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The COMBO dual therapy stent in patients presenting with acute ST-elevation myocardial infarction: a one-year follow-up study

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KEYWORDS

- clinical outcomes
- COMBO dual therapy stent
- endothelial progenitor cell
- primary percutaneous coronary intervention
- ST-elevation myocardial infarction

Abstract

Aims: The aim of this study was to evaluate the safety and efficacy of the COMBO dual therapy stent in patients with acute ST-elevation myocardial infarction (STEMI). We report the one-year clinical outcomes.

Methods and results: Patients with acute STEMI who underwent primary percutaneous coronary intervention (PCI) between November 2013 and March 2015 and received the COMBO dual therapy stent were enrolled in this prospective single-centre registry. The primary outcome was target lesion failure (TLF), defined as a combination of cardiac mortality, target vessel myocardial infarction (TVMI), or clinically driven target lesion revascularisation (TLR). A total of 117 patients received 147 COMBO dual therapy stents during the study period, and 9.4% of the patients presented with cardiogenic shock. Thrombolysis In Myocardial Infarction (TIMI) 3 flow post procedure was achieved in 98.5% of lesions. At one year, the TLF rate was 7.7%. The rates of cardiac mortality, TVMI, and TLR were 4.3%, 2.6%, and 3.4%, respectively. The incidence of definite/probable stent thrombosis was 4.3% at 12 months, with four of the five cases occurring within 30 days. The all-cause mortality was 5.1% at one year.

Conclusions: COMBO stent implantation during primary PCI for acute STEMI showed acceptable rates of TLF at one year, although the rates of early ST were not negligible. Further studies are warranted to evaluate the safety in a larger high-risk population.

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Abbreviations

DES	drug-eluting stent(s)
EPC	endothelial progenitor cell(s)
MI	myocardial infarction
PCI	percutaneous coronary intervention
ST	stent thrombosis
STEMI	ST-elevation myocardial infarction
TLF	target lesion failure
TLR	target lesion revascularisation
TVMI	target vessel myocardial infarction

Introduction

Drug-eluting stents (DES) have demonstrated a significant reduction in the rate of repeat revascularisation in comparison to bare metal stents. However, late stent failure is still an issue with the current generation of DES[1,2]. A major concern is the inhibitory effect of the antiproliferative drug on endothelial cell regeneration. This has resulted in delayed and incomplete endothelialisation of the stented segment. The regeneration of endothelial cells results from the local recruitment of adjacent cells or from an adhesion of bone marrow-derived endothelial progenitor cells (EPC)[3,4]. Previous studies with EPC capture technology have shown enhanced stent endothelialisation[5,6].

EPC capture on sirolimus-eluting stents augments endothelialisation. The presence of mature endothelium was higher in the EPC captured sirolimus-eluting stents (80%), in contrast to sirolimus elution alone (40%) at 14 days[7]. Similar high rates of endothelialisation were demonstrated on optical coherence tomography with the use of anti-CD34 sirolimus-eluting stents[8]. The inhibitory effect of sirolimus on smooth muscle cell proliferation will be sustained while accelerating the endothelial healing process. An early restoration of functional endothelium may be beneficial, especially in the setting of ST-elevation myocardial infarction (STEMI). The COMBO™ dual therapy stent (OrbusNeich Medical, Ft. Lauderdale, FL, USA) combines EPC capture technology with an antiproliferative, biodegradable sirolimus drug elution. This stent has shown similar rates of angiographic in-stent restenosis in comparison to the paclitaxel-eluting stent, and an overall low rate of clinical events in uncomplicated patients with stable angina[9]. In addition, the stent has demonstrated a unique late neointimal regression, with minimal restenosis and no late stent thrombosis (ST)[10]. Evidence of the safety and efficacy of the COMBO stent in patients presenting with STEMI is lacking. In the thrombogenic milieu of STEMI, hastening the process of vascular repair may lead to improved clinical outcomes. The aim of this study was to evaluate the clinical outcomes of patients with acute STEMI receiving the COMBO stent during primary percutaneous coronary intervention (PCI).

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Methods

STUDY DESIGN AND POPULATION

This was a prospective, single-centre, single-arm observational registry study from a tertiary care cardiac centre. The study was approved by the National Ethics Committee and Hospital Research Board. Consecutive patients who underwent primary PCI with the COMBO dual therapy stent between November 2013 and March 2015 were enrolled in this study. Patients were eligible if they were ≥18 years old with electrocardiographic evidence of acute STEMI. The study excluded patients with a contraindication to dual antiplatelet therapy, limited life expectancy (less than one year), and patients unwilling to give written informed consent.

STUDY DEVICE

The COMBO dual therapy stent is a balloon-expandable stent consisting of a 316L stainless steel alloy, with a strut thickness of 100 µm. It has an abluminal coating of a biocompatible, biodegradable polymer containing sirolimus (5 µg/mm) and a luminal covering of murine, monoclonal, anti-human CD34 antibody. The antibody specifically targets circulating EPC to accelerate endothelial coverage. The polymer degrades completely in 90 days. Fifty percent of the sirolimus is released in seven days, 75% in 10 days, and the rest is eluted within 30 days[8].

PROCEDURE

All patients in the study received dual antiplatelet therapy, which included a loading dose of 300 mg of aspirin and one of the following $P2Y_{12}$ receptor antagonists: 600 mg of clopidogrel (300 mg for those patients already receiving chronic clopidogrel therapy), 180 mg of ticagrelor, or 60 mg of prasugrel. Primary PCI was carried out in accordance with the current standard of practice. All patients received heparin anticoagulation, guided by an activated clotting time monitoring. The use of a glycoprotein IIb/IIIa receptor inhibitor and a thrombus aspiration device was at the discretion of the primary operator. The patients were subsequently maintained on 100 mg of aspirin indefinitely and on a $P2Y_{12}$ receptor antagonist for at least 12 months.

DATA COLLECTION AND STUDY ENDPOINTS

Baseline demographic and clinical characteristics were collected. The angiographic variables, procedural characteristics, and outcomes were analysed. Device success was defined as a successful COMBO dual therapy stent placement with Thrombolysis In Myocardial Infarction (TIMI) flow grade 2/3 post stenting and less than 10% residual stenosis. The one-month, six-month, and 12-month follow-ups were carried out by clinic visits or telephonic enquiry. These follow-ups were achieved in all of the patients in this study.

The primary outcome of interest was target lesion failure (TLF), defined as a combination of cardiac mortality, target vessel myocardial infarction (TVMI), or clinically driven target lesion revascularisation (TLR). Exploratory secondary outcomes of interest included in-hospital mortality, all-cause mortality, major adverse cardiac events (defined as the composite of all-cause mortality, MI, or ischaemia-driven target vessel revascularisation), the components of TLF, target vessel revascularisation and ST. Deaths that could not be attributed to another cause were regarded as cardiac deaths. MI was defined according to the third

universal definition of MI[11]. ST was classified according to the Academic Research Consortium criteria[12].

STATISTICAL ANALYSIS

Continuous data are expressed as means and standard deviations; discrete variables are given as absolute values and percentages. Data were analysed using the statistical software package SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 147 COMBO dual therapy stents were implanted in 117 patients during the study period. The baseline demographic and clinical characteristics are shown in **Table 1.** The mean age was 56±11 years and 90.6% of the patients were male. The most common risk factor for MI was current tobacco use (59.8%); 18.8% of the patients were diabetic. Cardiogenic shock was present in 9.4% of the patients. The left ventricular ejection fraction on the two-dimensional echocardiogram was 49±11%.

The lesion and procedural characteristics of the study population are defined in **Table 2**. The right coronary artery was the culprit vessel in 52.8% of the lesions, followed by the left anterior descending artery (41.9%). Initial TIMI flow 0/1 occurred in 87% of the lesions. Thrombus aspiration was performed in 88.9% of the patients. At the end of the procedure, 98.5% of the lesions achieved TIMI 3 flow. Device success was seen in all the patients.

Table 3 shows the clinical outcomes up to one year. TLF was recorded in 7.7% of the patients at one year. Cardiac mortality occurred in 4.3% of the patients. TVMI was observed in 2.6% and TLR was performed in 3.4% of the patients. The in-hospital mortality rate was 1.7%. The all-cause mortality rate was 5.1% at one year. Among the 117 patients included in the study, 91.5% were compliant with the dual antiplatelet therapy at the end of one year. Definite ST was seen in three patients (2.6%) and probable ST was seen in two (1.7%). The details of cases of ST are illustrated in **Table 4**.

Table 1. Baseline demographic and clinical characteristics.

Variable	Patients (n=117)
Age (years)	56±11
Male	106 (90.6%)
Hypertension	42 (35.9%)
Diabetes mellitus	22 (18.8%)
Dyslipidaemia	39 (33.3%)
Current tobacco use	70 (59.8%)
Family history of CAD	5 (4.3%)
Prior AMI	20 (17.1%)
Prior PCI	15 (12.8%)
Prior CABG	1 (0.9%)
Cardiogenic shock	11 (9.4%)
LVEF	49±11

Values are mean±SD or n (%). AMI: acute myocardial infarction; CABG: coronary artery bypass graft; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention

Table 2. Lesion and procedural characteristics.

Variable		Patients (n=117) Lesions (n=129)
$P2Y_{12}$ receptor antagonist	Clopidogrel	17 (14.5%)
	Prasugrel/ticagrelor	100 (85.5%)
Access	Femoral	62 (53%)
	Radial	55 (47%)
Culprit lesion location	LMCA	1 (0.8%)
	LAD	54 (41.9%)
	LCX	5 (3.9%)
	RCA	68 (52.8%)
	SVG	1 (0.8%)
Initial TIMI flow	0	106 (82.2%)
	1	6 (4.7%)
	2	9 (7.0%)
	3	8 (6.2%)
Lesion length (mm)		21.7±8.4
Number of stents per lesion		1.1±0.3
Average stent length (mm)		21.1±5.8
Average stent diameter (mm)		3.0±0.4
Final TIMI 3 flow		127 (98.5%)
Final TIMI 2/3 flow		129 (100%)
Adjunctive therapy in PCI	Glycoprotein IIb/IIIa receptor inhibitors	17 (14.5%)
	Aspiration thrombectomy	104 (88.9%)
IABP use		7 (6.0%)
Device success		129 (100%)
Multivessel CAD on presentation		65 (55.6%)
Multivessel PCI		2 (1.7%)
Staged PCI		26 (22.2%)
Staged CABG		3 (2.6%)

Values are mean±SD or n (%). CAD: coronary artery disease; IABP: intra-aortic balloon pump; LAD: left anterior descending artery; LCX: left circumflex artery; LMCA: left main coronary artery; PCI: percutaneous coronary intervention; RCA: right coronary artery; SVG: saphenous vein graft; TIMI: Thrombolysis In Myocardial Infarction

Table 3. Clinical outcomes at 30 days, 6 months, and 12 months.

	1 month (n=117)	6 months (n=117)	12 months (n=117)
Death	4 (3.4%)	4 (3.4%)	6 (5.1%)
Cardiac death	4 (3.4%)	4 (3.4%)	5 (4.3%)
MI	2 (1.7%)	3 (2.6%)	4 (3.4%)
TVMI	2 (1.7%)	3 (2.6%)	3 (2.6%)
Definite ST	2 (1.7%)	3 (2.6%)	3 (2.6%)
Definite/probable ST	4 (3.4%)	5 (4.3%)	5 (4.3%)
TLR	2 (1.7%)	4 (3.4%)	4 (3.4%)
TVR	2 (1.7%)	4 (3.4%)	4 (3.4%)
TLF	6 (5.1%)	8 (6.8%)	9 (7.7%)
MACE	6 (5.1%)	8 (6.8%)	11 (9.4%)

Values are n (%). MACE: major adverse cardiac events; MI: myocardial infarction; TLF: target lesion failure; TLR: target lesion revascularisation; TVMI: target vessel myocardial infarction; TVR: target vessel revascularisation; ST: stent thrombosis

Table 4. Narrative of cases with stent thrombosis.

	Baseline characteristics	Treated lesion	Timing of ST	Predisposing factors for ST	Angiographic findings	Treatment
1	58 years, male. LVEF: 55%	Proximal RCA. 3.5×33 mm	Acute. Immediate post PCI.	Non-absorption of antiplatelets due to profuse vomiting, hypotension.	Thrombus at the stented segment.	Thrombus aspiration, plain balloon angioplasty, glycoprotein IIb/IIIa inhibitor, volume replacement.
2	70 years, male. LVEF: 35%	Proximal LAD. 3.0×18 mm (IABP for haemodynamic support)	Acute. 2 hours post PCI	Heart failure, incomplete inhibition of platelet activation, probable clopidogrel resistance*.	Intravascular ultrasound: well expanded stent, no edge dissection or malapposition. MLA: 5.2 mm^2.	Thrombus aspiration, glycoprotein IIb/IIIa inhibitor, change to ticagrelor.
3	48 years, male. LVEF: 50%	Distal RCA. 3×33 mm	Late. 6 months post PCI	Drug non-compliance, DM.	Focal ISR with superimposed thrombus.	Drug-eluting balloon angioplasty
4	58 years, male. LVEF: 25%	Proximal LAD. 2.5×23 mm	Subacute. 15 days post PCI	DM, small vessel disease, low ejection fraction.	NA	NA
5	62 years, male. LVEF: 35%	Proximal LAD. 3.5×33 mm	Subacute. 7 days post PCI	Low ejection fraction.	NA	NA

Cases 4 and 5 had unexplained sudden deaths within the first month (probable ST). * Assays to confirm clopidogrel resistance were not performed. DM: diabetes mellitus; IABP: intra-aortic balloon pump; ISR: in-stent restenosis; LAD: left anterior descending artery; LVEF: left ventricular ejection fraction; MLA: minimum luminal cross-sectional area; NA: not applicable; PCI: percutaneous coronary intervention; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction

Discussion

This is the first reported study on the use of the COMBO dual therapy stent in patients with acute STEMI undergoing primary PCI. The implementation of this novel technology has shown acceptable clinical outcomes. The device success rate was high, and the primary endpoint of TLF occurred in 7.7% of the patients at one year. Definite ST occurred in three patients, two acute cases and one late case. The need for TLR in our cohort was low at 3.7% at one year.

Primary PCI is the reperfusion strategy of choice in patients with acute STEMI, and the use of DES in this setting has consistently been shown to reduce the incidence of target vessel revascularisation[13]. Although vascular smooth muscle cell proliferation and neointimal hyperplasia are effectively inhibited by the antiproliferative drug, the vessel healing at the culprit site is often incomplete and delayed[14]. The most important aspect of vascular repair is surface endothelialisation, and its delay is associated with an increased risk of ST. Bone marrow-derived circulating EPC have regenerative capacities and play an important role in the repair of endothelium after injury. EPC are mobilised in large numbers from the bone marrow during STEMI, occurring within the first few hours of the event, and they peak at day seven[15]. During primary PCI, implanting stents with luminal anti-human CD34 antibody coating may optimally harness the increased levels of circulating EPC and accelerate endothelial healing. These are designed to attract circulating EPC onto the stent surface and, with time, these EPC will differentiate into a functional endothelial lining over the stent. This concept has been shown to be promising with the Genous™ stent (OrbusNeich Medical)[6]. The Genous stent has demonstrated acceptable clinical outcomes in various studies[16-18]. In spite of the beneficial pro-healing effects of EPC capture, there was a trend of higher target vessel failure with the Genous stent in comparison to first-generation DES[19]. The in-stent late loss in patients who received the Genous stent was 0.87±0.67 mm, similar to the bare metal stent[20]. This prompted the development of a COMBO dual therapy stent, which combines the properties of enhanced vascular repair and antiproliferative drug elution with sirolimus[7,8].

The REMEDEE trial and the REMEDEE registry have shown favourable outcomes with the use of the COMBO dual therapy stent[9,21]. However, our study is the first to assess the preliminary safety and efficacy of the COMBO dual therapy stent in a specific patient cohort with acute STEMI. The TLF rate of 5.1% at one month, 6.8% at six months, and 7.7% at one year is encouraging, given that this is a high-risk population. TLF was mainly driven by cardiac mortality. In the REMEDEE registry, a total of 1,000 patients were enrolled, and more than two thirds (69.6%) underwent elective PCI. The primary endpoint of TLF occurred in 5.7% of the patients at one year[21]. When compared to the outcomes from other studies using the current generation of DES in the setting of STEMI, the one-year TLF and TLR rates of the COMBO dual therapy stent in our study were similar to those of the everolimus-eluting stents[22]. Major adverse cardiac events were higher in our study when compared to those from the biolimus-eluting stent reported by Tomai et al[23]. This could be explained by the much higher incidence of cardiogenic shock, an important predictor of adverse outcome, in our cohort (9.4%) in comparison to the 3.8% reported by Tomai et al.

The incidence of definite/probable ST in our study was 3.4% at one month and 4.3% at one year, which is higher than anticipated. In the COMBO dual therapy stent, early restoration of functional endothelium and the presence of a biodegradable polymer are expected to result in an overall low rate of ST. However, the risk is not eliminated, as the pathophysiology of ST is complex and multifactorial. The common potential mechanisms for early ST are patient-related (acute coronary syndrome presentation, high

platelet reactivity, diabetes mellitus, low ejection fraction), lesion-based (thrombus containing, small vessel, long lesions), or stent-related factors (edge dissections limiting inflow or outflow, stent underexpansion). The most important risk factor for late and very late ST is a premature discontinuation of antiplatelet therapy[24]. The majority of the cases of ST in our study were clustered within 30 days (four of the five cases), in the setting of STEMI. Patients with acute coronary syndrome are at an increased risk of early ST in view of the marked inflammation and enhanced platelet reactivity. Similar findings were observed in the REMEDEE registry, where 303 patients underwent urgent PCI for acute coronary syndrome, and five of the six cases of early ST occurred in the setting of acute coronary syndrome[21]. In the EXAMINATION trial, the incidence of definite/probable ST was 0.9% in the everolimus-eluting stent group and 2.5% in the bare metal stent group. The majority of the study population (97%) were in Killip class I and II in the EXAMINATION trial[25]. In contrast, the incidence of cardiogenic shock, an important predictor of adverse outcome and contributing factor to ST, was high in our cohort (9.4%). Hence, the reported increased incidence of ST in our registry should be interpreted with great caution considering the high-risk patient cohort and the small sample size. This should be evaluated further in a larger cohort.

Individuals with acute STEMI represent a cardiac emergency, and blood flow in the culprit vessel needs to be restored at the earliest opportunity. During primary PCI, it is often difficult to assess completely a patient's suitability for the standard recommended duration of dual antiplatelet therapy[26]. Therefore, the accelerated endothelial regeneration and pro-healing benefits of the COMBO stent may be a safer option, if the need for an early interruption of dual antiplatelet therapy is warranted during the follow-up (urgent non-cardiac surgery, active bleeding, or drug non-compliance). The risks of ST may then be potentially low. The current guidelines do not recommend short dual antiplatelet therapy duration with the use of a COMBO dual therapy stent. The outcome of the REDUCE (NCT02118870) study is eagerly anticipated and will clarify the safety of a shorter, three-month duration of a dual antiplatelet regimen with the use of the COMBO stent.

The combination of EPC capture and antiproliferative drug elution is a rational and an attractive concept. The efficacy and safety of the COMBO dual therapy stent is currently being evaluated in the HARMONEE study (NCT02073565), under the framework of the joint Japan-US Harmonization-By-Doing initiative, for approval of commercial use in both the USA and Japan. The patients to be enrolled include those with stable angina, unstable angina and stabilised non-STEMI. They are randomised to receive the COMBO dual therapy stent versus the current-generation everolimus-eluting stent.

Study limitations

This was an observational registry study with inherent limitations and without a control group. The study enrolled a relatively small number of patients. However, it represents the outcome of consecutive patients in an actual clinical setting. Although it is a single-centre study and the findings may not be generally applicable to all healthcare facilities, the management in our centre is in accordance with the current standard of practice. The study assessed only the clinical outcome; the novel concept of EPC capture was not evaluated. In addition, routine follow-up coronary angiography to evaluate strut coverage and late lumen loss was not performed.

Conclusions

Clinical outcomes with the use of a COMBO dual therapy stent in patients who undergo primary PCI for acute STEMI are acceptable, although the rates of early ST were not negligible. These preliminary real-world observational data suggest the feasibility of future randomised trials to test the expanded indications for this novel stent in high-risk patients.

Impact on daily practice

EPC capture technology is unique as it facilitates rapid endothelialisation. The COMBO dual therapy stent has shown a low rate of clinical events in uncomplicated patients with stable ischaemic heart diseases. In this prospective single-centre registry, the use of the COMBO dual therapy stent in acute STEMI showed acceptable rates of TLF at one year. The higher incidence of early ST mandates further assessment in a larger study cohort. Further, our findings provide a platform for future evaluation of the COMBO dual therapy stent in a randomised controlled trial against the current-generation DES in an all-comers STEMI population.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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