

## CLINICAL RESEARCH

## Clinical Trials

# Actinomycin-Eluting Stent for Coronary Revascularization

## A Randomized Feasibility and Safety Study: The ACTION Trial

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<b>OBJECTIVES</b>	We sought to demonstrate the safety and performance of the actinomycin D-coated Multilink-Tetra stent (Guidant Corp., Santa Clara, California) in the treatment of patients with single de novo native coronary lesions.
<b>BACKGROUND</b>	Drug-eluting stents (DES) releasing sirolimus or paclitaxel dramatically reduce restenosis. The anti-proliferative drug, actinomycin D, which is highly effective in reducing neointimal proliferation in preclinical studies, was selected for clinical evaluation.
<b>METHODS</b>	The multi-center, single-blind, three-arm ACTinomycin-eluting stent Improves Outcomes by reducing Neointimal hyperplasia (ACTION) trial randomized 360 patients to receive a DES (2.5 or 10 $\mu\text{g}/\text{cm}^2$ of actinomycin D) or metallic stent (MS). The primary end points were major adverse cardiac events (MACE) at 30 days, diameter stenosis by angiography, tissue effects, and neointimal volume by intravascular ultrasound (IVUS) at six months. When early monitoring revealed an increased rate of repeat revascularization, the protocol was amended to allow for additional follow-up for DES patients. Angiographic control of MS patients was no longer mandatory.
<b>RESULTS</b>	The biased selection of DES patients undergoing IVUS follow-up invalidated the interpretation of the IVUS findings. The in-stent late lumen loss and that at the proximal and distal edges were higher in both DES groups than in the MS group and resulted in higher six-month and one-year MACE (34.8% and 43.1% vs. 13.5%), driven exclusively by target vessel revascularization without excess death or myocardial infarction.
<b>CONCLUSIONS</b>	The results of the ACTION trial indicate that all anti-proliferative drugs will not uniformly show a drug class effect in the prevention of restenosis. (J Am Coll Cardiol 2004;44:1363-7) © 2004 by the American College of Cardiology Foundation

Restenosis after stent implantation remains a major limitation of efficacy. Drug-eluting stents (DES) with sirolimus (1) and paclitaxel (2) have significantly reduced restenosis in simple lesions, compared with the metallic stent (MS). Actinomycin D affects the "S" phase of the cell cycle by

forming a stable complex with double-stranded deoxyribonucleic acid inhibiting ribonucleic acid synthesis and is a powerful inhibitor of cell proliferation (3). To create the eluting stent, actinomycin was coated onto the stainless-steel Multilink Tetra stent in a polymer. We aimed to test the safety and efficacy of two doses of actinomycin D compared with the MS.

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## METHODS

**Study design.** This was a prospective, randomized, parallel, three-arm, single-blind trial with two doses of drug compared with control. The protocol was approved by the ethics committees of all the participating institutions, and all patients gave written, informed consent.

**End points.** The primary safety end points included major adverse cardiac events (MACE) at 30 days and local tissue

**Abbreviations and Acronyms**

DES	= drug-eluting stent
IVUS	= intravascular ultrasound
MACE	= major adverse cardiac events
MI	= myocardial infarction
MS	= metallic stent
QCA	= quantitative coronary angiography
TSR	= target site revascularization
TVF	= target vessel failure

effects (incomplete stent apposition, persisting dissection, edge stenosis, and thrombus formation) at 6 months. MACE was defined as a composite of death, myocardial infarction (MI) (more than three times the upper limit of normal creatine kinase levels), and revascularization (surgery or percutaneous coronary intervention) attributed to the target site (the stented and 5-mm persistent segments). When target vessel (the vessel containing the target site) revascularization was included in MACE, the composite end point was renamed “target vessel failure” (TVF).

The primary performance end points were the reduction of in-stent volumetric burden assessed by intravascular

ultrasound (IVUS) and reduction of target site diameter stenosis by quantitative coronary angiography (QCA) at six months.

The secondary performance end points were TVF at 6 and 12 months and angiographic binary restenosis at 6 months.

**Power calculation and sample size.** To detect a difference of 6.6% in diameter stenosis and of 11.5 mm<sup>3</sup> in intimal hyperplasia, with a significance level of 0.05 and 90% power, 110 patients would be needed in each of the three arms. A sample size of 120 patients was chosen.

**Patient selection.** Patients with stable angina pectoris or silent ischemia and a single de novo lesion in a native coronary artery ≥3.0 mm and ≤4.0 mm in diameter that could be covered by an 18-mm stent were enrolled. Randomization was done by a telephone allocation service.

**Study device.** The three components of the investigational device were the Multilink Tetra stent, a polymeric coating, and an anti-proliferative drug—actinomycin D (3)—in two doses (2.5 and 10 μg/cm<sup>2</sup> of metal stent surface area). The eluting profile of actinomycin D is targeted to release 80% of drug in 28 days. Stents were 18 mm in length and 3.0, 3.5, or 4.0 mm in diameter.

**Table 1.** Baseline Clinical and Angiographic Characteristics

	MS (n = 118)	DES	
		AcD 2.5 μg/cm <sup>2</sup> (n = 120)	AcD 10 μg/cm <sup>2</sup> (n = 119)
Age (yrs)	60 ± 10	61 ± 11	60 ± 11
Male gender	78	78	80
Previous MI	41	38	37
Diabetes mellitus*	5	15	11
Treated dyslipidemia	53	58	54
Treated hypertension	50	49	45
Current smoker	30	23	29
Angina pectoris by CCS class†			
I	7	4	4
II	34	34	35
III	21	21	23
IV	15	14	13
Target coronary artery			
LAD	37	44	42
RCA	42	40	35
LCx	21	16	23
Lesion type			
A	7	7	2
B1	23	21	29
B2	66	64	64
C	4	8	5
Reference vessel diameter, baseline (mm)	2.83	2.84	2.91
Lesion length (mm)	11.3	11.6	10.7
MLD, baseline (mm)	1.00	1.01	1.04
Diameter stenosis, baseline (%)	64	64	63

There were no significant differences in the baseline clinical and angiographic characteristics between the three groups, with the exception of diabetes (\*difference [95% confidence interval] in incidence of diabetes—control vs. 2.5 μg/cm<sup>2</sup>: -9.9% [-17% to -2.3%]; control vs. 10 μg/cm<sup>2</sup>: -5.8% [-12% to 1.02%]). †Angina was defined according to the system of the Canadian Cardiovascular Society (CCS). In the 2.5- and 10-μg groups, there were seven and eight lesions receiving two actinomycin D stents, respectively. Data are presented as the mean value ± SD or percentage of patients.

AcD = actinomycin D; DES = drug-eluting stent; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; MLD = minimal luminal diameter; MS = metallic stent; RCA = right coronary artery.

**Table 2.** Serial Quantitative Coronary Angiographic Analyses

	MS	DES			
		AcD 2.5 $\mu\text{g}/\text{cm}^2$	p Value	AcD 10 $\mu\text{g}/\text{cm}^2$	p Value
Angiographic follow-up	65 (55%)	114 (95%)		115 (97%)	
In-stent					
MLD, post-intervention (mm)	2.64 $\pm$ 0.34	2.77 $\pm$ 0.45	0.02	2.82 $\pm$ 0.43	0.002
MLD, f/u (mm)	1.88 $\pm$ 0.58	1.76 $\pm$ 0.70	0.25	1.90 $\pm$ 0.68	0.87
Late loss (mm)	0.76 $\pm$ 0.43	1.01 $\pm$ 0.58	0.001	0.93 $\pm$ 0.58	0.03
Restenosis (%)	11	25	0.03	17	0.38
Edges					
Proximal MLD, post-intervention (mm)	2.60 $\pm$ 0.53	2.73 $\pm$ 0.58	0.12	2.79 $\pm$ 0.56	0.02
Proximal MLD, f/u (mm)	2.32 $\pm$ 0.60	2.22 $\pm$ 0.67	0.35	2.26 $\pm$ 0.76	0.58
Proximal late loss (mm)	0.28 $\pm$ 0.38	0.51 $\pm$ 0.52	0.002	0.53 $\pm$ 0.61	<0.001
Proximal restenosis (%)	3	5	0.71	14	0.02
Distal MLD, post-intervention (mm)	2.31 $\pm$ 0.56	2.40 $\pm$ 0.58	0.32	2.41 $\pm$ 0.58	0.25
Distal MLD, f/u (mm)	2.23 $\pm$ 0.53	2.05 $\pm$ 0.61	0.05	1.99 $\pm$ 0.64	0.009
Distal late loss (mm)	0.08 $\pm$ 0.31	0.35 $\pm$ 0.50	<0.001	0.43 $\pm$ 0.57	<0.001
Distal restenosis (%)	2	4	0.65	6	0.26
Target site*					
DS (%)	35 $\pm$ 15	40 $\pm$ 18	0.08	40 $\pm$ 19	0.05
Restenosis (%)	14	26	0.06	28	0.04
Vessel segment					
RD, f/u (mm)	2.76 $\pm$ 0.58	2.71 $\pm$ 0.55	0.58	2.78 $\pm$ 0.48	0.81
DS, f/u (%)	37 $\pm$ 13	41 $\pm$ 18	0.11	41 $\pm$ 18	0.06
Restenosis rate (%)	14	27	0.04	28	0.04
Median time of angiographic f/u (days)	162 $\pm$ 53	161 $\pm$ 40	NS	160 $\pm$ 41	NS

\*Target site diameter stenosis was the primary performance end point in the intention-to-treat analysis.  
DS = diameter stenosis; f/u = follow-up; RD = reference diameter; other abbreviations as in Table 1.

**QCA and IVUS.** The QCA and IVUS analyses were performed as previously described (4,5). Coronary aneurysms were angiographically defined as localized coronary artery dilation  $\geq 1.5$  times the reference diameter (4).

**Statistical analysis.** All analyses were based on the intent-to-treat principle. For continuous variables, the mean value  $\pm$  SD was presented; differences between the treatment groups were evaluated with the Student *t* test. Discrete variables were expressed as counts and percentages and were analyzed with the Fisher exact test. Event-free survival times were analyzed using the Kaplan-Meier method. Differences between the groups were compared with the use of both the Wilcoxon and log-rank tests.

## RESULTS

**Patient baseline characteristics.** In total, 360 patients were randomly assigned to receive a DES with a dose of 2.5  $\mu\text{g}/\text{cm}^2$  (n = 120) or 10  $\mu\text{g}/\text{cm}^2$  (n = 121) or a MS (n = 119). Three patients were de-registered because they did not receive either a DES or control stent. Baseline clinical and angiographic characteristics are presented in Table 1. The significant difference in minimal lumen diameter after the procedure between the MS and DES groups could not be accounted for by procedural differences.

**Procedural characteristics and clinical outcomes in the hospital and at one month.** The procedural success rate was 99%. In-hospital MACE was confined to the four patients (1.1%) with non-Q-wave MI. The MACE rates at

30 days ranged from 0.8% to 2.5%, without differences between groups.

However, early monitoring of a subset of 39 DES patients revealed an increased rate of target site revascularization (TSR), suggesting that the investigational device was not performing as intended. After the sponsor informed the principal investigator and the Data Safety Monitoring Board, the following recommendations were made: 1) accelerated angiographic follow-up for DES patients; 2) a second angiographic and clinical follow-up visit six months later; 3) possible re-intervention for moderate restenosis ( $>30\%$  DS); 4) extension of clopidogrel administration for at least a further six months for DES patients; and 5) angiographic and IVUS follow-up was no longer mandatory for MS patients, as primary performance end points could not be reached. Consequently, only 65 of 118 MS patients underwent imaging, and 101 had clinical follow-up at 6 months.

**Angiographic outcomes.** The in-stent and in-lesion late loss and restenosis rates at six months were higher in both DES groups than in the MS group (Table 2). Aneurysm formation was infrequent, with two cases (3.1%) in the MS group and five (2.2%) in the DES groups.

**Clinical outcomes at 12 months.** At 12 months, MACE and TVF were higher in the DES than in the MS patients, mainly due to increased TSR (Table 3). Of the 2 deaths, the 1 with a MS was sudden at 44 days, and the 1 with low-dose DES was due to MI at 306 days. After 30 days, there were 2 additional non-Q-wave MIs in the low-dose and 1 in the

**Table 3.** Most Severe (Hierarchical) and Total Count of Cardiac Events Up to 12 Months in Each Treatment Group

	DES				
	MS (n = 104)*	AcD 2.5 $\mu\text{g}/\text{cm}^2$ (n = 120)†	p Value	AcD 10 $\mu\text{g}/\text{cm}^2$ (n = 119)‡	p Value
Death	1 (0.8)	1 (0.8)	NS	0	NS
Myocardial infarction					
Q-wave	0	0	NS	0	NS
Non-Q-wave	1 (1.0)	2 (1.7)	NS	4 (3.4)	NS
Target site revascularization					
CABG	1 (1.0)	0	NS	5 (4.2)	NS
PCI	11 (10.6)	37 (30.8)	<0.001	41 (34.5)	<0.001
Hierarchical MACE‡	14 (13.5)	40 (33.3)	<0.01	50 (42.0)	<0.001
Event-free survival	90 (86.5)	80 (66.7)		69 (58.0)	
Target vessel revascularization (CABG and PCI)	3 (2.9)	4 (3.3)	NS	1 (0.8)	NS
Target vessel failure§	17 (16.3)	44 (36.7)	<0.001	51 (42.9)	<0.001
Total count of events	16	45		61	

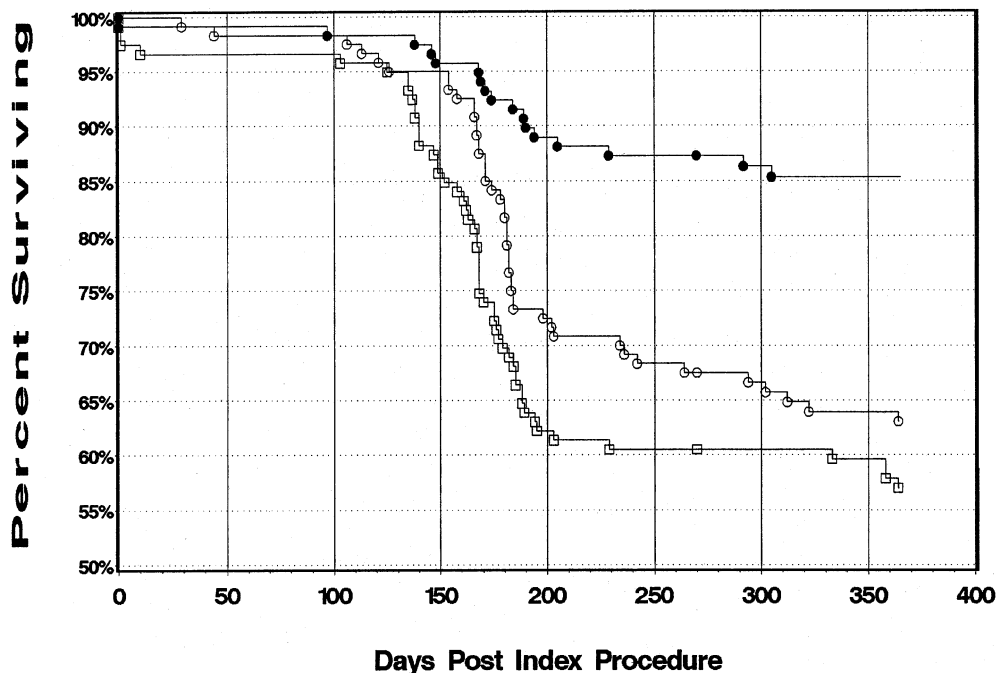
\*Follow-up was no longer mandatory for the MS group; therefore, for 14 patients no follow-up was available. †For five and three patients in the 2.5- and 10- $\mu\text{g}/\text{cm}^2$  group, respectively, no follow-up case report forms have been received; however, these patients have been contacted and all are alive and had no other MACE in the 12-month follow-up time frame. ‡Includes death, myocardial infarction, target site revascularization. §Includes death, myocardial infarction, target site revascularization, and/or target vessel revascularization. Data are presented as the number (%) of patients.

CABG = coronary artery bypass grafting; MACE = major adverse events; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

high-dose DES arm. To 1 year, there were 14 DES patients who had a second re-intervention, and in 2, a third re-intervention (Fig. 1).

**IVUS outcomes.** There was late-acquired incomplete stent apposition in six patients in the low-dose group and seven in

the high-dose group. At variance with the angiographic findings, there were apparently no differences between groups in volumetric obstruction measured by IVUS. This discrepancy is the result of a biased selection of DES patients undergoing IVUS during follow-up, as demon-



**Figure 1.** Kaplan-Meier estimates of survival free of repeated target site revascularization up to 365 days among patients who received actinomycin-eluting 2.5 and 10  $\mu\text{g}/\text{cm}^2$  stents and those who received the metallic stent. The rate of event-free survival was significantly higher in the control stent group than in the actinomycin stent groups ( $p < 0.05$  by both the Wilcoxon and log-rank tests). **Solid circles** = control (n = 104); **open circles** = drug-coated, 2.5  $\mu\text{g}/\text{cm}^2$  drug-eluting stent (n = 120); **squares** = drug-coated, 10  $\mu\text{g}/\text{cm}^2$  drug-eluting stent (n = 119).

**Table 4.** Incidence of Vessel Segment Restenosis in Patients With and Without Intravascular Ultrasound

	MS	DES	
		AcD 2.5 $\mu\text{g}/\text{cm}^2$	AcD 10 $\mu\text{g}/\text{cm}^2$
Patients with IVUS	4/39 (10.3)	23/89 (25.8)	22/93 (23.7)
Patients without IVUS	5/26 (19.2)	8/25 (32.0)	11/23 (47.8)
	*p = 0.47	p = 0.61	p = 0.037

\*Fischer exact test. Data are presented as n/N (%).

IVUS = intravascular ultrasound; other abbreviations as in Table 1.

strated by the higher binary “vessel segment” restenosis rate (32% and 47.8%) in the DES patients who did not undergo IVUS follow-up, compared with those who did (25.8% and 23.7%) (Table 4). This biased selection invalidated interpretation of the IVUS findings.

## DISCUSSION

This trial showed that while in-hospital and one-month outcomes were similar in each group, by six months there was increased restenosis, late lumen loss, and TSR in the DES arm. Despite this increased rate of restenosis, mortality and MI rates were very low.

The safety of the polymer was demonstrated in the porcine coronary model, where the histologic response was similar to MS to 180 days. Drug-eluting stents with four doses of actinomycin D (2.5, 10, 40, and 70  $\mu\text{g}/\text{cm}^2$ ) were evaluated in preclinical studies in the porcine coronary model by angiography, histomorphometry, and histopathology at 28 days. At this time, all vessels were patent, and there was marked suppression of neointimal formation above the stent with all doses. Neointimal thickness above the internal elastic lamina was decreased in all dose groups compared with the MS control. Medial thinning and necrosis were observed in the high-dose groups, as was positive remodeling. Intimal fibrin deposition and inflam-

mation were present with all doses, but most marked with the higher doses. Based on these preclinical findings, the two lower doses were considered safe for further evaluation in humans, with three months of data pending, which was the practice for MS extended to DES at the time. This trial has demonstrated that 28-day animal data do not provide sufficient information to judge the safety and efficacy of DES.

**Conclusions.** This trial demonstrates that not all anti-proliferative drugs are effective in the prevention of restenosis. It has become clear that promise in early preclinical studies (30 days) does not necessarily translate into clinical effectiveness at 6 months and that late safety animal data (90 days) is a prerequisite for clinical investigation (6).

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