Editorial

Treatment of coronary in-stent restenosis—evidence for universal recommendation?

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Coronary artery disease, clinically evident as stable angina, acute coronary syndrome (ACS) or ischemic cardiomyopathy is the leading cause for mortality in Western population. With widespread use of coronary revascularization the rate of death from myocardial infarction (MI) has decreased, whereas mortality from heart failure is rising. Percutaneous coronary intervention (PCI) initially performed as "plain old balloon angioplasty" (POBA) has established standards over the last 25 years with the introduction of bare-metal stents (BMS), drug-eluting stents (DES), drug-coated balloon (DCB) and scaffolds with concomitant antiplatelet therapy (1,2). However, despite the introduction of these innovations, restenosis remains the Achilles' heel of any PCI. Traditionally, coronary restenosis is defined as an angiographically detected reduction of ≥50% of vessel diameter at the site of a previously treated segment or its edges. Several surrogate parameters, like late lumen loss (LLL), minimal lumen diameter (MLD), target lesion revascularization (TLR), and target vessel revascularization (TVR) were introduced to better describe the nature of restenosis. With POBA the rate of restenosis, mainly driven by recoil and proliferative remodelling, was up to 30-60% at 6 months (3). BMS eliminated the issue of recoil but induced neointimal hyperplasia, and the term in-stent restenosis in 16-44% of cases (4). Detailed analyses revealed that restenosis after placement of BMS occurred in 42%, 21%, 30%, and in 7% as focal, diffuse, proliferative and total, respectively (5). The introduction of first-generation DES has substantially reduced both angiographic and clinical appearance of restenosis both in randomized clinical trials and in large-scale registries over 4 years (6). Second-generation DES are typically coated with new polymers and drugs resulting in fewer side-branch occlusion, less periprocedural infarction and restenosis rates (7). However, with widespread use of newer generation DES in complex lesions and "off-label" use rates of restenosis are still high at 12% (8). In-stent restenosis has traditionally been considered benign with recurrent symptoms but without any prognostic impact. However, several analyses revealed that 30-60% of patients develop ACS, predominantly with unstable angina and in 5% with ST-elevation myocardial infarction (STEMI) (9). The treatment strategy for restenosis has changed over 25 years and included conventional POBA, cutting or scoring balloon, BMS, vascular brachytherapy, same DES ("homo-DES"), different DES ("hetero-DES"), drug-eluting balloon (DEB) and even bypass surgery. POBA, with compliant or non-compliant balloons, was one of the first strategies used in patients suffering from restenosis. Despite reasonable outcomes in "focal" restenosis, long-term results of patients with diffuse pattern were less favourable. The use of a cutting balloon preventing slippage, ensured higher luminal gain and led to better clinical outcomes. The use of BMS for BMS restenosis ("sandwich technique") was supported by the fact of larger acute luminal gain. In RIBS I, comparing balloon angioplasty with BMS implantation for BMS restenosis, patients revealed better acute angiographic results as well as better long-term clinical outcomes in the subset of large vessels (>3 mm) and in the setting of restenosis affecting the stent edge (10). Clinical

and angiographic results with DES for BMS restenosis were superior to those with balloon angioplasty, BMS or brachytherapy in several randomized trials (11). Treatment of in-stent restenosis after DES is very challenging and is gaining momentum with the widespread use of DES in primary stenting. Initial experience revealed that the use of DES is associated with better outcomes than other techniques (12). The question whether the same stent or another stent will be superior was addressed in the ISAR-DESIRE 2 trial which not only confirmed that repeat DES implantation is safe for DES restenosis up to 1 year but also showed that using either SES or PES for DES restenosis has similar anti-restenotic efficacy (13). More recently, the concept of DCB for restenosis have been proven to be very effective in patients with both BMS as well as DES in-stent restenosis (14) with the advantage of avoiding multiple stent layers; DCB are noninferior to paclitaxel-DES and both DCB and paclitaxel-DES are superior to POBA (15).

Recently, the largest Bayesian network meta-analysis including 2,059 patients compared the effects of POBA, DES and DEB for the treatment of in-stent restenosis (BMS 42% and DES 58%) and revealed that surrogate endpoint parameter TLR was lowest in DEB and DES as compared to POBA without any significant difference between DES and DEB and without any significant difference between all three groups according to clinical endpoints for MI and mortality. On angiographic outcome analysis, DEB or DES also showed a significantly lower risk of binary restenosis at 6- to 9-month follow-up angiography than POBA (16).

Current literature reveals superiority of DES and DEB for the treatment of BMS in-stent restenosis, which is pointed out in the Guidelines by a recommendation, Class I, Level of Evidence A (1,2). However, in the future, the main issue will be how to deal with DES in-stent restenosis considering a penetration rate of 90%. The main limitation of trials addressing in-stent restenosis is the solely angiographic view on restenosis without a holistic perspective on this vexing problem. Underlying mechanisms of restenosis are complex and can be divided into lesion-specific, procedure-related and patient-related. There is evidence that high-risk patients (e.g., diabetics, end-stage renal failure, previous bypass graft surgery, arterial hypertension) ware prone to higher restenosis rates and that these factors should be taken into considerations when choosing a revascularization strategy (1,2). Regardless of treatment strategy these modifiable patient-related factors should be considered in the context of secondary prevention. Similarly, there is evidence that procedure-related factors are of utmost importance to avoid restenosis and stent thrombosis. Also anatomic features are important with increased likelihood of re-stenosis in the setting of saphenous vein graft disease, small vessel diameter, long lesions, bifurcation lesions, left main lesions and chronic total occlusion. Evaluated methods for prevention of in-stent restenosis and its recurrence consist of optimized implantation techniques, better stent design, improvements in reservoir design, development of bioabsorbable polymers, polymer-free drug delivery, fully biodegradable stents, stents eluting new pharmaceutical agents, and finally, gene therapy and prohealing therapy. Technical failure of the implantation with small post-procedural diameter, higher residual percent diameter stenosis, underexpansion, overexpansion, stent fracture, non-uniform distribution of stent struts and malapposition have all been associated with DES restenosis. Such shortcoming can be reduced with use of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) for procedure optimization (17). Advanced techniques such as fractional flow reserve (FFR), IVUS and OCT have greatly improved the ability to visualize re-stenosis and make quantitative assessments of functional relevance, neointimal thickness, neointimal volume, and MLD. Conversely, as the natural history of "asymptomatic" patients with angiographic restenosis with no ischemia is favorable (18), the so-called "oculostenotic reflex" should be avoided whenever possible. However, analysis of data on treatment strategies of in-stent restenoses with DES is characterized by small studies having variable results with "old-fashion" stents for first generation DES. To date, there have been no reports on the use of newer-generation DES for DES-restenosis. Subanalysis of RIBS III suggested that the use of second-generation DES was superior to first-generation DES, and that guidance with intracoronary imaging was associated with better long-term results (19,20). Recently, the RIBS V and RIBS IV trials reported superiority of DES for the treatment of BMS and DES restenosis as compared to DCB in terms of angiographic endpoints, but without a clear signal of clinical benefit over one specific DCB using iopromide as a hydrophilic spacer used in all comparing trials. It is important to note that any of these therapeutic strategies offer solutions for the failure of initially implanted opzimized stents. Thus, the treatment of restenosis is always associated with a natural delay of a success of the initial treatment. To optimize the dynamic process of restenosis treatment, there will be ongoing need to conduct studies on restenoses therapy with adaptable innovations. Current evidence should always be challenged

by newer strategies and revolutionary treatment strategies. Apart from stents and scaffolds it seems that better understanding of the biological nature of restenosis, specific drugs may be key to successful tackling of restenosis rather than placement of local devices such as stents. Whether drug delivery will be local or systemic needs to be shown in future trials, but regardless of any innovation and a motion towards personalized medicine an honest comparison to current standards remains the benchmark for new treatment to become standard.

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Footnote

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