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Cilostazol for RESTenosis Trial

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Specific Aim:

To evaluate whether cilostazol (Pletal) will prevent restenosis after stent implantation in a native coronary artery as evaluated by quantitative coronary arteriography



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Background:

- 1) Restenosis remains a significant problem
- 2) In a series of small trials cilostazol decreased restenosis by 1/3 to 2/3.



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Hypothesis:

Cilostazol will decrease restenosis, as measured by quantitative coronary arteriography, after successful placement of an intracoronary stent

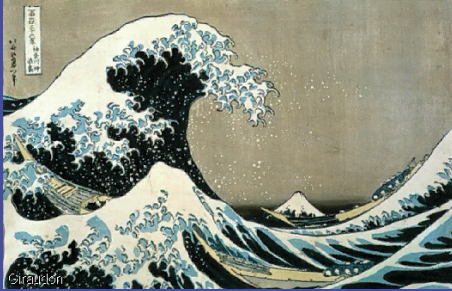


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Primary Endpoint:

Minimal luminal diameter at six months of the first lesion stented per patient as assessed by quantitative coronary arteriography at the angiographic core laboratory



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Secondary Endpoints:

- 1) Minimal luminal diameter in all lesions
- 2) Mean % diameter stenosis per patient and per stented lesion
- 3) Binary restenosis, defined as $>50\%$ DS, per patient and per stented segment
- 4) Target lesion revascularization
- 5) Major angiographic and clinical endpoints (MACE)



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Inclusion Criteria:

- 1) Target lesion is a de novo stenosis $>50\%$ and $<100\%$ DS by visual estimate
- 2) Successful, uncomplicated stent placement with $<10\%$ residual stenosis by visual estimate, with TIMI III flow, without dissection
- 3) Stented segment <40 mm by visual estimate
- 4) Age >18 years
- 5) Negative pregnancy test in women of child bearing potential and commitment to use contraception or abstinence for the duration of the study
- 6) Able to give informed consent
- 7) Able to return for a follow-up angiogram at 6 months



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Exclusion Criteria:

- 1) Prior PCI within 6 months
- 2) Thrombocytopenia defined as platelet level $<150,000/\text{ml}$
- 3) Known bleeding diathesis
- 4) Known intolerance to cilostazol, aspirin or clopidogrel
- 5) Acute MI with CK elevation to 3X ULN within 24 hours
- 6) Intraluminal thrombus at target lesion
- 7) Moderate to severe target lesion calcification
- 8) Target lesion encompassing side branches >2 mm in diameter
- 9) Heart failure or ejection fraction $<30\%$
- 10) Active peptic ulcer disease or GI bleeding
- 11) Renal insufficiency with creatinine > 2.5 mg/dL
- 12) Need for coumadin anticoagulation
- 13) Known hepatic dysfunction
- 14) Current participation in another randomized trial
- 15) Inability to return for follow-up angiography
- 16) Major life threatening illness
- 17) Patient taking cilostazol within last 6 month

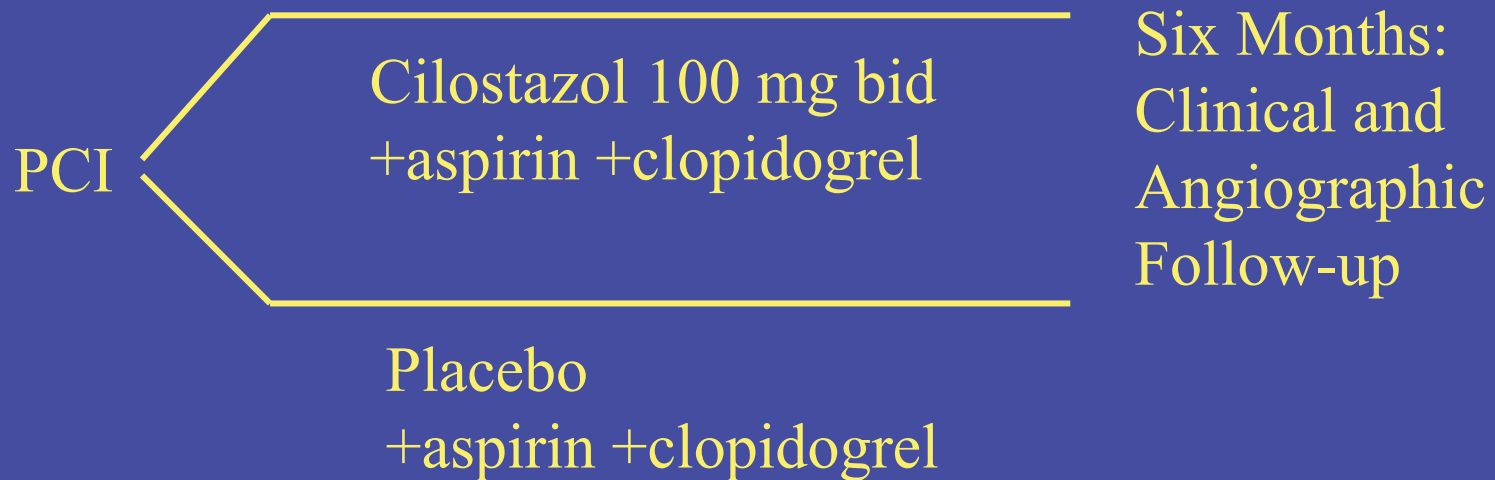


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Design:

- 1) Multicenter, randomized double blind clinical trial
- 2) 705 patients at 19 sites





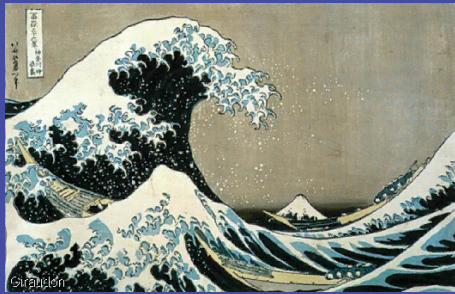
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Angiographic Methods:

Initial and follow-up angiograms used the same orthogonal views following nitroglycerin

Angiograms assessed by quantitative coronary arteriography in the core angiographic laboratory



Baseline Data

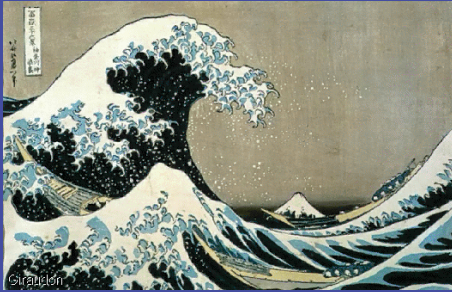
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Cilostazol (n=354)

Placebo (n=351)

Age	60 ± 11	60 ± 10
Females	83 (24%)	99 (28%)
Diabetes	82 (24%)	99 (28%)
Hypertension	230 (66%)	230 (66%)
Prior MI	75 (21%)	80 (23%)
Prior PCI	85 (24%)	88 (25%)
Prior CABG	43 (12%)	32 (9 %)
Site:		
LAD	152 (43%)	122 (35%)
Circumflex	78 (22%)	102 (29%)
RCA	115 (33%)	125 (36%)
Left Main	6 (2%)	0 (0%)

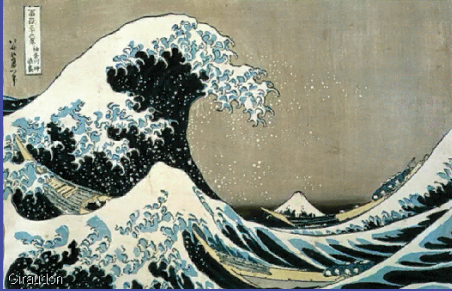


Angiographic Data

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	<u>Cilostazol (n=354)</u>	<u>Placebo (n=351)</u>	<u>P-Value</u>
<u>Baseline</u>			
Reference Diameter	2.70 ± 0.59	2.75 ± 0.59	0.41
Minimum Lumen Diameter	0.83 ± 0.38	0.88 ± 0.41	0.19
% Diameter Stenosis	68.28 ± 13.18	67.60 ± 13.04	0.56
<u>Procedure</u>			
Lesion Length	13.22 ± 8.60	13.35 ± 8.70	0.86
Number of Stents Deployed:			0.05
1	310 (88%)	315 (90%)	
2	36 (10%)	24 (7%)	
3	2 (1%)	9 (3%)	
<u>Post PCI</u>			
Minimum Lumen Diameter	2.75 ± 0.54	2.77 ± 0.50	0.59
% Diameter Stenosis	-0.17 ± 13.98	0.51 ± 14.65	0.39

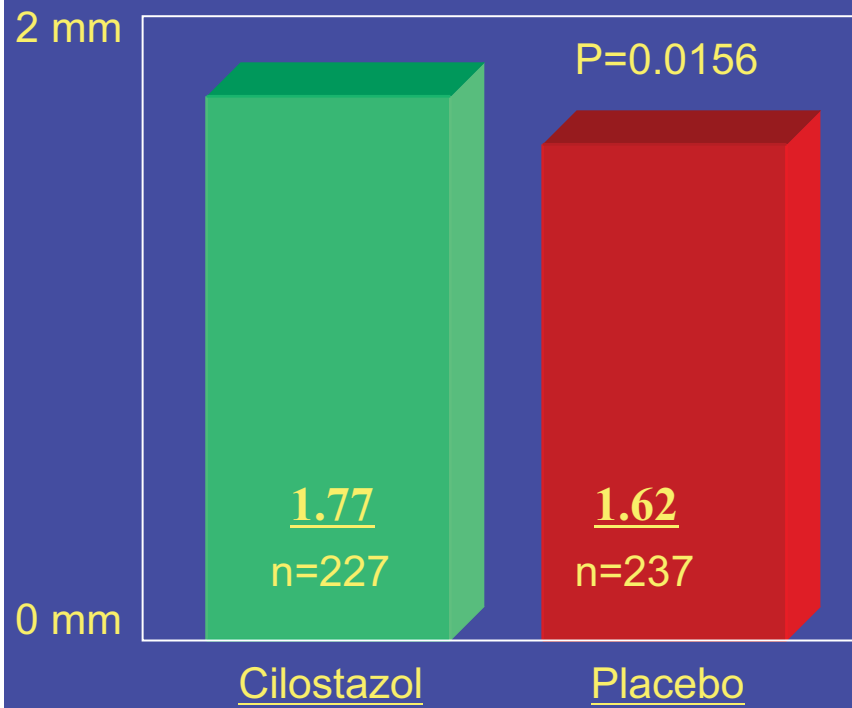


Angiographic Data

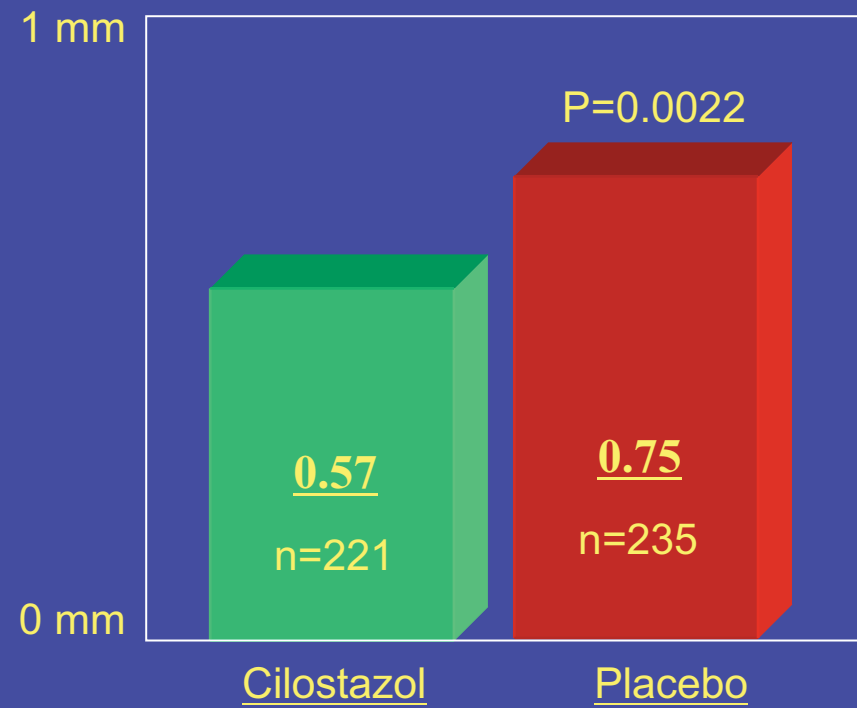
Primary Endpoint

In-Segment Results

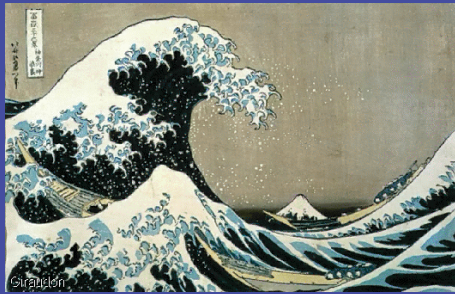
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Minimum Lumen Diameter

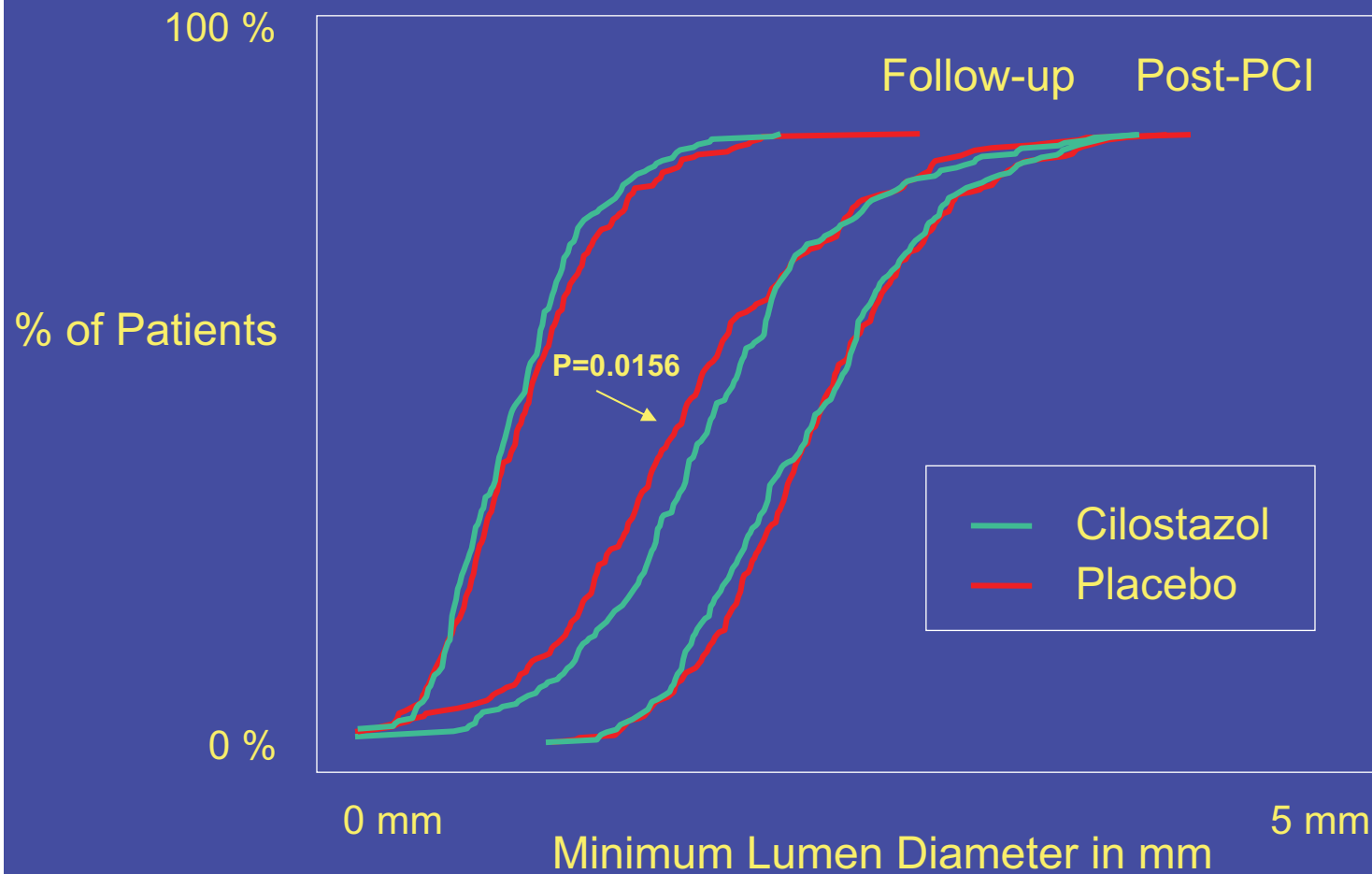


Late Loss Minimum Lumen Diameter



Angiographic Data In Segment

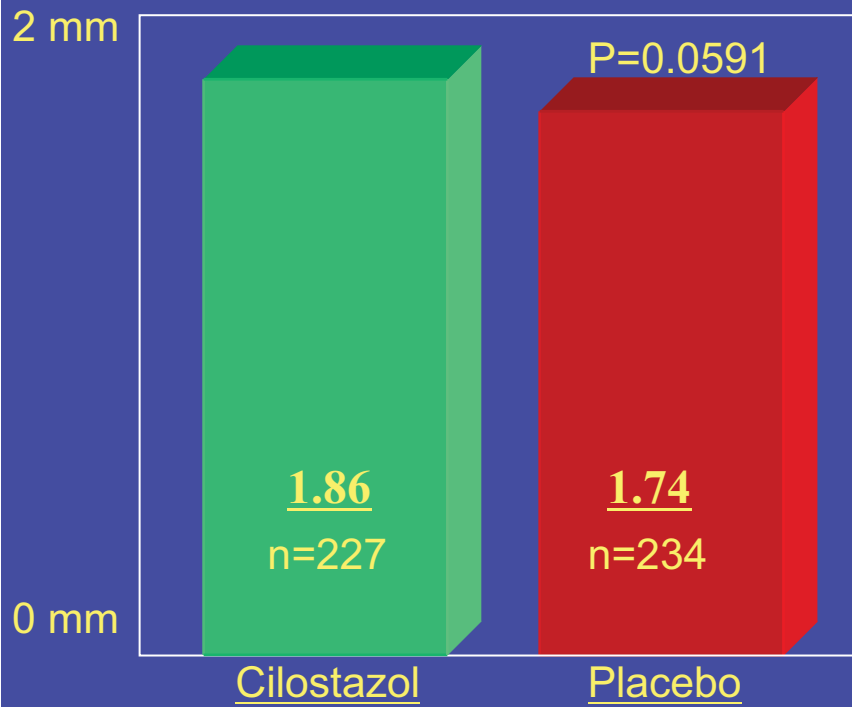
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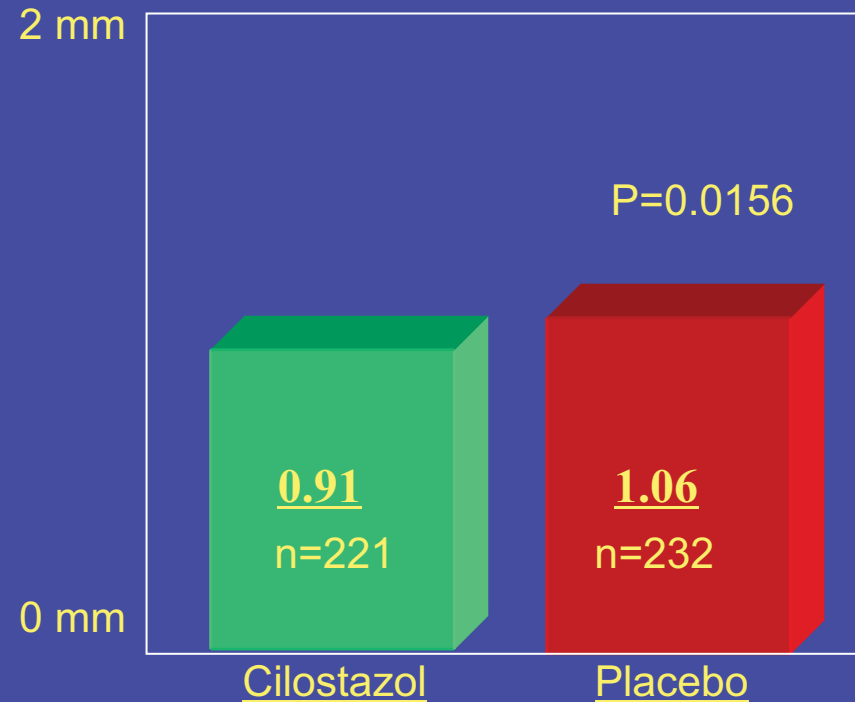


Angiographic Data In Stent Results

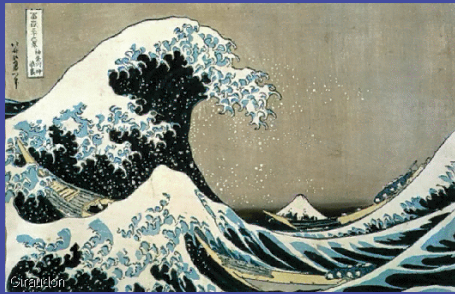
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Minimum Lumen Diameter

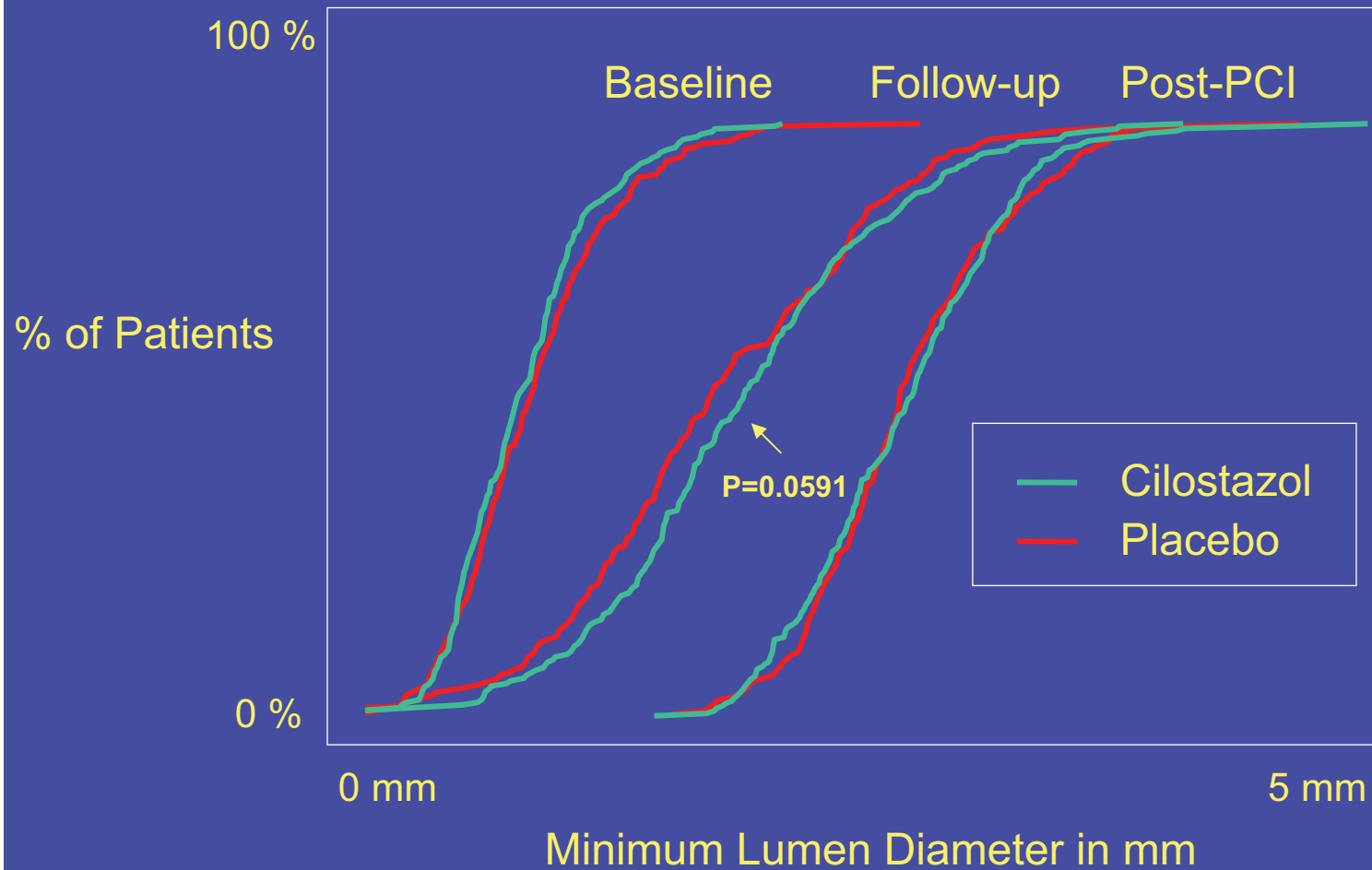


Late Loss Minimum Lumen Diameter



Angiographic Data In Stent

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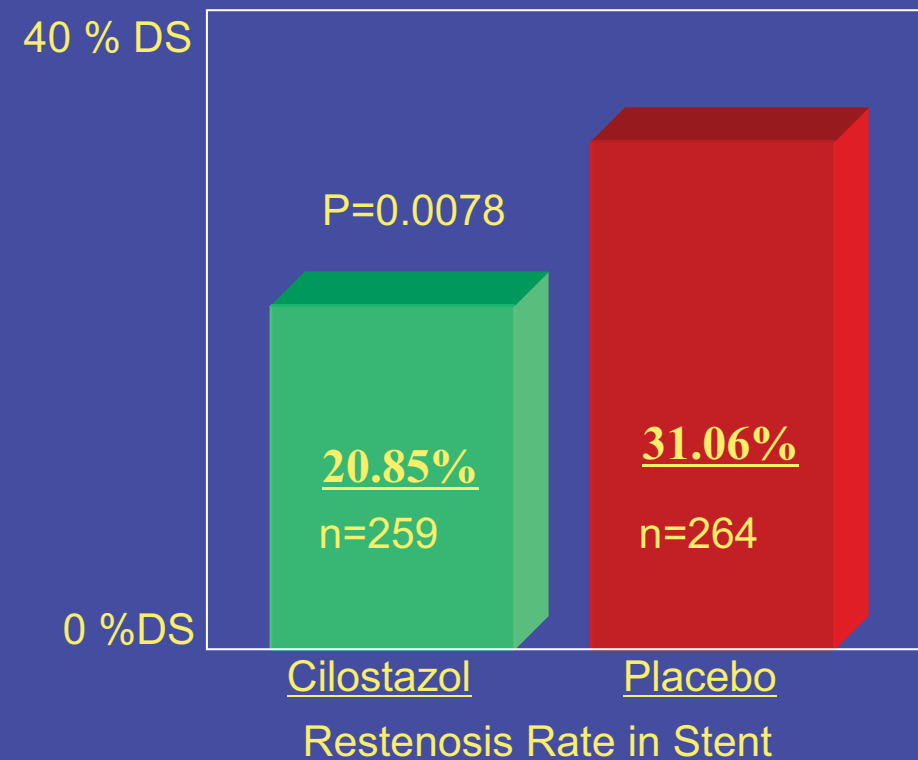
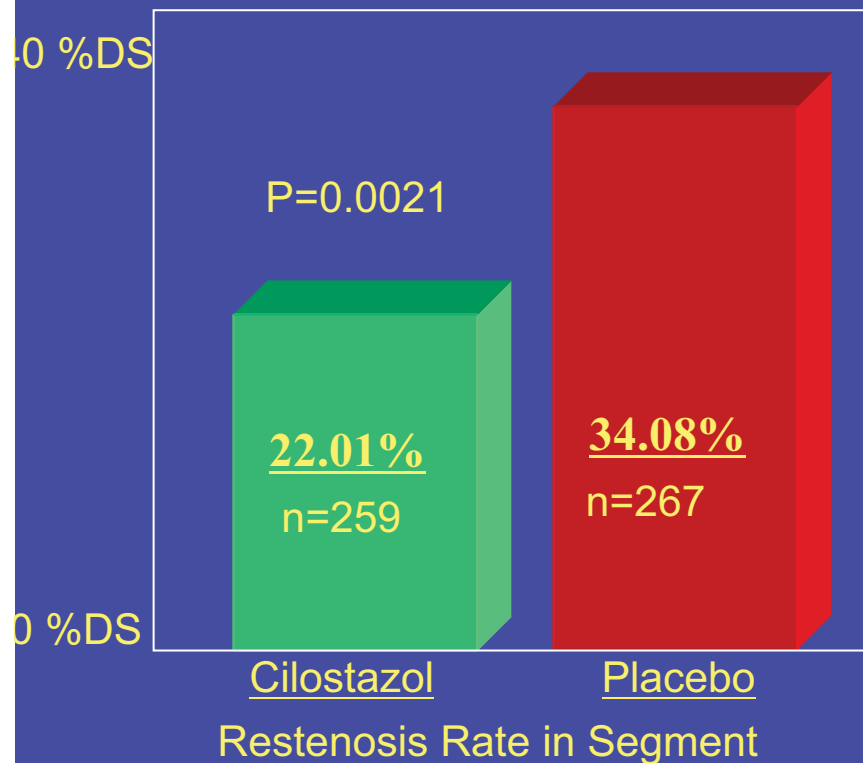
Restenosis Rate

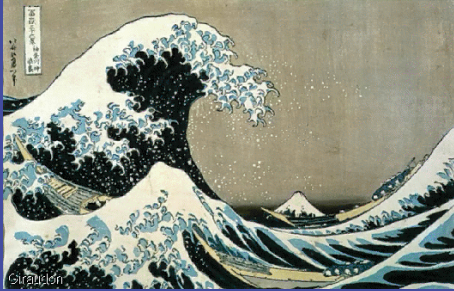
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RRR 35.4 %, 95% CI 32.0-40.3

RRR 32.9 %, 95% CI 29.6-36.6

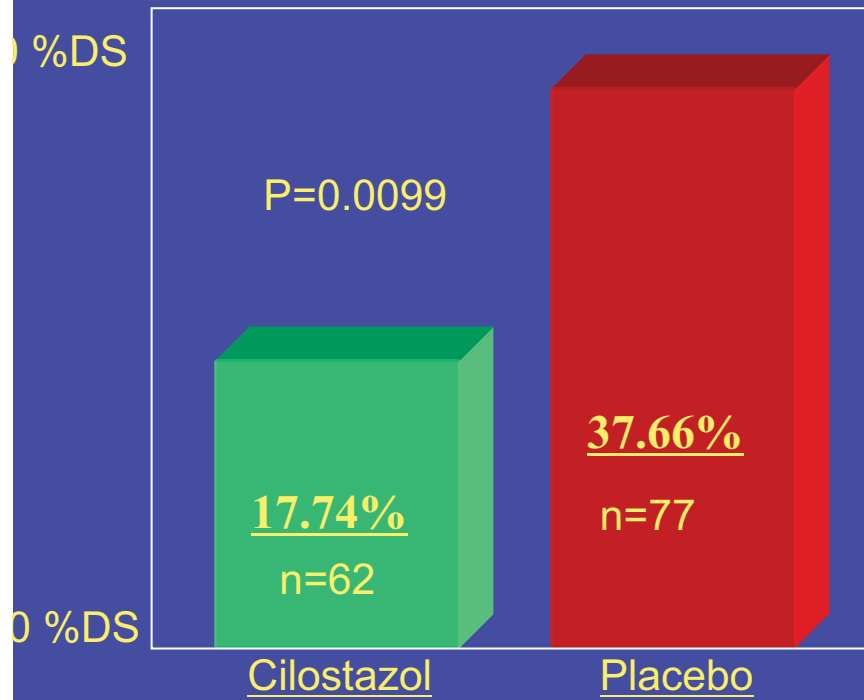




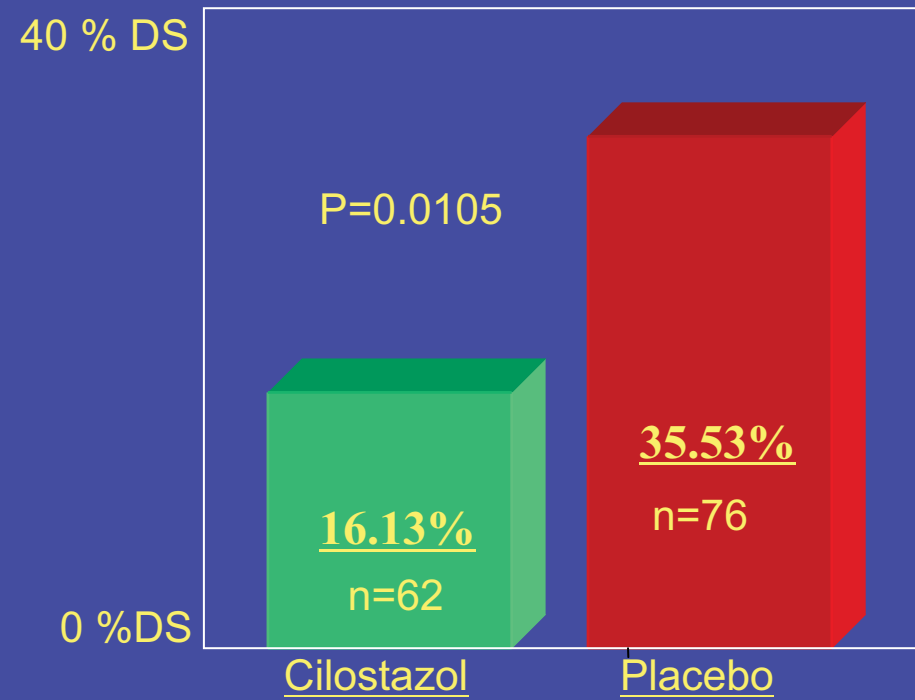
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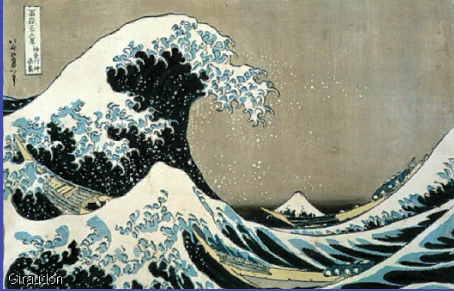
Restenosis Rate Diabetics



Restenosis Rate in Segment



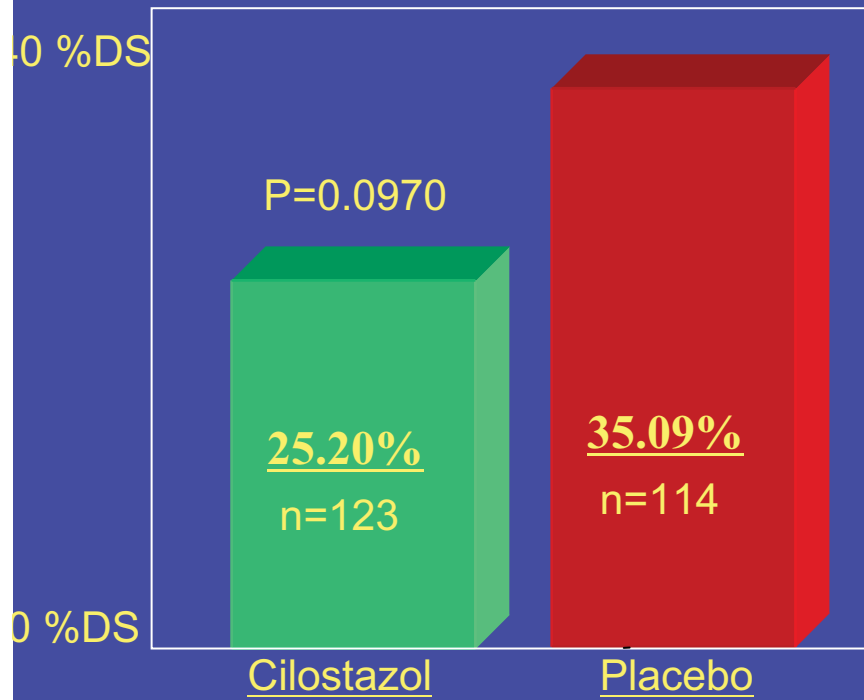
Restenosis Rate in Stent



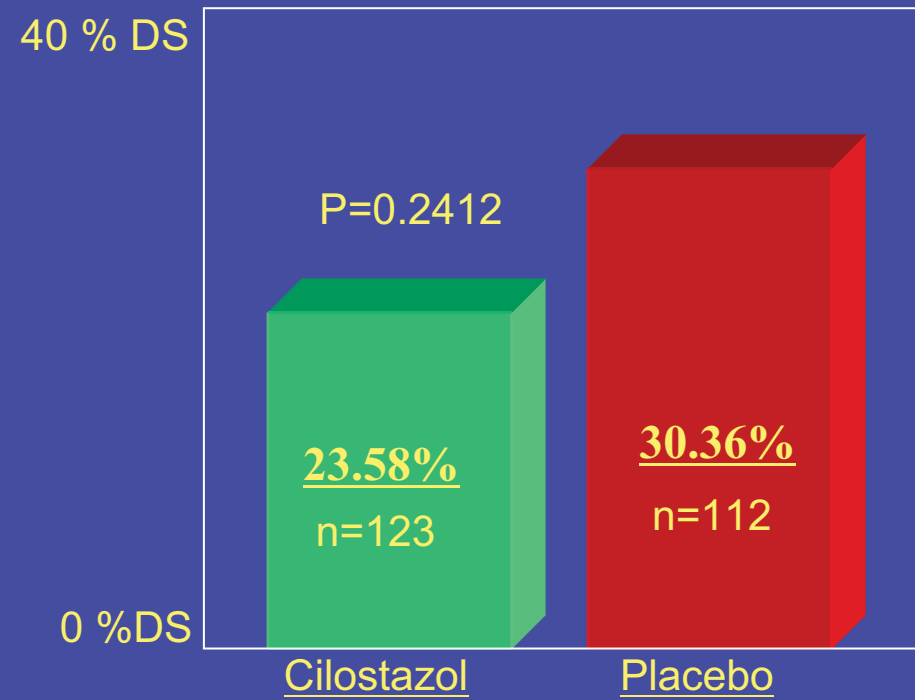
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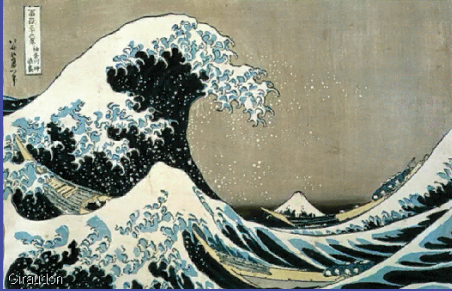
Restenosis Rate Vessels < 2.5mm



Restenosis Rate in Segment



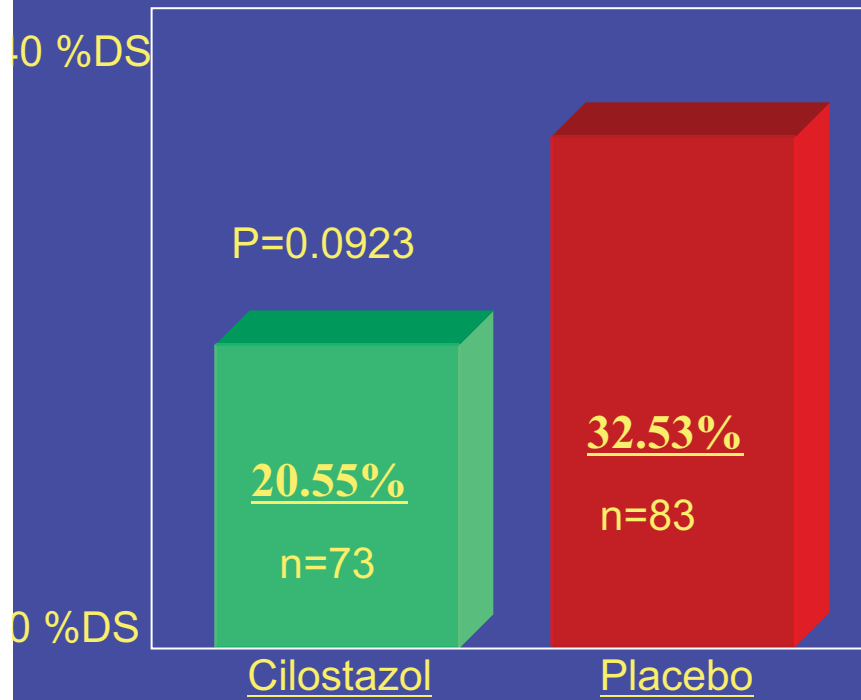
Restenosis Rate in Stent



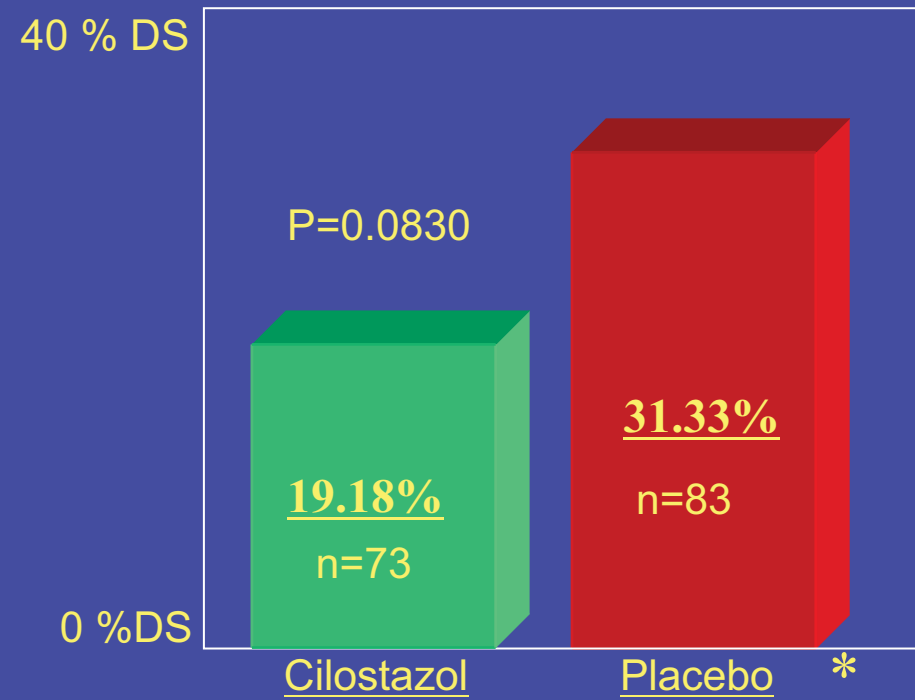
Restenosis Rate 3mm>Vessels > 2.5mm

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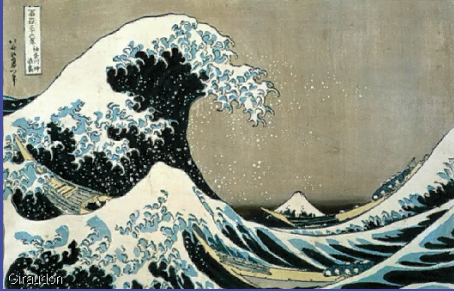
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Restenosis Rate in Segment



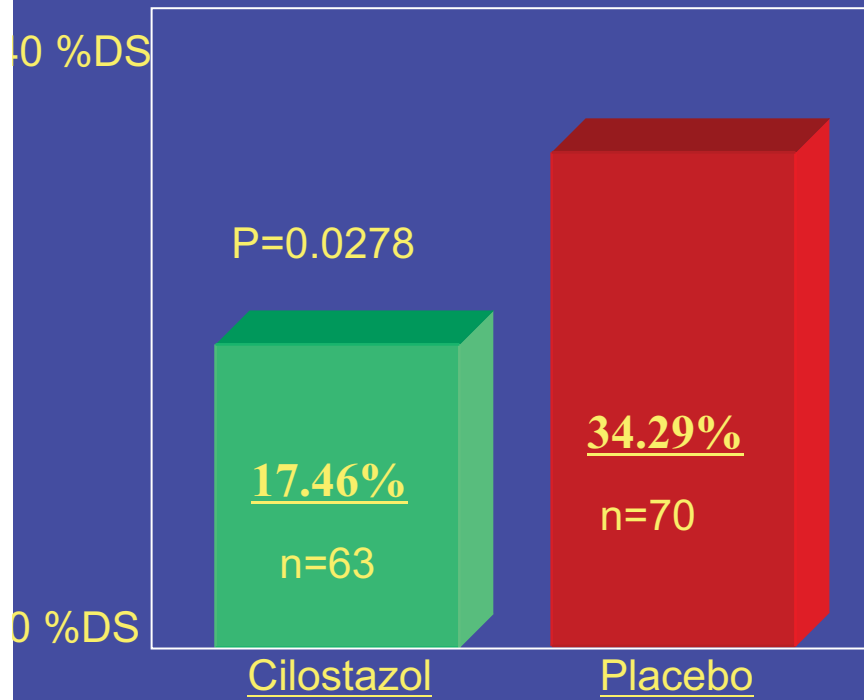
Restenosis Rate in Stent *



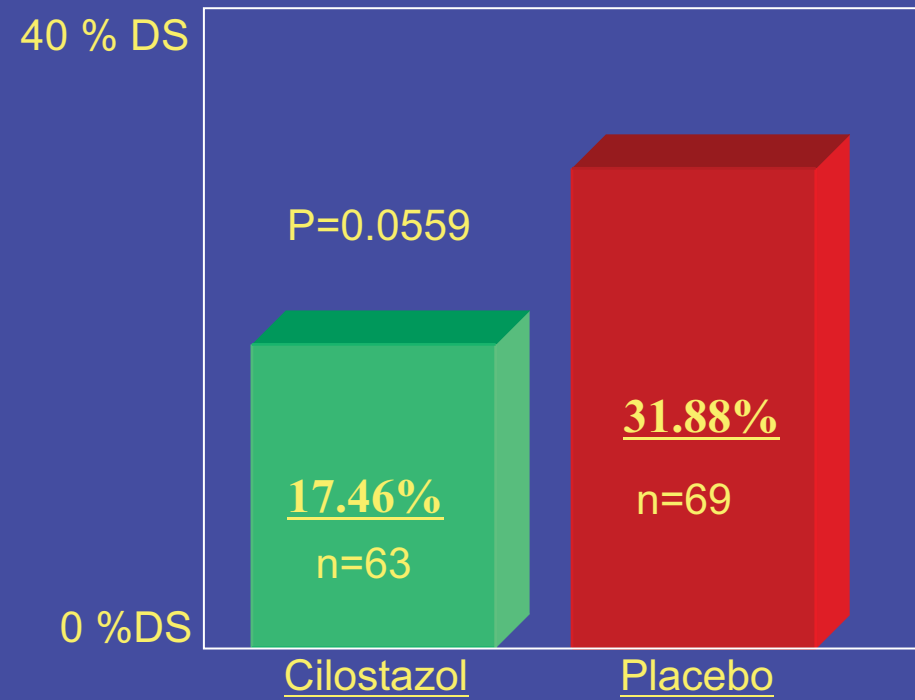
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Restenosis Rate Vessels ≥ 3 mm



Restenosis Rate in Segment



Restenosis Rate in Stent



Clinical Events

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	<u>Cilostazol</u> (n=354)	<u>Placebo</u> (n=351)	<u>P-Value</u>
Myocardial Infarction	13 (4%)	10 (3%)	0.53
Death	3 (1%)	2 (1%)	1.00
Target Vessel Revascularization	54 (16%)	56 (16%)	0.90
Stroke	5(1%)	2 (1%)	0.45



Safety

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	<u>Cilostazol</u> (n=354)	<u>Placebo</u> (n=351)	<u>P-Value</u>
Bleeding	11 (3%)	12 (3%)	0.82
Rehospitalization	14 (5%)	23 (7%)	0.17



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Conclusions

Cilostazol taken orally after successful PCI with stent placement significantly decreased the rate of restenosis, a benefit that extended to the diabetic and small vessel subgroups



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Other Roles for Cilostazol in Preventing Restenosis

- Non-stented lesions
- Peripheral vascular stents
- Carotid artery stents
- In addition to drug eluting stents



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Power Calculation:

Power calculation, $p < 0.05$, is based on an expected baseline restenosis rate of 30% and a treated rate of 20%. To achieve 80% power, 294 patients per arm are required. A second power calculation for the continuous variable of minimal luminal diameter (MLD) is based on an expected baseline MLD of 1.65 in the treated and 1.40 in the untreated. To achieve 90% power, 123 patients per arm are required.



Enrollment by Site

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186 Emory University Hospital

102 The Lindner Clinical Trial Center

63 William Beaumont Hospital

37 Crawford Long Hospital

35 American Cardiovascular Research
Institute

35 Melbourne Internal Medicine

31 Austin Cardiovascular Associates

30 Georgetown University Hospital

29 Saint Mary's Hospital

27 Piedmont Hospital

- 25 Abbott Northwestern Hospital
- 24 Florida Hospital
- 23 Midwest Cardiology Research
Foundation
- 18 Washington Hospital Center
- 14 Hartford Hospital
- 10 Brigham & Women's Hospital
- 10 Henry Ford Hospital
- 5 Mid-Ohio Heart Clinic Inc.
- 1 Medical College of Virginia
Hospital



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Angiographic Core Laboratory

ECG Core Laboratory

Data and Safety Monitoring Board

Endpoints

Site Monitors

John Mancini PI

Bernard Chaitman PI

Richard Shaw Chair

Ted Feldman

George Vetrovic

Marc I Chimowitz

Clinimetrics



Subgroup Data

Insegment

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	<u>Cilostazol</u> (n=354)	<u>Placebo</u> (n=351)	<u>P-Value</u>
<u>Follow-up MLD</u>			
Vessels 2.5	1.54 ± 0.63	1.31 ± 0.60	<0.01
Vessels 2.5-3 mm	1.73 ± 0.49	1.65 ± 0.67	0.62
Vessels ≥ 3 mm	2.22 ± 0.75	2.08 ± 0.82	0.66
Diabetes	1.71 ± 0.63	1.50 ± 0.81	0.07
Length 10	1.84 ± 0.65	1.71 ± 0.70	0.16
Length 10-15 mm	1.63 ± 0.63	1.61 ± 0.80	0.16
Length ≥ 15 mm	1.78 ± 0.78	1.49 ± 0.79	0.15



Subgroup Data

Instent

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	<u>Cilostazol</u> (n=354)	<u>Placebo</u> (n=351)	<u>P-Value</u>
<u>Follow-up MLD</u>			
Vessels 2.5	1.61 ± 0.68	1.46 ± 0.68	0.06
Vessels 2.5-3 mm	1.83 ± 0.55	1.75 ± 0.73	0.66
Vessels ≥ 3 mm	2.35 ± 0.83	2.17 ± 0.88	0.19
Diabetes	1.83 ± 0.71	1.60 ± 0.84	0.11
Length 10	1.94 ± 0.71	1.86 ± 0.77	0.39
Length 10-15 mm	1.74 ± 0.74	1.75 ± 0.85	0.71
Length ≥ 15 mm	1.84 ± 0.82	1.53 ± 0.80	0.04