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Outcomes Following Implantation of the Biolimus A9-Eluting BioMatrix Coronary Stent: Primary Analysis of the e-BioMatrix Registry

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Objectives: To assess the safety and efficacy of Biolimus A9-eluting stents (BES, BioMatrix™ and BioMatrix Flex™) in routine clinical practice. Background: The LEADERS randomized trial has documented equivalent efficacy and superior safety of the BES when compared to a first generation Sirolimus-eluting Cypher™ stent. Methods: 5,472 patients from 57 centers, treated with BES, were enrolled in an international multicenter registry and followed clinically up to 2 years. Results: Mean patient age was 63.2 ± 11 years, 24% of patients had diabetes, and 49.8% presented with an acute coronary syndrome. 99.3% of patients were discharged on dual antiplatelet therapy (DAPT), 83.3% remained on DAPT at 1 year and 30.6% at 2 years. The incidence of the composite primary end point [major adverse cardiac events (MACE) at 12 months] was 4.5% [cardiac death 0.9%, myocardial infarction 1.7%, clinically indicated target vessel revascularization (ci-TVR) 2.8%]. MACE incidence was 6.8% at 24 months (cardiac death 1.5%, myocardial infarction 2.4%, ci-TVR 4.3%). At 12 months, 32 patients (0.6%) had suffered at least one definite or probable stent thrombosis (ST), and 91 patients (1.7%) a major bleed (MB). Nine patients with ST (27.3%) and 7 patients with a MB (7.7%) died during the first year after the index procedure. Between 12 and 24 months after implantation, there were 18 (0.4%) additional MB and 8 (0.2%) additional ST. Conclusions: This large international cohort documents a low 12 and 24 months MACE incidence and a very low ST incidence in an unselected patient population undergoing BES implantation. The results are in keeping with those of the randomized controlled LEADERS trial. Even though ST with this stent was a rare event, it was still associated with significant mortality. MB remains a problem, and warrants improved tailoring of DAPT in recipients of drug eluting stents.

Key words: drug eluting stent; stent thrombosis; bleeding; dual antiplatelet therapy

INTRODUCTION

The recommended duration of dual antiplatelet treatment (DAPT) in recipients of drug eluting stents (DES) is 6–12 months as per current guidelines [1,2], but concern with late and very late stent thrombosis with the first Paclitaxel and Sirolimus eluting DES led some operators to advocate indefinite DAPT [3]. The availability of second generation drug eluting coronary stents,

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while maintaining the low target lesion revascularization (TLR) rates that were obtained with earlier devices, has represented a major step forward in terms of safety, and the Biolimus A9-eluting BioMatrix Flex ™ stent (Biosensors Europe, Morges, Switzerland) was conclusively demonstrated to be associated with significantly less very late stent thrombosis than the first generation Sirolimus-eluting Cypher ™ stent (Cordis Corporation, Bridgewater, NJ) [4–7]. The present registry was therefore designed to evaluate whether these excellent results could be replicated in routine clinical practice. Furthermore, the risk of bleeding as a cause of significant morbidity and mortality has led to renewed concern that intense and prolonged DAPT may negatively impact on prognosis [8,9] and routine use of platelet function testing, while a logical approach to the problem, has so far been disappointing in clinical practice [10,11].

While randomized trials have uniquely defined the risks and the benefits of coronary stenting in a variety of clinical settings [4–7,12,13], until now, they only rarely included any information on bleeding events. Their size has also meant that rare but important adverse events have often been difficult to quantify and analyze. Despite some methodological and statistical limitations in relation to potential reporting and selection biases, registries that enroll in a large number of centers and use broad inclusion criteria are more likely to provide a realistic estimation of the application of a given treatment in the general population, in particular when assessing rare events [14–16].

In this study, we analyzed the 12 and 24 months results of the 5,472 patients enrolled in the e-BioMatrix registry and treated with contemporary biodegradable polymer Biolimus A9™-eluting DES. In addition to the primary end point, defined as the incidence of major adverse cardiac events (MACE) at 12 months, the registry also analyzed, as predefined secondary end points, the incidence and consequences of both stent thrombosis (ST) and major bleeding (MB), as well as the incidence of MACE at 24 months.

MATERIALS AND METHODS

The e-BioMatrix Registry is a prospective, multicenter, observational registry designed to assess outcomes in a "real world, all-comers" patient population treated with either the BioMatrix™ or the BioMatrix Flex™ stent (BioMatrix, Biosensors Europe SA, Morges, Switzerland), a DES with a biodegradable polymer polylactic acid (PLA) coating containing the BA9™ drug (Biolimus A9).

The BioMatrix Flex is a more recent iteration with a platform design change providing improved flexibility. The registry was conducted in 57 centers and 15 countries (see Appendix A) where the Biolimus-eluting stent [BES] has been approved for commercial use. Baseline data were collected between April 2008 and August 2011 in eligible patients who received one or more BES.

Patients were included in the study if they had a clinical indication for percutaneous coronary intervention [PCI], with one or more coronary artery stenoses in a native coronary artery or a saphenous bypass graft that could be covered with one or multiple BioMatrix stents from 2.25 to 4.0 mm in diameter. There were no limitations as to the number of treated vessels, or the number, type and length of treated lesions. Patients were excluded from the registry if any additional stent(s) not of the BES type were implanted during the index procedure, or if any lesions were treated solely with other techniques (stand alone balloon angioplasty, atherectomy, etc.). There were no exclusion criteria related to clinical presentation. DAPT with aspirin and a P2Y12 blocker was recommended for 6–12 months.

The study complied with the declaration of Helsinki and was approved by all institutional ethics committees, whenever applicable for a registry. All patients provided written informed consent for participation in this registry, either before or as soon as possible after the procedure.

The baseline data collected for the e-BioMatrix registry included demographic information, cardiovascular history, comorbidity, lesion and procedure characteristics, and antithrombotic regimens. The patients were followed at 30 days, 6, 12, and 24 months by telephone contact and/or office visits.

Data were collected electronically at each participating center and stored in a central database (Merge Healthcare, Nancy France and e-Novex BVBA, Antwerp, Belgium). All data were checked for consistency, and electronic queries were used as required. 100% of patient consent forms were verified. All reported MACE, bleeding events and stent thromboses were monitored and checked against source documents. In nine of the participating centers, baseline parameters and source documents were fully monitored, representing 20% of the total patient population.

The analysis, presentations and publications of the e-BioMatrix registry results were planned and supervised by a Steering Committee (Appendix B). All MACE, bleeding events and stent thromboses were adjudicated by an independent Clinical Event Committee (Appendix B). The primary end point was the incidence of MACE at 12 months, a composite of cardiac death, any myocardial infarction (MI) and clinically indicated target vessel revascularization (ci-TVR). Pre-defined secondary end points included, among others, ST [Academic Research Consortium (ARC) definitions] [17], MB (STEEPLE definition) [18], the individual components of the primary end point and MACE at 24 months.

Definitions

Cardiac death was defined as any death due to an immediate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), un-witnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment. Q-wave MI was defined as the development of new, pathological Q-waves in two or more contiguous leads (as assessed by the CEC) with or without postprocedure CK or CK-MB levels elevation above normal. Periprocedural non-Q-wave MI was defined as the elevation of CK levels to >3 times the upper limit of normal, with CK-MB or troponin elevation if available, in the absence of pathological Q-waves. Spontaneous non-Q wave MI was diagnosed if symptoms and/or ECG changes were associated with elevated biomarkers (CK, CKMB or troponin) above the upper limit of normal.

Ci-TVR was defined as a repeat percutaneous intervention or bypass surgery of the target vessel associated with either a $\geq$70% vessel diameter reduction or a $\geq$50% diameter reduction together with angina and/or documented ischemia.

ST was classified as definite, probable, and possible according to ARC [17] and all relevant angiograms were reviewed by the CEC. Bleeding was classified as major [MB] or minor according to the STEEPLE definitions [18]. Staging of the index procedure was allowed when the second procedure was planned at the time of the initial procedure and was scheduled within 90 days, using study stents only. Chronic renal failure was considered present when preprocedure plasma creatinine was $\geq$2.95 mg/dl or 260 μmol/l.

Statistical Analysis

For all patients, standard descriptive statistics were used for baseline, lesion and procedural characteristic and for clinical results. Continuous variables are presented as mean $\pm$ standard deviation or median and range, and categorical variables are presented as numbers and percentages. Cumulative incidences of adverse clinical events were estimated using the Kaplan–Meier method. A list of potential predictors of MACE was established after production of descriptive statistics of the data, and included the following baseline patient characteristics: gender, age, presence of STEMI at presentation, diabetes mellitus, renal insufficiency, oral anticoagulant treatment and the Charlson comorbidity index.

In addition, the following lesion and procedural characteristics were considered as potential predictors: location of the target lesion in a saphenous vein graft, restenotic target lesion, complex target lesion (i.e., bifurcation lesion, in-stent restenotic lesion, lesion located in a saphenous vein (or arterial) graft or a chronically totally occluded lesion), total implanted stent length, multivessel PCI. Univariate and multivariate analyses were carried out using the Cox proportional hazards (Cox PH) model and R add-on package "survival" [19]. Covariate selection was performed according to Collett [20]. Along this selection procedure, statistical significance was considered to be reached when $P \leq 0.10$. The relationship between the logarithm of the hazard ratio and patient age was not linear and modeled using smoothing splines. All statistical analyses were performed with R 3.0.1.

RESULTS

From April 2008 to August 2011, in 57 centers in Europe, the Middle East, Russia, and North Africa, 5,653 patients provided informed consent. 181 patients were excluded because they did not meet exclusion/inclusion criteria. The study population therefore consisted of 5,472 patients. Baseline demographics, angiographic and procedure data and 12 and 24 months event rates are reported in Tables (I–IV), respectively. Mean patient age was 63.2 $\pm$ 11 years, 24% of patients had diabetes, 32.6% presented with unstable angina or non-ST-elevation MI (NSTEMI), and 17.1% with ST-segment elevation MI [STEMI].

A total of 5,167 patients underwent a single coronary revascularization procedure and 305 a planned staged procedure within 4.5 $\pm$ 5 weeks. A mean of 1.7 stents/patient was implanted. Compliance rates with DAPT were 98.2% at 30 days, 95.9% at 180 days, 83.3% at 12 months, and 30.6% at 24 months (Fig. 1). ESC guidelines were thus followed for 92.6% of elective procedures (DAPT duration $\geq$ 6 months) and 79.8% of acute coronary syndromes (ACS) patients (DAPT duration of 1 year). After discharge, temporary interruptions of DAPT were recorded in 1.1% of patients during the first 30 days (57/5, 378), in 1.7% of patients between days 31 and 180 (93/5, 363), and in 2.1% of patients between 181 and 12 months (114/5, 353). The 12- and 24-month clinical follow-up was obtained in 97.3% and 93.8% of patients, respectively.

The occurrence of MACE was 4.5% at 12 months and 6.8% at 24 months. Its individual components, stent thrombosis and major bleeding at different time points are given in Table III. Definite or probable ST occurred in 0.6% of patients at 12 months and 0.2% between 12 and 24 months. Of the 40 ST, 23 (58.5%) occurred during the first 30 days. MB occurred in 1.7% of patients at 12 months and 0.4% between 12 and 24 months. Although 41 of 109 MB (35.7%) occurred during the first 30 days, they were more

TABLE I. Baseline Characteristics of the Study Population

Variables	Study population ($n = 5,472$)
Age (years)	63.2 ± 11.0
Male, *n* (%)	4,126 (75.4)
Mean BMI (kg/m^2)	28.1 ± 4.7
History of prior MI, *n* (%)	1,362 (24.9)
History of PCI, *n* (%)	1,298 (23.7)
History of CABG, *n* (%)	398 (7.3)
Diabetes mellitus, *n* (%)	1,315 (24.0)
Insulin-dependent DM, *n* (%)	408 (31.0%)
Hypertension, *n* (%)	3,539 (64.7)
Hypercholesterolemia, *n* (%)	3,763 (68.8)
Current smoker, *n* (%)	1,441 (26.3)
Peripheral vascular disease, *n* (%)	369 (6.7)
Prior cerebrovascular disease, *n* (%)	311 (5.7)
Chronic renal failure, *n* (%)	160 (2.9)
(baseline plasma creatinine ≥ 2.95 mg/dl or 260 μmol/l)	
Anticoagulant treatment, *n* (%)	78 (1.4%)
Indication for PCI	
Stable angina/silent ischemia/asymptomatic	2,746 (50.2)
Acute coronary syndrome	2,723 (49.8)
Unstable angina	594 (21.8)
NSTEMI	1,190 (43.7)
STEMI	938 (34.5)
LVEF <40%, *n* (%)	302 (9.1)

LVEF: left ventricular ejection fraction (available for 3,337 patients).

TABLE II. Lesion and Procedure Characteristics

Type of lesion	
De novo (%)	7,458 (95.2%)
Any restenosis	375 (4.8%)
In-stent restenosis	307 (3.9%)
Bifurcation (%)	550 (7.0%)
Chronic total occlusion (>3 months, %)	194 (2.5%)
Left main (%)	183 (2.3%)
Bypass graft	113 (1.4%)
No. of treated vessels per patient (%)	
1 vessel	4,487 (82%)
2 vessels	866 (15.8%)
3+ vessels	119 (2.2%)
No. of treated lesions per patient (%)	
1 lesion	3,786 (69.2%)
2 lesions	1,191 (21.8%)
3 lesions	368 (6.7%)
4 +lesions	127 (2.3%)
No. of stents per patient (%)	
1 stent	3,140 (57.4%)
2 stents	1,415 (25.8%)
3 stents	583 (10.7%)
4 or more stents	334 (6.1%)
No. of staged procedures, %	305 (5.3%)
No. of stents per patient	1.7 ± 1.0
Total stent length/patient, mm	32.5 ± 21.4
Total stent length/lesion, mm	22.8 ± 11.1
Small diameter stent ($\leq$2.75 mm),%	2,669 (48.8%)
Antithrombotic medications, *n* (%)	
Preindex procedure	
Aspirin	4,767 (87.3)
Clopidogrel	4,248 (77.9)
Prasugrel	103 (1.9)
Ticlopidine	20 (0.4)
Peri-index procedure	
Heparin	4,978 (91.7)
IIbIIIa blocker	789 (14.5)
Bivalirudin	110 (2.0)
Platelet function tested during index admission, *n* (%)	36 (0.7)
Prescribed at discharge after index procedure	
Aspirin	5,435 (99.3)
Clopidogrel	5,288 (96.7)
Prasugrel	159 (2.9)
Ticlopidine	5 (0.1)

evenly distributed during the follow-up period than ST (Fig. 2).

Several pre-defined patient subgroups were analyzed for their relative risks of ST and MB (Fig. 3). Many patient subgroups appeared at increased risk for both adverse events, (especially the elderly, patients with renal failure, a history of bypass surgery, or those taking oral anticoagulants). Three patients with MB (2.8%) also suffered ST during the first year. This was different from a ST rate of 0.7% for patients without MB ($P < 0.05$). A multivariate analysis using the 24 months data was performed in order to identify the predictors of the primary end point (MACE) over the first year after stent implantation.

During the first 12 months, 87 of 91 patients with MB and all patients with ST were on DAPT at the time of the first event. Between 12 and 24 months, 6 patients out the 8 who had a first ST and 11 patients out of the 18 who had a first MB were on DAPT at the time of event. In total, mortality at 24 months was 27.5% (11/40) in patients with definite or probable ST and 9.1% (10/109) in patients with MB.

DISCUSSION

The 24 months analysis of the data collected in the e-BioMatrix registry confirms the excellent safety and efficacy profile of the BioMatrix family of stents in a population of patients undergoing PCI in routine clinical practice. The primary end point (MACE rate at 12 months) was reached by 4.5% of patients. This is lower than the 11% that was observed in the randomized LEADERS trial [5], most probably because of the selection of lower risk patients in e-BioMatrix, as suggested by the fact that the differences in MACE rates were most pronounced during the first 30 days (5.3% for LEADERS [4] vs. 1.2% for e-BioMatrix). Very late definite/probable ST was a rare event (0.2%), identical to the 0.2% rate of very late ST between 1 and 2 years observed in the BioMatrix Flex arm of the LEADERS trial [7].

TABLE III. Kaplan–Meier Estimates of Adverse Events Cumulative Incidences

	Up to 30 days % (*n*)	Up to 6 months % (*n*)	Up to 12 months % (*n*)	Up to 24 months % (*n*)
Available follow-up	99.2 (5,427)	98.3% (5,381)	97.3 (5,323)	93.8 (5,135)
MACE[a]	1.2 (64)	2.6 (143)	4.5 (243)	6.8 (358)
All death	0.3 (16)	1.0 (56)	1.8 (95)	3 (159)
Cardiac death	0.3 (14)	0.7 (38)	0.9 (51)	1.5 (78)
Acute myocardial infarction	0.9 (48)	1.3 (69)	1.7 (90)	2.4 (127)
Q wave	0.3 (16)	0.3 (18)	0.4 (24)	0.6 (34)
Non-Q wave	0.6 (32)	0.9 (51)	1.3 (68)	1.8 (95)
Any revascularization	0.8 (41)	2.8 (150)	5.3 (282)	8.1 (424)
CABG	0.0 (2)	0.2 (11)	0.5 (25)	0.8 (43)
PCI	0.7 (40)	2.6 (141)	4.9 (262)	7.4 (389)
ci-TVR[b]	0.3 (17)	1.2 (67)	2.8 (148)	4.3 (225)
TLF[c]	1.2 (64)	2.4 (132)	4.0 (212)	5.8 (307)
All Stent thrombosis (definite, probable, and possible)	0.4 (23)	0.7 (39)	0.9 (47)	1.3 (69)
Definite and probable	0.4 (23)	0.5 (29)	0.6 (32)	0.8 (40)
Definite	0.4 (20)	0.5 (25)	0.5 (28)	0.6 (34)
Major bleeding	0.8 (41)	1.4 (74)	1.7 (91)	2.1 (109)

[a]Major adverse cardiac events: cardiac death, any MI, and clinically indicated target vessel revascularization.
[b]Clinically indicated target vessel revascularization.
[c]Target lesion failure: a composite of cardiac death, MI, or ci-TLR.

TABLE IV. Relative Risks of Stent Thrombosis and Major Bleeding

	0–30 days	31 days–6 months	>6–12 months	>12–24 months
Stent thrombosis (ST) def/prob (%)	0.43	0.11	0.06	0.16
Major bleeding (MB) (%)	0.75	0.61	0.33	0.37
MB/ST ratio	1.74	5.55	5.5	2.31
On DAPT at end of period (%)	98.2	95.9	83.3	30.6

All percentages are Kaplan–Meier estimates derived from the number of patients for whom information on DAPT compliance is available ($n = 5{,}384$).

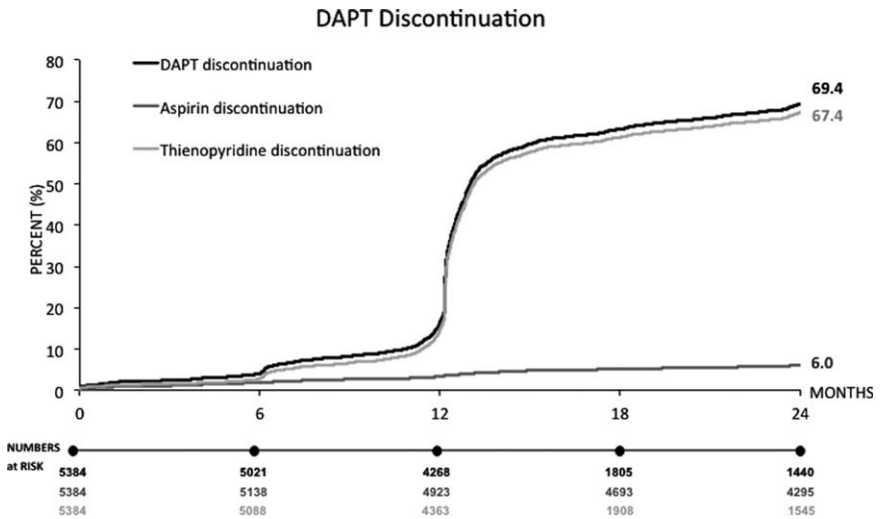


Fig. 1. DAPT, aspirin, and clopidogrel compliance.

The multivariate predictors of MACE (Table V) combined baseline clinical parameters (age and Charlson comorbidity index), and others related to the complexity and/or saphenous vein location of target lesions. Total implanted stent length was the only procedure parameter that was associated with MACE. Compliance with the DAPT regimen was good (86% overall adherence to ESC guidelines) associated with a maintained low MACE rate 2 years (6.8%). Importantly, no increase in definite/probable stent thrombosis

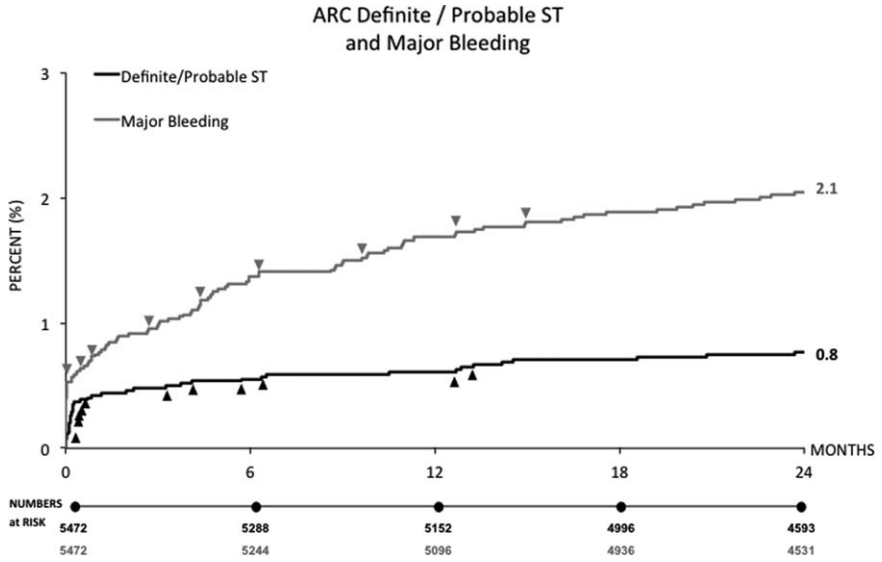
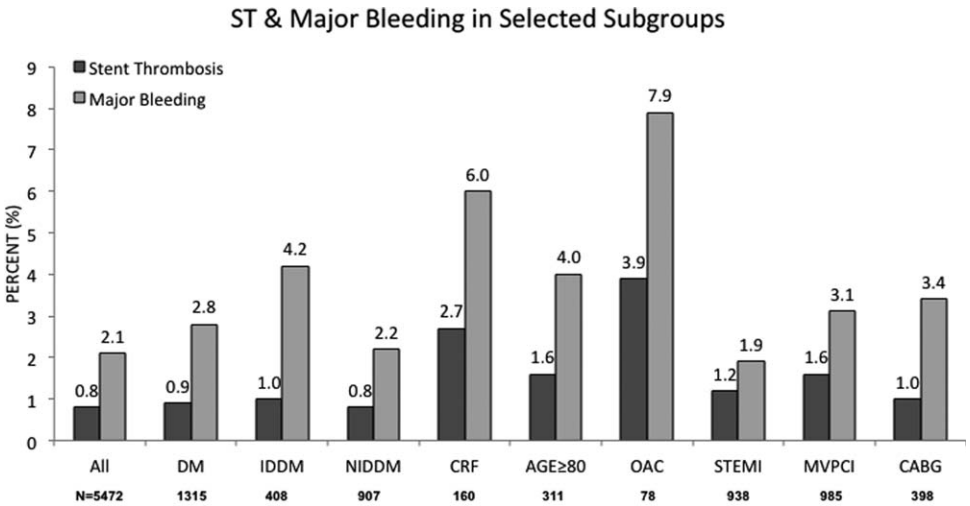


Fig. 2. Incidence of definite/probable stent thrombosis and major bleeding (arrowheads indicate events associated with death during the 24-month follow-up).



DM: Diabetes Mellitus, IDDM: Insulin-Dependent Diabetes Mellitus, NIDDM: Non-Insulin-Dependent Diabetes Mellitus, CRF: Chronic Renal Failure, OAC: Oral Anti-Coagulation , STEMI: ST-elevation Myocardial Infarction, MVPCI: Multi-Vessel Primary Coronary Intervention, CABG: Coronary Artery Bypass Graft

Fig. 3. Stent thrombosis and major bleeding at 24 months in selected subgroups.

(ST) was observed when a sizeable minority of patients switched from DAPT to single antiplatelet treatment at the time of the 6 months FU visit (Fig. 1). This was also observed in the LEADERS Trial, suggesting that in potential situations associated with bleeding, such as need for noncardiac surgery, there does not seem to be a significant risk for DAPT discontinuation after 6 months.

Our data confirm that, as is the case with other DES and BMS [14–16], most instances of ST occur early after the procedure (<30 days), and usually in patients who are on DAPT. All but two patients who developed definite or probable ST during the full 24 months follow-up period in the present series were on DAPT at the time of the event. As observed previously [6,14], ST is a very severe event, and 27.5% of patients who suffered definite or probable ST died during the follow-up period.

MB was also more frequent during the first weeks, but there was a more sustained incidence of MB

TABLE V. Predictors of MACE at 2 Years by Multivariate Analysis

	MACE		
Variables	HR	CI	*P*
Charlson comorbidity index[a]	1.42	1.18–1.71	<0.001
Total stent length	1.01	1.003–1.01	<0.001
Complex lesion[b]	1.44	1.12–1.86	0.005
Age[c]—linear	1.01	1.002–1.02	0.02
SVG target lesion	2.2	1.36–3.62	0.002

[a]The logarithm of the Charlson comorbidity index + 1 was entered to allow for linearity between the log hazard ratio and the predictor.
[b]Defined as any of the following: bifurcation lesion, in-stent restenotic lesion, lesion in a saphenous vein (or arterial) graft, or a chronically totally occluded lesion.
[c]The median age (64 years) was substracted from the age of patients so that the baseline hazard corresponds to the hazard of a 64-year-old patient.

throughout the 2-year follow-up period (Fig. 2). During the first year, 87 of 91 patients (95.6%) with MB were on DAPT at the time they suffered their first bleeding event. In total, 9.1% of patients who experienced a MB died during the follow-up period.

While the absolute numbers of deaths associated with ST and MB were not very different (11 and 10, respectively), together they accounted for only 13.2% of all deaths reported during the follow-up period. Only three patients (0.05%) in our series entered the vicious circle of suffering both definite/probable ST and MB during the entire follow-up period. This is in accord with data derived from platelet function testing [16,22–24], where an optimal level of platelet inhibition appears to exist, and a higher or lower effect of treatment is associated, respectively, either with bleeding or with stent thrombosis. In a large series of patients presenting with ACS and treated with stents, Manoukian et al. [25] showed that bleeding was associated with an increased risk of subsequent ST.

Early reports stressed the critical importance of DAPT compliance [26], and operators now take great care that patients fully understand this. In the future, progress is more likely to come from the selective use of more potent P2Y12 inhibitors, especially during the first 30 days after PCI, and perhaps from the use of platelet function testing, even though data from that field have so far been mostly disappointing [10,11]. Improved stent designs and shorter courses of DAPT should contribute to decrease the bleeding risks, as documented by several recent studies [27–30]. These suggest that, compared with short-duration DAPT, prolonged DAPT is associated with increased rates of MB but is not associated with an improved outcome in terms of death or myocardial infarction.

Clearly, the "one size fits all" approach for DAPT after stenting may soon be replaced by a choice of different strategies, based on patient demographics and presentation, procedure characteristics, and type of stent used.

Limitations

Several limitations should be underlined. First of all, the results reported here may have been affected by the type of bias inherent to all registries, namely the selective inclusion of lower risk patients, together with less exhaustive monitoring than that applied in randomized controlled trials, potentially contributing to an overall under-reporting of events. Also, although investigators were strongly encouraged to enroll all consecutive patients satisfying the inclusion/exclusion criteria, because written consent for participation could be obtained either before or after the index procedure, some patients with major complications during the procedure may not have been included. However, the event rates are similar to those of other postmarket registries [14,31,32]. and the high rate of patient follow-up deserves to be emphasized. Another limitation is that information regarding vascular access was not collected, and the relative merits of radial vs. femoral access in terms of bleeding and other adverse events cannot be analyzed. Also, the BARC classification was not available at the time the e-BioMatrix registry was designed, and bleeding was assessed using the STEEPLE classification; comparisons with some of the more recent series is thus rendered more difficult [13,15].

CONCLUSIONS

With a low MACE rate of 4.5% at 12 months, and 6.8% at 24 months, these data confirm that excellent results are obtained with the Biolimus A9-eluting stent in a large "real-world" registry recruiting from a representative international sample of 57 centers. The 12 months incidence of ST was low (0.6%) and even lower between 12 and 24 months (0.2%), while that of MB remained preoccupying (1.7% at 12 months and 0.4% between 12 and 24 months). In the future, individual tailoring of intensity and duration of DAPT, based on patient, procedure and stent characteristics, may contribute to further limiting the occurrence of these two very serious and sometimes fatal adverse events.

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APPENDIX A

List of Study Centers

Austria: Universität Innsbruck, *Bernhard Metzler*; Krankenanstalt Rudolfstiftung, Vienna, *Franz Weidinger*; KFJ Spital, Vienna, *Günter Christ*.

Czech Republic: Teaching Hospital, Brno, *Petr Kala*; Masaryk Hospital, Usti nad Labem, *Pavel Cervinka*.

Denmark: Roskilde Sygehus, Roskilde, *Steen Carstensen*.

Germany: Vivantes Klinikum, Berlin, *Stephan Kische*.

Ireland: St James Hospital, Dublin, *Niall Mulvihill*; Mater Misericordiae University Hospital, Dublin, *Niall Mahon*.

Jordan: The Jordan Cardiovascular Center, Amman, *Imad A. Alhaddad*.

Latvia: Pauls Stradins Clinical University Hospital, Riga, *Andrejs Erglis*.

Lithuania: Kaunas University of Medicine Hospital, Kaunas, *Ramunas Unikas*.

Morocco: Clinique Agdal, Rabat, *Assad Chaara*; Hôpital Militaire d'Instruction Mohamed V, Rabat, *Abdelali Boukili*.

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APPENDIX B

Members of the Clinical Event Adjudication Committee

Dr. Alaide Chieffo (Chair)
Prof. Dr. Adnan Kastrati (former Chair)
Dr. Jan Z Peruga
Dr. Tudor C. Poerner
Prof. Dr. Jochen Wöhrle
Prof. Dr. Peter Radke
Dr. Fina Mauri
Dr. Agustin Albarran
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