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Increased Rate of Stent Thrombosis and Target Lesion Revascularization After Filter Protection in Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

15-Month Follow-Up of the DEDICATION (Drug Elution and Distal Protection in ST Elevation Myocardial Infarction) Trial

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Objectives The purpose of this study was to evaluate the long-term effects of distal protection during percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI).

Background The use of distal filter protection during primary PCI increases procedure complexity and may influence lesion treatment and stent implantation.

Methods The STEMI patients were assigned to distal protection (DP) (n = 312) or conventional treatment (CT) (n = 314). Clinical follow-up was performed after 1, 6, and 15 months, and angiographic follow-up after 8 months. All target lesion revascularizations (TLRs) were clinically driven. We report the pre-specified end points of stent thrombosis according to the criteria of the Academic Research Consortium, TLR, and reinfarction after 15 months.

Results The total number of stent thrombosis was 11 in the DP group and 4 in the CT group (p = 0.06). The rate of definite stent thrombosis was significantly increased in the DP group as compared with the CT group, with 9 cases versus 1 (p = 0.01). Clinically driven TLRs (31 patients vs. 18 patients, p = 0.05) and clinically driven target vessel revascularizations (37 patients vs. 22 patients, p = 0.04) were more frequent in the DP group.

Conclusions In primary PCI for STEMI, the routine use of DP increased the incidence of stent thrombosis and clinically driven target lesion/vessel revascularization during 15 months of follow-up. (Drug Elution and Distal Protection in ST Elevation Myocardial Infarction Trial [DEDICATION]; NCT00192868) (J Am Coll Cardiol 2010;55:867–71)
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The DEDICATION (Drug Elution and Distal Protection in ST Elevation Myocardial Infarction) trial, evaluating the potential benefit of distal protection (DP) using a filter wire as an adjunctive to conventional treatment (CT) during primary percutaneous coronary intervention (PCI), found no benefit with respect to either primary or secondary end points (1).

Previous studies have similarly failed to show immediate, short-, or intermediate-term benefits of the adjunctive device (2–4), but potential long-term effects have not been reported.

In the DEDICATION trial, we also evaluated the effect of drug-eluting stents (DES) versus bare-metal stents (BMS), and therefore, we followed up all patients for 15 months (5). In the present study, we report pre-specified long-term end points of stent thrombosis, target lesion revascularization (TLR), and target vessel revascularization (TVR), reinfarction of the infarct-related artery, and death after 15 months.

Methods

Study design. The design of the DEDICATION trial was described previously (1,5). In brief, patients with symptoms lasting <12 h and with ST-segment elevation ≥0.2 mV in

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Abbreviations and Acronyms

BMS = bare metal stent(s)
CT = conventional treatment
DES = drug-eluting stent(s)
DP = distal protection
MACCE = major adverse cardiac and cerebral events
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TLR = target lesion revascularization
TVR = target vessel revascularization

≥2 contiguous leads were eligible for enrollment. The study protocol was approved by the local ethics committees, and all patients gave written informed consent.

Randomization and procedures. Patients were pre-treated with 300 mg aspirin, 300 to 600 mg clopidogrel, and 10,000 IU unfractionated heparin. A guide wire was advanced through the lesion, and pre-dilation was performed to visualize the peripheral vascular bed. If the operator predicted that a filter wire (EZ-Filter Wire, Boston Scientific, Natick, Massachusetts) or a SpiderX protection device (eV3, Inc., Minneapolis, Minnesota) could be advanced, randomization was performed stratified with regard to sex and diabetes mellitus.

Follow-up schedule. Clinical follow-up was performed at 1 and 6 months, and angiographic follow-up at 8 months. The TLR was considered clinically driven in case of angina and a diameter stenosis >50%, and in any case of a diameter stenosis >70%. A final clinical follow-up was performed at 15 months, 3 months after cessation of dual-antiplatelet therapy.

Study end points. The primary end point was the number of patients suffering a major adverse cardiac event (MACE), defined as stent thrombosis, TLR, TVR, nonfatal myocardial reinfarction, or death within 15 months. Stent thrombosis was characterized according to the Academic Research Consortium definitions as definite, probable, and possible (6). Myocardial infarction was defined as a total creatine kinase elevation ≥2 times the upper normal limit with a concomitant increase in creatine kinase-myocardial band mass blood concentration in the presence of an acute coronary syndrome, and reinfarction was present in case the recurrent myocardial infarction could be related (by electrocardiography or angiography) to the target vessel. Clinically driven TLR was defined as revascularization of the target lesion, in the presence of recurrent angina and a significant stenosis/occlusion of the infarct-related lesion. Nonclinically driven TLR was allowed in the absence of angina whenever the diameter restenosis was >70%. Finally, TVR was defined as revascularization either in the target lesion or in an area remote from the target lesion in the same coronary artery. The Clinical Events Committee adjudicated all serious events and stent thromboses.

Statistical analysis. Analyses were based on intention to treat. Categorical variables were analyzed by the chi-square test or by the Fisher exact test. Continuous variables were analyzed using the Mann-Whitney *U* test for unpaired samples. All p values were 2-sided.

Results

Baseline characteristics and procedural results. Baseline clinical and angiographic characteristics of the 626 patients were well matched (Tables 1 to 3). Of the patients assigned to DP, the filter wire was successfully advanced and unfolded distally to the lesion before stent implantation in 254 of 312 patients (81%). Pre-dilation was performed in 226 patients (71%) before filter placement. For pre-dilation, a 1.5-mm balloon was used in 32 patients (10%), a 2.0-mm balloon in 141 patients (45%), a 2.5-mm balloon in 50 patients (16%), and a 3.0-mm balloon in 3 patients (1%). The Spider-X system was used in 39 patients. In 58 patients (19%), none of the DP systems could be advanced to a sufficient landing zone.

Table 1 Baseline Clinical Characteristics

	Distal Protection (n = 312)	Conventional Treatment (n = 314)	p Value
Age, yrs	62 ± 12.3	63 ± 12.1	0.27
Male	232 (74.4)	226 (72.0)	0.53
Diabetes mellitus	28 (9.0)	37(11.8)	0.30
Hypertension	100 (32.1)	107 (34.1)	0.61
Treatment for hyperlipidemia	58 (18.6)	64 (20.4)	0.35
Current smoker	177 (56.7)	158 (50.3)	0.24
Family history of CAD	114 (36.5)	118 (37.6)	0.80
Previous myocardial infarction	20 (6.4)	20 (6.4)	1.0
Previous PCI/CABG	16 (5.1)	15 (4.8)	0.62
Symptom onset to arrival, min	200 (26–1,350)	199 (40–996)	0.98
Door-to-balloon, min	27 (3–104)	24 (3–92)	0.01
Symptom onset to balloon, min	233 (59–1,370)	222 (60–1,027)	0.55
Baseline cumulated ST-segment deviation, mV	1.1 (0.7–2.2)	1.3 (0.8–2.1)	0.13

Values are median ± SD, n (%), or median (range).
CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

Table 2 Baseline Angiographic Characteristics

	Distal Protection (n = 312)	Conventional Treatment (n = 314)	p Value
Number of diseased vessels			
1-vessel disease	198 (63)	194 (62)	
2-vessel disease	83 (27)	85 (27)	0.86
3-vessel disease	30 (10)	34 (11)	
Infarct-related artery			
RCA	139 (45)	152 (48)	
LAD	138 (44)	119 (38)	0.25
LCX	35 (11)	43 (14)	
Baseline TIMI flow grade			
0–1	209 (67)	213 (68)	0.87
2–3	103 (33)	101 (32)	
Angiographic lesion characteristics			
Reference vessel diameter, mm	3.50 (2.20–5.00)	3.50 (2.30–5.00)	0.25
Diameter stenosis, %	100 (30–100)	100 (50–100)	0.17
Minimal lumen diameter, mm	0.00 (0.00–3.15)	0.00 (0.00–2.00)	0.20
Visible thrombus	213 (68)	236 (75)	0.14

Values are n (%) or median (range).
LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

MACE. STENT THROMBOSIS. The rate of definite stent thrombosis was significantly increased in the DP group as compared with the CT group, with 9 cases versus 1 (p = 0.01). The only definite stent thrombosis in the CT group occurred at day 1 in a BMS. Of the 9 cases in the DP group (6 in BMS and 3 in DES), 5 occurred within the first month, and 4 occurred between 111 and 275 days from the initial intervention. The total number of stent thromboses, including probable and possible, was 11 in the DP group and 4 in the CT group (p = 0.06) (Table 4).

TLR. The rate of TLR was significantly increased in the DP group, 39 patients versus 22 patients in the CT group (p = 0.02), with a similar finding for the clinically driven TLR, 31 versus 18 patients (p = 0.05).

TVR. The rate of TVR was significantly increased in the DP group, 48 patients versus 26 patients in the CT group (p < 0.01), with a similar finding for the clinically driven TVR, 37 patients versus 22 patients (p = 0.04).

MYOCARDIAL INFARCTION. The rates of myocardial infarctions (9 patients vs. 6 patients) and of reinfarctions (7 patients vs. 3 patients) were not significantly different between the 2 groups.

DEATH. Mortality rates were similar in the 2 groups: 13 deaths in the DP group and 15 deaths in the CT group (p = NS).

MACE. The number of patients suffering any MACE was significantly increased in the DP group, 59 patients versus 40 patients in the CT group (p = 0.04) (Fig. 1).

Discussion

The STEMI patients randomly allocated to adjunctive therapy with filter protection had no benefit with respect to immediate, short-term (30 days), intermediate-term (6 months), or long-term (15 months) evaluation. On the contrary, after 15 months, we found a significantly increased rate of MACE in the DP group.

With respect to lack of benefit, the results are in accordance with those of previous studies evaluating distal pro-

Table 3 Procedural Results

	Distal Protection (n = 312)	Conventional Treatment (n = 314)	p Value
Use of GP IIb/IIIa inhibitor	301 (97)	302 (96)	0.36
Filter wire attempted	304 (97)	0	—
Filter wire success	254 (81)	0	—
Stent implanted	307 (98)	312 (99)	0.29
Drug-eluting stent	158 (51)	155 (49)	0.81
Stented length, mm	18 (6–60)	20 (8–107)	0.83
Stent diameter, mm	3.5 (2.0–5.0)	3.5 (2.0–5.0)	0.20
TIMI flow grade III post-procedure	295 (95)	268 (85)	0.01
IABP	4 (1)	6 (2)	0.75
Procedural success	309 (99)	310 (99)	0.69

Values are n (%) or median (range).
GP = glycoprotein; IABP = intra-aortic balloon pump; other abbreviation as in Table 2.

Table 4 Stent Thrombosis

	Distal Protection (n = 312)	Conventional Treatment (n = 314)	p Value
Any stent thrombosis	11, 3.5 (1.5–5.6)	4, 1.3 (0.0–2.5)	0.06
Definite stent thrombosis	9, 2.9 (1.0–4.7)	1, 0.3 (0.0–0.9)	0.01
Early (<30 days) stent thrombosis	5, 1.6 (0.2–3.0)	1, 0.3 (0.0–0.9)	0.06
Late stent thrombosis (>30 days)	4, 1.3 (0.0–2.5)	0	

Values are n, % (95% confidence interval).

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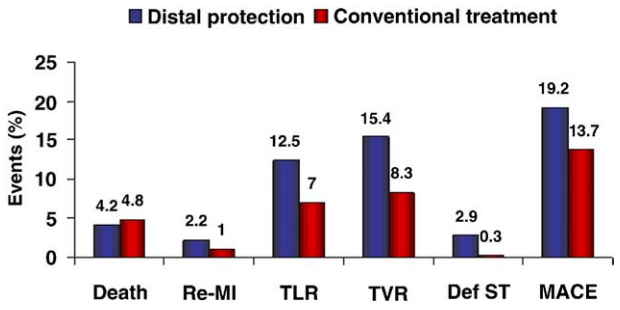

Figure 1 MACE Within 15 Months

Major adverse cardiac events (MACE) within 15 months are shown. The **blue bars** indicate distal protection; the **red bars** indicate conventional treatment. Def ST = definite stent thrombosis; Re-MI = myocardial infarct in the culprit vessel; TLR = target lesion revascularization; TVR = target vessel revascularization.

tection during primary PCI (2–4,7). Previous studies have evaluated end points immediately after the procedure, after 30 days, or after 6 months as the longest follow-up period. Our study is the first to extend follow-up to 15 months, thereby evaluating long-term outcome.

Increased rate of stent thrombosis. It is known that early stent thrombosis (occurring within 30 days) is relatively common with acute coronary syndromes, occurs with similar frequency after stenting with DES and BMS, and is predicted by inadequate pharmacotherapy, diffuse atherosclerosis, and suboptimal angiographic results (8). In the present study, patients were treated with dual platelet inhibition, and as the study was randomized, the 2 groups were presumed to be equal with respect to the amount of diffuse atherosclerosis.

In a study of embolic protection with filter wire during carotid stenting (9), 7.9% of cases had transient spasm in the vessel and 13.1% had nitroglycerine resistant flow impairment. Vessel diameter and flow were restored after removal of the filter, which was presumed to be responsible for the vessel spasm and flow impairment. In the present study, stenting was performed with the filter wire in place, and although the median values of vessel diameter and stent sizes were similar in the 2 groups, we cannot exclude that the filter wire in single cases might have caused vessel spasm, leading to an underestimation of the vessel diameter and to undersizing of the implanted stent, a known predictor of early stent thrombosis in acute coronary syndromes (8).

Dissection of the vessel wall at the site of filter deployment is another possible source of stent thrombosis (10). We did not find an increased rate of procedure complications in the DP group, but we cannot rule out that minor dissections not seen during the procedure while the filter is expanded in the vessel might be responsible for an increased number of acute and subacute stent thrombosis.

Finally, it might be speculated as to whether difficulties during retrieval of the filter might affect the stent apposition.

Increased rate of revascularization. An increased number of patients in the DP group experienced restenosis in the target vessel. Most of these occurred in the target lesion, but also an increased number of restenosis in the target vessel outside the treated lesion was seen. The use of a filter for embolic protection during primary PCI increases procedure complexity. Deployment of the filter may not be a problem in most cases with simple anatomy, but in cases with tortuous or calcified vessels or with very tight lesions, it might be not only a technical challenge but also associated with an increased risk of damaging the vessel. Pre-dilation with a small balloon might be necessary to overcome the problems in these complex lesions, and in our study, pre-dilation was performed in >70% of cases. However, pre-dilation might further increase the risk associated with placement of the filter, as minor dissections or intimal flaps created by the dilation might be aggravated when the filter has to pass through the dilated vessel segment. Therefore, it seems likely that the use of the filter might have created areas with damage of the intima, either in the perilesion area or more remote area.

As previously described for carotid stenting, nitroglycerine-resistant flow impairment occurred in >10% of cases (9). We did not register the rate of flow impairment during procedures, but it seems likely that at least some of the stents might have been placed while the visibility of the lesion was compromised, thereby increasing the risk of misplacing the stent.

Previous studies have suggested that the mechanical trauma to the artery during angioplasty itself might accelerate disease progression and the appearance of new narrowings in the arteries (11,12). As it must be assumed that potential trauma to the artery was more severe in the DP group, that might be another possible explanation why repeat revascularization was increased in this group.

Conclusions

The present randomized study found no benefit with respect to short-, intermediate-, or long-term angiographic or clinical end points. On the contrary, we found a significantly increased rate of adverse cardiac events within 15 months in the group of patients treated with routine DP. Together with the results of previous studies evaluating DP, the results of the DEDICATION trial demonstrate that routine use of a filter wire in its present form cannot be advocated and probably should be avoided with primary PCI for STEMI.

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