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ORIGINAL ARTICLE

Impact of vessel size, lesion length and diabetes mellitus on angiographic restenosis outcomes: Insights from the NIRTOP study

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Abstract

Background: The primary objective of the current analysis was to define the impact of vessel size, lesion length, and diabetes on clinical and angiographic restenosis following implantation of the NIRFLEX stent. *Methods and results:* Clinical and angiographic restenosis outcomes and multivariate predictors were compared between patients treated in 'small' (<3 mm, $n=113$ pts/133 lesions) versus 'large' (≥ 3 mm, $n=41$ pts/53 lesions) vessels; between 'tubular' (10–20 mm lesion length $n=49$ pts/51 lesions) versus 'discrete' (<10 mm lesion length $n=103$ pts/133 lesions) lesions; and between 'diabetic' ($n=30/35$ lesions) versus 'non-diabetic' ($n=128/156$ lesions) patients using the flexible closed-cell design 'bare-metal' NIRFLEX stent in patients with native coronary artery disease. At six month follow-up, target vessel revascularization (TVR) and target lesion revascularization (TLR) rates were significantly less frequent in the 'large' versus 'small' vessel group (2.4% versus 16.8% for TVR, $P=0.016$, 0% versus 12.4% for TLR, $P=0.022$). Likewise, angiographic late loss was lower in 'large' versus 'small' vessels (0.54 versus 0.70 mm, $P=0.05$). Lesion length affected MACE rates but not angiographic restenosis. Angiographic late loss was greater in diabetics compared to the non-diabetic group (0.89 versus 0.60 mm, $P=0.003$). Using a multivariate model, diabetes mellitus (odds ratio $=2.65$, $P=0.047$) and post-procedure in-stent MLD (mm) (odds ratio $=0.178$, $P=0.0019$) were major determinants of restenosis. *Conclusion:* Clinical and angiographic restenosis outcomes following NIRFLEX stent implantation were dependent upon vessel size, lesions length, post-procedural stent lumen dimensions, and the diabetic status.

Key Words: *Restenosis, stents, revascularization, stents, diabetes*

Introduction

The NIRTOP trial was designed to show equivalency in safety and effectiveness between the NIRFLEX and the NIRFLEX 'fused gold' Royal stent system in the treatment of native coronary artery lesions (1). The study showed that the 'bare-metal' NIRFLEX version was associated with superior angiographic results although had equivalent clinical outcomes (1). The study results also showed excellent angiographic and clinical outcomes for the bare-metal NIRFLEX stent configuration with very low rates of clinical and angiographic restenosis endpoints. Based upon prior observations, we assumed that the following parameters: vessel size, lesion length and diabetes status could have a biological impact upon restenosis outcomes in the NIRTOP trial (2–5). Those parameters could further improve or negate the favorable results obtained by bare metal stents. Thus, the primary objective of the current analysis was to define the impact of these parameters (e.g. vessel size, lesion length, and diabetes mellitus) on clinical and angiographic restenosis outcomes and to define the independent predictors for angiographic restenosis following implantation of the flexible closed-cells NIRFLEX stent in patients with obstructive atherosclerotic coronary disease.

Methods

Study population

The local ethics committees approved the study protocol. Written, informed consent was obtained

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from all patients at baseline and during follow-up angiography at 6 months after stent implantation. Patients were eligible if they had symptomatic coronary disease, with one or more *de novo* or non-stented re-stenotic lesions of the native coronary circulation suitable for stent implantation. The visually estimated reference vessel diameter was 2.5–4.0 mm, and lesion length $\leq$30mm. Angiographic exclusion criteria were excessive vessel tortuosity, unprotected left main disease, ostial or bifurcation lesions, chronic total occlusions, intraluminal thrombus, in-stent restenosis or any contraindication to emergency coronary artery bypass surgery. Although in the original study patients were randomized to receive either a 'fused-gold' (NIRFLEX Royal) or a 'bare' (NIRFLEX) stainless steel stent (Medinol Ltd, Tel Aviv, Israel), only patients who received the 'bare' (NIRFLEX) stainless steel stent were included in the current analysis. Clinical and angiographic restenosis outcomes and multivariate predictors for restenosis were distinguished and compared: (i) between patients treated in 'small' ($<$3 mm reference diameter) versus 'large' ($\geq$3 mm reference diameter) sized vessels; (ii) between patients treated in 'tubular' (10–20 mm lesion length) versus 'Discrete' ($<$10 mm lesion length) lesions, and (iii) between diabetic and non-diabetic patients. All patients received combination anti-platelet therapy, consisting of aspirin $>$100 mg per day for an indefinite duration and clopidogrel 300 mg pre-procedure and 75 mg once daily for 30 days post-procedure. Heparin was administered to achieve an activated clotting time of $>$250 s. A glycoprotein IIb/IIIa inhibitor was used at the discretion of the operator. Stent length and diameter were determined by visual estimation or quantitative coronary angiography (QCA) with a stent to distal reference vessel ratio of between 1:1 and 1.1:1.0. Direct stenting (without balloon pre-dilatation) was performed at the discretion of the operator. Stents were post-dilated, when necessary, using high-pressure balloon inflations to obtain optimal stent expansion.

QCA imaging

QCA was performed at pre- and post-procedure and at 6 months follow-up. Vessel size was determined as the average of proximal and distal diameters just prior to the coronary intervention. The 6 months follow-up angiography was performed in the same technique as above, with same angiographic angles that were taken pre- and post-stent implantation. Off-line QCA measurements were performed by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands) according to established methodology (6).

Definition of end points

For the current analysis the primary objective was to evaluate in-stent late loss (mm), loss index and binary restenosis at six month angiographic follow-up. 'Late loss' is the difference between MLD post-procedure and MLD follow-up'. 'Absolute gain' is the difference between MLD post-procedure and MLD pre-procedure. 'Late loss' index is the quotient of 'late loss' and 'absolute gain'.

Secondary end-points were the occurrence of MACE (death, myocardial infarction, and repeat target *lesion* revascularization), target lesion revascularization (TLR), target vessel revascularization (TVR) rates at 6 and 9 months follow-up. Binary angiographic restenosis was defined as $\geq$50% diameter stenosis by QCA within the stented segment. Target vessel revascularization was defined as repeat percutaneous or surgical revascularization procedures involving the original target vessel within six month of the index procedure.

Compliance to the study follow-up was as follows: 98.7% clinical at 150 days, 90.5% clinical at 180 days, and 88.5% angiographic at 180 days. At nine months (270 days) there was no systematic follow-up mandated by the study protocol but events were continued to be reported to the sites and thus to the Data Coordinating Center at Cardialysis.

Statistics

All data expressed as the mean value$\pm$SD. The analysis was performed on the actual stent received. Differences in normally distributed continuous variables were tested by the unpaired Student's *t*-test. Categorical data were assessed by Fisher's exact test. A *P*-value $<$0.05 was considered statistically significant. Univariate and multivariate analysis models used the logistic regression statistical model to predict binary restenosis outcomes. The model included all variables with $P<0.1$ in the univariate analysis model.

Results

Vessel size (Table 1)

One hundred and fifty-four patients (186 lesions) who were treated using the NIRFELX bare metal stent and underwent native vessel coronary angioplasty were included in the current analysis. Patient were distinguished based upon their target vessel size as 'small' vessels ($<$3 mm reference vessel diameter, $n=113$ pts/133 lesions) were compared to 'large' vessels ($\geq$3 mm reference vessel diameter, $n=41$ pts/53 lesions) results. There were no major differences in age, gender, vessel distribution (i.e. LAD versus non-LAD) between groups. However there was a strong trend towards a higher prevalence of

Table I. Characteristics and outcomes distinguished by vessel size.

	'Small <3 mm' ($n=113$ pts)	'Large ≥3 mm' ($n=41$ pts)	P value
Age (years)	60.4±10.6	58.9±10.4	0.43
Male gender	79.6%	85.4%	0.49
Diabetes mellitus	23.0%	9.8%	0.07
LAD	39.1%	34.0%	0.62
Lesion length (mm)	10.0±4.2	11.2±4.9	0.09
Multivessel disease (%)	50%	39%	0.16
RVD (mm)	2.48±0.32	3.38±0.34	<0.0001
Stent length (mm)	12.3±5.3	13.6±6.1	0.16
Post procedure			
In-stent MLD (mm)	2.29±0.34	2.90±0.37	<0.0001
Long-term outcomes @180 days:			
TVR	8.0%	2.4%	0.29
TLR	6.2%	0%	0.19
TVR not including TL	2.7%	2.4%	1.0
MACE	8.0%	4.9%	0.53
Long-term outcomes @270 days:			
TVR	16.8%	2.4%	0.016
TLR	12.4%	0%	0.022
TVR not including TL	5.3%	2.4%	0.68
MACE	15.0%	4.9%	0.10
Angiographic restenosis parameters @180 days			
Mean late loss (mm)	0.70±0.48	0.54±0.45	0.05
Loss index	0.52±0.39	0.34±0.31	0.005
Binary restenosis	22.2%	6.3%	0.013

diabetes mellitus among the 'small' versus 'large' vessel group (23.0% versus 9.8%, $P=0.07$). Multivessel disease was encountered in 50% of patients with 'small' versus 39% of patients with 'large' culprit lesions ($P=0.16$) (Table I).

Lesion length and stent length were comparable within both groups. As expected, the reference vessel diameter was greater for 'large' versus 'small' vessels (3.38±0.34 versus 2.48±0.32 mm, $P<0.001$). Accordingly, post procedure in-stent minimal lumen diameter was greater for 'large' versus 'small' vessels (2.90±0.37 versus 2.29±0.34 mm, $P<0.001$) but post-procedure percent diameter stenosis was similar for both groups (8.6% versus 9.2%, $P=$NS).

No deaths were observed during the study follow-up period. Technical success was 100% in both groups. Procedural success for both groups was 97% and 96% in 'large' vs. 'small' vessels ($P=$NS). Stent thrombosis rate was 0% among the two groups. In the 'large' vessel' group 95.1% of patients remained MACE-free at 270 days, compared to 85% in the 'small' vessel group ($P=0.10$). The majority of these events were repeat revascularization via PCI. Target vessel revascularization (TVR) and target lesion revascularization (TLR) rates were significantly less frequent in the 'large' versus 'small' vessel group (2.4% versus 16.8% for TVR at 270 days, $P=0.016$). Of note, during the same period target lesion revascularization (TLR) was observed in none (0%) of the large vessel group and in 12.4% of the 'small' vessel counterpart group ($P=0.022$). Non-TLR repeat revascularization rates were similar for both groups. One hundred and ninety-one lesions ($n=191$) were available for 6-month angiographic follow-up. The late loss at follow-up was lower in the 'large' compared to the 'small' vessels (0.54 versus 0.70 mm, $P=0.05$). The 'large' vessel group was also associated with a lesser loss index (0.34 versus 0.52, $P=0.005$) and binary restenosis rates (6.3% versus 22.2%, $P=0.013$).

Lesion length

Although overall angiographic restenosis did not differ between groups distinguished by length, the overall MACE rate was significantly higher in patients with longer lesions (Table II). Thus, MACE rate was greater at six month and appeared to be significantly higher at 270 days (20.4% versus 7.8%, $P=0.032$) in 'tubular' ($n=49$ pts/51 lesions) versus 'discrete' ($n=103$ pts/133 lesions) lesion length characteristics. This latter figure was only partially driven by more repeat revascularization events among patients with longer lesions.

Diabetes mellitus (Table 3)

Patient outcomes were further distinguished by their diabetic status (Table III). Thirty diabetic patients (35 lesions) were compared to 128 non-diabetic patients (156 lesions). There were no major differences in age, gender, vessel distribution (i.e. LAD versus non-LAD) between groups. Lesion length and stent length were comparable among both groups.

Table II. Characteristics and outcomes distinguished by lesions length.

	'Tubular 10–20 mm' ($n=49$ pts)	'Discrete <10 mm' ($n=103$ pts)	*P* value
Age (years)	61.3±10.6	59.5±10.5	0.33
Male gender	75.5%	85.4%	0.17
Diabetes mellitus	22.4%	18.4%	0.66
LAD	39.2%	37.6%	0.62
Lesion length (mm)	13.7±4.6	8.8±3.2	<0.001
RVD (mm)	2.79±0.54	2.71±0.52	0.37
Stent length (mm)	16.7±6.2	10.9±3.8	<0.001
Post procedure			
In-stent MLD (mm)	2.43±0.47	2.48±0.44	0.46
Long-term outcomes @180 days:			
TVR	8.2%	5.8%	0.73
TLR	4.1%	4.9%	1.0
TVR not including TL	4.1%	1.9%	0.59
MACE	12.2%	4.9%	0.18
Long-term outcomes @270 days:			
TVR	16.3%	10.7%	0.43
TLR	10.2%	7.8%	0.76
TVR not including TL	6.1%	3.9%	0.68
MACE	20.4%	7.8%	0.032
Angiographic restenosis parameters @180 days			
Mean late loss (mm)	0.66±0.47	0.63±0.47	0.71
Loss index	0.47±0.33	0.34±0.39	0.79
Binary restenosis	19.6%	16.2%	0.65

The reference vessel diameter tended to be greater for non-diabetics vs. diabetic patients (2.78±0.5 versus 2.53±0.53 mm, $P=0.07$). In the diabetic group 76.7% of patients remained MACE-free at 270 days, compared to 90.6% in the non-diabetic patients group ($P=0.06$). Target vessel revascularization (TVR) and target lesion revascularization (TLR) rates were greater in the diabetic versus non-diabetic group (26.7% versus 9.4% for TVR, $P=0.027$ and 16.7% versus 7.0% for TLR at 270 days, $P=0.14$). The late loss at follow-up was also greater in the diabetic compared to non-diabetics group (0.89 versus 0.60 mm, $P=0.003$). The diabetic group was also associated with more loss index (0.64 versus 0.42, $P<0.001$) and binary restenosis rates (32.1% versus 14.9%, $P=0.05$).

Table III. Characteristics and outcomes distinguished by diabetic status.

	Diabetics ($n=30$ pts)	Non diabetics ($n=128$ pts)	*P* value
Age (years)	58.9±11.1	60.2±10.4	0.53
Male gender	76.7%	82.8%	0.44
LAD	37.1%	37.2%	1.0
Lesion length (mm)	9.9±3.7	10.4±4.7	0.51
RVD (mm)	2.53±0.53	2.78±0.50	0.01
Stent length (mm)	12.9±5.4	12.9±6.0	0.95
Post procedure			
In-stent MLD (mm)	2.35±0.42	2.49±0.45	0.10
Long-term outcomes @180 days:			
TVR	13.3%	4.7%	0.10
TLR	10.0%	3.1%	0.13
TVR not including TL	6.7%	1.6%	0.16
MACE	13.3%	5.5%	0.13
Long-term outcomes @270 days:			
TVR	26.7%	9.4%	0.027
TLR	16.7%	7.0%	0.14
TVR not including TL	13.3%	2.3%	0.025
MACE	23.3%	9.4%	0.06
Angiographic restenosis parameters @180 days			
Mean late loss (mm)	0.89±0.38	0.60±0.48	0.003
Loss index	0.64±0.27	0.42±0.38	<0.001
Binary restenosis	32.1%	14.9%	0.05

Predictors of restenosis

Using a univariate model, the following variables were predictive for angiographic binary restenosis at six month follow-up: post-procedure in-stent MLD (mm), (odds ratio = 0.187, $P = 0.0018$), pre-procedural reference vessel diameter (mm), (odds ratio = 0.234, $P = 0.0035$), pre-procedural MLD (mm), (odds ratio = 0.162, $P = 0.0112$), and diabetes mellitus (odds ratio = 2.71, $P = 0.0336$).

In a multivariate analysis model, diabetes mellitus (odds ratio = 2.65, $P = 0.047$) and post-procedure in-stent MLD (mm), (odds ratio = 0.178, $P = 0.0019$), were the only independent determinants of angiographic binary restenosis.

Discussion

This analysis shows that clinical and angiographic restenosis outcomes following NIRFLEX bare stent implantation were primarily dependent upon vessel size parameters and/or vessel lumen dimension and the presence of underlying diabetes mellitus disease. The measured length of the treated lesion had an additional effect on overall MACE but did not have a significant impact on angiographic measures of binary restenosis and/or late loss. Our study also found very low rates of target vessel revascularization (e.g. 2.4%) and actually no event (e.g. 0%) of target lesion revascularization among patients with lesion located at larger (i.e. patients with reference vessel diameter ≥ 3 mm) coronary arteries. These patients comprised approximately one third of the patients enrolled into the NIRTOP study with enrollment criteria limited to vessel size between 2.5 and 4.0 mm. Likewise, binary restenosis and late loss/loss index values were very favorable for the 'large' vessel group using the bare-metal NIRFLEX stent in patients in native lesions coronary artery disease.

Previous studies have attempted to establish the relation between vessel size and restenosis outcomes in patients undergoing percutaneous coronary intervention (PCI), (2–4). Large sized vessels consistently showed better clinical and angiographic outcomes compared to smaller vessels (7). Although the pattern and distribution of restenosis was shown by intra-coronary ultrasonic studies to be similar for smaller versus large-sized vessels, it appears that larger diameter allows for maintaining a greater residual lumen in response to neointimal formation due to smooth muscle cell proliferation (8,9). Since optimal stent design may further diminish the neointimal response to stent implantation (10,11), favorable restenosis outcomes are to be expected primarily in large-sized vessels. Optimizing bare metal stent results and/or selection of patients/lesions at particularly lower risk for restenosis as potential candidates for treatment using bare metal stents, is still a relevant practice in many catheterization laboratories around the world. This matter is due to cost versus added clinical value and safety considerations that are being weighted among health authorities and clinicians in the current 'fragile' era of drug-eluted stents. Putting our sub-analysis results in perspective, we can use the results of the ENDEAVOR 2 as a reference study (12). Among patients with angiographic follow-up in the ENDEAVOR 2 study and using a zotarolimus as the eluted drug, in-stent and in-segment late loss values were 0.61 ± 0.46 mm and 0.36 ± 0.46 mm, respectively, and the rate of in-segment restenosis was 13.2% with Endeavor stent at 9-months follow-up. Although the patients enrolled in the aforementioned study were at higher risk of restenosis, this mentioning raises the issue of whether optimally designed bare metal stents (such as NIRFELX), that show favorable acute and long-term clinical performances, could serve as a viable and safe therapeutic option in lesions/patients subsets that are at lower risk for restenosis. The answer according to our data is most probably yes.

The interplay between restenosis and diabetes mellitus is a complex matter (13). Diabetic patients tend to have higher restenosis rates following implantation of bare metal stents and/or even drug-eluting stents (14,15). In fact, most of major pivotal 'bare metal' versus 'drug eluting' stents trials were not designed to establish the proof of principle that drug eluting stents are superior to newer generations of well designed bare-metal stents in terms of overall adverse cardiac events (16,17). In fact, a recently published pooled analysis of data from four pivotal trials comparing sirolimus-eluting stents and bare-metal stents, showed that in patients with diabetes, a significant difference in the survival rate was observed in favor of the bare-metal-stent group over the sirolimus-stent group with lower survival rate observed among diabetics, which was due to both cardiovascular and non-cardiovascular causes (18).

From the multivariate analysis model of our study, we learn that diabetic-related biological parameters 'govern' the process of restenosis by causing more late-lumen loss regardless of vessel size. The current study highlights a continued major limitation of NIRFLEX in treating diabetic patients as restenosis outcomes and late loss indices remain higher among these patients. Nonetheless, putting our data in perspectives, the results are far superior to those observed in the control bare metal stent diabetic arm of the low risk RAVEL study with equivalent demographic and angiographic parameters (19). In this study, event-free survival rate among diabetic patients was 52% for the BX VELOCITY bare metal stent arm at 180 days, a far worse outcome than the 86.7% event free survival rate observed for the NIRFLEX at the same period (20). Likewise, the target lesion revascularization rate at 6 months among diabetics was 36% for BX VELOCITY

versus only 10% in the NIRTOP study with comparable vessel size parameters (20). In the recently reported DIABETES trial, the MACE and TLR rates were 36.3 versus 11.3% ($P<0.001$) and 31.3 versus 7.5% ($P<0.001$) for BX VELOCITY versus Cypher stent at nine-month follow-up (21). Thus, the clinical results reported in the current analysis using NIRFELX in diabetics are in between those figures (e.g. 23.3% MACE rate and 16.7% TLR for NIRFLEX at 9 months).

Since progression of disease in untreated sites rather than restenosis *per se* is often the principle 'driver' for worse long-term adverse outcomes among diabetics, a major emphasis should be set to optimizing systemic treatment among these atherosclerotic patients (22). This goal should be accomplished using a comprehensive therapeutic approach directed towards metabolic normalization and vascular 'healing' in addition to local stent-based pharmacotherapy (23).

Study limitations

This is a retrospective sub-analysis that had no prespecified power calculation concerning its main theme (e.g. vessel size, lesion length and diabetes mellitus distinctions) with relatively small subgroups of patients. In addition, this analysis was underpowered to delineate differences between insulin treated and medicated diabetic patients and included no data about the adequacy of diabetes control and its influence on restenosis outcomes. In addition, it should be noted that according to the demographics of the patients, there is a strong tendency towards high prevalence of DM in small vessels compared to the large ones. (23.0% versus 9.8%, $P=0.07$). It is obvious that such differences may play a possible role in the favorable effect of this stent on the large vessels. Finally, the findings concerning vessel size are limited to the actual vessel/lesion dimensions that were tested in this trial and may be further modified in lesions located in smaller or larger vessels and/or more diffuse lesions. Ultimately, this study lacks systematic intravascular ultrasonic data that might have supported the angiographic findings that were presented in the current analysis.

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