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ORIGINAL ARTICLE

"Real World" Adhoc Percutaneous Coronary Interventions With Use of Sirolimus Eluting Stents: A Single Operator Experience and Long-term Follow-up

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KEY WORDS: *coronary artery disease; coronary angioplasty; coronary stents; drug-eluting stents; sirolimus-eluting stents; stent thrombosis; restenosis*

ABBREVIATIONS
ACT = activated clotting time
BMS = bare metal stents
CCS = Canadian Cardiovascular Society (classification of angina)
DES = drug-eluting stents
LAD = left anterior descending (coronary artery)
LCx = left circumflex (coronary artery)
LIMA = left internal mammary artery
LM = left main (coronary artery)
LVEF = left ventricular ejection fraction
MI = myocardial infarction
NSTEMI = non-ST elevation myocardial infarction
PCI = percutaneous coronary intervention
RCA = right coronary artery
SES = sirolimus eluting stents
STEMI = ST-elevation myocardial infarction
SVG = saphenous vein graft

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ABSTRACT

BACKGROUND: Drug eluting stents (DES) have ushered in a new era in percutaneous coronary intervention (PCI), curtailing significantly the restenosis rates compared with bare metal stents (BMS). However, their use has been plagued with the late stent thrombosis phenomenon.

OBJECTIVE: During a 5-year period, sirolimus-eluting stents (SES) were employed in 260 patients among 675 consecutive patients submitted to PCI by a single-operator with a uniform technique. The objective of this study was to assess the clinical and angiographic results and to report the incidence of stent thrombosis and the long-term outcome in these patients.

METHODS & PATIENTS: A consistent single-operator approach with 0.5 mm stent oversizing and high pressure (>12-18 bar) stent deployment was adopted, routinely combined with long-term dual antiplatelet therapy for at least a two-year period post-implantation. The study included 213 men and 47 women, aged 64±12 years, who presented with stable angina and/or positive exercise test (n=54), unstable coronary syndrome (n=125), or acute myocardial infarction (MI) (n=81). The dilated vessel was the left main stem (n=4), left anterior descending and/or its diagonal branch (n=178), the right coronary (n=103), the circumflex and/or its obtuse marginal branch (n=89), the ramus branch (n=10), a saphenous vein (n=11) or arterial (n=2) graft. Three groups were compared: 104 (40%) patients receiving SES alone (Group A), 122 patients receiving SES plus other DES (Group B), and 34 patients receiving SES plus BMS (Group C).

RESULTS: The majority (93.8%) of PCI procedures were performed adhoc during the same session of coronary angiography. All 3 groups had similar demographics, mean age (62-66 years), initial stenosis (88-89%) and mean ejection fraction (45-55%). Procedural success (99-100%) and residual stenosis (<0-10%) were also similar. Multivessel PCI and stenting was performed in 120 (46.3%) patients and multilesion PCI in the majority (89.2%) in this cohort. Overall, a mean number of 1.6±0.7 vessels and 3.1±1.6 (range, 1-9) lesions were dilated. A median of 2 stents (mean of 2.6±1.3 stents) were

Conflict of Interest: none declared

implanted in 260 patients; group A (patients receiving SES alone) received the least number of stents (1.7±0.7). There was one occurrence of subacute stent thrombosis in group C (0.4%). All patients received combined therapy with aspirin and clopidogrel, the latter administered for >24 months. Over 16.3±14.7 months of follow-up, survival free of events (death, MI, stroke, repeat revascularization and restenosis) was excellent at 98%, 96%, and 97% at 12 months and 95%, 90% and 97% at 24 months for groups A, B and C respectively; long-rank (Mantel-Cox) test p value= 0.27. Clinical restenosis rates were low in all 3 groups (0% vs 1.6% vs 5.9%) (p=NS). Possible very late stent thrombosis could be suspected in 1 patient (group B) who had sudden cardiac death at 32 months after the procedure.

CONCLUSION: In a consecutive series of 260 patients receiving SES and/or other stents, a uniform single-operator approach with 0.5 mm stent oversizing and high-pressure (>12-18 bar) deployment routinely combined with long-term dual antiplatelet therapy resulted in high procedural success (>99%), very low rate of subacute (0.4%) and late stent thrombosis (0.4%), very low clinical restenosis rates (0-5.9%) and overall excellent survival free of cardiovascular events at 1 and 2 years.

INTRODUCTION

Percutaneous coronary intervention (PCI) has been markedly facilitated by the use of drug eluting coronary stents (DES) which have a most favorable outcome with a significantly lower restenosis rate compared with bare metal stents (BMS) according to data from both randomized studies and registries.[1-3] However, over the recent several years we have poignantly become aware of a potentially serious problem, that of late stent thrombosis which has led to repeated major guideline revisions regarding the duration of dual antiplatelet therapy.[3-9] Over a 5-year period, a uniform approach with approximately 0.5 mm stent oversizing and high-pressure (>12-18 bar) deployment[10-12] was adopted by a single operator, routinely combined with long-term dual antiplatelet therapy and the clinical and angiographic results are presented in a prospective series of 260 consecutive patients receiving sirolimus eluting stents (SES) alone or SES combined with other DES and/or BMS.

PATIENTS AND METHODS

PATIENTS

Over the last 5 years, among 675 consecutive patients who were submitted to PCI by a single operator, 260 patients received SES alone or SES combined with other DES and/or BMS. The study included 213 men and 47 women, aged 64±12 years (range, 35-88) who presented with stable angina and/or positive exercise testing (n=54), acute coronary syndrome (n=125), or acute myocardial infarction (MI) (n=81) (Table 1). A history of previous MI (dated from 1 week to several years) was present in 32 patients, of previous PCI in 25 patients and a history of prior "bypass" surgery in 20 patients. Dilated vessels included the left main (LM) (n=4), the left anterior descending (LAD) and/or its diagonal branch (n=178), right coronary artery (RCA) (n=103), left circumflex (LCx) and/or its obtuse marginal branch (n=89), ramus intermedius (n=10), and venous (n=11) or arterial (n=2) grafts. Three groups were compared: 104 patients receiving a SES, 122 patients receiving a SES plus another DES and 34 patients who received a SES plus a BMS. Procedures were performed at an institution with cardiovascular surgery back-up. Possible complications and risks, as well the benefits of each procedure, and the availability of surgical "bypass" as an alternative method of revascularization were all made explicit to the patient and the patient's family, and informed written consent was obtained from the patient before the procedure.

As the majority (79%) of patients in this series had acute coronary syndromes admitted via the emergency room or transferred from other institutions, they routinely received loading doses of antiplatelet drugs (aspirin and clopidogrel) at least upon arrival in the emergency room. Also routinely upon admission all patients received a statin regardless of the cholesterol status. The primary end-point of the study was to assess the clinical and angiographic results and to report the incidence of stent thrombosis and the long-term outcome of these patients.

CORONARY ANGIOGRAPHIC ANALYSIS

Lesions were classified according to the American College of Cardiology-American Heart Association classification[13] and its subsequent modification.[14] Reference vessel and lesion diameters were measured with use of manual (n=206) or automated (n=54) calipers at selected frames at end-diastole in views showing the worst degree of stenosis without overlap and with the least foreshortening. The guide catheter filled with contrast was used as reference.

PCI PROCEDURE

All patients having an adhoc PCI procedure (n=244) received a bolus of 2500 units of heparin after vascular access was obtained usually from the right femoral artery. After completion of coronary angiography and before proceeding with PCI, additional heparin (5000 units) was administered. For elective PCI (n=16), an initial bolus dose of 7000 units of heparin was employed. For procedures lasting longer than 1 hour if the activated clotting time (ACT) could not be monitored additional

TABLE 1. Clinical and Anatomical Characteristics of 260 Consecutive Patients Receiving SES

Men/Women	213/47
Age (years)	64±11.7
Clinical presentation	
Stable angina/positive ETT	54
Unstable angina	125
AMI	81
STEMI	42
NSTEMI	39
Previous MI	32
Previous PCI	25
Previous CABG	20
Vessel(s)	
LM	4
LAD/D	178
LCx/OM	89
RCA	103
RI	10
SVG	11
LIMA/Rad	2
CTO	10
Number of vessels stented	1.6±0.7
One	140
Two	87
Three	33
Number of lesions	3.1±1.6
LVEF	50±11%
Initial stenosis	88±7%

AMI= acute myocardial infarction; CABG= coronary artery bypass grafting; CTO= chronic total occlusion; D= diagonal; ETT= exercise tolerance test; LAD= left anterior descending artery; LCx= left circumflex coronary artery; LIMA= left internal mammary; LM= left main; LVEF= left ventricular ejection fraction; MI=myocardial infarction; OM= obtuse marginal; PCI= percutaneous coronary intervention; Rad= radial (artery); RCA= right coronary artery; RI= ramus intermedians; SES= sirolimus eluting stents; SVG= saphenous vein graft

2000-3000 units of heparin was given, or if ACT was measured, heparin was given in doses needed to maintain the ACT >300 sec throughout the procedure. Mostly 6Fr or occasionally 7Fr sheaths and guiding catheters were used. A variety of rapid exchange balloon catheters were employed. Nonionic contrast agents were mainly used. Routinely 200 μg of intracoronary nitroglycerin was used initially before dilation, and repeated after each dilation to achieve maximal coronary vasodilation prior to final angiographic assessment estimated visually.

STENT IMPLANTATION

Coronary stents were implanted electively but also for coronary artery dissection of any degree observed visually. Monorail (rapid exchange) coronary angioplasty systems were utilized for all stent implants. Stent implantation was considered successful if residual stenosis was visually <10-20%, there was no discernible dissection or thrombus and the resultant flow was TIMI grade 3. Stent sizes ranged from 8 mm to 33 mm in length and 2.25 mm to 4.0 mm in diameter. In addition to the Cypher™ stent (Johnson & Johnson, Cordis Unit, Miami Lakes, Florida), the predominant types of stents used in these patients were the Endeavor™ (Medtronic Inc., Minneapolis, MN, USA), Xience™ (Abbott Vascular, Santa Clara, CA, USA), NirFlex™ (Medinol Ltd, Tel-Aviv, Israel), Genous™ (OrbusNeich Medical Technologies, Fort Lauderdale, FL, USA), and MGuard™ (InspireMD Ltd., Tel Aviv, Israel) stents. Lesions had been either predilated with undersized standard angioplasty balloons or direct stenting was performed, when deemed feasible, with no prior balloon dilation.

Routinely high-pressure inflation (>12-18 bar) and oversized (by approximately 0.5 mm) stents were employed.[10-12] As stents were mounted on high-pressure balloons and thus for stent deployment additional balloons for postdeployment inflation were not generally needed in the majority of patients. Stent deployment was assessed angiographically by visual estimation. Intracoronary ultrasound was not used. Vessels with reference diameter >2.25-2.5 mm were considered for stenting. Thromboaspiration was employed as needed with use of aspiration catheters for extraction of intraluminal thrombi. Bifurcation lesions were approached with a policy of provisional stenting with use of modified T-stenting and mini-crush techniques, depending on the presence or absence of ostial disease in the side-branch.[15]

For pre-planned procedures an attempt was made to use pretreatment with a 3-day regimen of aspirin (325 mg daily) and clopidogrel (75 mg daily); for patients not having been on aspirin or clopidogrel before the procedure, a dose of 300-500 mg of aspirin and a dose of 300 mg or occasionally 600 mg of clopidogrel was given the day of the procedure. For patients with angiographically demonstrated intracoronary thrombi, a platelet glycoprotein IIb/IIIa inhibitor (tirofiban or eptifibatide) was infused intravenously at an initial bolus dose and then continued at standard infusion rates for 24 hours. Administration of a IIb/IIIa agent was also considered for patients with balloon-induced coronary dissection, implantation of multiple stents, or angiographically high-risk coronary lesions, particularly in diabetic patients or patients with elevated troponin. Tirofiban was administered as an initial loading dose of 0.4 μg/kg/min and then decreased to infusion maintenance dose of 0.1 μg/kg/min at 30 minutes later. Eptifibatide was given

as an initial single bolus of 180 μg/kg, and the infusion at 2.0 μg/kg/min (or 1.0 μg/kg/min if the creatinine was elevated) was commenced concurrently with the first bolus. In cases of bleeding, the dose was decreased or the infusion discontinued.

Vascular sheaths were removed immediately after the end of the procedure and hemostasis was obtained with use of a hemostatic closure device (Angio-Seal™; St. Jude Medical, Inc, St. Paul, MN, USA) for all patients.

Procedural success for all procedures was defined as a residual stenosis <20% without a major cardiac event, including death, Q-wave myocardial infarction or need for emergency coronary artery bypass during hospital admission. Myocardial infarction was defined according with the universal definition of myocardial infarction criteria.[16]

POSTPROCEDURAL MANAGEMENT AND FOLLOW-UP

All patients received aspirin 325 mg once daily indefinitely, and clopidogrel 75 mg once daily for at least 2 years. Patients were followed up at the outpatient clinic or by their referring cardiologists. They routinely underwent exercise testing initially at 4 to 6 weeks and then at 3 and 6 months and annually thereafter. In diabetic patients, those unable to exercise or those with multivessel PCI, thallium scintigraphy was advised at 3-6 months and annually thereafter. Angiographic follow-up was not routinely obtained, but coronary angiography was performed only for clinical recurrence of angina or positive exercise testing or radionuclide scintigraphy. Restenosis was defined as clinical recurrence and/or objective evidence of ischemia by exercise testing or thallium scintigraphy and a diameter stenosis >50% at repeat angiography.

The consensus criteria of the Academic Research Consortium were adopted as general guidance for the definitions of clinical end points and stent thrombosis.[17] Particularly, overall cardiovascular outcome during long-term follow-up related to all *cardiovascular events* including death, MI, stroke, repeat revascularization and restenosis.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±SD and categorical variables as a percentage and/or as a numerical value. Differences between data in the three groups were determined by analysis of variance with Bonferroni posthoc correction for quantitative data and by the chi-square test and the z statistic for qualitative data; life table analysis was performed with use of the Kaplan Meier method and comparisons were made with the long rank test, all with use of the Statview 5.0.1 program (SAS Institute Inc., Cary, NS, USA). A statistically significant difference was accepted at a level of $p<0.05$.

RESULTS

PROCEDURAL CHARACTERISTICS

Clinical and angiographic characteristics of the study population are described in Tables 1 and 2. The majority (93.8%) of PCI procedures were performed adhoc during the same session of coronary angiography. Stenting was successful for all vessels attempted in 257 (98.8%) patients. Direct stenting (no balloon pre-dilation) was feasible for at least one vessel in 25 (9.6%) patients. Revascularization failed in one vessel (RCA) of each of two patients undergoing two- or three-vessel PCI due to inability to cross the lesion with the wire (n=1) or dilate the vessel with the balloon (n=1); in another patient attempted two-vessel PCI failed in one vessel (LCx) due to inability to cross the lesion with the wire, while a Cypher stent could not be advanced in the other vessel (diagonal branch) and another smaller DES (Endeavor Resolute) was successfully deployed instead.

Three groups were compared: 104 patients receiving SES alone (Group A), 122 patients who also received other DES (Group B) and 34 patients who received a SES plus BMS (Group C) (Table 2). The three groups had similar demographics, age, risk factors, initial vessel stenosis and left ventricular ejection fraction (Table 2). Lesion characteristics were different, as well number of stented vessels and lesions; with group A having the smaller number of vessels and lesions stented and thus receiving the least number of stents. The following stents were employed: Cypher alone (patients, n=104), Cypher plus Endeavor (n=118), and/or Xience (n=7), Nobori (n=1), Intrepide (n=1), NirFlex (n=9), Costar (n=5), MiniVision (n=1), Genous (n=55), MGuard (n=7), and Jostent (graft stent) (n=3) (Table 3). A median of 2 stents (mean of 2.6±1.3 stents; range, 1-8) were implanted in 260 patients. Single stents were used in 43 patients, 2 stents in 95 patients, and >3 stents in the remainder. There was one event of subacute stent thrombosis at 4 days after the initial procedure (Fig. 1). This was a patient who presented with inferolateral NSTEMI and coronary angiography revealed subtotal occlusion of both the RCA and an ectopic LCx originating from the proximal RCA; the LCx had long diffuse curved stenoses requiring the implantation of 3 cypher stents; a grafted stent was placed in the RCA due to local ectasia/aneurysm. Despite the administration of standard antithrombotic therapy and the addition of a IIb/IIIa agent (tirofiban), 4 days post-procedurally the patient developed acute symptomatology and ECG signs of an acute inferolateral STEMI. Repeat angiography showed total occlusion of the ectopic LCx, most likely due to previously unnoticed local dissection beyond the distal stent, successfully remedied with thromboaspiration (Export® AP catheter; Medtronic, Inc., Minneapolis, MN, USA) and implantation of a new stent (Endeavor Resolute 2.5/24 mm); the RCA stent was patent.

TABLE 2. Comparative Data in the Three Stent Groups

	SES	SES+other DES	SES+BMS	All Patients	P value
Patients	104	122	34	260	
Age (years)	62.5±12	64.8±11.8	65.8±10.7	64±11.7	NS
Coronary risk factors					
Smoking	48 (46%)	52 (43%)	13 (38%)	113 (43%)	NS
Hypercholesterolemia	85 (82%)	104 (85%)	28 (82%)	217 (83%)	NS
Hypertension	61 (59%)	79 (65%)	23 (68%)	163 (63%)	NS
Diabetes	42 (40%)	44 (36%)	12 (35%)	98 (38%)	NS
Lesion characteristics					
A	3 (2.9%)	0 (0%)	1 (2.9%)	4 (1.5%)	NS
B1	53 (51%)*	40 (32.8%)*	16 (47.1%)	109 (41.9%)	0.011*
B2	29 (27.9%)	42 (34.4%)	9 (26.5%)	80 (30.8%)	NS
C	19 (18.3%)*	41 (33.6%)*	8 (23.5%)	68 (26.2%)	0.016*
LVEF	51±12%	45±12%	55±8%	50±11%	NS
Vessels stented	1.3±0.5	1.8±0.8	1.6±0.6	1.6±0.7	<0.01
Lesions	2.1±0.9	3.95±1.7	3.1±1.4	3.1±1.6	<0.003
Stents	1.7±0.7	3.4±1.3	2.8±1.0	2.6±1.3	<0.001
Diameter stenosis	88±9%	88±7%	88±6%	88±8%	NS
Reference diameter (mm)	2.9±0.3	2.9±0.3	2.9±0.3	2.9±0.31	NS
Pre-intervention MLD	0.57±0.39	0.67±0.3	0.64±0.33	0.63±0.35	NS
Post-intervention MLD	2.9±0.3	2.9±0.3	3.00±0.3	2.9±0.33	NS
Use of IIb/IIIa agents	39 (38%)*	56 (46%)	22 (65%)*	117 (45%)	0.011*
Subacute thrombosis	0 (0%)	0 (0%)	1 (2.9%)	1 (0.4%)	NS
Complications	2 (1.9%)	13 (10.6%)	4 (11.8%)	19 (7.3%)	0.008
Clinical restenosis	0 (0%)	2 (1.6%)	2 (5.9%)	4 (1.5%)	NS
Very late stent thrombosis (possible) ***	0 (0%)	1 (0.8%)	0 (0%)	1 (0.4%)	NS

LVEF= left ventricular ejection fraction; MLD= minimal lumen diameter (mm); NS= non-significant
***relates to patient with sudden cardiac death at 32 months post-PCI

MULTIVESSEL AND MULTILESION PCI

Multivessel PCI and stenting was performed in 120 (46.3%) patients, 87 with two-vessel and 33 with three-vessel disease. However, among the 140 patients with single vessel disease, only 29 had single-lesions, the majority (89.2%) thus accounting for a preponderant multilesion PCI in this cohort. Overall, a mean number of 1.6±0.7 vessels and a mean number of 3.1±1.6 (range, 1-9) lesions were dilated. A mean number of 2.6±1.3 stents were implanted; a total of 43 (16.5%) patients received a single stent, while the majority (83.5%) received multiple stents. Group A (patients receiving SES alone) received the least number of stents (1.7±0.7) compared to the other two groups (Table 2).

ACUTE MYOCARDIAL INFARCTION

PCI was performed in 81 patients with acute myocardial infarction (MI), 42 with ST-elevation MI (STEMI) and 39 with non-ST elevation MI (NSTEMI). Primary PCI was performed in 28 patients and late PCI (24 hours to 1 week) in 14 patients with acute STEMI of anterior location in 19 and inferoposterior in 23 patients. Total occlusion was encountered in 24 and subtotal in the other patients. The dilated and stented vessels were the LAD in 43, the RCA in 16, the LCx in 18, SVGs in 3 and the LIMA in 1 patient. One additional patient, a 70-year-old lady with history of coronary artery bypass grafting (CABG) presented in cardiogenic shock; coronary angiography revealed critical left main and left circumflex

TABLE 3. Clinical Outcome of 260 Consecutive Patients Receiving SES

Initial success of stenting for all vessels attempted	257/260 (98.8%)
Procedural Complications	
Local dissections (managed with additional stenting)	11 (4.2%)
Vessel branch occlusion	1 (0.4%)
Bleeding	4 (1.5%)
Groin hematomas	3
Retroperitoneal bleeding	1
Vessel rupture & cardiac tamponade (managed with pericardiocentesis and grafted stent placement)	1 (0.4%)
Subacute stent thrombosis (at 4 days)	1 (0.4%)
In-hospital deaths (CS)	2 (0.8%)
Long-term follow-up (months)	16.3±14.7 (1-58)
Recurrent angina/ACS/MI	12 (4.9%)
Clinical restenosis	4 (1.6%)
Vessel revascularization (CABG)	2 (0.8%)
Deaths	3 (1.2%)
SCD (at 32 months) *	1
CD (post-CABG) (at 20 months)	1
NCD (colon carcinoma) (at 12 months)	1
CVA	3 (1.2%)
Bleeding	5 (2%)
Intracerebral	1
GI bleeding	1
Gingival bleeding	1
Petechiae	2
Overall stent thrombosis	2 (0.8%)

ACS= acute coronary syndrome; AMI= acute myocardial infarction; CABG= coronary artery bypass grafting; CD= cardiac death; CS= cardiogenic shock; CVA= cerebrovascular accident; D= diagonal (branch); ETT= exercise tolerance test; GI= gastrointestinal; LAD= left anterior descending; LCx= left circumflex; LIMA= left internal mammary artery; LM= left main; MI= myocardial infarction; NCD= non-cardiac death; NSTEMI= non-ST elevation myocardial infarction; OM= obtuse marginal (branch); PCI= percutaneous coronary intervention; Rad= radial (artery); RCA= right coronary artery; RI= ramus intermedius; SCD= sudden cardiac death; SES= sirolimus eluting stent(s); STEMI= ST-elevation myocardial infarction; SVG= saphenous vein graft

* Possible very late stent thrombosis by definition[17]

coronary artery lesions and total occlusion of the LAD with patent saphenous vein graft to the LAD which though had a subtotal occlusion after the anastomosis. PCI was successful in restoring patency both to LM/LCx with implantation of one stent and also to the distal LAD with implantation of a second stent via the SVG. Unfortunately, however, the patient succumbed despite successful recanalization 3 days later.

CHRONIC TOTAL OCCLUSION

Chronically totally occluded vessels were present in 10 (3.8%) patients; all but 4 had suffered a previous MI and subsequent functional testing had confirmed viable myocardium supplied by the occluded vessel; one patient had prior PCI and instent occlusion. All occluded vessels (LAD, n=5; RCA, n=2; LCx, n=3) were successfully crossed and dilated initially with conventional balloon angioplasty; stents were implanted in all patients. Local dissection and thrombus formation occurred in one patient, remedied with thromboaspiration and additional stenting. Restenosis was suspected in one patient developing angina CCS II symptoms at 6 months and repeat coronary angiography was recommended which the patient deferred. One patient suffered a non-cardiac death (colon cancer) at 12 months post-PCI.

USE OF IIB/IIIA AGENTS

A platelet glycoprotein IIb/IIIa inhibitor was used during the procedures in 117 (45%) patients, tirofiban in 80 patients and eptifibatide in 37 patients. A IIb/IIIa agent was mainly used for angiographically demonstrated coronary thrombi, local dissections, implantation of multiple (>3) and/or long stents, ectatic vessels with sluggish coronary flow, primary angioplasty and stenting of acute MI, or high-risk lesions in diabetic patients or lesions in venous grafts. Complications related to use of a IIb/IIIa agent included mostly local inguinal and gingival bleeding, but there were no cases of thrombocytopenia noted.

COMPLICATIONS

During PCI local dissections occurred in 11 (4.2%) patients and were managed with additional stent implantation; in one patient there was also local thrombosis noted in a dissected right coronary artery (RCA) which was recanalized from chronic total occlusion and thromboaspiration was successfully employed. Branch (PDA) occlusion occurred in one patient undergoing PCI and stenting of the distal RCA, resulting in small CK rise. Non-q wave myocardial infarction, as based on CK elevation, was noted in one additional patient. Vessel rupture leading to cardiac tamponade occurred in one patient having PCI performed in two vein grafts; a calcified diagonal branch ruptured during stenting just beyond the distal anastomosis of the graft. The patient was managed successfully with prompt pericardiocentesis and grafted stent placement; at the latest follow-up at 33 months he has been doing very well remaining free of angina symptoms. Subacute stent thrombosis

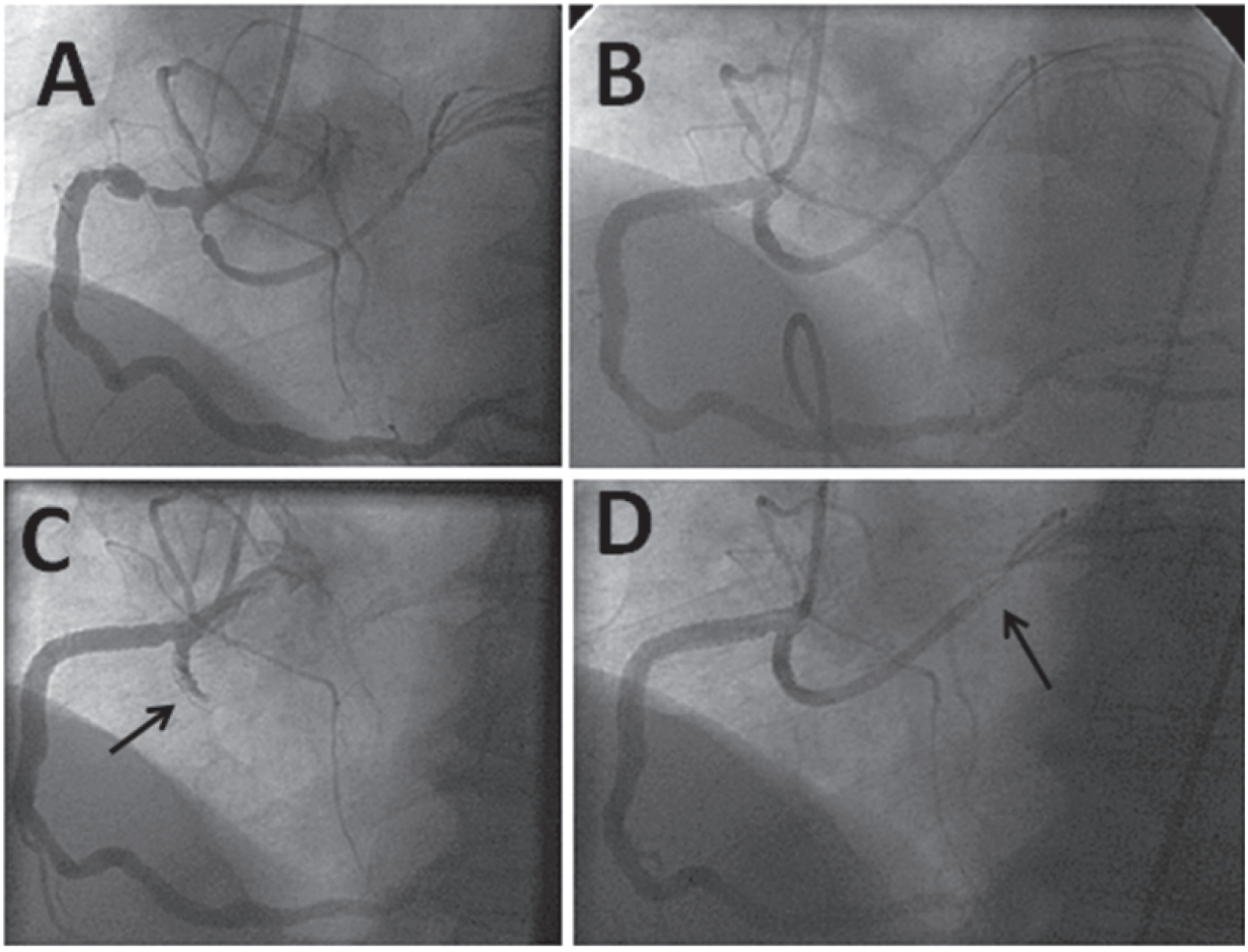


FIGURE 1. A 61-year-old patient who suffered an acute non-ST elevation infero-lateral myocardial infarction underwent coronary angiography, which revealed subtotal proximal occlusion of both the RCA (also followed by local aneurysmal dilatation) and an ectopic circumflex coronary artery (also having a distal critical stenosis) (panel A). Adhoc PCI and stenting were successfully performed with use of a grafted stent for the RCA and 3 Cypher stents for the circumflex to cover both the proximal and distal lesions (panel B). Despite having received loading doses of aspirin and clopidogrel and infusion of tirofiban, 4 days later the patient developed **subacute stent thrombosis** of the ectopic circumflex coronary artery (arrow, panel C), which was restored with thromboaspiration (panel D) and implantation of an additional stent at the distal lesion, just at the end of the previous stent (arrow, panel D). RCA= right coronary artery; PCI= percutaneous coronary intervention

occurred in one patient at 4 days, as discussed above, and was successfully managed with stent implantation (Fig. 1). Bleeding complications were observed in 4 patients receiving IIb/IIIa inhibitors, 3 groin hematomas and one retroperitoneal bleeding, the latter requiring blood transfusion. The no-reflow phenomenon occurred in two patients, significantly improved after intracoronary use of nitroglycerin and verapamil and intravenous administration of a IIb/IIIa agent; thromboaspiration of heavy thrombotic load was required in one additional patient for flow restoration.

Two in-hospital deaths occurred. One patient with prior CABG presenting with cardiogenic shock had a successful PCI of the native left main and circumflex coronary artery and the left anterior descending via a venous graft but finally succumbed 3 days later. Another patient presenting with lateral NSTEMI, initially successfully revascularized via a 2-vessel (circumflex and RCA) PCI procedure, developed heart failure and cardiogenic shock to which he succumbed 5 days later. Thrombocytopenia was not observed after administration of a IIb/IIIa agent in any patient. No patient in this series required emergency CABG.

LONG-TERM FOLLOW-UP

During long-term clinical follow-up, available in 244

(94.6%) patients, over 16.3±14.7 months, 12 (4.9%) patients had recurrent angina (Fig. 2) or acute coronary syndrome or MI, but restenosis was documented angiographically in only 4 (1.6%) patients, of whom 2 underwent CABG at 2 and 8 months after PCI respectively, while the other 2 were managed medically. One additional patient died suddenly at 32 months after PCI, by definition a suspect for "possible" very late stent thrombosis; this was an elderly gentlemen, aged 80 years, with prior CABG, who presented initially with inferior MI and underwent PCI and stenting of a subtotal occlusion of a saphenous vein graft to the RCA. There were two additional deaths, one cardiac (of pump failure one year after CABG) and one non-cardiac (of metastatic colon cancer) at 20 months and 12 months post-PCI respectively. Three (1.2%) additional patients suffered a stroke during follow-up. Bleeding occurred in 5 (2.1%) patients, including 1 intracerebral hemorrhage, 1 gastro-intenstinal bleeding, 1 gingival bleeding and 2 petechiae. Survival curve analysis with the Kaplan Meier method revealed excellent survival free of events (death, MI, stroke, repeat revascularization or restenosis) in all three groups (Fig. 3). Survival free from events was 98%, 96%, and 97% at 12 months and 95%, 90% and 97% at 24 months for groups A, B and C respectively; long-rank (Mantel-Cox) p value= 0.27.

DISCUSSION

"REAL WORLD" SINGLE OPERATOR EXPERIENCE WITH THE CYPHER STENT

In this prospective series of 260 patients receiving a SES with or without additional DES and/or BMS, the Cypher stent but also the other stents implanted (with the Endeavor Resolute and Genous stents as the predominant other non-SES stents) performed very well acutely and long-term over a mean follow-up of approximately 16 months. This was mainly a series of patients having an adhoc PCI (93.8%) during the same session as coronary angiography, with a preponderance of acute coronary syndromes (79.2%). The majority (89.2%) had multilesion PCI with 46.3% having two- or three-vessel disease with type B/C lesions in 98.5%. Of the 140 patients

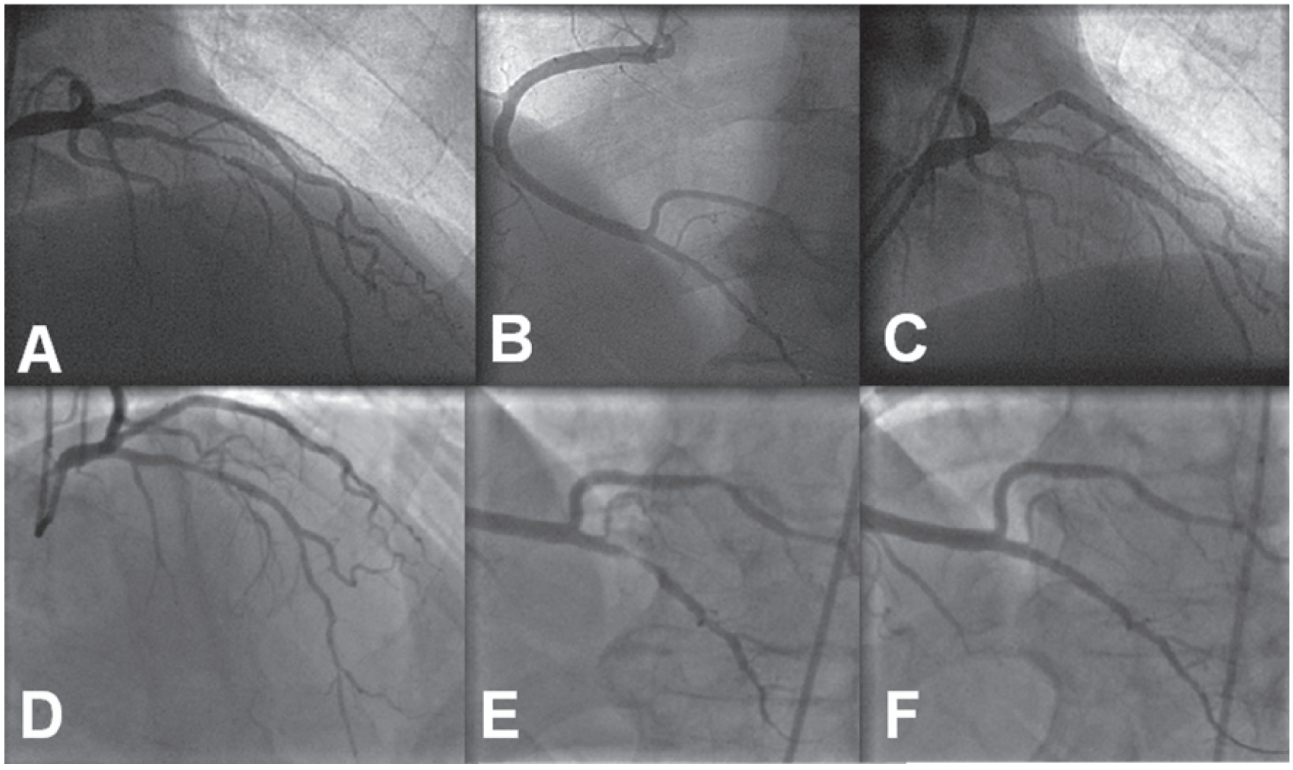
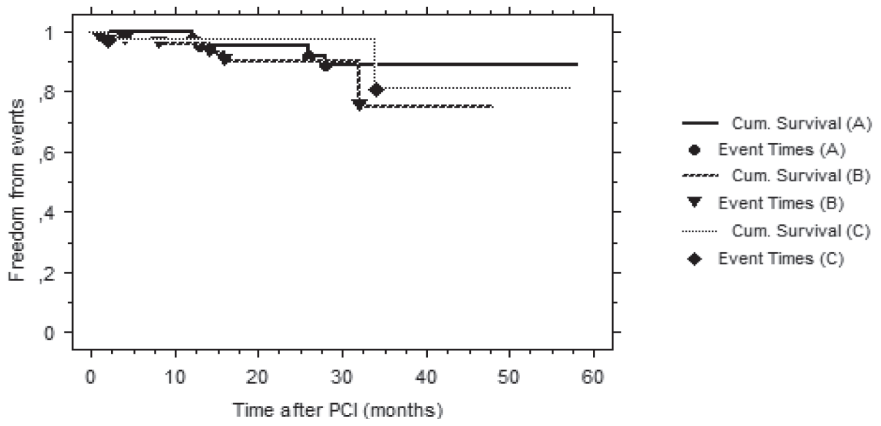


FIGURE 2. A 62-year gentleman with symptomatic ischemia (group A) in the territory of the LAD underwent PCI of a subtotal occlusion of the LAD (panel A) with implantation of a single Cypher stent (panel C). His RCA had no disease. Three years later the patient developed CCS class III angina symptoms leading to repeat coronary angiography which demonstrated patency of the LAD stent (panel D) and a new lesion of the PDA branch of the RCA (panel E). He received a new Cypher stent (panel F) and he has since been doing very well remaining asymptomatic at 18 months later. CCS= Canadian Cardiovascular Society (classification); LAD= left anterior descending coronary artery; PCI= percutaneous coronary intervention; PDA= posterior descending coronary artery; RCA= right coronary artery



Number at risk				
Group A	104	55	34	27
Group B	122	57	24	8
Group C	34	29	25	14

FIGURE 3. Kaplan-Meier analysis of cumulative survival of the three groups free from events (death, myocardial infarction, stroke, restenosis, repeat revascularization); survival free from events was 98%, 96%, and 97% at 12 months and 95%, 90% and 97% at 24 months for groups A, B and C respectively; long-rank (Mantel-Cox) p value= 0.27.

having single-vessel disease, only 29 had single lesions.

The PCI procedure was completely successful in revascularizing and stenting all vessels attempted in 257 (98.8%) of 260 patients; in 3 patients the procedure was partially successful with failure occurring in revascularizing one of two (n=2) or one of three (n=1) vessels attempted. Procedural complications comprised mainly local dissections in 11 (4.2%) patients, all managed successfully with additional stenting, one vessel rupture leading to cardiac tamponade promptly managed with pericardiocentesis and grafted stent implantation, and local bleeding in 4 patients managed conservatively. Subacute stent thrombosis developed in one (0.4%) patient and was also managed successfully at a repeat procedure.

The long-term course of this cohort was excellent with recurrent symptoms reported in 12 (4.9%) patients but restenosis was documented in 4 (1.6%). There occurred 3 deaths, one sudden, one cardiac and one non-cardiac, and 3 strokes during follow-up. While all patients were maintained on long-term dual antithrombotic therapy for at least 2 years, only 5 patients developed late hemorrhagic complications which were serious in 2 patients having cerebral and gastrointestinal bleeding, respectively. Long-term survival free of cardiovascular events (death, MI, stroke, repeat revascularization or restenosis) was excellent in all three groups: 98%, 96%, and 97% at 12 months and 95%, 90% and 97% at 24 months for groups A, B and C respectively (Fig. 2). The "dreaded" complication of late stent thrombosis could be suspected as possible in one (0.4%) patient who sustained sudden cardiac death at 32 months after the initial PCI procedure. Thus, the overall rate of stent thrombosis in this series was limited to 2 patients (0.8%).

CORONARY STENTING TECHNIQUE

The present study demonstrates in a series of 260 receiving a SES among 675 consecutive patients of a single-operator experience that SES implantation alone or combined with other DES and/or BMS by applying a uniform and consistent approach of oversizing and high-pressure deployment inflation, resulted in high procedural success, very low subacute stent thrombosis and very low clinical restenosis rates. Combined with long-term use of antiplatelet agents the late stent thrombosis phenomenon was almost eliminated; only one case of a patient with sudden death at 32 months meets the definition for "possible" very late stent thrombosis. Although these are results from a nonrandomized series of patients, they involve unselected patients and lesion types, with complex multilesion and multivessel PCI and thus reflect more accurately "real-world" practice in a large tertiary center, rather than randomized studies, with their selection bias and stringent selective criteria applied. These results are much better, albeit in a smaller cohort, than those recently reported in an observational retrospective study of a large patient population receiving different types of DES, whereby the incidence of late stent thrombosis ranged from 0.83% to 1.7% at two- and three-year follow-up.[18] They are also better than those of the SYNTAX trial which showed a 3.3% incidence of stent thrombosis at 1 year,[19] and of the ARTS II trial indicating a 3.8% incidence of stent thrombosis at 3 years.[20] Our patient population underwent complex multilesion and multivessel procedures with

implantation of multiple and long stents, features which apparently confer higher rates of stent thrombosis.[19,21,22] However, this was obviated and the difference noted, we believe, relates first to the technique adopted routinely in our study with stent oversizing and high-pressure stent deployment and second to the longer duration of antiplatelet therapy in our patients (>24 months vs >6-12 months).

Most importantly, compared to other studies, the present study reports on a more clinically relevant endpoint, which is the clinical, rather than the angiographic, restenosis rate. During long-term follow-up a patient-oriented cardiovascular end-point was utilized for evaluation, which included all death, MI, stroke, repeat revascularization and clinical restenosis, mostly following the consensus criteria of the Academic Research Consortium for DES study end-points.[17]

A small (13.1%) non-DES stent use rate in this series reflects an evolution over time with the exponential growth of DES use, due mainly to a significant reduction of the restenosis rates.[3] However, a major drawback of DES, the occurrence of late stent thrombosis, was highlighted a few years ago and threatened to limit the use DES in favor of BMS.[3-7] Nevertheless, the data accumulated todate offered some increased re-assurance with regards to the risks of this "dreaded" complication. Since then newer generation stent devices appeared and are being designed, promising to overcome the limitations of the first generation stents by providing improved flexibility and deliverability, better expansion, smoother angiographic appearance and possibly less thrombogenicity mainly by novel coatings or by being biodegradable, all leading to quicker, more simplified and, most importantly, safer procedures. [3,23] The technique of stent oversizing and high-pressure deployment adopted in this series, combined with prolonged dual antiplatelet agent use, has apparently contributed significantly to the very favorable acute and long-term results in this unselected patient cohort.

MULTIVESSEL AND MULTILESION PCI

The majority (89.2%) of patients in these series had multilesion PCI. A total of 46.3% had multivessel (two- or three-vessel) PCI. Even among the 140 patients having single-vessel disease, 111 patients had multiple lesions dilated and stented. The great majority (98.5%) of all lesions were complex type B/C lesions. Overall, a mean number of 1.6±0.7 vessels and a mean number of 3.1±1.6 (range, 1-9) lesions were dilated. The use of DES vs BMS in multilesion and multivessel PCI is favored in non-dedicated trials and registries with regards to repeat revascularization and major cardiac events, but randomized trials are lacking. [3] Importantly, comparing PCI using DES with CABG, the results from trials, including SYNTAX, favor CABG; clinical outcomes between PCI and CABG are only comparable among patients in the lowest SYNTAX score tercile,[3] although in the 5-year follow-up data from the ARTS II trial, safety of SES was comparable to CABG and superior to BMS, and the cardiac event rate was lower with BMS, but higher with CABG.[18,24] Nevertheless, one third of the events encountered in the SES group could have been prevented if stent thrombosis had been lower.[24] These not-withstanding, it appears that in patients with discrete and non-diffuse lesions and of course in those who refuse surgery or have high and prohibitive surgical risk scores, PCI with DES appears an important option.

ACUTE AND CHRONIC TOTAL OCCLUSION

PCI and stenting was successfully performed in 81 patients with acute MI, as primary (n=28) and late (n=14) PCI in 42 STEMI, and in 39 NSTEMI. Total culprit vessel occlusion was encountered in 24 and subtotal in the other patients. Despite initially successful revascularization, two in-hospital deaths occurred in patients presenting in cardiogenic shock and heart failure. During follow-up, MI recurred in 3 patients of whom one was submitted to CABG, one to non-target vessel PCI and the other treated medically; anginal symptoms developed in another 2 patients who deferred repeat coronary angiography; one patient died suddenly at 32 months. Studies examining the use of DES in patients with acute MI have indicated no significant difference between BMS and DES in terms of mortality and stent thrombosis, with DES leading to a significant reduction in repeat target lesion or vessel revascularization.[3,25] A recent study evaluated the 3-year long-term safety of SES in 2308 patients with acute coronary syndrome and found that these patients had a greater risk of early (first one year) adverse events (death, MI, stent thrombosis), but the risk of late (beyond the first year) events was similar to those without acute coronary syndrome.[26]

Chronic total occlusions were successfully treated in 10 patients (3.8%) in this series. All occluded vessels (100%) were successfully crossed and dilated initially with conventional balloon angioplasty; stents were implanted in all patients. Restenosis was only suspected in one patient who developed CCS class II symptoms at 6 months but deferred repeat coronary angiography. Stenting of chronically totally occluded vessels with DES as compared with BMS has been shown to be equally efficacious and safe in comparative trials, which though have demonstrated significantly reduced angiographic and clinical restenosis rates and target lesion or vessel revascularization with DES.[23,27]

ANTITHROMBOTIC AND STATIN THERAPY

All patients were receiving aspirin before and indefinitely after the revascularization procedures. All patients continued receiving additionally clopidogrel (75 mg daily) for at least 24 months after the procedure. An attempt was made for elective procedures to have the patient receive pretreatment with both aspirin and clopidogrel for 3 days before the scheduled procedure. This type of pretreatment strategy (>3 days) has been endorsed by several studies indicating a lower risk of

procedural non-Q-wave MI, in addition to the protection offered from subacute stent thrombosis.[28,29] However, the majority (79%) of patients in this series were patients with acute coronary syndromes admitted via the emergency room or transferred from other institutions and they all received loading doses of both antiplatelet agents at least upon their arrival in the emergency room. They also received a statin regardless of their cholesterol status and this may have contributed to the favorable outcome as suggested by recent data.[30,31] All these measures probably complemented a uniform and consistent approach of stent oversizing and high-pressure inflation, a strategy that can apparently optimize the clinical outcome of coronary stenting.[12]

In patients (n=117) with intracoronary thrombi, or dissections or angiographically high-risk lesions, particularly in diabetic patients, eptifibatide or tirofiban was administered with very favorable outcome. Most likely, early sheath removal with use of a closure device contributed to minimize bleeding complications particularly in this patient subgroup. Importantly, there were no events of thrombocytopenia noted in these patients. Cost constraints and concerns about the bleeding risk have by and large reduced the use of IIb/IIIa agents during PCI over the recent years, having also been supplanted by dual antiplatelet therapy given as pre-treatment or in a periprocedural loading scheme.[29]

With regards to the duration of dual antiplatelet therapy after DES implantation, due to the "dreaded" risk of late stent thrombosis, guidelines from cardiological societies have been updated more than once recently and the latest ones recommend at least one-year duration for this therapy.[8,9] Long before these clinical guidelines were issued, we have been advising our patients to continue receiving dual antiplatelet therapy for at least two years. This recommendation has most likely contributed to almost elimination of late stent thrombosis in our patient cohort, albeit without having all the data regarding patient compliance with dual antiplatelet therapy. "Possible" very late stent thrombosis may be suspected in only one patient who sustained sudden death at 32 months after the PCI procedure. Of course, there is concern of late bleeding problems and problems of patient handling when need for other surgical procedures emerges, but late bleeding occurred in a small number of our patients (Table 3), among whom only two (0.8%) had severe bleeding events and these were patients requiring triple antithrombotic therapy. However, studies have shown that even during the first year, life-threatening bleeding complications are not the main reasons for discontinuing dual antiplatelet therapy and this needs to be addressed in order to avoid unjustified discontinuation of what appears nowadays to be life-saving therapy for patients receiving DES.[32] Finally, with the new antiplatelet agents (prasugrel and ticagrelor) currently becoming available, the scenery of stent thrombosis in the future may not be the same.

STUDY LIMITATIONS

The study is limited by the lack of randomization. However, it reflects clinical practice in a uniform approach by a single operator. The results reported apply to the technique and type of stents (mainly the Cypher, Endeavor, Genous, Xience, NirFlex, Costar, MGuard, and Jostent stents) used in the study. Another limitation is the lack of routine angiographic follow-up, relying mainly on clinical grounds and exercise testing or radionuclide scintigraphy for initial detection of restenosis, subsequently confirmed by angiography. However, this approach avoids any unnecessary revascularization procedures usually triggered by the "occulostenotic reflex".[33] Also, the lack of intravascular ultrasound use in this series may be considered a limitation by some, but this was circumvented by oversizing and high-pressure stent deployment. Furthermore, current stent delivery systems utilize high-pressure balloons, which obviate the need for post-deployment extra dilatation. Overall, this proposed approach to coronary stenting appears more practical and cost-effective strategy by avoiding delay and costs incurred by use of ultrasound and extra balloons for additional high-pressure inflation. Finally, these results pertain to patients with a mean left ventricular ejection of 50% and may not relate to patients with more compromised left ventricular function.

CLINICAL IMPLICATIONS

The results of the present study indicate in a single-operator experience of 260 patients receiving SES alone or combined with other DES and/or BMS among 675 consecutive patients undergoing PCI that the technique of stent oversizing and high-pressure deployment with adjunctive therapy with aspirin and clopidogrel led to high procedural success (99%), very low rate of subacute (0.4%) or late stent thrombosis (0.4%), and a very low clinical restenosis rate (<6%). Pretreatment for at least 3 days before an elective procedure with the antithrombotic regimen of combined aspirin and clopidogrel or aspirin and clopidogrel loading for urgent PCI with selective periprocedural use of a IIb/IIIa agent may be an important adjunctive measure to reduce the acute complication rate during PCI and stenting. Long-term use of combined antiplatelet therapy with aspirin and clopidogrel drastically reduced the risk of late stent thrombosis without increasing the risk of serious late bleeding complications.

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