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Predictors of Restenosis Following Contemporary Subintimal Tracking and Reentry Technique: The Importance of Final TIMI Flow Grade

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Objectives: To identify predictors of restenosis after recanalization of chronic total occlusions (CTOs) with the Subintimal Tracking And Reentry (STAR) technique. Background: STAR is associated with high rates of restenosis but the associated factors are not clear. Understanding the underlying mechanisms may be important to improve STAR outcomes and possibly other contemporary CTO recanalization techniques utilizing extensive subintimal dissection and stenting. Methods: We retrospectively analyzed 211 lesions that underwent a STAR procedure (between 2002 and 2013) with a final Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3. One-hundred and nineteen lesions that received drug eluting stents (DES) and underwent follow-up angiography were included in the final analysis. Results: Of the 119 lesions treated with DES following STAR, 75 restenoses were observed (63.0%). Utilizing multivariate analysis, TIMI flow grade in the recanalized artery following stent implantation at the end of the index procedure was the only independent predictor of restenosis. Conclusions: Following recanalization of a CTO with STAR, final TIMI flow predicted future restenosis or reocclusion. As a bailout technique, STAR resulted in a high acute success rate with good safety and acceptable long-term results. When poor flow is observed following recanalization, and prior to stent implantation, a two-step strategy whereby a second procedure is performed at an interval to maximize coronary flow at the end of the procedure may be considered with the goal to reduce the risk of future restenosis or total vessel occlusion following STAR.

Key words: percutaneous coronary intervention; chronic total occlusion; coronary stenting; TIMI flow; restenosis

BACKGROUND

Despite a favorable risk-to-benefit ratio in experienced hands [1], percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) still remains a challenge [2–4], with the success rate not exceeding 90% even in the most proficient centers [5–7]. CTO treatment has been shown to improve symptoms [8] and outcomes [9–12]. Thus having a number of different techniques that can be employed in the treatment of CTO is essential in maximizing success.

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The subintimal tracking and reentry (STAR) technique was the first reported antegrade subintimal dissection and reentry (D/R) method to re-open occluded arteries [13,14]. Although this technique has some limitations, notably the inability to control the reentry point in the distal lumen and a high rate of restenosis, it did effectively demonstrate that blunt dissection through the subintimal space could rapidly and safely traverse even very long, tortuous, and calcified occluded segments without vessel perforation [13–17]. This demonstration provided the confidence to further explore the use of the subintimal space for therapeutic purposes [16]. STAR was integrated into a retrograde approach (e.g. Controlled Antegrade and Retrograde subintimal Tracking (CART)) [18–20], and a dedicated antegrade D/R system (CrossBoss^{TM} Catheter and Stingray^{TM} System) [21]. As a result of these advances and greater operator experience, success rates of CTO PCI have increased [7].

The increased use of STAR technique has raised certain concerns. Valenti et al. reported that a successful STAR procedure, regardless of the type of stent used, was associated with a high incidence of reocclusion (57%) [22]. Godino et al. proposed that the high restenosis/reocclusion rate was related to the length of the stented segment [15]. This hypothesis has been largely refuted in studies using more contemporary D/R techniques, such as reverse CART and the CrossBoss^{TM} catheter/Stingray^{TM} System, where both immediate angiographic results and long-term outcomes have been excellent despite stenting of an extended length within the subintimal space [23,24]. In contrast to STAR, these procedures typically end with a normal Thrombolysis in Myocardial Infarction (TIMI) flow grade in the treated vessel. Visconti et al., analyzing the outcome of successful STAR procedures where stenting was deferred, showed that the presence of spontaneous echo-contrast using intravascular ultrasound (IVUS) in the dissected segment (which reflects flow stasis and poor distal runoff) was associated with an increased risk of restenosis [25]. Based on these observations, we hypothesized that the adequacy of forward flow in the recanalized artery is one of the major determinants of long-term patency after subintimal recanalization. In order to test this hypothesis, we performed the following study.

METHODS

Among 211 lesions that underwent successful CTO recanalization with STAR technique (and subsequent stent implantation) in two centers (San Raffaele Hospital and EMO-GVM Centro Cuore Columbus, Milan, Italy), we retrospectively analyzed the subgroup that underwent follow-up angiography in order to determine the relationship of final TIMI flow to angiographic outcome. In order to avoid a possible confounder, we excluded all patients in whom bare metal stents (BMS) were implanted and utilized only the group receiving drug eluting stents (DES). CTO was defined as obstruction of a coronary artery with TIMI flow grade 0 and an estimated duration of at least 3 months [4]. Binary angiographic restenosis was defined as $\geq$50% luminal narrowing at follow-up angiography. The indications for index revascularization included symptomatic angina and/or evidence of inducible ischemia in the territory of the occluded artery. STAR was performed as previously described as a second-line procedure when first-line approaches had failed [13,14]. Storm cloud dissection was defined according to the previous description [14]. Heparin was administered in all cases to maintain an activated clotting time (ACT)$>$250 sec. After discharge, dual antiplatelet therapy (DAPT) was recommended for a minimum of 12 months for all patients. Flow in the recanalized artery was defined according to the TIMI grading system [26]. Angiographic success was defined as final TIMI flow ≥ 2 with residual stenosis $< 20\%$. Cases where successful recanalization of the main artery was achieved but with residual occlusion of a major branch, e.g. right coronary artery (RCA) and posterior descending artery (PDA) recanalization with failure to reopen the posterolateral branch (PL), were also included in the study. Two operators (MC and FF) independently reviewed angiograms. In order to assess the impact of stent implantation following STAR upon TIMI flow, we evaluated it at two time points: (1) after CTO recanalization and pre-dilatation but immediately before stent implantation and (2) upon completion of the procedure.

Statistical Analysis

Normally distributed continuous variables were expressed as mean ($\pm$SD), while median [interquartile range, IQR] was used to report skewed distributed variables. Respectively, independent Student's t test and Mann–Whitney U test were used to compare means between two groups, whilst ANOVA and Kruskal–Wallis tests were employed when more than two groups were analyzed. Categorical variables were expressed as absolute number (percentage) and analyzed by Pearson's chi-squared test or, when appropriate, by Fisher's exact test. Two-sided P-values $<$0.05 were used as a threshold for statistical significance.

Cox regression multivariate model for predictors of restenosis was used. We included variables demonstrating a significant association with restenosis and vessel reocclusion at univariate analysis as well as factors of clinical significance. To avoid multicollinearity, a "low-noise model" has been researched in which each predictor variable correlate at most only minimally with the other. In addition, the convention of limiting the number of independent variables to 1 for every 10 events was followed.

Hazard ratio (HR) and 95% confidence interval (CI) are reported.

RESULTS

Between 2002 and 2013, 211 CTO lesions were successfully recanalized with the STAR technique. One hundred thirty-two (132) lesions in 125 patients underwent angiographic follow-up, either as a scheduled procedure, or because recurrence of symptoms, or evidence of inducible ischemia. Of the 132 lesions, 13 had received a BMS on index procedure and were therefore excluded from the study population. One-hundred nineteen (119) lesions in 112 patients were included in final analysis (Figure 1). Six of 119 patients had previously undergone a failed CTO recanalization attempt at our center; however, none of these can be actually considered a "2-step procedure" intended as deferred stenting, as this practice was only recently started [25].

One in-hospital NSTEMI and 1 coronary perforation occurred; the case of perforation was successfully treated with conservative management. No cases of in-hospital or procedure-related death were reported; no patients needed urgent surgery, no cases of acute kidney injury occurred (mean contrast volume was 446 ± 176 ml).

Mean fluoroscopy time was 45 ± 20 min while procedural time was 135 ± 47 min.

In 37 patients (31%) repeat angiography was driven by symptoms; in 12 cases (10%) it was performed because of signs of silent ischemia; in 53 (45%) as a scheduled control. In 15 patients (13%), the reason of repeat coronary angiogram is missing.

The median time from index procedure to angiographic follow-up was 8.5 months [IQR 4.9–30.1]. Seventy-five restenoses in 67 patients (63% of lesions, 56% of the study population) were observed in the target vessel. There was total vessel occlusion in 33 cases (27.7%), diffuse severe restenosis in 9 (7.6%), and focal restenosis in 33 (27.7%, Fig. 1). Median time to restenosis was 179 [90–412] days; it was slightly shorter (135 [84–299] days) for occlusion. Compared to reocclusion, restenosis was more frequently associated with the presence of symptoms at repeat angiography, although the comparison did not reach statistical significance.

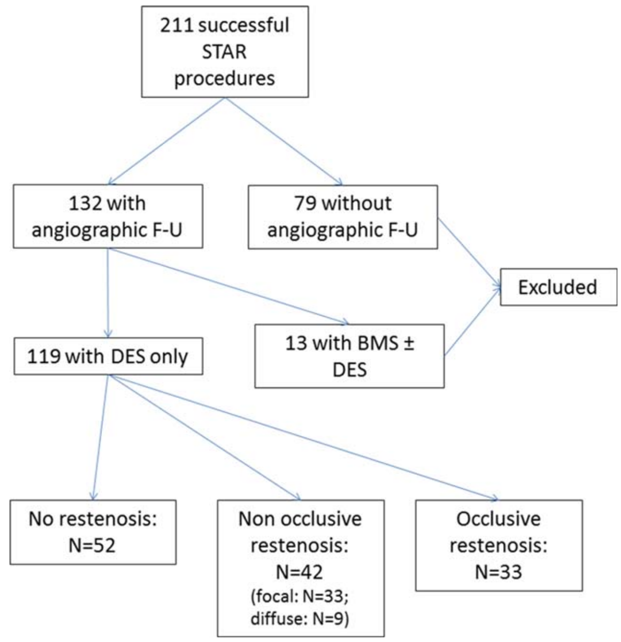

Fig. 1. Study population. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Restenosis was successfully treated in 48/67 (72%) patients. In 12 of the successfully treated patients (25%), symptomatic re-restenosis required a third intervention. At last follow-up angiography, the target vessel was patent in 100/119 lesions (84%), either primarily or after one or more repeat revascularizations.

Baseline clinical characteristics between patients with and without restenosis at follow-up angiography were similar (Table I). The RCA represented the target vessel in two-thirds of patients; and where possible, its bifurcation was left unstented (Table II). Second generation DES were used in a minority of patients (18.5%), due to their unavailability during most of the study period.

There was one instance of symptomatic acute vessel thrombosis successfully managed by repeat PCI at the level of a residual dissection. Two patients died suddenly during follow-up and were classified as cases of possible stent thrombosis; however, both patients had multi-vessel disease treated with multiple PCIs in addition to the index STAR procedure.

Final TIMI flow grade <3 (Table II, Fig. 2) was the only variable associated with increased incidence of target vessel restenosis at follow-up ($P = 0.02$). Of note, total stent length was similar between patients that suffered restenosis and patients that did not (72 ± 28 mm vs. 64 ± 32 mm respectively, $P =$ NS). Of nine patients with TIMI flow <3 who had no

TABLE I. Clinical Characteristics of Patients With and Without Subsequent Restenosis

	No restenosis ($n = 52$)	Any restenosis ($n = 67$)	P
Age	58.3 ± 10.1	61.5 ± 10.1	0.144
Male sex	50 (96.2)	62 (92.5)	0.304
Diabetes	10 (26.3)	12 (22.2)	0.650
Insulin use	2 (5.3)	4 (7.4)	0.682
Hypertension	28 (73.7)	43 (79.6)	0.503
Current smoking	8 (21.1)	11 (20.4)	0.575
Dyslipidemia	32 (84.2)	46 (85.2)	0.898
Family history CAD	15 (39.5)	26 (48.1)	0.410
Previous MI	14 (36.8)	27 (50)	0.211
Previous PCI	24 (63.2)	38 (70.8)	0.467
Previous CABG	15 (39.5)	21 (38.9)	0.955
Unstable angina	3 (7.9)	8 (14.8)	0.109
EF	53.9 ± 7.9	52.2 ± 9.4	0.342
CRF	0	2 (3.3)	0.242

CRF: chronic renal failure, CAD: coronary artery disease, CABG: coronary artery bypass grafting, EF: ejection fraction, MI: myocardial infarction.

TABLE II. Procedural Variables in Patients With and Without Restenosis

	No restenosis ($n = 52$)	Any restenosis ($n = 67$)	P
Vessel			
LAD/Diag	4 (7.7)	4 (6.0)	0.429
LCx/OM	16 (30.8)	19 (28.4)	0.321
RCA/PDA/PL	32 (61.5)	44 (65.7)	0.549
Contralateral collaterals	27 (77.1)	44 (83)	0.441
Severe calcifications	3 (7.7)	8 (14.8)	0.165
Storm cloud dissection	4 (7.7)	8 (11.9)	0.822
2nd generation DES	11 (21.2)	11 (16.4)	0.385
Stent length (mm)	64 ± 32	71 ± 28	0.501
Residual SB occlusion	10 (19.2)	21 (31.3)	0.135
Stented bifurcation	16 (30.8)	22 (32.8)	0.885
TIMI flow 3 pre-stenting	29 (55.8)	35 (52.2)	0.903
Final TIMI flow 3	43 (84.3)	43 (65.2)	0.020
12 months DAPT	36 (97.3)	51 (94.4)	0.643

LAD: left anterior descending artery, Diag: diagonal branch, LCx: left circumflex artery, PDA: posterior descending artery, PL: postero-lateral branch, OM: obtuse marginal branch, mm: millimetre.

restenosis at follow-up, in eight (89%) cases flow have improved to TIMI 3 at repeat angiogram.

TIMI flow grade immediately after recanalization and after stenting were closely correlated. Whilst 60/64 (93.8%) of patients with TIMI flow 3 after STAR and balloon dilatation were found to have TIMI 3 flow after stenting, only 3 of 14 patients with TIMI flow ≤ 2 following balloon dilatation achieved final TIMI 3 flow ($P < 0.001$). The rate of reocclusion after a final TIMI flow 3 was 19.8% (19/96) in this cohort of patients with angiographic follow-up compared with 62% in patients with final TIMI flow <3.

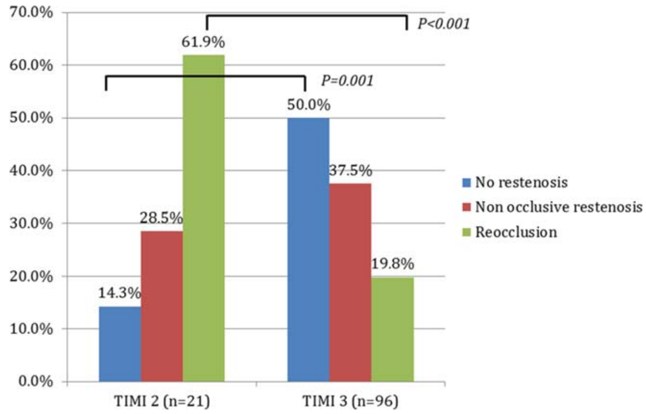

Fig. 2. Final TIMI flow grade and restenosis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

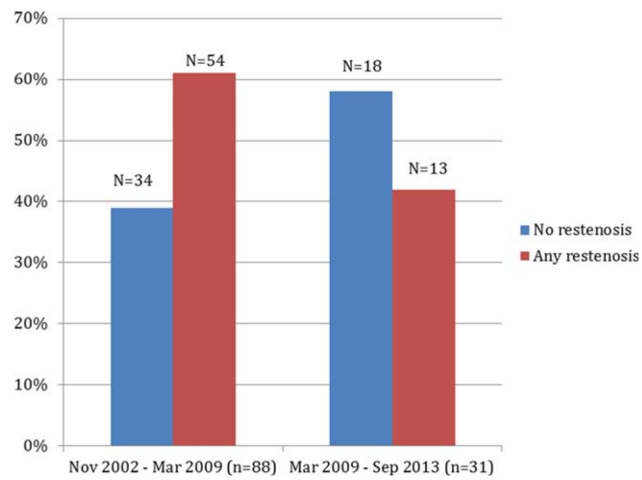

Fig. 3. Incidence of restenosis over time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Residual occlusion of a side branch ≥ 2 mm tended to be more common among patients who subsequently developed a restenosis, but the association was not statistically significant (Table II). Occasionally, spontaneous recanalization of an occluded side branch was observed at angiographic follow-up and occurred in eight patients (6.7%) in this cohort.

In order to assess the impact of evolving techniques and technology, we divided the population into quartiles based on the date of index procedure.

We observed a trend (41.9% vs. 61.4%, $P = 0.06$) for a reduced incidence of restenosis in the most recent quartile (March 2009 to September 2013) compared to the previous time points (Fig. 3). This observation is confounded by the shorter time to angiographic follow-up in this subgroup of patients (6 months [2.9–12.7]

TABLE III. Predictors of Restenosis and Reocclusion—Multivariate Analysis

Variable	HR for restenosis (95% CI)	*P*	HR for reocclusion (95% CI)	*P*
Final TIMI Flow 3	0.48 (0.25–0.92)	0.027	0.24 (0.08–0.69)	0.008
2nd generation DES	0.86 (0.45–2.65)	0.856	1.13 (0.21–6.12)	0.885
Stent length	1 (0.99–1.02)	0.586	0.99 (0.97–1.02)	0.561
Diabetes	0.78 (0.34–1.77)	0.740	1.09	0.906

vs. 11.1 [5.6–38.4]: $P = 0.044$) and by use of 2nd generation DES. Also in this last quartile TIMI flow <3 was significantly associated with restenosis and with occlusion.

When final TIMI flow, use of 2nd generation DES, stent length, and diabetes were combined in a Cox multivariate model, final flow retained its predictive value ($p<0.05$). The association became stronger when the model was applied only for the reocclusion events (all restenosis: HR 0.48 (0.25–0.92, $P = 0.02$; occlusion only: (HR 0.24 (0.08–0.69), $P = 0.008$). In fact, TIMI flow <3 was the only independent predictor of restenosis and reocclusion (Table III).

DISCUSSION

The STAR technique was an important advance in the history of percutaneous CTO treatment as it demonstrated that the subintimal space could be used therapeutically to recanalize the vessel. There have been concerns raised that the high restenosis rate after STAR [22] may be a direct consequence of subintimal stenting. If the cause of the high incidence of restenosis is, in fact, due to use of the subintimal space, newer CTO techniques, which are based on controlled subintimal dissection and reentry methods, also would be expected to be associated with this adverse outcome [18–21]. This, however, does not seem to be the case. Mogabgab et al. studied the long-term outcomes of 170 consecutive CTO PCI patients, of whom 60 were treated with the CrossBoss–Stingray device and 110 with other crossing strategies. Despite higher procedural complexity, patients treated with the dedicated D/R device had a similar rate of procedural success and comparable long-term outcomes to other, non-Cross Boss/Stingray strategies [27]. Additionally, although data are limited, long-term outcome measures with CART, reverse CART, and other retrograde D/R methods are promising [28]. Rinfret et al. have recently demonstrated from a cohort of 192 CTO patients successfully treated with a "hybrid approach," that the use of subintimal stenting did not adversely impact outcomes [29]. It is important to stress that even with the so-called "true to true lumen" recanalization procedures, inadvertent passage in the subintimal space is very frequent [30]. Thus, although the subintimal space is used for both STAR and more contemporary methods, outcomes, particularly with regards to restenosis and reocclusion rates, appear to be very different.

The main results of the current study strongly suggest that the final TIMI flow in the target vessel at procedural end is a major determinant of long-term patency (Fig. 4). Second stent length was not a predictor of subsequent restenosis.

It is important to note that the presence of extensive dissections in this setting appear to have a more benign clinical course (in comparison to traditional PCI). This finding is likely due in part to the fact that there are pre-existing collaterals to the CTO r myocardial region but also probably related to the fact that with the STAR technique, a wide reentry tear is induced that is less likely to lead to complete vessel occlusion in spite of a worrisome angiographic appearance. In situations when flow is compromised, it therefore may be more appropriate to defer stenting and consider a "second look" in order to assess the vessel healing at the dissection site after 2–3 months [25,31]. At this point (depending on the findings), it may be appropriate to proceed to stent implantation at the site of the original occlusion or to try a new recanalization attempt. In this regard, STAR might be considered a "two-step procedure," with the first step aimed at obtaining vessel patency and the second, treating restenosis (if it occurred). This concept is comparable to the idea of "preplasty" or "investment" procedure, as reported by Wilson et al., who described four cases in which CTO PCI initially failed, but in which modification of the plaque by subintimal dilatation at the initial procedure aided in a successful result at a second attempt a few weeks or months later [32].

Usually large dissections following recanalization with contemporary subintimal techniques (Fig. 5) are not appreciated angiographically because operators (correctly) avoid contrast injection at this juncture to avoid hydraulic extension of the dissection. However, with modern techniques and the control of the precise reentry point, flow is preserved, which is not necessarily the outcome with STAR.

There are a number of potential explanations for the occurrence of suboptimal TIMI flow following STAR:

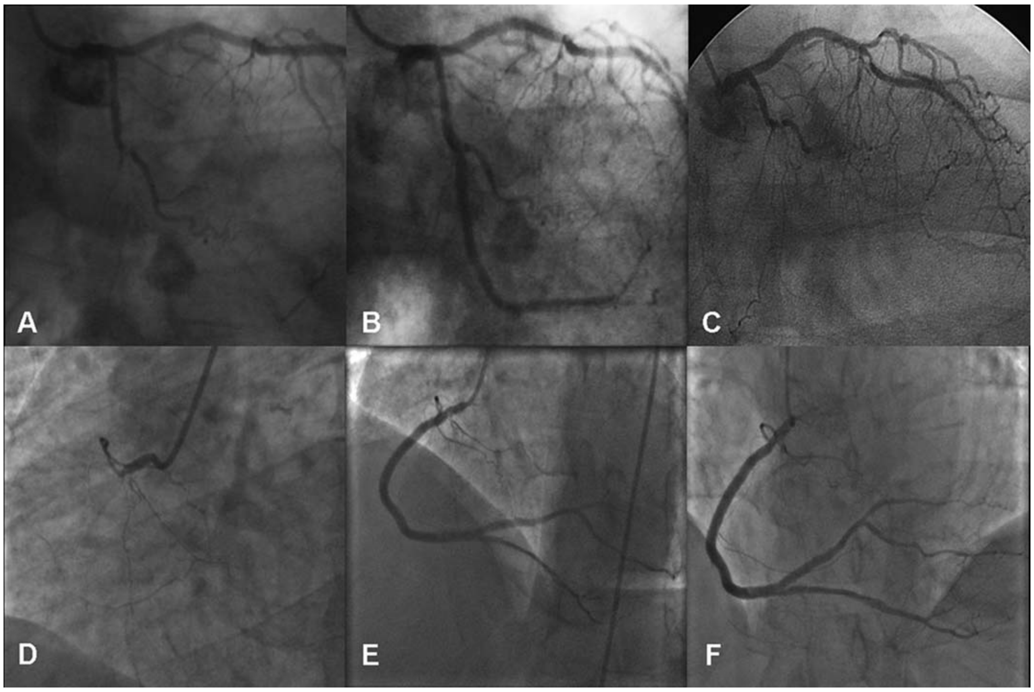

Fig. 4. Case examples. Top row: LCx occlusion (A) was recanalized with STAR (B), with TIMI flow 2 at the end of the index procedure; follow-up angiography showed occlusive restenosis. Lower row: RCA occlusion (D) successfully recanalized, with TIMI 3 final flow (E); a dissection flap is apparent in posterior descending artery (PDA). Six months follow-up showing vessel patency with increased number of small branches from PDA (F).

- Presence of a flow-limiting dissection flap: that extensive stenting does not always improve angiographic results strongly suggests that this mechanism does not provide the full explanation.
- A too distal reentry site, whereby the volume of myocardium supplied by the recanalized artery is too small to guarantee a good runoff: this mechanism would explain why, with precise control of the reentry point, flow is generally preserved at the end of the procedure. The presence of residual viability in the territory of restored flow could play a role.
- Residual dissections in side branches interfering with flow run-off.
- Procedural trauma following STAR causing microvascular obstruction (either due to extensive microembolic phenomena or peripheral vasoconstriction), which may result in continued impaired flow even after stenting flaps in the lumen.

It has been proposed that at least some of the restenosis observed following CTO recanalization might actually be due to clinically silent vessel thrombosis [15]; this mechanism is in agreement with the association between spontaneous echo-contrast in the recanalized vessel and subsequent reocclusion [22]. The vast majority of the patients in the present study were discharged with 12-months DAPT treatment. However, with the implantation of newer generation stents, a reduced course of DAPT is often prescribed [33]; the issue whether STAR procedures (and CTO PCI in general) may benefit from a prolonged and/or more aggressive platelet inhibition remains to be determined.

We had previously demonstrated that, when analyzing both conventional CTO PCIs and contrast-guided STAR procedures, stent length was an important predictor of restenosis [15]. These findings resulted in our technical modification to limit stent length to the site of the original occlusion. This relatively recent change was also intended to avoid side-branch compromise arising in the dissected segment (Fig. 6). In this study, stent length was not significantly correlated with angiographic outcomes, agreeing with data by Rinfret et al. [29]. As our clinical approach to limit stent length was only recently adopted, we cannot exclude the possibility that a clinical benefit of this approach will not become apparent in the future. A possible explanation of the discrepancies between the current analysis and our previous results may be that the requirement for long segments of stent implantation may be a marker of greater CTO complexity and may not have been

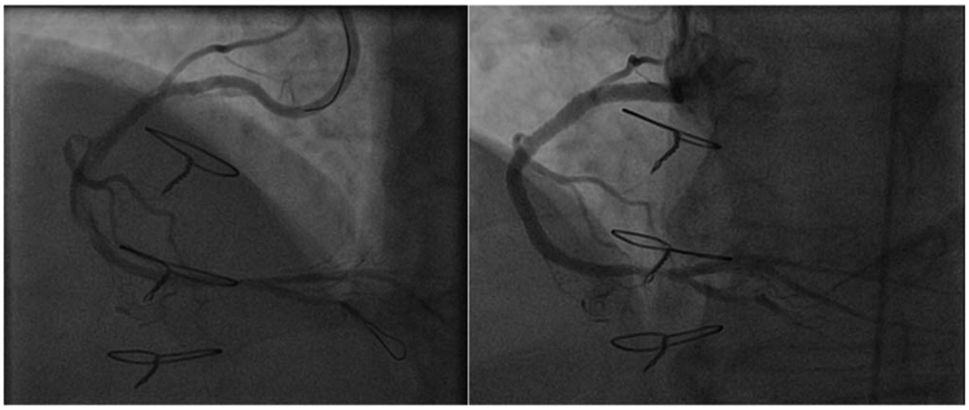

Fig. 5. Appearance of dissected vessel before stenting in a successful reverse CART procedure.

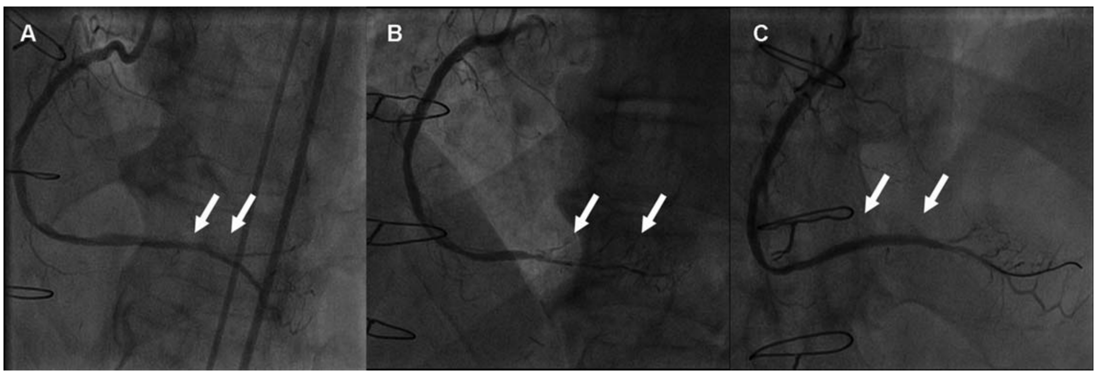

Fig. 6. Loss of small side-vessels after deferred stenting of a dissected segment. A: Result after index procedure, with TIMI 3 flow; One DES was implanted in the proximal part of the artery and a second look was scheduled in order to assess evolution of the dissected segment. B: 3 months later, the vessel was patent; FFR in the posterior descendent artery (PDA) was 0.6, so another stent was implanted. FFR in the mid PDA normalized, at the cost of losing all the small side-branches in the stented segment.

adequately captured by the multivariate model assessing predictors of restenosis. In the present study, we only included STAR patients (with a previously failed attempt using conventional techniques) and thus procedural complexity was probably greater than in our previous study.

Limitations

IVUS was only performed in a minority of cases of restenosis, representing a limitation; however, no unexpected findings were observed in those cases. We are aware that the high restenosis rate reported makes STAR a second-line strategy, reserved where other methods have failed. However, we believe that it is important to understand the reason why STAR is associated with worse outcomes, considering that many new techniques rely on the same principle, i.e. dissection and re-entry. We also believe that STAR, as a last option, may restore vessel patency when other methods have failed or when an occlusive dissection occurs during PCI: this technique should therefore be present in the interventionalist's armamentarium.

CONCLUSION

The current study suggests that the primary driver of restenosis and reocclusion after CTO recanalization with the STAR method is the final angiographic flow grade. Compared to more contemporary subintimal methods, STAR is limited by the fact that the final TIMI flow, due to unpredictability of the reentry site, may be suboptimal. Larger studies with longer follow-up are required to further define the principal drivers of restenosis following CTO recanalization. Long-term follow-up of CTO PCI with dedicated reentry devices will also shed light on difference in restenosis rates with various techniques. As a bailout technique, STAR results in an excellent acute success rate with good safety and acceptable long-term results. This may be enhanced when a contemporary "two-step strategy" is employed to maximize TIMI flow in the target artery following recanalization, reducing the risk of restenosis or total vessel occlusion.

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