One-year clinical follow-up of a registry evaluating a percutaneous revascularisation strategy combining a pre-specified simple selection process with the use of a new thin-strut bare cobalt-chromium stent

P.R. Stella, G. Pavlakis, P. Agostoni, H.M. Nathoe, S. Hoseyni Guyomi, B.J. Hamer, T.X. Wildbergh, P.A. Doevendans, E. Van Belle

Objectives. To evaluate clinical events in a specifically selected cohort of patients with obstructive coronary artery disease (CAD), using a new generation thin-strut bare cobalt-chromium coronary stent.

Methods. Patients with single- or multi-vessel, stable or unstable CAD eligible for percutaneous implantation of at least one bare cobalt-chromium stent were evaluated in a single-centre registry. Prospective pre-specified criteria for bare cobalt-chromium stent implantation in our centre were: any acute ST-elevation myocardial infarction (MI), otherwise 1) de novo coronary lesion, and 2) lesion length <20 mm, and 3) reference vessel diameter >2.6 mm, and 4) no diabetes, unless reference vessel diameter >3.5 mm. Endpoints, retrospectively collected, were death, MI and clinically driven target-lesion revascularisation (TLR) and target-vessel revascularisation (TVR) after 12 months.

Results. Between September 2005 and June 2007, 712 patients (48.7% one-vessel, 29.9% two-vessel, 20% three-vessel and 1.4% left main disease; 7.9% diabetics) were treated with 800 bare cobalt-chromium stents, for stable angina (40.9%), unstable angina (20.9%) or acute ST-elevation MI (38.2%). The procedural success rate was 99.3%. Peri-procedural MI rate was 2.2% in the semi-elective group. At 12 months there were 17 deaths (2.4%), of which nine non-cardiac, 20 (2.8%) MI, 19 (2.7%) TLR and 29 (4.1%) TVR. Early and late definite stent thrombosis occurred in four (0.6%) and three (0.4%) patients, respectively.

Conclusion. A strategy aimed at minimising drug-eluting stent use and combining a pre-specified simple selection process with the use of a new thin-strut bare cobalt-chromium stent is safe and effective at one-year clinical follow-up. (Neth Heart J 2010;18:486-92.)

P.R. Stella
G. Pavlakis
P. Agostoni
H.M. Nathoe
S. Hoseyni Guyomi
B.J. Hamer
T.X. Wildbergh
P.A. Doevendans
E. Van Belle
Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands

Correspondence to: P.R. Stella
Department of Cardiology, University Medical Center Utrecht, Room E.01.207, PO Box 85500,3508 GA Utrecht, the Netherlands
E-mail: p.stella@umcutrecht.nl

Percutaneous coronary interventions (PCI) are a valuable addition to treatment regimens in modern cardiology.[1-3] The use of intracoronary metallic stents has improved results over balloon dilatation alone and has become standard care for patients undergoing PCI.[4] However, in-stent restenosis, leading to recurrence of symptoms, has been the major drawback of bare metal stents (BMS).[5] Drug-eluting stents (DES) were introduced in an attempt to overcome this problem and, due to the improved effectiveness in preventing restenosis, DES implantation has rapidly grown to up to 80% of cases in some countries.[6]

However, recently there have been concerns about their long-term safety,[7] due to an increase in late stent thrombosis, possibly linked to delayed endothelialisation of the stent struts. Delayed endothelial cell growth is due to a non-selective inhibitory action of the drug on targeting both smooth muscle cell proliferation and endothelial cell regeneration.[8] Moreover, DES definitely increases the cost of PCI when compared with BMS and debate is ongoing over the long-term cost-effectiveness of these devices.[9]

The beneficial clinical data on DES are mainly derived from trials comparing DES with first-generation thick-strut stainless steel BMS. However, outcomes can be different between stents depending on material and design.[10-13] Stents with thinner struts have shown less restenosis and less repeated interventions.[14,15] This effect may be due to more rapid re-endothelialisation after deployment of thinner-strut stents, reducing vascular injury and inflammation.[14-16] With the progressive development of BMS manufacturing, the use of cobalt-chromium alloy has appeared promising. This alloy has shown good biocompatibility and appeared to limit the adverse proliferative response seen with other alloys.[9-11] In addition, cobalt-chromium compared with stainless steel allows reduction in strut thickness with increased flexibility, conserving both radial strength and deliverability.[17]

Our aim was to evaluate the clinical outcome of a cohort of patients undergoing PCI, in whom the decision to use a new generation thin-strut bare cobalt-chromium coronary stent was pre-specified according to 'non-DES' criteria.

Methods

This was a single-centre registry, based on a prospective pre-specified simple selection process used to discriminate between BMS or DES implantation, and retrospective data collection. The centre consensus agreement[18] limited the use of BMS to patients with the following pre-specified criteria: any acute ST-elevation myocardial infarction (MI), otherwise 1) de novo coronary lesion, and 2) lesion length <20 mm, and 3) reference vessel diameter >2.6 mm, and 4) no diabetes, unless reference vessel diameter >3.5 mm. Exceptions, with use of BMS also out of these criteria, occurred in case of predicted or suspected inability of patients to comply with long-term (one year) double antiplatelet therapy or in case of expected survival <6 months.

In this registry the Skylor thin-strut bare cobalt-chromium stent (Invatec S.p.A., Roncadelle [Brescia], Italy) was used as BMS. As the stent was already CE approved, marketed and commercially available at the beginning of the study, no formal informed consent, apart from the one related to the procedure, was requested.

Procedures

All angioplasty procedures were performed according to routine practice. According to the daily routine, direct stenting and post-dilatation were allowed and left to the discretion of the operator. Patients who received different types of stents in the index vessel were excluded. All patients were treated with standard optimal medical therapy, consisting of aspirin (at least 80 mg/day lifetime) and clopidogrel (75 mg/day after loading dose of 300 or 600 mg for at least one month up to one year in case of acute coronary syndromes). Use of β-blockers, ACE inhibitors, calcium antagonists, statins and nitrates were administered if clinically indicated.

Stent characteristics

The Skylor stent is a thin-strut bare cobalt-chromium stent with a multiple mono-type closed cell design. Strut thickness differs according to the diameter of the stent implanted: 70 μm for small vessel stents (2.00, 2.25 or 2.50 mm in diameter), 80 μm for medium vessel stents (2.75, 3.00 and 3.50 mm in diameter) and 95 μm for large vessel stents (4.00, 4.50 and 5.00 mm in diameter).[19]

Data collection

All PCI performed were recorded in a local data management system. Data input included medical history, risk factors, medication use, peri-procedural data and clinical follow-up. For this analysis all patients who underwent PCI involving at least one Skylor stent between September 2005 and June 2007 were included. Active follow-up by phone call following a pre-specified questionnaire is routinely performed in our institute for all patients treated with PCI at one and 12 months after the index procedure.

Endpoint definitions

If an event occurred, careful review of the in-hospital data or requirement of data from other hospitals were performed in order to classify the event. All deaths were considered cardiac unless a clear noncardiac cause could be established. Specifically, any unexpected or unwitnessed death was considered of cardiac origin. Myocardial infarction was defined as anginal symptoms associated with creatine kinase levels >3 times the upper limit of normal and concurrent elevation of creatine kinase-MB above the upper limit of normal (according to local reference values). All reported repeated interventions in the stented segment (including the stent and the 5 mm proximal and distal to the stent) were classified as target lesion revascularisation (TLR). Repeated interventions in the same vessel were reported as target vessel revascularisation (TVR). Major adverse cardiac events (MACE) were defined as a combined endpoint of death, MI (including peri-procedural MI) and TVR. Stent thrombosis was defined according to the Academic Research Consortium criteria.[20]

Table 1. Baseline patient characteristics.

	Patients (n=712)
Age (years)	64±13
Male gender	530 (74.4)
Risk factors	
- Diabetes	56 (7.9)
- Hypertension	238 (33.4)
- Hypercholesterolaemia	257 (36.1)
- Current smoking	156 (21.9)
- Family history	247 (34.7)
- Previous myocardial infarction	154 (21.6)
- Previous PCI procedure	106 (14.9)
- Previous coronary bypass surgery	51 (7.2)
Previous cerebrovascular accident	36 (5.1)
Baseline angina status	
- Stable	291 (40.9)
- Acute coronary syndrome	149 (20.9)
- Acute ST-elevation myocardial infarction	272 (38.2)
Extent of disease	
- One vessel	347 (48.7)
- Two vessels	213 (29.9)
- Three vessels	142 (20.0)
- Left main	10 (1.4)
Left ventricular function	
- Poor	21 (3.0)
- Moderate	213 (29.9)
- Normal	478 (67.1)

Values are presented as numbers (%) or mean ± SD.

Table 2. Procedural data.

	Procedures (n=712) Lesions (n=785)
Procedures with 1 Skylor stent	603 (84.6)
Procedures with 2 Skylor stents	85 (11.9)
Procedures with >2 Skylor stents	8 (1.2)
Average stent length (mm)	15.5±6.2
Average stent diameter (mm)	3.1±0.3
Procedural success	707 (99.3)
Type of PCI	
- Single vessel	639 (89.7)
- Multi-vessel	73 (10.3)
Index vessel	
- Left anterior descending artery	334 (42.5)
- Right coronary artery	278 (35.4)
- Circumflex artery	148 (18.9)
- Left main coronary artery	10 (1.3)
- Bypass graft	15 (1.9)
Lesion type (ACC/AHA classification)	
- A	120 (15.3)
- B1	336 (42.8)
- B2	201 (25.6)
- C	128 (16.3)

Values are presented as numbers (%) or mean ± SD. PCI=percutaneous coronary intervention.

Statistical analysis

Continuous data are reported as means and standard deviations. Dichotomous data are reported as numbers (percentages). Due to the observational, non-randomised nature of this study, only descriptive statistics are reported. For every endpoint evaluated, 95% confidence intervals (CI) of the incidence rate were calculated, using dedicated software (Confidence Interval Analysis, Version 2.0.0, available at: http://www.medschool.soton.ac.uk/cia/main.htm, access: 26 February 2009).

Results

Baseline characteristics and in-hospital clinical outcomes

A total of 712 consecutive patients treated with PCI involving deployment of at least one Skylor stent were included. Baseline patient characteristics are shown in table 1. In total 800 Skylor stents were implanted. Procedural data are shown in table 2. One Skylor stent was implanted in 603 (84.6%) of the cases and two stents in 85 (11.9%). In five PCIs, four Skylor stents were used, and in one PCI, seven Skylor stents were implanted (these six procedures concerned technically challenging chronic total occlusions). The procedural success rate was 99.3% (95% CI 98.1 to 99.9%): in three PCIs the stent could not be delivered at the lesion site; additionally one PCI in a saphenous venous graft was complicated by perforation of the vessel treated, which was successfully managed with deployment of a covered stent; a second PCI was complicated by catheter-induced (type E) left main dissection, successfully treated with uneventful urgent coronary artery bypass surgery, which was also the sole TLR in-hospital. There were four in-hospital deaths (0.6% [0.1 to 1.4%]). Three patients died in the catheterisation laboratory, all presenting with an acute MI complicated by cardiogenic shock and

Table 3. Follow-up data.

	Patients (n=712)
In-hospital adverse events	
- Death	4 (0.6)
- Peri-procedural MI (in semi-elective group)	10/440 (2.2)
- Cerebrovascular accident	1 (0.1)
- Target lesion revascularisation	1 (0.1)
- Access site complications	8 (1.1)
Cumulative 30-day adverse events	
- Death	4 (0.6)
- Myocardial infarction	14 (2.0)
- Cerebrovascular accident	1 (0.1)
- Target lesion revascularisation	6 (0.8)
- Target vessel revascularisation	6 (0.8)
- Definite early stent thrombosis	4 (0.6)
- Probable early stent thrombosis	1 (0.1)
Cumulative 12-month adverse events	
- Death	17 (2.4)
- Myocardial infarction	20 (2.8)
- Cerebrovascular accident	1 (0.1)
- Target lesion revascularisation	19 (2.6)
- Target vessel revascularisation	29 (4.1)
- Major adverse cardiac events	59 (8.3)
- Definite early and late stent thrombosis	7 (1.0)
- Probable early and late stent thrombosis	4 (0.6)
- Possible stent thrombosis	4 (0.6)

Values are presented as numbers (%).

referred while intubated and under inotropic support. Another patient underwent successful primary PCI for acute anteroseptal MI and, because of haemodynamic instability, he was transferred to the coronary care unit, were he died two days later because of ventricular tachyarrhythmia (probably due to early stent thrombosis). There were ten peri-procedural MIs (2.2% [1.2 to 4.1%]) in the semi-elective group (440 patients, 291 stable and 149 unstable).

Thirty-day clinical outcomes
One-month clinical events are shown in table 3. There were five repeated PCI procedures between hospital discharge and one month, one of which occurred because of TLR caused by dissection

which was missed at the index procedure. The remaining four procedures (0.6%) were due to early stent thrombosis, all causing an acute MI.

Twelve-month clinical outcomes
One-year clinical events are presented in table 3. There were three patients lost to follow-up at 12 months (0.4%). The overall mortality rate was 2.4% (95% CI 1.3 to 4.2%) with four additional cardiac deaths (0.6%, all possible stent thromboses) between one and 12 months of follow-up and nine (1.3%) noncardiac deaths (all due to tumours). The total rate of MI was 2.8% (2.1 to 4.5%), with six additional MIs (all considered late stent thromboses, three definite and three probable) between one and 12 months. The rate of TLR was 2.7% (1.8 to 4.4%) including three PCIs performed for definite late stent thrombosis and ten revascularisation procedures performed for recurrent ischaemia. The rate of TVR was 4.1% (2.8 to 6.1%). Overall, out of the 29 TVR procedures, 28 were again percutaneous, while one was surgical. The overall rate of definite and probable stent thrombosis was 1.5% (0.9 to 3.1%), including five early cases and six late cases. Overall MACE rate was 8.3% (6.7 to 11%).

Discussion
Drug-eluting stents are more effective than BMS in reducing restenosis and preventing repeated revascularisation procedures,[6] mainly by limiting intimal hyperplasia,[21] with similar early rates of death or nonfatal MI. However, concern is growing that delayed endothelialisation, incomplete neointimal healing, late acquired stent malapposition or hypersensitivity reactions after the implantation of DES may lead to increased rates of late adverse events, such as cardiac death and MI, due to the occurrence of stent thrombosis.[7,8]

In order to minimise late thrombotic events with the use of DES, an extended dual antiplatelet regiment is recommended for at least 12 months. However, the bleeding risks associated with prolonged dual antiplatelet therapy[22,23] and the increased costs for the healthcare system[9] should be taken into account. Moreover, a substantial proportion of patients have contraindications to prolonged antiplatelet therapy, or are already taking oral anticoagulants or cannot afford the increased cost of clopidogrel, in countries where this drug is not reimbursed. Such a prolonged dual antiplatelet therapy may be specifically valuable in patients who are at increased risk for stent thrombosis after DES implantation, such as those with diabetes, renal failure, long lesions and bifurcation disease.[24,25] Patients with these characteristics generally also have an increased risk for in-stent restenosis thus potentially getting the greatest benefit from DES in terms of reduction of restenosis. However, independently from clopidogrel use, in randomised trials as well as

Table 4. Literature on bare cobalt-chromium coronary stents.

Stent type	Follow-up duration (months)	Patients (n)	Procedural success (%)	TLR (%)	TVR (%)	MACE (%)	TVF (%)	Stent thrombosis (%)
MultiLink Vision[17]	6	268	99.0	4.3	5.1	6.2	6.7	-
Medtronic Driver[35]	9	298	98.3	7.0	8.1	8.4	8.1	0
Medtronic Driver[36]	6	202	98.0	9.4	-	12.4	-	0.5
Arthos Pico[37]	12	203	98.0	-	8.9	15.0	-	2.0
Invatec Skylor[38]	9	150	97.0	6.0	-	8.0	12.4	1.4

MACE=major adverse cardiac event, TLR=target lesion revascularisation, TVF=target vessel failure, TVR=target vessel revascularisation. Each endpoint was defined according to the specific study.

in large registries, very late stent thrombosis (occurring more than one year after stent implantation) is more common after DES than BMS implantation.[7,26] Thus, in 'real-world' patients the selective use of BMS can be adequately justified, when safety is the first issue. Nonetheless, the overall efficacy of BMS is sub-optimal as compared with DES.

The detection of selected subgroups of patients and lesions where BMS can perform well with a low rate of repeated revascularisations appears a reasonable alternative. Some data from registries and post-hoc analyses of randomised controlled trials suggest that BMS favourably compare with DES in lesions located in large coronary vessels (defined as vessels in which a stent >3.0 mm in diameter was implanted).[27-29] Angiographic superiority of DES remains solid, even in comparison with the newer generation BMS. In a recent randomised trial, angiographic parameters of restenosis were significantly lower in the DES group versus a thin-strut cobalt-chromium stent (late loss: 0.18±0.40 versus 0.58±0.51 mm). Though the angiographic performance of BMS in this trial was good. Furthermore, no statistically significant clinical differences between the two groups were apparent at 12 months (the trial, however, was definitely underpowered for this endpoint): freedom from target vessel failure at 12 months was 72% for DES patients and 68% for BMS patients.[30]

Other categories where conflicting results with DES still exist are patients with acute ST-elevation MI and lesions in saphenous vein grafts. Regarding acute ST-elevation MI, recent registries have shown no clear superiority of DES over BMS in terms of long-term repeated revascularisations,[31] raising even doubts on a possible increase in long-term mortality after DES placement.[32] However, in a recent meta-analysis of randomised trials, the use of DES significantly reduced the short-term rate of TVR without impact on mortality.[33] Regarding vein graft stenting, the data comparing DES with BMS are scarce and even more conflicting. In a secondary post-hoc analysis of a randomised trial the use of DES was found to be associated with increased long-term mortality as compared with BMS.[34] Nevertheless, these data need further verification.

In light of all these issues, it is obvious that in the modern era of interventional cardiology there is a place for the newest generation of BMS. In the aforementioned subgroups of patients in whom the use of DES does not seem completely beneficial or is based on contradictory trials, as well as in patients with relative or absolute contraindication to prolonged antiplatelet therapy, the new generation of thin-strut cobalt-chromium BMS fills the gap with very good efficacy. Currently, according to our present policy, providing that the patients do not have an acute ST-elevation MI and are able to comply with double oral antiplatelet therapy for one year, DES should be reserved for the following indications: 1) in-stent restenosis, 2) diabetes mellitus with reference vessel diameter <3.5 mm, 3) small vessel disease (reference vessel diameter <2.6 mm), and 4) lesions with length >20 mm. Our registry confirms that this policy, based on a pre-specified simple selection process to discriminate between BMS or DES implantation, provides very good results with a new generation BMS. This new generation class of cobalt chromium thin-strut bare metal stents has been adequately tested in several registries and in a variety of clinical settings. In each of these studies, newer generation BMS seem a safe and effective treatment modality (table 4).[17,35-38] Besides these promising results, there are also some technical advantages related to these BMS. Since cobalt chromium is about 75% stronger than stain-

less steel, it allows the stent to have thinner struts, thus increasing pushability, flexibility, deliverability and trackability (potentially making the PCI procedure simpler and faster), while maintaining radial strength and radiological visibility.

A final proof of the substantial similarity in effectiveness and superiority in safety of these new generation BMS as compared with DES will come from the ongoing BASKET PROVE randomised trial, performed specifically in lesions in large coronary vessels and planning to enrol more than 2000 patients.[39]

Limitations

We acknowledge that this is a single centre registry. Lack of randomisation is the major limitation, together with retrospective data collection. Furthermore, patients did not undergo systematic angiographic follow-up; they received a control angiogram only if clinically indicated. Thus there is no angiographic evaluation of the performance of the stent. On the other hand, it is well known that routine angiographic follow-up tends to inflate the rate of repeated revascularisation procedures due to the so-called 'oculo-stenotic' reflex.[40] ■

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