INDIAN HEART JOURNAL 66 (2014) 345–349

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ihj

Sponsored Article

Safety and efficacy of the Yukon Choice Flex sirolimus-eluting coronary stent in an all-comers population cohort

E. Xhepa, T. Tada, S. Cassese, L. King, I. Ott, M. Fusaro, A. Kastrati, R.A. Byrne*

Deutsches Herzzentrum, Technische Universität, Lazarettstrasse 36, 80636 Munich, Germany

Keywords:
Percutaneous coronary intervention
Bioresorbable-polymer drug-eluting stent
Stent thrombosis

ABSTRACT

Aims: The use of biodegradable-polymer drug-eluting stents has been shown to provide favorable results when compared with durable polymer drug-eluting stents and long-term follow up data have recently shown significant reductions in terms of very late stent thrombosis.

Aim of the present study was to assess the safety and efficacy profile of a novel biodegradable polymer DES, the Yukon Choice Flex sirolimus-eluting stent.

Methods: We report here the one-year clinical outcomes associated with the use of the Yukon Choice Flex sirolimus-eluting stent in an all-comers patient population. The present stent represents a further refinement of the stent platform tested in the ISAR TEST 3 and 4 randomized clinical trials. A total of 778 consecutive patients undergoing implantation of this stent were enrolled in the present observational study and prospectively followed for one year.

Results: The use of the Yukon Choice Flex stent in a patient population with complex coronary lesion morphology was associated with optimal immediate angiographic results. At one year follow up the rates of death, myocardial infarction, definite stent thrombosis and ischemia-driven target lesion revascularization were respectively 2.4%, 1.9%, 0.3% and 11.3%.

Conclusions: The use of the sirolimus-eluting biodegradable polymer Yukon Choice Flex stent in an all-comers population of patients with complex coronary artery disease is associated with a favorable safety and efficacy profile up to one year follow up.

1. Introduction

The introduction of drug-eluting stents (DES) in clinical practice has led to a drastic reduction in the rates of restenosis and the need for repeat revascularization procedures.[1–3] However, an increase in the incidence of very late stent thrombosis associated with the use of early generation DES compared with BMS has been reported,[4,5] particularly among patients with off-label indications.[6,7] Despite the increase in the

* *Corresponding author*. Tel.: +49 89 1218 4577.
E-mail address: kastrati@dhm.mhn.de (A. Kastrati).

http://dx.doi.org/10.1016/j.ihj.2014.05.003

occurrence of very late thrombotic events seems relatively limited in absolute terms, owing to the poor outcomes associated with this clinical entity, considerable efforts have been directed to clarify its underlying pathobiological mechanisms and to reduce its incidence. Animal experiments and human autopsy studies have shown that very late stent thrombosis is related to delayed arterial healing and remodeling of the stented vessel owing to ongoing inflammation.[8–11] Particularly, the persistence of the polymer coating on the stent surface after completion of the drug-elution process, has been shown to act as a trigger for a chronic inflammatory response, which delays the process of stent coverage and predisposes to late thrombotic events.[12,13] Since the function of the polymer coating is limited to that of a reservoir which allows for drug loading and modification of the release kinetics of the antiproliferative drug, the use of biodegradable polymer coatings, which undergo a process of absorption once their role has been served, seems particularly attractive, since it would eliminate the stimulus for the chronic inflammatory response, leading to a more favorable tissue healing profile and potentially reducing the rates of very late stent thrombosis.

Accordingly, biodegradable polymer DES have been developed and compared with durable polymer DES in randomized clinical settings and the favorable outcomes associated with their use have provided support to the initially hypothesized advantages associated with their use.[14–16] Owing to these favorable results, great interest and hope has been associated with this new generation of stents, which could further improve the safety and efficacy of percutaneous coronary interventions (PCI).

We report here the one-year outcomes associated with the use of a novel biodegradable polymer DES, the Yukon Choice Flex sirolimus-eluting stent (Translumina Therapeutics), in an unselected population cohort.

2. Methods

Patients presenting with ischemic symptoms or signs of myocardial ischemia in the presence of ≥50% coronary stenosis were considered eligible, provided that written, informed consent by the patient or her/his legally authorized representative was obtained. Besides age ≥18 years, there were no adjunctive exclusion criteria to patient enrollment in this prospective observational study.

The Yukon Choice Flex stent is a new generation stent consisting of a cobalt–chromium backbone (79 μm thickness) and a biodegradable polymer (polylactic acid) applied on the stent surface, which allows a controlled release of the antiproliferative drug followed by a bioresorption process of the polymer coating over a period of 6–9 weeks. The eluted drug is represented by sirolimus, a highly effective and widely tested agent with immunosuppressive and antimitotic properties, which has consistently shown superior outcomes compared with the paclitaxel-eluting stent platforms in terms of neointimal proliferation inhibition and repeat revascularization procedures.[17,18]

During the procedure, patients were given intravenous aspirin, heparin or bivalirudin; glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator. After the intervention, all patients received aspirin indefinitely, clopidogrel, prasugrel or ticagrelor for at least 12 months and other cardiac medications according to the judgment of the patient's physician [β-blockers, ACE (angiotensin-converting enzyme)-inhibitors, statins etc.]. Patients remained in the hospital for at least 48 h. Blood samples were drawn every 8 h for the first 24 h and daily afterward for the determination of cardiac markers (CK, CK-MB, Troponin T) and blood cell counts (hemoglobin, hematocrit, platelet count, white blood cell count). Daily recording of ECG was also performed until discharge.

Relevant data were collected and entered into a computer database by specialized personnel of the Clinical Data Management Center. Baseline and post-procedural cineangiograms were forwarded to the Quantitative Angiographic Core Laboratory (DeutschesHerzzentrum, Munich, Germany) for assessment by experienced operators. Angiographic image acquisition of the target lesion was done after intracoronary administration of nitroglycerin and the measurements were performed in the same single worst view projection. The offline quantitative coronary angiographic analysis was performed with an automated edge-detection system (QAngio XA 7,1; Medis, Medical Imaging Systems). The contrast filled, nontapered catheter tip was used for calibration. The reference diameter was measured by interpolation. Minimal lumen diameter was measured within the stent and within the 5 mm proximal and distal edges of the stent. Quantitative analysis was performed in the in-stent area (in-stent analysis) and in the in-segment area including the stented segment, as well as both 5 mm margins proximal and distal to the stent (in-segment analysis). Qualitative morphological lesion characteristics were characterized by standard criteria.[19]

2.1. *Statistical analysis*

Categorical variables are summarized as counts or proportions (%) whereas continuous variables are expressed as mean ± SD or median with 25th and 75th percentiles. Data distribution was tested for normality using the Kolmogorov–Smirnov test. Survival was assessed using the Kaplan–Meier method.

3. Results

3.1. *Baseline characteristics and procedural results*

A total of 778 consecutive patients undergoing coronary implantation of the Yukon Choice Flex sirolimus-eluting stent in our center were enrolled in the present study and considered for the present analysis.

Baseline clinical characteristics of the patient population are shown in Table 1. Overall, there is a high prevalence of coronary risk factors and 26.1% of patients had diabetes mellitus. Moreover, a high percentage of patients (40.9%) displayed unstable coronary syndromes and multivessel disease was present in 83% of the patient population.

A total of 1440 lesions were treated (1.85 lesions/patient). Baseline angiographic characteristics are displayed in Table 2 and are notable for a high prevalence of complex lesion

morphology (73.5% type B2/C lesions). Implantation of the stent was successful in all lesions and the immediate angiographic outcomes were excellent (Table 3). The mean stented length was 26.9 ± 12.9 mm.

3.2. *Clinical outcomes*

Clinical follow up was performed for all patients up to one-year.

During the first 30 days of follow up, 6 (0.8%) patients died, 4 (0.5%) patients suffered a transmural myocardial infarction and 7 (0.9%) patients suffered a non-transmural myocardial infarction; a sub-acute stent thrombosis occurred in 2 (0.3%) patients. Death or myocardial infarction occurred during the first 30 days in 15 (1.9%) patients.

By 12 months, 19 (2.4%) patients died, 4 (0.5%) patients suffered a Q-wave myocardial infarction and 11 (1.4%) patients a non Q-wave myocardial infarction; ischemia-driven target lesion revascularization occurred in 163 (11.3%) lesions. Death or myocardial infarction at 1-year follow up occurred in 32 (4.1%) of patients (Table 4)

4. Discussion

In this prospective observational study we report the 1-year clinical outcomes associated with the use of the Yukon Choice Flex sirolimus-eluting coronary stent in the treatment of coronary artery disease. The study cohort represents an all-comers patient population, thereby reflecting real clinical practice and allowing to test the device in a real-world setting. Accordingly, the study population comprised a cohort of patients with complex coronary lesion morphology (73.5% type B2/C lesions according to the ACC/AHA classification), a high prevalence of diabetes mellitus (26.1%), multivessel disease (83.0%) and of unstable coronary syndromes (40.9%).

The safety and efficacy of coronary artery stent platforms is modulated by each of their components, namely the stent design, the anti-proliferative drug and the presence and type of polymer. The performance of the precursor of the present biodegradable polymer DES was previously tested in the prospective, randomized ISAR TEST 3 and ISAR TEST 4 trials, as part of the ISAR (individualizable drug-eluting stent system to abrogate restenosis) stent project, aiming at investigating novel DES coatings with high restenotic efficacy and without the untoward effects of durable polymer coatings.[14,15,20,21] The biodegradable polymer DES used in these trials, displayed a pre-mounted, sand blasted, 316L stainless steel microporous backbone which was coated on site with a mixture of rapamycin, biodegradable polymer and shellac resin. The Yukon Choice Flex sirolimus-eluting stent represents an evolution of the previous stent used in the ISAR TEST 3 and 4 trials. The main differences are represented by the standardization of the coating process, which is now performed on an industrial basis and the use of a cobalt–chromium backbone, with

Table 1 – Baseline patient characteristics.

Age (years), mean ± SD	68.2 ± 10.7
Male	580 (74.6)
BMI, mean ± SD	27.8 ± 4.6
Diabetes	203 (26.1)
Insulin-requiring	70 (9.0)
Tablet-controlled	111 (14.3)
Hypertension	527 (67.7)
Hyperlipidemia	620 (79.7)
Current smoker	129 (16.5)
Prior MI	202 (25.9)
Prior PCI	398 (51.2)
Prior bypass surgery	71 (9.1)
EF, mean ± SD	52.9 ± 11.5
Clinical presentation	
STEMI	86 (11.1)
NSTEMI	111 (14.3)
Unstable angina	121 (15.5)
Stable angina	452 (58.1)
Silent ischemia	8 (1.0)
Coronary disease	
Single vessel	132 (16.9)
Two vessel	203 (26.1)
Three vessel	443 (56.9)
Multivessel disease	646 (83.0)

Values shown represent numbers (percentages) unless otherwise indicated.
BMI, body mass index; MI, myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 2 – Baseline angiographic characteristics.

Target vessel	
Left main	35 (2.4)
LAD	621 (43.1)
LCX	354 (24.6)
RCA	421 (29.2)
Venous bypass	6 (0.4)
Arterial bypass	3 (0.2)
Ostial lesion	339 (23.5)
Bifurcational lesion	467 (32.4)
Total occlusion	173 (12.0)
Chronic occlusion	80 (5.6)
Complex morphology[a]	1059 (73.5)

Values shown represent numbers (percentages).
LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.
[a] Defined as type B2/C by AHA/ACC classification.

Table 3 – Lesion and procedural characteristics.

Lesion length, mm	17.2 ± 10.5
Reference diameter, mm	2.87 ± 0.53
MLD, pre-procedure, mm	0.91 ± 0.49
Stenosis, pre-procedure, %	68.5 ± 14.8
Maximum balloon diameter	3.12 ± 0.58
Balloon-to-vessel ratio	1.11 ± 0.09
Maximal balloon pressure, a.t.m.	14.8 ± 3.35
Stented length, mm	26.9 ± 12.9
Stent diameter, mm	3.04 ± 0.47
MLD post, mm	2.56 ± 0.55
Stenosis post, %	14.2 ± 10.6

Data are shown as mean ± SD.
MLD, minimal lumen diameter.

Table 4 – Clinical follow-up data at 1 month and 1-year.

	30 days	1-year
Death	6 (0.8)	19 (2.4)
Myocardial infarction	11 (1.4)	15 (1.9)
Q-wave	4 (0.5)	4 (0.5)
Non Q-wave	7 (0.9)	11 (1.4)
Death/MI	15 (1.9)	32 (4.1)
Definite stent thrombosis	2 (0.3)	2 (0.3)
TLR		163 (11.3)
Re-PCI		156 (10.8)
CABG		7 (0.4)

Values shown are numbers (percentages).
CABG, coronary artery bypass grafting; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, Percutaneous coronary intervention; TLR, target lesion revascularization.

highly engineered strut and cell design, which guarantees increased stent flexibility without compromising its radial strength. The modification of the stent platform was undertaken in an attempt to overcome some of the limitations associated with the use of stainless steel stent platforms and in particular to improve stent deliverability, especially in case of unfavorable lesion characteristics, such as vessel tortuosity, complex lesion anatomy and lesion calcifications.

The results of the present study show that the use of this stent platform is feasible and associated with optimal immediate angiographic results. Moreover, despite the complexity of the clinical and angiographic profile of the present patient population, its use is associated with a favorable 1-year safety and efficacy profile. Compared with the Resolute All Comers Trial,[22] a large randomized non-inferiority trial with minimal exclusion criteria comparing two new-generation durable polymer DES, we observed a lower rate of myocardial infarction (1.9% versus 4.2%) and definite stent thrombosis (0.3% versus 0.75%) at 1-year follow up; instead, the rate of target lesion revascularization was higher in our study (11.3% versus 3.65%). A possible explanation for the observed difference might be provided by the higher grade of severity of coronary artery disease in the population included in the present study (multivessel disease 83% versus 58.8%; mean lesion length 17.2 mm versus 12.0 mm).

The biodegradable nature of the polymer could be expected to confer superior outcomes associated with the Yukon Choice Flex sirolimus-eluting stent compared with the previous generation of durable polymer DES, especially in terms of the incidence of very late in-stent thrombosis. Despite biodegradable polymer DES being initially developed with this precise finality, a clear superiority with respect to durable polymer DES in terms of reductions of definite stent thrombosis was not immediately evident in the randomized controlled trials comparing durable and biodegradable polymer stent platforms.[23,24] Indeed, the clinical advantage associated with the use of biodegradable polymer DES is expected to emerge only during long term follow up, after complete absorption of the polymer. Accordingly, large numbers of patients and long follow up periods are required to capture differences in terms of a relatively rare phenomenon such as very late stent thrombosis. However, evidence of a favorable pattern of arterial healing associated with the use of biodegradable polymer DES, was already reported in an optical coherence tomography substudy of the LEADERS Trial, reporting more complete stent strut coverage in the group of patients treated with the biodegradable polymer DES compared with those treated with durable polymer DES at 9 months follow up.[25] More recently, a pooled analysis of individual patient data from the three major randomized trials comparing bioresorbable-polymer and durable polymer DES (ISAR TEST 3, ISAR TEST 4 and LEADERS Trials) with an extended follow up up to 4 years, showed for the first time a significant reduction in terms of definite stent thrombosis in favor of biodegradable polymer DES.[26] These conclusions received further support by the recent release of the 5-year follow up data of the LEADERS Trial, which confirm a significant superiority of the biodegradable polymer DES compared with the durable polymer DES, driven primarily by the reduction in the incidence of very late thrombotic events.[27] In our study, a very low incidence of definite stent thrombosis events (0.3%) was observed. The one year follow up of the present observational study does not allow to capture eventual benefits in terms of very late thrombotic events. Despite the lack at the present moment of a clear proof of benefit in terms of very late thrombotic event reduction, it seems reasonable to hypothesize that the incorporation of a biodegradable polymer could represent an adjunctive favorable characteristic of the present stent platform. However, definite conclusions in this regard require a direct comparison of the present stent platform with durable polymer DES in a randomized clinical setting.

Routine control angiography was not part of the present study, thereby no definitive conclusions can be drawn relating to the antirestenotic efficacy of this stent platform. However, the low event rates and the favorable clinical follow up of the present population represent an indirect proof of the antirestenotic efficacy of this stent platform.

In conclusion, this prospective observational study shows that the use of the Yukon Choice Flex sirolimus-eluting stent in an all-comers patient population with complex coronary lesion morphology is feasible and associated with a favorable 1-year safety and efficacy profile. Its use could therefore represent a valuable adjunct in the field of the contemporary interventional cardiology.

Conflicts of interest

Dr. Kastrati is holder of patents regarding stent surface and DES technology.

REFERENCES

1. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet*. 2007;370:937–948.
2. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356:1030–1039.
3. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-

analysis of randomized trials and observational studies. *Circulation*. 2009;119:3198–3206.
4. Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. *J Am Coll Cardiol*. 2008;52:1134–1140.
5. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356:989–997.
6. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA*. 2007;297:2001–2009.
7. Marroquin OC, Selzer F, Mulukutla SR, et al. A comparison of bare-metal and drug-eluting stents for off-label indications. *N Engl J Med*. 2008;358:342–352.
8. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. *Circulation*. 2008;118:1138–1145.
9. Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol*. 2007;27:1500–1510.
10. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation*. 2009;120:391–399.
11. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193–202.
12. Byrne RA, Joner M, Kastrati A. Polymer coatings and delayed arterial healing following drug-eluting stent implantation. *Minerva Cardioangiol*. 2009;57:567–584.
13. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109:701–705.
14. Mehilli J, Byrne RA, Wieczorek A, et al. Angiographic restenosis investigators–test efficacy of rapamycin-eluting stents with different polymer coating S. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J*. 2008;29:1975–1982.
15. Byrne RA, Kastrati A, Kufner S, et al. Angiographic Results: test efficacy of 3 limus-eluting stents I. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4). *Eur Heart J*. 2009;30:2441–2449.
16. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet*. 2008;372:1163–1173.
17. Wessely R, Schomig A, Kastrati A. Sirolimus and paclitaxel on polymer-based drug-eluting stents: similar but different. *J Am Coll Cardiol*. 2006;47:708–714.
18. Wessely R, Blaich B, Belaiba RS, et al. Comparative characterization of cellular and molecular anti-restenotic profiles of paclitaxel and sirolimus. Implications for local drug delivery. *Thromb Haemost*. 2007;97:1003–1012.
19. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease. Implications for patient selection. Multivessel Angioplasty Prognosis Study group. *Circulation*. 1990;82:1193–1202.
20. Wessely R, Hausleiter J, Michaelis C, et al. Inhibition of neointima formation by a novel drug-eluting stent system that allows for dose-adjustable, multiple, and on-site stent coating. *Arterioscler Thromb Vasc Biol*. 2005;25:748–753.
21. Steigerwald K, Merl S, Kastrati A, et al. The pre-clinical assessment of rapamycin-eluting, durable polymer-free stent coating concepts. *Biomaterials*. 2009;30:632–637.
22. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med*. 2010;363:136–146.
23. Byrne RA, Kastrati A, Massberg S, et al. Biodegradable polymer versus permanent polymer drug-eluting stents and everolimus- versus sirolimus-eluting stents in patients with coronary artery disease: 3-year outcomes from a randomized clinical trial. *J Am Coll Cardiol*. 2011;58:1325–1331.
24. Stefanini GG, Kalesan B, Serruys PW, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet*. 2011;378:1940–1948.
25. Barlis P, Regar E, Serruys PW, et al. An optical coherence tomography study of a biodegradable vs. durable polymer-coated limus-eluting stent: a LEADERS trial sub-study. *Eur Heart J*. 2010;31:165–176.
26. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J*. 2012;33:1214–1222.
27. Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From a Durable versus ERodable Stent Coating) randomized, noninferiority trial. *JACC Cardiovasc Interv*. 2013;6:777–789.