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Transferability of data between different drug-eluting stents

Michael Magro[1], MD; Yoshinobu Onuma[1], MD; Sigmund Silber[2], MD; Patrick W. Serruys[1]*, MD, PhD

1. Department of Interventional Cardiology, Thoraxcentre, Erasmus MC, Rotterdam, The Netherlands; 2. Cardiology Practice and Hospital, Munich, Germany

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The introduction of drug-eluting stents (DES) for the treatment of coronary artery disease has considerably influenced the market size and growth rates for coronary stents. Companies are continuously striving to develop stents that are the safest and most effective with the goal of being market leaders. Since a considerable number of stents have been developed to date, and head-to-head comparisons in medical literature indicate the ones with the best results, it is no surprise that last generation DES systems tend to be an iterative progression from the previous successful generation. As a result, regulatory bodies including the Food and Drug Administration (FDA) and Conformité Européene (CE), who are consulted by the companies during a new DES development, have to decide whether the changes made to the stent system are significant or not. This in turn will directly influence the amount of additional non-clinical and/or clinical testing that is needed to support the safety and efficacy of the modified DES. Differences in decisions taken between the regulatory bodies is not unknown in this situation, and stems from our lack of understanding concerning what constitutes significant and non-significant change.

Guidelines from the FDA[1] and CE[2] refer to changes or modifications in the various components of the stent system to come to a conclusion as to whether the new stent is novel (innovative) or simply equivalent with minor modifications from the previous device. In principle, novel DES with unique characteristics dissimilar to any currently approved coronary stent should be tested extensively, since its ultimate effect on clinical outcome is unknown and unpredictable. On the other hand, slight modification in one component or in the manufacturing methods of a stent system needs limited investigation prior to approval, since such changes are not expected to affect the clinical outcome in a negative way. Thus, a spectrum of intensity of required investigations exists; these range from: pharmacokinetic tests, benchmark tests, animal studies, first-in-human and fully randomised clinical trials for novel stent systems, registries, or even just transferability of data (from literature) from old stent to the new stent system in the case of minor modifications. Therefore, the classification of the new stent system has a tremendous impact on the amount of investigations – and therefore the time and money required – which in turn affect the competitiveness of the stent once it makes it to the production line of the company.

To understand the significance of a change in a DES system we need to evaluate the importance of that particular component in the performance of the stent. Probably the best form of analysis of such a change would be a randomised controlled trial (RCT) sufficiently powered for demonstration of superiority or non-inferiority – of at least one year and preferably with five-year follow-up – comparing two stents which differ only in the component under investigation in terms of clinical endpoints as defined by the Academic Research Consortium.[3] In essence, target vessel revascularisation (TVR) is a measure of effectiveness of the device while myocardial infarction and cardiac mortality is a measure of its safety. Short of that, imaging endpoints that have been validated as surrogate markers of clinical outcome can be utilised. However, such endpoints are only accepted for "certain second generation DES…in specific populations or in specific vessel or lesion types"[1]. Although histopathological animal studies are an important part of the work-up in an innovative stent system, the short-term results do not provide sufficient information to judge the safety and efficacy of a DES as demonstrated in the ACTION trial[4].

** Corresponding author: Department of Interventional Cardiology, Thoraxcentre, room Bd589, PB412, Erasmus Medical Centre, Dr. Molewaterplein 40, 3000 CA Rotterdam, The Netherlands*

E-mail: p.w.j.c.serruys@erasmusmc.nl

Drug type

The type of drug used, is the most well known component which affects clinical outcomes. In the recent SPIRIT trials, everolimus eluting stents were shown to be superior to paclitaxel eluting stents[5]. Although the major difference between the two-stent systems is the drug, the likely explanation of fewer periprocedural myocardial infarctions may be due to other stent characteristics, including smaller strut size (81 µm vs 132 µm), thinner polymer thickness (7.8 µm vs 16 µm) and less polymer webbing which could have resulted in less side branch compromise.

Polymer and drug release profile

The drug release profile which depends on the drug dose, chemical composition and drug/polymer composition as well as the way it is applied to the stent platform also influences stent performance. The release kinetics of the drug are also proportional to the surface area, and inversely proportional to the membrane thickness. Thus, application of a studied drug/polymer to a stent with different design and/or different strut thickness and surface area may change the performance of the new DES. In PISCES, variable dose and release kinetics were shown to affect neointimal hyperplasia as demonstrated with the lowest in-stent late loss observed with the 10 µg and 30 µg doses in 30-day release groups respectively.[6]

Most of the other stent systems use a polymer that coats the stent surface and a polymer/drug combination in specific weight-to-weight ratio which determines the release profile of the drug. The impact of a novel durable polymer matrix (Biolinx™) which prolongs zotarolimus elution (despite same dose) in the Endeavor Resolute DES system was assessed in the Resolute trial[7].

Fourth-generation DES currently under development employ an ultra-thin biodegradable abluminal polymer that delivers a very low dose of paclitaxel to the wall of the treated vessel, and no polymer or drug on the inner surface of the stent. Being a major, significant change, the stent is undergoing complete evaluation, including pivotal trials.

Material composition of stent platforms

The alloy or modifications made to the composition of the stent platform is known to affect stent performance as exemplified in the NUGGET study, which showed worse angiographic and IVUS parameters at six months in the gold-coated NIR when compared to same uncoated stainless steel stent.[8]

A new platinum chromium alloy in the Promus Element, which uses the same drug and polymer as in Xience V (or PROMUS), was considered significant by the FDA and is thus being investigated in the PLATINUM trial, a single, blind, safety/efficacy randomised trial with parallel assignment to the PROMUS (cobalt chromium) and PROMUS Element. Is this truly a novel change, or is it iterative? Will CE mark be awarded, or will the decision be the same as the FDA's? Will the $10 million being spent for an RCT be money down the drain, or will it enlighten us to better understand the significance of alloy change?

Differences in strut thickness and stent design

Also in the bare metal stent (BMS) era, a randomised, multicentre trial showed significant differences in one year event free survival, freedom from myocardial infarctions and diameter stenosis at six months of 1,147 patients who received one of five stainless steel stents with different stent designs (Inflow, Multi-Link, NIR, Palmaz-Schatz and PURA-A)[9]. The degree of scaffolding, recoil, flexibility and deliverability of the stent are dependent on the stent design, and can influence procedural success rates as well as long term performance of the stent. Surface properties of particular stent designs can also be different, and may influence the stent interaction within the vascular wall in terms of vascular injury and inflammatory response. In DES the mechanism is modified by the anti-proliferative action of the drug but we can still hypothesize that the stent design influences procedural success.

The effect of strut thickness and the combination with stent design were studied in the ISAR-STEREO studies. Two stents with comparable BMS designs, but with stent thickness of 50 µm and 140 µm, were compared[10]. The incidence of angiographic restenosis and TVR were less in the thin strut group. In a second study, two different stent designs, a multi-link stent and a BX Velocity stent with different strut thickness (50 µm vs 140 µm), were compared. The incidence of angiographic restenosis was again lower in the thin strut group, as was TVR[11]. In both studies, no significant differences was observed in the combined incidence of death and MI at one year between the groups. These studies suggest that stent thickness may be a more important contributor than design for efficacy, at least in BMS. In DES, the newer continuous cell design and thin struts (0.0038") in Taxus Liberté were shown to be non-inferior to historic controls using the multi-link design with thicker (0.0052") struts in Taxus Express in the ATLAS trial[12]. Although the Liberté group had significantly more complex lesions, there was improved procedural performance with the newer stent as measured by lower procedure time, decreased bail-out and geographic miss as measured by quantitative coronary angiography. Here again, the combination of both strut thickness and stent design has influenced these results.

Changes in the design of the multi-link system and in the stent delivery system in Xience PRIME (Abbott Vascular) aimed at improving deliverability and flexibility of the everolimus eluting stent (Xience V) were considered iterative by the CE, while the FDA requested a registry pre-marketing. Improvement in the delivery system theoretically enhances procedural performance of the stents. The regulatory bodies limit the requirements to testing the delivery system using the intended DES/delivery system combination.

Differences in quality of manufacture of a stent can theoretically effect stent performance *in vivo* – a plausible explanation for the poorer outcome for the CoStar stent in the COSTAR II trial when compared to the same stent's previous safety and efficacy[13]. Critical process parameters should be controlled or monitored to ensure batch reproducibility and to minimise batch variability. If for example a stent is manufactured at one site by one company, can we assume that the end product is the same? Do minor differences in quality affect clinical results?

As such, the ultimate performance of a stent system depends on the contribution of each of the components and/or manufacturing standards individually – but also is affected by their combination – which could be either additive, synergistic, counteractive or the mixture of the three.

With the increasing number of companies investing in the development of newer stent systems, our regulatory bodies, scientific community and industry need to agree on which data can be transferable and which data has to be re-acquired. We need to stimulate collaboration of the interested parties to look into how the various components of the stent systems, and their combination, affect success or otherwise of a DES, to provide more robust scientific evidence for decisions taken by regulatory bodies which should then be unanimous. For this goal, a more uniform, homogenous and reproducible interpretation of registries and randomized controlled trials would be desirable.[14]

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