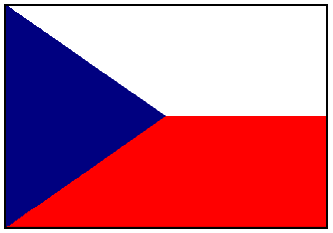

In-Stent Restenosis. How to treat it?

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MINISTRY OF EDUCATION, YOUTH AND SPORTS

EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND
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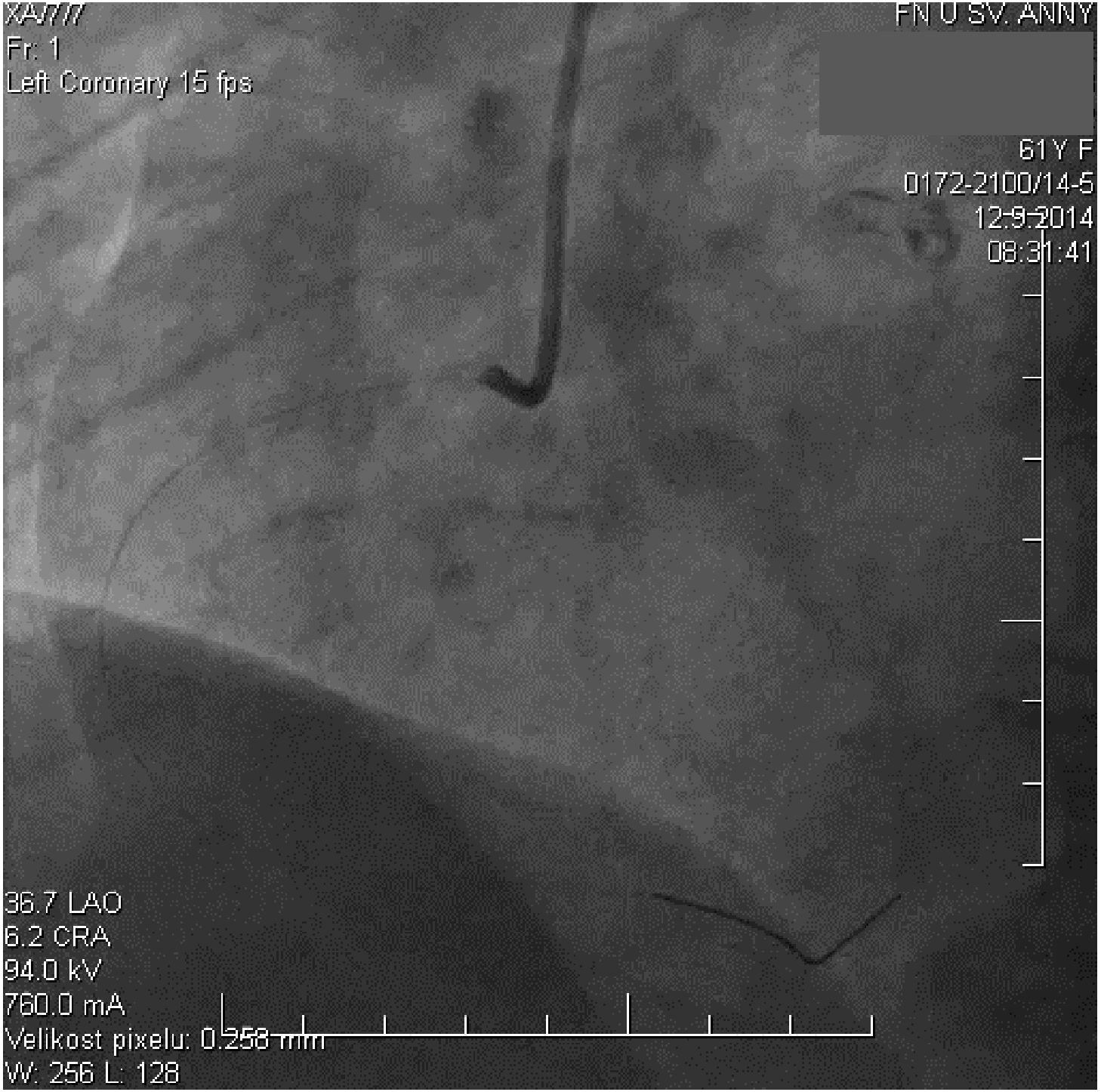
2007–13
OP Research and Development for Innovation

Nothing to disclose

In-Stent Restenosis

- **neointimal hyperplasia**
- **20-35% after BMS, 5-10% after DES**
- **treatment- local aplication of antiproliferative drugs:**
  - drug-eluting stents (DES)
  - drug-eluting baloons (DEB)



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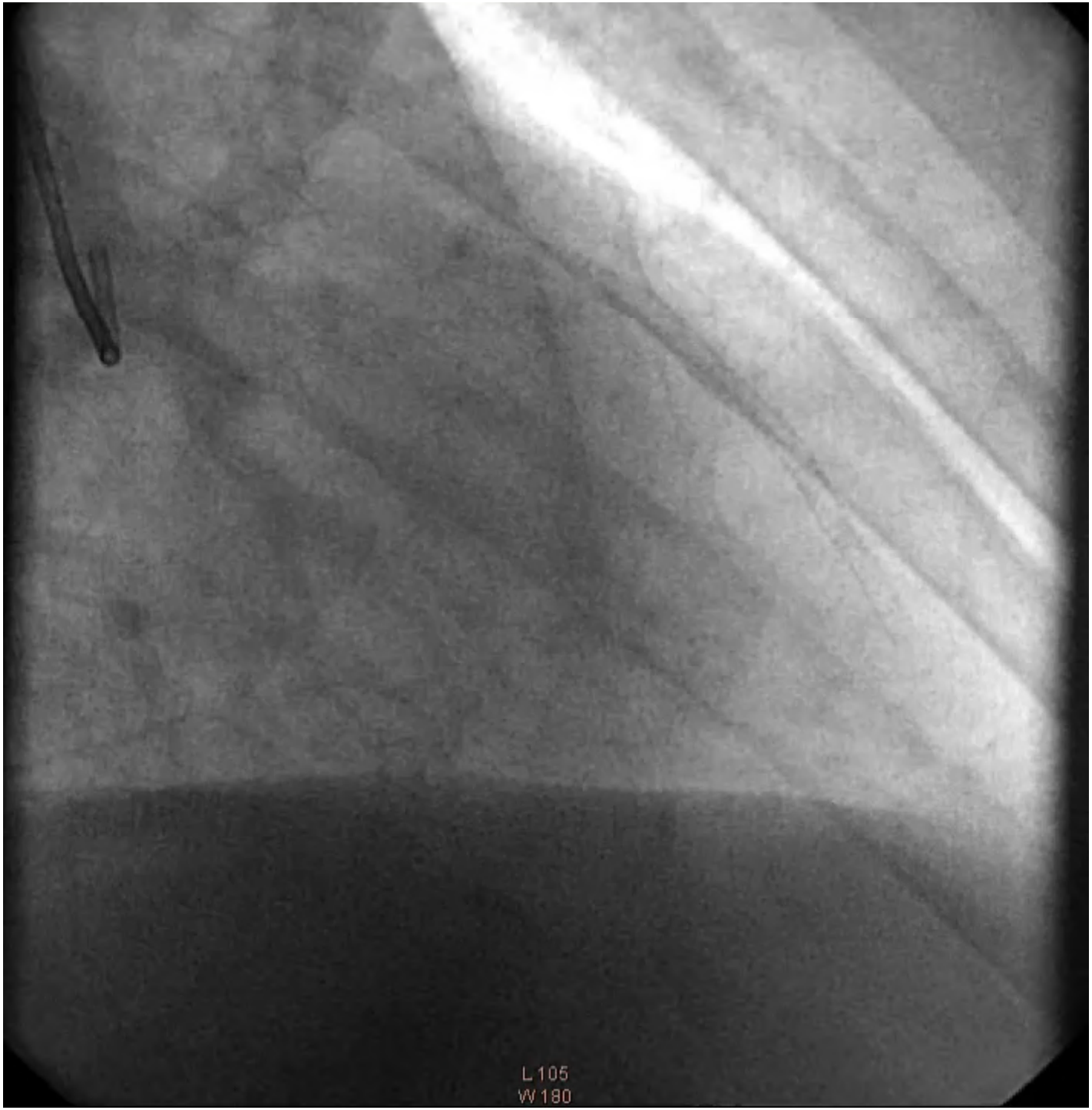
Focal



Diffuse

Occlusive

4.2014	1 BMS
8.2014	POBA
9.2014	1 DES
4.2015	1 DES, DEB
9.2015	1 DES, DEB
4.2016	2 DEB
2.2017	2 DES, DEB

DEB vs 1st generation DES

- **effect of BMS-ISR treatment by PEB against 1st generation DES proved**

- **PEPCAD II:** signif ↓ 6 M LLL, tendency to ↓binary restenosis and MACE against PES

- **2nd generation DES with sirolimus derivates like everolimus (EES) more efficient in treatment of de-novo lesions**

Circulation
Cardiovascular Interventions

Comparison of the Efficacy of Paclitaxel-Eluting Balloon Catheters and Everolimus-Eluting Stents in the Treatment of Coronary In-Stent Restenosis: The Treatment of In-Stent Restenosis Study

Leos Pleva, Pavel Kukla, Pavlina Kusnierova, Jana Zapletalova and Ota Hlinomaz

Circ Cardiovasc Interv. 2016;9:
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TIS trial

- **Randomized, prospective trial**

- **Aim:**

To compare the treatment of **in-BMstent restenosis** by drug-eluting balloon catheters using paclitaxel (**PEB**) with 2nd generation drug-eluting stents using everolimus (**EES**)

TIS trial

Inclusion criteria:

- Pts treated for BMS-ISR in one center 2012-14
- BMS-ISR >50% DS
- Informed consent signed

Exclusion criteria:

- Prognosis < 12 months
- Limited possibility to perform control angio after 12 M (advanced renal failure etc)
- Long-term dual antiplatelet treatment not possible

TIS trial

- **136 pts with BMS-ISR**
- 2 groups

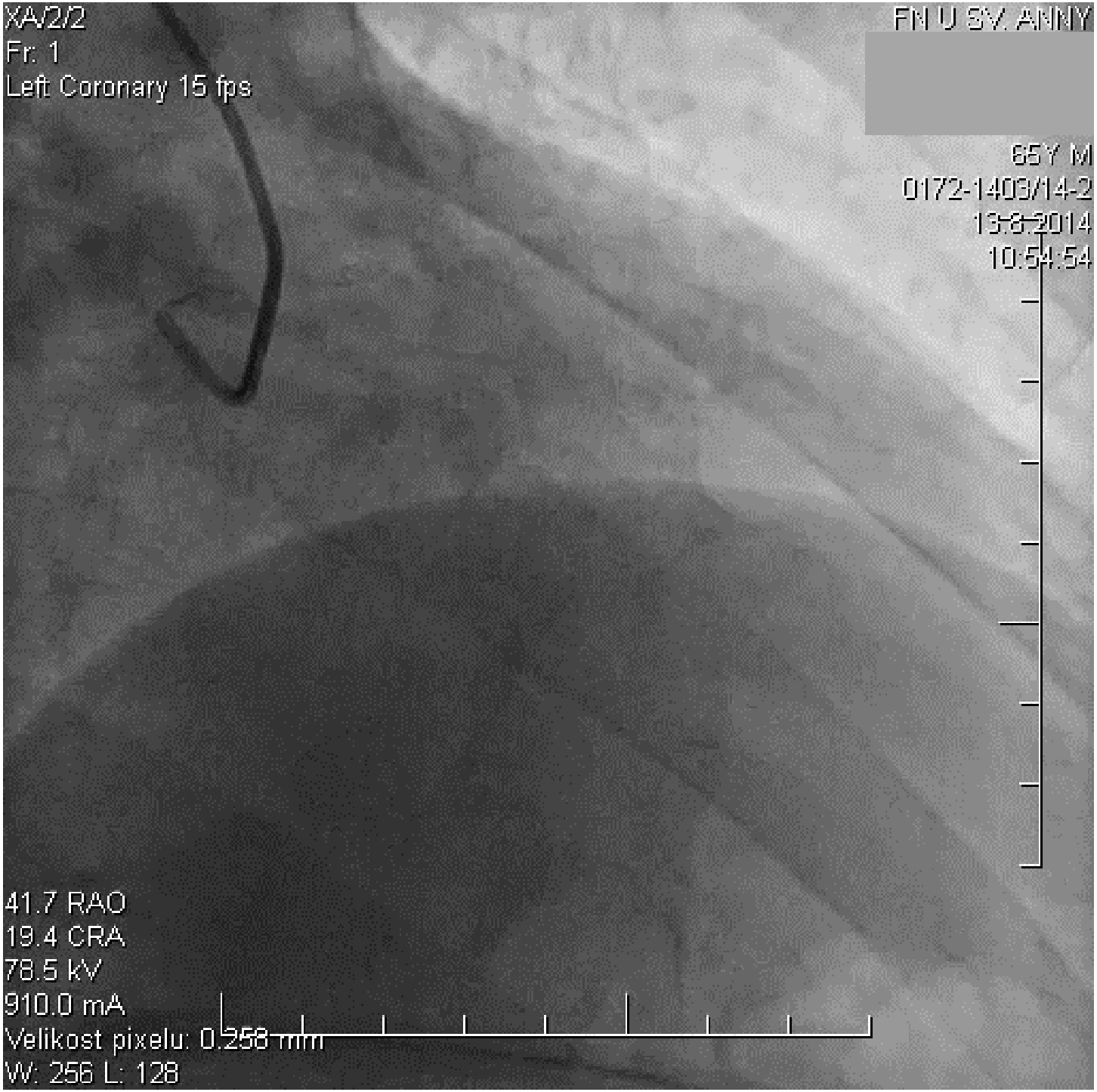
  iopromide-coated PEB (Sequent Please)

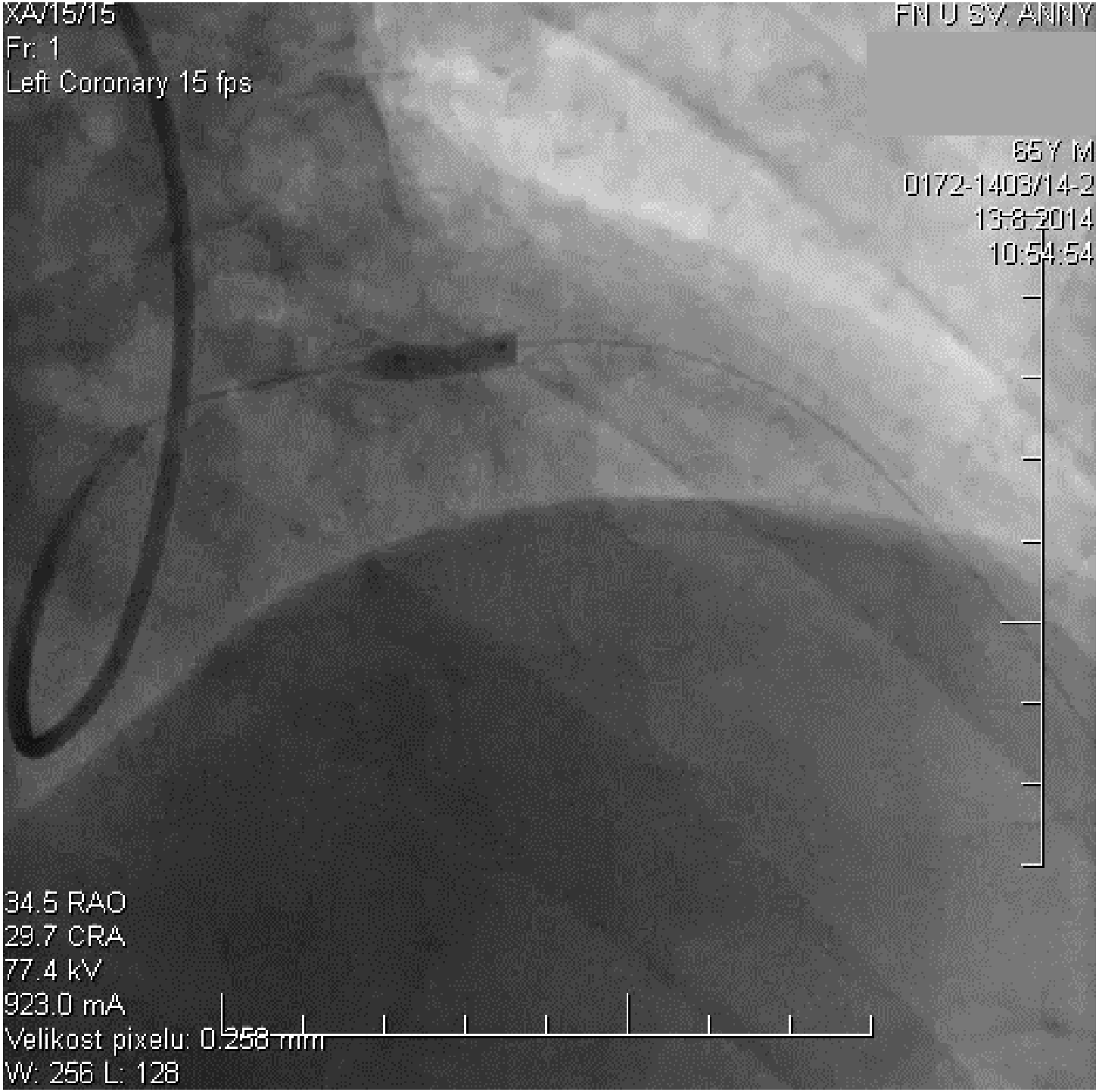
  vs.

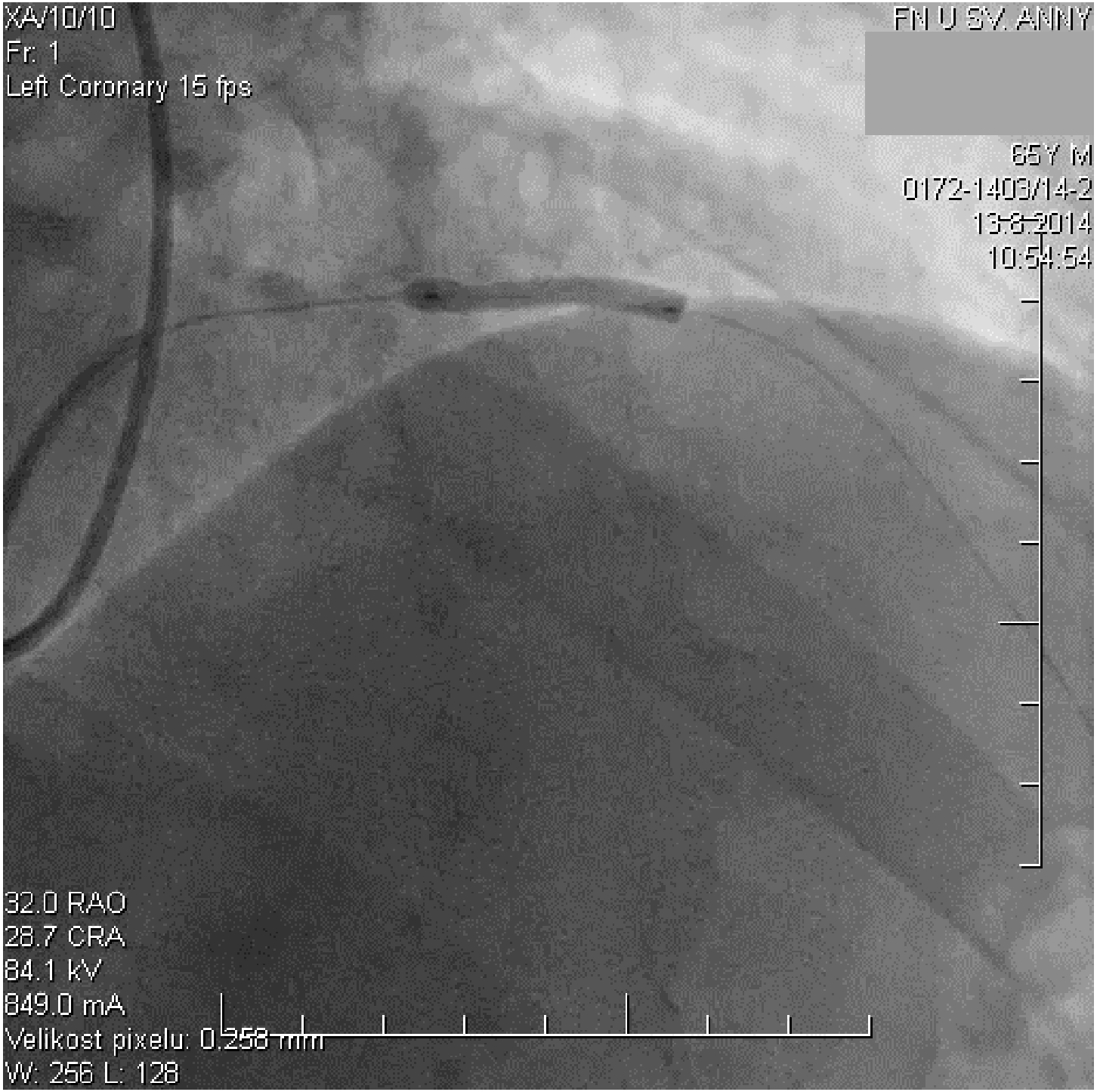
  everolimus-eluting stent (EES; Promus, Pt/Cr)
- **Primary end-point:** 12 M late lumen loss (LLL)
- **Secondary end-points:**

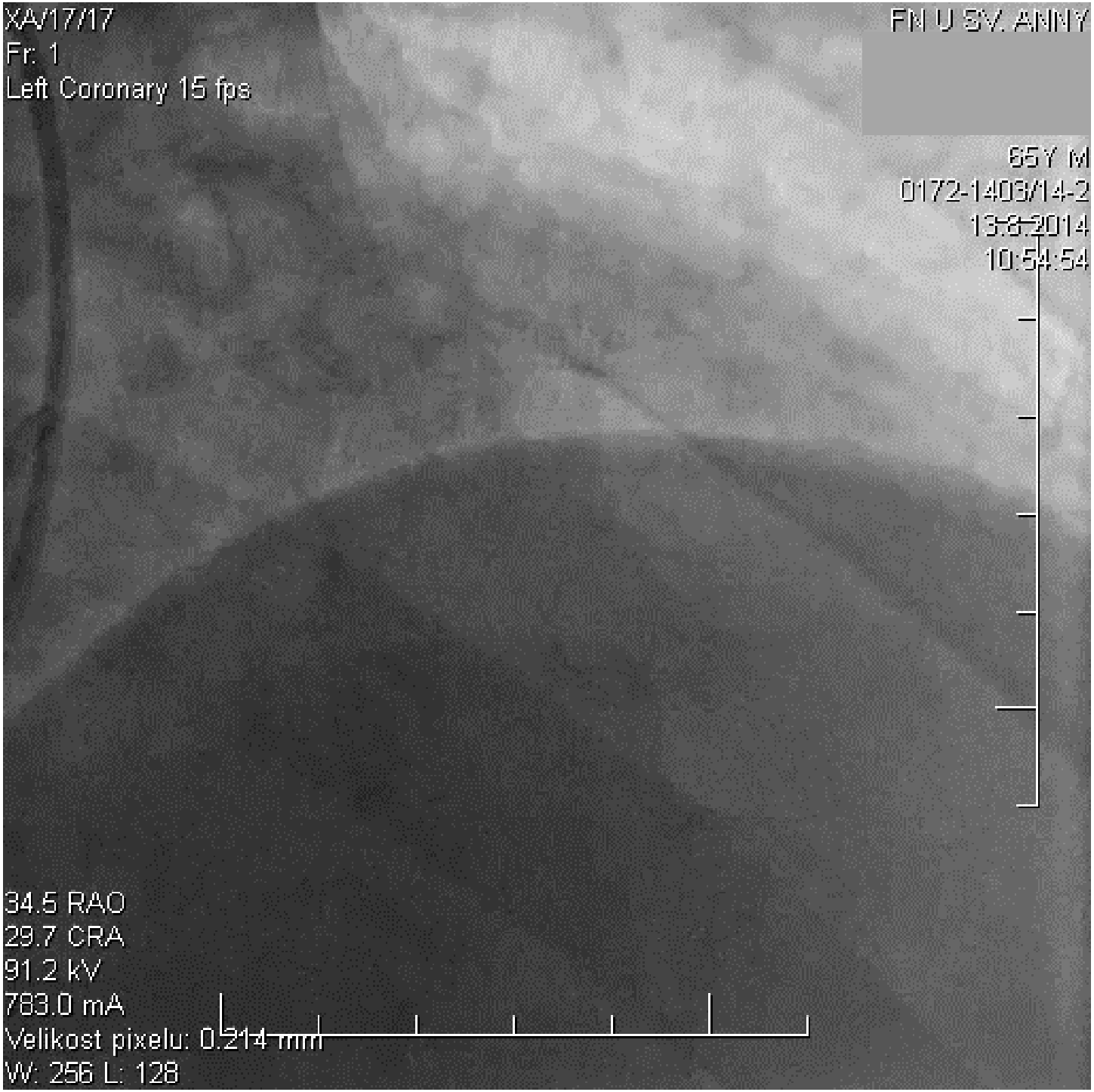
  12 months binary restenosis

  MACE (CV death/nonfatal MI/TVR)
- **non-inferiority study**


XA/2/2
Fr: 1
Left Coronary 15 fps
FN U SV. ANNY
65Y M
0172-1403/14-2
13:8:2014
10:54:54
41.7 RAO
19.4 CRA
78.5 kV
910.0 mA
Velikost pixelu: 0.258 mm
W: 256 L: 128


XA/15/15
Fr: 1
Left Coronary 15 fps
FN U SV ANNY
65Y M
0172-1403/14-2
13.8.2014
10:54:54
34.5 RAO
29.7 CRA
77.4 kV
923.0 mA
Velikost pixelu: 0.258 mm
W: 256 L: 128


XA/10/10
Fr: 1
Left Coronary 15 fps
FN U SV. ANNY
65Y M
0172-1403/14-2
13.8.2014
10:54:54
32.0 RAO
28.7 CRA
84.1 kV
849.0 mA
Velikost pixelu: 0.258 mm
W: 256 L: 128


XA/17/17
Fr: 1
Left Coronary 15 fps
FN U SV. ANNY
65Y M
0172-1403/14-2
13.8.2014
10:54:54
34.5 RAO
29.7 CRA
91.2 kV
783.0 mA
Velikost pixelu: 0.214 mm
W: 256 L: 128

TIS trial

- **Clinical 6 months and 12 months visit**
- **12 months angio with QCA**

Baseline characteristics

	PEB	EES	p
Patients, n	68	68	
ISR lesions, n	74	74	
Males/Females	43 (63,24%) / 25 (36,74%)	46 (67,65%) / 22 (32,35%)	0,589*
Age, years	65,6 ±10,9†	65,5 ±10,6†	0,930†
Ejection fraction, %	49,74 ±11,95†/50,0‡	49,57± 11,44†/50,0‡	0,956‡
Diabetes mellitus	17 (25,00%)	18 (26,47%)	0,844*
Renal insufficiency	2 (2,94%)	7 (10,29%)	0,165§
2VD/3VD	38 (55,88%)	41 (60,29%)	0,602*
Multi ISR	4 (5,88%)	5 (7,35%)	1,000§

† mean ± SD; ‡ median

Baseline PCI

	PEB	EES	p-value
ACS (STEMI/NSTEMI)	45 (66,18%)	50 (73,53%)	0,350*
Stable AP	23 (33,82%)	18 (26,47%)	
Lesion type B2/C	51 (68,92%)	47 (63,51%)	0,487*
Stent diameter, mm	3,18 ±0,43/3,0‡	3,20 ±0,41†/3,0‡	0,609#
Stent length, mm	22,65 ±11,70†/19,0‡	19,39 ±9,27†/16,0‡	0,077#

† mean ± SD; ‡ median

In-stent restenosis

		PEB	EES	p
ACS, STEMI/NSTEMI		24 (35,29%)	25 (36,76%)	0,098*
Time of ISR, months		12,10±8,47†/9,0‡	16,51±9,49†/24,0‡	0,009#
ISR:	I (focal)	30 (40,54%)	21 (28,38%)	0,266*
	II (diffuse)	34 (45,95%)	35 (47,30%)	
	III (proliferative)	5 (6,76%)	8 (10,81%)	
	IV (occlusive)	5 (6,76%)	10 (13,51%)	
Cutting predilatation		16 (21,62%)	5 (6,76%)	0,010*
ISR; PEB/EES diameter, mm		3,32 ±0,39/3,5‡	3,31 ±0,43†/3,5‡	0,989#
ISR; PEB/EES length, mm		22,53 ±8,13†/20,0‡	28,47 ±12,76†/24,0‡	0,001#
Postdilatation, atm		14,84 ±2,77†/16,0‡	14,11 ±2,45†/12,0‡	0,093#
2nd stent implantation		11 (14,86%)	11 (14,86%)	1,000*

† mean ± SD; ‡ median

Pre- and post-PCI QCA

	PEB	EES	p
Preprocedural parameters:			
Minimal lumen diameter, mm	0,92±0,45†/1,00‡	0,79±0,48†/0,77‡	0,062§
Reference diameter, mm	2,64±0,47†/2,63‡	2,66±0,45†/2,66‡	0,672§
% Diameter stenosis	71,8±13,9†/70,0‡	78,0±13,4†/76,0‡	0,007§
Postprocedural parameters:			
Minimal lumen diameter, mm	2,18±0,39†/2,13‡	2,51±0,38†/2,49‡	<0,0001§
Reference diameter, mm	2,79±0,41†/2,79‡	3,01±0,40†/2,96‡	0,006§
Acute gain, mm	1,25±0,54†/1,12‡	1,72±0,47†/1,69‡	< 0,0001§
% Diameter residual stenosis	19,5±7,4†/20,0‡	16,3±5,9†/16,0‡	0,005§

12 months QCA and clinical follow-up

	PEB	EES
12-M visit	68	68
12-M QCA-pts	63/ 92,6% (95% CI: 83,7% -97,6%)	62/ 91.2% (95% CI: 81.78–96.69)
12-M QCA- lesions	69/ 93,2% (95% CI: 84,9% - 97,8%)	68/ 91,9% (95% CI: 83,2% - 97%)

p = 0,753

12 months QCA parameters

	PEB	EES	p
Minimal lumen diameter, mm	2,09±0,57†/2,13‡	2,07±0,80/†2,23‡	0,481§
Reference diameter, mm	2,81±0,48†/2,81‡	2,96±0,50†/2,86‡	0,188§
% Diameter stenosis	26,2±18,0†/22,0‡	30,9±24,6†/21,5‡	0,816§
Late lumen loss, mm	0,09±0,44†/0,02‡	0,44±0,73†/0,19‡	0,0004 §
Binary restenosis (%DS>50%)	6 (8,7%)	13 (19,12%)	0,078♯

§ nonparametric Mann–Whitney U test

Subgroup analysis of 12 months LLL

		PEB	EES	p §
ISR length >10 mm	LLL (mm)	0,16±0,50†/0,05‡	0,53±0,67†/0,26‡	0,0002
Vessel diameter < 3 mm	LLL (mm)	0,12±0,48†/0,05‡	0,42±0,63†/0,16‡	0,003
Diabetes mellitus	LLL (mm)	0,12±0,33†/0,06‡	0,48±0,86†/0,12‡	0,254

12 months clinical follow-up

	PEB	EES	p
MACE all	7 (10,29%)	13 (19,12%)	0,213§
CV death	1 (1,47%)	1 (1,47%)	1,000§
Nonfatal MI	1 (1,47%)	1 (1,47%)	1,000§
TVR	5 (7,35%)	11 (16,18%)	0,110§
Definite stent thrombosis	1 (1,45 %)	0 (0%)	1,000♯
Event-free survivors	61 (89,71%)	55 (80,88%)	0,110§

TIS trial summary

- **Non-inferiority but also superiority of PEB vs EES**
- **12 months LLL in PEB group significantly lower vs EES group**
- **No significant difference in Binary restenosis and 12 months MACE**

RIBS V trial

- 190 pts with BMS-ISR
- iopromide-coated PEB (Sequent Please) vs. EES (Xience, Co/Cr)
- 9-M angio(QCA) and 12-M clinical follow up

	PEB	EES	p
MLD, mm	2,01+/- 0,6	2,36 +/-0,6	p < 0,001
%DS	25+/-20%	13+/-17%	p < 0,001
LLL, mm	0,14+/- 0,5	0,04+/- 0,5	p = 0,14
binary ISR	9,5%	4,7%	p = 0,22
12 M MACE	8%	6%	p = 0,6

Alfonso, J Am Coll Cardiol 2014; 63: 1378-86

DES-ISR

- **More neoatherosclerosis**
- **Treatment of DES-ISR: worse results than in BMS-ISR**

- **Habara et al:**

  subanalysis – signific ↑ LLL (0,18 vs. 0,05mm; p = 0,03) and binary restenosis (9,1 vs. 1,1%, p= 0,04) vs BMS-ISR

- **SeQuent Please World Wide Registry:**

  signific ↑ TLR (9,6 vs. 3,8%; p<0,001) and MACE (11,3 vs. 5,6%; p<0,001) vs BMS-ISR

- **DEB ~ DES**

BVS Restenosis (ScR)

Subanalysis of GHOST-EU registry:

- 14 ScR - 3,6%; 60% focal, 20% diffuse
- Due to: underexpansion (in diffuse), 1x geografic miss
- treatment: 45% DEB, 35% DES, 15% POBA – NC postdilatation, another BVS (1x) 5%

Conclusions

- High minimal lumen diameter (MLD)
- PEB similar to DES
- Different types of PEB and DES
- PEB better when ≥2 stent layers
- DES better when edge disease
- OCT, IVUS

Summary

- **BMS-ISR** **PEB, DES**
- **DES-ISR** **PEB, another DES**
- **ScR** **PEB, DES (OCT)**

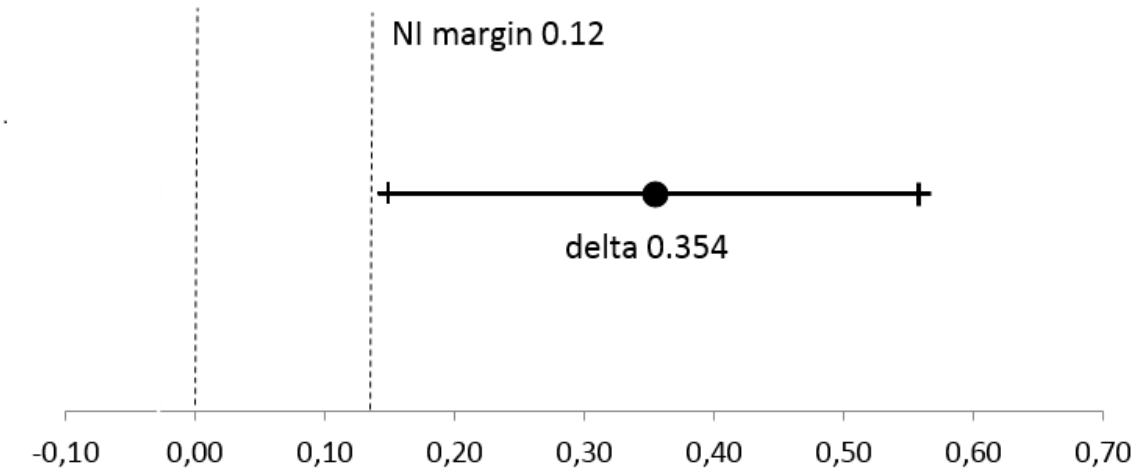
Restenosis in BVS (ScR)

- **Most trials - endpoints: TLF (CV death +TV-MI+ TLR)**
- **ABSORB II :** TLF 5%
- **ABSORB III:** TLF 7,4% /12M - non-inferior vs. EES
- **GHOST EU registry:** TLF 2,2% - 1M and 4,4% - 6M, 1 year prediction - 10%

Logistic regression analysis

	Adjusted OR	95% CI	p
Diabetes mellitus (1=yes, 0=no)	2,045	0,611 – 6,842	0,246
Renal insufficiency (1=yes, 0=no)	-	-	0,999
Type B2/C lesion (1=yes, 0=no)	1,661	0,528 – 5,224	0,386
PEB =1 / EES =2	3,132	1,058 – 9,269	0,039
Vessel diameter <3 mm (1=yes, 0=no)	2,283	0,558 – 9,343	0,251
ISR length >10 mm (1=yes, 0=no)	1,975	0,587 – 6,646	0,272

Non-inferiority study



The 2-sided 95% confidence interval for the difference between treatments in LLL (0,149 - 0,558) and the non-inferiority margin (0,12) non-inferiority but also superiority of PEB vs EES

Event-free survival