Meeting the Unmet – The Cre8 Polymer-free Drug-eluting Stents Technology

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Abstract

The use of first-generation drug-eluting stents (DES) has been associated with safety concerns such as very late stent thrombosis. Today, with the release of newer DES, there is a need for comparative studies of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) to demonstrate their value in patients with high risk of restenosis such as diabetic patients. In a satellite symposium presented at EuroPCR 2014, the Cre8™ DES was discussed. The Cre8 device has a number of unique clinical features, including polymer-free technology, abluminal reservoir technology and bio-inducer surface that ensure effective neointima suppression and rapid endothelialisation. The efficacy of the Cre8 DES has been demonstrated in the International randomised comparison between DES Limus Caribostent and Taxus drug-eluting stents in the treatment of de novo coronary lesions (NEXT) randomised clinical study, with equivalent efficacy in the diabetic and general populations, a unique finding. Ongoing clinical studies such as Investig8 and the Tel Aviv Medical Center (TLVMC) Cre8 study have confirmed the efficacy of the device in patient populations with a high proportion of diabetic patients. The Demonstr8 randomised trial has shown almost complete Cre8 strut coverage at three months with a numerical advantage versus bare metal stent (bare metal stents [BMS] – comparator device) at one month. In addition, use of the Cre8 DES may enable a shorter duration of dual antiplatelet therapy (DAPT) following PCI. The Cre8 DES therefore represents a significant advance in stent technology and may be particularly useful in challenging clinical settings

Keywords

Percutaneous coronary intervention (PCI), polymer-free drug-eluting stent, Cre8

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Percutaneous coronary intervention (PCI) involving stenting is routine practice, and involves either bare metal stents (BMS) or drug-eluting stents (DES), which allow controlled release of antiproliferative drugs at the arterial wall.¹ However, the persistence of durable polymers in first-generation DES led to numerous problems including inflammation, delayed arterial healing, aneurysm formation and mechanical disruption. All of which resulted in potential stent thrombosis.² More recently, advances in technology have resulted in the emergence of DES with novel features to enhance efficacy and safety, including the Cre8™ polymer-free DES (Alvimedica). A satellite symposium, chaired by Dr Didier Carrié of Rangueil Hospital (Toulouse, France) and Marco Valgimigli of Erasmus Thoraxcenter (Rotterdam, The Netherlands), was held at EuroPCR on May 21st 2014 in Paris. The objectives of this symposium were to review clinical study data for the Cre8 DES, understand the unmet needs in DES clinical performance for PCI in everyday practice and to understand the added efficacy and safety value of the polymer DES technology.

Dr Carrié began by introducing the Cre8 technology and reviewing published clinical data. The Cre8 DES uses a proprietary polymer-free drug release system (Abluminal Reservoir Technology), which comprises reservoirs on the outer surface of the stent. These enable controlled drug elution that is directed exclusively towards the vessel wall. The Cre8 DES utilises a formulation of sirolimus plus an organic acid, Amphilimus™, that enhances bioavailability and drug distribution to the entire vessel wall. Studies of a rabbit model show that the Cre8 DES has steady release kinetics compared to other commercially available DES (see *Figure 1*), reaching peak drug concentration during the first few days, 50 % drug elution in approximately 18 days, 65–75 % drug elution within 30 days and complete drug elution within 90 days.³ Its optimised permeability allows a homogeneous distribution inside the vessel wall and a uniform action on the whole tissue, enabling an optimal balance between safety and efficacy. After drug release, the Cre8 could be considered a bare metal stent (BMS). Cre8 is covered with a bio-inducer surface made of pure carbon, which is

Figure 1: Cre8™ Kinetic Release

* Cre8 implants in rabbit model

Source: Moretti, 2012³

biocompatible and does not produce any late inflammatory stimuli inside the treated segment, reducing inflammatory response and lowering the risk of device thrombogenicity.

Clinical data in support of the efficacy of the Cre8 DES has been obtained from the NEXT clinical study, which enrolled 323 patients with ischaemic myocardial symptoms related to de novo lesions in native coronary arteries, in 11 European sites.⁴ These were randomised 1:1 to the Cre8 or the Taxus Liberté stent. The primary endpoint was six-month angiographic in-stent late lumen loss (LLL). Although the trial was a non-inferiority trial, the Cre8 demonstrated superiority over the Taxus Liberté stent. In-stent LLL was significantly lower in the Cre8 group (0.14 mm vs 0.34 mm, p non-inferiority

Figure 2: Six-month In-stent Lumen Loss in the NEXT Clinical Study

LLL = late lumen loss. Source: Carie 2012.⁴

<0.0001 , p superiority <0.0001). Clinical endpoints (cardiac death, myocardial infarction, target lesion revascularisation, and stent thrombosis) up to 12 months did not differ significantly between the two groups. The most surprising finding of this study was that the LLL in the diabetic subgroup was comparable to that obtained in the overall population, a finding that had not been seen before with DES (see Figure 2). Only one stent thrombosis was seen in each group. The study concluded that the Cre8 stent in de novo lesions showed significantly lower in-stent LLL at six months than the Taxus Liberté stent, with a trend toward better 12-month clinical safety and efficacy results.

Dr Carrié ended his presentation by stating that the Cre8 unique features and initial clinical results have identified it as a possible step forward in DES development for both safety and efficacy ■

Clinical Programme Update

Dr Gennaro Sardella of the University of Rome (Italy) presented an update on the ongoing studies in the Cre8 clinical program, beginning with an overview of DES development. The first-generation BMS were suboptimal in terms of both efficacy and safety. The second-generation BMS had improved safety profiles but little improvement in efficacy was seen. The advent of the DES resulted in a substantial improvement in efficacy, but first generations of DES had safety issues. Now, with the emergence of newer DES, an optimal balance of efficacy and safety is being achieved, although efficacy in diabetics remains an unmet need.

The features of the Cre8 DES that enhance its safety are the polymer-free platform, which avoids all the established drawbacks associated with the presence of polymer interface with blood flow or vessel wall; the bio-inducer surface that ensures optimal haemo-compatibility vs lumen blood flow, and an abluminal reservoir that controls and directs drug elution to the vessel wall. The polymer-free platform, together with the amphiphilic formulation of sirolimus and organic acid, enhancing drug bioavailability and permeability, contribute to the superior efficacy of Cre8.

Following the demonstration of efficacy and safety in the NEXT clinical trial, the next steps in the Cre8 clinical development program are a randomised clinical trial, Demonstr8, and a real-world study in the

diabetic population, Prove Abluminal Reservoir Technology Clinical benefit in all comers patients (PARTicip8).

The Demonstr8 study

The rationale for the Randomised comparison between a DES and BMS to assess neointimal coverage by optical coherence tomography (OCT) examination (Demonstr8) study⁶ was that millions of stable patients undergoing PCI with BMS implantation have taken one-month dual anti-platelet therapy (DAPT), followed by aspirin monotherapy to optimise safety and efficacy of PCI procedure according to European guidelines. A longer duration of DAPT is required with DES use, since incomplete endothelial stent strut coverage and malapposition is considered a predictor of stent thrombosis. Furthermore, heterogeneity of healing is commonly seen in DES.⁶ However, after complete drug elution, the Cre8 becomes a BMS and interacts with blood and tissue as a standard BMS. The Demonstr8 study therefore aims to show non-inferiority of the Cre8 in terms of stent strut coverage evaluated with optical coherence tomography (OCT) at three months after stent implantation compared with a well known BMS (Vision Multilink).⁷ It has been hypothesised that if endothelial coverage is comparable at three months, the Cre8 could be treated as a BMS at this stage; i.e. only aspirin would subsequently be needed.

The study recruited 38 patients with ischaemic myocardial symptoms related to de novo lesions in native coronary arteries, in six European

Figure 3: Case Example from the Demonstr8 Study Showing Complete Coverage of the Cre8 Stent, with a Thin Layer of Neointima

sites.⁹ The primary endpoint was the percentage of sections with a Ratio of Uncovered to Total Stent Struts per Cross Section (RUTTS) score < 30 % at three-month non-inferior to Vision Multilink percentage of sections with RUTTS score < 30 % at one month. The 35 patients suitable for analysis have led to the evaluation of 17,000 struts in 2000 analysed sections. RUTTS scores <30 % were seen in 99.78 % of patients receiving a Cre8 DES and 99.55 % of patients receiving a BMS. In terms of secondary endpoints, OCT analysis showed superiority of the Cre8 group in terms of mean neointima thickness at months one and three (0.08 ± 0.03 mm in Cre8 group vs 0.18 ± 0.10 mm in BMS group; $p < 0.0001$; see Figure 3). In conclusion, results to date from this study

show that Cre8 has an excellent safety profile, with low RUTTS scores and low neointima thickness.

The PARTicip8 Trial

The PARTicip8 clinical observational prospective study aims to involve around 1000 'real world' patients with ischaemic myocardial symptoms related to de novo lesions in native coronary arteries, in 30 European sites.⁸ One hundred patients from a pre-specified diabetic subgroup will be submitted to angiographic follow up. The primary endpoint is a composite of cardiac death, target vessel myocardial infarction (MI) and clinically indicated TLR at six months. The recruitment was closed in December 2013 with an increased number of patients from the initial plan – 1250 patients.

The Investig8 Trial

The Multicentric and retrospective registry in real-world patients with polymer-free drug eluting stent Cre8 (INVESTIG8) study aims to collect clinical evidence of Cre8 performance from around 1,000 patients in a maximum of 15 European centres. The primary endpoint is the incidence of a composite of cardiac death, target vessel MI and clinically indicated target lesion revascularisation (TLR) at 12 months (major adverse cardiac events (MACE) at 12 months); secondary endpoints are the incidence of a composite of all deaths, all MI and any revascularisation at 12 months, as well as the incidence of stent thrombosis.

Interim analysis of data from 346 patients showed that 34.68 % of the patients had diabetes and 90.8 % had target lesions classified B2 or C according to the American College of Cardiology (ACC)/ American Heart Association (AHA) classification. The results to date are extremely positive with MACE in only 4.6 %

In conclusion, available data from ongoing clinical studies show that Cre8 has excellent efficacy, without compromising safety, for a broad range of patients. ■

Clinical Programme Update

The Tel Aviv Medical Center Cre8 Study

Dr Shmuel Banai of the Tel Aviv Medical Center Israel began by summarising the current limitations of DES: the risk of late stent thrombosis and the inferior efficacy in patients with diabetes. In addition, non-homogeneous coverage of the metal struts due to breaks and cracks of the polymer may lead to inflammatory reactions in the vessel wall, promoting instant stent restenosis (ISR), as well as platelet reactivation, leading to stent thrombosis. Inflammation plays a key role in coronary development and progression in diabetic patients.^{9,10} In scanning electron microscopy (SEM) studies, inhomogeneous distribution of coating was recognised in all DES types examined.¹¹ Furthermore, balloon expansion of first and second generation DES disturbs the polymer surface and can cause detachment of microparticles.¹² The clinical implication of damaged polymers may have been under-recognised and may have a substantial impact on clinical outcomes of patients receiving these stents, especially in diabetic patients. Polymer-free DES may overcome these limitations.

The TLVMC Cre8 study was a prospective, single arm open label non-randomised single-centre study and aimed to evaluate the safety

and efficacy of the Cre8 stent in the all-comer population. The end points were death, MI, stroke, unplanned PCI and clinically driven TLR at 30 days, six and 12 months. Between Nov 2012 and Aug 2013, 215 patients were enrolled and 319 stents implanted. One-year follow-up data are available on all 215 patients. Five patients were diagnosed as non-ST elevation MI (NSTEMI), only one of which had focal in-stent restenosis in an right coronary artery (RCA) in which four Cre8 DES were implanted; in the other four patients, the non-STEMI events were related to a new lesion in a different coronary artery. A total of nine patients underwent clinically indicated PCI. Only one required TLR, in which the lesion was successfully treated with a drug-eluting balloon. Among the remaining eight, none required PCI to the index coronary artery. These data demonstrate a very low incidence of MACE, suggesting an excellent safety profile. The very low incidence of clinically driven TLR also suggests high clinical efficacy.

Dr Banai concluded by stating that polymer-free DES appear to represent a new and improved generation of DES, but that this needs to be confirmed by larger clinical trials and extended clinical experience. ■

PCI in Everyday Clinical Practice: What is Still Unmet in DES Performance?

Dr Marco Valgimigli of the Erasmus MC Thoraxcenter in Rotterdam, the Netherlands, began by summarising the unmet needs in DES performance. These were long-term outcomes, performance in patients with diabetes mellitus and requirement for DAPT. An observational study comparing the effectiveness of revascularisation strategies found that, among older patients with multivessel coronary disease that did not require emergency treatment, there was an initial survival advantage among patients who underwent PCI as compared with patients who underwent coronary artery bypass grafting (CABG), but in the long-term, the advantage switches to CABG.¹³ The more severe the coronary disease, the worse is the comparative effect of PCI. The results of the SYNTAX trial also showed an initial survival advantage with PCI, as long as the anatomy is not too complex.¹ The FREEDOM trial reported that irrespective of complexity, CABG is superior to PCI in diabetic patients.¹⁴ However, stent technology has improved since these studies were undertaken. The SPIRIT IV trial demonstrated the benefits of the second generation DES, although all the advantages of the Xience™ stent in the first year were associated with non-diabetic patients.¹⁵ The EXCEL trial aimed to provide important information on whether the use of second-generation DES would make PCI more competitive in comparison to CABG in a complex patient population. In 2014, enrolment in the EXCEL trial was however capped at 1900 rather than the planned 2600. No other randomised studies are currently planned or ongoing with respect to the performance of second generation DES as compared to CABG. Hence, a full understanding how newer generation DES may fill the gap to CABG in current practice, remains unmet.

In terms of DAPT requirement the general consensus is that patients receiving DES should take DAPT for a minimum of 6/12 months or even more. This represents a significant disadvantage in an increasingly

elderly and frail patient population, for whom the bleeding risk is at least as high as the ischaemic risk. The current treatment paradigm is BMS + one month of DAPT or DES + long-term DAPT. However, there is no evidence from major clinical studies to support DAPT duration of more than 12 months following DES implantation.^{16–19} Current guidelines suggest that patients at high bleeding risk should be given a BMS followed by DAPT for 30 days. However, a safe DES followed by DAPT of short duration may be a better option. The ZEUS study, which randomised patients to a zotarolimus-eluting stent or a BMS, suggested that DAPT duration should be personalised. For example, modelled according to the patient's clinical risk profile and not by stent type. The study found a higher risk of MI in the BMS group. A post-hoc analysis found that these MIs were largely type 1 (spontaneous MI) but also type 4b (stent thrombosis), illustrating the power of late loss inhibition in a high-risk population. Studies have demonstrated that the most important predictor of late stent thrombosis is the RUTTS score.⁶ Data from the Demonstr8 trial have shown that the Cre8 DES is associated with a very high percentage of struts with a RUTTS score <30 % (99.78 % of patients) indicating very good stent coverage. Hence, studies designed to prove the safety of a reduced DAPT duration after Cre8 implantation would be welcome to further understand if DAPT duration should be driven by patients' characteristics and not stent type as long as new generation technology DES is employed.

In conclusion, what is unmet in DES technology is our capability to prove their value under current market conditions. There is a need for studies looking at long-term outcomes, especially in patients with diabetes. There is also a need for studies comparing the efficacy and safety of current DES with that of CABG. In addition, we need to prove that DES efficacy does not necessarily mean longer duration of DAPT. The duration of DAPT should be tailored to the patient and not to the stent. ■

Cre8 in Diabetic Patients

Dr Rafael Romaguera of the University of Barcelona (Spain) discussed the question of whether the Cre8 stent can make a difference to patients with diabetes. He began by examining the causes of DES failure in diabetic patients. Compared with control smooth muscle cells, those cultured under high glucose conditions require more than 10x as much sirolimus concentration to achieve similar suppression.²⁰ Differences in vascular cell metabolism are also seen between diabetics and non-diabetics. In a basal setting, glucose and lactate account for approximately 30 % of energy, whereas 70 % of adenosine triphosphate (ATP) generation is derived from fatty acid oxidation. However, in diabetes, as glucose uptake and oxidation are impaired, the heart is coerced to use fatty acid almost exclusively for ATP generation. The Amphilius™ technology employed in the Cre8 DES, in which the immunosuppressive drug is formulated with a long chain fatty acid, may enhance drug concentration, homogeneity and stability into the vascular cell.

While BMS show a characteristic luminal response involving a rapid increase in LLL over the first six months, due to inflammation and followed by a levelling out,^{21,22} the first and second generation DES showed persistent inflammation and a continued increase in LLL after six months

Figure 4: Durable Inflammation of Durable Polymers

LLL = late lumen loss; DES = drug-eluting stents; BMS = bare metal stents. Source: Kimura, 1996, Kimura, 2002, Byrne, 2011 and Byrne, 2009.^{21–24}

(see Figure 4).^{23,24} Theoretically, the Amphilius™ formulation in the Cre8 DES may represent an advantage in diabetic patients with increased fatty acid metabolism. The absence of polymer may also avoid late events

related to persistent inflammation. This has been demonstrated in the clinical trial setting, where the LLL in diabetes subgroup was comparable to that obtained in the general population (see Figure 2).⁴

The Randomised trial comparing reservoir-based polymer-free amphiphilic-eluting stents vs everolimus-eluting stents with durable polymer in patients with diabetes mellitus (RESERVOIR) trial is a prospective, randomised-controlled, single-blind, two-arm, multicentre clinical evaluation that aims to compare the Cre8 Stent implantation to polymer-based everolimus-eluting stent in diabetic patients (n=112).

The primary endpoint is neointimal hyperplasia as determined using OCT. Secondary endpoints include percentage of uncovered struts, percentage of malapposed struts, maximum areas of obstruction and angiographic LLL.²⁵

In summary, the PCI of patients with diabetes remains challenging, even with the second generation of DES. The Cre8 has demonstrated promising efficacy in patients with diabetes; however, the results need to be confirmed by the ongoing RESERVOIR trial, as well as future clinical trials. ■

Cre8 in Non-comer Patients

Professor Pieter Stella on the University Medical Centre, Utrecht, (the Netherlands) discussed non-comer or non-regular patients. Patients taking oral anticoagulant therapy have acute management issues during the PCI procedure such as choice of vascular access site and anticoagulant and antiplatelet therapy management. Long-term management issues risks of bleeding, stroke, target vessel revascularisation and stent thrombosis. Patients aged over 80 years represent a growing patient population for whom the reduction in mortality and MI rates with DES relative to BMS is particularly marked.²⁶ Patients with DAPT issues present numerous issues, including length of treatment duration, cost, potential side effects, risk of late stent thrombosis and bleeding complications. However, 70 % of the issues associated with DAPT issues could be prevented with new stents such as Cre8 (see Figure 5).²⁷

The stent of choice in non-comer patients according to standard practice is the BMS. However, the Cre8 offers an alternative in the form of a DES with a very safe profile, an abluminal drug, rapid but limited neo-endothelialisation, limited neo-intima and low LL.

Professor Stella considered the clinical evidence in support of the Cre8 DES and presented a case of a male patient aged 78 years, admitted for treatment of colon cancer. He presented with acute coronary syndrome with inferolateral leads on ECG. A Cre8 stent was implanted and four weeks of DAPT prescribed. The stent was examined by OCT at four weeks. OCT revealed a small neointimal layer and no uncovered struts. The patient proceeded to colon surgery and two years later had no angina, no TLR and was taking only aspirin. In terms of scientific evidence, the NEXT and Demonstr8 clinical trials have been discussed. The ReCre8

Figure 5: Principal Causative Factors of Stent Restenosis in Patients on Dual Antiplatelet Therapy

Source: Byrne, 2014.²⁷

trial is an investigator initiated all comers study. It is a prospective, randomised multicentre study that aims to recruit around 2,200 patients. Patients will be randomised to the resolute integrity DES (MDT) or Cre8. The study will also investigate the use of DAPT for three months vs one month in elective PCI. Clinical follow up will be at 12 months and three years, and the primary endpoint will be all MACE. ■

Summary and Concluding Remarks

Dr Carrié ended the symposium by stating that there remains an unmet need for clinical data demonstrating the value of new generation DES, particularly in terms of long-term outcomes and in patients with diabetes. The NEXT clinical study has proven high Cre8 efficacy in diabetics. Ongoing clinical studies such as Investig8 and the TLVMC Cre8™ study have confirmed the efficacy of the device in all comers patients with a high proportion of diabetic patients (35 % and 38 % respectively). Ongoing evaluations will provide further

evidence in this challenging setting. The Demonstr8 randomised trial has provided evidence in support of the excellent safety profile of the device, showing almost complete Cre8 strut coverage at three months. Single-centre experiences have suggested that Cre8 may enable a shorter duration of DAPT following stent implantation, although further studies are needed to confirm this finding. In conclusion, the unique features of the Cre8™ stent have provided high efficacy and safety in challenging clinical settings. ■

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