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Clinical

Clinical Outcomes One Year and Beyond After Combination Sirolimus-Eluting Endothelial Progenitor Cell Capture Stenting During Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction ☆

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ABSTRACT

Background/purpose: Primary percutaneous coronary intervention (PCI) during acute ST-segment elevation myocardial infarction (STEMI) represents a thrombotic milieu and is associated with delayed healing after stenting. The pro-healing combination sirolimus eluting endothelial progenitor cell (EPC) capture stents encourage early endothelialization after stenting and may be beneficial in the STEMI population. We aim to evaluate the clinical outcomes one year and beyond for patients with STEMI who received the combination sirolimus eluting EPC capture stents during primary PCI.

Methods/material: All STEMI patients implanted with combination sirolimus eluting EPC capture stents during primary PCI from November 2013 to December 2016 were enrolled. The primary outcome was target lesion failure (TLF) at in-hospital, one-month, one-year and beyond one year.

Results: A total of 260 consecutive STEMI patients (283 lesions) were implanted with 313 combination sirolimus eluting EPC capture stents during primary PCI. Mean age was 56.1 ± 11.2 years and 88.8% were male. One in ten patients (10.9%) had cardiogenic shock on presentation, 7.3% needed mechanical ventilation and 7.7% had intra-aortic balloon pump inserted. A total of 97.9% of lesions achieve final TIMI 3 flow. Device success was seen in all patients. At extended follow up period (median 23.4 months), the clinical outcomes were TLF 8.8%, major adverse cardiovascular events 10.8%, cardiac mortality 4.2%, target vessel myocardial infarction 3.4%, target lesion revascularization 3.8%, and definite stent thrombosis 1.9%.

Conclusions: This study demonstrated acceptable clinical outcomes for an all-comers STEMI patients undergoing primary PCI with the use of combination sirolimus eluting EPC cell capture stents.

1. Introduction

Percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI) is more challenging as compared to stable patients with ischemic heart disease. STEMI represents a heightened thrombotic milieu and is associated with delayed healing at the culprit vessel after stenting [1,2]. Endothelialization is a critical step in vascular healing after stent implantation. Drug eluting stent (DES) inhibits neointimal hyperplasia but its benefit was hampered by late stent failure due incomplete endothelialization [3–5]. Anti-proliferative drug released by monotherapy DES non-selectively inhibits both smooth muscle cells hyperplasia and endothelial cells proliferation leading to delayed vascular healing [3]. This remained a concern even with contemporary DES with thinner struts, biodegradable polymer and alternative drug compound [6,7].

The combination sirolimus eluting endothelial progenitor cell (EPC) capture stents have been designed to overcome the limitation of monotherapy DES. Regeneration of endothelial cells to cover the luminal surface of newly implanted stents was derived from the local recruitment of adjacent cells or from adhesion of circulating EPC derived from the bone marrow [8,9]. Anti-CD34 monoclonal antibodies are able to capture circulating EPC to promote stent strut coverage in animal model and human ex-vivo shunts studies with acceptable clinical outcomes [10–13]. Genous bio-engineered R stents with EPC capture technology was shown to be feasible and safe to use during primary PCI for STEMI [14,15]. The novel design of the dual therapy stents combines anti-CD34 antibodies with anti-proliferative sirolimus drug elution. The

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stent elutes sirolimus into the vessel wall preferentially from abluminal surface that effectively induce smooth muscle inhibition without negatively affecting EPC recruitment. As a result, early endothelialization was better demonstrated in dual therapy stents as compared to monotherapy sirolimus DES [4,16]. The combination sirolimus eluting EPC capture stents had been evaluated in post-marketing all-comers registry but there is still paucity of data in the STEMI population [17,18]. The objective of this study was to evaluate the long term clinical outcome of patients with acute STEMI receiving the combination sirolimus eluting EPC capture stents during primary PCI in the real-world setting.

2. Methods

2.1. Study design and population

This is an observational registry study of all consecutive STEMI patients who were implanted with the combination sirolimus eluting EPC capture stents during primary PCI from November 2013 to December 2016 in a tertiary care cardiac center. The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the National Ethics Committee and Hospital Research Board.

2.2. Study device

The combination sirolimus eluting EPC capture stent is a 316 L stainless steel platform with stent strut thickness of 100 μm. The stent luminal surface is coated with immobilized anti-CD34 monoclonal antihuman antibody that increases EPC adhesion to cell surface. The abluminal surface is a bioresorbable polymer matrix containing antiproliferative agent sirolimus (5 μg/mm) that release 50% of its total dose in 7 days, 75% of its total dose in 10 days the remaining drugs in 30 days. The layer of bioresorbable polymer matrix undergoes complete polymer degradation in 90 days [16].

2.3. Procedure details

Pre-hospital electrocardiograms (ECG) were obtained in the ambulance en-route to the emergency department and transmitted to the emergency department where decision for primary PCI was made. Patients were considered for primary PCI if they presented within 12 h of symptoms onset. All patients received dual anti-platelet therapy (DAPT) prior to transfer to the catheterization lab, which included loading dose of 300 mg aspirinand$P2Y_{12}$ receptor antagonists (600 mg clopidogrel, 180 mg ticagrelor or 60 mg prasugrel). Primary PCI was carried out as per current standard of practice. All patients received intracoronary heparin guided by activated clotting time monitoring. Manual aspiration thrombectomy, glycoprotein IIb/IIIa usage, intraaortic balloon pump (IABP) insertion and the use of stents type (including sirolimus eluting EPC capture stents) were at the discretion of the primary operators. For this study, only the patients implanted with the sirolimus eluting EPC capture stents were analyzed. DAPT was administered for at least 12 months for all patients post STEMI, followed by long term single antiplatelet agent.

2.4. Data collection, study definitions and study endpoints

Baseline demographics, clinical characteristics, and procedural data were collected retrospectively. Angiographic data was analyzed offline using qualitative comparative analysis (QCA) by a member of the study team. This is an ongoing observational registry. In-hospital, one-month, one-year and beyond one year's clinical outcome data were collected by telephone contacts, clinic visits, electronic medical records and registry database. Data were extracted and analyzed up to 31st January 2018. Cardiogenic shock was defined as systolic blood pressure of <90 mm Hg for >30 min or the use of inotropic support. Device success was defined as the successful delivery of the device to the target lesions and attainment of final diameter stenosis <20% with TIMI grade 2 or 3 flow. Procedural success was defined as device success without the occurrence of death, myocardial infarction (MI) or repeat revascularization of the target lesion during the hospital stay. The primary endpoint of the study was the occurrence of TLF, defined as a combination of cardiac mortality, target vessel myocardial infarction (TV-MI), or clinically driven target lesion revascularization (TLR). Additional endpoints included stent thrombosis (ST), major adverse cardiac events [MACE, defined as the composite of all-cause mortality, any myocardial infarction, or ischemia driven target vessel revascularization (TVR)] and the individual components of TLF and MACE. Deaths that could not be attributed to another cause were regarded as cardiac death. ST was classified according to the Academic Research Consortium criteria [19].

2.5. Statistical analysis

Categorical and quantitative data were presented in frequency/percentage and mean ± standard deviation (SD), respectively. Time to TLF were presented using Kaplan-Meier event curve. Patients were censored if they had an event (TLF), died or lost to follow up. Independent predictors of TLF were identified using multivariate Cox proportional-hazard regression model to adjust for confounders and demographics. Data were analyzed with IBM SPSS 21.0. All statistical tests were conducted at 5% level of significance.

3. Results

A total of 313 combination sirolimus eluting EPC stents were implanted in 260 patients (284 lesions) during study period. In-hospital, one-month and one-year outcome data was available for 260 (100%), 258 (99.2%) and 243 (93.5%) of patients respectively. Seventeen patients who were lost to follow up at 1 year were all non-residents. Median follow up time was 23.4 months (interquartile range 12.9 to 34.7 months) for longer-term follow up. The baseline demographics are depicted in Table 1. Mean age was 56.1 ± 11.2 years and 88.8% (n = 231) were men. Approximately two-thirds of the patients

Table 1
Baseline demographic and clinical characteristics.

Variables	Patients (n = 260)
Age (years)	56.1 ± 11.2
Male	231 (88.8)
Hypertension	107 (41.2)
Diabetes mellitus	82 (31.5)
Dyslipidaemia	172 (66.2)
Current tobacco use	139 (53.5)
Strokes or TIA	11 (4.2)
PVD	8 (3.1)
COPD	2 (0.8)
CKD	10 (3.8)
Prior MI	39 (15.0)
Prior PCI	17 (6.5)
Prior CABG	8 (3.1)
Cardiogenic shock	28 (10.9)
Mechanical ventilation	19 (7.3)
Hemoglobin (g/dL)	15.2 ± 5.7
Creatinine (mmol/L)	88.0 ± 41.3
$P2Y_{12}$ Antagonist use	
Clopidogrel	42 (16.2)
Ticagrelor	40 (15.4)
Prasugrel	178 (68.5)
Pre-discharge LVEF ≥ 50	108 (41.5)

Data are presented as mean ± standard deviation (SD) or n (%).
TIA = transient ischemic attack; PVD = peripheral vascular disease; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction.

(66.2%) had hyperlipidemia, 41.2% had hypertension and 31.5% were diabetics. The prevalence of active tobacco use was 53.5%. A total of 116 (44.6%) patients presented with anterior STEMI. One in ten patients (10.9%) had cardiogenic shock on presentation, 7.3% needed mechanical ventilation and 7.7% had IABP inserted. Clopidogrel was used in 16.2% of patients as opposed to 83.8% patients who received novel $P2Y_{12}$ antagonist.

The lesion and procedural characteristic were shown in Table 2. Initial TIMI 0/1 flow was observed in 84.0% of lesions. Manual aspiration thrombectomy was performed in 206 patients (79.2%) and 14.6% of patients received glycoprotein IIb/IIIa. A total of 97.9% of lesions achieved final TIMI 3 flow. Device success was seen in all patients. Four patients were complicated by stent edge dissection. All the dissection cases were successfully treated with deployment of another combination sirolimus eluting EPC capture stent (n = 3) and balloon angioplasty (n = 1) over the dissected segment. Two-thirds (62.3%) of the patients had multi-vessel coronary artery disease, where 24.7% and 2.7% went for subsequent staged PCI and coronary artery bypass graft surgery, respectively.

Table 3 shows the clinical outcomes at different time points. TLF occurred in 3.4%, 4.2%, 6.5% and 8.8% during in-hospital, one-month, one-year and at extended follow-up. During short and long-term follow-up, TLF was mainly driven by cardiac deaths. MACE was 8.2% at one-year and 10.8% at extended follow up. Two patients died of non-cardiac causes. Definite ST was seen in 5 (1.9%) patients (3 acute ST, 1 late ST and 1 very late ST) and probable ST in 2 (0.8%) patients. Three cases of acute ST, occurred within 2 h of primary PCI, 2 were due to ineffective antiplatelet therapy and 1 was due to stent under expansion as observed on optical coherence tomography (OCT). Antiplatelet non-adherence was the culprit of one late definite ST at 6 months. There was only one very late definite ST attributed to active tobacco use at 3 years follow-up. The two cases of sudden cardiac deaths occurring at 7 days and 15 days post event in our study were attributed to probable ST. When cardiogenic shock was excluded from the analysis (n = 232), TLF occurred in 0.8%, 1.7%, 3.9% and 6.5% during in-hospital, 1-month, 1-year and at extended follow-up (Table 3). TLF after excluding cardiogenic shock was mainly driven by TLR.

On multivariate Cox regression model, cardiogenic shock was the only predictor of TLF (adjusted hazard ratio 4.881, 95% CI 1.877–12.694, $p = 0.001$, Table 4). Clopidogrel use did not influence the individual clinical outcomes on univariate analysis and was not found to be predictive of TLF on multivariate Cox regression model.

Table 2
Lesion and procedural characteristics.

Variables	Patients (n = 260) Lesions (n = 283)
Radial puncture	136 (52.3)
IABP usage	20 (7.7)
Thrombectomy	206 (79.2)
Glycoprotein IIb/IIIa usage	38 (14.6)
Contrast amount (ml)	99.4 ± 34.4
Culprit lesion location	
Left main	2 (7)
Left anterior descending artery	124 (43.8)
Right coronary artery	142 (50.2)
Left circumflex artery	15 (5.3)
Initial TIMI flow	
0	210 (74.2)
1	21 (7.4)
2	23 (8.1)
3	28 (10.0)
Final TIMI 2/3 flow	283 (100.0)
Final TIMI 3 flow	275 (97.2)
Lesion length (mm)	21.8 ± 10.0
Post-reference vessel diameter (mm)	3.08 ± 0.49
No of stents per lesion	1.10 ± 0.2
Average stent length (mm)	21.8 ± 6.5
Average stent diameter (mm)	3.01 ± 0.36
Device success	260 (100.0)
Multi-vessel CAD	160 (62.3)
Staged angioplasty	63 (24.2)
Staged coronary artery bypass graft surgery	7 (2.7)

Data are presented as mean ± standard deviation (SD) or n (%).
IABP = intra-aortic balloon pump; TIMI = thrombolysis in myocardial infarction; CAD = coronary artery disease.

Table 3
Clinical outcomes.

Total cohort (n = 260)				
Clinical outcome, n (%)	In-hospital	1-Month	1-Year	Longer-term
All-cause death	6 (2.3)	8 (3.1)	11 (4.2)	13 (5.0)
Cardiac death	6 (2.3)	8 (3.1)	10 (3.8)	11 (4.2)
Any MI	3 (1.2)	4 (1.5)	8 (3.1)	12 (4.6)
TV-MI	3 (1.2)	3 (1.2)	6 (2.3)	9 (3.4)
Definite/probable ST	3 (1.2)	5 (1.9)	6 (2.3)	7 (2.7)
Definite ST	3 (1.2)	3 (1.2)	4 (1.5)	5 (1.9)
TLR	3 (1.2)	3 (1.2)	6 (2.3)	10 (3.8)
TVR	3 (1.2)	3 (1.2)	7 (2.7)	12 (4.6)
TLF	9 (3.4)	11 (4.2)	17 (6.5)	23 (8.8)
MACE	9 (3.4)	12 (4.6)	20 (7.7)	28 (10.8)
Excluding cardiogenic shock (n = 232)				
All-cause death	0 (0)	2 (0.8)	4 (1.7)	5 (2.2)
Cardiac death	0 (0)	2 (0.8)	3 (1.3)	4 (1.7)
Any MI	2 (0.8)	3 (1.3)	7 (3.0)	11 (4.7)
TV-MI	2 (0.8)	2 (0.8)	5 (2.2)	8 (3.4)
Definite/probable ST	2 (0.8)	4 (1.7)	5 (2.2)	6 (2.6)
Definite ST	2 (0.8)	2 (0.8)	3 (1.3)	4 (1.7)
TLR	2 (0.8)	2 (0.8)	5 (2.2)	9 (3.9)
TVR	2 (0.8)	2 (0.8)	6 (2.6)	11 (4.7)
TLF	2 (0.8)	4 (1.7)	9 (3.9)	15 (6.5)
MACE	2 (0.8)	5 (2.2)	13 (5.6)	19 (8.2)

MI = myocardial infarction; TV-MI = target vessel myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization; TLF = target lesion failure; MACE = major adverse cardiovascular events.

4. Discussion

This study reports the long term clinical outcome on the use of the combination sirolimus eluting EPC capture stents in patients who underwent primary PCI for STEMI. The overall primary endpoint of TLF at one year and longer-term (median 23.4 months) follow-up was 6.5% and 8.8% respectively. There were 5 cases (1.9%) of definite ST and 2 cases (0.8%) of probable ST. Device success rate was 100%.

The healing patterns of culprit vessels after stenting for STEMI are different from stable coronary artery disease. Stenting with DES during STEMI carries the risk of late stent failure due to delayed endothelial healing [2,20]. Although there are no direct mechanistic studies to date, it is postulated that using pro-healing stents that ensure early restoration of vascular healing may be beneficial in the setting of STEMI. In addition, EPCs are mobilized in large numbers from bone marrow and peak at day 7 following STEMI [21]. EPC capture technology

Table 4
Multivariate Cox regression model for target lesion failure.

Variables	Adjusted HR	95% CI	*p*-Value
Cardiogenic shock	4.881	1.877–12.694	0.001
Age	1.044	0.995–1.096	0.081
Diabetes	0.900	0.314–2.580	0.844
Anterior MI	0.822	0.306–2.212	0.698
Clopidogrel use	0.385	0.082–1.793	0.224
Lesion length	0.991	0.944–1.041	0.732
Post reference vessel diameter	0.731	0.226–2.362	0.731

HR = hazard ratio; CI = confidence interval; MI = myocardial infarction.

during this period will harness the elevated circulating EPC and encourage endothelialization. Previous experience with EPC capture stents in STEMI showed good clinical outcomes with no reported late ST [14]. The combination sirolimus eluting EPC capture stent increase EPC adhesion on the surface of DES while maintaining therapeutic level of the anti-proliferative drug to inhibit smooth muscle proliferation. In animal study, the presence of early mature endothelium was higher in the dual therapy stents as compared to monotherapy DES [4]. Combination sirolimus eluting EPC capture stent stents also had the least amount of neointimal thickness demonstrated by OCT as compared to monotherapy DES [16]. A longitudinal sequential assessment using OCT in the EGO-COMBO study demonstrated near to 100% stent coverage by 9 months and a unique neointimal regression healing pattern with low major adverse cardiac event (MACE) rate at 36 months follow up [22]. The recently published HARMONEE trial is the first randomized controlled trial to compare the combination sirolimus eluting EPC capture stent against best-in-class everolimus DES in patients with stable angina, unstable angina and stabilized non-STEMI. The OCT study in the trial showed superior strut coverage and more homogenous tissue covering the struts with the combination sirolimus eluting EPC capture stent as compared to everolimus DES [23].

The proof-of-concept REMEDEE trial found that combination sirolimus eluting EPC capture stents were non-inferior to paclitaxel DES in terms of angiographic in-stent restenosis and an overall low rate of clinical events in patients with uncomplicated coronary artery disease [24]. One-year TLF rate in the REMEDEE trial was 8.9% in the combination sirolimus eluting EPC capture stent group and 10.2% in paclitaxel DES but this study was not powered to detect differences in clinical outcomes. Among 1000 patients enrolled in the single-arm all-comers post-market REMEDEE Registry, low TLF rates at one year (5.7%) and two years (8.5%) after combination sirolimus eluting EPC capture stent placement was observed [17]. In the REMEDEE Registry cohort, TLF were mainly driven by TLR at one-year (4.3%) and two years (5.9%). However, the low number of patients with acute coronary syndrome (ACS) and STEMI at presentation in the REMEDEE registry (ACS 30.4%, STEMI 19.9%) infer a lower clinical event rates as compared to higher risk STEMI population [17,18]. STEMI is a known predictor of cardiac deaths and early ST after PCI [20]. The STEMI subgroup of the REMEDEE registry (n = 199) had similar one-year TLF rate (6.5%) as our cohort (6.5%) but with lower incidence of cardiac deaths (2.0%) as compared to4.3% in our STEMI cohort [18]. Our patients had higher prevalence of cardiovascular risk factors as compared to the REMEDEE Registry's STEMI subgroup (diabetes 31.5% vs. 11.1%, hypertension 41.2% vs. 36.7%, hypercholesterolemia 66.2% vs. 41.2%, active smokers 53.5% vs. 30.7%). After excluding patients with cardiogenic shock, our study observed a similar rate of TLF (6.5%) and cardiac death (1.7%) at long term follow up beyond one-year as compared to the REMEDEE registry.

Current generation of DES has consistently shown improvement in MACE and repeat revascularization when compared with bare metal stent (BMS) and first-generation DES in the setting of STEMI [25–27]. The event rates in our study were consistent to those of other studies using everolimus DES in the STEMI population. The TLR was 3.3% in the XIENCE V USA post market surveillance trial at one year and 2.9% in the EXAMINATION trial at two years. [26,28]. However, the MACE rates were higher in our study as compared to that reported by Tomai et al. using biolimus DES with degradable polymer (one-year MACE 3.2%) and the COMFORTABLE-AMI trial (two years MACE 4.3%) [27,29]. Such differences are likely due to the higher risk profile of our study population with 10.9% of patients in cardiogenic shock at presentation as compared to 3.8% in the study by Tomai et al. Moreover, 7.3% of our patients needed mechanical ventilation and 7.7% required IABP support; while only 7.0% of the patients in COMFORTABLE-AMI trial were in Killip II–IV class. The HARMONEE randomized pivotal registration trial was the first study that did a head-to-head comparison between combination sirolimus eluting EPC capture stent and new generation everolimus DES in patients with ischemic coronary artery disease and included non-ST segment elevation ACS. Both groups showed no difference in TLF rates at one year (6.6% Combo, 4.2% everolimus DES, $p = 0.268$), which was also comparable with our study [23]. With the combination sirolimus eluting EPC capture stent showing non-inferiority compared to the everolimus DES with mechanistically superior strut coverage, this trial seeks registration for commercial use of combination sirolimus eluting EPC capture stent in both US and Japan.

Due to large thrombus burden and high platelet activity, the risk of ST is greater in patients with STEMI [1,20]. The anti-CD34 antibodies with EPC capture technology in combination sirolimus eluting EPC capture stent was designed to promote vessel healing. Definite ST was seen in 5 (1.9%) patients (3 acute ST, 1 late ST and 1 very late ST) and probable ST in 2 (0.8%) patients (1 died at home, 1 died of ventricular fibrillation in the emergency department). In the REMEDEE registry, 4 out of 6 cases of definite/probable ST at one year occurred in the patients with STEMI (2.0% ST rate in STEMI subgroup) [17]. Definite/probable ST rate at two years was 1.3% for everolimus DES in the EXAMINATION trial and 3.2% for biolimus DES in the COMFORTABLE-AMI trial [26,27]. The ST rates were higher in our study than those reported in current literature but this could be attributed to the worse risk profile of our STEMI population as discussed earlier.

All our patients received DAPT with a minimum intended treatment period of 12 months after primary PCI. A total of 83.9% patients received the novel $P2Y_{12}$ inhibitors (prasugrel 68.5% and ticagrelor 15.4%). However, in the urgent setting of STEMI, it is challenging to thoroughly evaluate the potential barriers that may limit the treatment duration of DAPT [30]. The outcome of the REDUCE trial (NCT02118870) comparing 3 months and 12 months of DAPT in post ACS patients may provide data to support a potential use for COMBO stents in patients who may not tolerate longer duration of DAPT. It is also crucial to extend follow-up beyond 1 year after primary PCI in order to assess the long-term safety profile of DES after completion of the routinely recommended 12-month DAPT regimen. In our study, TLF and ST rates of 8.8% and 2.7% respectively at 23.4 months follow up were considered to be very acceptable.

5. Study limitations

This was an observational study with inherent limitations without a control group but it represents the insight of the real-world clinical outcome after combination sirolimus eluting EPC capture stent implantation in STEMI. It was one of the largest cohort of STEMI patients treated with combination sirolimus eluting EPC capture stent with a longer-term follow-up beyond one year. We identified several study limitations that can lead to bias. Firstly, we did not perform propensity-score matching or other approaches to adjust for confounders known to affect clinical outcomes in STEMI patients. Secondly, event adjudication was done by the local hospital team in an unblinded observational cohort. Thirdly, there was absence of an independent QCA core laboratory for angiographic analyses. Lastly, there was no mechanistic observation supporting the role of the novel EPC technology in clinical outcomes in this study.

6. Conclusions

This study demonstrated acceptable clinical outcomes for an all-comers STEMI patients undergoing primary PCI with the use of combination sirolimus eluting EPC capture stents. Future large randomized trials are needed to investigate the mechanistic characteristics and long term efficacy and safety profile of combination sirolimus eluting EPC capture stent in STEMI patients.

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