



Downstream effects of coronary drug-eluting stents: promising prophecy or incidental surveillance?

Evaluation of: Krasuski RA, Cater GM, Devendra GP et al. Downstream coronary effects of drug-eluting stents. *Am. Heart J.* 162, 764–771 e1 (2011). The remote effects of the cell-cycle inhibitors eluted from drug-eluting stents (DES) on downstream vessel architecture, remain controversial. The single-center cohort study reported by Krasuski *et al.* compared the incidence of angiographic *de novo* stenosis and the need for intervention in downstream vessels following proximal stent implantation, within 1 year of patients receiving a DES and bare-metal stent (BMS) from their registry, enrolling consecutive patients with percutaneous coronary intervention (PCI). DES use was associated with reduced risk of *de novo* stenosis and need for intervention in the overall cohort (Risk ratio [RR]: 0.39; 95% CI: 0.19–0.73; $p < 0.01$ for *de novo* stenosis, RR: 0.45; 95% CI: 0.21–0.85; $p = 0.01$ for need for intervention) and after propensity-matching (RR: 0.36; 95% CI: 0.14–0.82; $p = 0.01$ for *de novo* stenosis; RR: 0.41; 95% CI: 0.16–0.97; $p = 0.04$ for need for intervention). These findings may be explained by the remote effects of drugs released from DES, or may just be the result of individual differences in the progression of atherosclerosis.

KEYWORDS: cell-cycle inhibitors ■ downstream vessels ■ drug-eluting stent

Cell-cycle inhibitors, such as sirolimus or paclitaxel have been shown to be effectively delivered by drug-eluting stents (DES) with compelling evidence of their antirestenotic efficacy after intracoronary stenting [1]. Despite their profound antiproliferative actions and their clinical utility in reducing in-stent restenosis, systemic administration of cell-cycle inhibitors was accompanied by high rates of side effects, even in short duration of use [2,3]. In contrast, local drug delivery at the site of vascular injury via a polymer-coated stent, is an elegant solution to achieve effective local drug concentration in the absence of deleterious side-effects. DES have impressively proven efficacy in reducing restenosis after intracoronary stent implantation over a bare-metal stent (BMS), in a large numbers of patient subsets [1]. In fact, neointimal growth has been reported to be less with rapamycin-eluting stents compared with BMS with adjunct oral rapamycin therapy [3], providing evidence for the greater efficacy of localized drug delivery.

Recent studies suggest that implantation of DES may result in endothelial dysfunction in the peri-stent area, especially in distal position of the implanted stent [4,5]. Pharmacokinetic studies indicate that DES not only cause drug transfer to the vessel wall at the contact site, but also within the surrounding tissue and within remote organs [6,7]. Therefore, some of the newer generation DES are designed to achieve selective drug

transfer at the vessel wall with minimal remote effects. Technological innovations supporting these goals include the application of highly lipophilic drugs or the use of abluminal stent coatings [8,9]. However, several studies also suggested that the cell-cycle inhibitors might also possess anti-atherogenic properties [10–12]. Therefore, it may be hypothesized that the release of antiproliferative compounds from DES may also affect molecular conditions relevant to atherosclerosis progression within the vasculature, distal to the implantation site. In a recent observational study led by Krasuski *et al.*, the authors attempted to address this controversial issue that was lacking sufficient attention in previous prospective clinical trials [13].

Summary of methods & results

Krasuski *et al.* studied data from the Cleveland Clinic Interventional Registry, which is single-center observational registry of patients undergoing percutaneous coronary intervention (PCI), enrolling 29,487 patients between January 1992 and June 2009. The authors identified 734 patients implanted with a single stent to a single proximal vessel as an initial PCI and then returned for a second PCI due to symptomatic coronary artery disease within a year. Of these patients, 596 patients had no angiographical lesions in downstream vessels at first stent implantation, with an accompanying control artery free from angiographical stenosis. After

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excluding 133 patients due to chronic total occlusion, procedural failure, prior bypass grafting to the stented artery and intentionally staged procedure, 121 patients with DES implantation and 343 patients with BMS were used for this study. Propensity matching was performed on the entire cohort and identified 89 DES and 89 matched BMS patients.

The authors examined the incidence of angiographical *de novo* stenosis >25% and need for intervention in both downstream and control vessels within 12 months following initial PCI. Downstream territory was determined as sites distal from initial stenting in treated vessels, and control vessels were selected by researchers in untreated vessels, to match the site of target lesions in initial PCI.

The main finding of the study was that implantation of DES was associated with a risk reduction in the incidence of *de novo* stenosis in downstream vessels, for both the entire cohort population (relative risk [RR]: 0.39; 95% CI: 0.19–0.73; $p < 0.01$) as well as the propensity-matched cohort (RR: 0.36; 95% CI: 0.14–0.82; $p = 0.01$). In control vessels, there were no significant differences in the incidence of *de novo* stenosis between patients receiving DES or BMS in entire cohort (RR: 0.53; 95% CI: 0.20–1.21; $p = 0.14$) and the propensity-matched cohort, respectively (RR: 0.99; 95% CI: 0.26–4.07; $p = 0.99$). In terms of need for interventions after initial PCI, the use of DES was associated with a reduced risk in both the entire cohort (RR: 0.45; 95% CI: 0.21–0.85; $p = 0.01$) and the propensity-matched cohort (RR: 0.41; 95% CI: 0.16–0.97; $p = 0.04$). Again, no difference was detected in control vessels among the entire cohort (RR: 0.99; 95% CI: 0.35–2.45; $p = 0.98$) and the propensity-matched cohort, respectively (RR: 2.1; 95% CI: 0.44–14.8; $p = 0.36$). Furthermore, the use of DES was the only significant predictor of *de novo* stenosis (Hazard ratio [HR]: 0.39; 95% CI: 0.19–0.75; $p < 0.01$) and need for intervention (HR: 0.47; 95% CI: 0.20–0.99; $p = 0.02$) after initial PCI in the analysis using a multivariable Cox proportional-hazard regression model.

In their discussion, the authors note that despite the presence of an important limitation in applying a nonrandomized, relatively small sized, single-center cohort design, a consistent result was obtained with mandatory quality assurance using multiple analytic techniques. The authors concluded that patients receiving DES appear less likely to develop downstream

stenosis and have less repeat interventions compared with patients receiving BMS, suggesting a beneficial effect of downstream drug delivery.

Discussion

The major strength of the study performed by Krasuski *et al.*, is that it is the first report evaluating the progression of downstream atherosclerotic lesion formation, after index stent implantation. By comparing the incidence of downstream lesion progression with the consecutive need for new interventions among patients receiving DES or BMS, the current study provides an intriguing hypothesis relevant to all patients receiving such devices. In fact, the authors thoroughly discussed their findings of reduced downstream lesion progression after DES implantation in light of previous trials evaluating the impact of systemic treatment using agents applied on contemporary DES, which provided clear evidence that there are measurable systemic drug effects in remote organs following oral drug application [2,3]. As a consequence, the hypothesis that the targeted delivery of high drug concentrations using DES devices may result in significant accumulation of the drug distal to the stented segment, seems reasonable and true.

Despite the controversial reports about the molecular effects of antiproliferative agents used on contemporary DES, their broad anti-inflammatory actions may indeed result in a delay of lesion progression at the short-term (1 year), as reported in the current study. Nevertheless, this highly important issue requires thorough investigation in dedicated clinical trials, accompanied by fundamental basic research, before it can be acknowledged as an evidence based fact.

First, as reported in the study by Krasuski *et al.*, the freedom of downstream atherosclerotic disease during the index procedure is difficult to define, as early local atherosclerotic changes require sophisticated imaging tools for their detection [13]. On the other hand, these precursors of atherosclerotic plaque burden remain a highly relevant factor pertaining to the development of stenotic atherosclerotic lesions and the need for future interventions.

Second, although distal stent edge lesions <5 mm from the initial stent were excluded in the definition of downstream *de novo* stenosis, the same lesions were included as targets for new interventions distal to the implanted stent. Considering the substantially higher in-segment restenosis rate of BMS compared with DES, new interventions might have been

overestimated in the event of initial BMS implantation.

Third, downstream *de novo* stenosis was defined as a new lesion >25% of luminal narrowing, instead of lesions of >50% stenosis commonly used as threshold for binary stenosis in contemporary angiographic studies. Although this definition may support the detection of apparent atheroma progression, the inherent drawback in angiographic studies is the overestimation of irrelevant luminal changes, resulting in an increase of false-positive counts.

Fourth, despite extensive adjustment for potential confounding factors using multiple analytic techniques, others may have been underestimated in the current study. The higher rate of lipid-lowering medications in the DES group (67.8 vs 40.4%; $p < 0.01$) suggests that patients with DES might benefit from medications, such as statins, that are known regressors of atherosclerotic disease.

Last, the 1-year follow-up, as reported in the study by Krasuski *et al.*, may be too short to represent the full spectrum of lesion progression irrespective of stent implantation.

Regardless of these drawbacks, the current study highlights a forgotten chapter in the surveillance of patients receiving DES versus BMS, which was driven by innovative ideas and undertaken in a large registry of consecutive patients undergoing stent implantation, in a well recognized center. Therefore, the study performed by Krasuski *et al.* deserves complete reflectance

by researchers and professionals in the field of interventional cardiology.

Future perspective

As the current study is hypothesis-generating in nature, future studies should be designed to specifically address the progression of atherosclerotic lesions distal to the implantation site of either DES or BMS. Innovative invasive imaging modalities such as intravascular ultrasound and optical coherence tomography, as well as non-invasive imaging, may provide useful information on the characterization of atherosclerotic plaques prior to and after stent implantation. Furthermore, as the authors describe in their article, the pharmacokinetics and pharmacodynamics of drug delivery in the downstream coronary artery should be investigated on a molecular level, accompanied by a randomized clinical trial including patients of clearly definable atherosclerotic plaque burden in the absence of pure surrogate end points.

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Executive summary

- Research by Krasuski *et al.* reported that implantation of drug-eluting stents (DES) was associated with reduced risk of *de novo* stenosis and need for intervention in downstream vessels as compared with implantation of bare-metal stents. These findings suggest a beneficial effect of downstream drug delivery from DES.
- The current study is hypothesis-generating in nature and should be interpreted with caution with respect to the conclusions drawn.
- Further research is warranted to specifically address the issue of downstream vascular effects after implantation of DES.

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