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REVIEW

Spot Stenting is Preferable in Long Diffuse Coronary Lesions: Possible Incremental Value of Physiologic and Intracoronary Imaging Modalities

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KEY WORDS: *coronary artery disease; long lesions; diffuse coronary disease; spot stenting; percutaneous coronary intervention; coronary angioplasty*

Abbreviations
BMS = bare-metal stents
DES = drug-eluting stents
FFR = functional flow reserve
ISR = in-stent restenosis
IVUS = intravascular ultrasound
MACE = major adverse cardiac events
NIRS = near-infrared spectroscopy
OCT = optical coherence tomography
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
TLR = target lesion revascularization

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ABSTRACT

The treatment of long and diffuse coronary lesions with percutaneous coronary intervention (PCI) has been problematic since the era of plain balloon angioplasty. With the advent of bare-metal stents (BMS), long and multiple stents were used to completely cover the diseased segments in order to improve outcomes. Lesion length has been proven to be a factor related to higher rates of restenosis and target lesion revascularization (TLR) and the risk was further increased by the multiplicity of implanted stents. Covering the lesion with the least number of non-overlapping stents might reduce the risk of restenosis. This strategy, called *spot stenting*, was initially tested in the BMS era to treat discrete high-grade disease within moderately diseased vessel segments and has been shown to significantly reduce restenosis rates. Drug-eluting stents (DES) have been consistently shown to reduce restenosis and the need for TLR and thus provide improved clinical efficacy compared with BMS. However, even with DES, diffuse disease and long lesions are still associated with an increased risk of restenosis, need for TLR and major adverse cardiac events (MACE). A major long-term concern regarding DES is the potential for stent thrombosis which is increased after complex procedures with implantation of longer, multiple and overlapping stents. Data are limited but recent reports suggest that even when DES are used, selective stenting of only the severely narrowed areas of long lesions reduces the risk of MACE compared to full lesion coverage. The data supporting the spot stenting approach along with some considerations regarding the technique are presented herein.

THE CHALLENGE OF LONG CORONARY LESIONS WITH DIFFUSE DISEASE

The treatment of long diffuse coronary lesions with percutaneous coronary intervention (PCI) has been problematic. Since the era of plain old balloon angioplasty, lesion length has been a factor related to higher rates of restenosis and target lesion revascularization (TLR). The advent initially of bare-metal stents (BMS) and soon afterwards of drug-eluting stents (DES) reduced TLR but still efficacy is suboptimal and safety concerns remain.

A. BARE – METAL STENT PERIOD

In the BMS era, multiple and long stent implantation for long, diffuse lesions was associated with a high incidence of diffuse in-stent restenosis (ISR).[1,2] Diffuse ISR is however a major risk factor for malignant recurrent ISR, and therefore full lesion coverage with traditional stenting is associated with a poor clinical outcome.[3] Kobayashi et al reported a relationship between length of stented segment and restenosis: 24%, 35%, and 47% for segment lengths <20 mm, 20–35 mm, and >35 mm, respectively.[2] The treatment of diffuse ISR is exceedingly problematic with recurrence rates of 42-80% that frequently necessitate multiple additional PCIs or coronary artery bypass grafting.[4] The investigators of the New Approaches to Coronary Intervention (NACI) registry have suggested that stenting of long coronary lesions (>20 mm) involves significantly higher rates of the need for repeat TLR than more discrete lesions. Multivariate analysis showed that each 1-mm increase in lesion length was associated with an increased relative risk of 1.014 (95% confidence intervals-CI, 1.004-1.025) for TLR at 1 year.[5] A series by Kastrati et al examined the contribution of lesion length to restenosis as opposed to stent length per se.[1] In multivariate analysis, lesion length was found to be an independent risk factor for restenosis with the risk further increased by multiple and overlapping stent placement that were also independent risk factors of restenosis. Stented segment length did not show any independent effect. It was concluded that long lesions represent an independent risk factor for restenosis after coronary stent placement and that a possible way to reduce the risk would be to cover the lesion with a minimal number of non-overlapping stents.[1]

Spot stenting, defined as the selective stenting of only the most severely narrowed parts of long, diffuse lesions has been proposed as an alternative PCI strategy in this setting.[6,7] Colombo et al compared spot stenting to a traditional stenting strategy for long and diffuse coronary artery disease. Outcomes of a consecutive series of 130 long lesions (>15 mm) in 101 patients treated with intravascular ultrasound (IVUS) guided PCI and spot stenting were compared with those of a traditionally stented matched group of patients. Coronary angioplasty was performed with a balloon to vessel ratio of 1:1, according to the IVUS media-to-media diameter of the vessel at the lesion site, to achieve prespecified IVUS criteria: lumen cross-sectional area ≥5.5 mm^2 or ≥50% of the vessel cross-sectional area at the lesion site. The stents were implanted only in the vessel segments where the IVUS criteria were not met. In the spot stenting group, stents were implanted in 67 of 130 lesions, and the mean stent length was shorter than that of lesions in the matched traditional stenting group (10.4±13 mm vs. 32.4±13 mm, p <0.005). The 30-day major adverse cardiac event (MACE) rate was similar (5%) for both groups. Angiographic restenosis was 25% with spot stenting, as compared with 39% with the usual technique (p <0.05). At 6-month follow-up, MACE and TLR rates were lower with spot stenting (22% vs. 38%; p <0.05 and 19% vs. 34%, p <0.05 respectively). Thus, IVUS guided spot stenting with BMS was associated with good acute outcome and significantly reduced angiographic restenosis and follow-up adverse event rates compared to traditional stenting.[6]

B. DRUG-ELUTING STENT PERIOD

Randomized clinical trials and registries which included complex coronary lesions found that DES reduce the need for revascularization and thus provide superior clinical efficacy in routine practice compared with BMS.[8] DES implantation for small vessel disease or long lesions with multiple stents is efficacious for reduction of restenosis rates and TLR rates compared with BMS implantation.[9,10] In the DES era, interventionalists implant stents to cover the entire atherosclerotic lesion, that is, the stented segment length tends to be longer than the lesion length and the use of multiple, overlapping DES has been considered a suitable approach in clinical practice.[11,12] However, stent length, number of stents, and the use of overlapping stents have all been associated with an increased risk of restenosis, thombosis and stent fracture.[13-16] Coronary artery lesion length is still an independent predictor of restenosis following PCI with DES.[17] Recently, Raber et al reported an increased risk of both TLR and composite end-point of death and myocardial infarction in patients with overlapping DES compared to patients with single or multiple, but not overlapping stents.[14] DES overlap occurs in >10% of patients undergoing PCI in routine clinical practice and is associated with impaired angiographic and long-term clinical outcome, including death or myocardial infarction.[14]

Notably, stent thrombosis has been shown to occur very long after the index procedure.[15] In the Bern and Rotterdam study, stent thrombosis was reported to occur in a continuous rate of 0.4-0.6% per year for up to 4 years without diminution.[18] Previous data including a meta-analysis of 10 randomized studies demonstrated that stent length is a risk factor for acute and late stent thrombosis and MACE.[19] Suh et al also reported that stent length was one of the predictors of stent thrombosis and that the threshold of stent length for predicting DES thrombosis was 31.5 mm.[20] The SYNTAX trial showed a stent thrombosis rate of 3.3% at 1 year which suggests that complex procedures with implantation of longer and multiple DES to treat multi-vessel disease and fully cover atherosclerotic lesions may be associated with an increased risk for stent thrombosis.[21] Polymer hypersensitivity reactions, positive remodeling with late acquired malapposition, delayed arterial healing, late stent fracture, and endothelial dysfunction are a few of the possible causes of the increased risk of very late stent thrombosis with first generation DES.[22,23] It has been shown that even a small (>0.14%/year) incremental risk of thrombosis with DES might be sufficient to outweigh the benefit of restenosis prevention and favor BMS use for the

overall PCI population.[24] To address these issues concerning first generation DES, new DES have been developed with novel materials, designs, and delivery systems, with improved biocompatible polymers, and new antiproliferative agents compared with their predecessors.

Because treatment of hemodynamically non significant lesions is not indicated, the adoption of selective stenting with DES of only hemodynamically significant stenoses in the context of diffuse disease with variable severity is logical in clinical terms. Katritsis et al compared spot stenting to a strategy of full stent coverage for long and diffuse lesions when first generation DES are used.[25] Consecutive patients (n=179) with long (>20 mm) coronary lesions of non uniform severity and indication for PCI were randomized to full lesion coverage with multiple, overlapping stenting or spot stenting of hemodynamically significant lesion parts only, defined as diameter stenosis >50% as measured by quantitative coronary angiography (QCA). At 1-year follow-up, MACE were significantly fewer among patients with spot stenting compared to full coverage with DES (5.6% vs 15.6%, p = 0.031). At 3 years, MACE were also significantly fewer (7.8% vs 20%, p=0.019) and a Cox proportional hazard model showed that the risk for MACE was almost 60% lower in patients with spot stenting compared to those with full stenting (hazard ratio 0.41, 95% CI 0.17 - 0.98, p = 0.044).[25] The results were similar at long-term follow up (2-7 years) when it was demonstrated that the risk for MACE was almost 65% lower among patients with spot stenting.[26] The authors concluded that in the presence of diffuse disease of non uniform severity, selective stenting of only the significantly narrowed parts of the lesion confers better long-term results compared to total lesion coverage with first generation DES.

DISCUSSION

The abovementioned data, albeit limited, indicate that a minimalistic approach of spot stenting is preferable to the "full metal jacket" or "normal to normal" approach with both BMS and DES. As stented length increases the risk for restenosis and stent thrombosis also increases, since the innate morphology and physiology are disrupted by unnecessary metal, polymer and drug. It is a fact that in diffuse and uniformly severe disease full lesion coverage with stents is frequently necessary (Fig. 1). The comparison of spot stenting to full stent coverage is meaningful for long and diffuse lesions of non uniform severity. The studies are limited and there is no study comparing the two techniques with second generation DES, which are at least as effective and probably safer compared to first generation DES. This has been demonstrated in a recently published network meta-analysis of 49 randomized controlled trials (including 50844 patients) comparing PCI outcomes between different DES or between DES and BMS. Second generation cobalt – chromium everolimus –eluting stents had the lowest rate of stent thrombosis within 2 years of implantation compared to first generation DES but also compared with BMS.[27] If this finding is confirmed in further randomized trials, it would be a paradigm shift. Furthermore, recent data suggest that

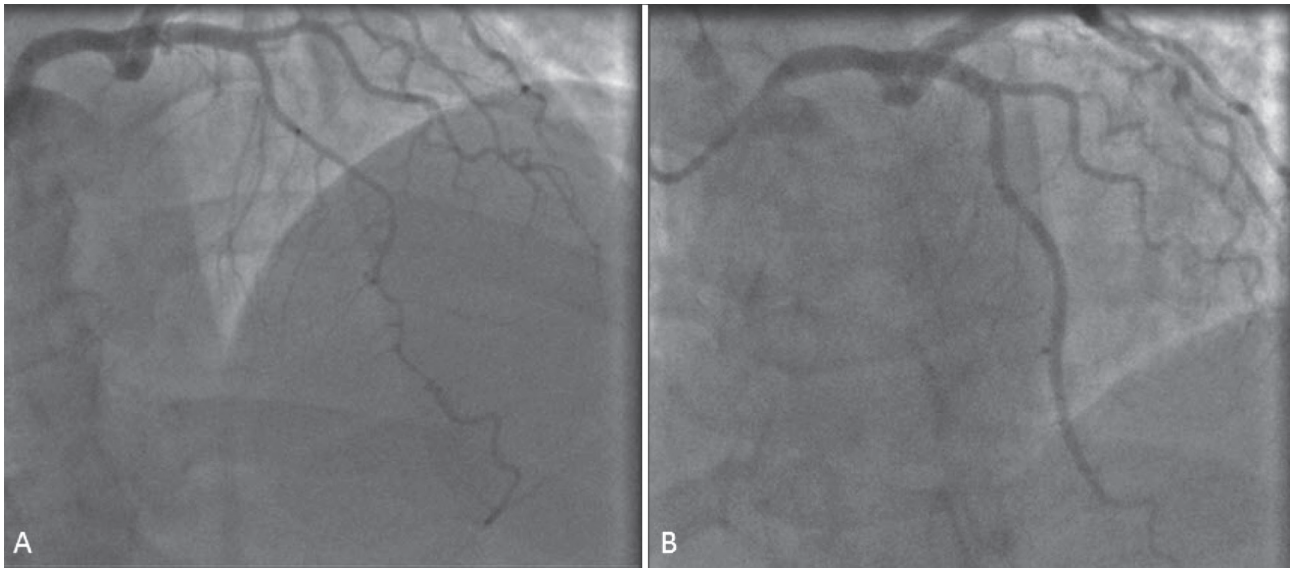

FIGURE 1. A. An example of long, diffuse and uniformly severe disease of the left anterior descending artery, responsible for an acute coronary syndrome with anterior wall ischemia. **B.** The lesion was treated by full lesion coverage with DES since in this case spot stenting was not possible.

compared to durable polymer everolimus-eluting DES, other second generation DES, such as zotarolimus and biolimus eluting, are probably equally safe and effective, making a class effect possible regarding this issue.[28,29] For the time being, data are lacking to answer the question whether spot stenting would still be preferable to full lesion coverage when second generation DES are used. The same question should also be answered for DES with bioabsorbable polymer and for the upcoming fully bioabsorbable DES.

A traditional "normal to normal" stenting approach is simpler, probably faster, less intellectually demanding and perhaps leads more easily to an optically "perfect" angiographic result. However, even with the limited existing data, spot stenting has been shown to be superior because optimal outcomes are obtained if stents are implanted only to treat functionally significant disease as shown in the FAME trial.[30] In this multi-center trial, 1005 patients with multi-vessel disease were randomized to undergo PCI with implantation of DES either guided by angiography alone or guided by functional flow reserve (FFR) measurements in addition to angiography. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was ≤0.80. At 1 year, MACE and each of their individual components (death, myocardial infarction and the need for repeat revascularization) were reduced by 30% - 40% in patients randomized to FFR-guided PCI compared with those randomized to standard angiographic guidance. Furthermore, patients randomized to angiography guidance had PCI performed on a significantly greater number of lesions, resulting in greater stent number and length.[30] At two years of follow-up, the superiority of FFR-guided versus angiography-guided PCI persisted as combined rates of death, nonfatal myocardial infarction, and revascularization were 17.9% versus 22.4%, respectively. For lesions deferred on the basis of FFR >0.80, the rate of myocardial infarction was 0.2% and the rate of revascularization was 3.2% after 2 years (Table 1).[31] The value of FFR to guide stenting decisions was also demonstrated by the recent publication of FAME 2 trial where in patients with stable coronary artery disease and functionally significant stenoses, FFR-guided PCI plus the best available medical therapy decreased the need for urgent revascularization as compared with the best available medical therapy alone.[32] The FAME 1 and 2 trials established FFR as the best currently available method to evaluate the functional significance of coronary lesions and therefore FFR is recommended for PCI guidance in stable patients in the recent myocardial revascularization guidelines.[33]

In the main studies comparing spot stenting to traditional stenting, Colombo et al used IVUS, while Katritsis et al used QCA for spot stenting guidance.[6,25] However, these techniques are not accurate to assess the physiologic significance of lesions. QCA is inherently inferior to IVUS and as very recently shown in the FIRST study anatomic measurements by IVUS show only a moderate correlation with the FFR values, while the optimal cutoff for an IVUS measured minimal lumen area to detect FFR ≤0.80 is vessel diameter dependent and not yet adequately standardized and validated.[34] Concerning diffuse disease it should be noted that FFR is not only a means to gain a functional assessment *per vessel* but also *per vessel segment* and thus can guide complex PCI in case of diffuse disease.[35] In the FAME trial, FFR was measured with a coronary pressure guidewire at maximal hyperemia induced by intravenous adenosine, administered at a rate of 140 μg/kg/min through a central vein. In the case of diffuse atherosclerosis punctuated by focal areas of more severe stenosis, or in the case of more than one stenosis within the same artery, pressure pullback recordings during hyperemia were performed and stenting was indicated for lesions with sudden pressure drops (ΔP>10-15 mmHg) during pullback (Table 2).[30,35] FFR is therefore a technique supported by robust clinical data that can guide a spot stenting approach. It should be noted that it is not indicated for PCI in cases of patients with acute myocardial infarction nor to evaluate the hemodynamic significance of infarct-related artery stenoses for several days post-infarction, since FFR would be high because of stunning and edema of the infarcted territory.[36] After their resolution, which means at least 5 days later depending on the infarct extent and patient related factors, FFR could be applied with a similar ischemia threshold value as in stable patients to assess the hemodynamic significance of residual or recurrent stenoses.[36,37]

Further anatomic details provided by intracoronary imaging techniques such as IVUS (Fig. 2) or even better optical coherence tomography (OCT), which has a much higher resolution, could further optimize spot stenting PCI by controlling for inadequate stent apposition, tissue protrusion, intraluminal thrombus and edge dissection.[38] Near-infrared spectroscopy (NIRS) combined with IVUS is also a promising novel imaging modality that could add to spot stenting technique precision in order to avoid incomplete coverage of lipid core plaques and thus minimize the risk of intra-procedural complications and post-procedural adverse events.[39] It should be kept in

TABLE 1. Results of the FAME trial at 1 and 2 years.[30,31]

	Angiography guided PCI	FFR guided PCI
Stenting	All lesions	If FFR ≤0.80
Stents per patient	2.7±1.2	1.9±1.3
1- year MACE*	18.3%	13.2%
2- year MACE*	22.4%	17.9%

FFR = functional flow reserve; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention
*MACE: Death, non fatal myocardial infarction or repeat revascularization.

TABLE 2. Algorithm for FFR use to guide spot stenting in non uniform diffuse disease with serial lesions.[30,35]

1) Advance pressure wire at the most distal part of the coronary artery	
2) Induce hyperemia by IV adenosine and measure FFR	If FFR >0.80 → no stenting is needed. If FFR ≤0.80 → proceed to pullback under fluoroscopy
3) Decision to stent according to pullback results	If the pressure decline is gradual due to diffuse disease → optimal medical treatment If sudden pressure drops (ΔP>10-15 mmHg) are found during pullback → spot stent
4) Stenting sequence	The most "severe spot" should be stented first and pullback repeated to check the other lesions By stenting the most severe lesion the gradient of other lesions may increase. This is much more common when distal lesions are stented first than vice versa
5) Control	Check the final result with another final pullback recording to check stented and other artery segments. Measure final distal FFR

FFR = functional flow reserve

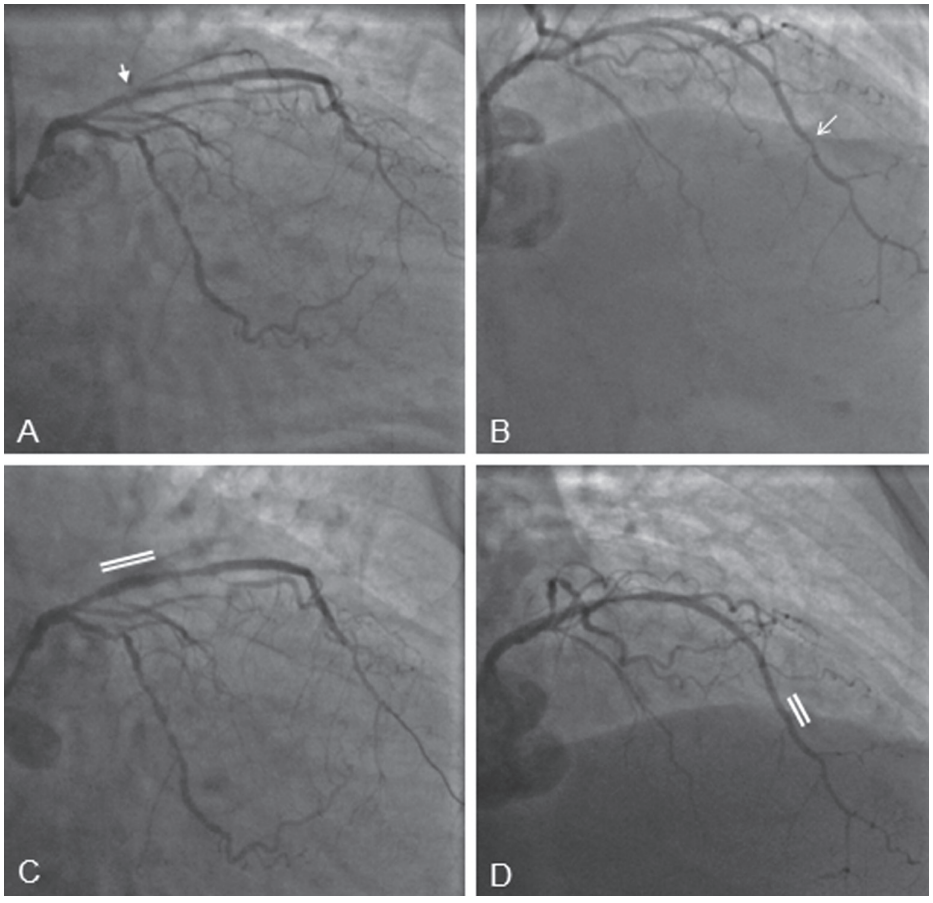

FIGURE 2. Spot stenting example. **A & B:** Proximal and mid LAD segments are diffusely diseased but there is more severe narrowing just distal to the first septal branch (panel **A**, arrow) and at the distal LAD (panel **B**, arrow). **C & D:** Following IVUS which was performed to determine the length of the stent for proximal and mid LAD, a 3×12 mm stent was implanted to treat only the focal proximal lesion and a 2.5×9 mm stent to treat the focal distal lesion and the final results are shown in panels **C & D** (white parallel lines).

mind though that intracoronary imaging modalities always add considerably to the procedural cost and their use (if, which one and why) depends on availability and should be decided on a case-by-case basis.

CONCLUSION

A minimalistic approach of spot stenting seems preferable to the "full metal jacket" approach for PCI in case of long lesions and diffuse coronary artery disease. As stented length increases the risk for restenosis and stent thrombosis increases since metal, polymer and drug disrupt the innate morphology and physiology. Angiography ± QCA, IVUS, OCT, NIRS and FFR can help guide the spot stenting approach depending on the experience of each catheterization laboratory. Stents should be implanted only to treat functionally significant disease, which is best documented by FFR that can reliably measure the functional significance of lesions per vessel but also per vessel segment. Spot stenting could be further optimized by the use of intracoronary imaging techniques which should be decided on a case-by-case basis.

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