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Optimal duration for dual antiplatelet therapy with COMBO dual therapy stent

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The COMBO stent (OrbusNeich Medical BV, the Netherlands) is a stainless-steel platform with the biodegradable abluminal coating containing antiproliferative sirolimus (5 mg/mm) and the luminal stent surface covered with anti-CD-34 antibody. The CD-34 antibodies essentially capture endothelial progenitor cells resulting in rapid re-endothelialization of the treated segment. This characteristic was initially demonstrated in *in-vitro* models, and its safety proven in the larger randomized clinical trials with dual therapy stents.[1–3] The REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus-coatED bio-Engineered StEnt) Trial was the first human trial comparing COMBO stents to the paclitaxel drug eluting stents (Taxus Liberte, Boston Scientific, Marlborough, Massachusetts). High initial procedural success, low revascularization rates, and low stent thrombosis rates were observed in all these patient populations. The trial protocol dictated a dual antiplatelet therapy (DAPT) for a duration of 6 months in elective cases and for 12 months in patients diagnosed with an acute coronary syndrome (ACS).

DAPTs bear the risk of bleeding events after successful percutaneous coronary intervention (PCI) and are independently associated with an increased mortality and morbidity.[4,5] The European Society of Cardiology (ESC) Guidelines on dual antiplatelet therapy in coronary artery disease (CAD) currently encourage every effort in minimizing such bleeding complications, and an optimized DAPT regimen is inherent in circumventing this risk.[6]

Several studies investigated the use of DAPT (ASA and clopidogrel) for three months in patients with stable CAD.[7,8] However, these trials used the Endeavor zotarolimus-eluting stent in the 3-month DAPT arms.[6]

We hypothesised that the novel characteristics of the COMBO stent allowed a safe reduction in the proposed duration of DAPT to three months in patients with stable coronary artery disease. Furthermore, we attempted to provide more insight into the clinical outcomes of patients treated with the COMBO Stent on different DAPT regimens.

This study was a monocentric, prospective clinical trial among patients receiving the COMBO dual therapy drug-eluting stent (DES). This study was investigator-initiated and free of industry financial support.

A total of 108 patients successfully treated with the COMBO stent in routine clinical practice were enrolled to the trial. Informed consent for participation in the registry was obtained immediately after successful COMBO stent implantation. All patients were included to this study in a consecutive manner, i.e., the first half were allocated to the 6 months DAPT group, while the second half comprised patients receiving DAPT for three months. The exclusion criteria outlined patients unable to take part in the follow up visits, as well as in cases where the life expectancy was less than one-year, or where existing clinical states required prolonged (i.e., longer than six months) DAPT regimens such as ACS, myocardial infarction or complex coronary revascularisations. Patients requiring therapeutic anticoagulation or triple therapy were also excluded from the study.

Patients were contacted after 180 days and after one year by telephone or during scheduled clinic visits. If the patients could not be reached by telephone, general practitioners or treating cardiologists were contacted to provide details concerning the current clinical state of the patient. Standard questionnaires were used to evaluate the clinical status and any adverse events. These include questions on all events including death, myocardial infarction (MI), stroke, rehospitalisation with the need of revascularisation and any bleeding events. If the patients were hospitalized due to adverse events, hospital records were obtained to assess its severity.

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Major adverse cardiac events (MACE) including death due to all-cause, stroke, MI and target lesion revascularisation (TLR) were defined as the primary outcomes of the study. The diagnosis of MI was based on the third universal definition of MI.[9] Stent thrombosis was defined according to Academic Research Consortium criteria.[10] Any repeat revascularisation by PCI or coronary artery bypass grafting (CABG) of the target lesion was defined as TLR. The PCI and stent implantation were considered as successful if postprocedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 and < 20% residual stenosis could be achieved. The secondary endpoint of the study were bleeding events. The severity was assessed according to BARC criteria.[11] All clinical events that occurred before the discharge were defined as in-hospital adverse events.

Continuous variables with a normal distribution are present as mean ± SD, continuous variables with a non-normal distribution as median (interquartile range) and categorical variables as frequency (%). The Mann-Whitney test was used to compare categorical variables. Time-to-event analyses, which were based on all available follow-up data, were performed using the Kaplan–Meier estimates.

All statistical analyses were performed using; $P \leq 0.05$ (two-tailed) was taken to indicate statistical significance. We used MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; 2015) to calculate the statistical results of the study.

A total of 108 patients were included to our study at the University Medical Centre Mannheim, Heidelberg University, Germany, between August 2014 and September 2016. The baseline characteristics are shown in Table 1. The mean age of the patient was 68 ± 11 years, with a male predominance in both groups. The incidence rates for diabetes mellitus, arterial hypertension, smoking history and hyperlipidaemia were similar in both groups without any significant differences. The 3-month DAPT group had significantly higher rates of patients with chronic kidney disease (29.1% *vs*. 5.55%; $P = 0.0019$). Other baseline demographics such as history of previous MI or CABG, as well as stroke were identical in both the groups. A comparison of echocardiographic indices revealed no significant statistical differences. The bleeding risk, as assessed by the HASBLED score was slightly higher in the first group (1.98 *vs*. 1.75), however without any statistical significance ($P = 0.262$).

The main characteristics are listed in the Table 2. The burden of CAD was similar in both the groups. Some trends are obvious, however without statistical significance: LAD was target lesion more frequent in the 6 months group (34.5% *vs*. 50.9%; $P = 0.0894$); RCX (29.1% *vs*. 17.0%; $P = 0.1441$) interventions were more common in the first group. Data concerning the number of stents, length and

Table 1. Baseline demographics.

	3 month DAPT	6 month DAPT	*P* value*
Patients, *n*	55	53	
Male	60%	73.6%	0.1406
Age, yrs	68.04 ± 11.03	68.28 ± 11.19	0.8082
Body mass index, kg/m^2	30.20 ± 8.03	28.39 ± 5.05	0.2794
Diabetes mellitus	41.8%	35.8%	0.5307
Hyperlipidaemia	40%	39.62%	0.895
Chronic kidney disease	29.1%	5.66%	0.0019
NYHA class of heart failure	1.43 ± 1.35	0.47 ± 0.86	0.001
Hypertension	76.4%	84.9%	0.2738
History of smoking	43.6%	47.2%	0.7161
Family history of coronary artery disease	12.7%	9.43%	0.6011
Previous myocardial infarction	24.1%	18.9%	0.5216
Previous CABG	3.64%	7.55%	0.4116
Previous stroke	9.09%	7.54%	0.7341
CCS class	1.76 ± 1.31	1.58 ± 0.81	0.3357
Ejection fraction			
> 50%	63.6%	73.6%	0.2737
31%–50%	20%	20.8%	0.9242
< 30%	5.45%	1.89%	0.3801
HASBLED	1.98 ± 1.06	1.75 ± 0.85	0.2962

Data are presented as mean ± SD or *n* (%). *Mann-Whitney Test. CABG: coronary artery bypass graft; CCS: Canadian Cardiovascular Society Grading of Angina; DAPT: dual antiplatelet therapy; NYHA: New York Heart Association Heart Functional Classification.

Table 2. Descriptive morphology of coronary artery disease and periprocedural characteristics.

	3-month DAPT	6-month DAPT	*P* value*
Vessel disease, %			
1-vessel disease	36.36	43.39	0.4619
2-vessel disease	27.27	26.41	0.9214
3-vessel disease	36.36	30.18	0.5030
Target vessel, %			
LAD	34.5	50.9	0.0894
RCX	29.1	17.0	0.1441
RCA	32.7	30.18	0.7800
Bypass graft	3.63	1.89	0.6320
Degree stenosis, %	81.45	83.28	0.3867
Stent details			
Number	1.3636	1.1321	0.0975
Diameter, mm	2.88	2.80	0.2033
Length, mm	18.96	19.73	0.1200
Direct stenting	65.5%	45.3%	0.0375

*Mann-Whitney test. DAPT: dual antiplatelet therapy; LAD: left anterior descending artery; RCA: right coronary artery; RCX: ramus circumflexus.

Table 3. In-hospital and one year clinical follow–up.

	3 month DAPT	6 month DAPT	*P* value*
In-hospital follow up			
Death	0	0	-
Myocardial infarction, %	0	1.89	0.4693
Stroke	0	0	-
MACE, %	0	1.89	0.4693
Target lesion revascularisation, %	0	1.89	0.4693
Severe bleeding complications	0	0	-
Hospitalisation > 3 days, %	50.90	26.41	0.0101
6 months follow up			
Death, %	1.82	0	0.4856
Myocardial infarction, %	0	1.89	0.4693
Stroke	0	0	-
MACE, %	1.82	1.89	0.9828
Target lesion revascularisation, %	0	1.89	0.4693
Bleeding, %			
Minor (BARC 1, 2)	0	3.77	0.4693
Major (BARC 3–5)	0	0	-
One year follow up			
Death, %	3.63	0.0	0.3646
Myocardial infarction, %	0	1.89	0.4693
Stroke, %	1.82	0	0.4856
MACE, %	10.9	5.66	0.3494
Target lesion revascularisation, %	1.82	3.77	0.5924
Bleeding, %			
Minor (BARC 1,2)	1.82	7.55	0.3402
Major (BARC 3–5)	0	0	-

*Mann-Whitney Test. BARC: The Bleeding Academy Research Consortium Score; DAPT: dual antiplatelet therapy; MACE: major adverse cardiac events.

diameter also corresponded between the groups. A significant difference between the groups could, however, be established in situations where direct stent implantation occurred without previous vessel balloon dilatation: 65.5% in the first group and 45.3% in the second group ($P = 0.0375$).

Definitive stent thrombosis occurred in a single case; a patient from the 6 months DAPT group developed MI within 24 h of intervention due to acute stent thrombosis with the need for target vessel revascularisation. Post-interventional bleeding was not observed during in-hospital stay.

The six months follow up was performed in the whole study population. A total of three patients died during the first six months, with one patients' death attributed to a non-cardiac cause. Two minor bleeding events (BARC 1–2) occurred in the 6 months group of patients, the 3-month group did not present with any bleeding complications.

At the 12-months follow-up, a 10.9% MACE rate was observed in the 3-months group and 5.66% in the 6 months group ($P = 0.3494$). The rate of TLR was respectively 1.82% and 3.77% ($P = 0.5924$). The total bleeding rate was 1.82% in the 3 months group and 7.55% in the 6 months group ($P = 0.3402$). No severe bleeding events (BARC 3–5) were reported among any patients included in this study (Table 3).

The optimal duration of DAPT after PCI for stable CAD is still not clearly defined. Additionally, there are few studies focussed on stable CAD patients undergoing PCI and exposed to different DAPT regimes. The current ESC DAPT guidelines are heterogeneous for stable CAD patients undergoing PCI.[6]

It is well known that prolonged DAPT has been associated with higher major bleeding rates,[12] with the reported incidence of major and minor bleeding anywhere between 1.8% to 5.1% in the current patient population. A higher incidence of bleeding episodes can impact patients' compliance and could result in the premature discontinuation of DAPT.[12,13]

In addition to bleeding risk, DAPT regimens are also influenced by the type of stent used. The first generation of DES with paclitaxel surface drug benefitted from extended DAPT, reducing risk of stent thrombosis and MACCE.[14,15] Shortened DAPT duration had generally overall lower rates of bleeding yet higher rates of stent thrombosis as compared to the prolonged DAPT regimens. However, this adverse effect was significantly attenuated with the use of the newer generation of DES.[16] The RESET trial with zotarolimus-eluting stents showed the non-inferiority of a 3-months DAPT treatment regime when compared to 12 months of DAPT treatment.[8] The same conclusion of noninferiority was highlighted in the other zotarolimus-eluting stent study—OPTIMIZE Trial.[7] Zotarolimus-eluting stents were used in both studies and the comparison was made between 3-months and 12-months groups. A lack of other randomized controlled studies with newer generation DES, comparing 3-month and 6-months of DAPT in the stable CAD patient, naturally leads to the question if 3 months of DAPT is non-inferior in all such cases.

In the Combo Stent non-inferiority study (REMEDEE Trial), all subjects were treated with DAPT for at least 6 months up to a duration of 12 months.[2] Our study is perhaps the first of its kind that summarizes trial data on the clinical outcomes of patients with the Combo dual therapy stent treated with three months of DAPT. The promulgated dual therapy concept of promoted epithelisation has led us to believe that patients receiving the COMBO stent are suitable for a shortened course of DAPT. However, the small size of our patient population restricts the power of

our study to suitably clarify this claim on COMBO stents. We observed the number of adverse events and could not find any statistical significance. However, some observations are obvious: observed TLRs were not associated with DAPT duration: the single case of stent thrombosis occurred during the first 24 hours, while other TLRs occurred after 6 months of DAPT. We also observed a higher bleeding rate, without statistical significance in the six months DAPT group. It is clear that our results are not applicable to the other types of DES and that our study is not powered enough to recommend a 3-month DAPT regimen for the COMBO stent. However, we believe that our findings can be a new challenge for future large randomized controlled studies to clarify if a 3 months DAPT regimen is non-inferior to a 6 months DAPT regimen.

Our clinical trial compared different DAPT regimes in patients receiving the COMBO stent. We observed after a follow-up of 12 months, that a shortened DAPT regimen was safe and efficient.

One of the main limitations is the monocentric design of the study and the lack of blind randomization. Therefore, the therapy regime was not blind and was familiar both to the investigators and to the study participants. The results of the study should be interpreted with caution in light of the small sample size. The events' rate was relatively low and needs to be evaluated in large multicentre registries.

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