ELSEVIER

Cardiovascular Revascularization Medicine 12 (2011) 220–227

CARDIOVASCULAR REVASCULARIZATION MEDICINE

Long-term follow-up of multivessel percutaneous coronary intervention with drug-eluting stents for de novo lesions with correlation to the SYNTAX score☆

Robert T. Gerber[a,b,*], Alfonso Ielasi[a], Rasha Al-Lamee[a,b], Azeem Latib[a,b], Flavio Airoldi[a], Massimo Ferraro[b], Luca Ferri[a], Giorgio Bassanelli[a], Cosmo Godino[a,b], Andrew S.P. Sharp[a,b], Alaide Chieffo[a], Mauro Carlino[a], Matteo Montorfano[a], Giuseppe M. Sangiorgi[a,b], Antonio Colombo[a,b]

[a]*Catheterisation Laboratory, San Raffaele Hospital, 20132, Milan, Italy*
[b]*EMO GVM Centro Cuore Columbus, 20145, Milan, Italy*

Received 20 July 2010; received in revised form 10 October 2010; accepted 13 October 2010

Abstract

Background: Stent thrombosis (ST) and restenosis are concerns after percutaneous coronary intervention (PCI). Limited information exists concerning clinical and angiographic outcomes following multiple stent insertion. We therefore present the long-term outcome from drug-eluting stent (DES) insertion and correlate this with the Syntax score.

Methods and Results: Between April 2002 and 2006, all patients that underwent multilesion PCI (defined as ≥4 DES) were included for analysis, and follow-up commenced from the point where the fourth stent was inserted. Three hundred and seventy-four patients were identified, comprising 1972 lesions; 99% had clinical (30±16 months), and 72% had angiographic follow-up. The mean number of stents implanted was 5.7±1.9 and with length of 137±50 mm and Syntax Score of 24±8. The Syntax score (SS) did not predict major adverse cardiac events (MACE) at long-term follow-up, which occurred in 33% in the low SS (<22), 34% intermediate SS (22–32) and 40% in the high SS (>33); *P*=ns. However, the number of stents implanted correlated with events [MACE: 12% (4 DES), 35% (4–6 DES), 61% (>6 DES)]. There were 11 (2.9%) definite and probable ST: four acute and subacute, three late, and four very late.

Conclusions: This study demonstrates an acceptable occurrence of myocardial infarction, death, repeat revascularisation, and ST in patients with multivessel de novo lesions, which had better correlation with the number of DES inserted than the Syntax score.

Keywords: Drug eluting stents; Restenosis; Stent thrombosis; Revascularisation

1. Introduction

The approach to the treatment of multivessel coronary disease (MVD) has evolved significantly in recent years [1]. Several observational and randomised studies have shown equivalence between percutaneous and surgical revascularisation [2–4]. These findings in conjunction with randomised trials demonstrating less neointimal proliferation with drug-eluting stents (DES) compared to bare metal equivalents (BMS) [5,6] has encouraged more liberal use of DES by operators in long and complex coronary lesions [7,8]. This practice occurred despite the pivotal trials enrolling a small percentage of patients with 2–3-vessel disease with

☆ Conflict of interest: none.

* Corresponding author. EMO GVM Centro Cuore Columbus, Milan, Italy. Tel.: +39 02 481 2920; fax: +39 02 48193433.
E-mail address: rtgerber@gmail.com (R.T. Gerber).

1553-8389/10/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.carrev.2010.10.002

Table 1A
Baseline clinical characteristics of all de novo lesions treated with ≥4 DES

	Total (*n*=374)	DES=4 (*n*=124)	DES 4–6 (*n*=155)	DES >6 (*n*=95)
Age	63±11	65±11	63±10	62±10
Men %	332 (89%)	102 (82%)	144 (92%)	86 (91%)
Hypertension	254 (68%)	89 (72%)	99 (64%)	66 (69%)
Diabetes	113 (30%)	32 (25%)	47 (30%)	34 (36%)
Family history	176 (47%)	58 (47%)	74 (48%)	44 (46%)
Hyperlipidaemia	233 (63%)	79 (64%)	96 (62%)	58 (61%)
Current smoker	69 (18%)	10 (8%)	34 (22%)	25 (26%)
Unstable angina	101 (27%)	34 (27%)	44 (28%)	23 (24%)
Mean creatinine (mg/dl)	1.04±0.79	0.96±0.23	1.14±1.19	0.97±0.29
Renal impairment (Cr >1.25 mg/dl)	43 (11%)	16 (13%)	16 (10%)	11 (12%)
Prior CABG	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prior MI	161 (43%)	50 (40%)	77 (50%)	34 (36%)
Left ventricular ejection fraction	53±8%	54±8%	53±8%	53±9%
1-Vessel disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2-Vessel disease	155 (41%)	63 (51%)	65 (42%)	27 (28%)
3-Vessel disease	219 (59%)	61 (49%)	90 (58%)	68 (72%)
Mean SYNTAX score	24.3±8.4	21.8±7.1	25.2±8.1	26.1±9.8

only one lesion treated with up to 2 stents per patient. The so-called off-label use of these stents has resulted in conflicting reports as to the safety of these devices in lesions involving bifurcations [9], chronic total occlusions, in-stent restenosis, and the left main stem [10–12]. Furthermore, recent concerns of DES safety with regard to stent thrombosis (ST) has resulted in changes to guidelines and the risk of ST after multiple DES implantation with current interventional practice is still unknown [13]. The recently reported follow-up from the randomised SYNTAX study (Taxus Drug Eluting Stent versus Coronary Artery Bypass Surgery For the Treatment of Narrowed Arteries) [14], which enrolled patients with multivessel disease and left main stem stenosis, demonstrated equivalence between percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) in terms of its composite primary end point of major adverse cardiac and cerebrovascular events (MACCE). The inevitable risk attributable to the discontinuation of clopidogrel after 1 year of implantation adds further concerns. To date, few studies have addressed these issues in MVD; we therefore conducted a retrospective observational study investigating the long-term impact of multiple DES implantation (defined as ≥4 DES) in relation to Syntax score on clinical and angiographic outcomes.

2. Methods

All consecutive patients referred for multivessel stenting between April 14, 2002 (first day DES usage available for standard clinical practice in our institutions), and April 14, 2006, were included in the analysis. Patients were included from the date when the fourth stent was inserted, whether this was placed in an index procedure or after a staged procedure. The decision to include patients with ≥4 DES was based upon this being the median number of DES implanted in the SYNTAX trial as well as previous data from our group on the midterm outcome of >4 DES in the same patient [15]. We believe this would provide us with a more valid bench mark to compare our data against as well as providing a good "real world" assessment of the SYNTAX score with longer clinical follow-up. There were no exclusion criteria and patients had stable or unstable angina or silent ischemia demonstrable by noninvasive stress testing.

Coronary angioplasty was performed by standard techniques using either the femoral or radial approach and a loading dose of clopidogrel (300 mg), ticlopidine (400 mg) or aspirin (300 mg) was administered if not pretreated. Thienopyridine administration was continued as a maintenance dose the day after the procedure for a minimum of 6 months. (Maintenance-

Table 1B
Baseline lesion and procedural characteristics

	Total (*n*=374)
IIb/IIIa (% of patients)	112 (30%)
IABP (% of patients)	32 (9%)
IVUS (% of patients)	82 (22%)
Left main stem	46 (12%)
Chronic total occlusions	93 (25%)
Bifurcations	171 (45%)
Inhospital death	2 (0.5%)
Non-Q-wave MI	27/374 (11%)
In-hospital repeat PCI	1 (0.3%)
In-hospital repeat CABG	0 (0%)
CK-MB post procedure (U/L)	18±34
	Total lesions (*n*=1972)
Lesion Type A	32 (1.6%)
Lesion Type B1	352 (17%)
Lesion Type B2	948 (48%)
Lesion Type C	606 (31%)
Lesion Type B2/C	1554 (79%)
Baseline RVD (mm)	2.61±0.66
Baseline MLD (mm)	0.86±0.53
Baseline lesion length (mm)	14.3±9.6
Final RVD (mm)	3.04±0.57
Final MLD (mm)	2.63±0.59
Balloon-to-artery ratio	1.20±0.50
Mean balloon pressure (atm)	21±8

Table 2A
Clinical and angiographic outcomes of de novo lesion treated with ≥4 DES according to SYNTAX score using the tertiles from the Syntax Trial [14]

Patients	SYNTAX Score <22 (*n*=165)	SYNTAX Score 23-32 (*n*=156)	SYNTAX Score >33 (*n*=48)	
Clinical follow-up (30±16 months)	164 (99%)	154 (99%)	100%	
Angiographic follow-up (9±6 months)	118 (72%)	113 (72%)	39 (81%)	
No. of DES	5.6±1.9	5.7±1.8	6.1±2.3	*P*=.07
DES length (mm)	132±51	138±45	152±58	*P*<.05 (<22 vs. >33)
Death	9 (5%)	10 (6%)	3 (6%)	*P*=.93
Cardiac death	4 (2%)	7 (4%)	3 (6%)	*P*=.40
Follow-up MI	5 (3%)	7 (4%)	1 (2%)	*P*=.66
TLR per patient	39 (24%)	34 (22%)	14 (29%)	*P*=.57
TVR per patient	50 (30%)	45 (29%)	16 (33%)	*P*=.84
Overall MACE	55 (33%)	53 (34%)	19 (40%)	*P*=.72

dose clopidogrel 75–150 mg, Ticlopidine 250 mg twice daily). The decision to perform PCI instead of CABG was based on (a) referring cardiologist opinion, (b) patient's preference, and (c) suitability to obtain an adequate revascularization with PCI. During the PCI procedure, patients received either intravenous bivalirudin or unfractionated heparin (100 IU/kg) to maintain an activated clotting time between 250 and 300 s. All coronary stents were implanted at pressures >12 atm, and full coverage of the angiographic lesion was attempted in all cases. Bifurcations were treated with either modified T, crush or Culotte techniques. Intra-aortic balloon pump, glycoprotein IIb/IIIa inhibitors, and intravascular ultrasound (IVUS) guidance was performed at the operators' discretion.

2.1. Quantitative coronary angiographic analysis

Coronary angiograms were analysed using a validated edge detection system (CMS, version 5.2, MEDIS, The Netherlands). The reference vessel diameter (RVD), minimum lumen diameter (MLD), and lesion length were measured on the pre and post angiogram and at follow-up.

2.2. End points and definitions

The primary endpoint of this study was the occurrence of immediate and long term follow-up major adverse cardiac events (MACE). The secondary endpoints were angiographic restenosis and stent thrombosis rates. MACE was defined as a composite end point comprising death, myocardial infarction (MI), target vessel revascularisation (TVR) and target lesion revascularisation (TLR). Deaths were classified as either cardiac or noncardiac. Cardiac death was defined as any death due to a cardiac cause (e.g., MI, low-output failure, fatal arrhythmia), procedure-related deaths, and death of unknown cause. Non-Q-wave MI was defined as an elevation of serum creatine kinase (CK) that was two times the upper limit of normal with a concomitant doubling in (CK) MB isoenzyme in the absence of pathological Q waves. Restenosis was defined as >50% luminal narrowing at the segment site (stent and 5 mm proximal and distal) demonstrated at the follow-up angiography, regardless of clinical symptoms. TLR was defined as any revascularisation performed on the treated segment or within 5 mm of the stent edges; TVR was defined as any reintervention performed on the treated vessel considering also treatment of any segment within the left coronary system for an index lesion of the left main stem. ST was defined on the basis of the Academic Research Consortium definitions [16].

2.3. Follow-up

Clinical follow-up was performed by either telephone contact or office visit and curtailed on October 14, 2007. Angiographic follow-up was suggested between 8 and 12 months after stenting unless clinically indicated at an earlier time.

2.4. Syntax scores

Syntax scores were calculated from the pre-intervention index angiograms in de-novo lesion only (i.e. excluding bypass graft interventions and PCI for in stent restenosis). Scores were calculated by four independent scorers (A.I, R. A-L., L.F, G.B) who were blinded from the final outcomes from the study population. The scorers had all completed the syntax score evaluating tutorial and determined the final scores for each angiogram from the Syntax score Web-based calculator at www.syntaxscore.com. In the entire group, five patients did not have Syntax scores calculated as the baseline angiograms were insufficient and excluded. The de novo Syntax group was further subdivided into low (<22), intermediate (22–32) and high (>33) Syntax scores as described in the Syntax study [14]. Additionally, this cohort was separated into the tertiles of risk as calculated for this population [low (<18), intermediate (19–28) and high (>29)]. Long-term outcomes were also determined according to the number of DES implanted with three subgroups created according to the first, median and third quartiles from the population (4 DES; 5–6 DES; >6 DES).

2.5. Statistical methods

Categorical variables are expressed as raw numbers and percentages. Continuous variables are presented as mean±1 S.D. Comparisons between groups of categorical data were performed with chi-square testing. Univariate odds ratio and

95% confidence intervals. SPSS version 13 (SPSS, Chicago, Illinois, USA) and Instat version 3 (San Diego, CA, USA) were used for data analysis and figures were plotted on Graph pad (San Diego, CA, USA). All *P* values were two-sided and considered significant if $P<.05$.

3. Results

A total of 374 patients were treated comprising 1972 lesions with three-vessel disease in 59% of the patients, and an unprotected left main stem lesion in 12%. The baseline clinical characteristics for the entire population are displayed in Table 1A with the lesion and procedural characteristics Table 1B. The mean stent number per patient was 5.6±1.9 with a length of 137±50 mm; 25% chronic total occlusions, 45% bifurcations. The mean Syntax score for the group was 24.3±8.4; in five patients syntax scores were not calculated. Procedures tended to involve complex lesions (lesion B2/C: 79%) with high rates of intra-vascular ultrasound (22%), IIb/IIIa (30%) and intra-aortic balloon pump (9%) use (Table 1B). Of the procedures, 17% were staged, and the mean time was 7.7±9.0 months between procedures; 5.2 lesions were treated per patient, and the number of bifurcation lesions per patient was 2.1. Severe calcification was documented in 406 (20.6%) of the lesions. There were 2 in-hospital deaths: one due to acute ST and subsequent MI and the other due to renal infarction several days post procedure. There were two episodes of repeat PCI: one was the aforementioned case of acute ST, and the second presented with chest pain 3 h post procedure and angiography demonstrated re-occlusion of the previously patent chronic total occlusion (CTO) of the right coronary artery. In-hospital CABG was not required in any patients.

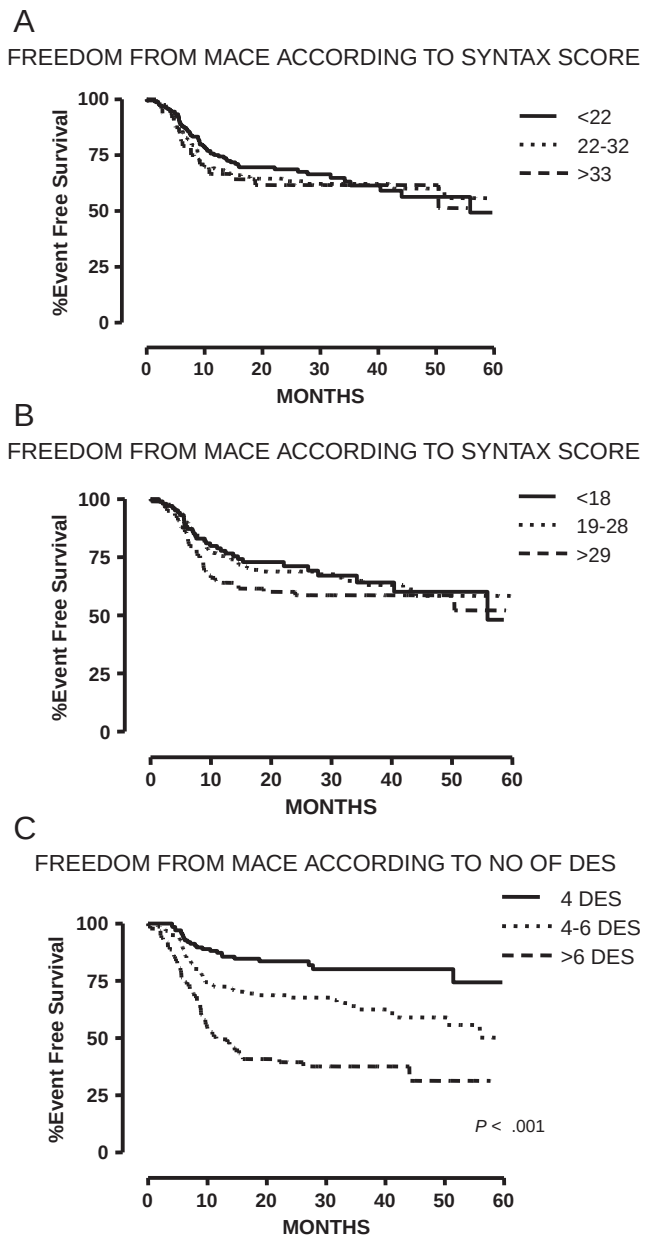

Fig. 1. (A–B) Kaplan-Meier curves for freedom from events in the de novo Syntax Group. (A) According to Syntax Score Tertile from the Syntax Trial [14] (<22, straight lines; 22–32, dotted lines; >33, dashed lines). (B) According to Syntax Score Tertile from this ≥4 DES Cohort (<18, straight lines; 19–28, dotted lines; >29, dashed lines). (C) According to number of DES implanted (4 DES: straight lines; 4–6 DES dotted lines lines; >6 DES dashed lines).

3.1. Long-term follow-up in relation to number of DES and Syntax score

Clinical follow-up was performed in >99% at a median time interval of 30 months with angiographic follow-up at 9±6 months. Angiographic follow-up tended to be higher in patients who had higher Syntax scores. The overall MACE, TLR, TVR, ST, death and follow-up MI rates according to the Syntax score tertiles was not significantly different (Syntax score MACE: <22 (33%) vs. 22–32 (34%) vs. >33 (40%); $P=.72$; Table 2A; Fig. 1A]. This was also the case if the tertiles were calculated according to the scores obtained for this population of patients instead of using the scores derived from the Syntax study [Syntax score MACE: <18(31%) vs. 19–28 (33%) vs. >29 (41%); $P=.32$; Table 2B; Fig. 1B]. Additionally, there was no difference in ST, death and follow-up MI rates according to the number of DES inserted. However, MACE, TLR and TVR rates were significantly different according to the number of DES implanted [MACE: 4 DES (12%) vs. 4–6 DES (35%) vs. >6 DES (61%); $P<.001$; Table 2C; Fig. 1C].

3.2. Stent thrombosis

At the end of follow-up there were 11 (2.9%) episodes of definite and probable stent thrombosis (ST). The time line, patient characteristics and concomitant antiplatelet therapy at the time of ST is shown in Table 3 and Fig. 2.

3.2.1. Acute and sub-acute ST

There were 4 episodes and 2 patients died. One death was a consequence of the ST and the other patient had a possible ST months later and died from heart failure.

Table 2B
Clinical and angiographic outcomes of de-novo lesion treated with ≥4 DES according to SYNTAX score using the tertiles from this cohort of patients

Patients	SYNTAX Score <18 (*n*=103)	SYNTAX Score 19-28 (*n*=165)	SYNTAX Score >29 (*n*=101)	
Clinical follow-up (30±16 months)	102 (99%)	164 (99%)	100 (99%)	
Angiographic follow-up (9±6 months)	73 (71%)	118 (72%)	78 (77%)	
No. of DES	5.3±1.8	5.6±1.8	6.3±2.1	*P*<.001 (<18 vs. >29) *P*<.01 (19–28 vs. >29)
DES Length (mm)	125±48	136±46	152±54	*P*<.001 (<18 vs. >29) *P*<.05 (19–28 vs. >29)
Death	6 (6%)	10 (6%)	6 (6%)	*P*=.99
Cardiac death	3 (3%)	6 (4%)	5 (5%)	*P*=.74
Follow-up MI	4 (4%)	7 (4%)	3 (3%)	*P*=.82
TLR per patient	25 (25%)	34 (21%)	29 (29%)	*P*=.32
TVR per patient	29 (28%)	47 (28%)	36 (36%)	*P*=.40
Overall MACE	32 (31%)	55 (33%)	41 (41%)	*P*=.32

3.2.2. Late definite and probable ST

Two patients had definite ST and both patients were taking dual antiplatelet therapy (DAT) at the time, and one patient died as a consequence. The one case of probable ST occurred in a patient who was admitted with pancreatitis, had all antiplatelet therapy suspended, and went onto to have a fatal MI 6 days after discontinuation of DAT.

3.2.3. Very late definite and probable ST

Two patients had very late definite ST and both were not taking DAT. One of these patients was not compliant with therapy and the other had a large gastrointestinal bleed and stopped all antiplatelets 12.5 months post procedure and suffered an ST. There were two probable ST occurring 3 and 4 years post procedure with one patient on aspirin monotherapy only and the other on DAT.

4. Discussion

The main findings of this study are the following: (1) an acceptable incidence of death and MI from multivessel stenting in these complex patients; (2) the Syntax score did not correlate with occurrence of events at follow-up; (3) the number of stents implanted predicted the occurrence of events during follow-up.

At the outset widespread use of PCI for multivessel disease was limited due to concerns about the high repeat revascularisation rates and so CABG tended to be the favoured treatment. The MACE rate of the current study is higher than our prior experience with multivessel stenting [17] (31–41% vs. 22%), these differences are easily explained when considering the more complex patients treated (3.3 vs. 5.6 stents per patient) and the longer follow-up (6.5 vs. 30 months).

The recently reported Syntax study has attracted much attention as the PCI arm performed as well as CABG in terms of hard clinical end points such as death, stroke and MI (12 months PCI vs. CABG: 7.6% vs. 7.5%; 24 months: 10.8 vs. 9.6%). However, the revascularisation rates were much higher in the PCI arm reflecting the higher MACCE (12 months PCI vs. CABG: 17.8% vs. 12.1%, *P*=.002; 24 months: 23.4 vs. 16.3%, *P*<.001) [14]. The overall MACE at 24 months was much lower than that reported in this study. Of interest, in patients with a high Syntax score (>33) the 2

Table 2C
Clinical and angiographic outcomes of de novo lesions according to number of drug eluting stents implanted

Patients	DES=4 (*n*=124)	DES 4–6 (*n*=155)	DES >6 (*n*=95)	
Clinical Follow-up (30±16 months)	123 (99%)	153 (99%)	100%	
Angiographic Follow-up (9±6 months)	73 (59%)	118 (76%)	83 (87%)	
No. of DES	4	5.4±0.5	8.4±1.9	*P*<.001
DES length (mm)	103±24	134±29	186±61	*P*<.001
SYNTAX score	22±7	25±8	26±10	*P*<.001 4 DES vs. 4–6 and >6
Death	3 (2%)	13 (8%)	6 (6%)	*P*=.11
Cardiac death	2 (2%)	9 (6%)	3 (3%)	*P*=.18
Follow-up MI	2 (2%)	9 (6%)	3 (3%)	*P*=.18
TLR per patient	10 (8%)	33 (21%)	45 (47%)	*P*<.0001
TVR per patient	11 (9%)	47 (30%)	54 (57%)	*P*<.0001
Overall MACE	15 (12%)	55 (35%)	58 (61%)	*P*<.0001
Stent thrombosis				
Acute	1 (0.8%)	1 (0.6%)	1 (1%)	*P*=.94
Subacute	0 (0%)	1 (0.6%)	0 (0%)	*P*=.49
Late definite and probable	0 (0%)	1 (0.61%)	2 (2%)	*P*=.21
Very late definite and probable	0 (0%)	4 (2.6%)	0 (0%)	*P*=.06

Table 3
Clinical and procedural characteristics from patients with late and very late definite & probable stent thrombosis

	1 Late definite	2 Late definite	3 Late probable	4 Very late definite	5 Very late definite	6 Very late probable	7 Very late probable
Ongoing DAT	√	√	×	×	×	×	√
Months since index PCI	5	5	2	12.5	12.5	57	34
No. of stents	10	7	5	5	5	5	5
Stent length (mm)	149	192	125	150	100	163	133
Vessels treated	3	3	2	2	3	3	3
Lesions location of ST	OM	LAD	Unknown	RCA	OM	Unknown	Unknown
CTO	No	No	No	Yes	No	No	No
Bifurcation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
IN LAB complication	No	No	No	No	No	No	No
Any LMS stenting	Yes	No	Yes	No	No	No	No
Gender	M	M	M	M	M	M	M
Age, y	81	80	82	58	60	52	61
LVEF, %	60	50	44	60	55	40	50
DM	Yes	No	Yes	No	No	No	No
Creatinine (mg/dl)	1.2	0.9	1.5	0.95	0.83	1.0	1.04
MI (procedural)	No	Yes	No	No	No	No	No
DEATH	No	Yes	Yes	No	No	Yes	No

DAT, dual antiplatelet therapy.

year MACCE rate was 28.2% once again lower than our reported MACE in the high Syntax group cohort (40%). These differences may be accounted for by the fact that the number (4.4 vs. 6.1) and length (85 vs. 152 mm) of stents were much higher in the present study compared to Syntax. Furthermore, the follow-up was longer and so one would naturally expect additional events with the progression of coronary atherosclerotic disease. In addition, we had a high rate of angiographic follow-up which has been shown to trigger an increase in the revascularisation rate. The present study did not demonstrate a correlation with Syntax score and event free survival. This could be due to a limitation in the reproducibility of the score amongst scorers; however, the score has been tested outside the core-lab setting and the reproducibly amongst cardiologists is sufficient [18]. Interestingly, in the present study, the mean Syntax score is very low compared to previous publications (24 vs. 30). The explanation for this may be that in the Syntax trial more left main stem and bifurcations procedures were performed than in our study (SYNTAX vs. Gerber: LMS 39% vs. 12%, bifurcation 72% vs. 45%). There is a greater weighting of the score for these particular complex lesions which potentially explains the differences in the scores. There is only one study outside the confines of the Syntax trial that has demonstrated that the Syntax score was able to predict the occurrence of adverse events when applied to the ARTS II patients [19]. In

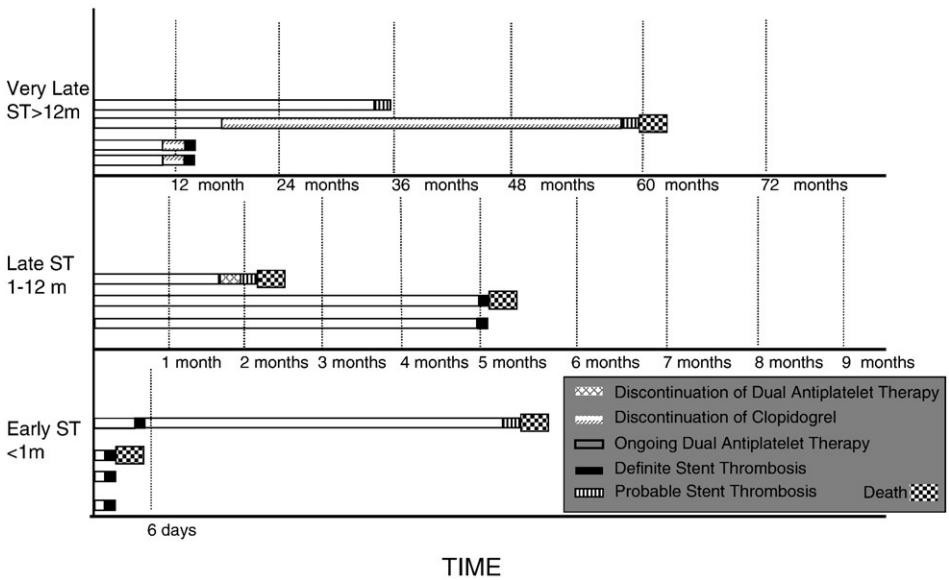

Fig. 2. Timeline to development of stent thrombosis in all patients who suffered definite or probable stent thrombosis. The antiplatelet regimen at the time of stent thrombosis is depicted: crossed lines-no antiplatelet therapy; diagonal lines-aspirin monotherapy; hollow boxes-dual antiplatelet therapy. Outcomes shown as: death-black and white boxes; definite stent thrombosis-black squares; probable stent thrombosis-black stripes.

a recent publication from our group, on the long-term outcome of patients receiving full metal jacket (FMJ) stenting defined as DES lengths >60 mm, the 3-year revascularization rate was 23% similar to that reported in the high syntax score group [20].

A unique feature of this study is the demonstration that the number of DES implanted correlated with events, and is of importance, as this may provide an alternative simpler method of predicting event free survival in patients with complex multivessel disease who undergo multivessel PCI. The explanation for this may simply be that the number of DES is just a marker highlighting the patients with more diffuse coronary artery disease who are generally sicker.

There have been numerous reports on multiple DES insertion, but numbers used have been less than in this report with the mean number of stents per patient ranging from 2.5 to 3.5 [17,21–24] and with follow-up confined to 6–12 months. MACE rates were 15% [21] and 22% [17] at 6 months, 8.3% [22] and 15% [23], at 12 months and 10% [24] and at 24 months. Only one study reported clinical events out to 3 years and demonstrated sustained superiority of DES over BMS during the follow-up period (MACE 12% vs. 37%), but unfortunately, there was no information on the number of stents used in the DES arm [8].

The overall stent thrombosis rate was relatively low (2.9%) in this cohort of patients that had multivessel PCI. The definite and probable very late ST rates were higher (2.4% vs. 0%) in the 4–6 DES group; this was borderline significant. Three of the four patients in that group were not taking dual antiplatelet therapy a feature which may have been contributory to the development of ST [25].

4.1. Limitations

This study reports observational non-randomised data. The choice of stent, adjunctive medical treatment and revascularisation strategy was left to the discretion of the operators and, so, could introduce specific bias, which may mask any confounding factors for the development of adverse events.

5. Conclusion

This observational study provides valuable information on the long-term outcome from multiple stent implantation in complex coronary artery disease. The low mortality and MI rate is encouraging, but the high repeat revascularisation rate needs further investigation. In this cohort of patients that had more than 4 DES implanted the Syntax score did not appear to predict as well the long-term freedom from events as did the number of stents implanted.

References

[1] Van Domburg RT, Lemos PA, Takkenberg JJ, Liu TK, van Herwerden LA, Arampatzis CA, Smits PC, Daemen J, Venema AC, Serruys PW, Bogers AJ. The impact of the introduction of drug-eluting stents on the clinical practice of surgical and percutaneous treatment of coronary artery disease. Eur Heart J 2005;26:675–81.

[2] Bari Investigators. The final 10-year follow-up results from the Bari randomized trial. J Am Coll Cardiol 2007;49:1600–6.

[3] Serruys PW, Ong ATL, Van Herwerden LA, Sousa JE, Jatene A, Bonnier JJRM, Schönberger JPMA, Buller N, Bonser R, Disco C, Backyx B, Hugenholtz PG, Firth BG, Unger F. Five year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: The final analysis of the arterial revascularization therapies studies (ARTS) randomized trial. J Am Coll Cardiol 2005;46: 575–81.

[4] Park DW, Yun SC, Lee SW, Kim YH, Lee CW, Hong MK, Kim JJ, Choo SJ, Song H, Chung CH, Lee JW, Park SW, Park SJ. Long-term mortality after percutaneous coronary intervention with drug-eluting stent implantation versus coronary artery bypass surgery for the treatment of multivessel coronary artery disease. Circulation 2008;117: 2079–86.

[5] Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.

[6] Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003;108:788–94.

[7] Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, O'Shaughnessy CD, DeMaio S, Hall P, Popma JJ, Koglin J, Russell ME. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA 2005;294:1215–23.

[8] Kelbaek H, Klovgaard L, Helqvist S, Lassen JF, Krusell LR, Engstrom T, Botker HE, Jorgensen E, Saunamaki K, Aljabbari S, Thayssen P, Galloe A, Jensen GV, Thuesen L. Long-term outcome in patients treated with sirolimus-eluting stents in complex coronary artery lesions: 3-year results of the scandstent (stenting coronary arteries in non-stress/benestent disease) trial. J Am Coll Cardiol 2008;51:2011–6.

[9] Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR, Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. Circulation 2004;109:1244–9.

[10] Applegate RJ, Sacrinty MT, Kutcher MA, Santos RM, Gandhi SK, Baki TT, Little WC. "Off-label" stent therapy: 2-year comparison of drug-eluting versus bare-metal stents. J Am Coll Cardiol 2008;51:607–14.

[11] Qasim A, Cosgrave J, Latib A, Colombo A. Long-term follow-up of drug-eluting stents when inserted for on- and off-label indications. Am J Cardiol 2007;100:1619–24.

[12] Chieffo A, Park S-J, Meliga E, Sheiban I, Lee MS, Latib A, Kim Y-H, Valgimigli M, Sillano D, Magni V, Zoccai GB, Montorfano M, Airoldi F, Rogacka R, Carlino M, Michev I, Lee C-W, Hong M-K, Park S-W, Moretti C, Bonizzoni E, Sangiorgi GM, Tobis J, Serruys PW, Colombo A. Late and very late stent thrombosis following drug-eluting stent implantation in unprotected left main coronary artery: a multicentre registry. Eur Heart J 2008;29:2108–15.

[13] Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation 2007;115:1440–55 [discussion 55].

[14] Serruys PW, Morice M-C, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW, For the SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.

[15] Ioannis I, Sangiorgi GM, Stankovic G, Corvaja N, Vitrella G, Ferraro M, Colombo A. Results and follow-up after implantation of four or

more sirolimus-eluting stents in the same patient. Catheter Cardiovasc Interv 2005;64:436–9.

[16] Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es G-A, Gabriel Steg P, Morel M-a, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. On behalf of the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

[17] Orlic D, Bonizzoni E, Stankovic G, Airoldi F, Chieffo A, Corvaja N, Sangiorgi G, Ferraro M, Briguori C, Montorfano M, Carlino M, Colombo A. Treatment of multivessel coronary artery disease with sirolimus-eluting stent implantation: immediate and mid-term results. J Am Coll Cardiol 2004;43:1154–60.

[18] Garg S, Girasis C, Sarno G, Goedhart D, Morel M-A, Garcia-Garcia HM, Bressers M, van Es G-E, Serruys PW. The Syntax score revisited: a reassessment of the Syntax score reproducibility. Catheter Cardiovasc Interv 2010;75:946–52.

[19] Valgimigli M, Serruys PW, Tsuchida K, Vaina S, Morel M-A, van den Brand M, Colombo A, Morice MC, Dawkins K, De Bruyne B, Kornowski R, Servi S, Guagliumi G, Jukema J, Mohr F, Kappetein A-P, Wittebols K, Stoll H-P, Boersma E, Parrinello G. 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; 99:1072–81.

[20] Sharp ASP, Latib A, Ielasi A, Larosa C, Godino C, Saolini M, Magni V, Gerber RT, Montorfano M, Carlino M, Michev I, Chieffo A, Colombo A. Long-term follow-up on a large cohort of "full-metal jacket" percutaneous coronary intervention procedures. Circ Cardiovasc Intervent 2009;2:416–22.

[21] Tsagalou E, Chieffo A, Iakovou I, Ge L, Sangiorgi GM, Corvaja N, Airoldi F, Montorfano M, Michev I, Colombo A. Multiple overlapping drug-eluting stents to treat diffuse disease of the left anterior descending coronary artery. J Am Coll Cardiol 2005;45:1570–3.

[22] Degertekin M, Arampatzis C, Lemos P, Saia F, Hoye A, Daemen J, Tanabe K, Lee C, Hofma S, Sianos G, McFadden E, van der Giessen W, Smits P, de Feyter P, van Domburg R, Serruys P. Very long sirolimus-eluting stent implantation for de novo coronary lesions. Am J Cardiol 2004;93:826–9.

[23] Arampatzis C, Hoye A, Lemos P, Saia F, Tanabe K, Degertekin M, Sianos G, Smits P, van der Giessen W, McFadden E, Van Domburg R, De Feyter P, Serruys PW. Elective sirolimus-eluting stent implantation for multivessel disease involving significant LAD stenosis: one-year clinical outcomes of 99 consecutive patients—the Rotterdam experience. Catheter Cardiovasc Interv 2004;63:57–60.

[24] Lee C, Park K, Kim Y-H, Hong M-K, Kim J, Park S-W, Park S. Clinical and angiographic outcomes after placement of multiple overlapping drug-eluting stents in diffuse coronary lesions. Am J Cardiol 2006;98:918–22.

[25] Airoldi F, Colombo A, Morici N, Latib A, Cosgrave J, Buellesfeld L, Bonizzoni E, Carlino M, Gerckens U, Godino C, Melzi G, Michev I, Montorfano M, Sangiorgi GM, Qasim A, Chieffo A, Briguori C, Grube E. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation 2007; 116:745–54.