

Stent for chronic total coronary occlusions: benefits and drawbacks after the introduction of drug-eluting stents

Chronic total occlusion (CTO) is a common finding on diagnostic coronary angiography and constitutes one of the most challenging lesion subsets in interventional cardiology. The introduction of dedicated guidewires and the development of new techniques have improved the success rate in the crossing of CTO lesion while the use of bare-metal stents and drug-eluting stents has dramatically reduced the occurrence of restenosis and the need for target lesion revascularization in the short- and mid-term after CTO recanalization. However, new unsolved issues regarding the use of drug-eluting stents in CTO that might impact on long-term outcomes are emerging. The aim of this article is to review the current stage of knowledge on the application of stents in the treatment of CTO with a particular attention to the new complications associated with drug-eluting stent use in complex lesions.

KEYWORDS: aneurysm ■ bare-metal stent ■ chronic total occlusion ■ drug-eluting stent ■ stent fracture ■ stent malapposition

Chronic total occlusion (CTO) of the coronary arteries is a common finding on diagnostic coronary angiography (~35%) and percutaneous coronary intervention (PCI) for CTO actually represents as many as 15% of all angioplasty procedures at high-volume centers [1,2]. Despite remarkable advances in the procedural techniques in the last 15 years, due to improved equipment and operator experience, CTOs are still one of the most challenging lesion subsets in interventional cardiology. Historically, the main reasons for failure of CTO recanalization were the failure to cross the lesion with a guidewire and the higher rate of restenosis and reocclusion compared with non-occlusive lesions. The introduction of dedicated guidewires and the development of new techniques have improved the success rate in the crossing of CTO lesions while the use of drug-eluting stents (DES) has dramatically reduced the occurrence of restenosis and the need for target lesion revascularization (TLR) [3,4]. Concerns regarding the long-term complications of DES implantation (late restenosis and stent thrombosis) are emerging. The aim of this article is to review the current stage of knowledge on the application of stents in the treatment of CTO.

Benefit of late patency of chronic total occlusion lesions

Several studies have demonstrated the benefit of a late patency of CTO lesions in terms of symptoms, improving quality of life, recovery of hibernating myocardium, avoiding coronary

artery bypass graft (CABG) and prognosis [5-7]. In a retrospective study, on 870 patients with 885 CTO lesions, Hoyer *et al.* demonstrated that the successful PCI of CTO was associated with an improved survival rate and a lower incidence of major cardiovascular events (MACE) at 5-year follow-up [8]. Subsequently, Valenti *et al.* demonstrated that the survival benefit after successful CTO treatment was mainly driven by the differences in the outcome of patients with multivessel disease (MVD) who underwent complete revascularization [9]. Indeed, patients with a single CTO without MVD had a very low mortality whatever the results of the PCI attempt. Thus, a recent consensus document from the EuroCTO Club has underlined that reopening of a CTO should be considered in the presence of symptoms or objective evidence of viability/ischemia in the territory of the occluded artery with the aim of improving symptoms and prognosis; a PCI strategy should also be used in patients with MVD in the absence of significant left main disease and when the other lesions are suitable for PCI [3].

It is important that the vessel should remain open after recanalization of CTO as the consequent reocclusion may not be supported by collateral circulation as shown by Zimarino [10] and Werner [11,12]. Owing to the higher restenosis and reocclusion rates in CTO PCI with the BMS as compared with the treatment of no CTO lesions, the routine use of DES in such lesions has become the standard approach [7-9].

Andrea Leo¹, Simona Giubilato¹, Marco Bacà¹, Rocco Antonio Montone¹ & Giampaolo Niccoli^{1*}

¹Department of Cardiovascular Medicine, Catholic University of the Sacred Heart, Largo A Gemelli, 0168, Rome, Italy

*Author for correspondence:

Tel.: +39 063 055 535

Fax: +39 063 015 4444

gniccoli73@hotmail.it

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Plain old balloon angioplasty versus BMS implantation & predictors of restenosis in BMS era

For the first time, the introduction of bare-metal stents (BMS) has led to a decrease in restenosis and reocclusion rate in CTO PCI and has conferred a long-term survival advantage after successful CTO treatment. Several randomized trials [13–21] have demonstrated the superiority of stenting over balloon angioplasty in the setting of CTO. A recent meta-analysis [22] of the nine trials directly comparing BMS placement with balloon angioplasty has shown that stent implantation was associated with a lower rate of vessels reocclusions (6.8 vs 16%), angiographic restenosis (41.1 vs 60.9%) and the need for repeated revascularization (17 vs 32%) versus balloon angioplasty without stent. Furthermore, this meta-analysis, including 1409 patients, clearly demonstrated the benefits of stent implantation at midterm clinical follow-up (6 months) with a MACE rate of 23% in the stent group versus 35.4% after balloon angioplasty, mainly owing to the reduction of repeated revascularizations without significant differences in the rate of death. The benefit of stent strategy was also maintained at long-term follow-up (from 2 to 6 years), with a lower incidence of MACE in the stent group compared with the balloon angioplasty group (30.7 vs 45.5%) (FIGURE 1).

Nevertheless, even after BMS introduction, restenosis, reocclusion and repeated revascularization rates remained unacceptably high compared with non-CTO lesions treated with BMS. In the Total Occlusions Study of Canada (TOSCA), restenosis and reocclusion rates after BMS implantation in successfully treated CTO lesions were as high as 50 and 10%, respectively, compared with those after treatment of no CTO lesions [16]. In the series by Elezi *et al.*, the restenosis rate was 43% after stent implantation in CTO versus 27% in non-occlusive lesions. Of note, this higher rate of restenosis was associated with a worse prognosis, a trend versus a higher mortality and a significant increase in the need for repeated revascularization procedures [23].

Several angiographic, functional and intracoronary ultrasound predictors of reocclusion and restenosis after BMS implantation for CTO have been reported. Among angiographic parameters, stent length, number of implanted stents, balloon:vessels diameter ratio and a smaller final postprocedural minimal lumen diameter (MLD), have been shown to be the major determinants of target vessel failure (TVF) in CTO PCI. A study by Rau *et al.*, reported four variables independently correlated with the rates of restenosis and reocclusion [24]: the presence of dissection after balloon angioplasty; the size of post-stenting MLD; the length of the stented

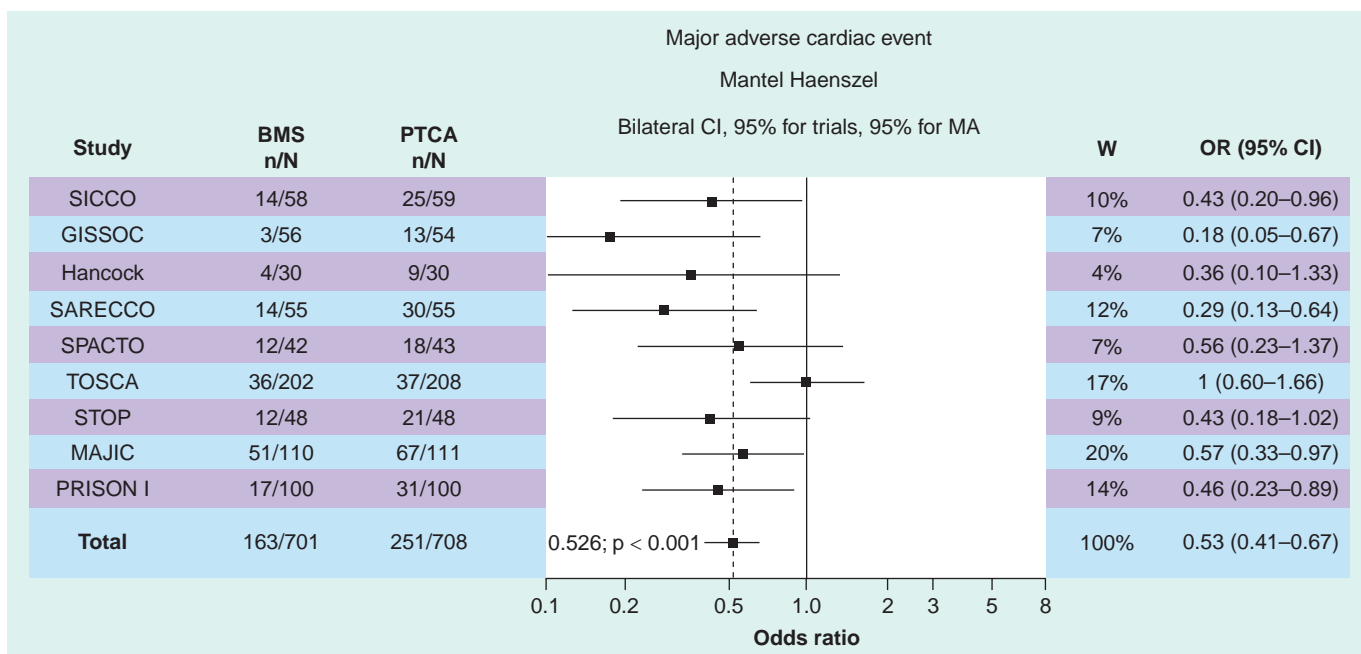


Figure 1. Comparison of the risk of major cardiovascular events. Comparison of the risk of major cardiovascular events (composite of death, myocardial infarction and repeated revascularization) in patients with chronic total occlusion treated with BMS versus PTCA in each study and in the overall population, demonstrating odds ratio and 95% CIs. BMS: Bare-metal stent; MA: Meta-analysis; OR: Odds ratio; PTCA: Percutaneous transluminal coronary angioplasty; W: Weight. Data adapted from [22].

vessel segment; and the balloon:vessels diameter ratio for final stent expansion. In particular, the risk of restenosis and reocclusions associated with the procedural dissection of the vessels, a common complication of CTO stenting, was five-times higher than that observed in patients without this complication. The post-stenting MLD showed a cut-off value of 2.54 mm, and a MLD less than this value was associated with a rate of restenosis and occlusions of approximately 50% higher than that observed in patients with a MLD greater than 2.54 mm. The rate of restenosis and reocclusion correlated with the stented vessel segment length, with a 4.6-times higher risk if the total stented length was up to 26 mm and a 6.5-times higher risk if it exceeded 26 mm. The last variable independently associated with restenosis and reocclusion was balloon:vessels diameter ratio for final stent expansion, with a higher risk for a balloon:vessel diameter ratio for final stent expansion less than 1.00. The study by Sallam *et al.* confirmed these results and also showed the predictor value of two other variables [25], the number of stents for lesion and the final percentage of diameter stenosis even if, at the multivariable analysis, the only independent predictor of reocclusion was total stent length (OR: 1.45; $p = 0.0069$).

Werner *et al.* have analyzed the functional predictors of TVF in a cohort of 111 patients with CTO lesions by functional assessment by Doppler and pressure recordings after recanalization [11,26]. In this study, the authors demonstrated that the risk of reocclusion was predicted by a low fractional flow reserve (FFR) but not by an impaired coronary flow velocity reserve (CFVR) after percutaneous transluminal coronary angioplasty.

Moreover, the association between intravascular ultrasound (IVUS) parameters, after successful CTO PCI, and the occurrence of restenosis has been evaluated in a study by Werner *et al.* In this study the only IVUS predictor of restenosis at 6-month angiographic follow-up was a smaller minimum stent area that occurred more frequently in occlusions without compensatory vessel enlargement.

DES versus BMS

The use of DES has led to a dramatic decrease in the restenosis and reocclusion rate after angioplasty of native *de novo* coronary lesions, suppressing neointimal proliferation. In consideration of the antiproliferative properties of these stents, some registries have evaluated and demonstrated both safety and efficacy of DES

for treatment of CTO showing a very low restenosis and reocclusion rate compared with those reported in previous studies in BMS era [27,28].

Several studies have compared the clinical outcomes and the angiographic results of patients with CTO treated with BMS or with DES [29–41]. In most cases, they were observational nonrandomized studies in which CTO treated with DES were compared with CTO treated with BMS in previous registries. In the first of these studies, Hoyer *et al.* studied 56 patients successfully treated for CTO lesions with sirolimus-eluting stent (SES) and 28 patients treated with BMS [29]. In-hospital MACE (including death), nonfatal myocardial infarction (MI) and repeat target vessel revascularization (TVR) are not recorded, and at 1-year follow-up, the cumulative event-free survival was 96.4% for the SES group versus 82.8% in the BMS group. At 6 months of angiographic follow-up, the binary restenosis rate was 9.1% and the occlusion rate was 3% in the SES group.

In another study, Ge *et al.* evaluated 122 patients who underwent revascularization with SES for CTO lesions and compared their cumulative rate of MACE at 6-months follow-up with that of 259 patients treated with BMS in the 24 months before SES introduction [30]. The cumulative rate of MACE was 16.4% in the SES group and 35.1% in the BMS group ($p < 0.001$). Compared with the BMS group the rate of TLR and TVR were significantly lower in the SES group (TLR: 7.4 vs 26.3%; TVR: 9 vs 29%). By Cox regression analysis, BMS implantation; lesion length (>20 mm) and baseline reference vessel diameter (<2.8 mm) were identified as predictors of MACE during 6-months follow-up.

In a nonrandomized prospective study, Nakamura *et al.* analyzed 60 patients with CTO who underwent SES implantation and 120 patients who underwent BMS implantation without significant differences in baseline clinical and angiographic characteristics [31]. In this study, the estimated probabilities of freedom from MACE and repeat revascularization were 58% in BMS and 97% in SES at 12 months follow-up. The SES group had a lower restenosis and occlusion rate than the BMS group on angiographic follow-up at 6 months (2 vs 32% and 0 vs 6%, respectively). Moreover, at angiographic follow-up the SES group had significantly larger luminal diameters and a smaller late loss than the BMS group.

Two studies by Werner *et al.* have evaluated CTO patients treated with paclitaxel-eluting stents (PES) compared with BMS [32,33]. In

2004, Werner *et al.* published a study in which 48 patients with CTO treated with PES were compared with 48 matched patients with CTO previously treated with BMS. The 1-year MACE (cardiac death, periprocedural and late Q-wave MI, non-Q-wave MI and TLR) rate was 12.5% in the PES group and 47.9% in the BMS group ($p < 0.001$). This difference was mainly due to a reduced need for repeat revascularization. During angiographic follow-up for all patients at 6 months, the restenosis rate was 8.3% with PES versus 51% with BMS ($p < 0.001$). There was only one late reocclusion with PES (2.1%) as compared with 23.4% with BMS, with a reduction of late loss by 84% compared with BMS. MLD was significantly higher and late loss lower in the PES group.

In 2006, Werner *et al.* published a study that compared 82 consecutive patients with CTO recanalized with PES and 82 clinically and lesion matched patients treated with BMS. In 21 of 82 patients treated with PES, additional lesions in the artery not directly related to the original occlusion site were treated with BMS (hybrid group). These patients were compared with 21 BMS control subjects (hybrid control group) regarding the study end points. Patients were divided up into four groups, PES, PES control, hybrid and hybrid control, and the incidences of MACE during 12-month follow-up were 13.3, 56.7, 33.3 and 61.9%, respectively. This study confirmed the benefit of DES implantation in terms of clinical outcome, owing to a lower TLR (10 vs 53.4%). There was only one late reocclusion with PES as compared with 21.7% with BMS. In the BMS group, diabetes, stent length and stent number were significant predictors of TVF, while the duration of occlusion and diameter stenosis were not independent predictors. However, taking all 81 patients treated with a PES, the hybrid approach was the single significant predictor of TVF. Thus, the use of a BMS for remote lesions within the target artery to cover distal dissections or additional distal lesions resulted in a considerably higher TVF and MACE rate as compared with the group with exclusive PES use.

The study by Migliorini *et al.* enrolled 92 patients who underwent DES implantation (47 with SES and 45 PES) for the treatment of 104 CTO lesions, and compared them with a matched control group, consisting of 26 patients with 27 CTO lesions [34]. The 6-month MACE event rate was lower in the DES group as compared with the BMS group (9.8 vs 23%; $p = 0.072$). The 6-month

angiographic follow-up revealed a restenosis rate per lesion of 19 and 45% in DES and BMS, respectively ($p < 0.001$).

The Primary Stenting of Totally Occluded Native Coronary Arteries (PRISONS) II [35] was the only randomized prospective study that compared successful CTO PCI treated with SES or with BMS. In this study, 200 patients with CTO were enrolled. At 6-month follow-up the rate of MACE in the BMS was higher than in the SES (RR: 5.0; 95% CI: 1.77–14.11) as a result of a higher TLR (19 vs 4%) and TVR rates (22 vs 8%). At 12 months of clinical follow-up, the rate of cardiac events in the BMS group was higher than in the SES group (RR: 2.67; 95% CI: 1.31–5.45). Angiographic 6 months follow-up demonstrated that patients assigned to SES implantation had a larger in segment MLD (difference: 0.77 mm; 95% CI: 0.55–0.97) with less residual stenosis (difference: 21.0%; 95% CI: 14.9–27.0) compared with BMS implantation. As a result of these differences, the rate of binary in-segment restenosis and reocclusion in the SES group were lower than those in the BMS group.

Few studies have evaluated long-term outcomes (>1 year) of DES in the treatment of CTO [36–39]. In 2005, the results of 3 years clinical outcome of the PRISON II study were published [36]. A total of 3 years after total occlusion (>2 weeks) lesions treatment, implantation of SES was associated with a significant reduction in adverse clinical events compared with BMS (10 vs 34% in SES vs BMS group, respectively), with a lower rate of TVR (11 vs 30%, respectively) and TLR (7 vs 27%, respectively). No statistically significant differences were found in death, MI and stent thrombosis. These data were also confirmed in the 'real chronic total coronary occlusion' subgroup (>3 months). Although the highest benefit was achieved in the first year of follow-up, no significant differences in adverse events between 12 and 36 months were found. García-García *et al.* reported the 3-year clinical outcome after coronary stenting of CTO using SES in the patients of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry [37]. This study demonstrated that, after 3 years, the use of SES was not associated with significantly lower rates of TVR or MACE in patients with CTO compared with BMS, suggesting a phenomenon of late catch-up of TLR and other MACEs. In addition, in a smaller population, Shen *et al.* reported a similar outcome between SES and BMS after 5 years by a successful CTO recanalization, 15.6 and 11.8% of MACE rates in the BMS and SES

group, respectively ($p = 0.56$) [38]. However, in the SES group, there was a lower but statistically nonsignificant incidence of TLR.

These data were dissimilar to the study by Han *et al.*, which evaluated 1184 patients with successful recanalization of 'real chronic total coronary occlusion', 660 patients underwent DES implantation (53.8 and 46.2% in SES and PES, respectively) and 524 underwent BMS implantation [39]. In this study, the 5-year TVR- and MACE-free survival rates were significantly higher in the DES group than in the BMS group (81.6 vs 73.5% and 80.6 vs 71.5%; Log-rank $p < 0.001$ for all). However, no significant difference in 5 years global survival was found between the two groups (90.3 vs 89.6% for DES vs BMS, respectively). A summary of the angiographic and clinical outcomes found in these studies are reported in TABLES 1 & 2.

Overall, these studies demonstrated that DES implantation provides better results when compared with BMS, mainly due to a significant reduction of TVR in the midterm follow-up without any statistically significant difference in survival rates. Moreover, the data regarding the benefits of DES for CTO lesions at long-term follow-up are scarce and contrasting and further studies are needed to clarify this issue.

DES versus DES

In the literature, few studies have compared the differences between DES in the setting of CTO. In the first of these, Hoye *et al.* retrospectively analyzed a population of 133 patients treated with DES (76 with SES implantation and 57 with PES) and have compared those with a similar group of 26 patients treated with BMS [40]. At 400 days follow-up, the cumulative TVR-free survival was 80.8% for BMS versus 97.4 and 96.4%, respectively, in the SES and PES group, suggesting that both SES and PES use were associated with a lower rate of TVR. The study by Migliorini *et al.* confirmed the similar results obtained using PES or DES in CTO treatment [34].

In a further study, Jang *et al.* evaluated the differences in terms of safety and efficacy between SES (107 patients) and PES (29 patients) use in the treatment of CTO lesions [41]. In contrast with previous studies, they reported a significantly higher restenosis rate and late loss with PES compared with SES at 6-months follow-up (28.6 vs 9.4%; $p = 0.02$ and 0.8 vs 0.4 mm; $p = 0.025$, respectively). At 1 year, the cumulative MACE-free survival rate was 95.8% in the SES group compared with 85.8% in the PES

group ($p = 0.049$), suggesting a different effectiveness among the DES used. More recently, the hypothesis of a dissimilar benefit obtained using different DES in the treatment of CTO lesions was also suggested by the findings of the Multicenter Registry in Asia [42,43]. The most recent results of this registry were presented at the 21st annual Transcatheter Cardiovascular Therapeutics (TCT) scientific symposium [43]. This registry has evaluated 1148 patients with 1253 CTOs, successfully treated with different DES: 396 SES, 526 PES, 177 zotarolimus-eluting stent (ZES) and 66 Biolimus A9 (BES), 41 EPC capture (ECS) and 43 everolimus-eluting stents (EES). The MACE rate at 9 months revealed a higher efficacy of SES (3.6%), EES (2.4%) and BES (4.5%) compared with PES (6.7%), ZES (10.4%) and ECS (10.3%). Moreover SES, BES and EES demonstrated a lesser rate of angiographic restenosis compared with the other DES (4, 4.5 and 2.4 vs 12.3% for ZES, 10.3% for ECS and 6.7% for PES). The results of this Registry suggests the better clinical performance of SES and of the new BES and EES device in the treatment of CTO lesions (FIGURE 2).

Special issues with DES use in CTO

Even if the use of DES represents a revolutionary step toward improving outcomes after CTO lesions treatment, several issues concerning the use of these stents for off-label indications and for the treatment of complex lesions, such as CTO, are emerging.

■ Duration of dual antiplatelet therapy

Several years have elapsed since the introduction of the first DES, and the ideal duration of dual antiplatelet therapy remains to be determined, in particular interventional settings associated with a higher thrombotic risk, such as the treatment of CTO [44]. Current guidelines [45] recommend at least 12 months of clopidogrel in patients at low risk for bleeding and some cardiologists suggest continuing clopidogrel therapy beyond 1 year in patients at low risk of bleeding to prevent the most prominent and potential catastrophic complication of DES placement – late stent thrombosis. Of note, the 4% re-occlusion rate with SES in the PRISON II study might include some cases of late stent thrombosis, and a 3% late stent thrombosis rate has been reported in a series of consecutive CTOs treated with PES within 3 years of follow-up. While these data, together with the higher thrombotic risk

Table 1. Midterm clinical and angiographic outcomes of the patients in the included studies that have evaluated drug-eluting stent implantation in chronic total occlusion.

	Hoye et al. Research-Registry (2004)			Ge et al. MILAN Registry (2005)			Nakamura et al. (2005)			Suttorp et al. Prison II (2006)		
	BMS	DES SES	p-value	BMS	DES SES	p-value	BMS	DES SES	p-value	BMS	DES SES	p-value
No. of patients	28	56		259	122		120	60		100		
Minimum duration of CTO	>3 months			>3 months			>3 months			100		At least 2 weeks (>3 months in 45%)
CTO definition	All occlusions in a native vessel			TIMI flow grade 0			TIMI flow grade 0			TIMI flow grade 0 or 1		
Follow-up duration	1 year			6 months			6 months			1 year		
Death; n(%)	0 (0)	0 (0)	ns	3 (1.2)	3 (2.5)	ns	0 (0)	0 (0)	ns	1	0	ns
AMI; n (%)	0 (0)	1 (1.8)	ns	20 (7.7)	10 (8.2)	ns	3 (3)	0 (0)	ns	4	2	ns
TLR; n (%)				68 (26.3)	9 (7.4)	<0.001	27 (23)	1 (2)	0.001	21	5	<0.001
TVR; n (%)	5 (17.8)	1 (1.8)	<0.05	75 (29)	11 (9)	<0.001	36 (30)	2 (3)	0.001	24	9	0.004
MACE; n (%)	5 (17.8)	2 (3.6)	<0.05	91 (35.1)	20 (16.4)	<0.001	50 (42)*	2 (3)	0.001	24	5	<0.001
Antiplatelet regimen	All received 6 months dual antiplatelet therapy with clopidogrel in addition to aspirin			Pretreatment with 300 mg clopidogrel loading dose and clopidogrel or ticlopidin for at least 3 months for DES and 1 month for BMS			Pretreatment with 150 mg clopidogrel loading dose; therapy duration was not defined			Pretreatment with a loading dose of clopidogrel 300 mg and aspirin 80 mg followed by aspirin 80 mg once daily indefinitely and clopidogrel 75 mg daily for at least 6 months		
Angiographic follow-up and duration	No	Yes		Yes	Yes		Yes	Yes		Yes	Yes	
	6 months	6 months		6 months	6 months		6 months	1 year		6 months	6 months	
No. of patients; n (%)	33 (60)	33 (60)		208 (80.3)	101 (83.5)		116 (97)	40 (63)	45 (75)	100 (100)	100 (100)	
Late lumen loss (mm)	0.13 ± 0.46	0.13 ± 0.46		1.04 ± 0.87	0.28 ± 0.56	<0.01	1.36 ± 0.88	0.08 ± 0.1	0.1 ± 0.1	1.09 ± 0.91	0.05 ± 0.81	<0.00001
Re-occlusion; n (%)	1 (3)	3 (9.1)	ns	15 (6.6)*	3 (2.5)*	ns	7 (6)	0	0.001	13	4	<0.04
Restenosis; n (%)	3 (9.1)	3 (9.1)	ns	76 (33.3)*	11 (9.2)*	<0.001	37 (32)	1 (2)	0.001	41	11	<0.001
Stent thrombosis (%)	0	2	ns	0.4	0	ns	0	0	ns	0	2	0.49

*At 1 year follow-up.
 †Rate per lesion.
 AMI: Acute myocardial infarction; BMS: Bare-metal stent; CTO: Chronic total occlusion; DES: Drug-eluting stent; MACE: Major adverse cardiovascular event; ns: No significant; SES: Sirolimus-eluting stent; TIMI: Thrombolysis In Myocardial Infarction; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

Table 1. Midterm clinical and angiographic outcomes of the patients in the included studies that have evaluated drug-eluting stent implantation in chronic total occlusion (cont.).

	Migliorini et al. (2006)			Werner et al. (2006)			Werner et al. (2004)		
	BMS	DES SES PES	p-value	BMS	DES Taxus	p-value	BMS	DES Taxus	p-value
No. of patients	26	92		61	61		48	48	
Minimum duration of CTO	>3 months			At least 2 weeks (>3 months in 70%)			At least 2 weeks (>3 months in 69%)		
CTO definition	TIMI flow grade 0			TIMI flow grade 0 or 1			TIMI flow grade 0 or 1		
Follow-up duration	6 months			1 year			1 year		
Death; n(%)	0 (0)	2 (2.1)	ns	2 (3.3)	0 (0)	ns	2 (4.16)	1 (2.1)	ns
AMI; n (%)	0 (0)	0 (0)	ns	1 (1.7)	2 (3.28)	ns	1 (2.1)	2 (4.16)	ns
TLR; n (%)							21 (44)	3 (6)	<0.001
TVR; n (%)	6 (23)	7 (7.6)	0.027						
MACE; n (%)	6 (23)	9 (9.8)	0.072	34 (56.7)	8 (13.3)	<0.01	23 (47.9)	6 (12.5)	<0.001
Antiplatelet regimen	Pretreatment with aspirin (300 mg/day) and clopidogrel (loading dose 600 mg). Aspirin (300 mg daily) was continued indefinitely, whereas clopidogrel (75 mg daily) was continued for at least 6 months			All patients were on aspirin (100 mg) and received clopidogrel (75 mg) for 6 months starting on the day of the procedure in the Taxus group. In the BMS control group, clopidogrel was administered for 4 weeks			All patients received aspirin (100 mg) and, in addition, clopidogrel (75 mg) for 4 weeks after BMS and for 6 months after Taxus stents		
Angiographic follow-up and duration	Yes, 6 months			Yes, 1 year			Yes, 1 year		
No. of patients; n (%)	21 (81)	74 (80)		60 (98)	61 (100)		48 (100)	48 (100)	
Late lumen loss (mm)				1.26 ± 0.60	0.24 ± 0.6	<0.001	1.21 ± 0.7	0.19 ± 0.62	<0.001
Re-occlusion; n (%)	5 (23)*	9 (11)*	ns	13 (21.7)	1 (1.7)	<0.0001	11 (23.4)	1 (2.1)	<0.005
Restenosis; n (%)	10 (45)*	15 (19)*	<0.001	33 (55)	7 (11.7)	<0.001	25 (51.1)	4 (8.3)	<0.001
Stent thrombosis (%)				0	0	ns	0	0	ns

*At 1 year follow-up.

*Rate per lesion.

AMI: Acute myocardial infarction; BMS: Bare-metal stent; CTO: Chronic total occlusion; DES: Drug-eluting stent; MACE: Major adverse cardiovascular event; ns: No significant; SES: Sirolimus-eluting stent; TIMI: Thrombolysis In Myocardial Infarction; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

of CTO-treated lesions, appear to suggest the need of a longer duration of dual antiplatelet therapy, none of the trials that have tested this therapy for more than 12 months after DES implantation have shown a net benefit in reducing death or MI. However, no studies are specifically designed to assess the efficacy of a longer dual antiplatelet therapy in the setting of CTO-treated lesions, and interestingly, a majority of the studies regarding DES use in CTO have considered a short period of dual antiaggregant therapy. Further studies are needed to clarify this unsolved issue.

■ Late restenosis

Although the benefits of DES in the treatment of CTO lesion appear clear in the midterm outcome, the data on the long-term patency, especially in very long CTO lesions, are scant and contrasting. Of the four studies regarding long-term follow-up, two studies did not confirm the benefit of DES versus BMS while in the other two studies this benefit appears to be lower than that observed in the midterm follow-up. The difference between mid- and long-term outcomes after DES implantation for the treatment of CTO lesions might have at least two explanations. First, it is possible

that the more complex characteristics of CTO lesion treated with DES, usually detected in these studies (such as longer segments requiring a greater number of stents implanted and a longer overlapping, as well as smaller diameters of treated vessel), might affect the long-term DES patency. Conversely, several of these studies were not randomized with a BMS group as a historic control, thus, it cannot be completely excluded that the differences found between DES and BMS are due more to new procedural techniques used rather than the type of stent *per se*.

Second, the higher incidence of restenosis and reocclusion of DES-treated CTO lesions in the long-term studies might be due to a variety of complications associated with the long-term outcome of employment, including stent fractures, stent malapposition and aneurysm.

■ Stent fracture

Stent fracture is not a rare complication of DES implantation (5%), in particular with the use of Cypher stent [46] and in the setting of CTO (11.6%) [46-48]. In a recent post-mortem study by Nakamura *et al.* [48], the authors demonstrated that this complication was more common than previously reported

Table 2. Long-term clinical and angiographic outcomes of the patients in the included studies that have evaluated drug-eluting stent implantation in chronic total occlusion.

	García-García <i>et al.</i> Research-Registry (2007)			Rahel <i>et al.</i> Prison II (2008)			Han Yang <i>et al.</i> (2009)			Shen <i>et al.</i> Research-Registry (2009)		
	BMS	DES	p-value	BMS	DES	p-value	BMS	DES	p-value	BMS	DES	p-value
No. of patients	71	76		100	100		524	660		64	76	
Duration follow-up (years)	3			3			5			5		
Patients at follow-up (%)	96	87		98	96					95.5	96.4	
Minimum duration of CTO	At least 3-month			At least 2 weeks (>3 months in 45%)			At least 3-month			At least 3-month		
CTO definition	All occlusions in a native vessel			TIMI flow grade 0 or 1			TIMI flow grade 0			All occlusions in a native vessel		
Death n (%)	4 (5.6)	5 (6.6)	ns	4	4	ns	54 (10.4)	64 (9.7)	ns	7 (10.9)	9 (11.8)	ns
AMI n (%)	2 (2.8)	2 (2.6)	ns	3	5	ns				2 (3.1)	3 (3.9)	ns
TLR n (%)	8 (11.4)	6 (7.9)	ns	27	7	<0.001				8 (12.5)	5 (6.6)	ns
TVR n (%)	9 (12.7)	7 (9.2)	ns	30	11	<0.002	139 (26.5)	121 (18.4)	<0.001	9 (14)	9 (11.8)	ns
MACE n (%)	13 (18.3)	12 (15.8)	ns	34	10	<0.001	149 (28.5)	128 (19.4)	<0.001	14 (21.9)	19 (25)	ns

AMI: Acute myocardial infarction; BMS: Bare-metal stent; CTO: Chronic total occlusion; DES: Drug-eluting stent; MACE: Major adverse cardiovascular event; ns: Not significant; TIMI: Thrombolysis In Myocardial Infarction; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

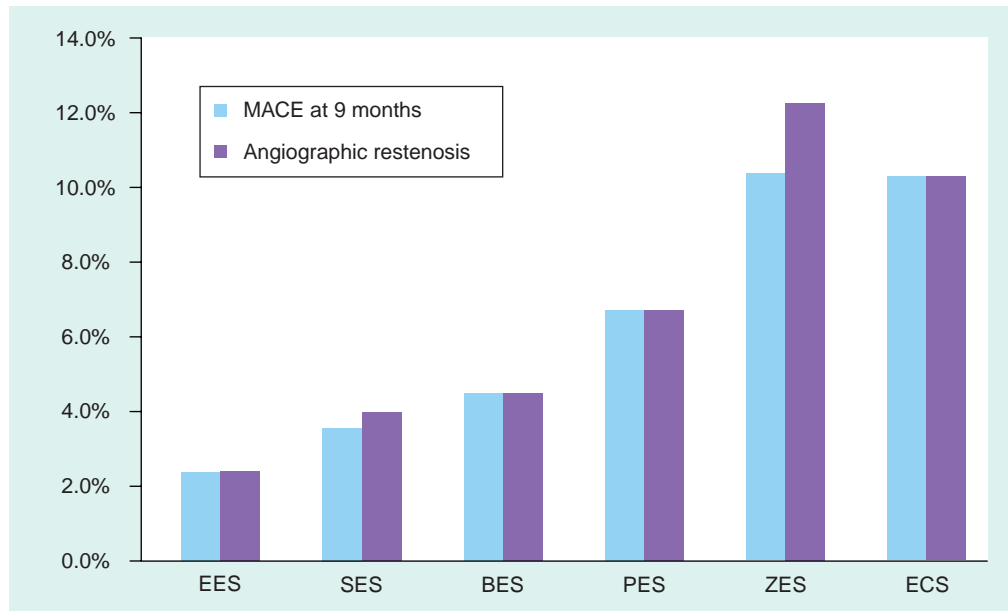


Figure 2. Comparison of the rate of MACE at 9 months and angiographic restenosis in patients with chronic total occlusion treated with different drug-eluting stents in the multicenter registry in Asia by Nakamura *et al.*

BES: Biolimus A9-eluting stent; ECS: EPC capture stent; EES: Everolimus-eluting stent; MACE: Major adverse cardiac event; PES: Paclitaxel stent; SES: Sirolimus-eluting stent; ZES: Zotarolimus-eluting stent. Data adapted from [43].

(29%) and that it was more often associated with Cypher implantation, longer stent length, greater number of stents for lesion and overlapped stents. However, a higher incidence of adverse events (restenosis and thrombosis) was only observed in a particular type of fracture with a gap in the body of the stent. In another study, Pompma *et al.* reported that stent fracture of Cypher occurred more frequently in the presence of complex lesions characterized by extensive calcification, angulation greater than or equal to 45°, lesion length greater than or equal to 20 mm, proximal vessel tortuosity, total occlusions and ostial location and was associated with a higher rate of need for revascularization. In addition, in the Approaches to Chronic Occlusions With Sirolimus-Eluting Stents/Total Occlusion Study of Coronary Arteries-4 (ACROSS/TOSCA-4) trial, studying a cohort of 200 consecutive CTO patients treated with SES, TLR was more common among 32 patients identified with stent fractures than patients without fractures (25.0 vs 6.7%; $p = 0.005$) [49]. Serial angiographic follow-up might be useful to detect stent fractures in patient treated for CTO lesions and, in those with angiographic evidence of this complication, a long-term dual antiplatelet therapy should be taken into account to avoid the occurrence of adverse events.

Stent malapposition & aneurysm

Several studies have reported late stent malapposition (LSM) in 4–5% of patients after BMS implantation [50,51]. Although DES dramatically reduced the rate of in-stent restenosis, the incidence of LSM after DES implantation appeared to be higher than in BMS-treated patients. The study by Hong *et al.*, confirmed these data and also demonstrated that total stent length and CTO lesions are independent predictors of LSM [52]. In this study, the incidence of LSM in CTO lesions was approximately 27.5%. Subintimal passage of the guidewire, creation of a false lumen, or stenting of the false lumen may result in injury to the adventitial layer during DES implantation of CTO lesions, contributing to LSM.

Moreover, although in this study LSM was not associated with any MACE during a follow-up of 10 months, a recent meta-analysis of Hassan *et al.* demonstrated that the risk of late stent thrombosis in patients with LSM was higher compared with those without LSM [53].

Massive plaque burden and severe calcification, commonly found in CTO lesions, represent well-known causes of stent malapposition to the vessel wall in this setting. Plaque debulking with high-speed rotational atherectomy or excimer laser might allow optimal stent apposition and reduce the incidence of adverse

events associated with stent malapposition. Indeed, a recent study, although conducted in the BMS era, demonstrated the safety and efficacy of a plaque debulking strategy in PCI for CTO involving a massive plaque burden or calcified plaque [54]. Comparing 266 patients randomly assigned to a debulking or non-debulking strategy, this study demonstrated that pre-stent plaque debulking of CTO was associated with a favorable midterm outcome (1-year-MACE rate: 27.5 vs 39.8%; $p = 0.033$) with a trend to lower TVR rate in the debulking group than in the nondebulking group (23.8 vs 34.6%; $p = 0.072$). Moreover, as suggested by recent studies, IVUS-guided stent implantation in the treatment of CTO lesions might be another chance to reduce the occurrence of this complication or to treat it later. Further studies will be needed to test these hypotheses.

Moreover, the late acquired incomplete stent apposition may be a precursor of aneurysm formation that may lead to rare but potentially dramatic complications such as stent thrombosis, coronary rupture or distal embolism. DES may be associated with a greater risk of aneurysm formation, in particular after CTO treatment [55]. DES, locally eluting antiproliferative drugs, can dramatically inhibit neointimal growth, suppressing restenosis, but can also potentially cause coronary aneurysms owing to delayed re-endothelialization secondary to the antiproliferative action, inflammatory changes of the medial wall and hypersensitivity reactions. This risk could be higher in CTO treatment due to the concomitant presence of other factors associated with physical vessel trauma and aneurysm formation, such as residual

dissection and deep arterial wall injury caused by oversized balloons or stents, high-pressure balloon inflations, atherectomy or excimer laser angioplasty, retrograde subintimal tracking or DES placement in false lumen [56].

Conclusion & future perspective

There is clear evidence that a persistent patency of treated CTO lesions determines a better outcome especially in patients with MVD. The introduction of BMS before and DES after have allowed the significant reduction of the incidence of restenosis in this setting and several studies have demonstrated how this translates into a reduction of MACE within the midterm follow-up, mainly due to a reduction of TLR rate. However, owing to the emerging concerns regarding long-term DES-related complications, the choice of DES type and the use of other strategies able to lower the number of implanted DES (such as IVUS-guided stent implantation and plaque debulking strategies) should be a topic for further research along with a better understanding of the pharmacological management of patients treated for a CTO with DES.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Chronic total occlusion (CTO) of the coronary arteries is a common finding on diagnostic coronary angiography (~35%) and in fact, percutaneous coronary intervention (PCI) for CTO represents as many as 15% of all angioplasty procedures at high-volume centers.
- The introduction of dedicated guidewires and the development of new techniques have improved the success rate in the crossing of CTO lesions, while the use of stent has dramatically reduced the occurrence of restenosis and the need for target lesion revascularization (TLR).
- The introduction of bare-metal stents (BMS) has led to a reduction in restenosis and reocclusion rate in CTO PCI and has conferred a long-term survival advantage after successful CTO treatment. Nevertheless, even after BMS introduction, restenosis, reocclusion and repeated revascularization rates remained unacceptably high compared with non-CTO lesions treated with BMS.
- Thus, several studies have compared the clinical outcomes and the angiographic results of patients with CTO treated with BMS or with DES; DES implantation provides better results when compared with BMS, mainly due to a significant reduction of TVR in the mid-term follow-up without any statistically significant difference in survival rates. The data about the benefits of DES for CTO lesions at long-term follow-up are insufficient and contrasting.
- There are several issues regarding the use of DES for off-label indications and for the treatment of complex lesions, such as CTO, and results on long-term DES use are emerging: the ideal duration of dual antiplatelet therapy remains to be determined; the higher incidence of restenosis and reocclusion of DES-treated CTO lesions in the long-term studies might be due to a variety of complications associated with the long-term outcome, including stent fractures, stent malapposition and aneurysm.

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