Optimal Implantation Strategies Using Drug-Eluting Stents for In-Stent Restenosis: Do We Know the Answer?

To the Editor:

We read with great interest the elegant but provocative study of Fujii et al.1 assessing mechanisms of drug-eluting stent (DES) failure in patients treated for in-stent restenosis (ISR). Focal recurrence after DES treatment occurred in 25% of patients. Eleven patients with ISR recurrence showed evidence of severe stent underexpansion on intravascular ultrasound (minimal stent area $\leq 5 \text{ mm}^2$ in 9 lesions, $<4 \text{ mm}^2$ in 7 lesions, and $<3 \text{ mm}^2$ in 4 lesions). Of interest, these findings were demonstrated despite the routine use of high inflation pressures ($\geq 14 \text{ atm}$ by protocol).

Because the study has major potential clinical implications, further details and some methodological considerations would be appreciated to better delineate the pattern of ISR in these patients.

First, it would be important to know the degree of stent expansion in relation to the reference vessel lumen area as depicted by intravascular ultrasound. Otherwise, although it is likely that most of these stents indeed presented with severe underexpansion, the relevance of these findings in patients with small vessels remains difficult to ascertain. In this regard, quantitative angiographic data of reference vessel size in patients with and without subsequent ISR would also be illustrative.

Second, in patients with imaging before DES implantation, it would be of help to know whether the underlying conventional stent already presented data of severe underexpansion to start with. If this is the case, the study results may reflect a relatively selected subset of patients with ISR.

Third, from a mechanistic point of view, it would be of major interest to determine whether the degree of maximal intimal hyperplasia was located precisely at the site showing the minimal stent area or, alternatively, whether intimal hyperplasia growth was evenly distributed along the DES. In the former scenario, a high shear stress could contribute to the genesis of restenosis, whereas in the latter, minimal stent area per se will emerge as the main player accounting for lumen narrowing.

Finally, from a pragmatic standpoint, it would be important to provide further therapeutic alternatives when significant DES underexpansion is detected by intravascular ultrasound after the procedure, because the systematic use of very high pressures ($18 \pm 4 \text{ atm}$ in this study) does not appear to prevent the occurrence of this phenomenon.

We fully agree with these investigators that the efficacy of DES in the treatment of patients with ISR is currently not completely established.2–5 Therefore, prospective controlled studies are warranted to further define the role of DES in the challenging setting of ISR.

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Circulation. 2004;110:e302
doi: 10.1161/01.CIR.0000141457.02676.FD
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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