

The COMBO stent: can it deliver on its dual promise?



Roisin Colleran¹, MB BCh; Michael Joner^{1,2*}, MD

1. Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; 2. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

By effectively suppressing neointimal hyperplasia (NIH), drug-eluting stents (DES) have proven highly successful in reducing in-stent restenosis (ISR) compared with bare metal stents. However, after their introduction into clinical practice, concern emerged regarding a possible excess of late adverse events with DES as compared with bare metal stents. In particular, late stent failure due to stent thrombosis (ST) may occur at a higher rate over the medium term, at least with early-generation devices¹.

Insights from autopsy studies and intravascular imaging in patients with late ST implicate two main factors in the pathogenesis of late ST, namely impaired device healing with delayed endothelialisation and accelerated atherogenesis within the stented segment²⁻⁴. When considering approaches to target the former, it is important to note that stent endothelialisation after vascular injury occurs in one of two ways - through local recruitment of adjacent endothelial cells or by recruitment of blood-derived endothelial progenitor cells (EPC), which adhere to the surface of the device and differentiate into mature endothelial cells⁵. Delayed healing after DES occurs as a result of persistent cell inhibition from potent antiproliferative drugs, with the pro-inflammatory effect of durable polymers on some devices playing a role.

Against this background, the “pro-healing” COMBO™ dual therapy stent (OrbusNeich, Hong Kong, China) was developed. It aims to accelerate device endothelialisation, while maintaining the suppression of NIH achieved by conventional monotherapy DES⁶. To expedite endothelialisation, the stent luminal surface is coated

with immobilised anti-CD34+ monoclonal antibodies, which target binding of CD34+ antigen on circulating EPC to promote cell surface adhesion. Meanwhile, sirolimus on the abluminal stent surface is eluted from a biodegradable polymer matrix. Sirolimus is fully eluted within 30 days and the biodegradable polymer within 90 days, with the aim of reducing polymer-induced inflammation.

Preclinical studies with the COMBO stent in porcine coronary arteries have shown promising results, with more rapid endothelialisation compared with early-generation DES and less NIH compared with newer-generation DES⁵. In terms of clinical studies, the randomised REMEDEE first-in-man trial compared the COMBO stent with the TAXUS™ Liberté™ paclitaxel-eluting durable polymer stent (Boston Scientific, Natick, MA, USA) for treatment of *de novo* coronary artery lesions in patients with stable angina, and showed comparable results in terms of the angiographic primary endpoint (late lumen loss)⁷. Clinical events at 12 months were low and comparable in both groups, with no safety concerns regarding late ST.

In this issue of the journal, Lee et al report results from a sub-study of the REMEDEE trial, examining differences in vascular healing assessed by optical coherence tomography (OCT) between the COMBO and TAXUS stents⁸.

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Vascular healing was determined by strut coverage and apposition, as well as neointimal morphological analysis by OCT at nine-month angiographic follow-up. Thirty-three patients were

*Corresponding author: Deutsches Herzzentrum München, Lazarettstrasse, 36, 80636 Munich, Germany.

E-mail: joner@dhm.mhn.de

included, 23 treated with the COMBO stent and 10 with the TAXUS stent. At nine months, both stent platforms were almost completely covered (98.5% for COMBO vs. 97.6% for TAXUS, $p=0.40$), with comparable neointimal volume and thickness. The main difference between devices was in the morphology of the neointimal tissue, with the COMBO stent displaying significantly more homogeneous tissue than the TAXUS stent (79.2% vs. 40.0%, respectively, $p=0.01$), and the TAXUS stent showing a trend towards more layered or heterogeneous tissue (0.0% vs. 20.0%, respectively, $p=0.08$). Because homogeneous tissue is characteristic of mature smooth muscle cell-rich NIH, whereas heterogeneous tissue is characteristic of more immature hypocellular neointima, the authors concluded that the results suggest a favourable healing profile for the COMBO stent⁹.

Although the authors should be congratulated for reporting this detailed subgroup analysis of patients with intravascular imaging surveillance, there are some important limitations, which should be considered when interpreting the results. First, there were a number of differences other than the presence or absence of EPC capture technology between the experimental and comparator devices, which may have affected healing. The devices were coated with different antiproliferative agents (sirolimus vs. paclitaxel), eluted from different polymers (one biodegradable vs. one durable), with different drug coating distributions (abluminal vs. circumferential). Second, tissue coverage by OCT is not an indication of completeness of vascular healing. While OCT can quantify neointimal coverage, standard OCT analysis is unable to distinguish between tissue types and cannot, therefore, differentiate degrees of tissue healing. Although not performed in this study, offline greyscale signal intensity (GSI) analysis of OCT images has been shown to be capable of distinguishing immature from mature neointimal tissue in the clinical setting, with one pilot study showing that only one quarter of DES neointimal tissue observed at six-month OCT surveillance represented mature intima⁹. However, it should be acknowledged that association of immature tissue type by GSI analysis with late adverse events has not been proven thus far; therefore, the clinical relevance of these surrogate imaging parameters remains unknown.

Some insight as to whether the potentially accelerated healing with the COMBO stent translates into clinical benefit in high-risk patients can be gained from a second study also published in this issue of the journal¹⁰. Ananthakrishna et al report the results of a prospective, single-centre study including 117 patients, with a total of 147 lesions treated with the COMBO stent in the setting of primary percutaneous intervention (PCI).

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The primary endpoint of target lesion failure (TLF) at one year – defined as a composite of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularisation (TLR) – occurred in 7.7% of patients, with the individual components occurring in 4.3%, 2.6% and 3.4%, respectively. Notably, the rate of definite ST was 2.6% at one year, despite the use of newer, more potent P2Y₁₂ receptor antagonists in 85.5% of patients: two

of the three cases occurred acutely – one immediately post PCI in a patient with cardiogenic shock and vomiting, another within two hours – with no explanation despite intravascular ultrasound. The third case occurred six months post PCI in the setting of non-compliance with dual antiplatelet therapy (DAPT).

Although the high rates of ST in this study are disappointing, they are difficult to interpret on account of the non-randomised nature of the study and inclusion of very high-risk patients. Randomised studies comparing second-generation DES with bare metal stents in the setting of primary PCI have shown lower rates of ST in both arms, with rates of definite ST of 0.5% and 1.9%, respectively, in the EXAMINATION trial, and 0.9% and 2.1%, respectively, in the COMFORTABLE-AMI trial^{11,12}. However, compared with patients enrolled in randomised trials, patients included in this registry were sicker on presentation: 9.4% of patients presented in cardiogenic shock compared with only 1.2% in EXAMINATION and, although the rate of cardiogenic shock was not reported in COMFORTABLE-AMI, only 6.7% of patients presented in Killip class II-IV¹². In addition, more patients in the registry had TIMI 0 flow on presentation (82.2% compared with only circa 50% in EXAMINATION and circa 68% with 0-1 flow in COMFORTABLE-AMI). Patients in this registry also had higher baseline cardiac risk profiles, with a higher incidence of previous MI (17.1% compared with approximately 5% in EXAMINATION and COMFORTABLE-AMI), previous PCI (12.8% compared with 4% in both EXAMINATION and COMFORTABLE-AMI), and multivessel disease (55.6% compared with 12.5% in EXAMINATION), with planned staged revascularisation in one quarter. Moreover, lesions were longer (mean length 21.7 mm vs. circa 18 mm in COMFORTABLE-AMI). There were also significant differences in procedural characteristics, with high rates of thrombus aspiration in the current registry (88.9% of patients compared with circa 65% in EXAMINATION and circa 63% in COMFORTABLE-AMI), and low use of GP IIb/IIIa inhibitors (14.5% compared with approximately half of patients in both EXAMINATION and COMFORTABLE-AMI). Finally, use of intra-aortic balloon counterpulsation was higher at 6.0% vs. 2.5% in COMFORTABLE-AMI. In the absence of a comparator group in the current study, then, one might conclude that the high rates of adverse events observed may be explained by the inclusion of such high-risk patients.

Looking to the future, more data are certainly required before the place of the COMBO stent in routine clinical practice is defined. In this respect, we await with interest the results of two ongoing randomised clinical trials of the COMBO stent. The investigator-initiated REDUCE trial is investigating the safety of a shorter duration of DAPT (three months) in 1,500 patients with ACS treated with the COMBO stent, compared with conventional therapy (12 months) (NCT02118870). The primary endpoint is a composite of all-cause mortality, myocardial infarction, ST, stroke, and bleeding at one year. The HARMONEE trial, which is designed to fulfil regulatory requirements for stent approval by two major agencies (the United States Food and Drug Administration

and the Japanese Pharmaceuticals and Medical Device Agency), will compare TVF rates at one year in 572 patients treated with the COMBO vs. the XIENCE® everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA) in the setting of stable and unstable angina and NSTEMI (NCT02073565). A secondary analysis will focus on intimal tissue coverage by OCT at one year.

Overall, the COMBO dual therapy, pro-healing sirolimus-eluting stent represents an appealing concept for patients who may benefit from reduced duration dual antiplatelet therapy – such as those at increased risk of bleeding, in need of non-cardiovascular surgery, or at risk of non-compliance – owing to its endothelial-capturing coating technology in combination with antiproliferative drug release to inhibit restenosis. However, there is a long road ahead and there are many scientific hurdles to be overcome before we may be satisfied that the COMBO stent can deliver on its dual promise.

Conflict of interest statement

R. Collieran reports support from the Irish Board for Training in Cardiovascular Medicine sponsored by MSD. M. Joner reports consultancy fees from OrbusNeich International, Biotronik and AUM Cardiovascular, Inc., and lecture fees from Biotronik, OrbusNeich, Boston Scientific, and AstraZeneca.

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