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Two-Year Outcomes after Utilization of the TAXUS Paclitaxel-Eluting Stent in Bifurcations and Multivessel Stenting in the ARRIVE Registries

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Aims: *Examine the incidence of clinical events after utilization of the TAXUS® Express® paclitaxel-eluting stent (PES) in multivessel and bifurcation coronary stenting in an unselected patient population.*
Methods and Results: *The ARRIVE Program compiled data on 7,492 patients receiving ≥1 TAXUS Express PES, including patients with multivessel stenting (MVS; n = 1,208) and bifurcation stenting (n = 575). Patients were enrolled at procedure start with no mandated inclusion/exclusion criteria; all cardiac events were monitored with independent adjudication of end-points. Compared to simple use (single vessel/single stent) patients undergoing native intervention (N = 2,698), MVS patients had significantly more baseline comorbidities. Both groups had higher 2-year rates of mortality (7.3% [MVS] and 7.5% [bifurcation] vs. 4.2% [simple-use], P < 0.001), myocardial infarction (5.5% and 4.6% vs. 2.2%, P < 0.001 and P = 0.002), target vessel revascularization (15.5% and 14.8% vs. 7.7%, P < 0.001), and Academic Research Consortium definite/probable stent thrombosis (4.3% and 4.4% vs. 1.4%, P < 0.001) than the simple-use group.*
Conclusions: *ARRIVE multivessel and bifurcation stenting patients have significantly higher clinical risk through 2 years compared to simple-use patients. In the absence of large randomized controlled trials in these populations, ARRIVE provides important insight into clinical outcomes over an extended period of time.* (J Interven Cardiol 2011;24:342–350)

Introduction

Multivessel stenting (MVS)[1,2] and stenting of bifurcation lesions[3] using drug-eluting stents (DES) are associated with higher technical difficulty, higher need for repeat revascularization, and higher stent thrombosis (ST) rates compared to treatment of simpler coronary lesions, although outcomes are better compared to treatment with bare metal stents.[4–6] The TAXUS ARRIVE Safety Surveillance Program captured usage patterns and outcomes in 7,492 patients, including 1,208 patients who underwent multivessel and 575 patients who underwent bifurcation stenting.[7,8] Using data from ARRIVE, we evaluated 2-year clinical outcomes after DES implantation in these complex lesion subsets and compared them to outcomes in patients receiving the same DES in simple coronary lesions.

Methods

Study Design, Data Collection, and Follow-up. The TAXUS® Express2® Coronary Stent System (Boston Scientific Corporation, Natick, MA, USA)[9]

This study was Supported by Boston Scientific Corporation, Natick, MA, USA.

Conflicts of Interest. Boston Scientific Corporation [BSC] Speaker's Bureau (JML, DAC); BSC Medical Advisory Board (DAC); BSC consulting fees (JML); St Jude Medical and Terumo speaker honoraria (ESB); Abbott Vascular and Infraredx research support (ESB); BSC full-time employment and stock ownership (TSB, RMS, KDD).

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and the TAXUS Peri-Approval Registry: A Multicenter Safety Surveillance (ARRIVE) Program have been described previously.[7,8] Briefly, 2 prospective, multicenter US safety surveillance registries (ARRIVE 1 [50 sites, February–May 2004] and ARRIVE 2 [53 sites, October 2004–October 2005]) were similarly designed to enroll consecutive patients treated with the TAXUS Express paclitaxel-eluting stent (PES). Both studies are registered on www.clinicaltrials.gov (Identifiers NCT00569491 and NCT00569751). No specific inclusion/exclusion criteria were mandated as patients receiving a TAXUS stent were included in the registry, whether or not they also received a non-TAXUS stent during the index procedure. Under a protocol approved by the local Institutional Review Board in conformity with the declaration of Helsinki and FDA guidelines, patients providing informed consent were enrolled at procedure initiation. Investigators were not limited to the criteria specified in the product labeling if they believed that DES treatment represented the patient's best therapeutic option and were not required to provide their indications for DES placement. Cardiac enzyme and electrocardiographic data were collected per local practice. Follow-up angiography was performed at operator discretion and was not required by the study protocol. Patient follow-up was scheduled via a clinic visit or telephone contact with a study research nurse at 30 days, 6 months, and 1- and 2-years after the index procedure.

Dual antiplatelet therapy (DAPT, aspirin and clopidogrel/ticlopidine) was begun before or immediately after intervention with aspirin recommended indefinitely and the thienopyridine recommended for 6 months per the directions for use. The relationship to the study device of reported major cardiac events (MCE, defined as cardiac death, myocardial infarction [MI], target vessel revascularization [TVR], target lesion revascularization [TLR, defined as "TAXUS-stent-related" TVR]) and ST was determined by an independent Clinical Events Committee (CEC; see reference 7 for CEC membership); an event was deemed related to the TAXUS stent if it occurred at the stented segment or if the relationship to the stent could not be excluded based on existing information.[7] Data were source verified for death, MCE, and ST along with an additional 10–20% per site random sampling of patients. An independent committee at the Harvard Clinical Research Institute also adjudicated ST per the Academic Research Consortium (ARC) definite/probable definition.[10]

Statistical Analysis. Simple proportions with 2-sided P values from Student's t-test (continuous variables, summarized as mean ± one standard deviation) or chi-square test (discrete variables, presented as frequencies and group percentages) were used for baseline variables. Statistical analyses of events were carried out based on the CEC assessment of relation to the TAXUS stent. Time-to-event curves were generated by the Kaplan–Meier product method (log-rank P value). All analyses were performed using SAS System Software, Version 8.0 or higher (SAS Institute, Cary, NC, USA); $P < 0.05$ was considered statistically significant. The bifurcation subgroup included all patients with bifurcation stenting. The MVS subgroup (mean of 2.1 vessels per patient) consisted of all patients in whom more than 1 vessel was stented at the index procedure. Patients with bifurcation lesions who were treated for lesions in more than 1 vessel were included in both subgroups. Each of these subgroups was compared to the simple-use cohort. Simple-use cases (N = 2,698), with or without diabetes, excluded one or more of the following: acute MI; bifurcation, cardiogenic shock, chronic total occlusion (CTO), prior brachytherapy, vein graft stenting, in-stent restenosis, large vessel (reference vessel diameter [RVD] > 3.75 mm), left main disease/stenting, long lesion (>28 mm), moderate/severe calcification, MVS, ostial lesion, renal disease (serum creatinine >3.0 mg/dL or dialysis), severe tortuosity, and small vessel (RVD < 2.5 mm) as classified by the investigator. Multivariable Cox models were developed using baseline clinical and angiographic characteristics and procedure-related variables (Appendix S1) in order to determine independent predictors of death, MI, TVR, and ST. Significant predictors were identified using backward selection; the threshold to stay in the model was set at 0.10.

Results

Patient and Procedural Characteristics. Of 7,492 total ARRIVE patients, 1,208 (16.1%) underwent MVS (MVS; 2,969 lesions) and 575 (7.7%) underwent bifurcation stenting (741 lesions); 164 of the patients with bifurcation stenting were also in the MVS subgroup. These patients were part of the ARRIVE expanded-use cohort (N = 4,794),[8] which consisted of cases with patient and/or lesion characteristics outside the simple-use subgroup (N = 2,698) who would

Table 1. Comparison of Baseline Patient and Lesion Characteristics in ARRIVE MVS, Bifurcation, and Simple Use Cohorts

Variable	Multivessel Stenting N = 1,208 Patients N = 2,969 Lesions	Bifurcation Use* N = 575 Patients N = 741 Lesions	Simple Use† N = 2698 Patients N = 3,112 Lesions	P Value Multivessel vs. Simple Use	P Value Bifurcation vs. Simple Use
Patient characteristics					
Age (years)	65.1 ± 11.7	63.3 ± 11.7	63.0 ± 11.5	<0.001	0.51
Male	67.4% (814)	69.4% (399)	65.9% (1,777)	0.35	0.10
Hypertension	77.8% (940)	76.7% (441)	75.4% (2,034)	0.10	0.51
Hyperlipidemia	78.8% (952)	76.5% (440)	74.4% (2,007)	0.003	0.29
Diabetes mellitus‡	36.3% (439)	29.4% (169)	29.8% (805)	<0.001	0.83
Oral medications	27.9% (337)	20.0% (115)	21.8% (589)	<0.001	0.33
Insulin	11.3% (137)	9.9% (57)	8.9% (241)	0.02	0.46
Smoking at baseline	21.6% (261)	24.3% (140)	24.2% (652)	0.08	0.93
Prior MI	37.8% (457)	36.9% (212)	26.9% (725)	<0.001	<0.001
Prior PCI	33.5% (405)	38.4% (221)	34.5% (930)	0.57	0.07
Prior stroke	7.1% (86)	5.9% (34)	5.0% (135)	0.01	0.37
Lesion characteristics					
RVD (mm)	3.0 ± 0.4 (2,968)	2.9 ± 0.4 (741)	3.0 ± 0.4 (3,110)	0.60	<0.001
Lesion length (mm)	15.6 ± 9.2 (2,955)	15.3 ± 8.9 (737)	13.7 ± 5.8 (3,103)	<0.001	<0.001
B2/C lesion	51.0% (1,512)	69.2% (513)	33.3% (1,035)	<0.001	<0.001
Diameter stenosis (%)	84.8 ± 10.6 (2,968)	85.4 ± 11.6 (741)	84.4 ± 10.4 (3,111)	0.18	0.02
Calcification§ (%)	19.9% (591)	20.8% (154)	0.0% (0)	<0.001	<0.001
Restenotic lesions (%)	3.7% (111)	5.0% (37)	0.0% (0)	<0.001	<0.001

Data are % (n) or mean ± SD (n); P values are chi-square test (binary) or t-test (continuous).
*134 patients in the bifurcation subgroup also belonged to the multivessel stenting cohort.
†Simple-use cases are defined in the Methods section.
‡Includes patients treated with diet/exercise plus those treated with oral mediations and/or insulin.
§Moderate plus severe.
MI = myocardial infarction; PCI = percutaneous coronary intervention; RVD = reference vessel diameter.

have met the criteria for inclusion in the TAXUS IV pivotal trial.[11] As shown in Table 1, MVS patients had significantly more baseline comorbidities and complex disease than the simple-use subgroup, including more diabetes, prior MI and stroke, and longer lesions. In the bifurcation cohort, however, patient characteristics overall were not significantly different from the simple-use subgroup although lesions were significantly more complex with more severe stenosis. Table 2 shows procedural data for the 3 patient groups. Predilatation, postdilatation, and side branch occlusion were more common in bifurcation lesions, although technical success, defined as successful delivery/deployment of the study stent to the target lesion without device malfunction, was achieved in almost all patients in all 3 groups.

Clinical Outcomes. Among ARRIVE MVS patients, clinical follow-up was available in 97% (1,174/1,208) at 1 year and 93% (1,128/1,208) at 2 years. Similar follow-up rates were achieved with bifurcation stenting patients (97%, 558/575 at 1 year and 94%, 538/575 at 2 years). Clinical outcomes through 2 years (Kaplan–Meier analysis) in the MVS, bifurcation, and simple-use cohorts are shown in Table 3 and Figure 1. All-cause and cardiac mortality, all MI, and ST were significantly higher in the more complex MVS and bifurcation groups compared to simple-use patients. Overall, these 2 subgroups had similar rates for 2-year target vessel failure (TVF, defined as cardiac death, MI, and TVR) that was 15.7% and 15.5% for the MVS and bifurcation subgroups, respectively, both significantly higher than in the simple-use cohort (7.8%, $P < 0.001$). For both cohorts TVF was driven by significantly higher rates of TLR compared to the simple-use subgroup (Fig. 1). In the bifurcation stenting group (data available for ARRIVE 2 only), simple stenting (stenting of the main branch without balloon angioplasty or stenting of the side branch) was performed in 55.3% (215/389) of lesions, whereas stenting of both branches was performed in 44.2% (172/389). The incidence of acute periprocedural MI was 1.0% (2/207) in the simple stenting and 3.6% (6/167)

Table 2. ARRIVE MVS, Bifurcation, and Simple Use Cohorts Procedural Characteristics

Variable	Multivessel Stenting N = 1,208 Patients N = 2,969 Lesions	Bifurcation Use* N = 575 Patients N = 741 Lesions	Simple Use† N = 2,698 Patients N = 3,112 Lesions
Clinical procedural success‡	95.2% (1,299)	95.7% (551)	98.1% (2,647)
Technical success§	99.1% (1358)	99.0% (570)	99.6% (2,689)
Implant success¶	94.6% (1291)	94.6% (545)	97.7% (2,637)
Predilatation	59.6% (1,770)	70.3% (521)	53.6% (1,667)
Vessel treated (lesion location)			
LAD	32.0% (950)	52.8% (391)	39.5% (1,228)
Circumflex	30.3% (901)	29.8% (221)	26.1% (812)
RCA	29.0% (861)	13.4% (99)	34.4% (1,072)
Left main	2.7% (79)	3.1% (23)	0.0% (0)
Graft	6.0% (178)	0.9% (7)	0.0% (0)
Vessels treated per patient			
1	0% (0)	96.3% (554)	100.0% (2,698)
2	92.5% (1,117)	3.5% (20)	0.0% (0)
≥3	7.5% (91)	0.2% (1)	0.0% (0)
Lesions treated per patient			
1	0% (0)	73.4% (422)	86.5% (2,334)
2	66.6% (804)	24.5% (141)	11.7% (315)
≥3	33.4% (404)	2.1% (12)	1.8% (49)
Stents per vessel	1.3 ± 0.6 (2,511)	1.4 ± 0.7 (594)	1.2 ± 0.5 (2,698)
Stents per lesion	1.1 ± 0.4 (2,911)	1.2 ± 0.5 (732)	1.1 ± 0.2 (3,108)
Total stent length per lesion (mm)	20.9 ± 10.7 (2,911)	21.0 ± 11.0 (732)	18.7 ± 7.1 (3,108)
Stents per patient			
1	3.0% (36)**	63.5% (365)	81.7% (2205)
2	51.2% (619)	27.7% (159)	15.6% (420)
≥ 3	45.8% (553)	8.3% (48)	2.4% (65)
Stent length per patient (mm)	50.3 ± 23.7 (1,208)	26.8 ± 14.9 (572)	21.6 ± 10.6 (2,698)
Prestenting TIMI flow (per lesion)			
0	3.9% (116)	3.5% (26)	2.3% (71)
1	2.8% (84)	3.9% (29)	3.1% (95)
2	10.6% (315)	12.6% (93)	12.4% (385)
3	82.7% (2,454)	80.0% (593)	82.3% (2,561)
Poststenting TIMI flow (per lesion)			
0	0.2% (7)	0% (0)	0.3% (8)
1	0.1% (3)	0% (0)	0.1% (2)
2	0.5% (15)	0.4% (3)	0.5% (16)
3	99.2% (2,942)	99.6% (738)	99.2% (3,086)
Postdilatation (per lesion)	37.0% (1,099)	53.2% (394)	31.6% (983)
Poststent balloon pressure (atm)	15.3 ± 3.8 (1,096)	14.0 ± 4.0 (391)	15.1 ± 3.9 (983)
Slow flow/no flow after PCI	1.8% (53)	1.5% (11)	1.2% (37)
Postprocedure % DS	1.1 ± 6.0 (2,964)	0.9 ± 4.4 (741)	0.7 ± 5.0 (3,112)
Side branch occlusion	1.0% (29)	2.4% (741)	0.9% (29)

Data are presented as % (n) or mean ± SD (N) (minimum, maximum).
*134 patients in the bifurcation subgroup also belonged to the multivessel stenting cohort.
†Simple use is defined in the Methods section.
‡Clinical procedural success was defined as mean lesion diameter stenosis <30%, a TIMI flow of 3 as visually assessed by the physician, and no in-hospital CEC-adjudicated events; N = 1,365, 576, and 2,699 for the multivessel use, bifurcation use, and simple use cohorts, respectively.
§Technical success was defined as a successful delivery or deployment of the study stent to the target lesion without device malfunction; N = 1,370, 576, and 2,699 for the multivessel use, bifurcation use, and simple use cohorts, respectively.
¶Implant success was defined as the percent of implant procedures exhibiting both procedural and technical success; N = 1,365, 576, and 2,699 for the multivessel use, bifurcation use, and simple use cohorts, respectively.
**In 44 patients, complete stent implantation data were not available.
CEC = Clinical Events Committee; DS = diameter stenosis; LAD = left anterior descending artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIMI = Thrombus In Myocardial Infarction.

Table 3. Death and Myocardial Infarction in ARRIVE Multivessel Use, Bifurcation Use, and Simple Use Cohorts

Clinical Event	Multivessel Stenting N = 1,208 Patients		Bifurcation Use* N = 575 Patients		Simple Use† N = 2,698 Patients		P Value Multivessel vs. Simple Use	P Value Bifurcation vs. Simple Use
	1 year	2 years	1 year	2 years	1 year	2 years		
Death	4.3 (51)	7.3 (85)	4.9 (28)	7.5 (41)	2.3 (60)	4.2 (108)	<0.001	<0.001
Cardiac	2.9 (34)	4.4 (51)	3.5 (20)	4.9 (27)	1.3 (33)	2.1 (54)	<0.001	<0.001
MI	3.6 (43)	5.5 (62)	2.5 (14)	4.6 (24)	1.4 (36)	2.2 (56)	<0.001	0.002
Q-Wave	1.3 (15)	1.7 (20)	0.5 (3)	0.9 (5)	0.5 (12)	0.7 (19)	0.005	0.63

Data are from Kaplan-Meier analysis and are expressed as % (n); P values are log-rank (0–2 years).
*134 patients in the bifurcation subgroup also belonged to the multivessel stenting cohort.
†Simple use is defined in the Methods section.
MI = myocardial infarction

in the complex stenting group, respectively (P = 0.15).

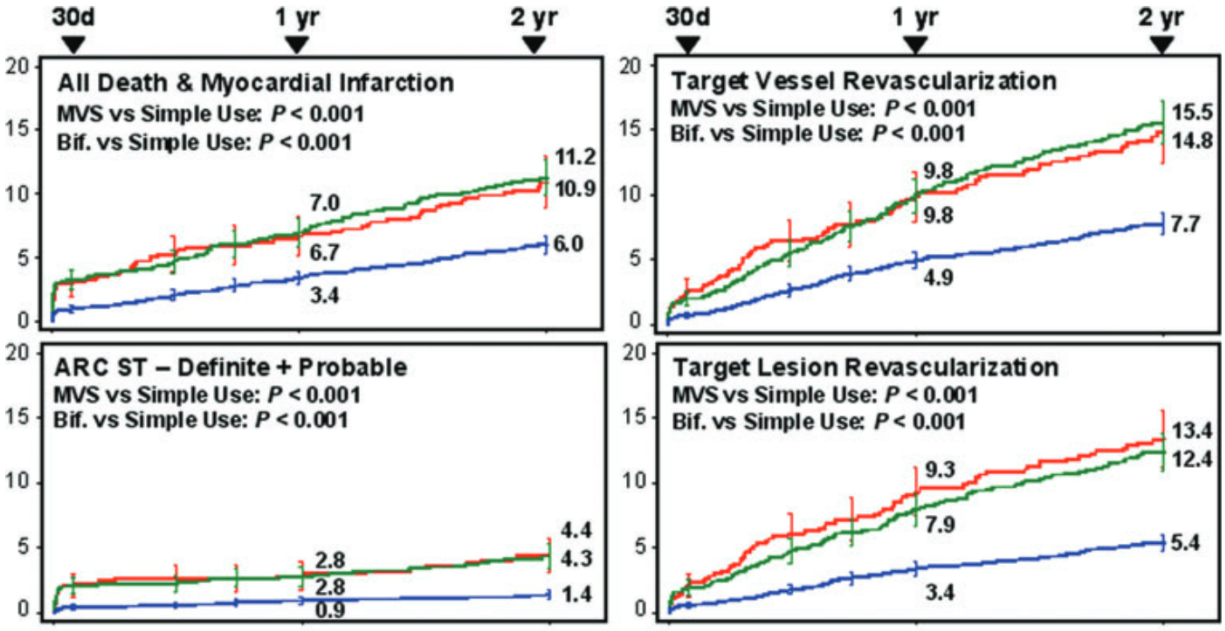
In the MVS cohort, early (0–30 days) ST was 2.1% (25/1208); late (31 days–1 year) ST was 0.7% (8/1181); and very late ST (VLST) was 1.5% (16/1088).[12] Of the 16 MVS patients with VLST, 11 were not on DAPT, 2 were on DAPT, and the DAPT status of the other 3 is unknown. Among the 49 ARRIVE MVS patients suffering an ST event, 5 (10.2%) underwent subsequent revascularization within 30 days, all of which were TLR performed within 7 days of the event (Table 4). In the bifurcation stenting group, early ST was 2.1% (12/574), late ST was 0.7% (4/558), and VLST was 1.5% (8/518).[12] Among 8 bifurcation stenting patients with VLST, 7 were not on DAPT and the DAPT status of one is unknown. Among the 24 bifurcation stenting patients with ST, 1 received a subsequent TLR within 7 days (Table 4). Early, late, and VLST were 0.4%, 0.5%, and 0.4%, respectively, in the simple-use subgroup.[12] At 1 year, 67.7% of all ARRIVE patients (4687/6927) were on DAPT with 53.1% (3487/6569) at 2 years.[12] Among MVS and bifurcation patients, the corresponding rates were 69.4% (767/1105) and 69.1% (357/517), respectively, at 1 year and 56.1% (583/1039) and 51.1% (250/ 489) at 2 years compared to 64.7% (1640/2534) and 50.9% (1243/2442) in the simple-use cohort.

Multivariate Analysis. Table 5 shows multivariate predictors for all death, MI, TVR, and ST through 2 years among ARRIVE MVS and bifurcation use patients. In both cohorts predictors of mortality were patient, lesion, and procedure based whereas MI and TVR predictors were mostly lesion based. Renal disease (7.5-fold among MVS patients and 6.3-fold among bifurcation patients) and discontinuation of thienopyridine use before 6 months (7.3-fold for MVS and 8.5-fold for bifurcation) posed the highest risk for death. Multivariate analysis of the overall ARRIVE population showed that MVS was not a significant predictor of 2-year death, MI, revascularization, or ST[8]; outcomes were similar when the analysis was carried out with MVS forced into the model. Bifurcation stenting was found to be a significant predictor of TLR (1.4-fold) among all ARRIVE patients.[8]

Discussion

The ARRIVE registries collected data through 2 years on 7,492 "real-world" patients who received the TAXUS Express PES in routine clinical practice, including 1,208 patients who underwent MVS and 575 patients who received a stent for a bifurcation lesion. The MVS subgroup had significantly more comorbidities and a higher risk of clinical events through 2-year follow-up than the subgroup of simple-use patients (N = 2,698) who would have been eligible for the TAXUS IV pivotal trial.[11] While bifurcation patient characteristics overall were not significantly different from the simple-use subgroup, lesions were significantly more complex with more severe stenosis and these patients also suffered significantly more clinical events. The 2-year TVF rate, driven by TLR, was 15.7% for MVS and 15.5% for bifurcation, both significantly higher than the observed rate for the simple-use cohort (7.8%, P < 0.001).

With increasing use of DES, the percutaneous treatment of multivessel coronary artery disease has rapidly evolved. During 5 years of follow-up of the Arterial Revascularisation Therapies Study, part II (ARTS II) registry patients receiving DES had similar incidence



Days	0	30	180	365	730
All Death & Myocardial Infarction					
MVS	1208	1194	1158	1100	1058
Bifurcation	575	570	551	524	509
Simple Use	2698	2689	2627	2583	2493
Stent Thrombosis (ARC Def/Prob)					
MVS	1208	1205	1166	1110	1072
Bifurcation	575	573	553	526	511
Simple Use	2698	2695	2639	2593	2505

Days	0	30	180	365	730
Target Vessel Revascularization					
MVS	1208	1203	1159	1045	987
Bifurcation	575	572	546	493	471
Simple Use	2698	2692	2630	2537	2399
Target Lesion Revascularization					
MVS	1208	1203	1160	1061	1007
Bifurcation	575	572	548	496	473
Simple Use	2698	2692	2632	2557	2435

Figure 1. Death/MI, ST, and revascularization through 2 years in the ARRIVE multivessel stenting, bifurcation stenting, and simple-use subgroups. Cohorts were ARRIVE multivessel stenting (N = 1,208, green line), ARRIVE Bifurcation Stenting (N = 575, red line), and ARRIVE Simple-use (N = 2,698, defined in the Methods section, blue line). Target lesion revascularization (TLR) was defined as "TAXUS-stent-related" target vessel revascularization, given the absence of a central angiographic core laboratory. Stent thrombosis (ST) is per ARC definite/probable definitions.[10] P values (log-rank) are for the comparison between MVS and simple-use cohorts and between bifurcation and simple-use cohorts; error bars are ±1.5 SE.

of major adverse cardiac events with patients who underwent coronary artery bypass graft (CABG) surgery in the ARTS I trial and significantly lower incidence of major adverse cardiac events than the bare metal stent arm of the ARTS I trial.[1] However, they had higher need for repeat coronary revascularization (20.3% vs. 8.6%),[1] suggesting that restenosis remains an important limitation of currently available DES platforms. In the Synergy Between Percutaneous Coronary Intervention (PCI) with TAXUS and Cardiac Surgery (SYNTAX) trial the 12-month need for TVR in patients with 3-vessel (without left main) disease was 14.6%.[2] This is higher than 12-month TVR in the ARRIVE MVS group (9.8%), and likely reflects less-complex disease in ARRIVE. In SYNTAX, where an average of 4.6 stents were placed per patient, ST at 12 months was 3.3%; in the ARRIVE MVS cohort with an average of 2.7 stents per patient the ST rate was 2.8% and in the ARRIVE simple-use cohort ST was 0.9%. These results highlight the increased risk of ST after MVS and the importance of high compliance with DAPT regimens.[13] In the angiography-guided multivessel

Table 4. Revascularization Within 30 Days Post Initial Stent Thrombosis Event in ARRIVE Multivessel and Bifurcation Subgroups

Time of Initial ST Post Index Procedure*	Multivessel Stenting		Bifurcation Use†	
	N‡	TLR§	N‡	TLR§
ST 0–30D	25	8.0% (2)	12	0.0% (0)
ST 0–1D	9	22.2% (2)	3	0.0% (0)
ST 2–30D	16	0.0% (0)	9	0.0% (0)
ST >30D–1Y	8	0.0% (0)	4	0.0% (0)
ST >1Y–2Y	16	18.8% (3)	8	12.5% (1)
All ST	49	10.2% (5)	24	4.2% (1)

Values are n or percent (n).
*Only a patient's first ST event is counted here; ST is defined as ARC definite/probable[10].
†134 patients in the bifurcation subgroup also belonged to the multivessel stenting cohort.
‡N = number of ST in the time interval.
§TLR within 30 days of initial ST event, defined as "TAXUS-stent-related" TVR, given the absence of a central angiographic core laboratory to perform quantitative coronary angiography; all TVR were TLR and all occurred within 7 days of the ST event.
D = days; TLR = target lesion revascularization; TVR = target vessel revascularization; ST = stent thrombosis; Y = years

PCI arm of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study, 2-year TVR from stenting was 12.7% in contrast to 15.5% among ARRIVE MVS patients; this may reflect a healthier patient population in FAME (2-year mortality was 3.8% vs. 7.3% in ARRIVE).[14] In fact, patient selection may be particularly important for improving clinical outcomes in MVS patients. In the ARRIVE MVS cohort, renal disease (7.5-fold) and left main stenting (3.3-fold) were strong independent predictors of mortality. Several studies have shown that higher angiographic disease complexity is associated with higher risk post-PCI, suggesting that CABG may be an attractive treatment option for such patients. The SYNTAX score, recently developed as a comprehensive angiographic scoring system to assess patients undergoing PCI for complex coronary lesions,[15] has shown good predictive capacity in several patient populations,[1,16,17] though with moderate reproducibility.[18]

Treatment of coronary bifurcations has also recently undergone significant evolution with single-stent techniques (stenting of the main branch with provisional balloon angioplasty/stenting of the side branch) emerging as the treatment of choice due to lower periprocedural acute MI and lower restenosis rates compared to routine 2-stent techniques.[3,19–21] At 9.8%, 12-month TVR in the ARRIVE bifurcation group compares favorably with rates observed with a sirolimus-eluting stent in the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) study (6.2% to 6.8% TVR at 6 months)[22] and with PES in the BBC ONE (British Bifurcation Coronary Study: Old, New, and Evolving Strategies) trial (8% to 13% at 9 months).[19] All 3 studies reported higher TVR than in the Nordic Bifurcation study (1.9% at 6 months).[20] Most prior studies reported short-term outcomes; ARRIVE demonstrates that the need for repeat TVR remains high during the second year post stenting (5.0%). In the ARTS II registry, stenting of bifurcation lesions had similar outcomes to stenting of nonbifurcation lesions with the exception of ST, which was higher in bifurcations (4.6% vs. 2.1%).[23] Improved techniques, equipment, and patient selection could enhance outcomes in this challenging patient group. Use of thinner stent struts might reduce the risk for periprocedural MI and possibly for repeat TVR.[24] Several dedicated bifurcation stents are currently being developed,[25] although deliverability of these higher profile devices can be challenging.[26] The main limitation of the current study is its observational nature and the lack of a control group. The monitoring level in ARRIVE was lower than standard for traditional randomized, controlled trials (RCTs), although the outcome data are concordant with those from RCTs with 100% monitoring.[7,8] The SYNTAX score[15] of the ARRIVE registry patients was not available and higher angiographic disease complexity, as assessed by the SYNTAX score, is known to be associated with higher risk for subsequent events.[1,16] Analysis was based on site visual assessments of angiographic data rather than a core angiographic laboratory. The incidence of smaller (non-Q) MI may have been underestimated, because the protocol did not mandate serial cardiac enzyme or electrocardiographic measurements. While these limitations must be noted, these large cohorts of MVS and bifurcation stenting patients with complex disease provide an important data source for a group of patients who are typically not included in large RCTs.

Conclusion

ARRIVE patients undergoing multivessel or bifurcation stenting had expectedly higher TVF rates, driven by TLR, than patients undergoing simple native coronary artery stenting. In the absence of a large RCT in

Table 5. Multivariate Predictors of Major Events at 2 Years in the ARRIVE MVS and Bifurcation Use Subgroups

	Multivessel Stenting (N = 1,208) Hazard Ratio (95% Confidence Interval)				Bifurcation Use (N = 575) Hazard Ratio (95% Confidence Interval)			
Variable	All Death*	MI	TVR†	ST‡	All Death*	MI	TVR†	ST‡
Renal disease	7.52 (3.96, 14.26)[a]	NS	NS	NS	6.27 (1.94, 20.33)	NS	NS	NS
Thienopyridine <6 m§	7.30 (4.67, 11.40)[a]	NS	NS	2.74 (1.51, 4.98)	8.52 (4.30, 16.88)[a]	NS	NS	4.25 (1.89, 9.59)
Left main stenting	3.25 (1.50, 7.06)[a]	NS	NS	NS	4.86 (1.99, 11.88)[a]	NS	NS	NS
Graft stenting	2.79 (1.16, 6.73)	NS	NS	NS	NS	NS	NS	NS
CHF	2.61 (1.44, 4.71)	NS	NS	NS	NS	NS	NS	NS
RVD <3 mm	2.48 (1.43, 4.32)	NS	NS	NS	2.49 (1.14, 5.43)	NS	NS	NS
Bifurcated lesion	2.11 (1.24, 3.61)[a]	NS	NS	NS	NS	NS	NS	NS
Stroke, previous	2.10 (1.13, 3.90)	NS	NS	NS	NS	NS	NS	NS
Lesion calcification	1.86 (1.18, 2.93)	NS	NS	NS	NS	NS	NS	NS
MI, previous	1.74 (1.11, 2.73)[a]	NS	NS	2.63 (1.47, 4.70)	NS	2.91 (1.26, 6.72)	NS	NS
Stent inflation pressure ≤14 atm	1.69 (1.07, 2.66)	NS	NS	NS	NS	NS	NS	NS
Lesion length >28 mm	NS	2.81 (1.64, 4.81)	NS	2.08 (1.12, 3.87)	NS	3.36 (1.39, 8.11)	NS	NS
ISR stenting	NS	2.29 (1.10, 4.76)	1.75 (1.08, 2.86)[b]	NS	NS	NS	NS	NS
Ostial lesion	NS	1.93 (1.06, 3.52)	NS	NS	0.33 (0.15, 0.77)	NS	NS	NS
Multivessel disease	NS	1.87 (1.08, 3.24)	1.65 (1.21, 2.26)	NS	NS	NS	NS	NS
Smoking at baseline	NS	1.78 (1.02, 3.12)	NS	NS	NS	NS	NS	NS
Hypercholesterolemia	NS	0.51 (0.29, 0.90)	0.66 (0.46, 0.94)[b]	0.44 (0.24, 0.81)	NS	NS	NS	NS
Multiple stents per lesion	NS	0.33 (0.12, 0.93)	NS	NS	NS	NS	NS	NS
Brachytherapy, prior	NS	NS	4.89 (1.44, 16.67)	NS	NS	NS	NS	NS
Tortuosity, severe	NS	NS	2.04 (1.22, 3.43)[b]	NS	4.01 (1.14, 14.17)	NS	NS	NS
Multiple overlapping stents	NS	NS	1.91 (1.37, 2.66)[b]	NS	NS	NS	1.82 (1.08, 3.07)[b]	NS
LAD as target vessel	NS	NS	1.50 (1.07, 2.10)[b]	NS	NS	NS	NS	NS
Age >70 years	NS	NS	0.64 (0.46, 0.89)[b]	NS	1.96 (1.04, 3.69)	NS	NS	NS
Multivessel stenting	NS	NS	NS	NS	2.70 (1.30, 5.59)[a]	NS	NS	NS
CTO stenting	NS	NS	NS	NS	NS	5.83 (1.55, 21.95)	NS	NS
Lesion type B2/C	NS	NS	NS	NS	NS	0.32 (0.13, 0.79)	0.48 (0.29, 0.790[b]	NS
Postprocedure dilatation	NS	NS	NS	NS	NS	NS	1.78 (1.08, 2.93)[b]	NS

Variables listed reached statistical significance ($P < 0.05$). See Table 1 for method and baseline variables used for modeling (n = 40 variables).

* [a]denotes variable is significant for cardiac death; significant variables for cardiac death also include insulin requiring diabetes in the multivessel stenting cohort (1.99 [1.06, 3.75]) and left main disease in the bifurcation use cohort (0.23 [0.06, 0.93]).

†b denotes variable is significant for TLR; significant variables for TLR also include preprocedure TIMI = 0 in the bifurcation cohort (2.22 [1.05, 4.68]).

‡Definite or probable by ARC definitions.[10]

§Patient was not receiving clopidogrel/ticlopidine at the 6-month visit.

ARC = Academic Research Consortium; CHF = congestive heart failure; CTO = chronic total occlusion; ISR = in-stent restenosis; MI = myocardial infarction; LAD = left anterior descending artery; NS = not significant; TLR = target lesion revascularization.

these populations, ARRIVE provides important insight into clinical outcomes over an extended period of time.

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References

1. Serruys PW, Onuma Y, Garg S, et al. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. J Am Coll Cardiol 2010;55:1093–1101.
2. Serruys PW, Morice M-C, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–972.
3. Katritsis DG, Siontis GC, Ioannidis JP. Double versus single stenting for coronary bifurcation lesions: A meta-analysis. Circ Cardiovasc Interv 2009;2:409–415.
4. Beohar N, Davidson CJ, Kip KE, et al. Outcomes and complications associated with off-label and untested use of drug-eluting stents. JAMA 2007;297:1992–2000.
5. Applegate RJ, Sacrinty MT, Kutcher MA, et al. 3-year comparison of drug-eluting versus bare metal stents. JACC Cardiovasc Interv 2009;2:231–239.
6. Ko DT, Chiu M, Guo H, et al. Safety and effectiveness of drug-eluting and bare-metal stents for patients with off- and on-label indications. J Am Coll Cardiol 2009;53:1773–1782.
7. Lasala JM, Cox DA, Dobies D, et al. Usage patterns and 2-year outcomes with the TAXUS express stent: Results of the US ARRIVE 1 registry. Catheter Cardiovasc Interv 2008;72:433–445.
8. Lasala JM, Cox DA, Lewis SL, et al. Expanded use of the TAXUS Express stent: 2-year insights on safety from the 7500-patient ARRIVE registry program. EuroIntervention 2009;5:67–77.
9. Abizaid A, Chan C, Lim YT, et al. Twelve-month outcomes with a paclitaxel-eluting stent transitioning from controlled trials to clinical practice (the WISDOM Registry). Am J Cardiol 2006;98:1028–1032.
10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: A case for standardized definitions. Circulation 2007;115:2344–2351.
11. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–231.
12. Lasala JM, Cox DA, Dobies D, et al. Drug-eluting stent thrombosis in routine clinical practice: 2 year outcomes and predictors from the TAXUS ARRIVE registries. Circ Cardiovasc Intervent 2009;2:285–293.
13. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005;293:2126–2130.
14. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 2010;56:177–184.
15. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: An angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–227.
16. Valgimigli M, Serruys PW, Tsuchida K, et al. Cyphering the complexity of coronary artery disease using the Syntax score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. Am J Cardiol 2007;99:1072–1081.
17. Capodanno D, Di Salvo ME, Cincotta G, et al. Usefulness of the SYNTAX score for predicting clinical outcome after percutaneous coronary intervention of unprotected left main coronary artery disease. Circ Cardiovasc Interv 2009;2:302–308.
18. Garg S, Girasis C, Sarno G, et al. The SYNTAX score revisited: A reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv 2010;75:946–952.
19. Hildick-Smith D, de Belder AJ, Cooter N, et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions: The British Bifurcation Coronary Study: Old, new, and evolving strategies. Circulation 2010;121:1235–1243.
20. Steigen TK, Maeng M, Wiseth R, et al. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: The Nordic bifurcation study. Circulation 2006;114:1955–1961.
21. Brilakis ES, Berger PB. Treatment of coronary bifurcations: Might less be more? Eur Heart J 2008;29:704–706.
22. Colombo A, Bramucci E, Sacca S, et al. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: The CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. Circulation 2009;119:71–78.
23. Routledge HC, Lefevre T, Colombo A, et al. Three-year clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: Insights from the Arterial Revascularisation Therapies Study, part II (ARTS II). EuroIntervention 2009;5:190–196.
24. Tanigawa J, Barlis P, Dimopoulos K, et al. The influence of strut thickness and cell design on immediate apposition of drug-eluting stents assessed by optical coherence tomography. Int J Cardiol 2009;134:180–188.
25. Verheye S, Agostoni P, Dubois CL, et al. 9-month clinical, angiographic, and intravascular ultrasound results of a prospective evaluation of the Axxess self-expanding biolimus A9-eluting stent in coronary bifurcation lesions: the DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) study. J Am Coll Cardiol 2009;53:1031–1039.
26. Ormiston JA, Lefevre T, Grube E, et al. First human use of the TAXUS Petal paclitaxel-eluting bifurcation stent. EuroIntervention 2010;6:46–53.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1: Baseline Characteristic Variables Used in Predictor Modeling.

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