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Current Treatment of In-Stent Restenosis

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Management of patients with in-stent restenosis (ISR) remains an important clinical problem. Although drug-eluting stents (DES) have drastically reduced the incidence of ISR, treatment of DES-ISR is particularly challenging. ISR mainly results from aggressive neointimal proliferation, but recent data also suggest that neoatherosclerosis may play an important pathophysiological role. Intracoronary imaging provides unique insights to unravel the underlying substrate of ISR and may be used to guide repeated interventions. In this paper, we systematically reviewed clinical trial data with currently available therapeutic modalities, including DES and drug-coated balloons, in patients presenting with ISR within bare-metal stents or DES. (J Am Coll Cardiol 2014;63:2659–73) © 2014 by the American College of Cardiology Foundation

Treatment of patients with in-stent restenosis (ISR) remains a challenge (1). Bare-metal stents (BMS) are still frequently used during percutaneous coronary intervention, although they are associated with relatively high restenosis rates, especially when used in complex clinical and anatomic scenarios (2). Factors associated with the current use of BMS include the unaffordable price of drug-eluting stents (DES) in certain geographic areas, concerns about a high risk of bleeding in relation to a requirement for prolonged dual antiplatelet therapy after DES, and a perceived low restenosis risk in large coronary vessels. Accordingly, treatment of patients with BMS-ISR continues to represent a significant therapeutic burden in routine clinical practice in many catheterization laboratories around the world (1,2).

The introduction of DES has drastically reduced the occurrence of severe neointimal proliferation, the dominant cause of restenosis after stent implantation (3). This decrease translated into important reductions in clinical need for subsequent repeat revascularization (4,5). However, first-generation DES were plagued by safety concerns related to a small, but clinically relevant, increase in the risk of very-late stent thrombosis (6). Recently, however, the adoption of newer-generation DES and their unrestricted use in clinical practice has proven that these devices are not only more effective (7) but also safer (8,9) compared with first-generation DES. Nevertheless, DES are not immune to restenosis. In fact, routine angiographic surveillance after unrestricted use of newer-generation devices demonstrates rates of angiographic restenosis of approximately 12% (7). Of additional concern, the treatment of patients with DES-ISR has proven to be particularly challenging (1,10).

In the present review, we discuss currently available therapeutic strategies for the management of patients with ISR. We performed a systematic review to identify all randomized clinical trials published on this subject (11–39). Results of the most recent trials, especially those assessing novel modalities, are critically discussed in the light of previous evidence. In addition, we review recent developments relating to delineation of the underlying substrate accounting for late stent failure. Notably, recent pathological studies demonstrated that "neoatherosclerosis" represents a common substrate in patients with late stent failure (40). In this regard, progress in intracoronary imaging techniques was able to unravel the underlying pathological substrate of ISR in vivo (1). This information may be used to select and tailor interventions to tackle the underlying putative mechanisms and also to optimize results of these repeated interventions.

Methods

A search in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials was performed (without language restrictions) from 1995 through November 30, 2013. In addition, abstract lists and conference proceedings from the 2013 scientific meetings of the American College of Cardiology, the European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, the American Heart Association, and the World Congress on Cardiology were searched. We used, as search limits, the following: humans, randomized controlled trial, "coronary restenosis" and "in-stent restenosis" (Medical Subject Headings). Reference lists from these papers were also reviewed for additional studies.

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Abbreviations and Acronyms

BA = balloon angioplasty
BMS = bare-metal stent(s)
DCB = drug-coated balloon(s)
DES = drug-eluting stent(s)
ISR = in-stent restenosis
OCT = optical coherence tomography

Only randomized clinical trials comparing therapeutic modalities in patients with ISR were included (29 randomized studies in total [11–39]).

Relevant Clinical and Anatomic Issues

Definition. The definition of ISR remains an angiographic one: namely, recurrent diameter stenosis >50% at the stent segment or its edges (5-mm segments adjacent to the stent) (41,42). Angiography not only allows determination of ISR severity but also its morphological pattern. The Mehran system permits a morphological classification of BMS-ISR lesions (pattern I, focal; pattern II, diffuse; pattern III, proliferative; and pattern IV, occlusion) and can predict the need for repeat revascularization after intervention (19%, 35%, 50%, and 98%, respectively) (42). This classification scheme also has prognostic value in patients with DES-ISR (43). In addition, the American College of Cardiology/American Heart Association classification has been validated in patients with ISR: B2-C lesions are not only more frequently associated with suboptimal acute results, but also with a higher restenosis rate and poorer long-term clinical outcomes (44).

Clinical presentation. In terms of clinical presentation, ISR had traditionally been thought to represent a relatively benign clinical entity, with predominantly stable clinical presentation and largely satisfactory acute results with repeat interventions (1,45). This was in keeping with the prevailing etiologic paradigm suggesting that the progressive homogeneous smooth muscle cell proliferation constituted the universal substrate of ISR. More recent studies, however, suggest that patients with ISR frequently present with unstable symptoms and, in fact, many of them exhibit elevations of cardiac markers fulfilling diagnostic criteria for myocardial infarction (7,46).

Whether acute coronary syndrome presentations are more common with DES-ISR remains unknown. However, a shift in the underlying pathological substrate toward restenotic lesions with a higher proportion of in-stent atherosclerotic plaque, the so-called neoatherosclerosis (40), means that this hypothesis deserves further investigation (Fig. 1). Conversely, the natural history of "asymptomatic" patients with angiographic restenosis seems favorable (47). Therefore, treatment of asymptomatic patients (the so-called "oculostenotic reflex") should be avoided whenever possible (48,49). In some cases, however, very severe ISR (>75% diameter stenosis according to quantitative coronary angiography) has also been considered a clinical indication for repeat revascularization. Currently, the functional significance of ISR may be readily evaluated in the catheterization laboratory by using the pressure wire, and prospective studies have validated the use of fractional flow reserve for clinical decision making in these patients (50). Notably, the clinical outcome of patients with ISR with deferred interventions based on a fractional flow reserve >0.75 is excellent (51). This diagnostic strategy is especially attractive in patients with angiographically moderate or ambiguous ISR.

Type of underlying stent: BMS-ISR versus DES-ISR. Accumulating evidence strongly suggests that there are significant differences between ISR that occur after BMS compared with those seen after DES (1,10,52). Time of presentation, morphological patterns, underlying substrate, and response to interventions largely differ in patients with BMS-ISR and DES-ISR (1,52). This finding is consistent with observations that the time course of neointimal accumulation differs considerably after DES compared with after BMS (53,54), which reflects a manifestation of delayed arterial healing that seems to characterize the vascular response after DES implantation (55). Moreover, compared with BMS-ISR, DES-ISR tends to exhibit a focal pattern, often affecting the stent edges. This outcome may be because the overall high suppression of neointimal growth by DES means that technical problems, including geographic miss phenomenon or strut fractures, are relatively more important contributing factors in patients with DES-ISR (1,45). In addition, neoatherosclerosis occurs not only more frequently, but also earlier in patients with DES-ISR compared with those with BMS-ISR (40) (Table 1).

Underlying substrate. Assessing the main underlying cause of ISR may be critical for guidance and optimization of these repeated interventions (1,45). In many patients, underlying mechanical problems explain the subsequent development of ISR. These tend to be preventable and, more importantly, if adequately recognized, they may be corrected during reinterventions. Underexpansion is considered a major factor triggering ISR after either BMS or DES implantation (56,57). This problem may be due to stent underdeployment as a result of undersizing or due to the use of low deployment pressures (57). Conversely, resistant underexpansion may be caused by the presence of underlying heavily calcified lesions that prevent adequate stent expansion despite high dilation pressures. In other patients, however, ISR is detected in well-expanded stents. In selected patients, stent misplacement or stents not fully covering the underlying lesion may explain the appearance of focal ISR. "Candy wrapper" angiographic appearance is typical of geographic miss, particularly in patients treated with DES or brachytherapy (58). In this scenario, the sharp contrast between the excellent appearance in the stent lumen (effective suppression of neointimal growth) and the focal-edge restenosis (negative remodeling, plaque growth, or both) accounts for this distinctive angiographic pattern.

Stent fractures may also trigger focal ISR or even stent thrombosis. Fractures are more frequent in the right coronary artery and occur more frequently in some DES types (1,59). Repeat stent implantation is frequently advocated