Treatment of In-Stent Restenosis — Back to the Future?

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Percutaneous transluminal coronary angioplasty has become the most frequently used method for myocardial revascularization.[1] The use of uncoated coronary-artery stents during percutaneous intervention has decreased the incidence of acute complications and improved the outcome of patients,[2] but restenosis within the stent compromises the long-term results. As a consequence, the prevention and treatment of in-stent restenosis have become priorities in interventional cardiology.

Drug-eluting stents, which markedly reduce in-stent restenosis,[3] have relegated all other therapeutic approaches to the background. However, it is gradually emerging that rates of late restenosis after the use of drug-eluting stents are higher than initial experience suggested, particularly in patients who have complex lesions or are at high risk for complications (e.g., those with multivessel disease or diabetes). In such cases, rates of binary in-segment restenosis are 8.9 to 18.9%.[4,5] Recently, the problem of late thrombosis (>1 month after the procedure) has further dampened initial enthusiasm and has reduced the indiscriminate use of first-generation drug-eluting stents. As a result, interventional cardiologists have tended to revert to more predictable devices (e.g., uncoated stents or ones that are coated with so-called inert compounds, such as silicon carbide and titanium–nitride–oxide), which are designed to decrease acute surface thrombogenicity. Thus, in-stent restenosis is likely to remain an important clinical issue.

Catheter-based drug delivery was originally developed by Harvey Wolinsky to prevent restenosis after balloon angioplasty.[6] In the 1990s, extensive research was carried out to improve catheter-based, site-specific (or local) intraarterial delivery of drugs.[7] However, studies in animals and humans showed marked variability of site-specific uptake in the arterial wall and a quick washout of the compounds that were being studied,[8,9] so clinically convincing results could not be demonstrated. These difficulties favored the development of stent-based drug delivery.

In this issue of the *Journal,* Scheller et al. compare routine balloon angioplasty with angioplasty using a drug-coated balloon catheter for the treatment of in-stent restenosis.[10] Conceptually, the advantage of this technique is that the drug (in this case, the antiproliferative compound paclitaxel) is administered to the vessel wall without the use of a stent coated with a biostable polymer as a platform for delivery. As a result, the acute neointimal and vascular injury from the procedure is not prolonged by persistent exposure to the drug-carrier platform, which may generate a persistent inflammatory and immunologic reaction.

Although the study by Scheller et al. involved only 52 patients and must be considered a pilot trial, the results are intriguing. As compared with the use of an uncoated angioplasty balloon in the control group, the use of a paclitaxel-coated balloon significantly inhibited neointimal proliferation, as assessed by quantitative coronary angiography. The primary end point was angiographic in-segment late luminal loss, which was defined as the change in the minimal luminal diameter between the measurement performed immediately after the procedure and at 6 months. The mean (±SD) late luminal loss was 0.74±0.86 mm in the group treated by simple angioplasty, as compared with 0.03±0.48 mm in the group treated with the paclitaxel-coated balloon (P=0.002). In absolute numbers, this mean value for late luminal loss is one order of magnitude smaller than values obtained with the use of either intracoronary radiation (0.35±0.68 mm) or first-generation drug-eluting stents (0.32 mm [0.03 to 0.74 mm]) to inhibit neointimal growth.[11,12]
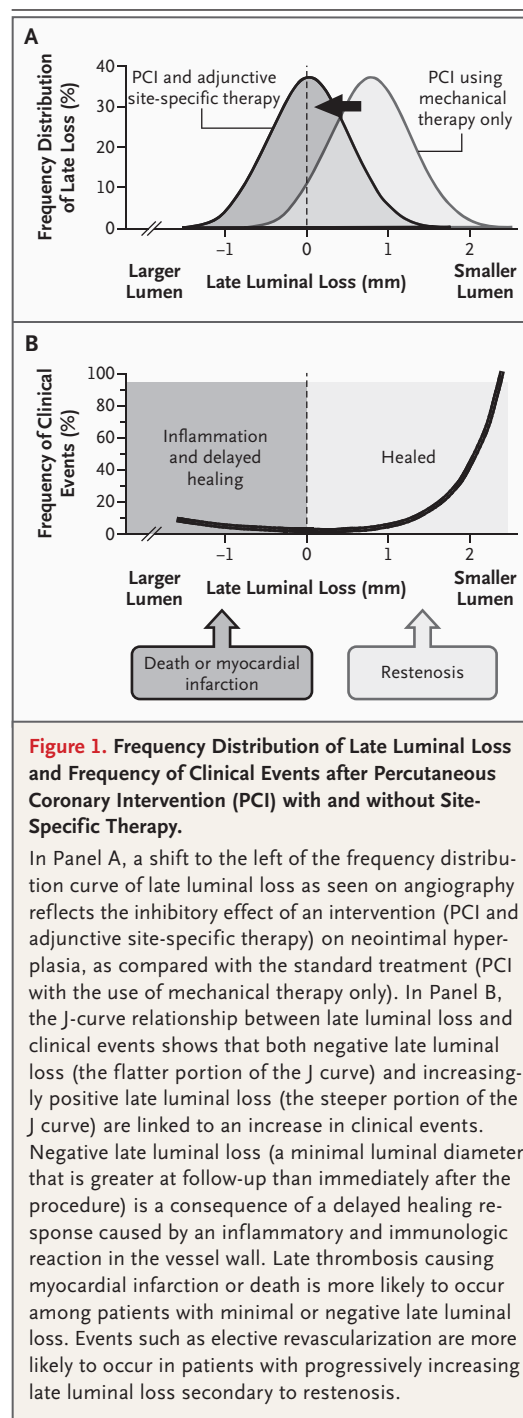
Various elements may have contributed to this significant effect. First, the selection of the highly lipophilic cytostatic drug paclitaxel allows for good penetration and persistence in tissue. Second, a proprietary technique for coating the balloon surface provided good adhesion of the compound to the balloon without noticeably affecting its mechanical properties. The coating appears to have allowed the loaded drug to reach the lesion and to have delivered the compound to the vascular wall within the duration of the balloon inflation (mean time, 81.5±48.7 seconds). According to the protocol, patients with calcification of lesions were excluded from the trial, and procedural predilation was suggested, presumably to

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avoid increased surface friction and mechanical damage to the balloon coating. Third, the type of lesion selected for study in this trial — in-stent restenosis — is rather homogeneous histologically. The neointimal tissue has low cellularity and an extracellular matrix rich in proteoglycans,[13] which may provide an ideal composition for drug absorption. Balloon-catheter angioplasty for previously untreated atherosclerotic and calcified lesions with variable levels of injury after angioplasty may present a more challenging setting owing to more unpredictable uptake of the drug.[9]

With regard to safety, the results of the intention-to-treat analysis seemed acceptable, even though myocardial infarction with a fatal outcome was classified as "possibly related" to treatment with the drug-coated balloon. Per-protocol or as-treated analysis revealed a further myocardial infarction in the coated-balloon group. The second event occurred in a patient who was assigned to the uncoated group and erroneously treated with a drug-coated balloon.

Whether these preliminary observations can be expected to translate into a significant clinical benefit is not clear. We are gradually learning from the long-term follow-up of trials of first-generation drug-eluting stents that the curvilinear relationship between late luminal loss and the rate of restenosis (as well as clinical restenosis) may be lost over time.[14] As a result, a promisingly low or even negative angiographic measurement of late luminal loss may not be associated with a favorable long-term clinical outcome (Fig. 1). This dissociation may be due to persistent incomplete healing of the vessel[15] as a consequence of an ongoing inflammatory and immunologic reaction in the vessel wall.[16] In addition, it is crucial to realize that this trial was carried out with the use of only a short-term (1 month) regimen of dual antiplatelet therapy. It will be necessary to complete a long-term assessment of these patients, as well as to plan a clinically oriented trial, to exclude an increased risk of serious late clinical events (death and myocardial infarction).

It appears to be clinically evident that after site-specific drug treatment, the healing response of the vessel and the duration of antiplatelet therapy are interconnected. Dual antiplatelet coverage should be maintained until complete healing and vessel reendothelialization have been achieved.[15] The integration of preclinical,[17] pathological,[15] and clinical studies in humans, including the as-

Figure 1. Frequency Distribution of Late Luminal Loss and Frequency of Clinical Events after Percutaneous Coronary Intervention (PCI) with and without Site-Specific Therapy.

In Panel A, a shift to the left of the frequency distribution curve of late luminal loss as seen on angiography reflects the inhibitory effect of an intervention (PCI and adjunctive site-specific therapy) on neointimal hyperplasia, as compared with the standard treatment (PCI with the use of mechanical therapy only). In Panel B, the J-curve relationship between late luminal loss and clinical events shows that both negative late luminal loss (the flatter portion of the J curve) and increasingly positive late luminal loss (the steeper portion of the J curve) are linked to an increase in clinical events. Negative late luminal loss (a minimal luminal diameter that is greater at follow-up than immediately after the procedure) is a consequence of a delayed healing response caused by an inflammatory and immunologic reaction in the vessel wall. Late thrombosis causing myocardial infarction or death is more likely to occur among patients with minimal or negative late luminal loss. Events such as elective revascularization are more likely to occur in patients with progressively increasing late luminal loss secondary to restenosis.

sessment of characteristics of drug release (both in vitro and in vivo),[18] is essential to allow for the prediction of the vascular healing response in vivo and the determination of long-term safety. Such analyses will lay the groundwork for the systematic development of both drugs and delivery methods.

In conclusion, the report by Scheller et al. suggests that catheter-based drug delivery is a potentially promising approach to in-stent restenosis and demonstrates that old avenues of investigation may yield new solutions to persisting problems. Although these data are preliminary and do not yet confirm the clinical validity of this approach, it may be that we can make progress in this field by going "back to the future."

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Professionalism — The Next Wave

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In their Medical Education article in the October 26 issue of the *Journal*, Stern and Papadakis make a number of observations about professionalism and the learning environments in which medical training occurs.[1] Like a growing number of medical educators, they recognize that considerable learning (some think most) takes place outside the domain of the formal curriculum and that such learning involves indoctrination in the unwritten rules of studenthood and medical practice.

Some medical schools and residency programs have acknowledged the existence of alternative, or shadow, domains of learning, whose lessons are sometimes collectively called the "hidden curriculum," and have accepted responsibility for both understanding and modulating the effects of these domains on students' knowledge, skills, and values. Included in this broadened curriculum are the lessons students learn as they witness conflicts between the expectations and ideals articulated in professional codes[2] and the behavior of individual physicians (particularly faculty members) and organizations as both go about the daily and concurrent work of medicine and education.

As we work to define, instill, and appraise professionalism as a core standard and competency, it is critical that we keep three interrelated questions in mind. First, how do we effectively define and assess something that is transmitted in a variety of learning environments through a wide