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CORONARY ARTERY DISEASE

One-Year Outcome of Small-Vessel Disease Treated with Sirolimus-Eluting Stents: A Subgroup Analysis of the e-SELECT Registry

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Objectives: *To investigate the characteristics and one-year outcomes following sirolimus-eluting CYPHER Select Plus stent (SES) implantation in small (SmVD) and non-small vessel disease (NSmVD) in the international e-SELECT registry.*

Background: *Large-scale registry data are lacking on DES outcomes in SmVD treatment.*

Methods: *There were 4,700 SmVD (at least one vessel with estimated reference vessel diameter [RVD] < 2.5 mm, excluding 283 patients with unknown RVD vessels) and 10,139 NSmVD only patients.*

Results: *The SmVD population was older, with more women, diabetics, and vessels treated, higher mean Charlson Comorbidity Index score (CCI), shorter lesions, and less STEMI presentation. The 1-year stent thrombosis (ST) rate (primary end-point), was significantly higher (1.3% vs. 0.7%) in SmVD versus NSmVD, mainly driven by early events. One-year major adverse cardiac event (MACE), myocardial infarction (MI), and clinically indicated target-lesion revascularization (TLR) rates were significantly higher in SmVD although death and major bleeding rates were similar in both groups. Complication rates were similar between pure (3,188 patients; only RVD < 2.5 mm) and mixed (1,795 patients; some RVD < 2.5 mm or unknown RVD) SmVD. Multivariate predictors for 1-year MACE in SmVD included saphenous vein graft or bifurcation lesions, major bleeding, any antiplatelet therapy discontinuation within 1 month, age, number of stents implanted, CCI, acute coronary syndrome, and insulin-dependent diabetes mellitus.*

Conclusion: *SES implantation for SmVD occurs more frequently in women, diabetics, and those with multivessel disease and comorbidities. One-year ST, MACE, MI, and clinically indicated TLR rates are higher, although low overall, in SmVD or mixed SmVD patients while death rates are similar to NSmVD.* (J Interven Cardiol 2013;26:163–172)

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Introduction

From approximately one-third to over one-half of percutaneous coronary intervention (PCI) is targeted at significant disease in small coronary artery segments, defined as those with estimated reference vessel diameter (RVD) under a threshold ranging from 2.5 mm to 3 mm depending on the study.[1–5] PCI of small coronary artery segments, relative to that of larger caliber vessels, is significantly and directly associated with an increased risk of major adverse cardiovascular events (MACE), including restenosis and stent thrombosis (ST).[6–9] Some studies have reported higher rates of target vessel revascularization in small compared to large vessels even with comparable postprocedural minimal in-stent lumen areas, which could be a consequence of the greater proportions of higher risk baseline clinical and lesion characteristics, including diabetes, multivessel disease (MVD), diffuse disease, and chronic total occlusion, among patients with small-vessel disease (SmVD).[1,10] The clinical relevance and management, including medical therapy, PCI, and coronary artery bypass graft surgery (CABG) of SmVD is influenced by lesion location, amount of myocardium at risk, and occlusion severity.[11] CABG for revascularization of small coronary vessels is limited by high rates of technical failure.[12] For PCI of SmVD, various devices and techniques have been used over time; however, it was not until the introduction of drug-eluting stents (DES) that outcomes in this challenging higher-risk setting were greatly improved,[1,2,13–25] likely because, compared with large vessels, small vessels have a smaller postprocedural luminal area that is less able to accommodate neointimal hyperplasia.[25,26] Data on large "real-world" experiences with PCI of SmVD have been lacking and therefore this study is aimed at investigating the characteristics and 1-year outcomes and predictors of MACE following sirolimus-eluting CYPHER stent (SES, Cordis Corporation, Johnson and Johnson, Bridgewater, NJ, USA) implantation in SmVD relative to those in non-SmVD (NSmVD) in the international e-SELECT registry, which was conducted in 320 hospitals throughout 56 countries, recruited 15,147 patients, and has been the subject of 5 publications focused on different clinical subsets.[27–31]

Methods

The design, execution, and data analysis of the e-SELECT registry has been previously described.[27–31] The e-SELECT registry included 320 medical centers in 56 countries. Baseline data were collected between May 2006 and April 2008 in consecutive and eligible patients who underwent implantation of $\geq$1 CYPHER Select Plus (Cordis Corporation, Johnson and Johnson, Bridgewater, NJ, USA) SES according to standard practice and procedural techniques. The protocol specified very few inclusion or exclusion criteria. Although lesions could be pretreated with any technique or device (such as balloon angioplasty, cutting balloon, or atherectomy), implantation of SES in each target lesion during index procedure was mandatory. All postoperative medical management, including antithrombotic therapy, was prescribed according to usual local practice. The protocol was approved by the ethics committee of each participating medical center, and the patients granted their consent to participate in the registry. Patients for whom the collection of dependable follow-up information was unlikely and those who received a stent other than a CYPHER SES during the index procedure were excluded. RVD was visually estimated by angiography, and small vessels were defined as those with an RVD $\leq$ 2.5 mm. The primary end-point of the registry was a composite of definite and probable ST at 1 year of follow-up, as defined by the Academic Research Consortium.[32] Secondary end-points at 1 year included rates of major bleeding (MB) according to the STEEPLE (Safety and efficacy of Enoxaparin in PCI) definition,[33] cardiac and noncardiac death, myocardial infarction (MI), and MACE (defined as any death, MI, or target lesion revascularization [TLR]). Of 15,122 all-comer patients in the e-SELECT registry, treatment of SmVD, defined as at least one vessel with estimated RVD $\leq$ 2.5 mm and excluding cases with unknown RVD, was done in 4,700 patients (31%; 7,318 lesions; 8,443 stents), although treatment of NSmVD only was performed in 10,139 patients (67%; 12,204 lesions; 14,508 stents); proportions of cases with multiple stents, approximately 19%, and of overlapped stents among multiple-stent cases, approximately 87%, were similar for both groups. There were 3,188 with pure SmVD (RVD $\leq$ 2.5 mm only) and 1,795 with

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mixed SmVD (some vessel with RVD $\leq$ 2.5 mm or unknown RVD, the latter amounting to 283 patients). In the overall e-SELECT registry, 98.2% of patients were eligible for follow-up at 12 months. Of these 92.0% underwent follow-up at a mean follow-up of 370.4 $\pm$ 124.7 days. As previously reported for the e-SELECT registry, at 1 year (the follow-up length), the reported compliance with dual antiplatelet therapy (DAPT) as recommended by the European Society of Cardiology guidelines was 86.3%.[27]

Statistical Analysis. For all patients, standard descriptive statistics were used for baseline, lesion, and procedural characteristics and for clinical results. Continuous variables are presented as mean $\pm$ SD and compared using the Student's t-test, and categorical variables are presented as numbers and percentages and compared using the chi-square test. Cumulative rates of adverse clinical events were calculated with event-specific adjusted denominators, therefore all patients experiencing an event within 360 days or followed up for at least 330 days after index procedure contributed to the denominator. There was no censoring. MACE-free survival curves were constructed by the Kaplan–Meier life-table method, and compared by the log-rank test. Predictors of major adverse cardiac events were identified by univariate and multivariate analyses with Cox proportional hazards model. The following baseline covariates with >15% missing values were excluded from analysis: creatine kinase-MB isoenzyme (CK-MB) or troponin levels greater than upper limit of normal preprocedure; hemoglobin level preprocedure; left ventricular ejection fraction (LVEF), maximum inflation pressure, and platelet count. Baseline demographic, angiographic, clinical, and procedural covariates were identified by univariate analysis as significantly correlated ($P < 0.05$) with MACE, namely Charlson Comorbidity Index (CCI), saphenous vein graft (SVG)[34] target lesion, MB, age, number of stents implanted, total stent length, bifurcation lesion, in-stent restenosis (ISR) target lesion, any deviation from continuous DAPT up to 1-month follow-up, acute coronary syndrome (ACS), diabetes mellitus (DM), insulin-dependent DM (IDDM), MVD, maximum lesion length, index procedure-related ST, previous CABG, bypass graft lesion, chronic pulmonary disease, chronic Vitamin K antagonists (AVK) treatment, total number of lesions treated, major or minor bleeding, postdilation, moderate to severe renal disease, multisent-treated patient, diabetes with retinopathy, neuropathy or nephropathy, multilesion-treated patient, calcification, history of prior MI, ostial location, American College of Cardiology/American Heart Association (ACC/AHA) lesion morphology class B2 or C, unprotected left main target lesion, history of hyperlipidemia, and predilatation. Following the rule of 20 events per predictor, 13 of the most clinically meaningful univariate parameters with $P < 0.05$ (first 13 in the aforementioned univariate predictors) were included in the multivariate analysis. All statistical analyses were performed with SAS (version 9.1 or higher software, SAS Institute, Cary, NC, USA).

Results

As shown in Table 1, the SmVD patient population was older (63.2 years vs. 61.7 years, $P < 0.001$), with a higher proportion of women (28.4% vs. 22.9%, $P < 0.001$), diabetics (34.1% vs. 28.6%, $P < 0.001$), and higher mean CCI (1.1 $\pm$ 1.4 vs. 1.0 $\pm$ 1.3, $P < 0.001$) and had more vessels treated (1.3 vs. 1.1, $P < 0.001$). Patients with SmVD presented less often with ST-segment Elevation Myocardial Infarction (STEMI) (5.8% vs. 7.6%, $P < 0.001$), and had shorter lesions (19.1 mm vs. 20.8 mm, $P < 0.001$). The rate of ARC-defined "definite or probable" ST was significantly higher in the SmVD group (1.3% vs. 0.7%, $P < 0.001$), mainly driven by a higher incidence of early (0–30 days) ST (0.9% vs. 0.4%, $P = 0.002$; Fig. 1). The incidence of MACE (any death, MI, or TLR, 5.4% vs. 4.0%, $P < 0.001$), MI (2.4% vs. 1.5%, $P < 0.001$), and clinically indicated TLR (2.7% vs. 1.8%, $P < 0.001$) was significantly higher at 1 year in patients with SmVD, respectively (Fig. 2). The MACE-free survival rate at 1 year was significantly lower in SmVD than that in NSmVD (Fig. 3). The incidence of death (1.7% vs. 1.5%, $P = 0.287$) and MB (1.0% vs. 0.8%, $P = 0.218$) was similar in both groups. There was a numerical trend of increasing MACE rate with decreasing RVD (Fig. 4). The pure SmVD group had a higher proportion of women (30.6% vs. 23.5%, $P < 0.001$), with more prior PCI (33.1% vs. 30.1%, $P = 0.028$), higher mean CCI (1.2 vs. 1.1, $P = 0.026$), more STEMI (6.5% vs. 4.7%, $P = 0.0119$), fewer number of vessels or lesions treated (1.1 vs. 1.6, $P < 0.001$, and 1.2 vs. 2.3, $P < 0.001$, respectively), and smaller RVD (2.4 mm vs. 2.8 mm, $P < 0.001$). However, the MACE-free survival rate at 1 year was not significantly different between the pure and mixed SmVD groups (Fig. 5); the MACE-free survival rate at 1 year in the mixed

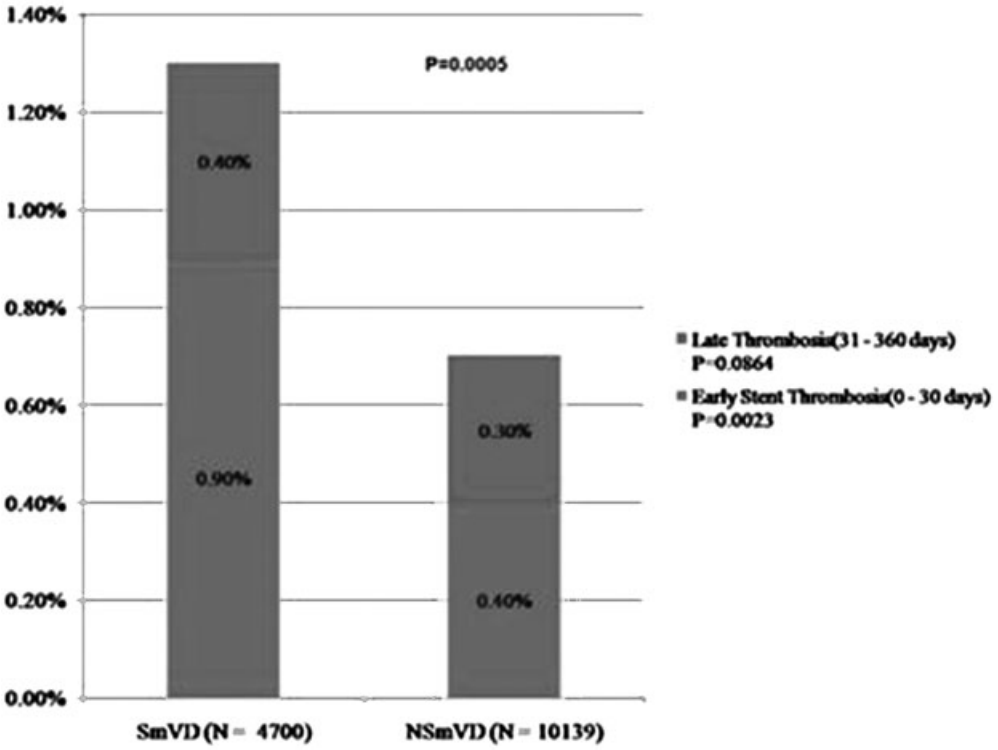

Figure 1. Histogram representation of definite/probable stent thrombosis according to the ARC definitions comparing the small-vessel disease and non-small-vessel disease subsets of the e-SELECT registry.

SmVD was significantly lower than that in NSmVD group (Fig. 6). The multivariate predictors for MACE in the SmVD group at 1 year included SVG or bifurcation target lesions, MB, any deviation from continuous DAPT up to 1-month follow-up, age [years], number of total stents implanted, CCI, ACS, and IDDM; (Table 2). Stent overlap was not a univariate predictor for MACE at 1 year (Hazard Ratio (HR) 1.05, 95% Confidence Interval (CI) 0.68–1.61, $P = 0.833$).

Discussion

This study of one of the largest cohorts of SmVD ($\leq$2.5 mm estimated RVD) confirms that SES implantation for SmVD occurs more frequently in women, diabetics, those with MVD, and comorbidities. Death rate at 1 year is similar to that of patients with NSmVD, and although incidence of MACE, MI, clinically indicated TLR, and ST is higher in patients with SmVD, and in those with mixed SmVD, it remains low overall. The proportion of SmVD treated in the e-SELECT registry, 31%, is within the range of previously reported ones in real-world interventional cardiology studies.[35] As further supported by this study, patients with smaller vessels have higher frequency of several characteristics, including DM and MVD that have been associated with a poorer outcome after stent implantation;[1,36,38] smaller coronaries also are more common in certain groups of patients including women and Asians.[19] The lower frequency of STEMI presentation in the SmVD versus NSmVD group (5.8% vs. 7.6%, $P < 0.001$) stands in contrast to a previous report[37] on a large cohort of 798 STEMI patients in whom approximately 50% of culprit lesions were located in smaller vessels (<3 mm). The increased risk of MACE in small relative to large vessels has been seen in previous studies[6–9] and in this study is mainly due to increased MI, ST, and TLR rates in SmVD patients, although the death rate is similar between the SmVD and NSmVD groups. Despite the remarkably low values for late lumen loss documented in DES studies, there remains a relationship between vessel size and restenosis, with increased restenosis rates in smaller vessels; the same is true for ST. Several studies, both randomized and nonrandomized, and subanalyses of all-comer studies have

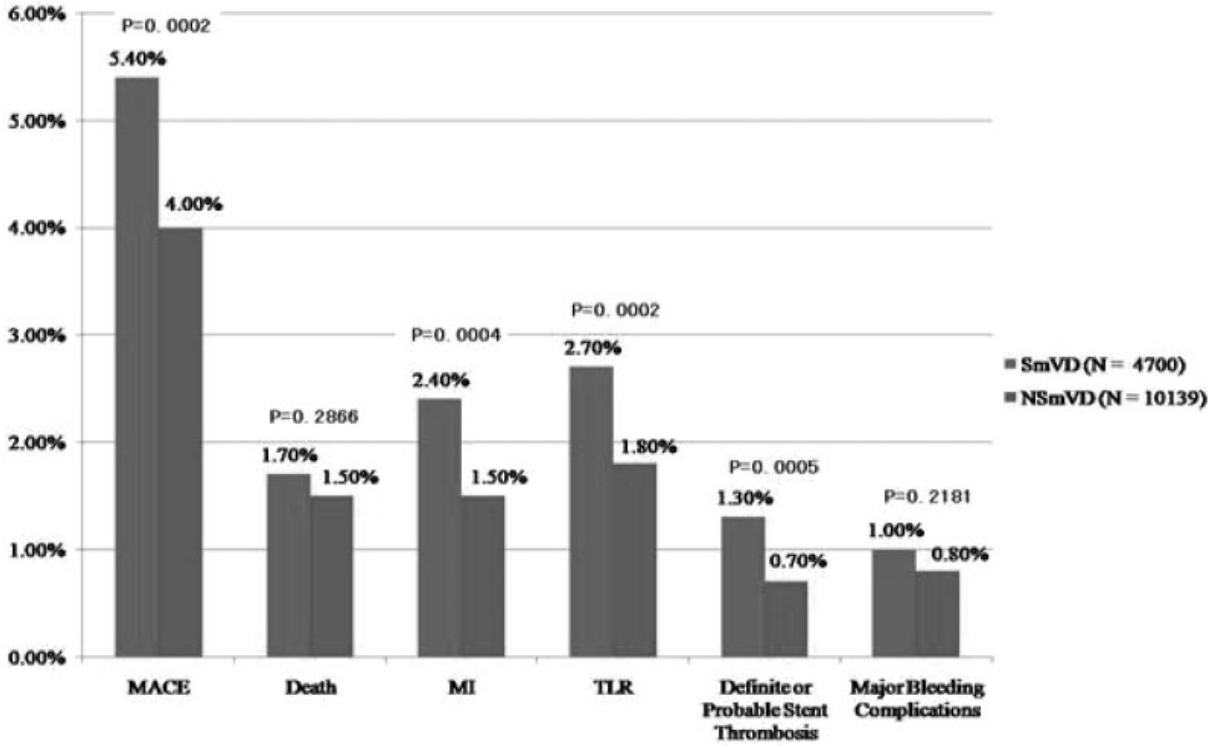

Figure 2. Major adverse clinical events at 1 year.

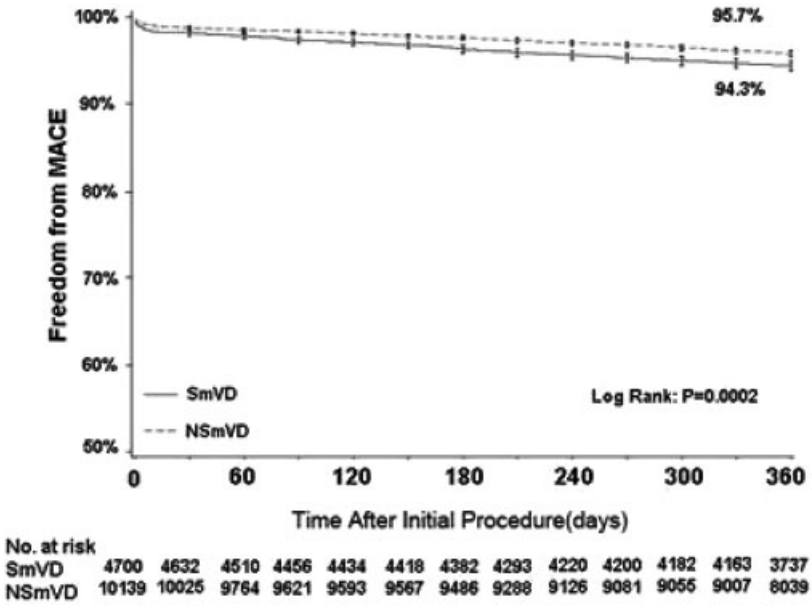

Figure 3. MACE-free survival curves at 1 year comparing patients with SmVD and NSmVD.

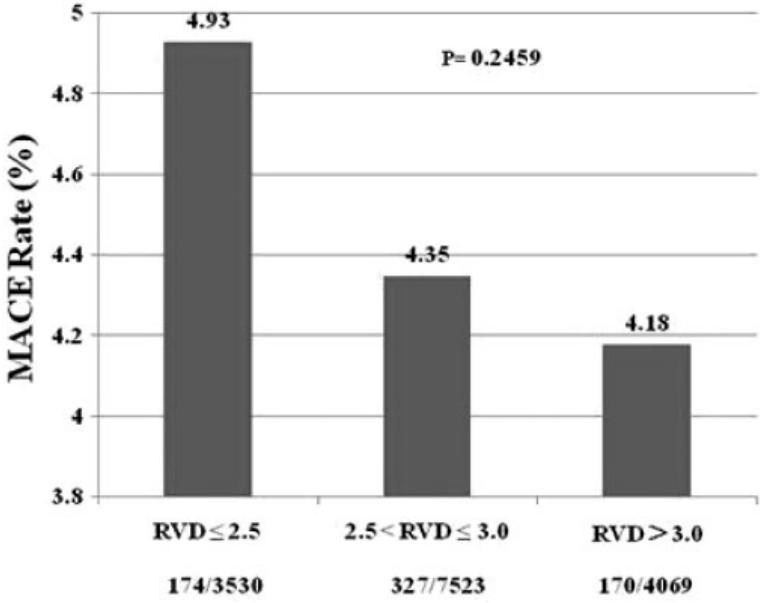

Figure 4. Correlation between MACE and RVD.

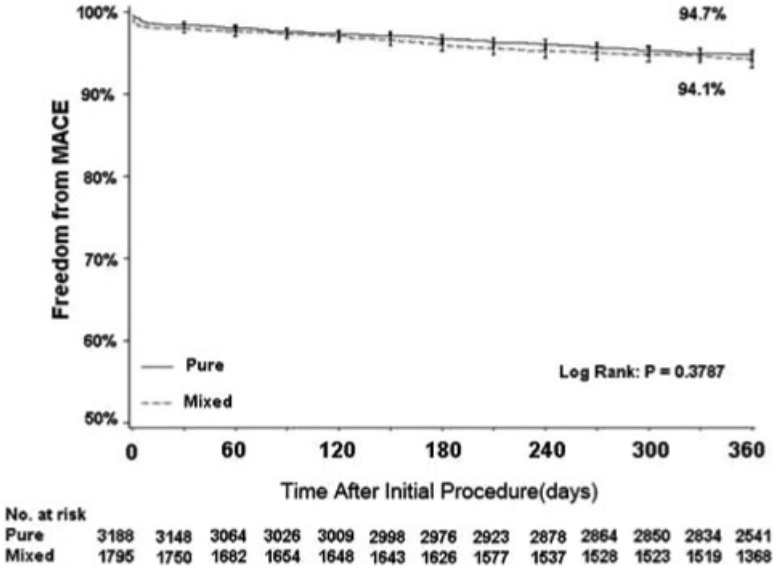

Figure 5. MACE-free survival curves at 1 year comparing patients with pure and mixed SmVD.

supported better outcomes in small vessels with SES, and in direct and indirect comparisons to PES.[15,38–45] Although some interventionists support balloon-only angioplasty for SmVD treatment,[46,47] SES has shown consistent benefit and lower rates of complications than alternative treatments[12,38–40,42,48–51] even when using, as was not the case in this study, 2.5 mm stents in vessels with <2.5 mm diameter,[40,44,52,53] or in patients with diabetes and very small coronary vessel (<2.1 mm) disease,[15] or even relative to thinner-strut bare metal stents (BMS) or DES.[17,54] In terms of the potential for improving outcomes of PCI in SmVD, studies have shown that specific baseline clinical and angiographic characteristics are predictive of the different rates of MACE, including restenosis, seen for various lesion/patient subsets.[39] Diabetes, for instance, exacerbates the negative impact on outcomes of smaller vessel size,[39,55,56,57] and insulin treatment was a multivariate predictor of in-segment restenosis in the Taxus in Real-life Usage Evaluation (TRUE) registry.[4] In this study IDDM was identified as one of the multivariate predictors of 1-year MACE. Hausleiter et al.[55] and Iijima

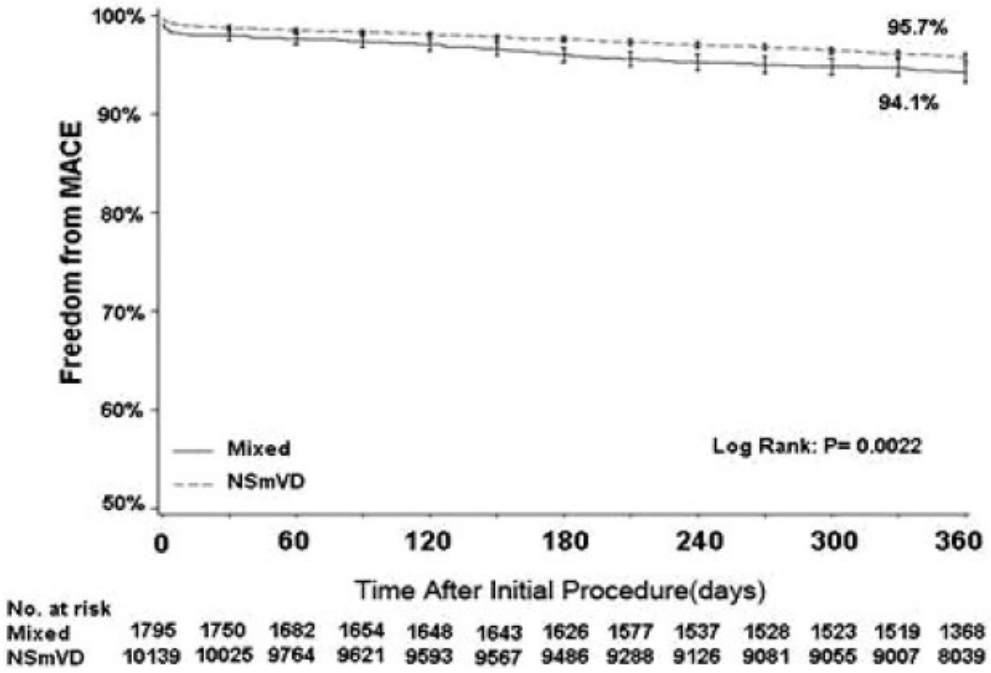

Figure 6. MACE-free survival curves at 1 year comparing patients with mixed SmVD and NSmVD.

Table 1. Baseline Patient and Procedural Characteristics of the SmVD and NSmVD Groups

	SmVD N = 4,700	NSmVD N = 10,139	P-value
Age (years)	63.2 ± 11	61.7 ± 11	<0.001
Male (%)	71.6	77.1	<0.001
Prior PCI (%)	32.4	32.2	0.86
Prior CABG (%)	10.7	8.3	<0.001
Prior MI (%)	31.6	32.6	0.23
Hypertension (%)	69.0	66.8	0.008
Hyperlipidemia (%)	70.8	67.3	<0.001
History of smoking (%)	51.0	54.8	<0.001
Diabetes mellitus (%)	34.1	28.6	<0.001
Insulin treated DM (%)	29.2	25.8	0.015
LVEF < 30% (%)	3.0	2.6	0.32
Charlson Comorbidity Index score	1.1 ± 1.4	1.0 ± 1.3	<0.001
STEMI (%)	5.8	7.6	<0.001
Number of vessels treated	1.3 ± 0.5	1.1 ± 0.4	<0.001
RVD (mm)	2.6 ± 0.4	3.1 ± 0.3	<0.001
Number of lesions treated	1.6 ± 0.8	1.2 ± 0.5	<0.001
Lesion length (mm)	19.0 ± 10.6	20.8 ± 12.0	<0.001
Number of stents/patient	1.8 ± 1.0	1.4 ± 0.7	<0.001
Number of stents/lesion	1.16 ± 0.42	1.19 ± 0.47	<0.001
Mean stent diameter (mm)	2.6 ± 0.2	3.1 ± 0.3	<0.001
Total stent length (mm)/lesion	24.2 ± 12.1	26.0 ± 13.7	<0.001
Lesions with predilatation (%)	67.5	62.3	<0.001
Stents with postdilatation (%)	33.1	37.8	<0.001
DAPT postprocedure (%)	97.1	97.3	0.33

Table 2. Multivariate Predictors of MACE at 1 Year in the SmVD Group

Predictors of MACE to 360 days Multiple CoxPh regression	Hazard ratio [95% CI]	P-value
Charlson Comorbidity Index	1.11 [1.06–1.16]	<0.001
SVG target lesion	3.63 [2.01–6.58]	<0.001
Major bleeding	3.35 [1.69–6.63]	<0.001
Age (years)	1.02 [1.01–1.03]	0.002
Number of stents implanted	1.20 [1.06–1.35]	0.003
Bifurcation lesion	1.55 [1.10–2.17]	0.011
Any deviation from continuous DAPT (up to 1-month follow-up)	2.26 [1.18–4.32]	0.014
ACS	1.38 [1.06–1.80]	0.016
Insulin-dependent diabetes mellitus	1.94 [1.05–3.60]	0.034

et al.[57] identified total stent length as a predictor of restenosis in SmVD treated with BMS; however, stent length was not among multivariate predictors of in-segment restenosis in a study of small vessel lesions (<2.75 mm) treated with PES.[4] In a Korean study of 1,269 lesions in small coronaries (≤2.8 mm), lesion length was a powerful predictor of restenosis and MACE, with multiple overlapping stents in very long SmVD (lesion length ≥60 mm) being associated with a high risk of SES failure.[58] In this study total stent number but not total stent length or stent overlap was a multivariate MACE predictor in SmVD. The CCI score which captures cardiovascular status is a MACE predictor as reported by Hausleiter et al.[55] which identified ACS at admission and LVEF as predictors of early adverse clinical outcomes in BMS-treated SmVD. Age was a MACE predictor of MACE in this and another report.[10] As in this study, Iijima et al.[57] identified bifurcation lesion as a MACE predictor. PCI of SVG is associated with worse outcomes and high incidence of ISR.[5] The finding in this study that DAPT discontinuation during the first month postindex procedure is a predictor of 1-year MACE is consistent with previous reports[59] and underscores the importance of DAPT use particularly during the first month postindex procedure; however, the finding that bleeding is also a MACE predictor in SmVD PCI calls for caution in the use of DES in the setting of patients at high risk for bleeding. This study showed that the MACE-free survival rate at 1 year was not significantly different between the pure and mixed SmVD groups; it was also significantly lower in mixed SmVD than in NSmVD which, to our knowledge, has not been previously reported in the literature. This finding has potential clinical significance. In clinical practice, patients with mixed vessel size (combined RVD ≤ 2.5 mm and RVD > 2.5 mm) are common, and to avoid unnecessarily increasing MACE one needs to consider the severity of lesion stenosis and the territory of ischemia of the SmVD before treating the lesion.

This study is limited by the fact that the Cypher stent has been withdrawn from markets in most countries; however, SES are extensively used in many places around the world, and the lessons learned from this study may also be suitable for treatment of SmVD with other limus-eluting stents. The study was an international multicenter registry, and the inclusion and exclusion criteria nonetheless allow for an analysis with lessened confounding. Because of the extensive multinational and multicenter nature of the registry study, the RVD was visually estimated without quantitative coronary angiography analysis, which does not allow validation of the actual vessel sizes included in the groups studied. However, the vessel size threshold used is not uncommon and the majority of small vessels treated were of similar estimated RVD, namely 2.5, as reflected by the standard deviation of 0.2. Also, although follow-up was conducted for 1 year, which does not address very late safety, i.e., events occurring beyond 1 year, the results of this international multicenter large-cohort study of outcomes after PCI of SmVD show favorable efficacy and safety of SES implantation in unselected patients and consistency with previous similar smaller studies. Only unadjusted rates of clinical events were compared between vessel size groups because the emphasis was on comparative epidemiology of SmVD and outcome predictors. Analyses also included pure and mixed SmVD groups which underscored the findings with the overall SmVD cohort (i.e., that including pure and mixed cases).

Conclusion

This large cohort study of SmVD confirms that SES implantation for SmVD occurs more frequently in women, diabetics, and those with MVD and

comorbidities. The incidence of MACE, MI, clinically indicated TLR, and ST is higher in patients with SmVD, whether pure or mixed SmVD, although it remains low overall. Death rate at 1 year is similar between SmVD and NSmVD. The multivariate predictors of 1-year MACE include SVG or bifurcation target lesions, MB, any deviation from continuous DAPT up to 1 month follow-up, age (years), number of total stents implanted, CCI, ACS, and IDDM.

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