

JUPITER II:
double blind randomized comparison
of Janus Tacrolimus eluting stent
with the Tecnic Carbostent

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Thoraxcenter, Erasmus MC, Rotterdam, Netherlands

06 September 2005
11:13-18
Stockholm (Green Zone)

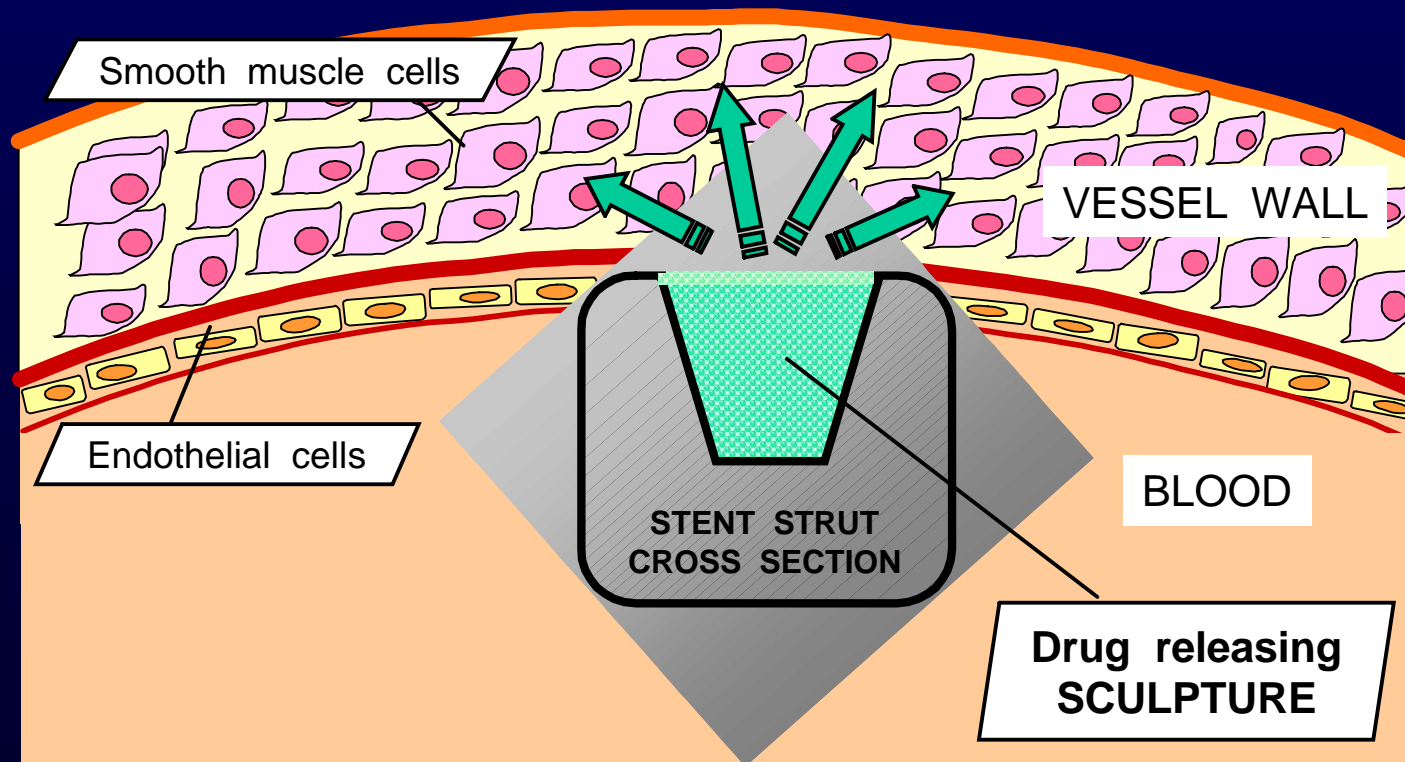
This presentation is exciting ! Why?

- Because we are dealing with the first European eluting stent produced by a European company.
- Because the stent platform is original, not using a coating of durable polymer for elution, but rather a large mechanical reservoir.
- Because the drug offers a therapeutic window and inhibits more selectively the SMC before affecting the endothelial cell.
- Because when pooling **Jupiter 1a** (50 control, 50 DES a trial without direct stenting) with **Jupiter 1b** (the trial presented today), we have a **statistically significant** reduction in TLR from **13.5% to 6.3%** (a relative reduction of **53% in TLR**, data not presented today).

JANUS CARBOSTENT THE DRUG RELEASING MACHINE

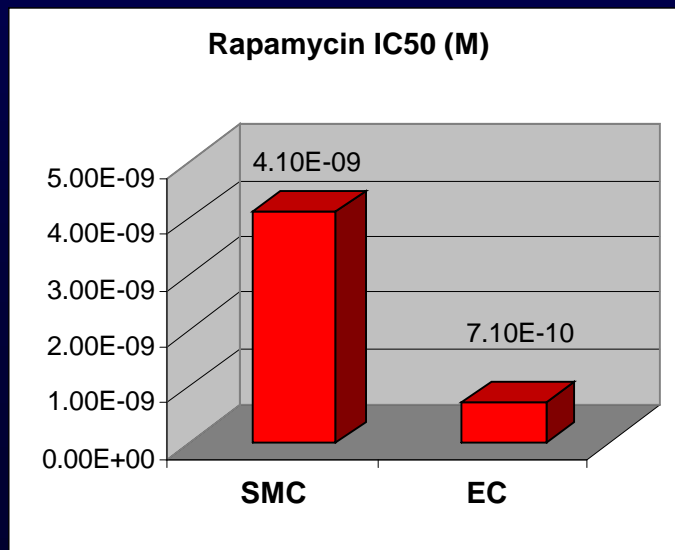
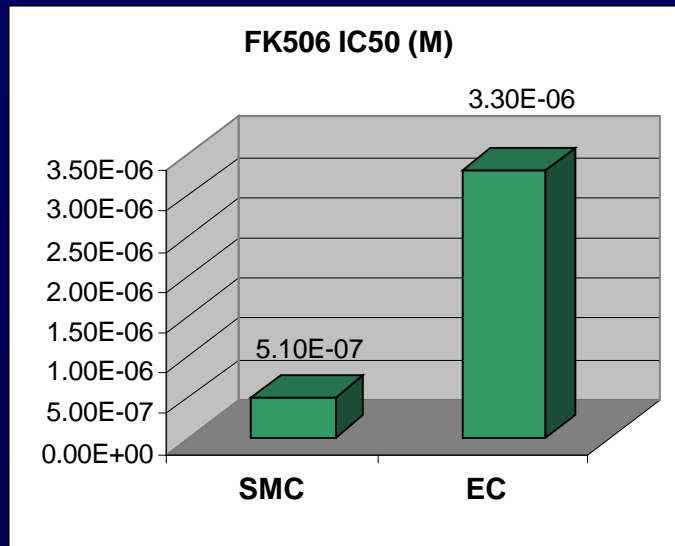
JANUS CARBOSTENT IS:

- *RELEASING DRUG DIRECTLY TOWARD THE VESSEL TISSUE*
- *STABLE NON THROMBOGENIC SURFACE TOWARD THE BLOOD*
- *NO DRUG IS RELEASED INTO THE BLOOD*



Tacrolimus' SMC selectivity: A Smart Drug

(Mohacsi PJ, et al. J Heart Lung Transplant 1997; 16: 484)



- Studies with human smooth muscle (SMC) and endothelial cells (EC) showed SMC selectivity of FK506.
- Rapamycin has higher potency for ECs compared to SMCs.
- FK506 may improve reendothelialization of damaged vessel wall.

The lower the IC50, the more active the drug.

C. Matter, Th. Lüscher (Zürich)

Stockholm ESC, 06 September 2005

TACROLIMUS (FK506)

- Tacrolimus is 100 times less potent than sirolimus in smooth muscle cell inhibition but has less detrimental effect on endothelial function.
- Therefore, it has been perceived as an alternative eluting drug.
- However, Jomed has failed to develop a Tacrolimus program (insufficient dose, poor kinetic profile cracking of ceramic coating)
- Animal work recently performed at the Thoraxcenter with stent coated with very slowly biodegradable polymer has shown a potent inhibitory effect on neointimal hyperplasia at 28 days and at 90 days with excellent healing and endothelialization.

This presentation is disappointing ! Why?

- **The trial was completed in December 2004.**
- **8 months later, the “6-month” angiographic follow-up - the primary endpoint - is still not available- even the baseline angiography is reported as “visually” evaluated.**
- **It is unusual to present chronologically the secondary endpoint prior to the primary endpoint !!**

Considering the late loss of the sample size of the trial?

How often made the power calculation?

(Invited Lecture, ESC, 2004, Pg. 64, with citation: *Journal of Clinical Pharmacy and Therapeutics* 2001; 54: 420)

Expected late loss (mm)	Sample size	
	70%	80%
0.6	235	190
0.5	107	93
0.4	61	52
0.3	41	32
0.2	28	28
0.1	21	17

166?

Study Endpoint

Primary endpoint:

- Assessment of in-stent and peri-stent "Late Lumen Loss (LLL)" at 6 month follow-up by Quantitative Coronary Angiography (QCA)

Secondary endpoints:

- Assessment of binary angiographic follow-up
- MACE at discharge
- Clinically driven TLR
- Incidence of stent thrombosis at 6 months

The primary endpoint should be single (not multiple).

MACE is mentioned, but not defined.

- **Death – cardiac or non cardiac?**
- **MI – 2 or 3 × CK/CKMB?**
- **TLR – all TLR or clinically-driven? If only clinically-driven TLR is considered as MACE, then the MACE rate at 6 months (strictly censored at 180 days or including an angiographic window of 2 to 4 weeks?) would be 1.9% in Janus versus 0.6% in Tenic...**

6-month Angiographic vs. Clinical TLR

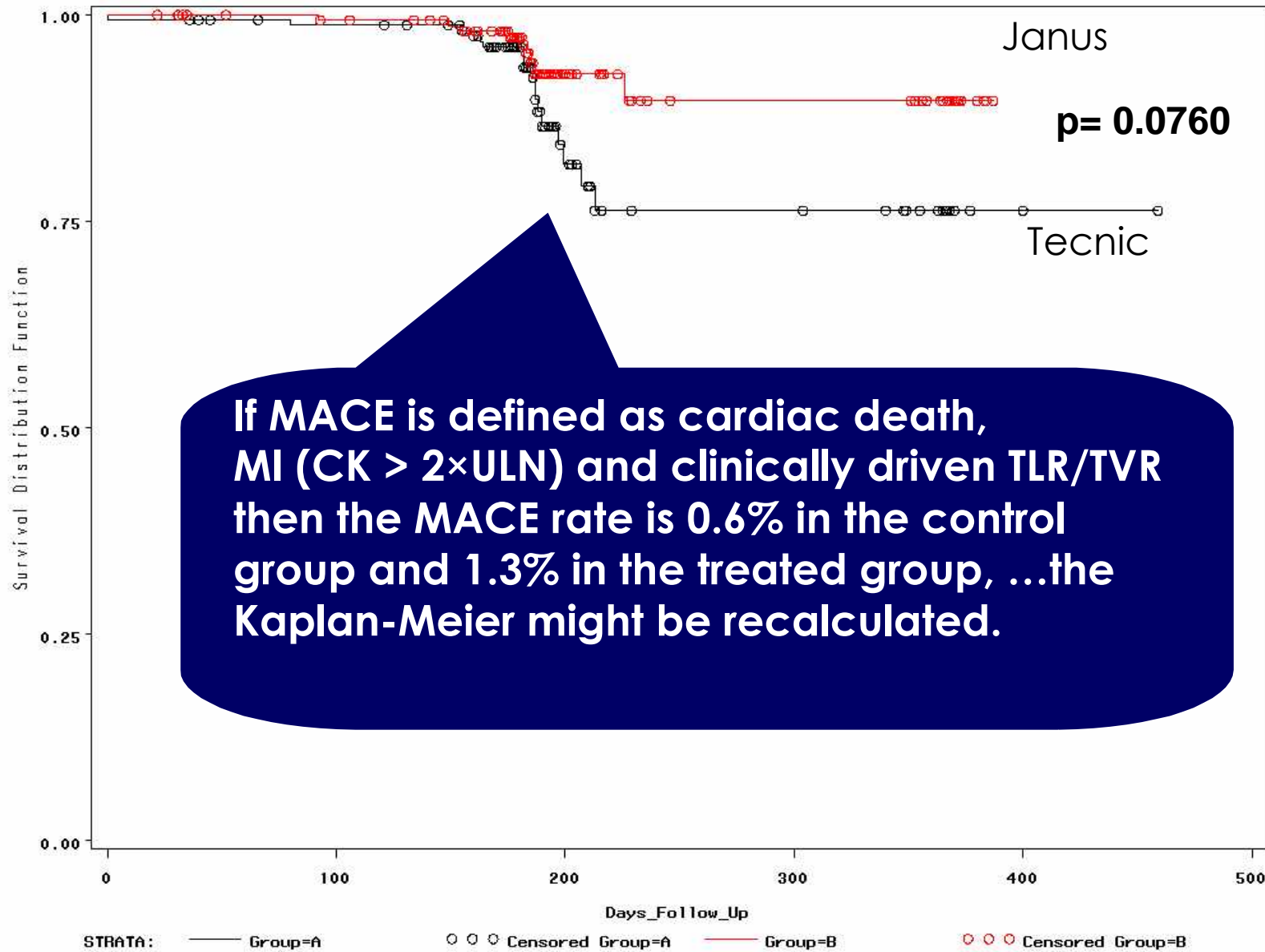
	TECNIC 160 patients	JANUS 157 patients
INTERVENTION (area)	17 (17)	9 (9)
Angiographic TLR *	10.0% (16)	4.4% (7)
Clinical TLR **	0.6% (1)	1.3% (2)

* Patients treated without symptoms at the scheduled 6-month follow-up

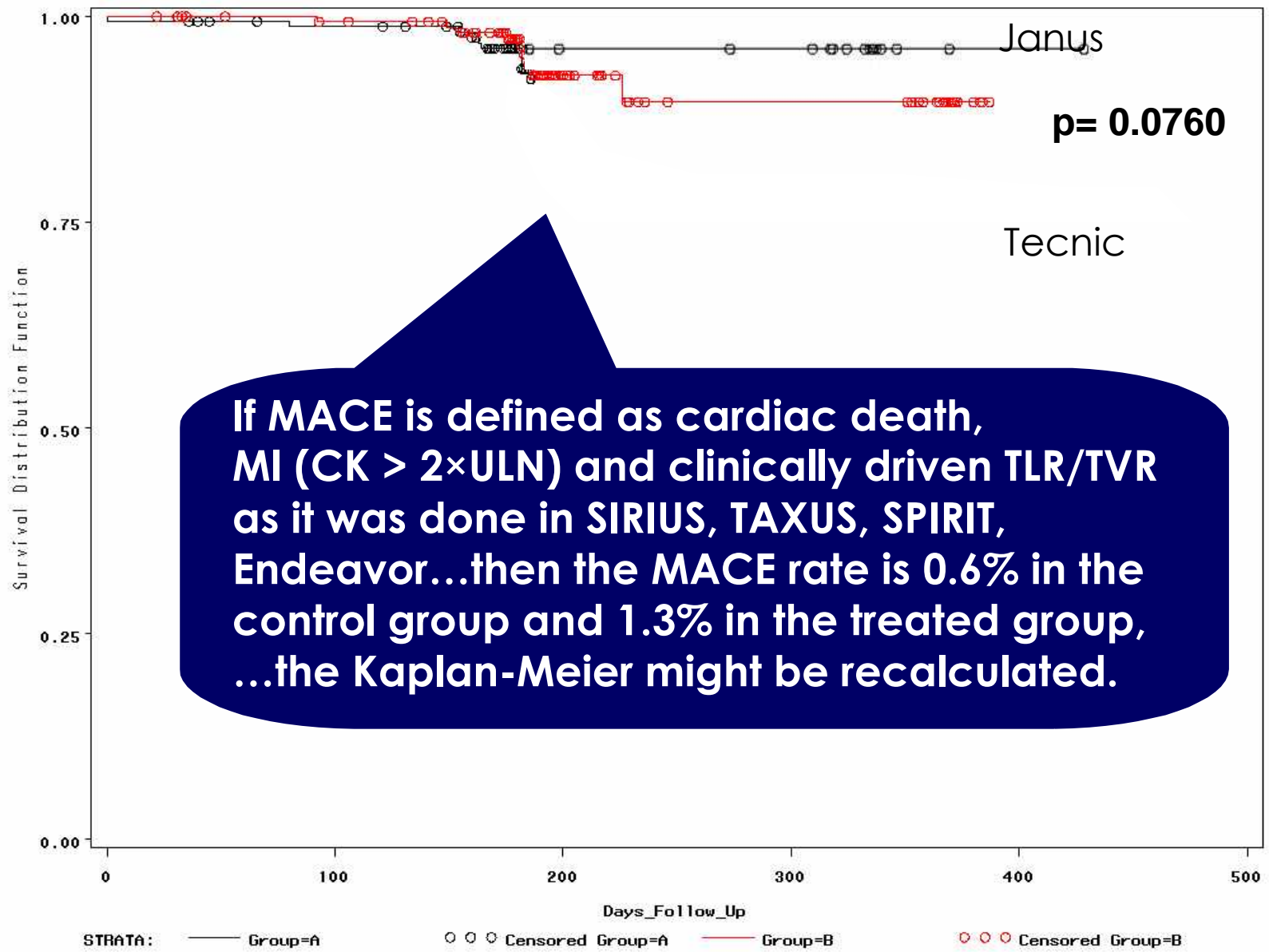
** **Patients treated with symptoms at unscheduled follow-up**

In the control group, only 6% (1/17) and in the treated group only 22% (2/9) of all the TLR's are apparently clinically-driven or justified. Are all the other TLR's the result of the oculo-stenotic reflex?

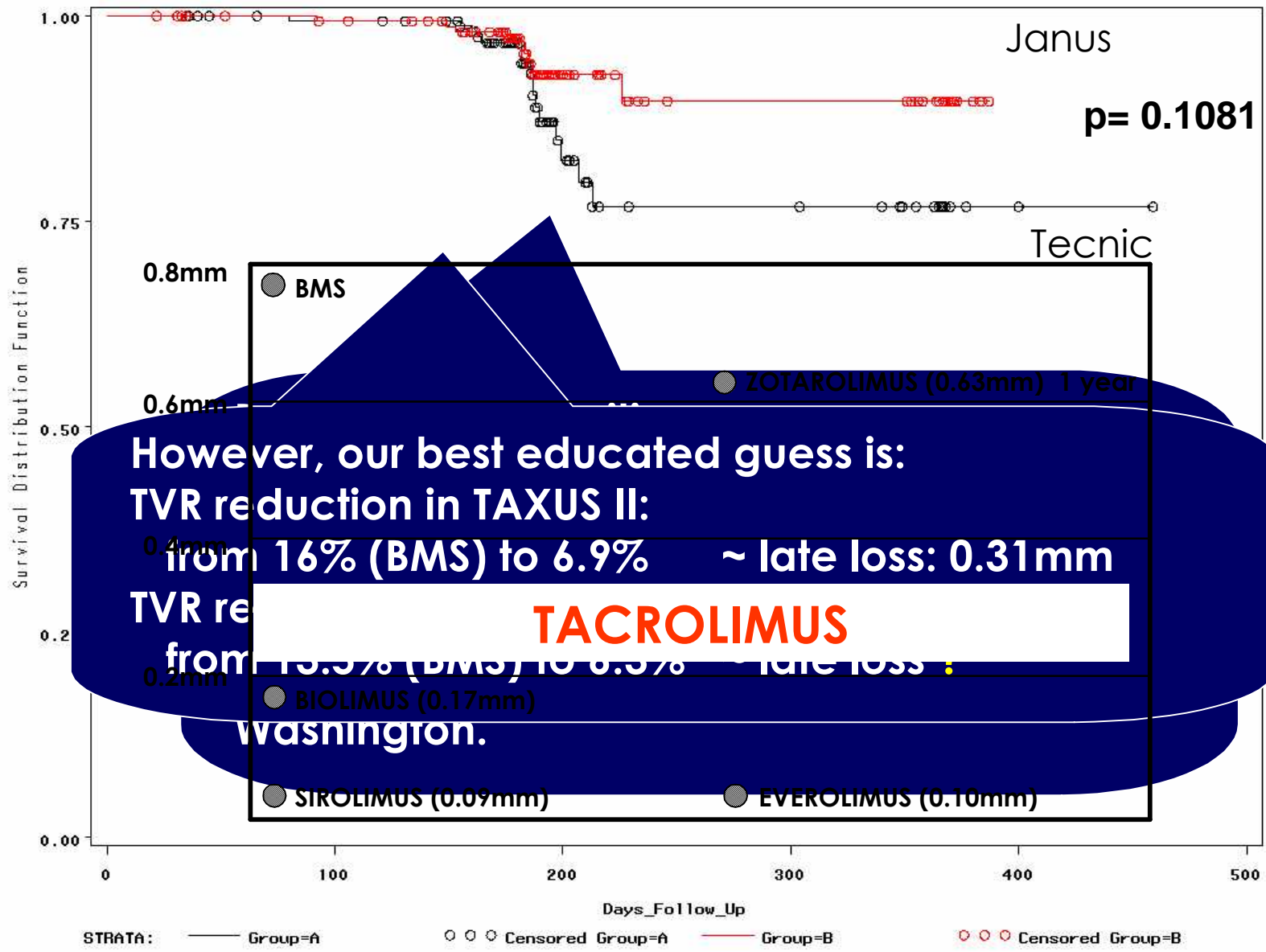
Freedom from stent-related MACE



Freedom from stent-related MACE



Freedom from stent-related TLR



Backup slides

Stent Thrombosis (Acute, Subacute & Late)

	TECNIC	JANUS
Acute Thrombosis (n)	0.5% (1/163)	0% (0/163)
Sub-acute Thrombosis (n)	0% (0/161)	0% (0/160)
Late Thrombosis (n)	0% (0/160)	0.6% (1/157)*

* Patient with two vessels treated (RCA prox and LAD prox) respectively with Janus 3.0x15 mm and 3.0x25 mm.

After three months the patient was hospitalized with Q-wave AMI. At angiography a thrombus related to subocclusive hyperplasia in LAD was detected and treated by Re-PTCA+DES stent and Reopro.

Clinical Events at 6 months:

JUPITER II & JUPITER I – Beta

	Group A 207 patients	Group B 208 patients	P-Value
Death (n)	0%	0%	-
Cardiac Death	0%	0%	-
MI (all) (n)	0%	0.5% (1)	.9999
Q-Wave	0%	0%	-
Non Q-Wave	0%	0.5% (1)	.9999
TVR (all) (n)	13.5% (28)	6.3% (13)	.0130
CABG	0%	0%	-
Re-PTCA	4.8% (10)	3.4% (7)	.4514
Re-PTCA + stent	8.7% (18)	2.9% (6)	.0112

Conclusion (I)

- Early clinical outcomes demonstrate high procedural and lesion success together with low rate of MACE in both groups;
- The analysis performed on 6 month clinical follow-up shows again a low MACE rate in both groups with a more favorable rate of 6.4% for Janus stent;
- The occurrence of MACE in Jupiter II study is mainly related to TLR. The incidence of events such as death, AMI or CABG is negligible;

Conclusion (II)

- **The 6-month clinical efficacy of Janus stent is expressed by a reduction of 46% of TLR in respect to Tecnic stent however this difference is not statistically different;**
- **Janus stent exhibits very high safety profile, as demonstrated by the extremely low thrombosis rate, confirming all previous clinical results with Tecnic and other Carbofilm coated stents.**

Visual Estimation !!!

Trial was completed in December 2004.
Why is the pre-procedural angiography not yet quantified?

Pre-Procedure	TECNIC	JANUS	P-Value
Pre-Procedure Diameter (mm)	1.38	1.40	0.576
Minimum Luminal Diameter (mm)	1.03±0.65	1.02±0.56	0.9017
Lesion Length (mm)	11.83±3.76	12.30±3.85	0.2465

The QCA pre treatment indicated that we are dealing with BENESTENT-like vessel. In MUSIC using Palmaz-Schatz stent, the TLR rate was 5.7% like in this trial.

Baseline Clinical Characteristics (I)

	TECNIC	JANUS	p value
N° of enrolled pts (332)	166	166	
N° of analyzed pts (326)	163	163	
Male	75.5%	75.5%	.9999
Age (yrs)	64.0 ± 10.0	64.0 ± 9.7	.9461
<u>Clinical Status</u>			
Asymptomatic			.6081
Silent Ischemia			.5324
Stable Angina			.4908
Unstable Angina			.3783
MI			.2795
<u>CAD</u>			
Single vessel disease	60.7% (99 pts)	61.3% (100 pts)	.9096
Multivessel disease	39.3% (64 pts)	38.7% (63 pts)	.9096

On baseline characteristics, p values should not be applied, since we are not testing a hypothesis. The differences between the groups should be reported together with the 95% CI.

Clinical Events at 6-month follow up

	TECNIC 160 patients	JANUS 160 patients	P Value
Only Stent			
Death (n)			
Mortality			
Q1			
TVR			.1747
Only Stent-rev			.1125
CABG		0.6% (1*)	.4953
Re-PTC	2.5% (4)	3.2% (5)	.7484
Re-PTC or Stent	8.1% (13)	2.5% (4)	.0433

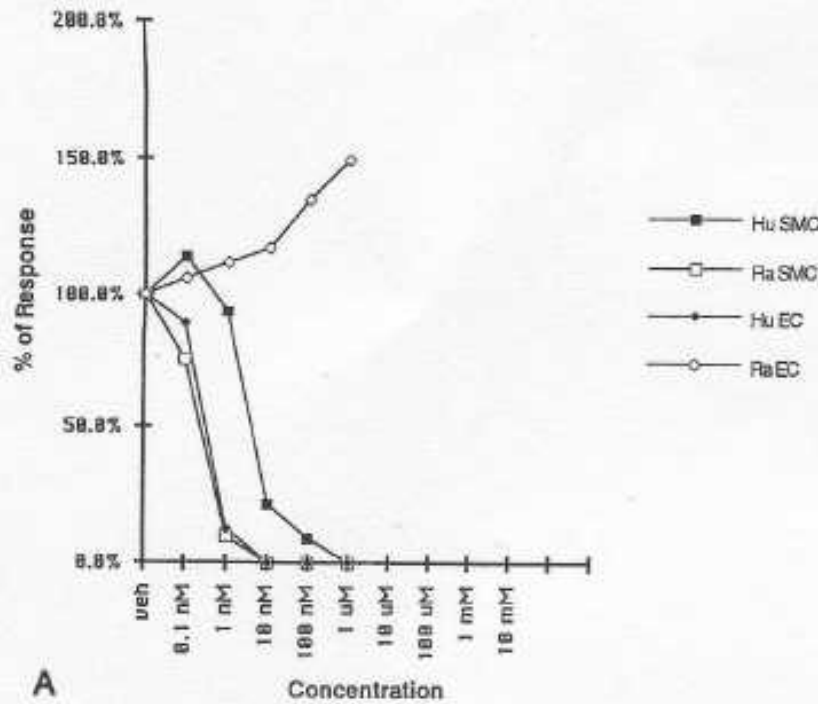
In this session, the presentation of the primary end point was expected; angiographic follow-up should be available before clinical follow-up - it is unusual to present chronologically the secondary end point prior to the primary end point.

* Not Standardized

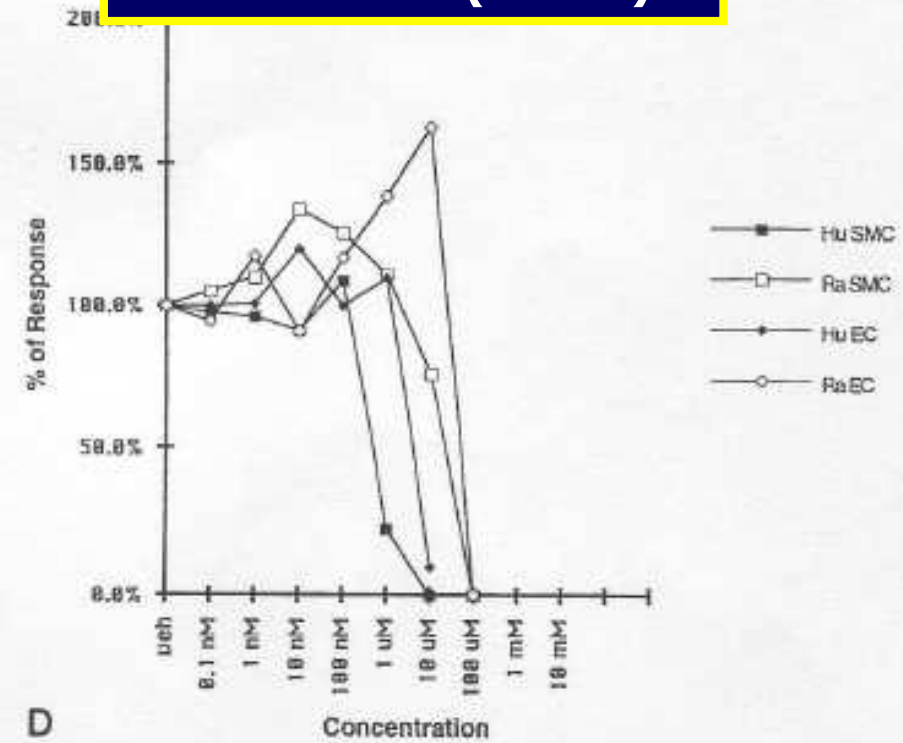
Study Objective

Evaluation of safety and effectiveness
of Janus Tacrolimus Eluting Carbostent
in Direct Stenting, as compared to
Tecniv Carbostent

Rapamycin



Tacrolimus (FK506)



Endothelial Cell Growth Factor

Paul J. Mohacsi, MD, David Tüller, Beatrice Hulliger,
and Peter L. J. Wijngaard, PhD

Mohacsi PJ, et al. J Heart Lung Transplant 1997; 16: 484

Stockholm ESC, 06 September 2005

Procedural Success

	TECNIC	JANUS	P value
Lesion Success	99.5% (185/186 les)	99.5% (185/184 les)	.9999
Procedure Success	99.4% (174/175 les)	99.4% (175/176 les)	.9999

Lesion Success	Residual diameter stenosis <20% (by visual estimate) after stenting procedure
Procedure Success	Final diameter stenosis of <20% without any MACE

Study Management

Principal Investigator:

- Marie-Claude Morice

Independent DSMB and CEC:

- Bartorelli, MD
- Badano, MD
- Naftel, MD

Angiographic Core Lab:

- Bio Imaging
Leiden, Netherlands

Industry sponsor:

- Sorin Biomedica Cardio
Saluggia, Italy

Investigators by Country

COUNTRY	INVESTIGATOR
FRANCE (2)	Prof. Carrié - Toulouse Prof. Massy - Paris
THE NETHERLANDS (3)	Dr. Aengevaeren-Nijmegen Prof. Serruys - Rotterdam Dr. De Winter - Amsterdam
BELGIUM (3)	Dr. De Bruyne, Dr. Wijns - Aalst Dr. Verheye - Antwerp Dr. Dubois - Leuven
GERMANY (3)	Prof. Neumann, Prof. Bestehorn - Bad Krozingen Dr. Hoffmann - Berlin Dr. Hempel - Dresden
SPAIN (1)	Prof. Macaya - Madrid
U.K. (2)	Prof. Di Mario, Prof. Ilsey - London
ITALY (1)	Dr. Cremonesi - Cotignola
AUSTRIA (1)	Prof. Pachinger - Innsbruck
SWITZERLAND (1)	Prof. Amann - Zurich

Study Design

Multicenter, European Double blind, randomized 1: 1
Patients with ≤ 2 de novo lesions in a maximum of 2
native coronary arteries

Tecnic

166 patients with 189 lesions

Janus

166 patients with 191 lesions

Follow-up

- 1, 12, 24 months: Clinical
- 6 months: Clinical & Angiographic

Major Inclusion/ Exclusion Criteria

Inclusion Criteria:

- Patients > 18 years willing to participate in the study, after signature of informed consent
- Angina CCS class I, II, III, IV (stable)
- Angina Braunwald Class B & C I-II-III (unstable)
- Documented Silent ischemia
- Acute MI over 72 hours (non Q-wave)
- Lesions suitable for direct stenting technique
- Target vessel \varnothing 2.7 to 4.0 mm
- Lesion length \leq 20 mm
- Target lesion stenosis \geq 50% and \leq 100% (TIMI I)

Exclusion Criteria:

- Acute MI within 7 days (Q-wave)
- LVEF \leq 40%
- Less than 1 year life expectancy
- Angiographic evidence of massive thrombus in the target lesion
- Ostial lesions
- Left Main with >50% disease
- Unprotected Left Main
- Total occlusion
- In-stent restenosis
- Lesions involving bifurcation and/or collateral vessels with \varnothing >2 mm

Study Medications

Pre-Procedure

Clopidogrel: 300 mg the day of procedure as loading dose

Aspirin: >100 mg (Patients without oral aspirin treatment should receive 500 mg i.v. of soluble aspirin before procedure)

During Procedure

Heparin: IV boluses in order to have ACT ≤ 250 sec

Nitroglycerin or ISDN: 0.1 – 0.3 mg of nitroglycerin or 1 – 3 mg of ISDN

GPIIb/IIIa receptor antagonist: under judgment of the Investigator

Post Procedure & After Discharge

Clopidogrel: 75 mg once daily

For at least 2 months

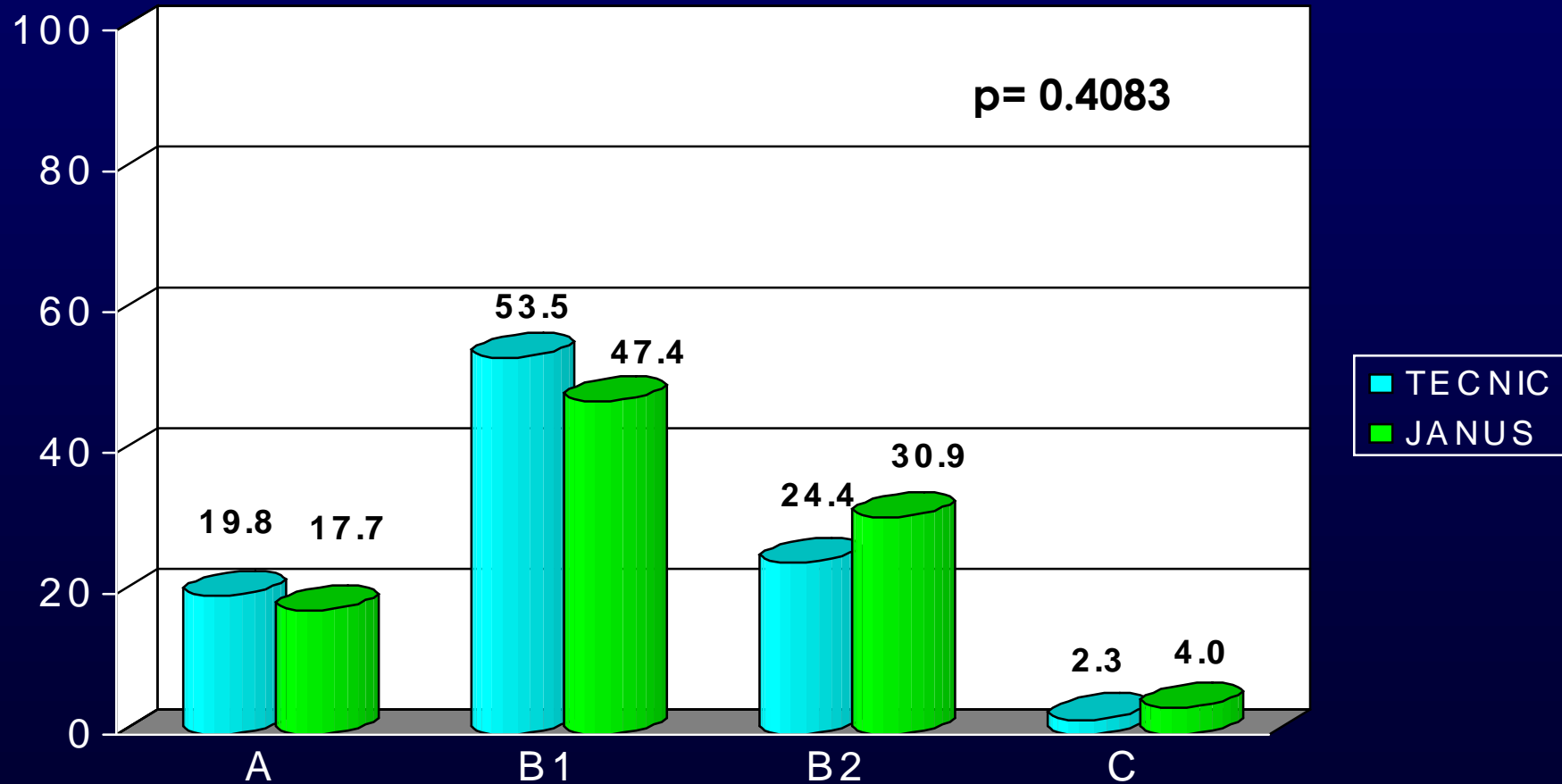
Aspirin: ≥ 75 mg indefinitely

Target lesion Characteristics (I)

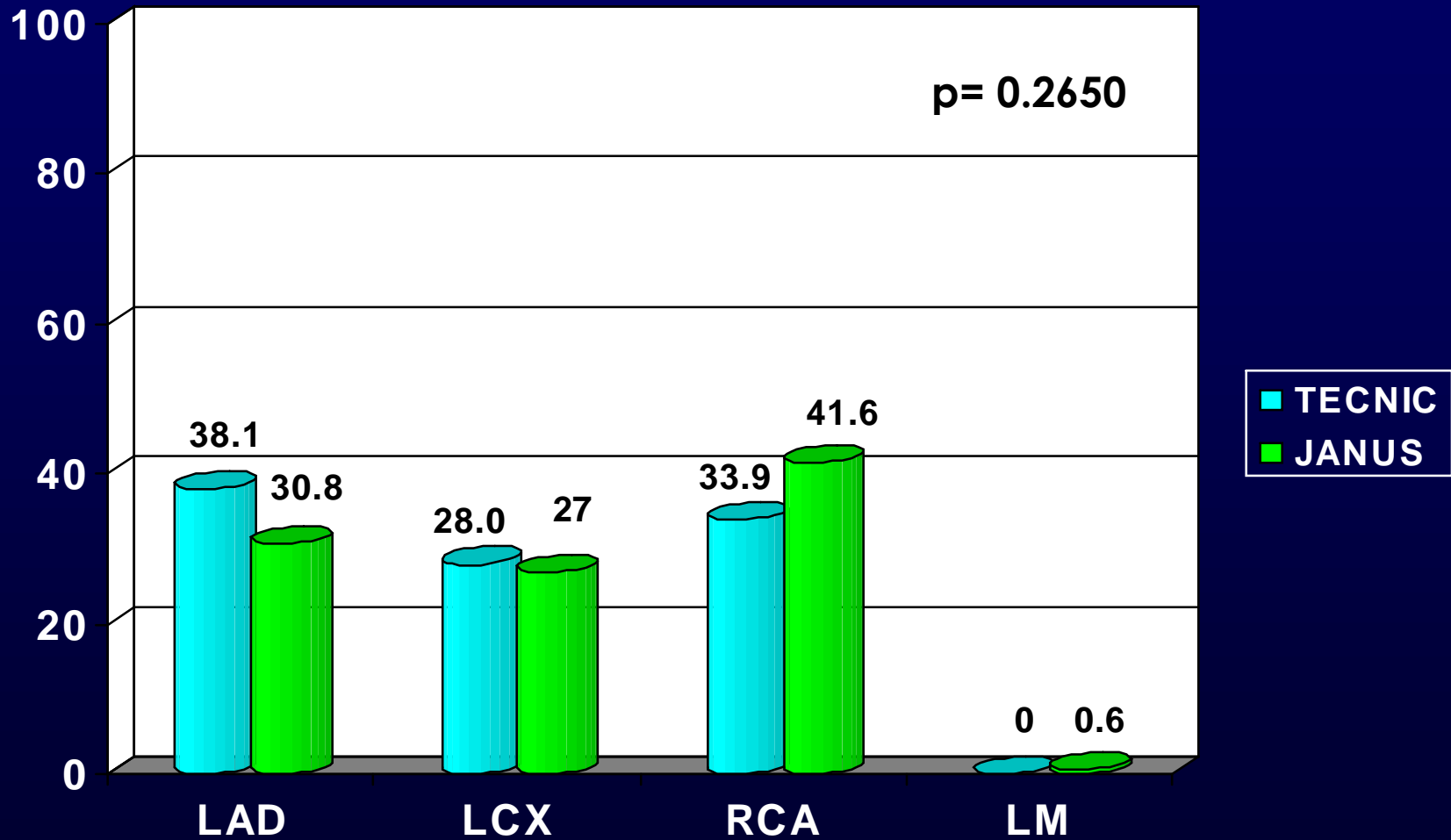
	TECNIC	JANUS	p value
N° of lesions (371)	186	185	
De Novo	98.9% (184/186)	99.5% (184/185)	.9999
Concentric	55.0% (93/169 les)	48.3% (86/178 les)	.2109
Eccentric	45.0% (76/169 les)	51.7% (92/178 les)	.2109
Calcification	17.2% (32/186 les)	24.3% (45/185 les)	.0909
Tortuosity	6.5% (12/186 les)	13.5% (25/185 les)	.0232
Bifurcation	0%	3.2% (6/185)	.0148
Ostial Lesion	0.5% (1/186)	1.1% (2/185)	.6230
Total Chronic Occlusion	0%	1.1% (2/185)	.1551

Target lesion Characteristics (II)

ACC/AHA Lesion Classification (% of lesions)



Target lesion Characteristics (III)



Cumulative 1 month Clinical Events

	TECNIC 161 patients	JANUS 160 patients	P-Value
MACE (n)	0.6% (1)	0%	.9999
Death (n)	0%	0%	-
Cardiac Death	0%	0%	-
MI (all) (n)	0.6% (1)	0%	.9999
Q-Wave	0%	0%	-
Non Q-Wave	0.6% (1*)	0%	.9999
TLR (all) (n)	0%	0%	-
CABG	0%	0%	-
Re-PTCA (n)	0%	0%	-
Re-PTCA + stent (n)	0%	0%	-

Clinical Events at 6-month follow up

	TECNIC 160 patients (compl. 98.2%)	JANUS 157 patients (compl. 96.9%)	P-Value
Only Stent-Related MACE (n)	10.6% (17)	6.4% (10)	.1747
Death (n)	0%	0.6% (1*)	.4953
Cardiac Death	0%	0.6% (1*)	.4953
MI (all) (n)	0%	0.6% (1)	.4953
Q-Wave	0%	0.6% (1)	.4953
Non Q-Wave	0%	0%	-
TVR (all) (n)	10.6% (17)	6.4% (10)	.1747
Only Stent-related TLR (n)	10.6% (17)	5.7% (9)	.1125
CABG	0%	0.6% (1*)	.4953
Re-PTCA	2.5% (4)	3.2% (5)	.7484
Re-PTCA + stent	8.1% (13)	2.5% (4)	.0433

* Not Stent Related

Procedural Characteristics

	TECNIC (186 les; 193 stent)	JANUS (185 les; 200 stent)	P value
% of direct stenting	99.1%	99.7%	.217
Direct stenting success	99.3%	100%	.9999
# Stent/patient	1.18 ± 0.45	1.23 ± 0.52	.3598
# Stent/lesion	1.04 ± 0.19	1.09 ± 0.35	.0969
Mean Stent Diameter (mm)	3.22 ± 0.25	3.23 ± 0.25	.6197
Stent max pressure (atm)	13.9 ± 3.3	13.7 ± 3.0	.4082

Baseline

Characteristics (I)

In baseline clinical characteristics, there are asymptomatic (thus without symptom and without ischemia; why they are treated?) and patient with silent ischemia 8.6% vs. 6.7%. (these by definition asymptomatic).

On baseline characteristics, p values should not be applied, since we are not testing a hypothesis. The differences between the groups should be reported together with the 95% CI.

N° of enrolled pts

N° of analyzed pts

Male

Age (yrs)

Clinical Status

Asymptomatic

Silent Ischemia

Stable Angina

Unstable Angina

MI

CAD

Single vessel disease

Multivessel disease

	NUS	p value
	166	
	163	
	75.5%	.9999
	± 9.7	.9461
		.6081
		.5324
		.4908
		.3783
		.2795
		.9096
		.9096

Baseline Clinical Characteristics (II)

	TECNIC	JANUS	p value
<u>Risk factors</u>	163	163	
Smokers	39 (23.9%)	38 (23.3%)	.2603
Diabetes			.6701
ID Diabetes			.1862
NID Diabetes			.7503
Hypertension			.2128
Hypercholesterolemia			.6328
Family history of CAD	28.2% (46 pts)	27.5% (46 pts)	.8068

On baseline characteristics, p values should not be applied, since we are not testing a hypothesis. The differences between the groups should be reported as well as the 95% CI.



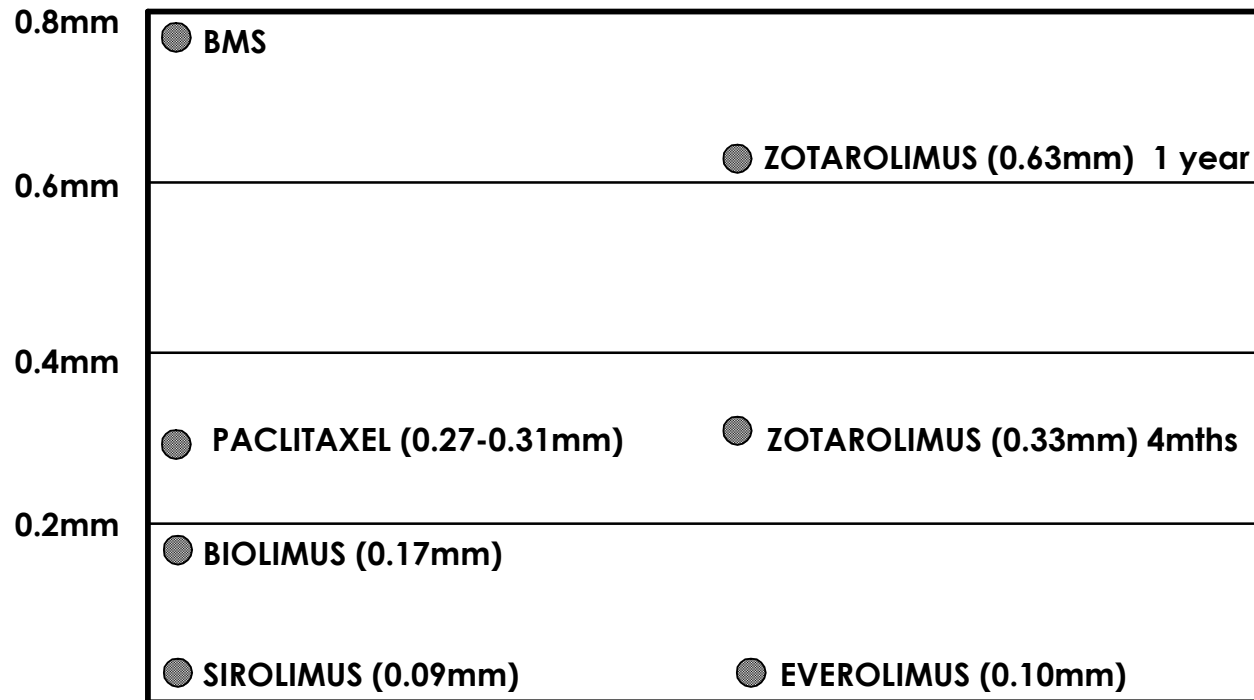
Conclusion (II)

- The 6-month **clinical efficacy** of Janus stent is expressed by a reduction of 44% of TLR in respect to Tecnic stent however the results are not statistically different;

By augmentation of 100% (from 0.6 to 1.3% in clinically-driven TLR XXX secondary end point in the weeks XXX.

- Janus stent exhibits very low thrombogenicity as demonstrated by the results of the study confirming all previous studies and other Carbofilm coated stents.

TACROLIMUS



This presentation is exciting ! Why?

- Because we are dealing with the first European eluting stent produced by a European company.
- Because the stent platform is original, not using a coating of durable polymer for elution, but a rather large mechanical reservoir.
- Because the drug offers a therapeutic window and inhibits more selectively the SMC before affecting the endothelial cell.
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