ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2019 Apr 15; 7(7):1103-1109.
https://doi.org/10.3889/oamjms.2019.241
eISSN: 1857-9655
Clinical Science

Real World Experience of a Biodegradable Polymer Sirolimus-Eluting Stent (Yukon Choice PC Elite) in Patients with Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Angioplasty: A Multicentric Observational Study (The Elite India Study)

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Citation: Verma B, Patel A, Katyal D, Singh VR, Singh AK, Singh A, Kumar M, Nagarkoti P. Real World Experience of a Biodegradable Polymer Sirolimus-Eluting Stent (Yukon Choice PC Elite) in Patients with Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Angioplasty: A Multicentric Observational Study (The Elite India Study). Open Access Maced J Med Sci. 2019 Apr 15; 7(7):1103-1109. https://doi.org/10.3889/oamjms.2019.241

Keywords: BPDES; STEMI; Percutaneous coronary intervention; Third generation stents; Drug-eluting stents; Deliverability; Stent thrombosis

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Received: 30-Jan-2019; **Revised:** 29-Mar-2019; **Accepted:** 30-Mar-2019; **Online first:** 14-Apr-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: The durable polymer drug-eluting stents (DPDES) reduce the risk of repeated target vessel revascularisation (TLR) compared with BMS, but are associated with increased risk of late adverse events. In broadly inclusive populations, the biodegradable-polymer drug-eluting stents (BPDES) have favourable results compared with DPDES in the long term. However, its use in primary angioplasty has not been adequately studied, and data of real-world clinical experience is lacking.

AIM: Aim of this study was to assess the safety and efficacy of Yukon Choice PC Elite sirolimus-eluting stent (a novel BPDES) in STEMI patients undergoing primary angioplasty.

METHODS: We have presented here one-year clinical follow-up data of the Yukon Choice PC Elite sirolimus-eluting stent in patients undergoing primary angioplasty. A total of 636 patients were enrolled in this single arm, prospective observational study from five centres.

RESULTS: This multicentric observational study showed excellent safety and efficacy profile of the novel device at one year follow up. The device-oriented composite endpoint (DOCE) of cardiac death, target-vessel reinfarction, and target-lesion revascularisation (TLR) was 2.7%, and the patient-oriented composite endpoint (POCE) of all-cause death, any myocardial infarction, and any revascularisation was 4.2% at one year. Definite or probable stent thrombosis rate was 0.6%, and no events were recorded beyond 6 months of follow up.

CONCLUSIONS: In patients with STEMI undergoing primary angioplasty, the use of Yukon Choice PC Elite (biodegradable polymer sirolimus-eluting stent) has excellent results at one year. It, therefore, represents an attractive alternative to second generation DES in this high-risk population.

Introduction

Primary percutaneous coronary intervention (PCI) is considered the gold standard of management in ST-segment elevation myocardial infarction (STEMI) [1], [2]. Coronary stenting with a bare-metal stent (BMS) is associated with a lower risk of reinfarction and target vessel revascularisation compared with balloon angioplasty alone [3]. The advent of drug-eluting stents (DES) has further reduced the in-stent restenosis and the risk of repeated target vessel revascularisation compared with BMS [4]. However, the first-generation DES, including the sirolimus and paclitaxel-eluting stents, have increased the risk stent thrombosis over the long term [5], [6]. These late adverse events are related to hypersensitivity reactions to the durable polymer which produces chronic inflammation and thereby delays endothelial healing and favour stent thrombosis [7], [8], [9]. This is especially important in

patients with STEMI because of plaque rupture, high thrombus burden and increased platelet activation [8], [10]. Moreover, there are chronic processes leading to delayed endothelial healing, vessel remodelling and stent malapposition [8], [11].

Second-generation DES were subsequently developed using thinner stent struts, more biocompatible polymers, and a lower dose of newer anti-proliferative agents (Everolimus and Zotarolimus). The most recent addition to the stent technology is the development of biodegradable polymer drug-eluting stents (BPDES), the third generation DES. These newer generation DES with more biocompatible or biodegradable polymer have been shown to have lower thrombogenicity compared to BMS in experimental studies [12]. However, the ideal DES for use in STEMI is still not clear as there is no conclusive evidence of superiority.

BP-DES degrades after completion of drug release and transforms functionally into BMS. This may improve arterial healing by removing the chronic source of inflammation, the durable polymer, present in all current second-generation DES. Consequently, BP-DES appears to be a novel solution for STEMI, by possibly reducing late ischemic events. We report here the one-year outcomes associated with the use of a novel biodegradable polymer DES, the Yukon Choice PC Elite sirolimus-eluting stent (Translumina Therapeutics, Germany), in STEMI population undergoing primary angioplasty. Recent studies with their use in all-comer populations have been encouraging [13], [14], [15]. However, there is a paucity of data regarding real world experience with this device in STEMI patients.

Methods

Patients

This was a prospective observational single arm study from five centres across India. Patients presenting with STEMI were screened for inclusion in the study. Patients were eligible for inclusion if: (1) they presented within 12 hours of symptom onset, or between 12 hours and 24 hours if they had persistent symptoms with evidence of ongoing ischemia; (2) procedures were completed with only Yukon Choice PC Elite DES. Patients were excluded if they had a contraindication to antiplatelet or anticoagulant therapy, undergone CABG, pregnant women and women of childbearing potential and known hypersensitivity to sirolimus, shellac or stainless steel. The study was conducted according to the Helsinki Declaration and the Good Clinical Practice Guidelines. Written informed consent was obtained from each patient before performing the PCI procedure.

Study Device

The Yukon Choice PC Elite stent is a third generation sirolimus-eluting stent (SES) from Translumina Therapeutics (Germany), now being manufactured in India. This is made up of surgical grade stainless steel (87 µm strut thickness) coated with a biodegradable polymer (polylactic acid, PLA) and sirolimus, which releases from the matrix of Resomer 202S and Shellac resin. It has a unique micro-porous stent surface, PEARL surface, which favours better endothelialisation. The drug is coated only abluminally with no drug or polymer on the luminal side of the stent. Sirolimus eluted from the abluminal side controls smooth muscle cell proliferation, while the luminal side promotes endothelialisation as there is no polymer or drug (acts like BMS). It has the least polymeric load of a biodegradable polymer, 1/4th of polymer present in conventional DES. The drug is released in 4-6 weeks, and polymer gets completely degraded in 60-90 days, and it essentially becomes a bare metal stent. Sirolimus has a broad therapeutic profile and flat dose-response curve leading to consistent and homogenous anti-proliferative and immunosuppressant properties. Sirolimus-eluting stents have consistently shown superior outcomes compared to the paclitaxel-eluting stent (PES) [16], [17] and zotarolimus-eluting stent (ZES) [18], whereas comparable safety and efficacy profile to the everolimus-eluting stent (EES) [19], [20]. However, sirolimus is temperature sensitive and get degraded at a temperature of > 30°C into an open-chain isomer (34-hydroxy sirolimus) retaining less than 10% of the immunosuppressive activity [21]. The Yukon Choice PC Elite is a cosmetically improved version of Yukon Choice PC stent, which is specially adapted for conditions of extreme temperatures particularly seen in the tropical regions. It comes with dual packing of the outer polystyrene box and inner aluminium pack. Additionally, it has a highly sensitive temperature monitoring device, the Tag Alert, which uses Sensitech Technology.

Study procedure

All the patients included in the study underwent loading with ticagrelor 180 mg, aspirin 300 mg and atorvastatin 80 mg in the emergency department and shifted to the catheterisation laboratory. The radial approach was the default access site in all patients undergoing primary angioplasty. During the angioplasty procedure, intravenous unfractionated heparin was used for anticoagulation, and glycoprotein IIb/IIIa inhibitors were used as a bail-out. Thrombosuction was used only in cases with large residual thrombus burden after opening the culprit artery with guidewire or balloon. After the intervention, all patients received aspirin indefinitely and clopidogrel, prasugrel or ticagrelor for at least 12 months. Patients remained in

the hospital for at least 48 h. Blood samples were drawn every 24 h for the determination of cardiac markers, blood cell counts and renal function test. Daily recording of ECG was also performed until discharge.

Follow up and study endpoints

Clinical follow-up visits were scheduled at day 14 and monthly after that up to one year. Frequent follow-up visits, telephonic conversation, reminder messages (SMS) and frequent group counselling sessions were organised to ensure better drug compliance, drug/dose adjustment and collecting data regarding adverse events. The primary endpoint of the study was device-oriented composite endpoint (DOCE) of cardiac death, target-vessel reinfarction, and target-lesion revascularisation (TLR) and the co-primary endpoint was patient-oriented composite endpoint (POCE) of all-cause death, any myocardial infarction, and any revascularisation at the 30-day, 6 months and 1-year of follow-up. The secondary endpoint of this study was the incidence of definite or probable stent thrombosis at the 30-day, 6 months and 1-year of follow-up. Additional secondary endpoints were major/minor bleeding and TLR rates.

Definitions

Clinical device success was defined as successful delivery and deployment of the first inserted stent and final diameter stenosis after stenting ≤ 50% by quantitative coronary angiography or visual assessment. Clinical procedure success was defined as clinical device success without the occurrence of serious cardiac events important for ischemia during hospitalisation. Any death was defined as cardiac unless an unequivocal noncardiac cause could be established. Stent thrombosis was defined as acute (< 24 h), subacute (24 h to 30 days), late (> 30 days to 1 year), and very late (> 1 year). It was further defined as per the ARC definition as definite, possible or probable stent thrombosis [22]. Target lesion revascularisation was defined as any clinically indicated repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion. Major and minor bleeding was defined using the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria [22]. Obesity was defined as body mass index > 25 kg/m^2 [23].

Statistical analysis

Descriptive analyses were performed. Categorical variables are expressed as number and percentage of patients. Continuous data are reported as mean ± SD.

Results

Baseline patient characteristics

A total of 636 patients were enrolled in the study. Clinical follow-up was completed in 634 (99.7%) patients at 30 days, 625 (98.2%) at 6 months, and 618 (97.1%) at 1 year, respectively. By the end of one year follow up 14 patients (2.2%) have died, and 4 patients (0.6%) were lost to follow up. The patient follows up is presented in Figure 1.

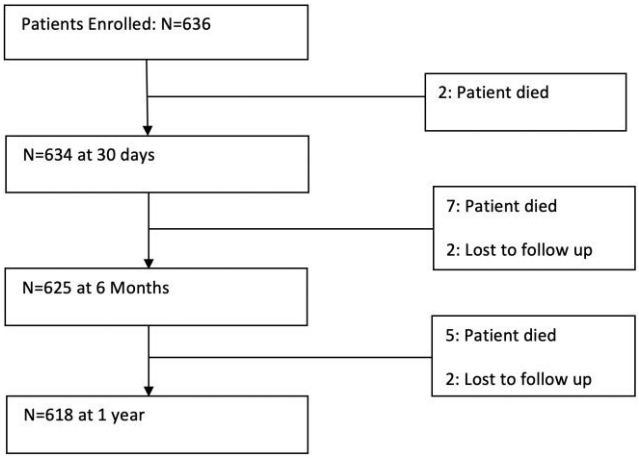

Figure 1: Patient flow and follow up through one year

The mean age was 53.9 years, and 79% of the patients were male. There was a high prevalence of coronary risk factors including hypertension (57.6%), smoking (43.8%), dyslipidaemia (40.8%), obesity (36.9%) and diabetes (20.9%). 3.3% had suffered myocardial infarction before the index event, and 2.8% have earlier undergone PCI. Mean LVEF (left ventricular ejection fraction) was ~47%. 4.8% of patients presented in cardiogenic shock and 16.9% were in Killip class II or more. Baseline characteristics are shown in Table 1.

Table 1: Baseline patient characteristics (N = 636)

Age (years), mean ± SD	53.9 ± 11
Male sex	504 (79.2)
BMI, mean ± SD	26.5 ± 6.2
Cardiovascular risk factors	
Obesity	235 (36.9)
Diabetes	133 (20.9)
Hypertension	368 (57.6)
Dyslipidemia	260 (40.8)
Current smoker	279 (43.8)
Family history of CAD	82 (12.8)
Prior MI	21 (3.3)
Prior PCI	18 (2.8)
LVEF, mean ±SD	46.9 ± 6.2
Cardiogenic shock	31 (4.8)
Killip class >I	108 (16.9)

Lesion and procedural characteristics

The mean door to balloon time was 56 minutes. The radial approach was the primary route of angioplasty (96%). LAD/diagonal was the infarct-related artery in half of the patients followed by RCA

(33%), and LMCA constituted 0.9% of the cases. The majority had single vessel disease (69%), and 6.6% had triple vessel disease. The mean diameter and mean length of the stent were 3.14 mm and 26.15 mm, respectively. Multiple stents were used overall in 16% of patients before hospital discharge and in 4% of patients during the index procedure. Direct stenting was done in 67% of the patients. Thrombosuction was used in 3.3% patients, and bail-out Gp IIb/IIIa inhibitor use was 10.5%. Clopidogrel (79%) was the most commonly prescribed DAPT (dual antiplatelet therapy) along with aspirin followed by ticagrelor (14%) and prasugrel (7%). Compliance to DAPT at one year was 94%. The device success rate was 99.3%, and the procedure success rate was 98.1%. Lesion and procedural characteristics are summarized in Table 2.

Table 2: Lesion and procedural characteristics (N = 636)

Door to balloon (minutes), mean ± SD	56 ± 11
Radial access	612 (96.2)
Infarct related artery	
Left main	6 (0.94)
LAD/Diagonal	309 (48.5)
LCX/Marginal	108 (16.9)
RCA	213 (33.4)
Multivessel disease	193 (30.3)
Reference vessel diameter (mm), mean ±SD	2.91 ± 0.25
Stented length (mm), mean ±SD	26.15 ± 6.35
Stent diameter (mm), mean ±SD	3.14 ± 0.28
Stent implanted per patient	1.18 ± 0.40
Multiple stents used	102 (16)
Thrombosuction	21 (3.3)
Direct stenting	426 (66.9)
Gp IIb/IIIa inhibitor use*	67 (10.5)
DAPT usage	
Clopidogrel	79%
Prasugrel	7%
Ticagrelor	14%
DAPT compliance at 1-year	94%
Device success	99.3%
Procedure success	98.1%

Clinical outcomes

At one-year clinical follow-up, 14 patients (2.2%) had died, including 9 patients (1.4%) who died of cardiac reasons. The device oriented primary endpoint (DOCE) was seen in 1.1% at 30 days, 2% at 6 months and 2.7% at the end of one year.

Table 3: Clinical follow up

Outcomes	30 days	6 months	1 year
All death	3 (0.5)	9 (1.4)	14 (2.2)
Cardiac de	3 (0.5)	7 (1.1)	9 (1.4)
MI (non-fatal)	2 (0.3)	4 (0.6)	5 (0.8)
Target vessel reinfarction	2 (0.3)	3 (0.5)	3 (0.5)
Any revascularization	5 (0.8)	9 (1.4)	11 (1.7)
TLR (clinical driven)	3 (0.5)	5 (0.8)	8 (1.2)
Device oriented endpoint β	7 (1.1)	13 (2)	18 (2.7)
Patient oriented endpoint §	9 (1.4)	19 (3)	26 (4.2)
Stent thrombosis *	3 (0.5)	4 (0.6)	4 (0.6)
Definite	2 (0.3%)	2 (0.3%)	2 (0.3%)
Probable	1 (0.15%)	2 (0.3%)	2 (0.3%)
Major and minor bleeding	3 (0.5)	7 (1.1)	9 (1.5)

The patient-oriented co-primary endpoint (POCE) was 1.4%, 3% and 4.2% at 30 days, 6 months and 1 year respectively. The target lesion re-infarction at one year was 0.5%, and the clinical driven TLR rate was 1.2%. Definite and probable stent thrombosis occurred in 2 patients each till 6 months follow up (total 4 patients, 0.6%). Both of the definite stent thromboses were sub-acute (early stent thrombosis). Beyond 6 months no additional case of stent thrombosis was seen. The major and minor bleeding rates at one year were 1.5%. The clinical outcomes are detailed in Table 3.

Discussion

To our knowledge, this is the largest study reporting the real-world experience of biodegradable polymer sirolimus-eluting stent in the STEMI population undergoing primary angioplasty. This prospective, observational multicentric study showed excellent safety and efficacy profile of Yukon Choice PC Elite with low rates of POCE, DOCE, TLR and overall stent thrombosis rates at one year follow up. The study cohort had a high prevalence of cardiovascular risk factors, cardiogenic shock and poor Killip class, thereby reflecting real clinical practice and testing the stent in a real-world setting. This novel device with enhanced biocompatibility, therefore, appears to be an attractive option in the STEMI population.

The Yukon Choice PC stent (Translumina therapeutics, Hechingen, Germany) consists of a unique microporous stainless-steel stent surface coated abluminally with sirolimus and a PLA biodegradable polymer. This sirolimus-eluting BP-DES has been found non-inferior to permanent polymer SES (Cypher) in the ISAR-TEST-3 study and permanent polymer EES (XIENCE V) or SES (Cypher) in ISAR-TEST-4 [13], [14]. Outcomes were non-inferior even at 3 years and 5 years follow up [24], [25]. The Yukon stent has also been shown to be non-inferior to the PES in diabetic patients (LIPSIA-Yukon trial) [26], [27]. Furthermore, the ISAR-TEST 5 trial showed that this strut had non-inferior results at one year and five years compared to a zotarolimus-eluting stent [28], [29]. The Yukon Choice PC Elite uses the same stent platform and design as Yukon Choice PC used in the ISAR TEST 3 and 4 trials. The major difference is a temperature control system present with the current device, as sirolimus is temperature sensitive.

We have experienced high device and procedural success rate using the Yukon Elite stent (99.3% and 98.1% respectively). This is comparable to a procedural success rate of 97.5% using EES in EXAMINATION Trial [30]. All the operators in this study report to have experienced exceptional manoeuvrability, deliverability and flexibility during stent deployment. Direct stenting was done in 67%, and it failed in 5.6% patients, which is considerably lower than previously reported with 2nd generation

DES (17-18%) [31], [32]. No case of failure of stenting, a mechanical complication related to stent or change over to different DES was seen. Given comparable efficacy of the contemporary DES, deliverability is certainly an important feature in relative superiority of stents. Unfortunately, deliverability data from randomised clinical trials are almost negligible, and therefore real-world experience is critical for determining relative deliverability. The excellent deliverability with Yukon Choice PC stent could be explained by widely spaced, thinner struts (87 μm) and newer improved stent delivery system.

There are limited studies comparing new-generation DES (n-DES) and BMS in the STEMI population. In the recent two trials-COMFORTABLE AMI trial (biolimus-eluting stent with biodegradable polymer versus BMS) and EXAMINATION trial (EES versus BMS) in STEMI-new-generation DES were convincingly superior to BMS [30], [33]. Meta-analysis of these trials showed a significant reduction in rates of target vessel re-infarction, TLR and stent thrombosis in the DES arm [34]. Moreover, this benefit was extended up to 2-year follow-up in both trials [35], [36]. More recently, the 5-year follow-up of EXAMINATION trial demonstrated a reduction in the patient-oriented endpoints, device-oriented endpoints, stent thrombosis and all-cause mortality with DES [37]. Stenting with new-generation DES is thus recommended over BMS for primary PCI [2]. The results of the present study confirm these findings with a favourable 1-year safety and efficacy profile. The overall mortality at one year (2.2%) was lower as compared to COMFORTABLE AMI (3.2%) and EXAMINATION trial (3.5%), and the cardiac death too was much lower (1.4% vs 2.9% and 3.2% respectively). The DOCE in our study was 2.7% at one year as compared to 4.3% in COMFORTABLE AMI, and 5.5% EXAMINATION trial and the POCE was 4.2% vs 8.4% and 11.9% respectively.

The BP-DES were designed to confer benefit particularly in terms of late adverse events compared to durable polymer DES. This is especially applicable in STEMI, where the risk of stent thrombosis is increased due to high thrombus burden, increased platelet activation and inflammation leading to delayed endothelial healing. Indeed, in a pooled analysis of three trials in STEMI, BP-DES led to significant reduction in TLR rates and trend towards reduction of definite or probable stent thrombosis [38]. In our study, the overall stent thrombosis rate was 0.6% (definite 0.3% and or probably 0.3%), with no event seen beyond 6 months. This was lower compared to 2.5% in COMFORTABLE AMI trial and 0.9% in EXAMINATION trial [30], [33]. In ISAR-5 trial, the incidence of definite/probable stent thrombosis was 1.1% in BPDES group and 1.2% in Zotarolimus arm at one year, and there was no stent thrombosis seen beyond one year [29]. Similarly, in COMFORTABLE AMI trial, there was no case of late definite stent thrombosis [35].

Study limitations

The strength of this study was a prospective design with a large number of STEMI patients from multiple centres. However, there were several important limitations too. First, it was an observational study, and a head-to-head comparison is required to confirm the safety and efficacy relative to other newer generation DES. Second, the limited follow up of one year does not allow capturing of very late stent thrombosis. However, recent studies with longer follow up in the STEMI population didn't show any stent thrombosis beyond one year [29], [35]. Third, there may have been underreporting of MI and TLR as follow-up angiography, and routine cardiac bio-marker estimation was not mandatory. However, asymptomatic MI and restenosis are usually associated with less clinical significance, and it is unlikely that they would have affected the final results of this study.

Furthermore, the excellent follow-up results represent indirect evidence of favourable effects of the stent used in the study. Fourth, the favourable results in our study may have been influenced by a greater proportion of direct stenting, shorter door-balloon time, experienced operators, predominantly radial approach and selective use of thrombosuction. Finally, there are reports to suggest that the incidence of stent thrombosis is relatively low in Asian populations [39] and thereby the results may not apply to other populations.

In conclusion, in patients with STEMI undergoing primary angioplasty, the use of Yukon Choice PC Elite (biodegradable polymer sirolimus-eluting stent) has excellent safety and efficacy profile at one year. It may, therefore, represent an attractive solution in this high-risk population. However, long-term follow is needed to determine safety in terms of very late adverse events.

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