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Safety and efficacy of the COMBO bio-engineered stent in an all-comer PCI cohort: 1-Year final clinical outcomes from the MASCOT post-marketing registry

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ABSTRACT

Background: The COMBO stent (OrbusNeich Medical, Ft. Lauderdale, Florida) is a new-generation bio-engineered drug eluting stent, combining an abluminal coating of a bioabsorbable polymer matrix for sustained release of sirolimus and luminal anti-CD34 coating for endothelial progenitor cell capture and rapid endothelialization.
Methods: The Multinational Abluminal Sirolimus Coated BiO-Engineered StenT (MASCOT) registry was a prospective post-marketing study conducted from June 2014–May 2017 across 60 centers globally. Patients were eligible if COMBO stent implantation was attempted, and they received dual antiplatelet therapy (DAPT) per local guidelines. Follow-up was conducted by trained research staff at 1, 6 and 12 months by phone or clinic visit to capture clinical events and DAPT cessation events. The primary endpoint was 1-year target lesion failure (TLF), composite of cardiac death, non-fatal myocardial infarction not clearly attributable to a non-target vessel, or ischemia-driven target lesion revascularization.
Results: A total of 2614 patients were enrolled over the study period with 96.7% completion of 1-year follow-up. The mean age of enrolled patients was 62.9 ± 11.2 years and 23.0% were female. Diabetes mellitus was present at baseline in 33.5%. A total of 56.1% patients underwent PCI for acute coronary syndrome (ACS). The 1-year primary endpoint of TLF occurred in 3.4% patients ($n = 88$). Definite stent thrombosis occurred in 0.5% patients ($n = 12$).
Conclusion: The MASCOT post marketing registry provides comprehensive safety and efficacy outcomes following contemporary PCI using the novel COMBO stent in an all-comer population. This platform is associated with low rates of 1-year TLF and ST.
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1. Introduction

Novel stent designs have remarkably improved percutaneous coronary intervention (PCI) outcomes over the last decade [1]. Second generation biocompatible drug eluting stents (DES) have significantly reduced the risk of intimal hyperplasia with very low incident rates of stent thrombosis (ST) [2]. Biodegradable polymer (BDP) stents have further decreased risk of hypersensitivity related to DES polymer and propensity for late ST [3,4]. Recent BDP stent trials have been associated with very low rates of target lesion failure (TLF) and ST [5,6–11]. Despite these tremendous advances, dual antiplatelet therapy (DAPT) is necessary for a mandatory period following PCI to reduce ST, but may result in adverse bleeding outcomes [12]. In this context, the most recent DES technology to generate interest is the COMBO Dual Therapy Stent that combines luminal endothelial progenitor cell (EPC) capture technology to act synergistically with abluminal sirolimus in a resorbable polymer matrix for faster endothelialization [13]. By antibody recruitment of EPCs to the site of vascular injury, an acceleration and enhancement of the normal endothelialization process occurs [14–16]. Functional endothelium is known to reduce inflammation, prevent thrombosis, inhibit smooth muscle cell migration, proliferation and the expression of extracellular matrix, along with maintaining blood flow through vasodilation of the vessel.

While the recent Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt (REMEDEE) registry has demonstrated low TLF up to 2-years in 1000 European patients undergoing PCI with the COMBO stent, bleeding outcomes and DAPT adherence post-PCI were not recorded [17,18]. In the current report, we present the main clinical outcomes from the Multinational Abluminal Sirolimus Coated BiO-Engineered StenT (MASCOT) registry (Clinicaltrials.gov identifier NCT02183454), in patients receiving COMBO DES across several global sites, with systematic follow up of DAPT cessation, and exploratory analysis of the associations between DAPT cessation and 1-year outcomes.

2. Methods

The MASCOT registry was a post marketing observational study conducted across 60 sites in Europe, Middle East, Asia and South America, to evaluate the long-term safety and performance of the COMBO stent in routine clinical practice. The study was managed by the Clinical Coordinating Center (CCC) at the Icahn School of Medicine at Mount Sinai (directed by RM) under the leadership of the Principal investigator (AC), Steering Committee and study sponsor (OrbusNeich Medical, Fort Lauderdale, Florida). The study sponsor managed the sites with respect to regulatory and contractual aspects. The CCC had full oversight of data entry in the electronic data capture (EDC) system, site monitoring, event adjudication and data analysis. The sponsor did not interfere with data analysis and presentation of results. The study was conducted in keeping with principles of the Declaration of Helsinki and Good Clinical Practice. All sites received local ethics committee approval or a waiver to participate in the registry. All patients provided written informed consent. The study was registered on clinicaltrials.gov (identifier NCT02183454). Enrollment occurred over 21 months from June 2014 to March 2016. One-year follow up was completed in May 2017. After quality control checks, the database was locked on September 15, 2017. Final analysis was conducted on September 28, 2017.

2.1. Study population

All consecutive patients undergoing PCI with attempted placement of at least one COMBO stent as part of routine clinical care were eligible for enrollment, as long as they did not meet any of the following exclusion criteria: PCI for treatment of ST, concurrent participation in another drug or device trial where routine angiographic follow up was planned, life expectancy <12 months, high probability for non-adherence to follow up due to social, psychological or medical reasons and refusal to participate in the registry. The study intended to enroll 2500 patents from a minimum of 50 centers globally.

2.2. Study device

The OrbusNeich COMBO bio-engineered sirolimus eluting stent (Fig. 1) is a dual therapy stent, which consists of a 316 L stainless steel alloy in a double helix strut design with a strut thickness of 100 μm. The stent is abluminally coated with a biodegradable biocompatible polymer containing sirolimus with a proprietary blend of two bioabsorbable urethane-linked poly(ether-ester) multi-block copolymers composed of glycolide (GA), lactide (LA), ε-caprolactone (CL), and polyethylene glycol (PEG) pre-polymer blocks. The coating matrix has been specially formulated to provide the required mechanical properties of a stent coating to allow for crimping and deployment, while allowing for a time release profile of the drug similar to the commercial Cypher DES (Cordis Corporation, Johnson & Johnson, Warren NJ). The total sirolimus drug content of the COMBO Stent is 5 μg/mm (0.75 μg/mm^2) stent length, approximately half the dose of the commercially available Cypher DES. Covalently attached to this matrix is a layer of murine monoclonal anti-human CD34 antibody, which specifically targets circulating CD34+ endothelial progenitor cells (EPCs). The stent is supplied premounted on a low profile rapid exchange balloon catheter delivery system compatible with a 0.014″ guidewire. Sirolimus is fully eluted from the stent within 30 days and the biodegradable polymer is fully resorbed within 90 days. The device received Conformité Européene mark in May 2013.

2.3. Study procedure

The PCI procedure was performed as per standard of care at each site. DAPT selection, intensity and duration, were at the discretion of the treating physician and according to local policy but was recommended for a period of 6–12 months in all patients, and 12 months in patients with ACS in accordance with European society of cardiology guidelines. There was no study-related formal requirement or recommended dose regarding post-procedural medication.

2.4. Follow-up and event reporting

Follow-up was conducted by telephone or clinic visit by designated research staff at each site at 30 days, 6 and 12 months post-PCI. Follow up included questions on cardiac status, DAPT adherence and reasons for cessation. The study utilized a web-based electronic data capture (EDC) system. All events were reported by the sites directly in to the EDC with upload of anonymized source documents. Site reported and triggered events were adjudicated by an independent clinical events committee (CEC) of physicians, and adjudicated events were entered in to the EDC. Along with clinical events, all DAPT cessation events were also adjudicated by an independent CEC and classified in to the following modes: discontinuation, disruption or interruption.

2.5. Endpoints and definitions

The primary endpoint of the study was device-oriented composite of 12-month TLF, defined as a composite of cardiac death, non-fatal myocardial infarction (MI) not clearly attributable to a non-target vessel or ischemia driven target lesion revascularization (TLR) by PCI or CABG. Secondary endpoints included TLF in-hospital, at 30 days and 6 months. The individual components of TLF, ST, target vessel and non-target vessel ischemia driven revascularization (TVR, NTVR) and stroke were assessed in-hospital, at 30 days, 6 months and 12 months. Major adverse cardiac events (MACE) and each of its components (all-cause death, any MI, any ischemia driven revascularization) were assessed in-hospital, at 30 days, 6 months and 12 months. Device success was calculated as the percentage of patients with successful delivery and deployment of the COMBO stent to the target lesion, final diameter stenosis ≤20% and final TIMI flow 3 by visual assessment. Procedural success was calculated as successful stent implantation without any peri-procedural complications.

Death, ST and ischemia driven TLR were adjudicated using the Academic Research Consortium definitions [19]. MI was defined using the third universal definition [20]. Bleeding was defined using the Bleeding Academic Research Consortium (BARC) definitions [21] – major bleeding as BARC 3 or 5, minor bleeding as BARC 2 and nuisance bleeding as BARC 1. DAPT cessations were categorized as discontinuation, disruption and interruption based on the Patterns of non-adherence to anti-platelet regimens in stented patients (PARIS) registry definitions [22]. Discontinuation was permanent physician-guided cessation, disruption was non-recommended cessation due to non-compliance or bleeding, and interruption was brief and necessary DAPT cessation for <14 days.

2.6. Statistical analysis

Categorical data are reported as numbers and frequencies, continuous data as means and standard deviations or medians and interquartile ranges. Clinical and DAPT cessation events were analyzed in a time to event manner using Kaplan-Meier methods and represented using time to event curves. Follow up was censored to last known follow-up or 12-months, whichever came first. Time dependent analyses were conducted to examine the effect of DAPT cessation on 1-year outcomes. Time dependent Cox regression models were adjusted for age, sex and center. Two sided p-values of <0.05 were considered significant. Statistical analyses were conducted using SAS version 9.4 (Durham, North Carolina) and Stata version 14.0 (College Station, Texas).

3. Results

The study population included for final analysis comprised 2614 patients enrolled across 60 sites. The study flow is shown in Supplementary Fig. 1. Table 1 presents the baseline characteristics of the patients. The mean age of patients was 62.9 ± 11.2 years including 23.0% females and 70.7% whites. The prevalence of traditional cardiovascular risk factors included 33.5% diabetes mellitus, 29.4% current smoking, 70.5% hypertension, 58.9% dyslipidemia and 6.5% chronic

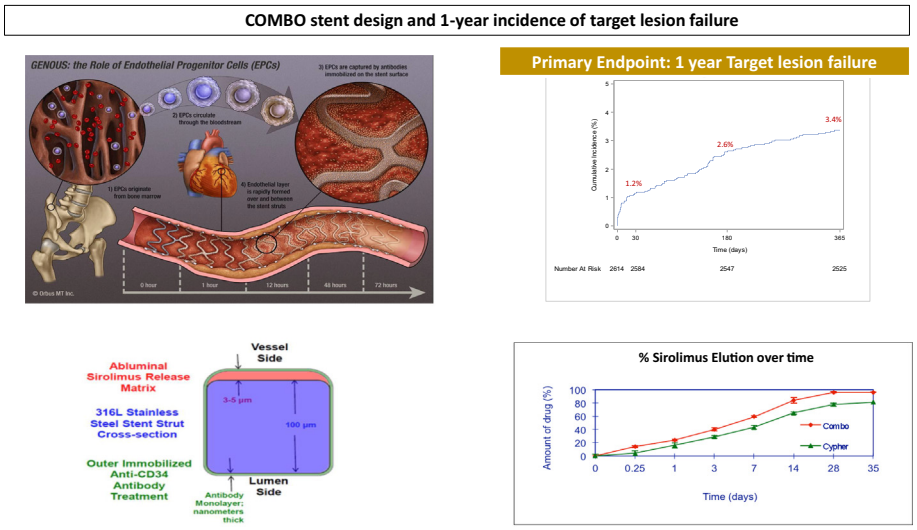

Fig. 1. COMBO stent design and 1-year incidence of the primary endpoint of target lesion failure.

kidney disease (CKD). Prior PCI was reported in 25.5% of enrolled patients and 23.1% had a history of prior MI. More than half of the patients (56.1%) underwent PCI for acute coronary syndrome (ACS), including 23.1% for ST segment elevation MI (STEMI) and 15.6% for non-STEMI (NSTEMI). With respect to patient risk factors associated with bleeding, approximately 6.9% patients had atrial fibrillation and 7.8% were discharged on chronic oral anticoagulation. Around 2.0% of patients had history of bleeding diathesis, prior bleeding needing transfusion or hospitalization, recent or concomitant bleeding with the PCI procedure or history of recent surgery. At discharge, one-third of patients were prescribed potent $P2Y_{12}$ therapy such as prasugrel or ticagrelor.

The procedural characteristics are shown in Table 2. Approximately 70.4% patients underwent radial access PCI with a median sheath size of 6 French. Vascular closure devices were successfully deployed in 18.2% of the patients. The primary anticoagulant used for PCI was unfractionated heparin, and glycoprotein 2b3a inhibitors were used in 10.7% patients. Overall 51.9% of the patients had multivessel disease including 9.8% patients with left main disease ≥50% and 20.3% with triple vessel disease. Multivessel PCI was performed in 17.8%.

Approximately 57.7% patients had American College of Cardiology/American Heart Association (ACC/AHA) type B2 or C lesions. Heavy calcification was present in 17.9%, thrombus in 17.1%, and approximately 4.5% patients had lesions with chronic total occlusions (CTO). Intravascular imaging with intravascular ultrasound or optical coherence tomography was used in 5.2% patients. At least one COMBO stent was successfully implanted in 2608 patients. The mean number of COMBO stents implanted was 1.29 ± 0.65, with a mean stent length 26.9 ± 17.8 mm and a mean stent diameter 3.2 ± 0.4 mm. Post-dilation was performed in 55.6% of all patients. The rate of device success per the study definition was 96.0%; with successful delivery and deployment of the COMBO stent to the target lesion in 99.7% patients, diameter stenosis ≤20% in 96.8% and TIMI 3 flow in 98.0%. Procedural success occurred in 97.5%. At least one COMBO stent delivery failure occurred in 9 patients (0.3%) due to failure to reach the target lesion ($n = 7$) or failure to cross the lesion ($n = 2$). At a lesion level, 3190 lesions were treated. Lesion level data are indicated in Supplementary Table 1.

One-year follow-up was completed in 96.7% patients. Clinical outcomes are shown in Supplementary Table 2. The primary endpoint of 12-month TLF occurred in 3.4% ($n = 88$) (Fig. 1), with 2.0% all-cause death, 1.4% cardiac death, 1.4% non-fatal MI not clearly attributable to a non-target vessel and 1.4% TLR (Fig. 2). MACE at 1-year occurred in 5.2% ($n = 137$) and stroke in 0.4% ($n = 11$). The incidence of 1-year major bleeding BARC 3 or 5 was 1.8% (Fig. 2). One-year definite ST occurred in 0.5% ($n = 12$), and definite or probable ST in 0.9% ($n = 24$). One-year incidence of TLF in the following important subgroups, patients on triple therapy, high and intermediate-high bleeding risk patients using the PARIS bleeding risk score, high ischemic risk patients using the PARIS thrombotic risk score, and in patients presenting with ACS is shown in Supplementary Table 3.

DAPT cessation outcomes are shown in Supplementary Fig. 2. Overall DAPT cessations occurred in 24.8% patients at 1-year including 21.7% DAPT discontinuations, 2.2% disruption and 0.9% interruption. In time-dependent models (Supplementary Table 4), physician guided DAPT discontinuation had no adverse effects on 1-year TLF (HR 1.20, 95% CI 0.47–3.10, $p = 0.70$) or MACE (HR 0.70, 95% CI 0.28–1.75, $p = 0.44$). DAPT disruption was associated with increased risk of 1-year MACE (HR 3.18, 95% CI 1.17–8.68, $p = 0.024$) but not TLF (HR 2.52, 95% CI 0.61–10.36, $p = 0.20$). No TLF or MACE events occurred subsequent to DAPT interruption.

4. Discussion

The MASCOT registry is the largest prospective global observational study of clinical events in patients undergoing PCI with the COMBO stent, including data on DAPT cessation and exploratory associations with 1-year outcomes in a time dependent manner. The main findings are as follows 1) COMBO stent implantation in all-comer PCI patients was associated with high rates of device and procedural success; 2) COMBO stent PCI was safe and effective in both ACS and non-ACS patients, including patients with higher baseline predisposition for bleeding; 3) At 1-year, the rate of TLF was 3.4%, with 1.4% incidence of cardiac death, 1.4% non-fatal MI not clearly attributable to a non-target vessel and 1.4% TLR; 4) incidence of definite ST was 0.5% and low through 1-year follow up; 5) With real world use of COMBO DES, physician recommended DAPT discontinuation occurred in only one-fifth of patients within 1-year, without increase in risk of TLF or MACE. Although the rates of non-physician recommended DAPT disruption were extremely low, disruption was associated with increased risk of 1-year MACE.

The COMBO stent has a combination of abluminal drug eluting technology with sirolimus in a biodegradable polymer coating, which resorbs within 90 days after implantation, along with the luminal endothelial progenitor cell capturing CD34 antibody coating for faster endothelialization [13]. Pre-clinical data have demonstrated that drug release from the COMBO stent is near complete at 30-days comparable to the Cypher stent [23], yet with a higher expression of endothelial cell adhesion molecules and low rates of neointimal hyperplasia.

Table 1
Baseline demographic and clinical characteristics.

	$N = 2614$
Age, years, mean ± SD	62.9 ± 11.2
Female sex	600 (23.0%)
Race	
• Asian	583(23.0%)
• Black	9(0.4%)
• Other	150(5.9%)
• White	1791(70.7%)
Body mass index (kg/m^2), Mean ± SD	28.1 ± 4.8
Diabetes mellitus	875(33.5%)
• Insulin treated diabetes mellitus	208(8.0%)
Current smoking	768(29.4%)
Hypercholesterolemia	1539(58.9%)
Hypertension	1842(70.5%)
Family history of CAD	652(24.9%)
Congestive heart failure	192(7.3%)
Chronic renal failure	170(6.5%)
Peripheral arterial disease	142(5.4%)
Previous stroke	113(4.3%)
Previous MI	605(23.1%)
Previous PCI	665(25.4%)
Previous CABG	138(5.3%)
AF/Flutter	180(6.9%)
Cardiac status	
• Asymptomatic	241(9.2%)
• NSTEMI	408(15.6%)
• STEMI	604(23.1%)
• Stable angina	905(34.6%)
• Unstable angina	456(17.4%)
Discharge medications	
Aspirin	2580(98.7%)
$P2Y_{12}$ inhibitor	
• Clopidogrel	1833(70.1%)
• Prasugrel	83(3.2%)
• Ticagrelor	687(26.3%)
• Ticlopidine	5(0.2%)
• None	5(0.2%)
Statin	2485(95.1%)
ACE inhibitors or ARB	1922(73.5%)
Beta-blockers	1991(76.2%)
Calcium channel blockers	565(21.6%)
Long-acting nitrate	502(19.2%)
Ranolazine	11(0.4%)
Anticoagulation	205(7.8%)
• Apixaban	11(5.4%)
• Dabigatran	18(8.8%)
• Rivaroxaban	10(4.9%)
• Warfarin	99(48.3%)
• Acenocoumarol or Other	34(16.6%)
Proton pump inhibitor	1354(51.8%)

Numbers are presented as N (%) unless indicated otherwise.
ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; NSTEMI, non-ST segment elevation MI; STEMI, ST segment elevation MI; PCI, percutaneous coronary intervention.

Table 2
Procedural patient characteristics.

	$N = 2614$
Arterial sheath size (Fr)	
• 4Fr	5 (0.2%)
• 5Fr	142 (5.8%)
• 6Fr	2156 (88.1%)
• 7Fr	140 (5.7%)
• 8Fr	5 (0.2%)
Radial access	1800(70.4%)
Vascular closure device successfully deployed	419(18.2%)
Number of vessels diseased	
• One	1258(48.1%)
• Two	825(31.6%)
• Three	531(20.3%)
Left main disease ≥50%	257(9.8%)
Left ventricular ejection fraction (%)	52.9 ± 11.6
Multivessel PCI	464 (17.8%)
Vessel treated	
• Left main	59 (2.3%)
• Left anterior descending artery	1349 (51.6%)
• Left circumflex artery	619 (23.7%)
• Right coronary artery	892 (34.1%)
• Bypass graft	42 (1.6%)
At least one ACC/AHA B2/C lesion	1509(57.7%)
At least one lesion with CTO	118(4.5%)
At least one lesion with heavy calcification	469(17.9%)
At least one lesion with thrombus present	448(17.1%)
PCI with combo stent in at least one lesion	2608(99.8%)
Total number of combo stents implanted, mean ± SD	1.29 ± 0.65
Total length of combo stents implanted (mm) for all lesions, mean ± SD	26.93 ± 17.83
Maximum diameter of largest combo stent (mm), mean ± SD	3.16 ± 0.43
IVUS or OCT use	136 (5.2%)
Total contrast (mL), Mean ± SD	172.0 ± 76.1
Peri-procedural medications	
Unfractionated heparin	2461 (95.4%)
Low molecular weight heparin	492 (19.1%)
Bivalirudin	19 (0.7%)
Glycoprotein IIB/IIIA inhibitors	279(10.7%)
Procedural complications	59(2.3%)
Complication type	
• Cardiac arrest	2(0.08%)
• Dissection (grade C or above)	6(0.23%)
• Perforation	6(0.23%)
• Distal embolization	4(0.15%)
• Side branch compromise	9(0.34%)
• No reflow (TIMI 0/1), sustained	1(0.04%)
• No reflow (TIMI 0/1), transient	1(0.04%)
• Slow reflow (TIMI 2), sustained	2(0.08%)
• Slow reflow (TIMI 2), transient	2(0.08%)
• Other	26(1.00%)

Numbers are presented as N (%) unless indicated otherwise.
ACC/AHA, American College of Cardiology/American Heart Association; CTO, chronic total occlusion; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

The predecessor of COMBO DES, the Genous stent, was shown to result in greater endothelialization in porcine coronaries [15], as well as faster endothelialization in human femoral extracorporeal AV shunts [16]. Further, Beijk et al. observed low rates of cardiac death, spontaneous MI and TLR with the Genous compared to paclitaxel eluting stents (PES) in patients at high risk of restenosis [24]. In the first coronary randomized controlled REMEDEE trial, Haude et al. noted lower rates of neointimal hyperplasia with COMBO stent compared to PES; the rate of in-stent late lumen loss with the COMBO stent was non-inferior to PES (0.39 ± 0.45 mm versus 0.44 ± 0.56 mm, $p = 0.0012$ for non-inferiority) [13]. The EGO-COMBO study showed a low 3-year rate of MACE with evidence of neointimal regression from 9 to 24 months after PCI with the Combo stent [25].

In keeping with these data, we observed a low rate of TLF in this all-comer population with more than half the enrolled patients undergoing PCI for ACS, one-fifth undergoing PCI for STEMI and 33.5% patients with diabetes mellitus. With respect to procedural characteristics, more than half of treated lesions were ACC/AHA B2/C type lesions with a mean stent length that was comparable to other contemporary BDP PCI studies. While the rate of intravascular imaging use was in keeping with use in real world cohorts [26], 56% stents were post-dilated, with final TIMI flow 3 in >97% and similarly high rates of procedural success. Our findings of low TLF were associated with low rates of all stent related endpoints – target vessel MI, ST and TLR. Indeed, the incidence of composite definite or probable ST and the rates of definite – acute, subacute or late ST were extremely low. These findings support the mechanistic synergy between SES technology in a resorbable polymer and EPC capture for superior efficacy outcomes.

Our findings are also consistent with the results of the REMEDEE registry, which has shown favorable outcomes with this stent platform

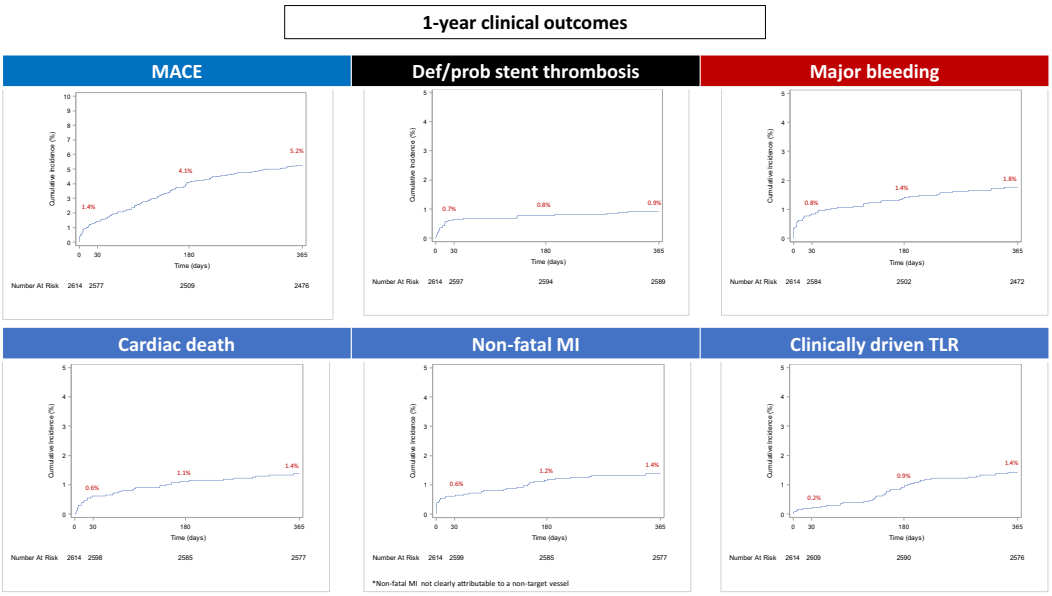

Fig. 2. Cumulative incidences from Kaplan Meier estimates of the first time to event occurrence of clinical adverse events during 1-year follow up.

up to 2 years [17,18]. The rate of 1-year TLF in that registry was 5.7%, which was mainly driven by 4.4% TLR, however, the rates of cardiac death were comparable to our study. The higher rates of TLR compared to our rates occurred in the setting of somewhat greater stable angina presentations but lower prevalence of diabetes mellitus. This difference in TLR rates between the two studies may be a function of differences in TLR endpoint reporting, whether clinically driven and unplanned or not; as well as a potential reflection of regional factors influencing patient presentation to hospital with recurrent chest pain. Nevertheless, lower event reporting from some sites cannot be excluded. In other sub-analyses from the REMEDEE registry, satisfactory TLF outcomes were noted with the COMBO stent in ACS patients and non-insulin treated diabetes mellitus (non-ITDM) patients, albeit ITDM patients had significantly high rates of TLF compared to non-DM patients [27,28]. The TLF results from the REMEDEE registry and the current study are also largely aligned and indeed somewhat superior to the results from contemporary BDP and metallic second-generation stent trials in mostly all comer patient populations [5–11]. A recent propensity adjusted analysis of the REMEDEE registry and the DUTCH PEERS TWENTE II cohorts showed similar rates of 2-year TLF (7.9% vs. 8.0%) [29].

While the REMEDEE registry demonstrates efficacy up to 2 years, bleeding and DAPT cessation outcomes during follow-up were not systematically recorded. In the current study, we noted that the incidence of major bleeding was 1.8% and minor bleeding was 2.4%. This was in the context of radial access for PCI in 70.4%, primary use of UFH for anticoagulation, ~10% use of 2b3a inhibitors and prescription of potent $P2Y_{12}$ therapy in under one third of patients. Conversely to our enrolled sample of patients who had some baseline risk factors for bleeding, the LEADERS FREE trial included all high bleeding risk patients who despite receiving only one month of DAPT, had a major bleeding rate of 7.2% [30]. However, 33% of LEADERS FREE patients were discharged on triple therapy and nearly 38% remained on oral anticoagulation up to 12 months.

Among the patients that discontinued DAPT based on physician recommendation, this was mainly for $P2Y_{12}$ inhibitors rather than aspirin. On the other hand, DAPT interruption occurred in only <1% of patients over the study period. Certainly, our rates of DAPT disruption and interruption are lower than that reported in the PARIS registry, where 9.8% disrupted DAPT and 4.6% interrupted DAPT at 1-year [22]. However, PARIS included two-thirds of US enrolled patients, who preferentially showed these behaviors, in contrast with European patients who displayed cessation rates nearer to our study [31]. Thus, geography and regional or cultural influences across the enrolling MASCOT sites, may provide some explanation for the modes and rates of DAPT cessation.

In exploratory time dependent analyses, DAPT discontinuation was not associated with greater risk for ischemic or bleeding outcomes in COMBO stent treated patients. Conversely DAPT disruption was associated with significant increase in risk for 1-year MACE. Patients with brief DAPT interruption did not experience any adverse outcomes during follow-up (Supplementary Table 4). These results are consistent with the findings from the PARIS registry indicating that physician assessment led decisions for DAPT cessation lowered risk whereas non-compliance and patient triggered decisions to stop DAPT without consultation resulted in increased hazard for clinical events [22]. Importantly, many enrolled patients had some risk factors for bleeding; in these patients the COMBO stent may have a particular role for permitting reduced DAPT duration without trade-off from increased ischemic events. Results from the COMBO REDUCE trial suggest that where necessary short DAPT duration of 3 months vs. 12 months in ACS patients treated with the COMBO stents may be a feasible approach [32]. We were however surprised by the low rate (5.6%) of DAPT discontinuations in this study within the first 6 months, despite current updates to the guidelines [33,34], which may be a reflection of physician equipoise until randomized data become available with this stent platform. Data from the recently presented HARMONEE trial (clinicaltrials.gov identifier NCT02073565) in 600 US/Japanese patients provide evidence for non-inferiority of this novel platform compared to best in class everolimus eluting stents [35]. Further data from two randomized controlled trials SORT OUT X (NCT03216733) and RECOVERY (NCT02542007) are awaited.

5. Limitations

MASCOT was a post-marketing observational study. There was no angiographic core laboratory for analysis of procedural data. We did not have angiographic follow up for detection of binary restenosis. Adherence to DAPT was estimated based on patient self-report without systematic pill counts.

6. Conclusions

The MASCOT post marketing registry provides comprehensive safety and efficacy outcomes following contemporary PCI using the novel

COMBO dual therapy stent. In all-comers, COMBO DES was associated with low rates of 1-year TLF, ST and MACE with high rates of device and procedural success. One in five patients had physician recommended DAPT cessation within the first year, which was not associated with increased risk of ischemic adverse outcomes. In addition to randomized trial evidence from the HARMONEE trial, the large-scale SORT OUT X trial will provide objective data with the COMBO stent compared to contemporary DES to facilitate wider uptake.

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Conflict of interest

Dr. Mehran has received institutional grant support from The Medicines Company, Astra Zeneca, Bristol-Myers Squibb/Sanofi, and Eli Lilly and Company/Daiichi Sankyo; and is a consultant to Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, Janssen Pharmaceuticals, Regado Biosciences, Maya Medical, Merck & Co., and The Medicines Company. Dr. Stephen Rowland, Ms. Debbie Morrell and Ms. Francesca Elmore are employees of OrbusNeich Medical, Ft.Lauderdale, Florida, USA. All other authors report no relevant conflicts of interest.

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