JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 15, 2015

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2015.10.013

EDITORIAL COMMENT

Drug-Coated Balloon Angioplasty for De Novo Stenosis

The Balloon is Back…Reloaded!*

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It seems obvious to many of us that if a stenosis could be effectively treated by angioplasty alone rather than stent implantation, this would be the best option over the long-term. Writing in *Circulation* in 1998 in a paper subtitled, "the balloon is back!" some experts called for a change of course away from routine stent implantation during percutaneous coronary intervention, advocating instead a strategy of systematic aggressive balloon angioplasty with provisional stent implantation when required (1). Ultimately, it was maintained, clear evidence should be generated that an alternative approach is superior before optimized angioplasty with provisional stenting should be abandoned. The passage of time has seen routine stent implantation supplant angioplasty as the default strategy for percutaneous coronary intervention. Nowadays, if a lesion can be stented, it usually is. So, why has the pursuit of balloon angioplasty been a vain undertaking? The reasons are not difficult to understand.

First, angioplasty alone results in varying degrees of vessel wall injury, ranging from intimal tears to frank medial dissection. Accordingly, a subset of treated patients is at risk of abrupt vessel closure. Routine stenting, however, seals dissections and flaps resulting in more predictable acute results. Second, vessel recoil and constrictive remodeling are dominant causes of restenosis after angioplasty. Routine stenting addresses both issues and results in greater acute gain and lower risk of subsequent restenosis compared with angioplasty alone. In addition, the advent of drug-eluting stent (DES) technology has almost eliminated the secondary problem of in-stent restenosis due to neointimal hyperplasia. Third, the proliferation of high-performance "me too" DES devices has driven the cost of stent technology downward to the point where unit cost in certain countries already approaches the $100 mark. This means that financial disincentives for stent implantation are increasingly less relevant. The rapid progress in stent technological development and the continual improvement in patient outcomes meant that further large-scale clinical trials investigating optimized angioplasty with provisional stent implantation were never performed, due to a perceived lack of clinical equipoise compared with routine stenting.

Drug-coated balloons are standard angioplasty catheters that are surface coated with active drug mixed with a spacer (or excipient) that facilitates transfer of the drug to the vessel wall (2). So, should we expect the fate of angioplasty with drug-coated balloons to be much better than that of its predecessor, plain balloon angioplasty? There are at least 2 reasons to believe that it might. First, the advent of effective dual antiplatelet therapy has been central to the success of contemporary percutaneous intervention (3), and current antiplatelet regimens are well-established and effective. This means that abrupt vessel closure after drug-coated balloon angioplasty in the setting of vessel wall dissection is likely to be less of an issue. Second, in common with DES therapy, angioplasty with drug-coated balloons

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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effectively targets neointimal hyperplasia and inhibits restenosis. Pre-clinical experience and clinical trials clearly show that a brief dilation (of just 30 to 60 s duration) can produce effective drug transfer as well as durable inhibition of restenosis (2).

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In this issue of *JACC: Cardiovascular Interventions*, Cortese et al. (4) study the outcome of 156 patients with de novo stenosis treated with drug-coated balloon angioplasty who underwent angiographic surveillance approximately 6 months after intervention. At the outset, only one-third (n = 52) had angiographic evidence of dissection after angioplasty, and most of these were classified as mild to moderate (n = 48) (type A to C according to National Heart, Lung, and Blood Institute definitions [5]). Accordingly, these were deemed not to require treatment. The main finding of the study was that the fate of these patients was encouraging, with a benign clinical course and a favorable appearance at surveillance angiography. Patients with severe or flow-limiting dissection (type D to F according to National Heart, Lung, and Blood Institute definitions [5]) following angioplasty were not considered for further angiographic analysis: every interventionalist knows that these patients must be treated promptly with stenting to ensure a favorable clinical course.

The observations of Cortese et al. (4) are important and reinforce the impression from trials of plain balloon angioplasty that mild to moderate dissection is associated with a benign clinical course (6,7). However, there are some important limitations that should be considered when interpreting the results. First and most importantly, although easy to use, angiography alone is a blunt tool for assessing coronary dissection. By pathology, dissections are defined as a separation of the intima/media from the underlying adventitia including a dissecting hemorrhage. It seems intuitive that the prognosis of "true" medial dissections is substantially different from intimal tears and flaps. However, it is likely not ideal to rely on an angiography-based system to classify and triage patients to provisional stent implantation. In this respect, the current study was underpowered to provide meaningful information on adverse clinical events, so caution must be exercised in interpreting the outcome data. Intravascular imaging modalities, such as optical coherence tomography or intravascular ultrasound, have higher sensitivity in detecting and classifying dissection and should be preferred (8). Second, the external validity of the data is limited due to the recruitment of selected patients at just 2 centers and the exclusion of patients with lesions in heavily calcified vessels or vessels >3 mm in diameter. Third, the angiographic data presented was not analyzed in a core laboratory. This affects internal validity. Finally, some of the authors' interpretations are open to question. In particular, the claim that paclitaxel release from drug-coated balloon angioplasty may facilitate vessel healing is speculative. In fact, our experience in animal studies suggested that successful drug transfer was almost invariably associated with features of delayed arterial healing characterized by loss of smooth muscle cells within the intima and media, prolonged fibrin deposition, and inflammation (2,9).

So, what is the future for drug-coated balloon angioplasty for de novo coronary disease? Although a strategy of optimized angioplasty with liberal use of intravascular imaging and provisional stenting holds promise, some skepticism persists. Despite many years of clinical experience with drug-coated balloons in certain parts of the world, its use in routine practice is not widespread. Most encouraging comparative efficacy data against DES is limited to studies enrolling patients with in-stent restenosis (10). In fact, the use of drug-coated balloon angioplasty for treatment of de novo stenosis is mostly restricted to selected enthusiastic adopters, and current clinical practice guidelines do not support their use for this indication (11). Two barriers in particular hinder more widespread adoption of this therapy. The first is the excellent clinical outcome seen with current-generation DES based on their thinner stent struts and lower metal footprint. This is nicely illustrated in a systematic review of coronary stent data from 158 trials by a recent stent task force. In this analysis, at 9 to 12 months, the median rates of repeat revascularization in studies with new-generation DES was 2.91% (interquartile range [IQR]: 1.67% to 5.94%), and the rate of stent thrombosis was only 0.47% (IQR: 0.28% to 0.72%) (12). The second is the considerable investment in bioresorbable stent technology as a means to improving late outcomes (13). Although bioresorbable stents might be considered a work-in-progress, iterative development of these devices will likely reduce opportunities for drug-coated balloon angioplasty in the future (14).

Ultimately, the findings of Cortese et al. (4) should provide an impetus for investment in further randomized clinical trials investigating angioplasty with drug-coated balloons. However, in exploring the late benefits of stentless technologies in clinical practice, we must not surrender the predictable acute results and the excellent midterm outcomes that we and our patients have come to expect with current-generation DES devices. For this reason, disruptive

technology such as drug-coated balloon angioplasty must be subject to clinical testing with the tools and techniques we know best. This requires random treatment allocation, sufficient statistical power to reliably detect superiority or noninferiority against DES, and the use of clinical endpoints accepted by academic and regulatory authorities. In the absence of such trials, it is difficult to envisage that the call "the balloon is back!" will gain widespread support in the contemporary era of percutaneous intervention.

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REFERENCES

1. Narins CR, Holmes DR Jr., Topol EJ. A call for provisional stenting: the balloon is back! Circulation 1998;97:1298–305.

2. Byrne RA, Joner M, Alfonso F, Kastrati A. Drug-coated balloon therapy in coronary and peripheral artery disease. Nat Rev Cardiol 2014;11:13–23.

3. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084–9.

4. Cortese B, Silva Orrego P, Agostoni P, et al. Effect of drug-coated balloons in native coronary artery disease left with a dissection. J Am Coll Cardiol Intv 2015;8:2003–9.

5. Dorros G, Cowley MJ, Simpson J, et al. Percutaneous transluminal coronary angioplasty: report of complications from the National Heart, Lung, and Blood Institute PTCA. Registry. Circulation 1983;67:723–30.

6. Hermans WR, Rensing BJ, Foley DP, et al., for the MERCATOR Study Group (Multicenter European Research Trial with Cilazapril after Angioplasty to prevent Transluminal Coronary Obstruction and Restenosis). Therapeutic dissection after successful coronary balloon angioplasty: no influence on restenosis or on clinical outcome in 693 patients. J Am Coll Cardiol 1992;20:767–80.

7. Albertal M, Van Langenhove G, Regar E, et al. Uncomplicated moderate coronary artery dissections after balloon angioplasty: good outcome without stenting. Heart 2001;86:193–8.

8. Radu MD, Raber L, Heo J, et al. Natural history of optical coherence tomography-detected non-flow-limiting edge dissections following drug-eluting stent implantation. EuroIntervention 2014;9:1085–94.

9. Joner M, Byrne RA, Lapointe JM, et al. Comparative assessment of drug-eluting balloons in an advanced porcine model of coronary restenosis. Thromb Haemost 2011;105:864–72.

10. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. Lancet 2015;386:655–64.

11. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2014;35:2541–619.

12. Byrne RA, Serruys PW, Baumbach A, et al. Report of a European Society of Cardiology–European Association of Percutaneous Cardiovascular Interventions Task Force on the Evaluation of Coronary Stents in Europe: executive summary. Eur Heart J 2015;36:2608–20.

13. Wiebe J, Nef HM, Hamm CW. Current status of bioresorbable scaffolds in the treatment of coronary artery disease. J Am Coll Cardiol 2014;64:2541–51.

14. Byrne RA, Kastrati A. Bioresorbable drug-eluting stents: an immature technology in need of mature application. J Am Coll Cardiol Intv 2015;8:198–200.

KEY WORDS angioplasty, dissection, drug-coated balloon