Cre8™ Unique Technology in Challenging Daily Practice

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Abstract

The use of drug-eluting stents (DES) has improved clinical outcomes in percutaneous coronary intervention (PCI) procedures. However, first-generation DES were associated with safety concerns arising from the persistence of durable polymers, including late stent thrombosis. The Cre8™ DES is a novel polymer-free stent designed to overcome these issues. In a presentation at EuroPCR 2014, two clinical cases were discussed. The first was a case of high bleeding risk; the second was the case of multivessel disease with a significant risk of stent restenosis. Together, these cases illustrated the complexity of decision-making in PCI in daily practice. In both cases, the Cre8™ DES offered a safe and effective solution to these challenging cases.

Keywords

Percutaneous coronary intervention, polymer-free drug eluting stent

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The use of coronary artery stents was first described in 1986, and percutaneous coronary intervention (PCI) involving stenting is now routine practice. However the problem of restenosis, caused by neointimal tissue growth, led to the development of drug-eluting stents (DES), which allow controlled release of antiproliferative drugs at the arterial wall.¹ The use of DES has significantly improved clinical outcomes compared to bare metal stents (BMS).^{2,3} But safety issues emerged with the use of DES. These were late stent thrombosis due to delayed arterial healing of the stented segment, characterised by inflammation at the stent site with uncovered stent struts.⁴ This is caused by the persistence of durable polymers used in first generation DES. Once the drug is fully eluted, the polymers continue to interact with the vascular endothelium.

Stent technology continues to evolve, and the development of second-generation DES with novel or biodegradable polymer coatings and/or bioabsorbable struts has improved the safety profile of DES.⁵ A symposium, chaired by David Antoniucci and Roxana Mehran, at EuroPCR

on 23rd May 2014 in Paris focussed on the Cre8™ DES (Alvimedica), a novel polymer-free stent designed to address the issues associated with early DES use (see *Figure 1*). The Cre8 features a polymer-free structure to reduce the risk of inflammation associated with durable polymers and the breakdown products of absorbable biopolymers. A drug delivery system, Abluminal reservoir technology, utilises a formulation of sirolimus and a fatty acid (Amphilimus™) that enhances bioavailability and drug distribution to the entire vessel wall (see *Table 1*). In addition, the bio inducer surface, a second-generation integral pure carbon coating, is designed to accelerate stent endothelialisation and strut coverage that reduces the risk of thrombosis. The NEXT clinical trial demonstrated the efficacy and safety of Cre8,⁶ and has suggested that this DES may be useful in cases with complex anatomy. This symposium aimed to demonstrate the use of Cre8 in patients with dual antiplatelet therapy constraints, to review the clinical issues related to patients undergoing PCI at high risk of restenosis and to understand PCI strategies for the above patients, through the discussion of two case studies. ■

Case Presentation 1

PCI in a Patient with Dual Antiplatelet Therapy Constraints

Professor Ahmed Khashaba of Ain Shams University in Cairo, Egypt, presented a case of a 45-year-old man with multiple cardiovascular (CV) risk factors; a smoker for 22 years, hypertension for five years and noninsulin-dependent diabetes for two years, with glycated

haemoglobin levels (HbA1c) of 7.1 percent. He also had chronic liver disease and bleeding oesophageal varices treated by endoscopic variceal ligation three weeks previously. He presented with a non-ST elevation myocardial infarction (NSTEMI). An electrocardiogram (ECG)

showed an infero-lateral ST depression and T-wave changes. Troponin testing was positive, and haemoglobin (Hb) levels were 9.9, indicating anaemia. The patient appeared to have a simple lesion – varifocal stenosis in the right coronary artery (RCA) followed by a mobile small thrombus in the RCA. Several issues needed addressing regarding the treatment of this patient. The interventional strategy was the selection of stent technology; DES, BMS, bio active stent (BAS) or bioresorbable scaffold (BVS); the intra-procedural adjunctive pharmacotherapy and the post-procedural dual antiplatelet therapy (DAPT) strategy. Two interventional cardiologists were invited to discuss how they would treat this patient.

Professor Giuseppe de Luca of Eastern Piedmont University in Novara, Italy, highlighted the high risk of bleeding complications in this patient. Major bleeding is an important cause of mortality in PCI procedures and is associated with a number of adverse effects, including stent thrombosis (see *Figure 2*). An observational cohort study found that discontinuation of DAPT was a major determinant of stent thrombosis within the first six months following treatment with DES.⁷ The highest negative impact of DAPT discontinuation was observed within seven days of discontinuation. For patients with high risk of bleeding complications, several potential strategies are available – balloon angioplasty, drug-eluting balloon (DEB), BMS or a pro-healing stent such as Genous or Avantgarde.

In addition, the reason for DAPT cessation has an impact on cardiovascular risk. Cessation may result from discontinuation resulting from physician recommendation, interruption for surgery followed by resumption of DAPT within 14 days, or disruption due to bleeding or noncompliance. The patterns of nonadherence to anti-platelet regimens in stented patients (PARIS) registry found that the hazard ratio for stent thrombosis was 0.39 following discontinuation ($p=0.137$); 0.64 following interruption ($p=0.664$) and 2.58 following disruption ($p=0.013$). The early risk for stent thrombosis due to disruption was substantial – a hazard ratio of 15.94 at 0–7 days ($p<0.001$). The effect was attenuated over time.⁸

Since this patient is therefore at high risk for stent restenosis, the Cre8 DES represents an attractive compromise between the risk of major bleeding and the risk of stent restenosis. In addition, the patient is young and may have multivessel disease, therefore an aggressive treatment strategy is warranted. Professor De Luca therefore recommended the following – pretreatment with DAPT (aspirin and clopidogrel 300 mg), PCI using a radial approach, fractional flow reserve (FFR) of the left anterior descending artery (LAD) to determine the degree of stenosis, administration of heparin, thrombectomy if required and direct stenting with Cre8, followed by postprocedural protamine and DAPT for three months.

Dr Holger Nef of the University of Giessen, Germany then provided his opinion on how he would treat the patient. Firstly, he made the observation that this is not a case of 1-vessel disease, the RCA is clearly stenosed but there may be intermediate stenosis of the left coronary artery (LCA), which may not have been detected by visual assessment. Dr Nef emphasised the limitations of visual assessment – in a study in which four experienced visual interventional cardiologists compared their visual assessment of lesions to FFR measurements, the experts classified lesions correctly only in approximately 50 % of cases each.⁹ Dr Nef considered that we have insufficient information about the lesions and need to see more. He therefore recommended FFR in the ramus circumflex (RCX). The FAME II clinical trial indicated that

Figure 1: Features of the Cre8™ Drug-eluting Stents

Table 1: Properties of the Amphilimus™ Technology

Specific properties/contributions	
m-Tor inhibitor drug	Organic acid (Amphiphilic carrier)
• Immunosuppressant	• Sustained drug elution timing
• Anti-proliferative action	• Modulated drug bioavailability
• Anti-microbial	• Raised homogeneous drug distribution
• Inhibitor of inflammatory cell activities	• Enhanced drug stability

Figure 2: Problems Associated with Major Bleeding Risk During Percutaneous Coronary Intervention

ASA = Aspirin; Clop = clopidogrel

FFR-guided PCI plus the best available medical therapy, as compared with the best available medical therapy alone, is the optimal strategy in stable coronary artery disease (CAD).¹⁰

In terms of the choice of stent, the use of a stent that is too short may damage the necrotic core, therefore intravascular imaging is needed. Two other factors should be taken into account; the patient has diabetes, a predictor of in-stent restenosis,¹¹ and also is at a high risk of bleeding. The Zotarolimus-eluting Endeavour sprint stent in Uncertain DES candidates (ZEUS) trial, an open-label randomised clinical trial involving 1,600 individuals, aims to assess whether the use of DES, followed by DAPT, is superior to BMS.¹² Outcomes at one year show that major adverse cardiac events (MACE) are lower for patients implanted with a DES compared with a BMS, with less target vessel revascularisation in the DES group and no difference in bleeding events between the two groups.¹³

Dr Nef recommended the following – clarification of the significance of the lesions in all vessels using FFR, use of intravascular imaging,

implantation of a DES and treatment with DAPT (aspirin and ticagrelor) for as long as needed but as short as necessary, not longer than six months.

Professor Khashaba returned to describe how he actually treated this patient. The major difficulty in this case was balancing the risk of bleeding against the risk of thrombosis and restenosis. The bleeding risk was calculated as a HAS-BLED score of four and a Glasgow-Blatchford gastrointestinal bleeding score of 10, indicating a high risk of bleeding. Risk factors for thrombosis/restenosis included the NSTEMI, visible thrombus, diabetes and a long atheroma. However this was in a large vessel (4 mm) with good distal vessel flow. The options were therefore balloon angioplasty, a BMS or a DES. In a patient with such a high bleeding risk, a stent needs to provide the safety of a BMS with the efficacy of a DES. The Cre8 DES (4.00 x 31 mm) was then chosen because of its decreased risk of stent thrombosis.¹⁴ The patient was kept only on aspirin because the risk of bleeding from the upper gastrointestinal tract is higher with clopidogrel.

Following stent implantation, the patient did very well, with no recurrence of variceal bleeding and a correction of anaemia.

However, 15 weeks later he experienced accelerating angina and anterior dynamic T-wave changes. A lesion in the LAD was detected, and a second Cre8 DES was implanted. FFR would have given this information prior to the initial procedure. A BMS was not considered appropriate because of the evidence of disease progression and the risk of restenosis. The risk of rebleeding was now low and the decision to use clopidogrel passed by a gastroenterologist. The risk of thrombosis was high because of the unstable angina, lack of visible thrombus, diabetes and the fact that the affected vessel was small (3 mm). However, the atheroma was not very long, and a good distal vessel flow was observed. Following stent implantation, short-term DAPT was recommended for three months (clopidogrel 75 mg every other day and aspirin 81 mg/day). This regimen kept the patient's P2Y12 reaction units (PRU) between 142–155 on serial measurements.

The take-home message from this case presentation was that patients with a high risk of bleeding represent a significant challenge during PCI, even with simple lesions. ■

Case Presentation 2

PCI in a Patient Undergoing PVI at High Risk of Restenosis

Dr Mathias Vrolix of Ziekenhuis Oost Limburg in Genk, Belgium, presented the case of a 57-year-old female who was obese (body mass index [BMI] 31.7); other risk factors included type 2 diabetes, a familial history of cardiovascular disease (CVD) and hypercholesterolaemia (LDL 3.6 mmol/L). The patient had a recent diagnosis of breast cancer and had undergone a lobectomy six weeks previously. Nodal metastasis had been detected and chemotherapy suggested. Exercise tolerance testing (ETT) was not performed because the patient presented with unstable angina. However, nothing specific was seen on an ECG. The patient was admitted to hospital for diagnostic coronary angiography, which revealed one lesion in the RCA as well as LCA lesions in the circumflex (CX) and LAD. This patient was therefore diagnosed with 3-vessel disease and a SYNTAX score of 14. The FFR in the RCA was 0.77, in the main stem LAD was 0.71 and FFR was not performed in the CX.

Professor de Luca proposed his treatment strategy. He calculated the patient's SYNTAX score as 26, a score that would have been a clear indication for coronary artery bypass grafting (CABG) several years ago. A recent meta-analysis of 14 clinical trials found that among diabetic patients with multivessel disease and/or left main disease, CABG is superior to DES in terms of mortality.¹⁵ However, in this case, the SYNTAX score of 26 is close to the borderline (23). The patient has mostly focal, not complex lesions. The patient is relatively young and has recent cancer with metastases. These factors, together with improved stent technology and DAPT, suggest that a DES may be the appropriate strategy, and the Cre8 stent would be a good choice. The chosen approach was therefore multistep revascularisation, firstly by direct stenting of the RCA and, a few days later, stenting of the left main (LM), LAD and CX. The first step should be administration of DAPT comprising aspirin and prasugrel or ticagrelor. A radial approach should be taken. Professor de Luca recommended the following – administration of heparin and glycoprotein IIb/IIIa inhibitors (bolus) for the LM PCI, implantation of a Cre8 stent, intravascular ultrasound (IVUS) imaging, postprocedural protamine and 12 months of DAPT.

Dr Nef then presented his opinion. This is a case containing three clear stenosis – the RCA is highly stenosed, and stenoses are evident in the LAD and LM. Numerous studies support the use of IVUS to determine the degree of stenosis.^{16–20} Dr Nef recommended the use of PCI, a decision that is supported by clinical evidence – the FREEDOM trial in patients with diabetes and advanced CAD concluded that coronary artery bypass grafting (CABG) was superior to PCI in terms of rates of myocardial infarction (MI) and death from any cause.²¹ But that significance between the two techniques was only achieved at five years. At up to two years there was no difference between PCI and CABG.²¹ In view of the potentially limited life expectancy of a patient with metastatic malignancy, PCI is therefore an attractive choice. In terms of stent choice, a registry study showed that in diabetic patients, DES are associated with half the risk of restenosis compared with BMS, with similar risk of death or MI within four years in both groups.²² The ABSORB Expand trial also demonstrated the benefits of a DES in diabetic subgroups.²³ In terms of stenting procedure, a simple without kissing balloon dilatation (FKBD) is recommended as this is associated with reduced use of contrast media and shorter procedure and fluoroscopy times.²⁴ Dr Nef therefore recommends a simple procedure involving one stent.

The discussion returned to Dr Vrolix, who outlined how he actually treated this patient. He would have offered CABG since the patient's life expectancy exceeded two years but the patient refused surgery. The culprit lesion was considered to be the lateral branch of the CX. The first step was peri-procedural management using femoral access and six French, aspirin 80 mg, clopidogrel 600 mg loading dose, heparin 70E/kg according to activated partial thromboplastin time (APTT). Step two was the PCI procedure for the lateral branch. A complication occurred – a fausse route in the lateral branch of the CX resulted in a dissection of the CX. The main stem and LAD were treated as follows – lesion preparation with compliant balloons, stenting of the LAD and then the main stem, 3 x 12 mm and 3.5 x 31 mm.

Figure 3: Cre8™ DES – Sirolimus Distribution Inside the Vessel Wall

In step three of the PCI procedure, the main stem was checked and a stent implanted in the posterior descendens RCA (DES, 2 mm, not Cre8). The lateral branch of the CX was rewired, using a Fielder XT guide wire and balloons. Stenting was impossible because of the angle of the lateral branch. A good angiographic result was seen after multiple ballooning. At six months follow-up the patient remained asymptomatic and chemotherapy was uneventful. There were no bleeding complications on DAPT, and DAPT was stopped at six months.

The Cre8 DES was well suited to this complex case. Its structure provides high radial strength, a necessary consideration for use in the main stem. It can be easily positioned and has demonstrated efficacy in diabetic patients.⁶ It employs a fatty acid, which acts as a permeation enhancer, in its formulation. Fatty acids are used

Figure 4: Factors to be Considered in Everyday Practice When Undergoing Percutaneous Coronary Intervention

to improve transdermal and skin delivery of drugs,²⁵ and cardiac fatty acid uptake is increased in diabetic mouse models.²⁶ This combination of drug and permeation enhancer leads to increased drug concentration in the tissue, allowing a homogeneous distribution and a uniform action on the whole tissue (see Figure 3). ■

Summary and Concluding Remarks

These presentations of two very different cases – one with a high bleeding risk and the other with highly stenotic lesions in different places. These illustrate the value of case studies. Clinical trials do not discuss specific cases, but in everyday practice we need to apply clinical trial data on a one-to-one basis. No single patient fits a standard profile, and numerous factors need to be considered before undergoing PCI. These include the patient's medical history, prognosis and clinical presentation, the available instruments, devices and imaging modalities and the experience of the cardiologist (see Figure 4). Furthermore, it can be seen that there is no consensus of opinion between experts.

The Cre8 DES could be a useful addition to the range of DES employed in complex PCI cases. Its polymer-free platform with abluminal reservoirs allow targeted and controlled drug elution. The Amphilius formulation enhances drug bioavailability and tissue permeability for optimal safety and efficacy. Furthermore, initial clinical data have demonstrated good safety and efficacy. However, data from larger prospective trials are required to ascertain the true effectiveness of the Cre8 DES in complex lesions. ■

- Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961–72.
- Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004;109:1942–7.
- Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315–23.
- Finn AV, Nakazawa G, Joner M, et al. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol* 2007;27:1500–10.
- Nikam N, Steinberg TB, Steinberg DH. Advances in stent technologies and their effect on clinical efficacy and safety. *Med Devices (Auckl)* 2014;7:165–78.
- Carrie D, Berland J, Verheye S, et al. A multicenter randomized trial comparing amphilius- with paclitaxel-eluting stents in de novo native coronary artery lesions. *J Am Coll Cardiol* 2012;59:1371–6.
- Airolidi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation* 2007;116:745–54.
- Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a randomised observational study. *Lancet* 2013;382:1714–22.
- Lindstaedt M, Spieker M, Perings C, et al. How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? *Int J Cardiol* 2007;120:254–61.
- De Bruyne B, Pijls NH, Kalesan B, et al., Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991–1001.
- Cutlip DE, Chhabra AG, Baim DS, et al., Beyond restenosis: five-year clinical outcomes from second-generation coronary stent trials. *Circulation* 2004;110:1226–30.
- Valgimigli M, Patilalakas A, Thury A, et al., Randomized comparison of Zotarolimus-Eluting Endeavor Sprint versus bare-metal stent implantation in uncertain drug-eluting stent candidates: rationale, design, and characterization of the patient population for the Zotarolimus-eluting Endeavor Sprint stent in uncertain DES candidates study. *Am Heart J* 2013;166:831–8.
- M. V. Bare metal vs. zotarolimus-eluting stent in uncertain drug-eluting stent candidates: a randomized controlled trial (ZEUS). Presented at: American College of Cardiology/ACC Scientific Session, March 31, 2014; Washington, DC.
- Moretti C, Loll V, Perona G, et al. Cre8 coronary stent: preclinical in vivo assessment of a new generation polymer-free DES with Amphilius formulation. *EuroIntervention* 2012;7:1087–94.
- De Luca G, Schaffer A, Verdoia M, et al. Meta-analysis of 14 trials comparing bypass grafting vs drug-eluting stents in diabetic patients with multivessel coronary artery disease. *Nutr Metab Cardiovasc Dis* 2014;24:344–54.
- Abizaid AS, Mintz GS, Abizaid A, et al. One-year follow-up after intravascular ultrasound assessment of moderate left main coronary artery disease in patients with ambiguous angiograms. *J Am Coll Cardiol* 1999;34:707–15.
- Ricciardi MJ, Meyers S, Choi K, et al. Angiographically silent left main disease detected by intravascular ultrasound: a marker for future adverse cardiac events. *Am Heart J* 2003;146:507–12.
- Jasti V, Ivan E, Yalamanchili V, et al. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation* 2004;110:2831–6.
- Fassa AA, Wagatsuma K, Higano ST, et al. Intravascular ultrasound-guided treatment for angiographically indeterminate left main coronary artery disease: a long-term follow-up study. *J Am Coll Cardiol* 2005;45:204–11.
- de la Torre Hernandez JM, Lopez-Palop R, Garcia Camarero T, et al. Clinical outcomes after intravascular ultrasound and fractional flow reserve assessment of intermediate coronary lesions. Propensity score matching of large cohorts from two institutions with a differential approach. *EuroIntervention* 2013;9:824–30.
- Farkouh ME, Domanski M, Fuster V. Revascularization strategies in patients with diabetes. *N Engl J Med* 2013;368:1455–6.
- Stenestrand U, James SK, Lindback J, et al. Safety and efficacy of drug-eluting vs. bare metal stents in patients with diabetes mellitus: long-term follow-up in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J* 2010;31:177–86.
- van Geuns JJ, de Jaegere P, Diletti R, et al. TCT-429 Short- and intermediate- term clinical outcomes after implantation of everolimus-eluting bioresorbable scaffold in complex lesions : a prospective single-arm study – ABSORB Expand trial. *J Am Coll Cardiol* 2013;62(suppl):B133.
- Niemela M, Kervinen K, Erglis A, et al. Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. *Circulation* 2011;123:79–86.
- Kim MJ, Doh HJ, Choi MK, et al. Skin permeation enhancement of diclofenac by fatty acids. *Drug Deliv* 2008;15:373–9.
- Chabowski A, Gorski J, Glatz JF, et al. Protein-mediated Fatty Acid Uptake in the Heart. *Curr Cardiol Rev* 2008;4:12–21.