1-Month or 3-Month DAPT in Women and Men at High Bleeding Risk Undergoing PCI

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ONE-MONTH VS. THREE-MONTHS DUAL ANTIPLATELET THERAPY IN WOMEN AND MEN AT HIGH BLEEDING RISK UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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Abstract

Background: In patients at high bleeding risk (HBR), short dual antiplatelet therapy (DAPT) after coronary stenting has been associated with fewer bleeding events and preserved ischemic protection. Whether these effects are affected by sex remains unclear.

Methods: Data from three prospective, international, single-arm studies (XIENCE Short DAPT Program) including HBR patients who underwent successful percutaneous coronary intervention (PCI) with implantation of a fluoropolymer-based cobalt-chromium everolimus-eluting stent (XIENCE, Abbott) were analyzed. The primary endpoint was the composite of all-cause death or any myocardial infarction (MI) at 1 year. The key secondary endpoint was Bleeding Academic Research Consortium (BARC) type 2 to 5 bleeding.

Results: Out of 3,364 patients, 1,154 (34.3%) were women. At 1 year, the rates of death or MI (7.6% vs 8.1%) and BARC 2-5 bleeding (9.5% vs 9.2%) were similar in women and men. After propensity score adjustment, 1- vs. 3-month DAPT conferred a similar risk of death or MI in women (7.5% vs. 7.6%, adj. HR 0.86, 95% CI 0.54-1.36) and men (8.1% vs. 8.0%, adj. HR 1.04, 95% CI 0.75-1.44; p-interaction=0.783). In both women and men BARC 2-5 bleeding events were lower with 1-month DAPT but the reduction in bleeding risk was not significant after propensity score adjustment (women: 7.1% vs. 11.2%, adj. HR 0.66, 95% CI 0.43-1.02; men: 8.5% vs. 9.7%, adj. HR 0.78, 95% CI 0.57-1.06; p-interaction=0.378).

Conclusions: Among HBR patients undergoing PCI with everolimus-eluting stent implantation, 1-month compared with 3-months DAPT was associated with a similar risk of ischemic events irrespective of sex. In both women and men, 1-month DAPT was associated with lower

occurrence of clinically relevant bleeding as compared to 3-months DAPT, although with no significant difference in bleeding risk after propensity score adjustment.

Key words: percutaneous coronary intervention; dual antiplatelet therapy; sex differences; women; drug eluting stent; high bleeding risk.

Abbreviations

BARC, Bleeding Academic Research Consortium.

CI, confidence intervals.

DAPT, dual antiplatelet therapy.

DES, drug-eluting stents.

HBR, high bleeding risk.

HR, hazard ratio.

PCI, percutaneous coronary intervention.

MI, myocardial infarction.

TLF, target lesion failure.

TVR, target vessel revascularization.

Clinical perspectives

- *What is Known?* Women undergoing percutaneous coronary intervention (PCI) are at higher bleeding risk as compared to men and might derive a clinical benefit from short dual antiplatelet therapy (DAPT).
- *What is New?* In both women and men at high bleeding risk undergoing PCI, the two different short DAPT regimens (1-month vs. 3-months DAPT) confer a similar risk for the composite of death and myocardial infarction. One-month DAPT seems to be associated with a lower bleeding risk than 3-months DAPT, irrespective of sex.
- *What is Next?* Due to the low proportion of women enrolled in this registry as well as in previous PCI trials, dedicated studies assessing the optimal DAPT duration in women are warranted.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is targeted at reducing the risk of thrombotic events in patients who undergo percutaneous coronary intervention (PCI) with drug-eluting stents (DES) implantation.[1,2] On the other hand, DAPT is associated with a higher risk of bleeding, which impacts mortality and morbidity and is related to the duration and intensity of the treatment.[3,4] Improvements in stent design and technology have led to a substantial reduction in thrombotic complications, allowing earlier DAPT discontinuation.[5–11] Several ischemic and bleeding risk scores have been developed and validated with the aim to identify high bleeding risk (HBR) patients, who account for about 40% of all subjects receiving DAPT and might benefit from reduced DAPT durations.[12,13] Nonetheless, optimal DAPT regimen after PCI remains debated.

Female patients are notably under-represented in clinical trials, leading to a suboptimal spread of novel therapeutic strategies in women.[14] Indeed, women present with higher bleeding risk following PCI as compared to men and could derive greater benefit from short DAPT.[15–17]

In a pooled dataset of 3 prospective studies enrolling HBR patients undergoing PCI with cobalt-chromium everolimus-eluting stents (the XIENCE Short DAPT program), 1-month and 3-months DAPT regimens were non-inferior to standard DAPT in terms of ischemic events reduction, with a potential to reduce bleeding risk.[18–21] The present analysis ought to compare sex-related differences in ischemic and bleeding outcomes among patients included in the XIENCE Short DAPT program.

Methods

Study design

This is a pre-specified sub-study within the XIENCE Short DAPT program, which consisted of three prospective, multicenter, single-arm studies conducted at 101 sites in the United States (XIENCE 90; NCT03218787), 58 sites in the United States and Canada (XIENCE 28 USA; NCT03815175), and 52 sites in Europe and Asia (XIENCE 28 Global; NCT03355742) from July 2017 to February 2020 (**Supplementary Tables 1-3**). The rationale, design, and principal results have been reported previously[15–17]. In brief, this clinical program investigated two different short DAPT durations after PCI with a fluoropolymer-based cobalt-chromium everolimus-eluting stent (XIENCE, Abbott). The XIENCE 28 and 90 studies were conducted with nearly identical protocols, differing only in the duration of DAPT. It was predetermined that data from the USA and Global studies of XIENCE 28 would be combined for analysis. The principal investigators with members of the executive and steering committees and the sponsor designed the protocol. National regulatory agencies and institutional review boards or ethics committees of participating sites approved the study protocol. An independent data monitoring committee provided external oversight to ensure public safety. All enrolled patients provided written informed consent.

Study population

Subjects who underwent successful PCI with the XIENCE stent were screened for eligibility. Patients had to fulfill at least one of the following inclusion criteria: age ≥75 years, chronic anticoagulant therapy, history of major bleeding in the previous 12 months, history of ischemic or hemorrhagic stroke, renal insufficiency (creatinine > 2.0 mg/dL or maintenance

dialysis), anemia (hemoglobin < 11 g/dL) and systemic conditions associated with an increased risk of bleeding including hematological disorders such as thrombocytopenia (platelet count < 100,000/mm^3) or coagulation disorders. Key exclusion criteria included presentation with ST-segment elevation myocardial infarction (MI), left ventricular ejection fraction <30%, implantation of a DES other than a cobalt-chromium everolimus-eluting stent in the previous 12 months, target lesion located in the left main, arterial or saphenous vein graft or in a previously implanted stent (in-stent restenosis), chronic total occlusion and target lesion treated with overlapping stents. The full list of inclusion and exclusion criteria is reported in **Supplementary Table 4**.

After index PCI, all patients received DAPT with aspirin plus a P2Y12 inhibitor. There were no restrictions on the choice of the P2Y12 inhibitor, but clopidogrel was recommended. The eligibility for discontinuing DAPT was assessed at 1 month in XIENCE 28 and at 3 months in XIENCE 90. Patients who had been adherent to treatment and free from MI, repeat coronary revascularization, stroke or stent thrombosis, discontinued the P2Y12 inhibitor and continued aspirin until the end of the study.

Follow-up was performed in-person or via telephone interviews at 1, 3, 6, and 12 months after index PCI in XIENCE 28, and at 3, 6, and 12 months in XIENCE 90. Patients from XIENCE 90 who were event-free and adherent to treatment at 1 month were retrospectively selected to match the XIENCE 28 event-free population.

Clinical outcomes

The primary endpoint was the composite of all-cause death or any myocardial infarction (MI) between 1 and 12 months after the index procedure.[22] MI was defined according to a modified Academic Research Consortium definition. The key secondary endpoint was Bleeding Academic Research Consortium (BARC) type 2 to 5 bleeding.[12] Additional secondary endpoints included target lesion failure (TLF; defined as the composite of cardiovascular death, target vessel MI, or clinically indicated target lesion revascularization), the individual components of the composite endpoints, definite or probable stent thrombosis, stroke, ischemic stroke, target vessel revascularization (TVR) and BARC type 3-5 bleeding. Definitions for the primary and secondary endpoints are provided in **Supplementary Tables 5-6**. All clinical events were adjudicated by an independent external committee.

Statistical analysis

The effects of 1-month versus 3-months DAPT on ischemic and bleeding outcomes were evaluated according to sex. Clinical and procedural characteristics of each group are summarized using means and standard deviations or median and interquartile range for continuous variables and counts and percentages for categorical ones. Chi-square and Student's t-test or Mann-Whitney *U* test were used to compare groups, as appropriate. The cumulative incidence rates for both primary and secondary endpoints were calculated with the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) were generated using unadjusted and multivariable adjusted Cox proportional hazard models. Because treatment arms were not randomized, adjusted risks for all endpoints were estimated using propensity score stratification into quintiles. Propensity scores (patients' estimated probability of receiving 1- or 3-month DAPT) were derived using a logistic regression model that included the treatment group as the

outcome and the selected baseline demographic, clinical, and procedural covariates as the predictors. The list of variables included in the propensity score model is reported in **Supplementary Table 7.**

The Markov Chain Monte Carlo multiple imputation method was used to handle missing data in the propensity score building. The Rubin's combination rule was used to integrate the final analysis with each of the 10 imputed data sets. All endpoints were tested for superiority with the Farrington-Manning method and a 1-sided alpha of 0.025. The stratification weight was based on the total sample size in each stratum relative to the overall sample size for both arms.

Heterogeneity of treatment effects was assessed across pre-specified subgroups using a generic version of the meta-analysis where each subgroup contributes a normalized treatment effect and its standard error. A landmark analysis at 3 months was performed to discriminate between events occurring in the period of actual treatment difference between the 2 DAPT groups (1-3 months) and thereafter (3-12 months).

All statistical analyses were performed with the R software, version 3.6.2 (R Foundation for Statistical Computing), or the SAS software, version 9.4 (SAS Institute).

Results

Patients characteristics

A total of 3,652 patients were enrolled in the XIENCE Short DAPT program from July 19, 2017, to February 7, 2020. Of these, 3,364 patients were free of ischemic events and adherent to treatment at 1 month (1,392 [41.4%] from XIENCE 28; 1972 [58.6%] from XIENCE 90) and

were included in this analysis. The study population comprised 2210 (65.7%) men and 1,154 (34.3%) women.

Baseline clinical and procedural characteristics in women and men are reported in **Supplementary Table 8**. The mean number of HBR criteria was 1.5 ± 0.7 in both sexes (p=0.108). Women tended to be older than men, more likely to have anemia and less likely to present with thrombocytopenia, renal insufficiency, and oral anticoagulant therapy. The proportions of prior PCI, prior coronary artery bypass grafting and prior MI were lower in women (**Supplementary Table 8**), which also presented with higher mean PARIS (6.6±2.3 vs. 5.8±2.2, p<0.001) and PRECISE-DAPT (30.1±11.3 vs. 25.0±11.3) bleeding risk scores. Following PCI, aspirin was administered in 87.2% of patients, with no significant differences based on sex, while clopidogrel was the most used P2Y12 inhibitor (83.7%).

In both women and men, patients receiving 1-month versus 3-months DAPT were more likely to be Asian or Hispanic and to suffer from chronic kidney disease and less likely to have hypertension, dyslipidemia and multivessel coronary artery disease (**Table 1**). Men receiving 1-month DAPT had higher bleeding risk than those in the 3-months DAPT group, as assessed through both the PARIS and the PRECISE-DAPT scores, while no difference in baseline bleeding risk between the two treatment groups was noted for women (**Table 1**).

Outcomes by sex

Kaplan-Maier incidences of the primary and secondary endpoints at 1 year in women and men are shown in **Figure 1** and **Supplementary Table 9**. The primary endpoint of all-cause death or MI occurred in 7.6% of women and 8.1% of men, with no significant difference

between the sexes (p=0.867; adj. HR 0.79, 95% CI: 0.60-1.05). The rate of BARC 2-5 bleeding was also similar between sexes (9.5% in women vs. 9.2% in men; p= 0.815, adj. HR: 1.03, 95% CI: 0.81-1.31). There was no significant difference in all other secondary endpoints. (**Figure 1** and **Supplementary Table 9).**

Outcomes by randomized DAPT duration in women and men

The cumulative incidence of all-cause death or MI at 1 year was similar between the 1-month and 3-months DAPT regimens irrespective of sex (log-Rank p=0.940 - **Figure 2** and **Supplementary Table 10**). Such result remained consistent after propensity score adjustment (women: 7.5% vs. 7.6%, adj. HR 0.86, 95% CI: 0.54-1.36; men: 8.1% vs. 8.0%, adj. HR 1.04, 95% CI: 0.75-1.44; p-interaction=0.783), as shown in **Table 2** and **Figure 3**. Both women and men exhibited lower BARC 2-5 bleeding with 1-month DAPT, although the reduction in bleeding risk was not statistically significant after propensity score adjustment (women: 7.1% vs. 11.2%, p<0.001, adj. HR: 0.66, 95% CI: 0.43-1.02; men: 8.5% vs. 9.7%, p<0.001, adj. HR: 0.78, 95% CI: 0.57-1.06; p-interaction=0.378) (**Table 2, Supplementary Table 10** and **Figures 2-3**). Similarly, BARC 3-5 bleeding was numerically lower with 1-month DAPT in both sexes with no significant differences after propensity score adjustment (women: 3.0% vs. 4.5%, p<0.001, adj. HR: 0.61, 95% CI: 0.31-1.19; men: 4.3% vs. 4.8%, p=0.006, adj. HR: 0.83, 95% CI: 0.53-1.29; p-interaction=0.535) (**Table 2, Supplementary Table 10** and **Figure 3**).

With regards to the other secondary endpoints, propensity score adjusted analysis found target vessel revascularization was more frequent with the 1-month DAPT regimen in women but not in men (p for interaction = 0.03, **Table 2**). For all other secondary endpoints there were no significant differences between treatment strategies by sex with no interaction between sex and treatment effect of the 1-month vs. 3-months DAPT strategies. (**Table 2**).

Landmark analyses

At the 1-3 months landmark analysis, 1-month DAPT conferred a lower risk of BARC 3-5 bleeding in women (0.7% vs. 2.5%, adj. HR 0.25, 95% CI: 0.07-0.89) and of BARC 2-5 bleeding in men (3.1% vs. 4.6%, adj. HR 0.61, 95% CI: 0.38-0.99), although there was no significant sex-treatment effect interaction (**Supplementary Table 11**). Between 3 and 12 months, no differences between the two DAPT regimens were observed in both women and men. (**Supplementary Table 11**)

Discussion

The main findings of this sex-stratified analysis of pooled data from three large prospective studies including HBR PCI patients treated with cobalt-chromium everolimus-eluting stents and subsequent short (1- or 3-month) DAPT followed by aspirin monotherapy are the following:

- Compared to men, women had a similar risk of both ischemic events and clinically relevant bleeding at one year.
- There was no difference in the primary outcome of all-cause death or MI between the two short DAPT regimens regardless of sex.
- In both women and men, 1-month versus 3-months DAPT was associated with lower occurrence of BARC 2-5 bleeding, although the reduction in bleeding risk was not significant after propensity score adjustment.

Even in the era of contemporary generation DES, women continue to exhibit poorer outcomes after PCI, primarily due to a higher incidence of bleeding when compared to their male counterparts.[16,23–25] Several sex-stratified analyses of large randomized trials have suggested women undergoing PCI present with higher prevalence of bleeding risk factors as compared to men.[15,17,24] In keeping with these findings, some baseline and procedural characteristics such as older age, higher prevalence of anemia and less common use of radial access potentially predisposing to higher bleeding risk have been observed in women of our population. However, no sex-related differences in bleeding events at one year were detected, which is likely due to the overall HBR nature of the study population. In fact, the incidence of major (BARC 3-5) bleeding episodes at one year in male patients (4.6%) was higher as compared to previous all-comers PCI studies (1.4% in GLOBAL LEADERS;[15] 2.2% in PROMETHEUS;[24] 1.3% in TWILIGHT[17]), and the findings of our analysis are in line with those of LEADERS-FREE and MASTER DAPT, showing no excess bleeding in women vs. men within patients at increased bleeding risk.[26,27]

While a reduction of bleeding with shorter DAPT regimens has consistently been reported in women, the effect of such therapy on ischemic outcomes varied by sex.[15,17,28–30] In studies comparing 1-month or 3-months DAPT followed by aspirin monotherapy with standard DAPT, no heterogeneity in treatment effect by sex has been found.[9,10,31,32] However, with regard to recent trials testing a strategy of short DAPT followed by P2Y12 inhibitor monotherapy versus standard DAPT, an individual patient-level meta-analysis including 24,096 patients showed a significantly lower risk of the composite of death, MI or stroke in women (HR 0.64, 95% CI: 0.46-0.89) but not in men (HR 1.00, 95% CI: 0.83-1.19, p for interaction = 0.02).[28] Similarly, in a pre-specified secondary analysis of the MASTER DAPT trial, which randomized HBR patients

to 1-month DAPT (followed by P2Y12 inhibitor monotherapy in over 70% of cases) or standard DAPT, a more pronounced reduction in the risk of MI in women compared to men within the short DAPT arm was observed.[27]

The XIENCE Short DAPT program had the original attribute to directly compare two different short DAPT regimens (1-month or 3-months DAPT) followed by aspirin monotherapy for up to one year in HBR patients, demonstrating a reduction in BARC 2-5 bleeding with the 1-month versus 3-months DAPT regimen without any corresponding rise in all-cause death or MI.[20,21] Notably, the "mandatory" short DAPT duration has been challenged in the last years with several studies confirming the feasibility of discontinuing aspirin at 1 month[33,34] or earlier[35] but few data supporting P2Y12 inhibitors withdrawal at one month. The present sex-stratified analysis confirms that the results observed in the overall population remain consistent in both women and men.

Putting together our findings with those of previous short DAPT trial, we can therefore conclude that short DAPT effectively tackles the excess bleeding risk associated with female sex as well as other HBR features Nonetheless, women remain consistently underrepresented in PCI trials.[36] Although the Xience Short-DAPT trial enrolled a higher percentage of women (34%) compared to previous investigations in this field[15,17,27,29,30], additional evidence regarding bleeding reduction strategies in women is warranted.

Study limitations

First, the proportion of women was smaller than men in our study (1,154 vs 2,210), leading to a potential underestimation of event rates in female patients (type II error). Second, the study was

non-randomized and although propensity score adjusted analysis is a valuable tool to compare the effectiveness of different treatment groups, the presence of unmeasured confounders cannot be excluded. Third, the study was not powered to evaluate differences in single ischemic endpoints including MI, stent thrombosis and stroke. Fourth, the inclusion of patients who were free of events at one month in the XIENCE 90 cohort might have led to an overestimation of DAPT adherence in this group and reduced the chance to detect differences in outcomes between the two strategies; however, the landmark analysis between 3 and 12 months provided consistent results. Fifth, HBR inclusion criteria used in the XIENCE Short DAPT program were defined before the Academic Research Consortium definition of HBR became available.[22] Finally, this analysis refers to HBR patients receiving cobalt-chromium everolimus-eluting stents and its results may not apply to the general PCI population.

Conclusion

Among HBR patients undergoing PCI with cobalt-chromium everolimus eluting stent, 1-month or 3-months DAPT, followed by aspirin monotherapy, led to a similar risk of ischemic events at one year irrespective of sex. In both women and men, 1-month DAPT was associated with lower occurrence of clinically relevant bleeding as compared to 3-months DAPT, however with no significant difference in bleeding risk after propensity score adjustment.

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Tables

Table 1. Baseline clinical and procedural characteristics by sex and DAPT regimen

	Women (N=1554)			Men (N=2210)		
	1-month DAPT N= 453 (39.3%)	**3-month DAPT N=701 (60.7%)**	**p-value**	**1-month DAPT N= 939 (42.5%)**	**3-month DAPT N=1271 (57.5%)**	**p-value**
High bleeding risk criteria						
Age >= 75 years	330 (72.8%)	504 (71.9%)	0.725	619 (65.9%)	788 (62.0%)	0.058
Chronic anticoagulant therapy	165 (36.4%)	241 (34.4%)	0.478	452 (48.2%)	564 (44.4%)	0.076
Anemia	96 (21.2%)	158 (22.5%)	0.590	105 (11.2%)	155 (12.2%)	0.470
History of stroke	45 (9.9%)	80 (11.4%)	0.430	100 (10.7%)	143 (11.3%)	0.661
Renal insufficiency	30 (6.6%)	40 (5.7%)	0.524	86 (9.2%)	117 (9.2%)	0.976
Thrombocytopenia	8 (1.8%)	7 (1.0%)	0.254	23 (2.6%)	31 (2.5%)	0.930
History of major bleeding	15 (3.3%)	24 (3.4%)	0.918	31 (3.3%)	33 (2.6%)	0.326
Number of HBR criteria	1.5±0.7	1.5±0.7	0.687	1.5±0.8	1.4±0.7	0.028
Clinical characteristics						
Age, years	76.9±8.5	76.5±9.1	0.396	75.5±8.3	74.3±9.4	0.002
BMI, kg/m^2	28.6±7.3	29.9±7.1	0.002	28.2±5.2	30.2±6.2	<.001
Race						
American Indian or Alaskan Native	0 (0.0%)	3 (0.4%)	0.556	2 (0.3%)	8 (0.6%)	0.510
Asian	43 (13.4%)	10 (1.4%)	<.001	83 (12.8%)	35 (2.8%)	<.001

Black or African American	15 (4.7%)	49 (7.0%)	0.153	21 (3.2%)	68 (5.4%)	0.037
Native Hawaiian or Pacific Islander	0 (0.0%)	4 (0.6%)	0.315	0 (0.0%)	1 (0.1%)	1.000
White	264 (82.0%)	618 (88.2%)	0.008	543 (83.7%)	1121 (88.2%)	0.006
Hispanic or Latino ethnicity	34 (8.0%)	19 (2.7%)	<.001	104 (11.7%)	37 (2.9%)	<.001
Hypertension	397 (87.6%)	640 (91.3%)	0.044	782 (83.3%)	1131 (89.0%)	<.001
Dyslipidemia	315 (69.5%)	564 (80.5%)	<.001	624 (66.5%)	1058 (83.2%)	<.001
Diabetes mellitus	171 (38.0%)	264 (37.7%)	0.922	341 (36.6%)	523 (41.2%)	0.029
Chronic kidney disease	268 (61.3%)	365 (52.7%)	0.004	363 (40.6%)	436 (34.5%)	0.004
Prior PCI	108 (23.8%)	188 (26.8%)	0.258	282 (30.0%)	419 (33.0%)	0.143
Prior CABG	18 (4.0%)	59 (8.4%)	0.003	94 (10.0%)	187 (14.7%)	0.001
Prior MI	63 (14.0%)	97 (14.1%)	0.982	164 (17.6%)	220 (17.6%)	0.990
Multivessel disease	152 (33.6%)	284 (40.5%)	0.017	421 (44.8%)	634 (49.9%)	0.019
Chronic coronary syndrome	283 (62.5%)	441 (62.9%)	0.881	634 (67.5%)	842 (66.2%)	0.530
Acute coronary syndrome	170 (37.5%)	260 (37.1%)	0.881	305 (32.5%)	429 (33.8%)	0.530
NSTEMI	92 (20.3%)	63 (9.0%)	<.001	153 (16.3%)	78 (6.1%)	<.001
Unstable angina	78 (17.2%)	197 (28.1%)	<.001	152 (16.2%)	351 (27.6%)	<.001
PARIS bleeding risk score	6.6±2.2	6.7±2.4	0.654	5.9±2.3	5.7±2.2	0.026
PARIS bleeding risk score [IQR]	6.0 (5.0-8.0)	6.0 (5.0-8.0)	0.817	6.0 (4.0-8.0)	5.0 (4.0-7.0)	0.043
PRECISE-DAPT bleeding risk score	30.8±10.8	29.7±11.6	0.104	26.1±11.2	24.3±11.3	<.001
PRECISE-DAPT bleeding risk score	30.0 (24.0-37.0)	29.0 (23.0-36.0)	0.125	25.0 (18.0-32.0)	24.0 (16.0-30.0)	<.001

[IQR]						
Procedural characteristics						
Number of lesions treated [IQR]	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.093	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.286
Number of vessels treated [IQR]	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.879	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.050
B2/C lesion	141 (31.1%)	237 (33.8%)	0.343	357 (38.0%)	450 (35.4%)	0.207
Bifurcation	50 (11.0%)	55 (7.8%)	0.066	111 (11.8%)	98 (7.7%)	0.001
Radial access	295 (65.1%)	351 (50.1%)	<.001	691 (73.6%)	677 (53.3%)	<.001
Number of stents per subject [IQR]	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.157	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.207
Total stent length, mm	25.9±13.4	25.6±14.5	0.676	27.8±14.9	25.6±13.5	<.001
Pre-procedure RVD, mm	3.0±0.4	2.9±0.5	0.917	3.0±0.5	3.0±0.5	0.346
Pre-procedure % DS	82.0±11.6	83.4±9.1	0.032	82.8±9.7	84.2±9.8	<.001
Antiplatelet therapy at discharge						
Aspirin	370 (81.7%)	653 (93.2%)	<.001	762 (81.2%)	1148 (90.3%)	<.001
Clopidogrel	379 (83.7%)	576 (82.2%)	0.511	825 (87.9%)	1036 (81.5%)	<.001
Prasugrel	3 (0.7%)	15 (2.1%)	0.048	11 (1.2%)	31 (2.4%)	0.031
Ticagrelor	71 (15.7%)	112 (16.0%)	0.890	103 (11.0%)	205 (16.1%)	<.001

DAPT: dual-antiplatelet therapy, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, MI: myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction.

Table 2. Primary and secondary endpoints by sex and DAPT regimen after propensity score adjustment

	Women (N=1154)				Men (N=2210)				
Outcomes	**1-month DAPT No. (%)**	**3-month DAPT No. (%)**	**Adjusted Hazard ratio[a] (95% CI)**	**p-value**	**1-month DAPT No. (%)**	**3-month DAPT No. (%)**	**Adjusted Hazard ratio[a] (95% CI)**	**p-value**	**Interaction p-value[b]**
All-cause death, or MI	32 (7.5%)	51 (7.6%)	0.86 (0.54 - 1.36)	0.520	71 (8.1%)	94 (8.0%)	1.04 (0.75 - 1.44)	0.801	0.783
All-cause death	17 (3.9%)	33 (5.0%)	0.71 (0.38 - 1.30)	0.260	47 (5.4%)	55 (4.8%)	1.11 (0.73 - 1.67)	0.633	0.269
Cardiovascular death	9 (2.1%)	18 (2.8%)	0.76 (0.33 - 1.73)	0.510	23 (2.7%)	31 (2.8%)	0.95 (0.54 - 1.69)	0.870	0.563
MI	16 (3.9%)	28 (4.3%)	0.86 (0.45 - 1.62)	0.642	24 (2.8%)	45 (3.8%)	0.78 (0.46 - 1.31)	0.351	0.658
Definite or probable ST	2 (0.5%)	3 (0.5%)	1.13 (0.18 - 7.21)	0.897	2 (0.2%)	3 (0.3%)	1.04 (0.16 - 6.74)	0.965	0.928
Stroke	3 (0.7%)	14 (2.2%)	0.26 (0.07 - 0.94)	0.040	8 (1.1%)	19 (1.6%)	0.54 (0.23 - 1.29)	0.167	0.447
Ischemic stroke	3 (0.7%)	14 (2.2%)	0.26 (0.07 - 0.94)	0.040	6 (0.8%)	16 (1.4%)	0.42 (0.16 - 1.15)	0.093	0.561
Target lesion failure	24 (5.7%)	34 (5.2%)	1.00 (0.58 - 1.72)	0.996	45 (5.2%)	67 (5.8%)	0.97 (0.65 - 1.44)	0.869	0.616
Target lesion revascularization	8 (1.8%)	6 (0.9%)	2.21 (0.74 - 6.58)	0.156	10 (1.3%)	20 (1.7%)	0.71 (0.32 - 1.57)	0.393	0.097
Target vessel revascularization	16 (4.0%)	11 (1.7%)	2.32 (1.05 - 5.15)	0.038	13 (1.8%)	35 (3.0%)	0.55 (0.28 - 1.06)	0.076	0.003
BARC 2-5 bleeding	31 (7.1%)	69 (11.2%)	0.66 (0.43 - 1.02)	0.062	72 (8.5%)	115 (9.7%)	0.78 (0.57 - 1.06)	0.117	0.378
BARC 3-5 bleeding	13 (3.0%)	29 (4.5%)	0.61 (0.31 - 1.19)	0.146	36 (4.3%)	57 (4.8%)	0.83 (0.53 - 1.29)	0.406	0.535

DAPT: dual-antiplatelet therapy, MI: myocardial infarction, ST: stent thrombosis

[a] Propensity stratified outcomes according to baseline serum creatinine, anticoagulation therapy, stroke, history of major bleeding, baseline platelet, baseline hemoglobin, BMI, hypertension, hypercholesterolemia, prior PCI, prior CABG, prior MI, multi-vessel disease, acute coronary syndrome, B2/C lesion, total lesion length, mean pre RVD, mean pre DS, bifurcation lesion, number of lesion treated, number of vessel treated, number of stents, total stent length, P2Y12 on discharged, PARIS risk score for major bleeding, PRECISE DAPT risk score for bleeding

[b] P value is obtained from the interaction test between diabetes and DAPT after applying multiple imputation and propensity score stratification

The percentages mentioned above represent K-M rates at 12 months after index procedure.

Figure Legends

Figure 1. Event rates at 1 year in women and men.

The cumulative incidences for all study endpoints in women (red bars) and men (blue bars) are reported, alongside with the unadjusted p-value for comparison between sexes.

BARC: Bleeding Academic Research Consortium; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction; PCI: percutaneous coronary intervention; TLF: target lesion failure; TLR: target lesion revascularization.

Figure 2. Cumulative incidence of death or MI and BARC 2-5 bleeding by sex and DAPT regimen.

Kaplan Maier curves for all-cause death or MI (panel A) and BARC 2-5 bleeding (panel B) from 1 month to 1 year after PCI, in women (red curves) and men (blue curves) in the 1-month DAPT (solid lines) and 3-months DAPT (dotted lines) groups, are reported.

BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; MI, myocardial infarction.

Figure 3. Effect of DAPT duration on outcomes in women and men.

The event rates for all-cause death or MI, BARC 2-5 and BARC 3-5 bleeding are reported, alongside with the adjusted HR for 1-month vs- 3-months DAPT in both women and men.

BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy; HR: hazard ratio; MI, myocardial infarction.