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### Dual-therapy stent technology for patients with coronary artery disease

*A great catch?*

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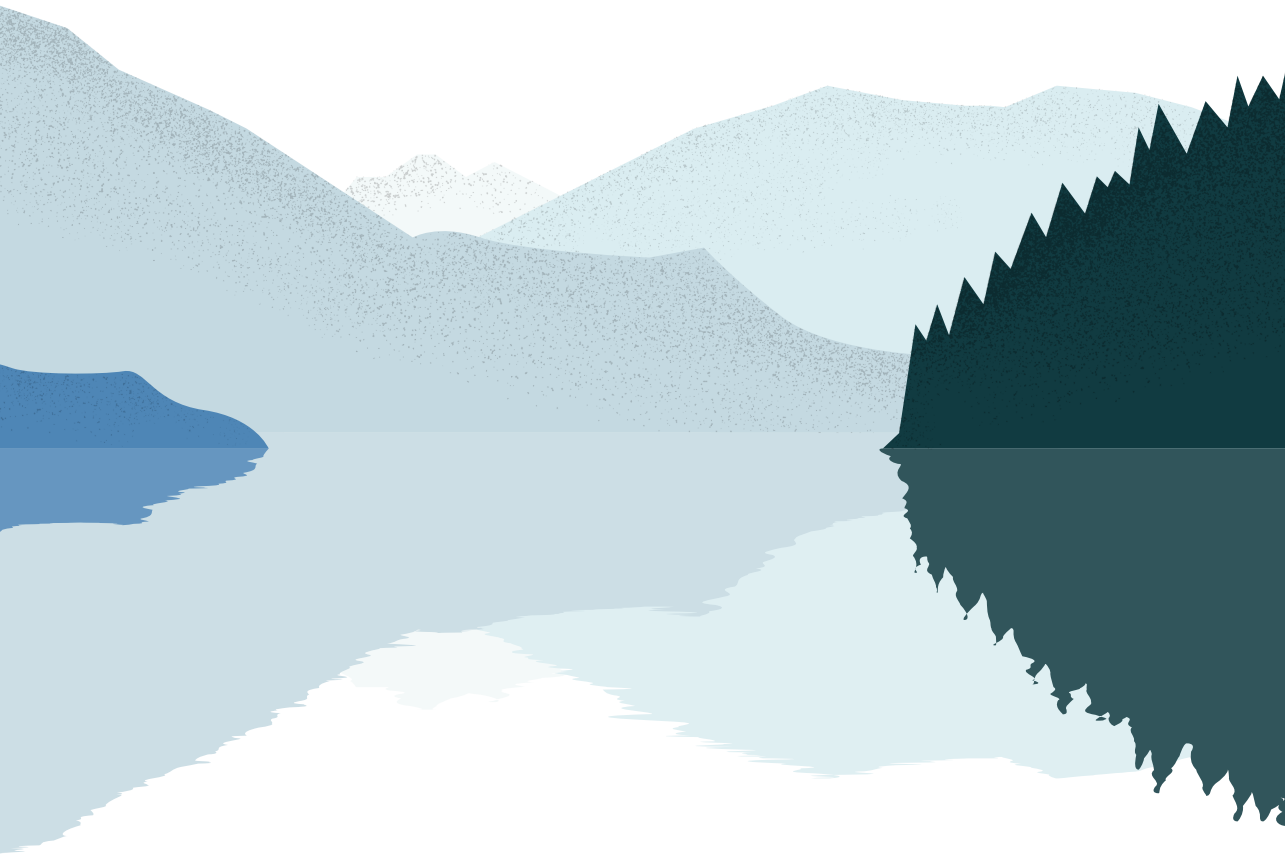
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# Chapter 6

## Two Year Clinical Outcomes of Patients Treated with the Dual-Therapy Stent in a Thousand Patient All-comers Registry



**Kalkman DN**, Woudstra P, Menown IB, den Heijer P, Suryapranata H, Iñiguez A, Arkenbout KE, van 't Hof AW, Muller P, Erglis A, Tijssen JG, Beijk MAM, de Winter RJ

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## ABSTRACT

**Objective** The dual-therapy stent combines an abluminal biodegradable drug-eluting coating, with a 'pro-healing' luminal layer. This bio-engineered layer attracts circulating endothelial progenitor cells that can differentiate into normal endothelium. Rapid endothelialization of the stent might allow safe short dual antiplatelet therapy. We aim to assess clinical outcomes in patients treated with this novel device at 2 year follow-up.

**Methods** A total of 1,000 patients were included in the REMEDEE Registry, to evaluate clinical outcomes after treatment with the dual-therapy stent. This prospective, multicenter, European registry included all-comers patients, which resulted in a high risk patient population. Target lesion failure (TLF), a combined endpoint consisting of cardiac death, target vessel myocardial infarction (tv-MI) and target lesion revascularization (TLR), at two year follow-up was the primary focus of this analysis. Subgroup analyses was performed according to Diabetic Mellitus (DM), gender, age, acute coronary syndrome, smoking, hypertension, hypercholesterolemia, previous stroke, peripheral vascular disease and chronic renal failure.

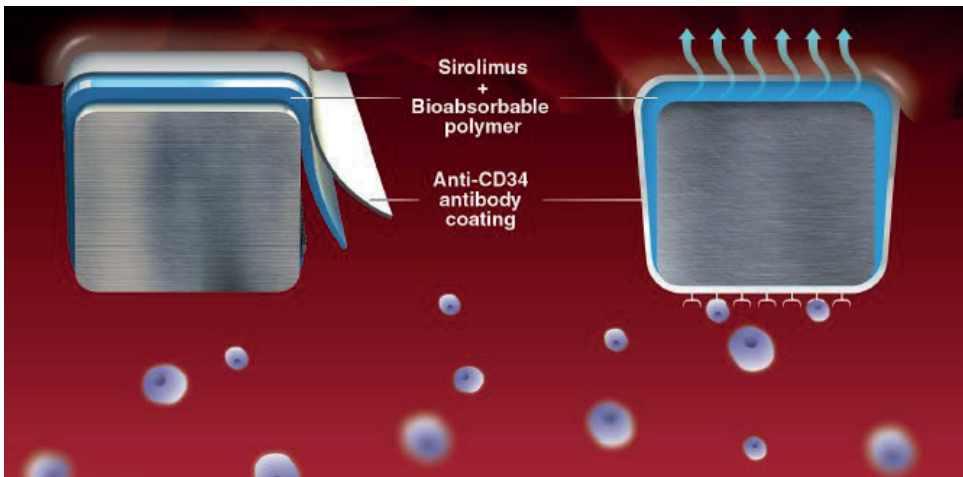
**Results** TLF at 2 years was observed in 84 patients (8.5%), with 3.0% cardiac death, 1.2% tv-MI and 5.9% TLR. Definite stent thrombosis at 2 years was 0.6%. In presence of DM or chronic renal failure, a higher TLF was observed.

**Conclusions** The dual-therapy stent shows favorable clinical outcomes from 12 months onwards. Two years after stent placement low TLF and very low stent thrombosis rates are observed in this large prospective all-comers cohort study. Clinicaltrials.gov identifier: NCT01874002.

## INTRODUCTION

Innovations in the field of drug-eluting coronary stent (DES) therapy are rapidly evolving. First-generation DES improved outcomes in terms of reduced rates of restenosis compared to bare metal stenting. (1)(2) Subsequently second-generation DES, with thinner stent struts, limus analog drugs and more biocompatible polymers, were designed to reduce the increased risk of late clinical events of DES. (3)(4)(5) The controversial term ‘third-generation’ DES is attributed to DES with newer (fully) biodegradable polymers and polymer free DES. These stents and also the bioabsorbable scaffolds try to minimize adverse outcomes. (6)(7)(8) However, no device has been able to eliminate in-stent neo-intimal hyperplasia, neoatherosclerosis and/or (very) late stent thrombosis.

The COMBO stent (OrbusNeich Medical B.V., the Netherlands) is the first dual-therapy stent (DTS), which combines the ‘traditional’ drug-eluting therapy (sirolimus in a biodegradable polymer) with an immobilized CD34 antibody that captures endothelial progenitor cells (EPC’s) from the circulation (**Figure 1**). These EPC’s can differentiate into endothelial cells on the luminal surface of the stent. (9) The hypothesis of this ‘pro-healing’ technique is that it may offer not only improved clinical outcomes, but also safe short use of dual antiplatelet therapy (DAPT). (10)(11)



**Figure 1** The COMBO stent design Illustration of the dual-therapy stent technology

The REMEDEE registry aims to provide more insight into the clinical outcomes with the COMBO stent in routine clinical practice and in an all comer setting. Currently only limited long-term data is available on clinical results with the DTS exceeding one year. (12) In this paper, we evaluate two year clinical results of the REMEDEE registry and analyze outcomes in different patient subgroups.

## **METHODS**

### **Registry design and patient population**

The study design of the REMEDEE Registry (*NCT01874002*) has been previously published. (13) In brief, the REMEDEE Registry is an investigator-initiated, prospective, European registry evaluating the first DTS, the COMBO stent. A total of 1,000 patients, in whom treatment with a COMBO stent in the setting of routine clinical care was attempted, were enrolled. DAPT was prescribed according to local guidelines. With only few exclusion criteria, a true all-comers patient population was targeted. At 30 days, 180 days, 1 and 2 year follow-up all patients were contacted for clinical follow-up by telephone call or during a scheduled outpatient clinic visit. All event documentation was collected and all events were adjudicated by an independent clinical event committee.

### **Endpoints and definitions**

In this 2-year follow-up analysis of the REMEDEE Registry, we evaluate target lesion failure (TLF), which is defined as the composite of cardiac death, target-vessel myocardial infarction (tv-MI) or target lesion revascularization (TLR). Tv-MI was defined as all myocardial infarctions (MI) unless in presence of documented proof that the infarction arose from a non-treated coronary vessel. TLR was defined as any repeat revascularization by percutaneous intervention of the treated lesion or coronary artery bypass grafting (CABG) of the treated vessel. Secondary endpoints were the individual components of the primary endpoint, target vessel failure (TVF) and stent thrombosis at 2 year follow-up. TVF was defined the composite of cardiac death, tv-MI and target vessel revascularization (TVR). TVR was defined as target vessel revascularization (any revascularization of the treated vessel by PCI or CABG). Stent thrombosis was defined according to the Academic Research Consortium (ARC) criteria ((14)).

### **Statistical analysis**

Categorical data are shown with counts and percentages, continuous variables are in mean  $\pm$  standard deviation, unless otherwise mentioned. For time-to-event data, Kaplan-Meier estimates were used for all endpoint analyses. Follow-up was censored at the last known date of follow-up, or at 24 months, whichever came first. A lost to

follow-up rate of <2% a year was deemed acceptable. All endpoints were evaluated in the unselected patient population, which consisted of all patients who were enrolled after signing an informed consent and in whom placement of a COMBO stent was attempted. Cox regression analysis was done to calculate hazard ratios for diabetic mellitus (DM) status, gender, age, acute coronary syndrome, smoking, hypertension, hypercholesterolemia, past stroke, peripheral vascular disease and chronic renal failure. Statistical analyses were performed using SPSS version 23.0 (Chicago, IL, USA).

## RESULTS

### Baseline characteristics

Between June 2013 and March 2014 a 1000 patients were enrolled in 9 European sites. The baseline characteristics are presented in **Table 1**. The mean age during baseline procedure was  $65 \pm 11$  years, and 26.1% of patients were female. At baseline, 58.0% of the patients had a history of hypertension, and 18.4% were diabetic. The registry included 30.4% of patients with an urgent indication for PCI. TIMI flow 0 was observed in 14.5% of patients and thrombus was present in 15.0% of the cases. In two patients the COMBO stent could not be placed. Mean stent length was  $21.4 \pm 10.5$ mm and mean diameter  $3.2 \pm 0.5$ mm.

### Clinical outcomes

Two year follow-up was obtained for 981 patients (98.1%). Events observed at 2 years after COMBO stent placement are listed in **Table 2**. TLF occurred in 84 patients (8.5%), as illustrated in the Kaplan-Meier curve of events found in **Figure 2**. Cardiac death was observed in 3.0% of patients (n=30), tv-MI in 1.2% (n=12) and TLR in 5.9% (n=58) (**Figure 3**). In 4 of the 5 cases of very late tv-MI angiography was performed which did not show stent thrombosis of COMBO, the 5<sup>th</sup> tv-MI was in a patient presenting with dyspnea and decompensation cordis, without chest pain but classified as non-ST-segment elevation MI. Echocardiography showed diffuse impaired LV function. Regional wall abnormalities could not discriminate location of MI, therefore the CEC classified as tv-MI. Due to absence of ST-segment elevation on inferior leads, (COMBO in RCA), the possibility of a ST was found less likely by the CEC.

A total of 70 patients underwent TVR (7.1%), resulting in a 9.7% TVF at two years. Definite stent thrombosis at 2 years occurred in 6 patients (0.6%). Five patients had ST within the first 9 days post procedure, one ACS-patient had a very late stent thrombosis at 380 days, shortly after DAPT cessation.



**Table 1.** Baseline characteristics

<b>Patient (N = 1000)</b>		
Age, yrs	65	±11
Female	26.1	
History of Diabetes	18.4	
Requiring insulin	6.4	
History of Hypertension	58.0	
History of Hyperlipidemia	56.2	
Family history of CAD	45.5	
Current smoker	24.1	
Chronic renal failure	6.1	
Prior myocardial infarction	25.3	
Prior percutaneous intervention	30.1	
Prior CABG	6.8	
Urgent indication for PCI	30.4	
<b>Lesions (N = 1255)</b>		
TIMI flow 0 pre-procedure	14.5	
Thrombus present and thrombus aspiration	15.0	10.8
AHA/ACC lesion type B2/C	58.9	
Lesion length, mm	15.0	12-20
Reference vessel diameter, mm	3.0	3.0-3.5
Percentage stenosis by visual estimate	90	80-99
Total stent length, mm	21.4	±10.5
Total stent diameter, mm	3.2	±0.5

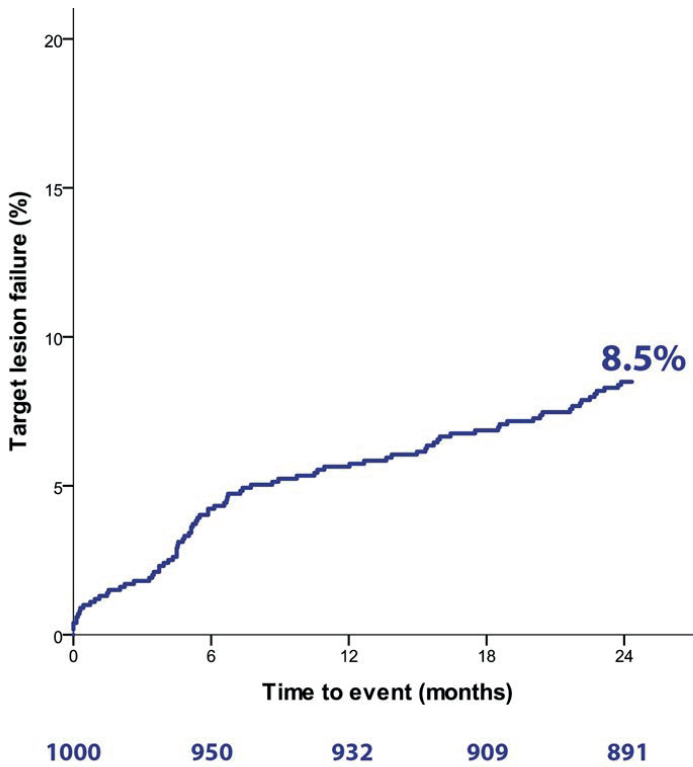
Values are valid %, mean ± SD, or median (interquartile range). CAD: coronary artery disease. CABG: coronary artery bypass graft. PCI: percutaneous coronary intervention. TIMI grade flow. AHA/ACC: American Heart Association/American College of Cardiology classification.

The influence of baseline patient characteristics (gender, age, cardiovascular risk factors, ACS, peripheral vascular disease and chronic renal failure) on two year clinical outcome is shown in **Figure 4**. The only significant univariate predictors of target lesion failure were diabetes HR 3.00 (95% CI: 1.93-4.66) and chronic renal failure HR 2.47 (95% CI: 1.31-4.67), although trends were seen with current smokers, ACS and peripheral vascular disease.

**Table 2.** Clinical endpoints at one and two year follow-up

	One year follow-up		Total two year follow-up	
	N=	(%)	N=	(%)
<b>TLF</b>	<b>57</b>	<b>(5.7)</b>	<b>84</b>	<b>(8.5)</b>
Cardiac death	17	(1.7)	30	(3.0)
Target vessel MI	7	(0.7)	12	(1.2)
TLR	43	(4.3)	58	(5.9)
TVR	48	(4.8)	70	(7.1)
TVF	62	(6.2)	96	(9.7)
Definite ST	5	(0.5)	6	(0.6)
Probable ST	1	(0.1)	1	(0.1)

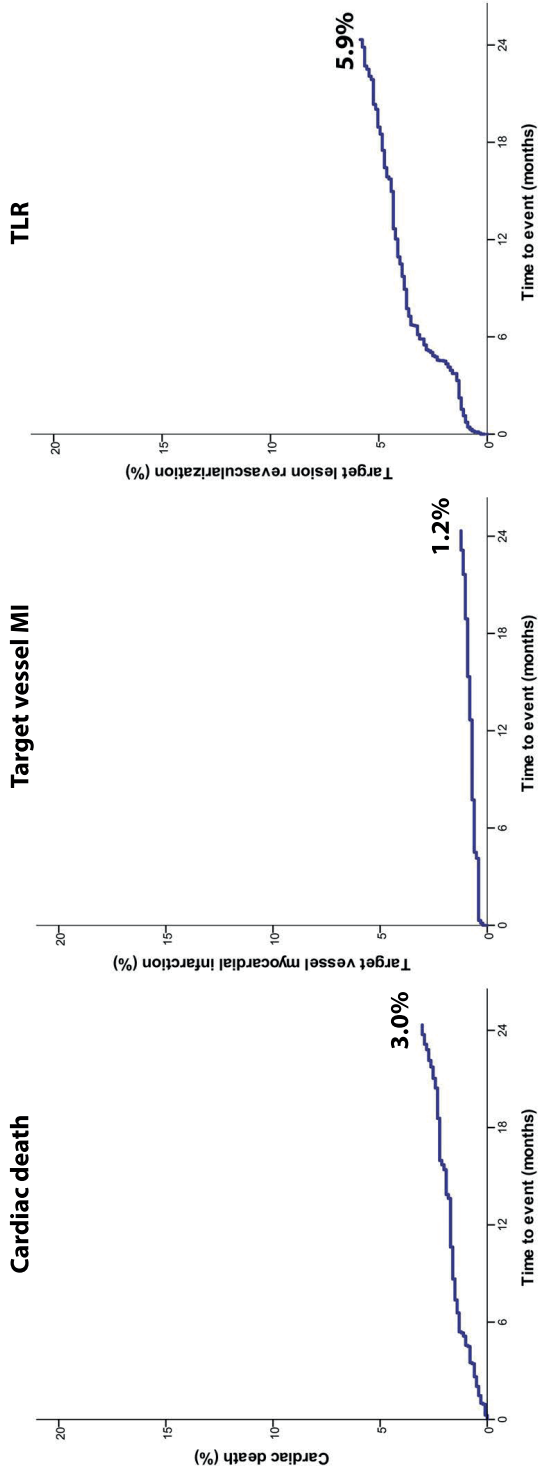
TLF: target lesion failure. MI: myocardial infarction. TVR: target vessel revascularization. TVF: target vessel failure. ST: stent thrombosis.



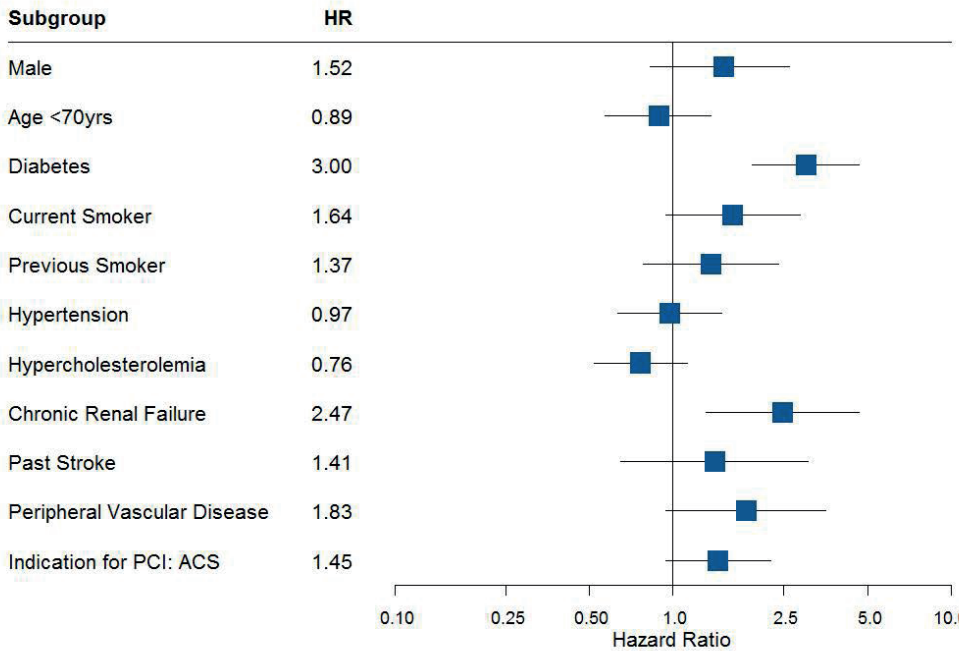
**Figure 2 Target lesion failure** Cumulative event rate of Target Lesion Failure by Kaplan-Meier method.







**Figure 3 Cardiac death, target vessel MI, target lesion revascularization by Kaplan-Meier method** A: Cumulative event rate of the individual endpoint cardiac death. B: Cumulative event rate of the individual endpoint target vessel related myocardial infarction. C: Cumulative event rate of the individual endpoint target lesion revascularization.



**Figure 4 Subgroups.** Hazard ratio (HR) of gender, age, diabetic status, smoking (current and previous), hypertension, hypercholesterolemia, chronic renal failure, previous stroke, peripheral vascular disease and acute coronary syndrome on target lesion failure at two year follow-up. PCI: percutaneous coronary intervention. ACS: acute coronary syndrome.



## DISCUSSION AND LIMITATIONS

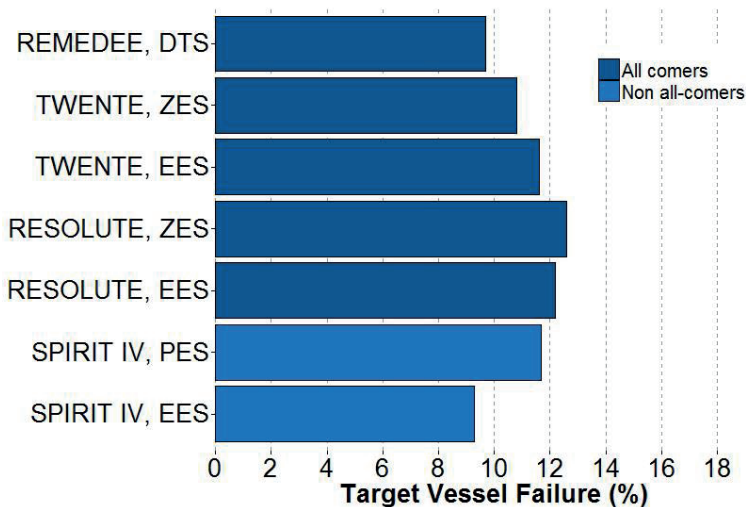
### Key findings

This study reports the clinical outcomes up to 2 year follow-up in a large prospective, all-comers cohort of patients treated with the COMBO stent. We found I) low rates of clinical events observed at 2 years after DTS stent implantation with an overall low percentage of the primary endpoint TLF of 8.5% and very late stent thrombosis in only one patient (0.1%), II) our subgroup analyses found that the DTS stent gave favourable results in several high risk patient groups although higher rates of target lesion failure were observed at 2 years in patients with diabetes mellitus and chronic renal failure higher rates of target lesion failure, III) the rate of target lesion revascularisation between 1 and 2 years follow-up was very low.

## Clinical implications

Currently only limited data are available on clinical outcomes with the DTS stent exceeding one year follow-up (12). The results presented in this study are in line with other newer generation DES (see **Figure 5**) such as the all-comers TWENTE (15) and RESOLUTE (16) all comers trials which compared a zotarolimus-eluting stent (ZES) (RESOLUTE, Medtronic, USA) with an everolimus-eluting stent (EES) (XIENCE V, Abbott Vascular, USA). In addition, compared with the 2 year outcomes of the more selected patient population SPIRIT IV trial, comparing a paclitaxel-eluting stent (PES) (TAXUS, Boston Scientific, USA) with an EES (XIENCE, Abbott Vascular, USA), reported similar outcomes. (17)

Stent thrombosis in the REMEDEE Registry was reassuringly low despite the all-comers design. In particular, very late stent thrombosis (between 12 and 24 months) occurred in only 0.1% of patients receiving the COMBO stent (which is lower than with the other devices above; EES varies 0.1-0.3, ZES 0.3% and PES 0.2%. (15–17) A recent meta-analysis by Nairooz et al. reports a two year stent thrombosis rate of the bioresorbable vascular scaffold of 2.1%.(18) The low ST rate at 2 years with the COMBO stent is a significant finding supporting the DTS technology hypothesis of low stent thrombosis risk due to early endothelialization of the stent, but caution should be taken and randomized data is needed to confirm these findings.



**Figure 5 Comparison of TVF at two year follow-up with other DES.** TVF: target vessel failure. DES: drug eluting stent. RR: REMEDEE Registry. DTS: dual therapy stent. RESOLUTE trial. TWENTE trial and SPIRIT IV trial. EES: Everolimus-eluting stent, ZES: Zotarolimus-eluting stent, PES: Paclitaxel-eluting stent.

## Neointimal regression

A recent study evaluating the healing pattern of the COMBO stent at 4 monthly groups (1:2:2:1 ratio from 2 to 5 months), 9 months and 24 months showed a new phenomenon not described earlier with any other DES: neointimal regression visualized by optical coherence tomography between 9 to 24 months. (12) This intimal hyperplasia regression has also been assessed by quantitative coronary analyses previously in the Genous stent (OrbusNeich BV, a BMS with EPC capturing layer). (19) These consistent findings may supports the hypothesis of the beneficial effect of rapid endothelialization and healthy maturation of the endothelial layer by means of EPC capture by the immobilized CD34 antibody at the stent surface. This study showed low TLR rate between one and two years (from 4.3% to 5.9%; a 1.6% increase). Moreover, these results emphasize the need for evaluation of long-term clinical results, exceeding one year follow-up, to make the true comparison of performance of these DES.

## Subgroups

Diabetes mellitus is a known risk factors for higher adverse outcome after PCI. (20) (21) We published one year clinical outcomes after COMBO stent placement of insulin treated DM, non-insulin treated DM and non-DM patients, with a clear signal of higher TLF in insulin treated DM. (22) And although patients with CKD often have DM, after multiple regression analyses in the DM group at one year, CKD was also independently associated with higher TLF. Clinical outcomes of patients with CKD and stent placement should further be explored.

## Future perspectives

The REMEDEE Registry will evaluate patients up to 5 years after COMBO stent placement, and thereby, will give further insight into the long-term treatment effect of DTS technology with COMBO. Currently the USA-Japan randomized HARMONEE trial, which evaluates clinical outcomes between EES (XIENCE family, Abbott Vascular) versus COMBO awaits completion of 1 year follow-up. This study will also obtain clinical follow-up up to 5 years too.

## Limitations

The main limitation of the REMEDEE Registry was the single-arm design. However, data collection was undertaken with great care to ensure optimum data quality. On site monitoring and full event documentation was collected for independent adjudication by the clinical event committee. Another limitation of the registry design is that the DAPT duration was not mandated by the registry's protocol, therefore the majority of patients received DAPT for one year. A potential benefit of the DTS would be illustrated more clearly if a short duration of DAPT (e.g. <6 months) after COMBO stent placement

would show the same low stent thrombosis rates. However, this study is the first large cohort to report on long-term results after COMBO stent in an all-comer patient population and provides new insight into the performance of DTS.

## **CONCLUSION**

Two year clinical results with the COMBO stent in the 1000 subject REMEDEE Registry have shown low rates of TLF, TVF and stent thrombosis. These results confirm the long-term clinical effectiveness of dual-therapy stent technology in an all-comers patient population.

## **Acknowledgments**

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## SUPPLEMENTAL MATERIAL

### Supplement I: Trial acronyms used in this manuscript.

**REMEDEE Registry:** Multicenter, Prospective, Clinical Outcomes after Deployment of the Abluminal Sirolimus Coated Bio-Engineered Stent (Combo Bio-Engineered Sirolimus Eluting Stent) Post Market Registry

**RESOLUTE trial:** Randomized, Two-arm, Non-inferiority Study Comparing Endeavor-Resolute Stent With Abbot Xience-V Stent

**TWENTE trial:** The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting Stent Study in Twente

**SPIRIT IV trial:** Clinical Trial: Clinical Evaluation of the XIENCE V® Everolimus Eluting Coronary Stent System

**HARMONEE trial:** Japan-USA Harmonized Assessment by Randomized, Multi-Center Study of OrbusNEich's Combo StEnt

