

**A Polymer-Free Dual Drug-Eluting Stent
in Patients with Coronary Artery Disease:
Randomized Trial Versus
Polymer-Based DES**

ISAR-TEST 2 Trial

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I have no conflicts of interest to disclose

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Long-term polymer residue in the coronary milieu is a consequence of current DES therapy and has been implicated in late adverse events

Avoidance of polymer imposes certain efficacy limitations related to suboptimal release kinetics of the active drug



The incorporation of a second active agent targeted at a different element of the restenotic response cascade is a potential option to enhance anti-restenotic performance in a polymer-free DES



Previous experience with an oestradiol + rapamycin-eluting stent did not show improved anti-restenotic efficacy



LATE-BREAKING CLINICAL TRIALS

Does Addition of Estradiol Improve the Efficacy of a Rapamycin-Eluting Stent?

Results of the ISAR-PEACE Randomized Trial

Tom Adriaenssens, MD, Julinda Mehilli, MD, Rainer Wessely, MD, Gjin Ndrepepa, MD, Melchior Seyfarth, MD, Anna Wiecek, PhD, Raisuke Iijima, MD, Jürgen Pache, MD, Adnan Kastrati, MD, Albert Schömig, MD

Munich, Germany

Objectives	This study aimed to assess the efficacy of a rapamycin plus 17- β -estradiol-eluting stent versus a rapamycin-eluting stent in patients with coronary artery disease.
Background	Estradiol promotes rapid re-endothelialization of coronary stents in animal models, but it is not known whether combining this drug with rapamycin represents an improved drug-eluting stent technology in terms of reduced lumen renarrowing.
Methods	In this randomized study, we enrolled 502 patients with de novo lesions in native coronary arteries who were randomly assigned to receive either a polymer-free, estradiol plus rapamycin-eluting stent (ERES) (n = 252) or a polymer-free, rapamycin-eluting stent (RES) (n = 250). The primary end point was in-stent late lumen loss in the follow-up angiography. Secondary end points were binary angiographic restenosis, target lesion revascularization, combined incidence of death and myocardial infarction, and incidence of stent thrombosis during 1 year after randomization. The study was designed to test for the superiority of the ERES compared with the RES with respect to in-stent late lumen loss.
Results	Late lumen loss (0.52 ± 0.58 mm vs. 0.51 ± 0.58 mm, $p = 0.83$), the incidence of binary angiographic restenosis (17.6% vs. 16.9%, $p = 0.85$), the incidence of target lesion revascularization (14.3% vs. 13.2%, $p = 0.72$), the combined incidence of death and myocardial infarction (7.9% vs. 8.0%, $p = 0.98$), and the incidence of stent thrombosis (0.8% vs. 1.2%, $p = 0.99$) were not significantly different between the ERES group and the RES group.



Probucol is a potent lipophilic antioxidant which has proven effects in reducing restenosis – both in animal models and clinical trials

We therefore developed a polymer-free probucol + rapamycin-eluting stent and sought to examine its efficacy in ISAR TEST-2

Ferns *Proc Natl Acad Sci* 1992

Schneider *Circulation* 1993

Tardif *NEJM* 1997

Tardif *Circulation* 2003



to compare the anti-restenotic efficacy of:

polymer-free probucol+rapamycin-eluting stent
(Dual-DES)

with

permanent polymer rapamycin-eluting stent
(Cypher)

and

permanent polymer zotarolimus-eluting stent
(Endeavor)

in patients with coronary artery disease



Inclusion Criteria

- “De novo” lesions in native coronary arteries
- Written informed consent

Exclusion Criteria

- Left main lesion
- Cardiogenic shock
- Comorbidities with a life expectancy < 12 months
- Contraindication to aspirin, limus agents, probucol, stainless steel, thienopyridines
- Pregnancy



Primary Endpoint:

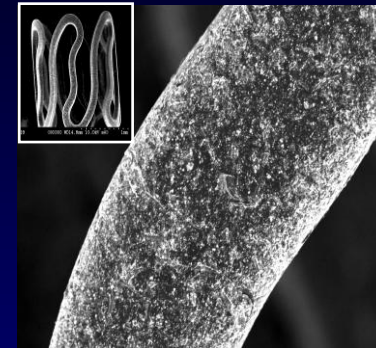
- in-segment binary angiographic restenosis (DS \geq 50%) at follow-up angiogram

Secondary Endpoints:

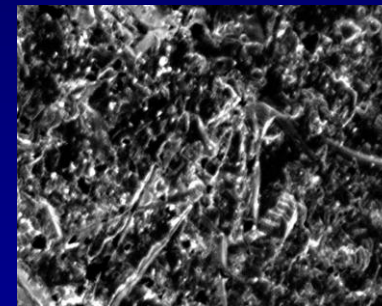
- in-stent late luminal loss
- need for target lesion revascularization due to restenosis in the presence of symptoms or signs of ischemia
- composite of death and MI
- incidence of stent thrombosis



- Probucol+rapamycin-eluting stent (Dual-DES)
- Rapamycin-eluting stent with permanent polymer (Cypher)
- Zotarolimus-eluting stent with permanent polymer (Endeavor)



100 μm



10 μm

Microporous thin-strut (87 μm) 316L SS
 Polymer-free; dual drug-eluting
 Developed in setting of ISAR Project



Study hypothesis:

Dual-DES, Cypher and Endeavor stents would have different anti-restenotic efficacy

Assumptions:

Power 80%; α -level of 0.05

To detect difference in proportions characterized by:

- average proportion of 11.7%
- variance of proportions of 0.14%

Needed sample size of:

245 patients in each of three groups

1007 patients enrolled to accommodate for possible missing follow-up angiographic data



Pre-specified analysis:

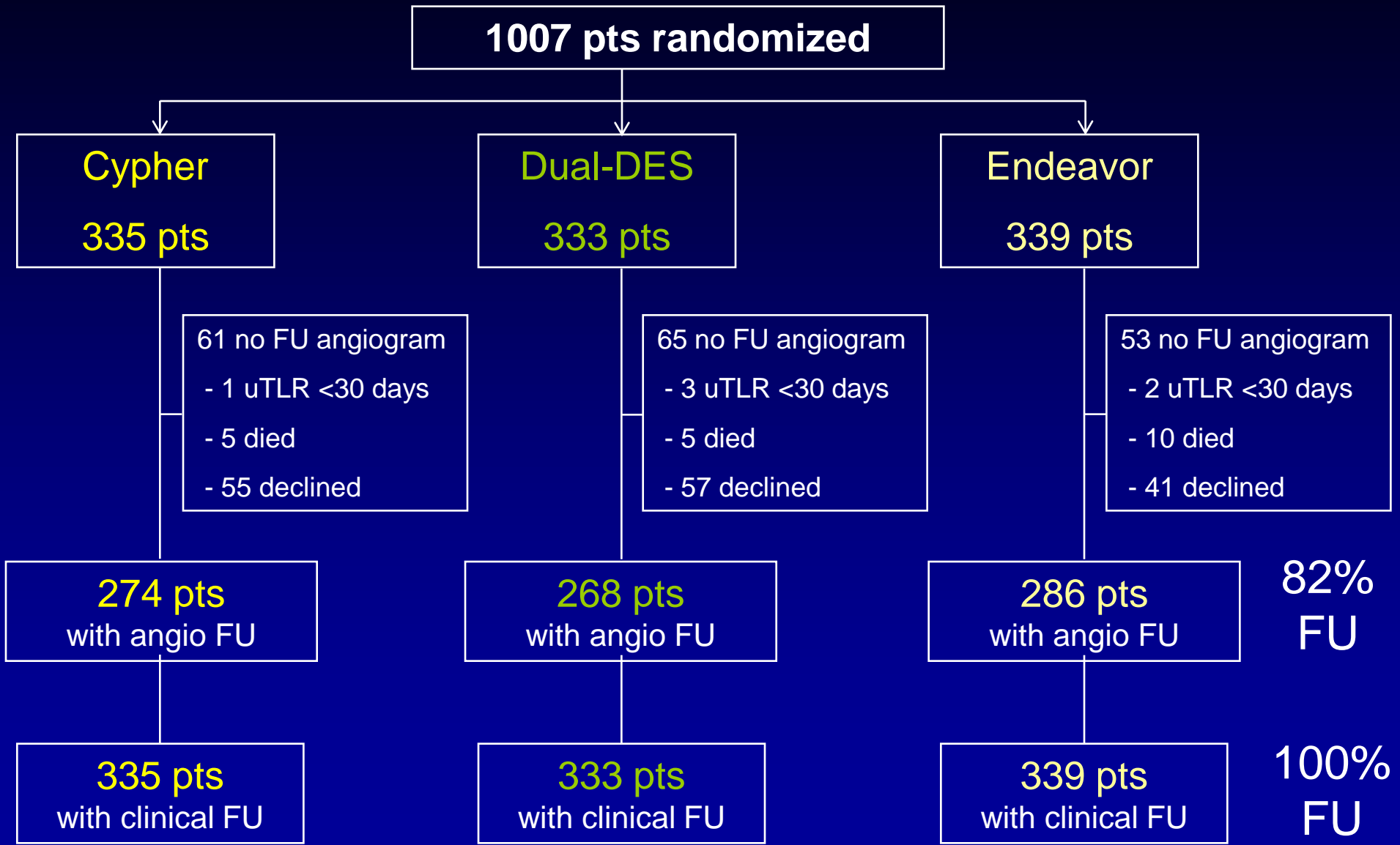
In the event of a significant difference in the primary analysis, two pre-specified analyses were planned to be performed:

Dual-DES versus Cypher

Dual-DES versus Endeavor

To account for multiple testing a p-value of <0.025 was considered statistically significant according to the Bonferroni method

Study Flow Chart





	Cypher (n=335)	Dual-DES (n=333)	Endeavor (n=339)
Age, years	67 ± 11	67 ± 11	67 ± 11
Women	23	23	25
Arterial hypertension	64	65	68
Diabetes	27	29	26
Current smoker	17	20	18
Hypercholesterolemia	69	63	66
History of MI	30	25	26
History of CABG	8	10	9



	Cypher (n=335)	Dual-DES (n=333)	Endeavor (n=339)
Acute MI	13	12	15
Unstable angina	25	30	30
Stable angina	61	58	56
LV ejection fraction (%)	52±12	53±12	55±10



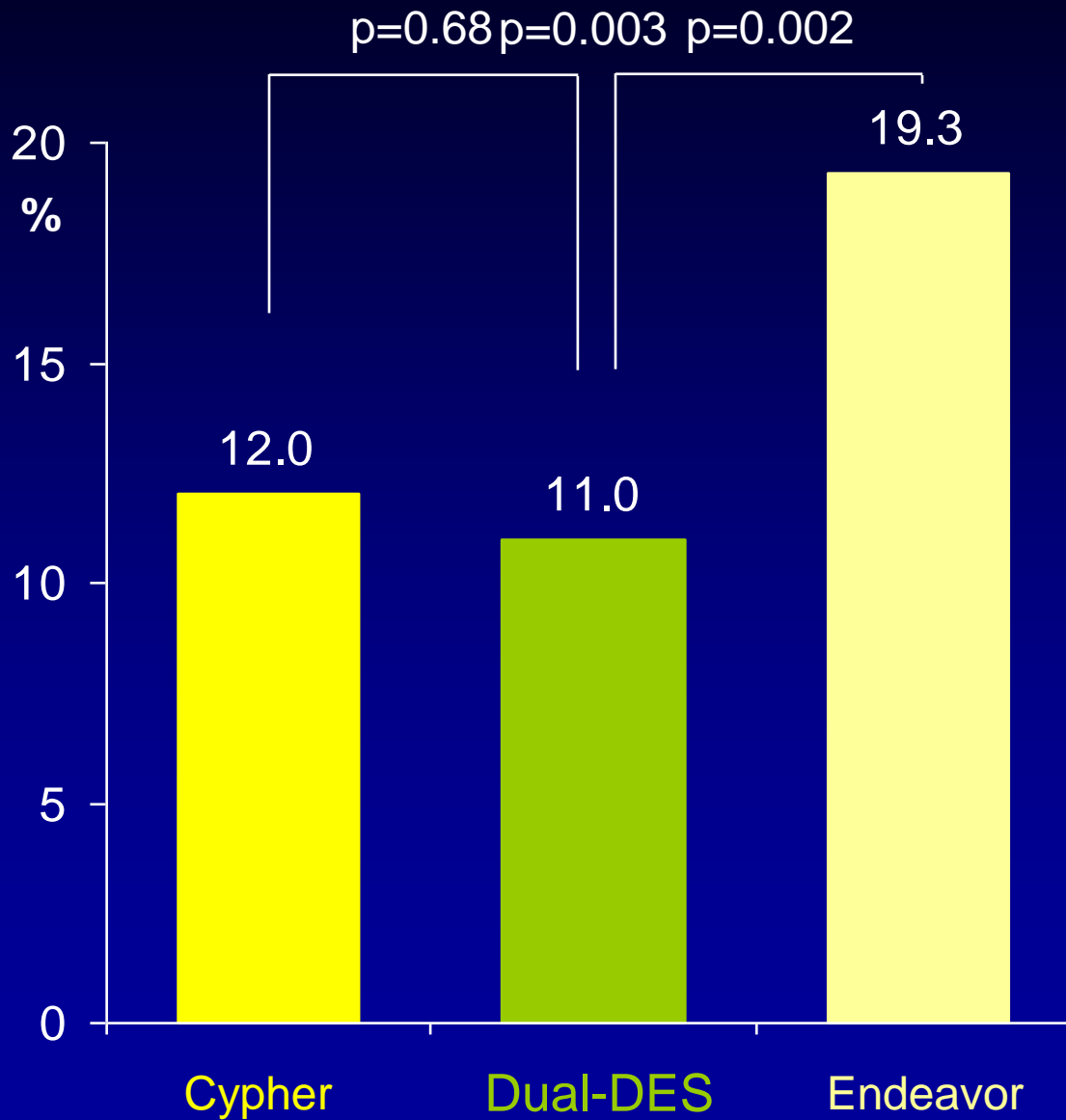
	Cypher	Dual-DES	Endeavor
Target vessel			
LAD	49	44	41
LCx	25	25	31
RCA	26	31	29
Multivessel disease	86	81	83
Complex lesions	73	70	75
Total occlusions	12	12	12



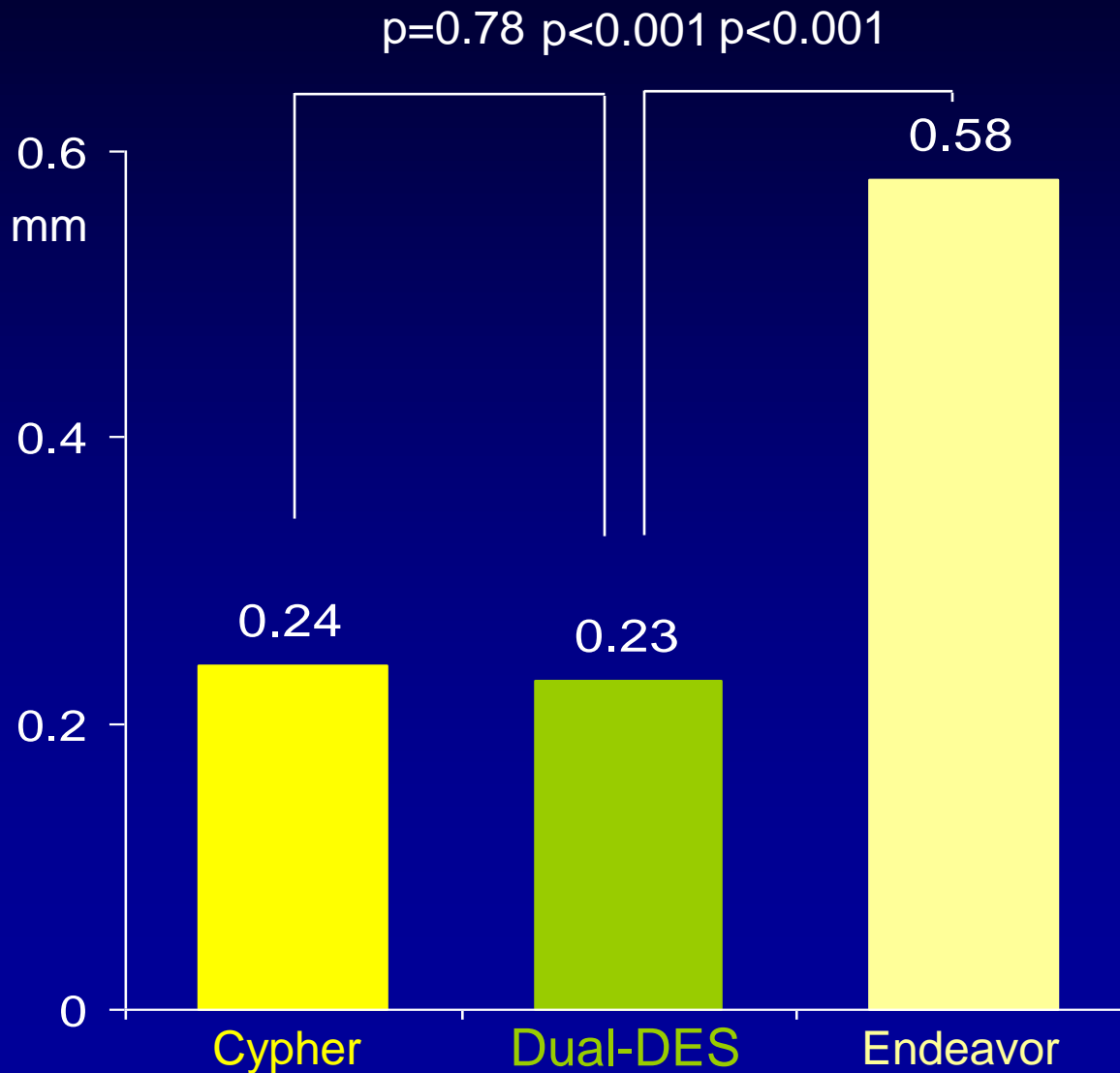
	Cypher (n=419)	Dual-DES (n=427)	Endeavor (n=420)
Vessel size, mm	2.75 ± .46	2.69 ± .52	2.71 ± .49
Lesion length, mm	14.8 ± 8.3	14.0 ± 8.2	14.7 ± 8.0
MLD before PCI, mm	0.97 ± .46	0.93 ± .47	1.00 ± .49
DS before PCI, %	64.7 ± 15.0	65.4 ± 14.6	63.4 ± 15.9
MLD after PCI, mm	2.55 ± .43	2.49 ± .48	2.51 ± .47
DS after PCI, %	10.8 ± 5.7	11.6 ± 5.0	10.7 ± 7.0

Data are mean ± standard deviation

Primary Endpoint: binary angiographic restenosis



Secondary Endpoint: in-stent late lumen loss



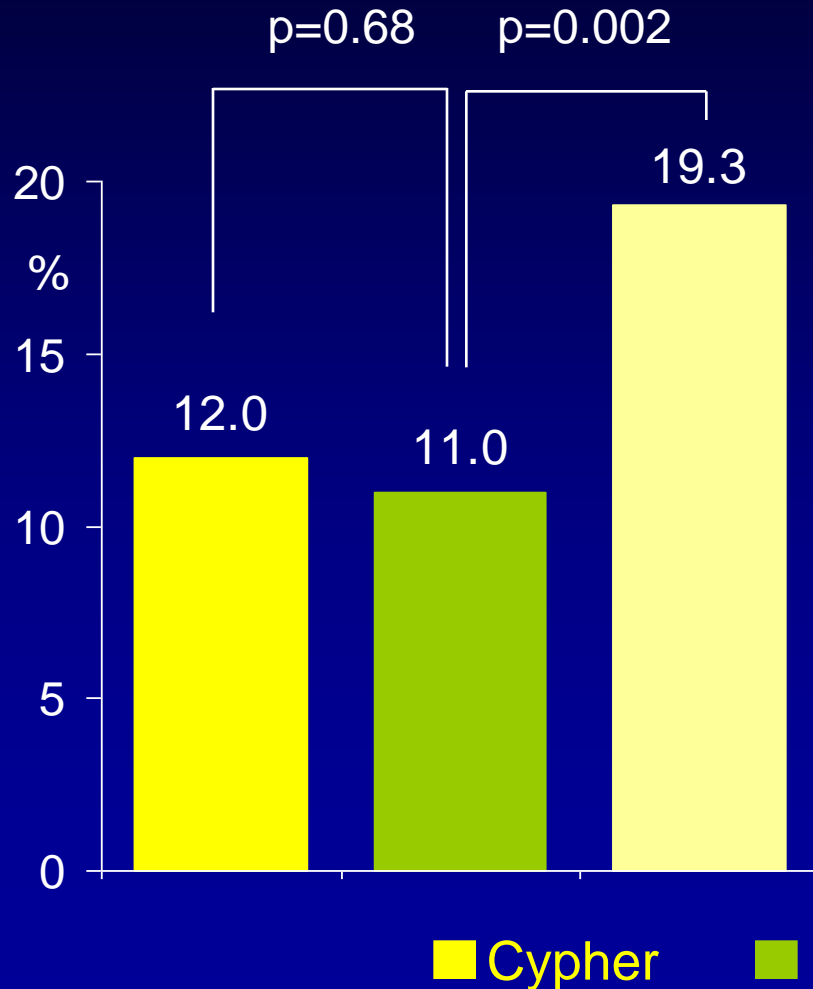


	Cypher (n=347)	Dual-DES (n=356)	Endeavor (n=343)
Late lumen loss, mm			
In-stent	0.24 ± .51	0.23 ± .50 [†]	0.58 ± .55
In-segment	0.23 ± .48	0.20 ± .52 [†]	0.35 ± .60
MLD, mm			
In-stent	2.32 ± .63	2.26 ± .64 [†]	1.95 ± .72
In-segment	1.99 ± .59	1.98 ± .59 [†]	1.79 ± .66
Diameter stenosis, %			
In-stent	20.1 ± 16.8	20.0 ± 17.1 [†]	30.0 ± 21.2
In-segment	31.8 ± 15.4	30.5 ± 16.6 [†]	35.3 ± 19.4

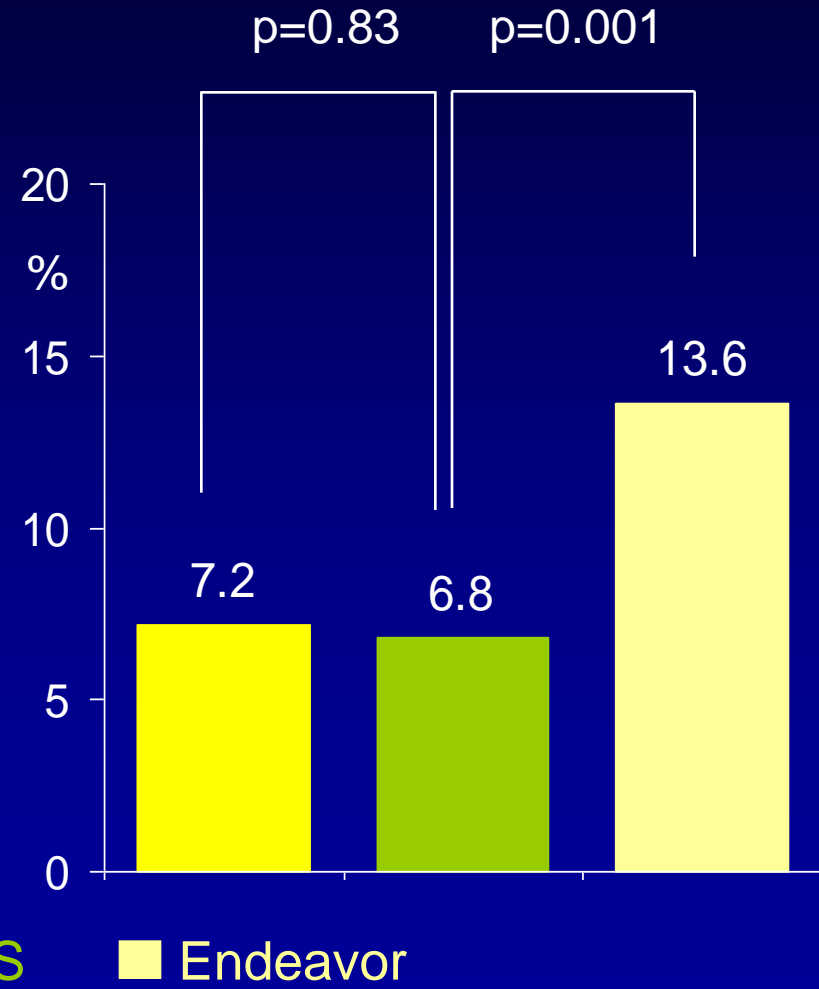
[†]p<0.001 for Dual DES vs. Endeavor



Angiographic restenosis

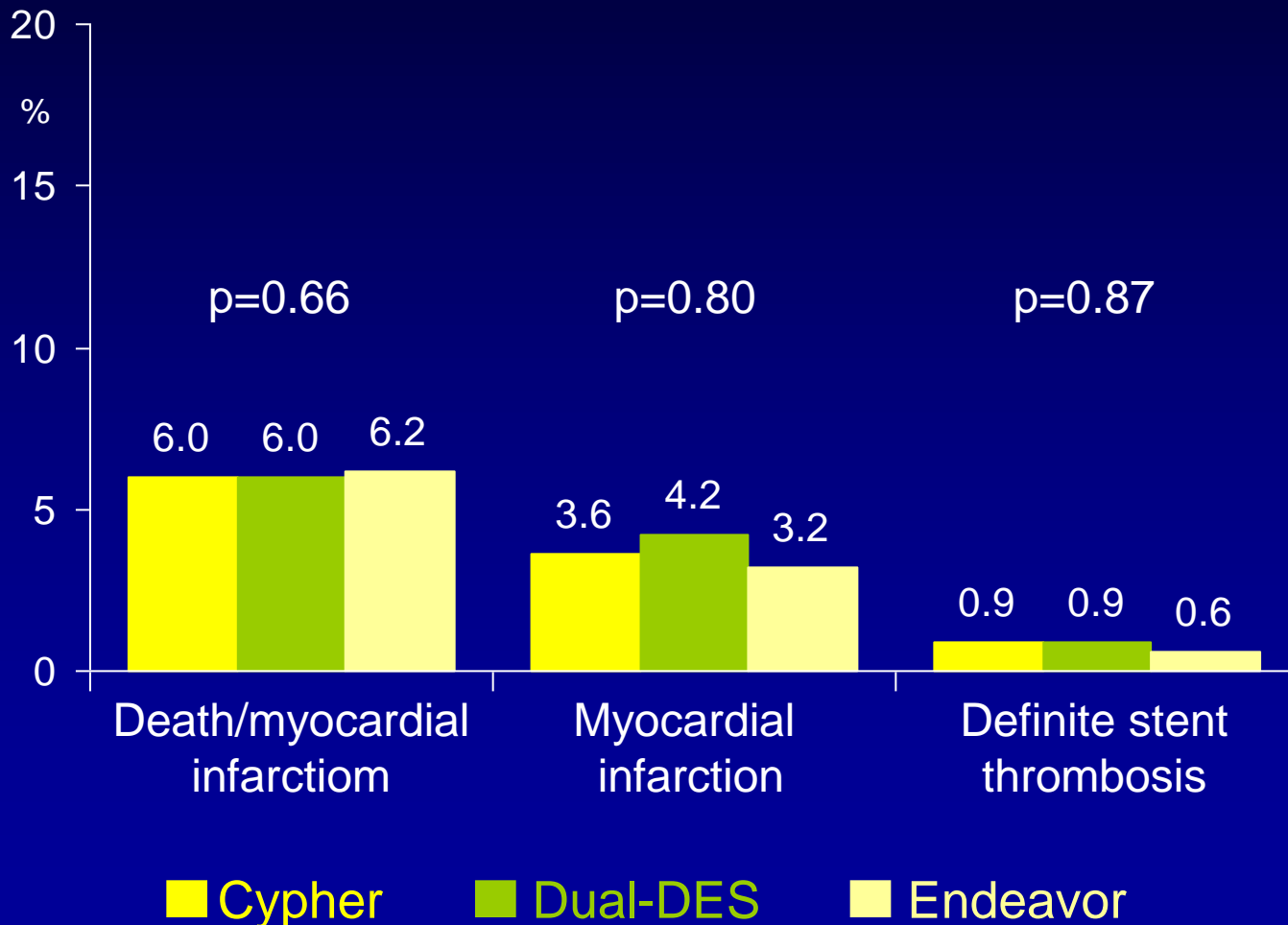


Clinical restenosis (TLR)





Incidence



Conclusions (1)



- This is the first report of successful outcome with a Dual-DES

- A novel probucol+rapamycin Dual-DES is associated with high anti-restenotic efficacy without recourse to permanent polymer

Conclusions (2)



- The efficacy of this Dual-DES platform is superior to that of the permanent polymer zotarolimus stent and comparable to that of the permanent polymer sirolimus-eluting stent
- Although avoidance of durable polymer has interesting potential long-term safety implications, durability of performance efficacy and accrual of putative clinical benefit remain subject to future investigation

Thank You



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