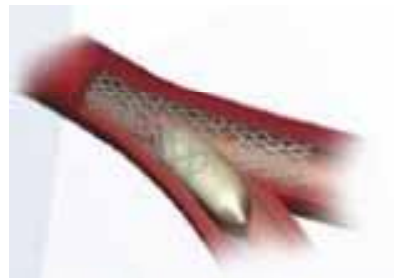


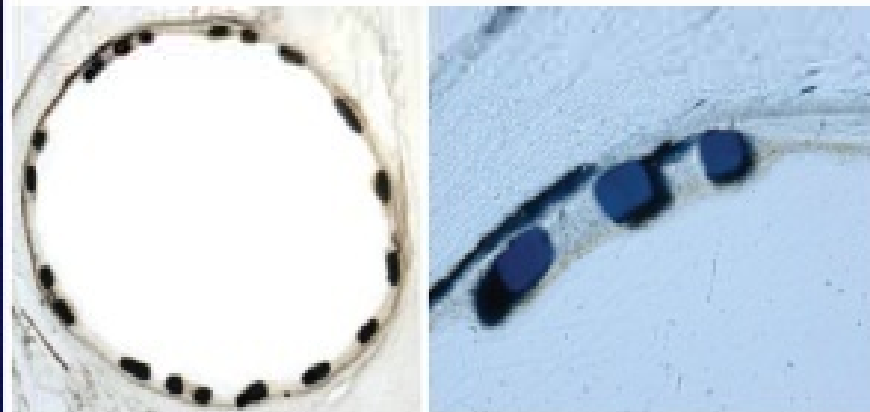
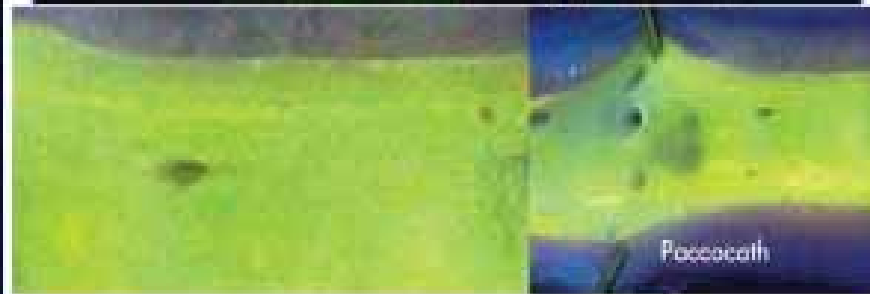
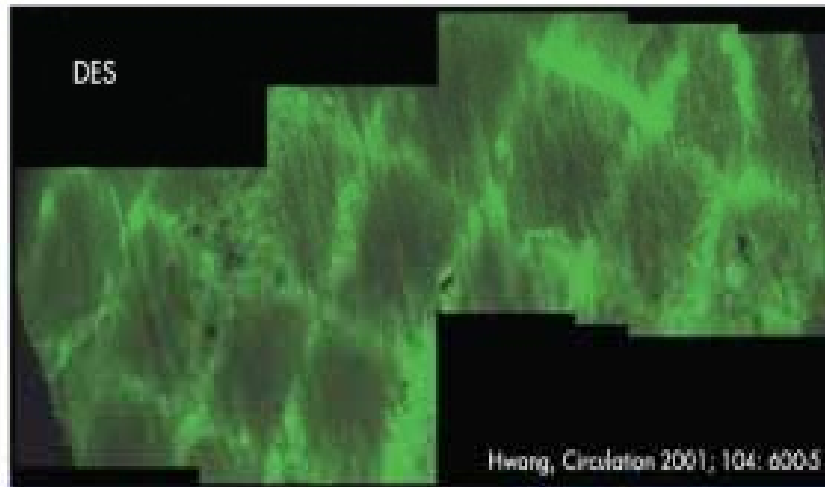
Drug Eluting Balloons for Bifurcation Lesions : Which Role ?

I Sheiban

University of Torino / Italy

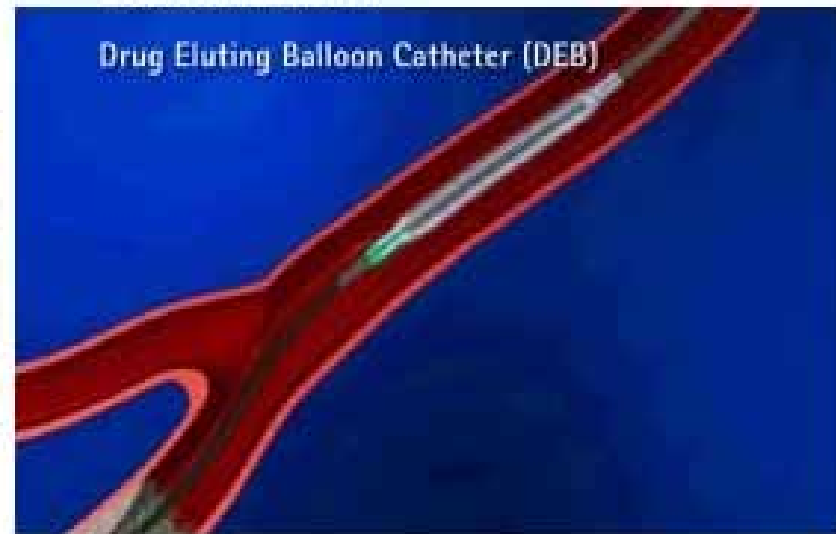
E-mail: isheiban@yahoo.com





Drug-Eluting Stent

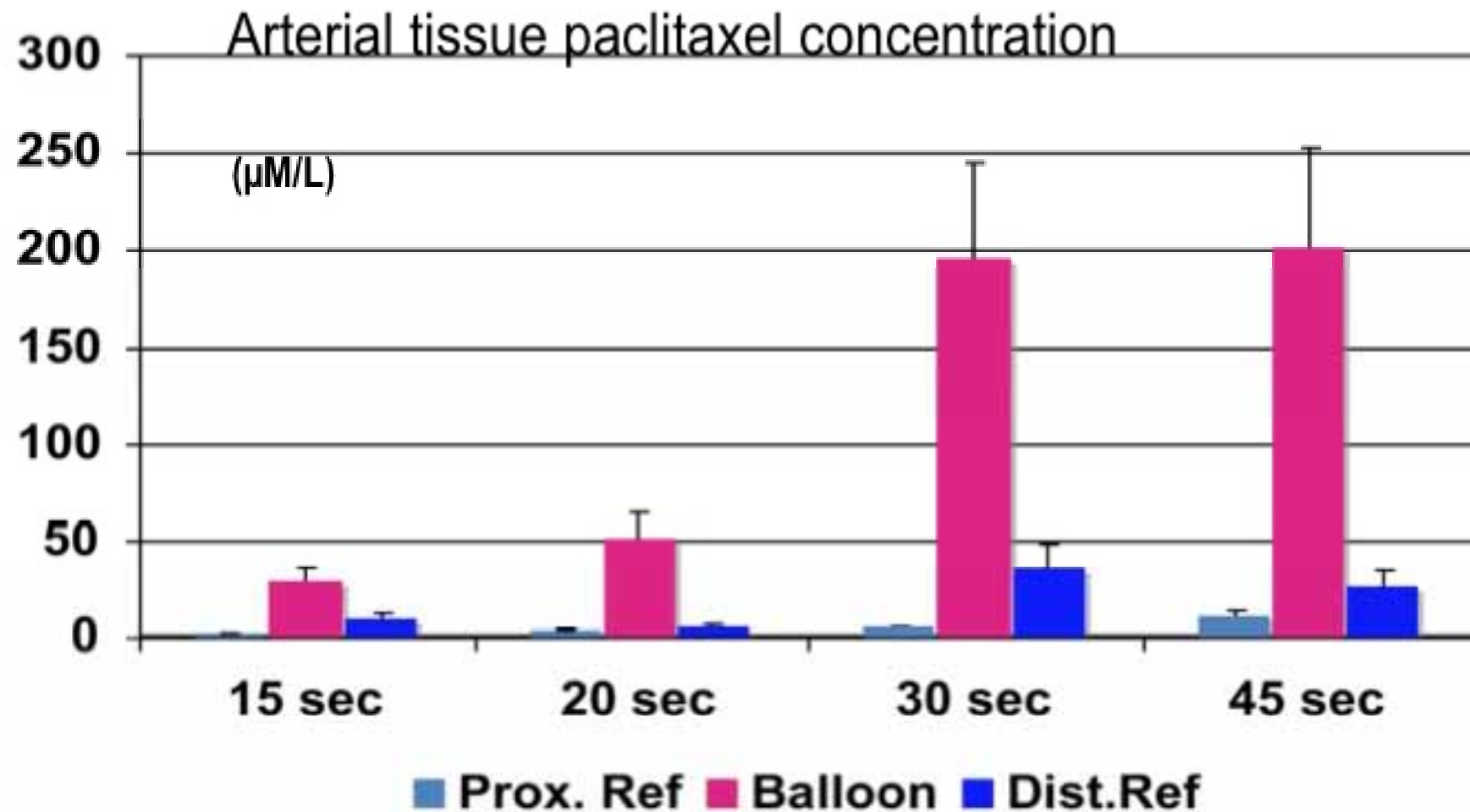
- Slow release
- Persistent drug exposure
- ~ 100 - 200 μg dose
- Polymer
- Stent mandatory



Drug-Eluting Balloon (PACCOCATH)

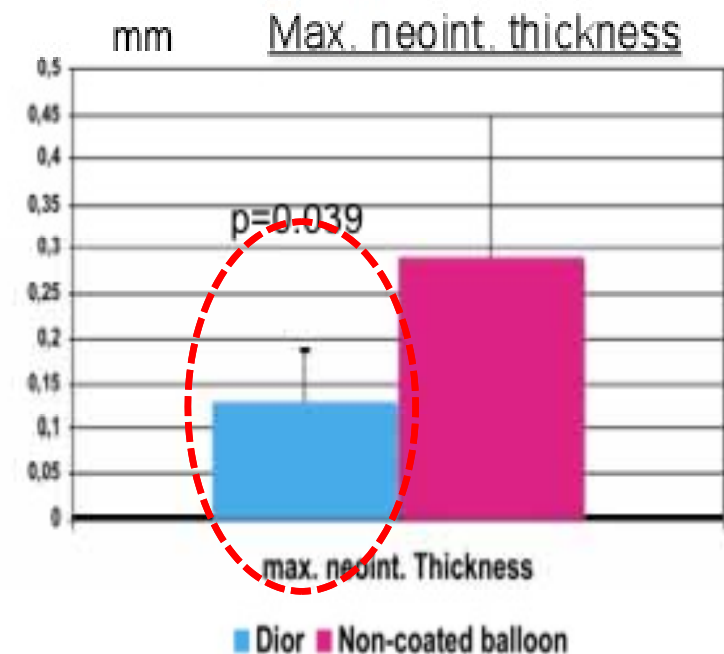
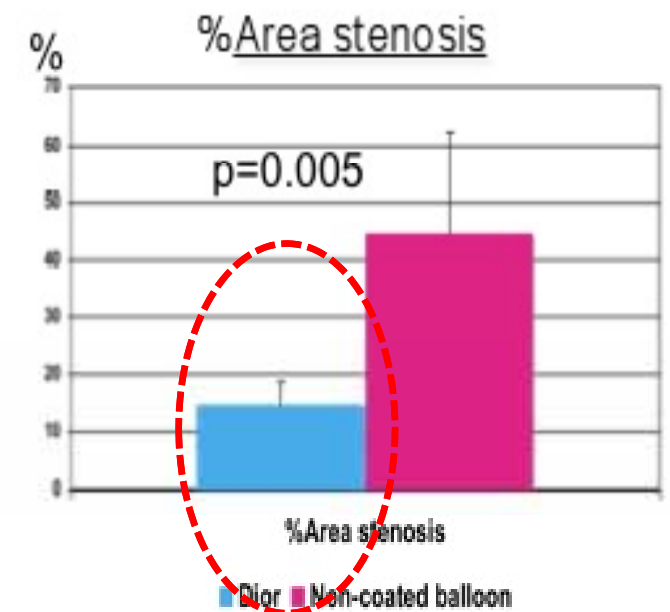
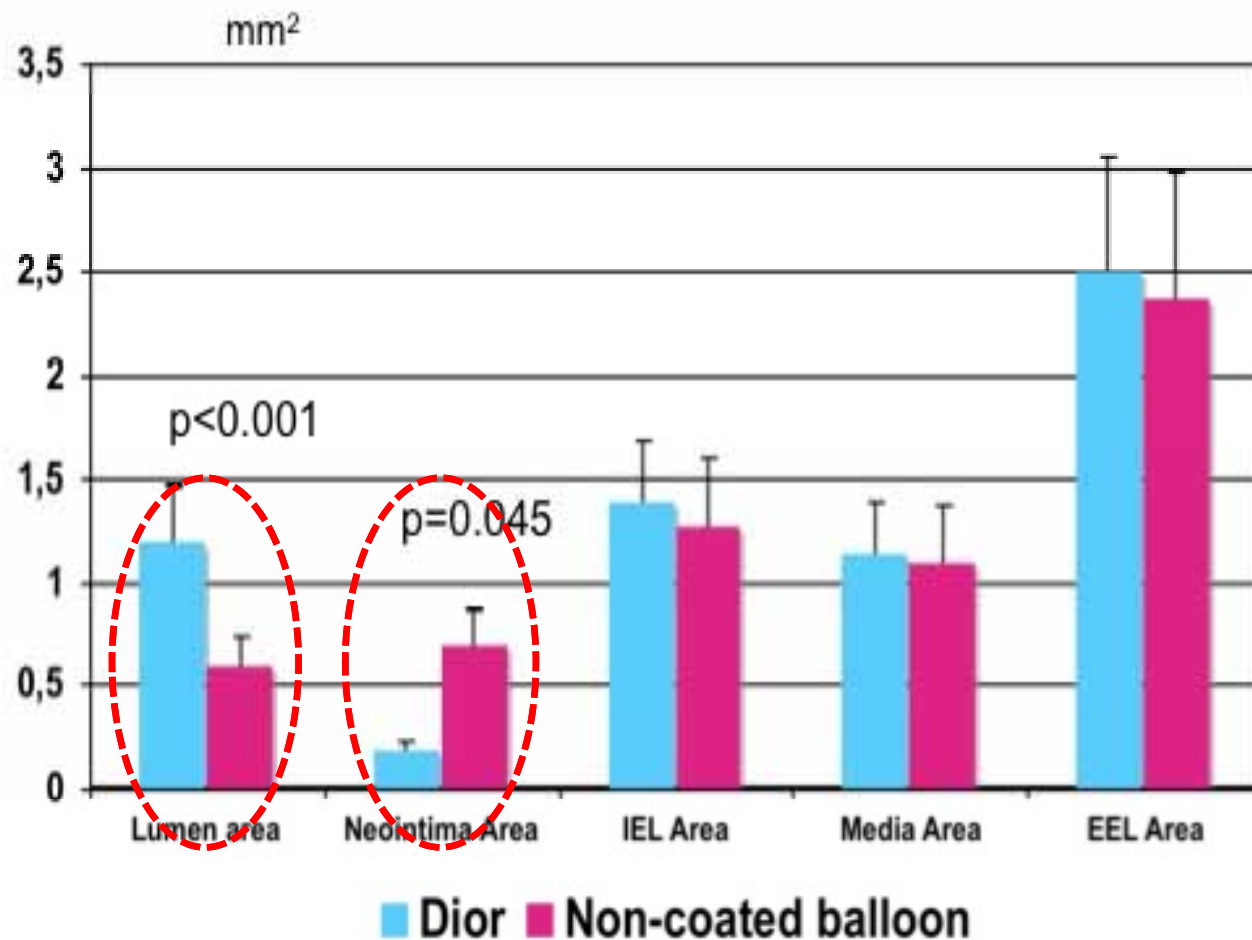
- Immediate release
- Short-lasting exposure
- ~ 300 - 600 μg dose
- No polymers
- Premounted stent optional

Time-dependent tissue concentrations of paclitaxel from the Dior balloon N=29**



** Gyöngyösi et al

Quantitative histological results N=12 **



****Gyöngyösi et al**

CE-certified Drug-Eluting Balloons (DEB)

Technology and Applications

Product*	Excipient	Company
DIOR-II	Shellac	EuroCor
In.Pact Falcon	Urea	Medtronic
Pantera Lux	BTHC	Biotronik
SeQuent Please	Iopromide	B Braun

***all are Paclitaxel-eluting DEB**

Appropriate Technique to use a Drug-Eluting Balloon (DEB)

DEB is a system for angioplasty deliver drug into the arterial wall.

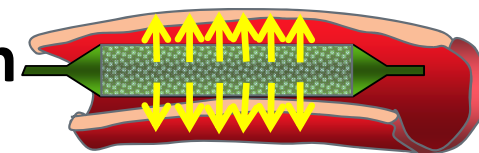
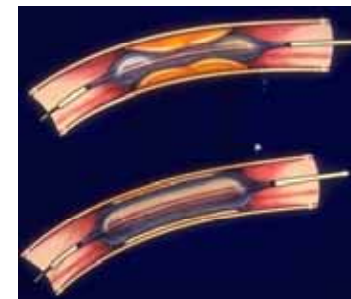
Consequently different steps should be followed:

1. *Predilate* the lesion with a conventional angioplasty balloon

2. Try to obtain a „*stent-like result*“ result with angioplasty

3. Choose a DEB a bit *longer* than the angioplasty balloon to avoid „geographical miss“.

4. *Inflate the DEB* to the nominal pressure and for the recommended inflation time.



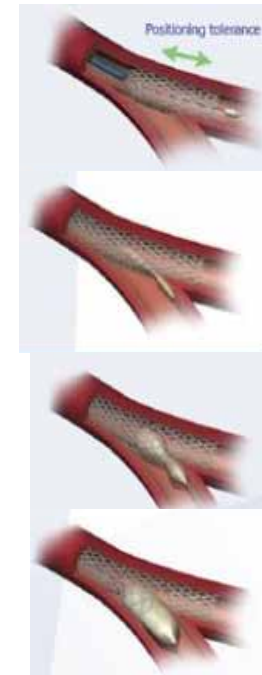
Potential Advantages of DEB

- **Local drug delivery over very short period of time : not weeks /months**
- **Avoid chronic inflammation due to absence polymers**
- **Better re-endothelialization: reduced dual antiplatelet therapy**
- **No distortion of original vessel anatomy (BIF)**
- **No double / triple metal layers in case of ISR or BIF**
- **Easy lesion crossing / deliverabilityby balloon only**

DEB & Bifurcation

What Are The Clinical Scenarios Where DEB Strategy Can Have a Clear Advantage ?

- **Vulnerable Plaque-AMI**
- **Bifurcation Lesions**
- **In-stent Restenosis**
- **Small Vessel Disease**



Where ST Risk is Potentially Increased with the use of DES

SOME Clinical Data on the use of DEB for :

- **ISR**
- **Bifurcation**
- **Small Vessels**
- **Native « De Novo » lesions**

Some Clinical Data on the use of DEB for :

- **ISR**
- Bifurcation
- Small Vessels
- Native « De Novo » lesions

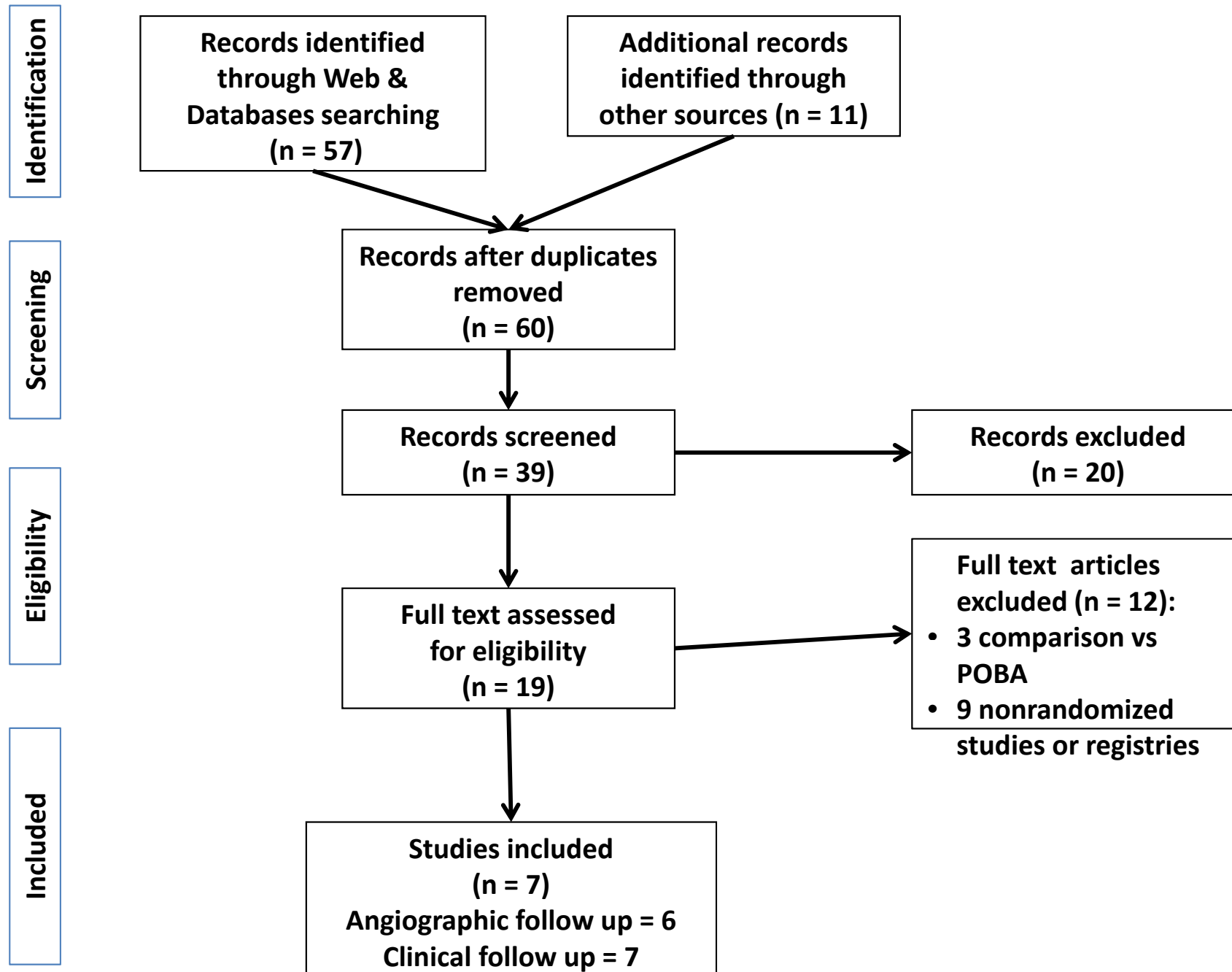
Drug-eluting Balloons (DEB) for In-Stent Restenosis after Bare Metal Stents (BMS) or Drug-eluting Stents (DES)

Product*	Excipient	Company	Study
DIOR-II	Shellac	EuroCor	VALENTINES-I
In.Pact Falcon	Urea	Medtronic	Registry
Pantera Lux	BTHC	Biotronik	PEPPER DELUX
SeQuent Please	Iopromide	B Braun	PEPCAD-II SES-ISR

Drug-eluting Balloons (DEB) for In-Stent Restenosis after Bare Metal Stents (BMS) or Drug-eluting Stents (DES)

DEB	Study	Time of TLR	TLR BMS-ISR	TLR DES-ISR
DIOR-II	VALENTINES-I	9 months	5.1 % (of 157 pats)	10.8 % (of 83 pats)
In.Pact Falcon	Registry	6 months	4.3 % (of 26 pats)	_____
Pantera Lux	PEPPER	12 months	2.4 % (of 41 pats)	17.1 % (of 35 pats)
	DELUX	6 months	2.0 % (of 277 pats)	6.6 % (of 248 pats)
SeQuent Please	PEPCAD-II	12 months	6.3 % (of 66 pats)	_____
	SES-ISR	6 months	_____	4.3 % (of 25 pats)
	WWR	9 months	3.8 % (of 730 pats)	9.6 % (of 457pats)

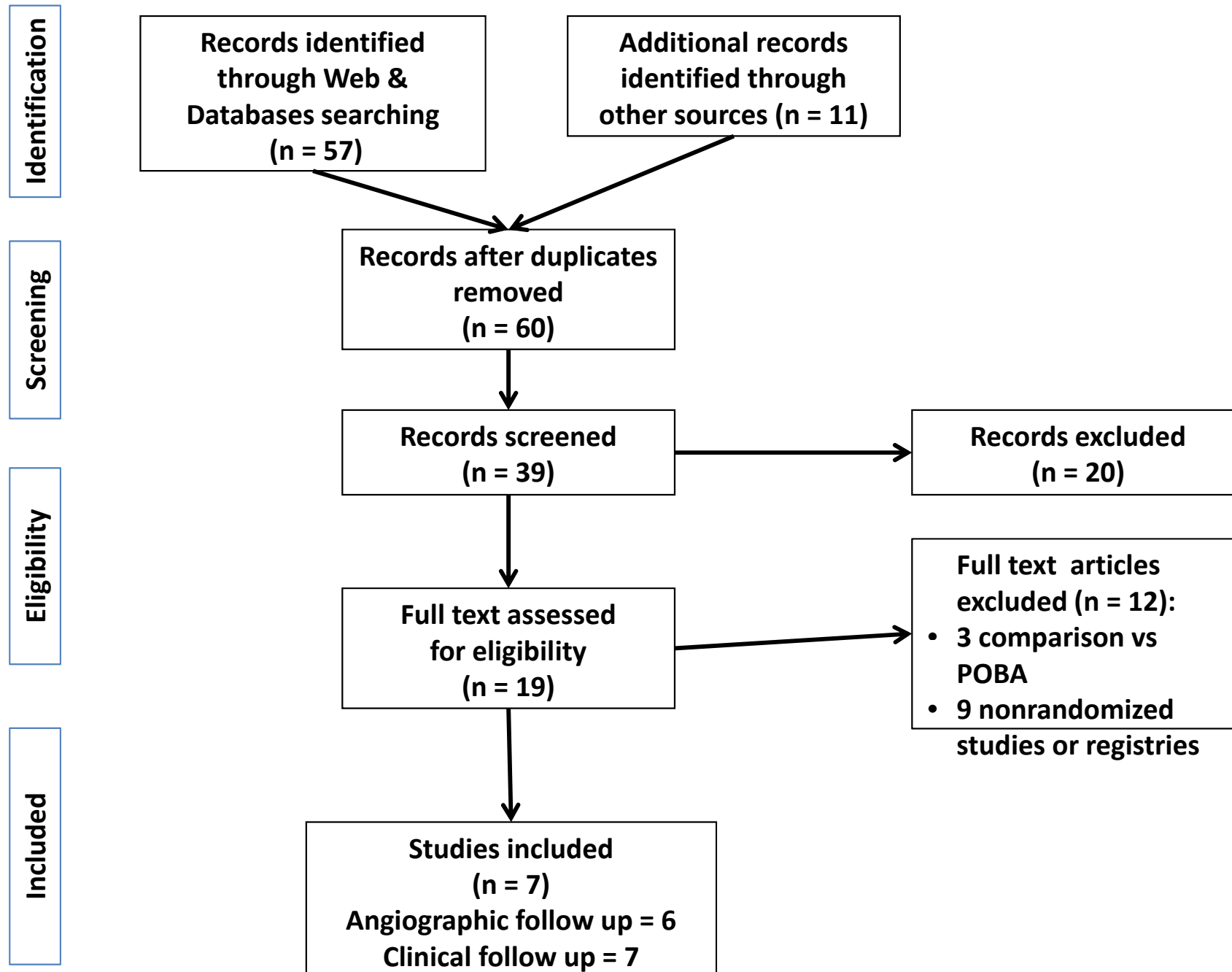
Drug eluting balloon versus drug eluting stent in percutaneous coronary interventions: insights from a meta-analysis of 1462 patients



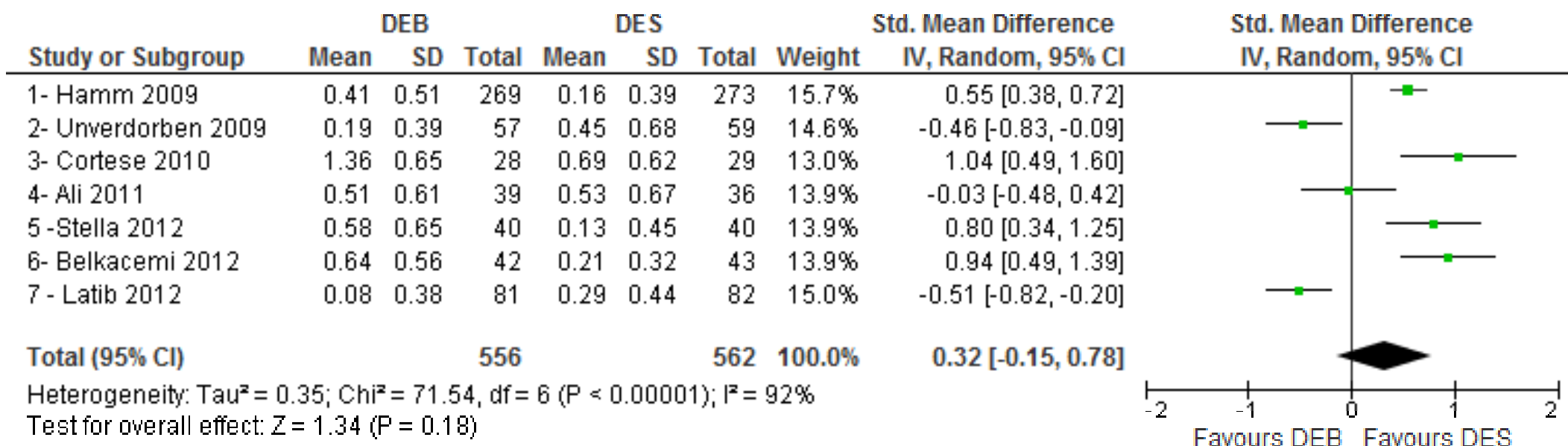
Drug eluting balloon versus drug eluting stent in percutaneous coronary interventions: insights from a meta-analysis of 1462 patients

Author	Year	Journal	RCT	Eponim	Patients	Inclusion criteria	Exclusion	Comparison	DEB	DES	Diabet es	AC S	Follow up	Angiogram hic follow up
Hamm	2009	AHA 2009	yes	PEPCAD III	637	De novo stenoses; CSA, UA, silent ischemia	STEMI, NSTEMI, CTO, ISR, bifurcation	DEB (plus 100% BMS) vs DES	SEQuent Please	Sirolimu s	175 (27.5%)	na	9 months	85.1%
Unverdorben	2009	Circulation	yes	PEPCAD II	131	ISR	STEMI, NSTEMI, bifurcation	DEB (plus 7,5% BMS) VS DES	SEQuent Please	Paclitax el	39 (29.8%)	33	12 months	88.6%
Cortese	2010	Heart	yes	PICCOLETO	60	Small vessels; de novo stenoses; CSA, UA, silent ischemia	STEMI, CTO, ISR, bifurcation	DEB (plus NA% BMS) VS DES	DIOR	Paclitax el	24 (40.0%)	na	9 months	95%
Ali	2011	Eurointervention	yes	PEPCAD IV	84	Diabetes; CSA, UA, silent ischemia	STEMI, CTO, ISR, bifurcation	DEB (plus 100% BMS) vs DES	SEQuent Please	Paclitax el	84 (100.0%)	10	6 months	89.3%
Stella	2012	Catheter Cardiovasc Interv	yes	DEBIUT	120	Bifurcations; de novo stenoses; CSA, UA, silent ischemia	STEMI, CTO	DEB (plus 100%BMS) vs DES	DIOR	Paclitax el	13 (10.8%)	na	12 months	100%
Belkacemi	2012	J Am Coll Cardiol	yes	DEBAMI	150	All comers STEMI	diabetes plus type C lesion, LM, 3 vessel disease	DEB (plus 100%BMS) vs DES	DIOR	Paclitax el	11 (7,3%)	150	6 months	84.7%
Latib	2012	J Am Coll Cardiol	yes	BELLO	182	Small vessels; de novo stenoses; CSA, UA, silent ischemia	STEMI, CTO, ISR, bifurcation	DEB (plus 21% BMS) VS DES	IMPACT	Paclitax el	74 (40,7%)	42	6 months	89.6%
Mieres	2012	Cardiovasc Rev Med	no	DEAR	316	Diabetes; CSA, UA, silent ischemia	STEMI	DEB (plus 95,6% BMS) VS DES	DIOR	miscellanea	316 (100.0%)	214	12 months	na

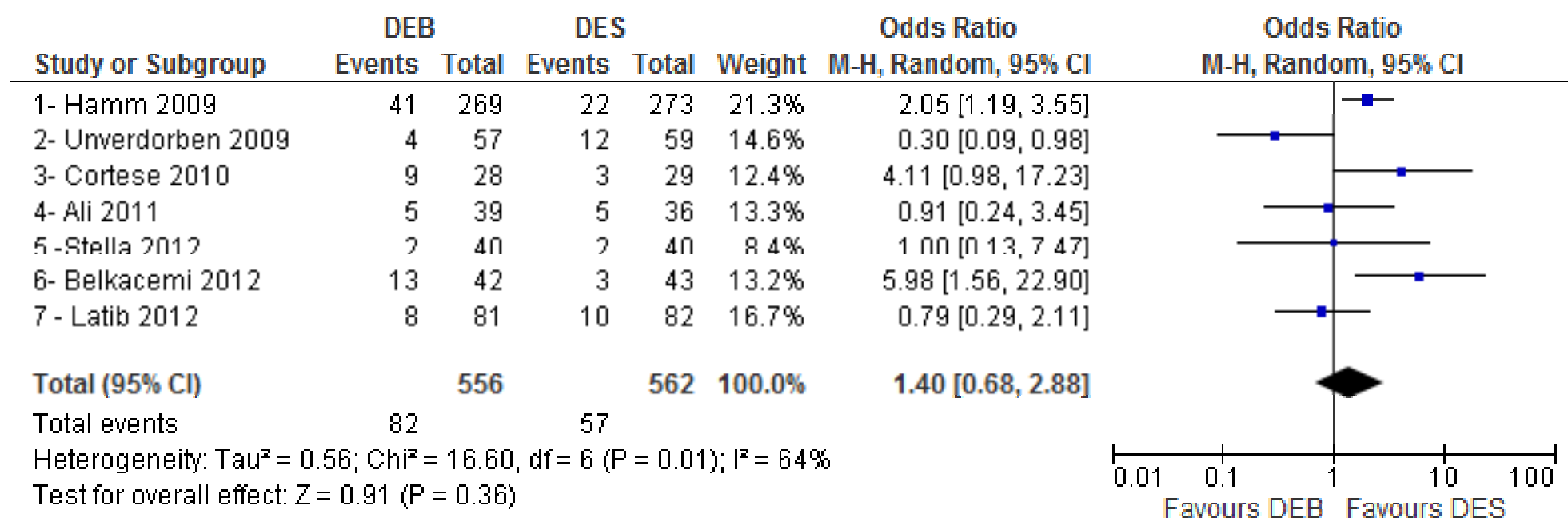
Drug eluting balloon versus drug eluting stent in percutaneous coronary interventions: insights from a meta-analysis of 1462 patients



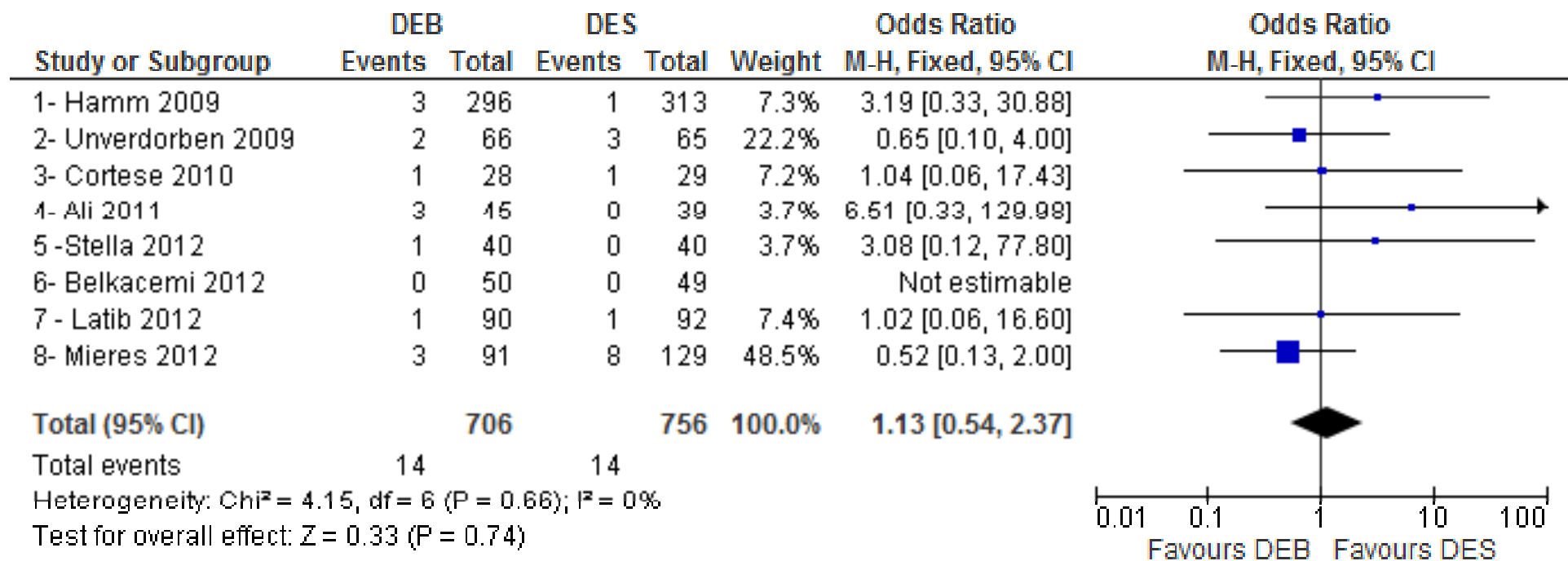
Late lumen loss



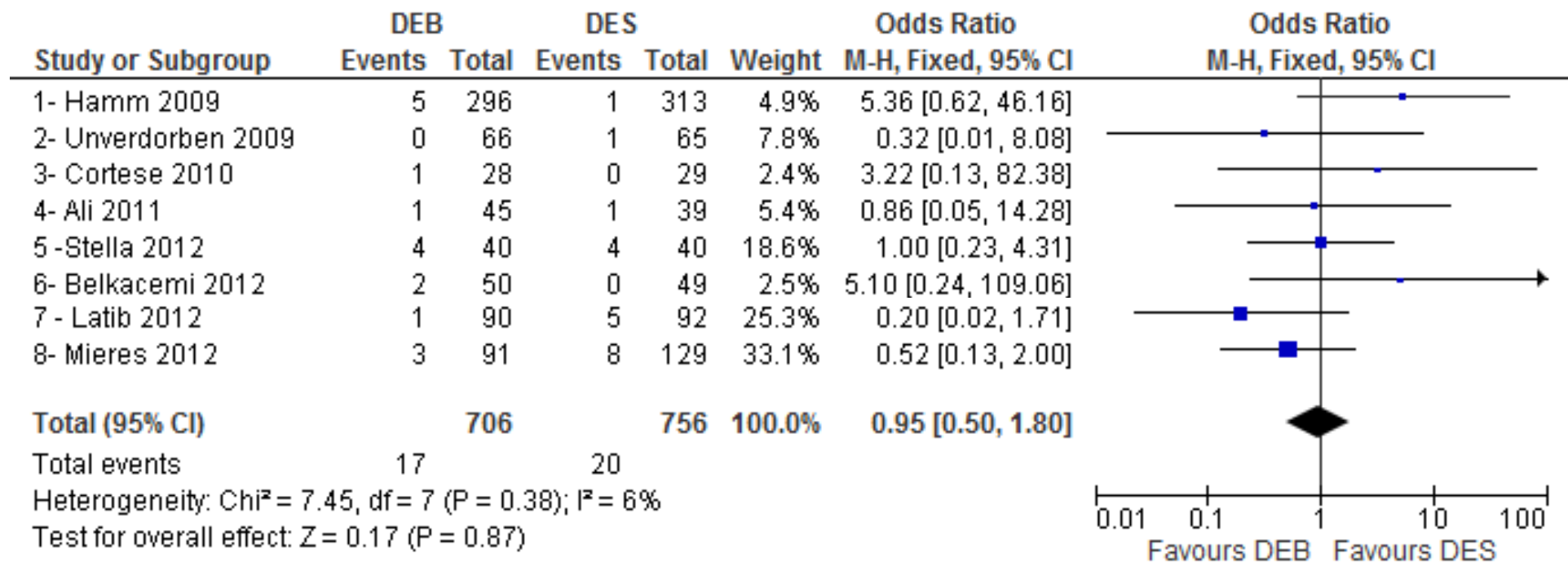
Binary restenosis



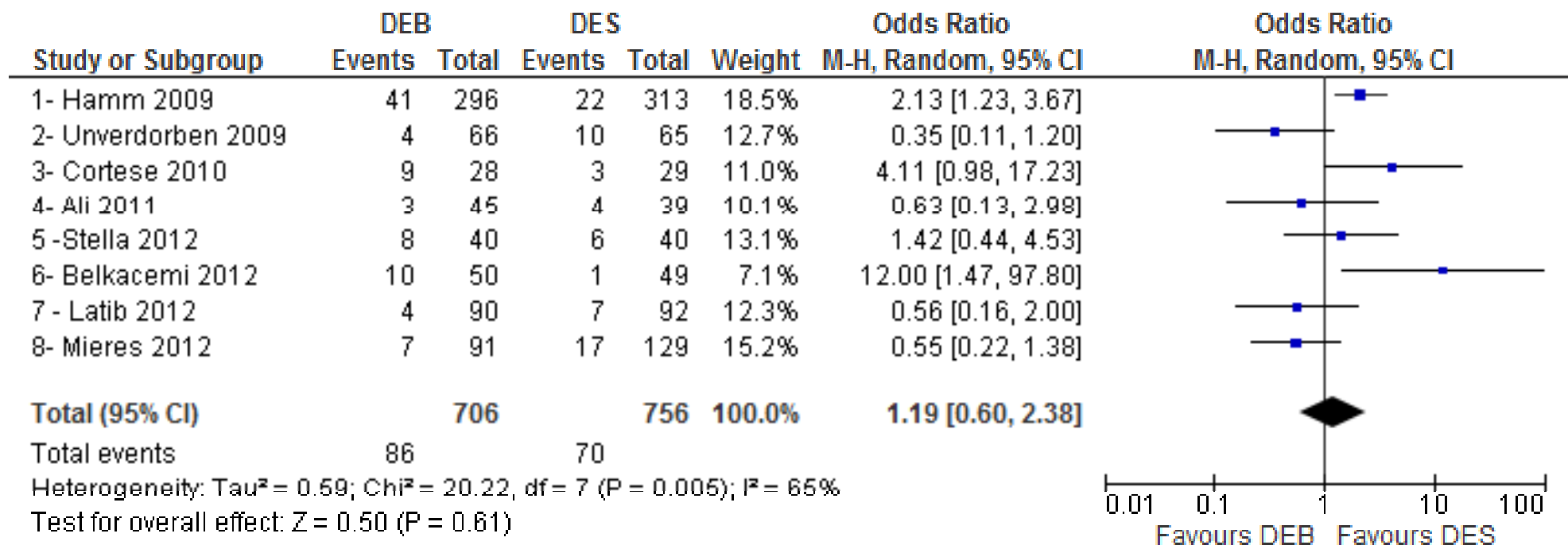
Overall death



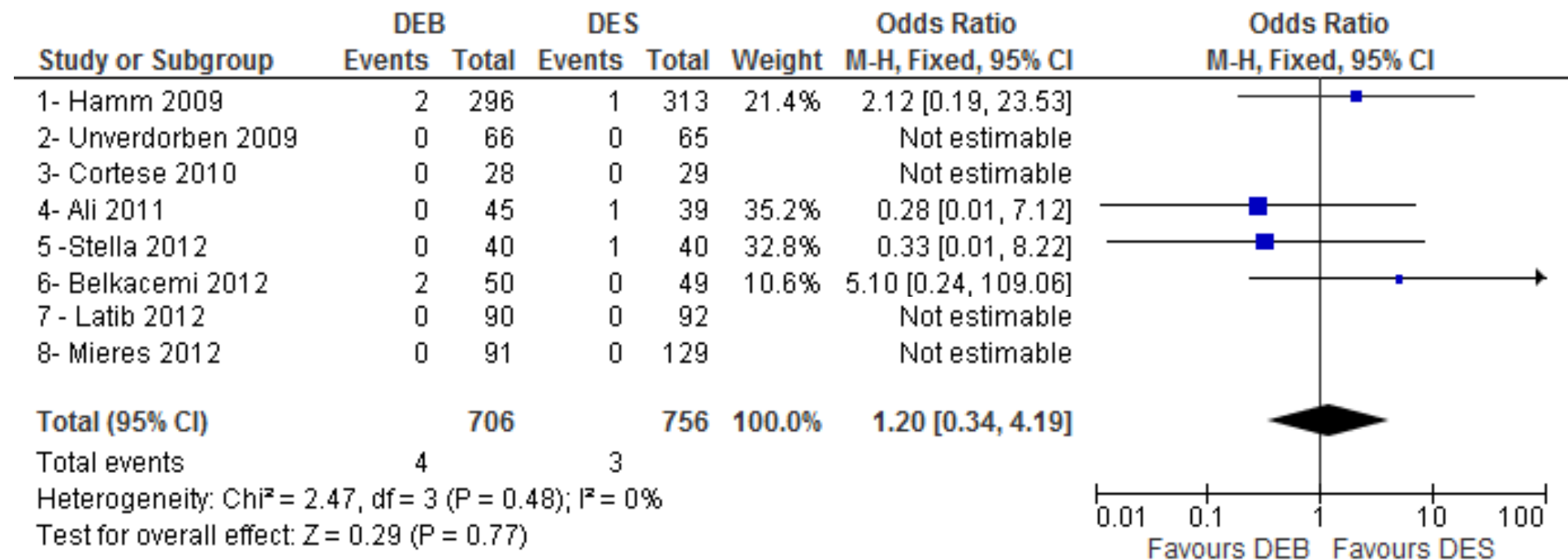
Myocardial Infarction



Target lesion revascularization



PCI vessel thrombosis





Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: William Wijns (Chairperson) (Belgium)*, Philippe Kolh (Chairperson) (Belgium)*, Nicolas Danchin (France), Carlo Di Mario (UK), Volkmar Falk (Switzerland), Thierry Folliguet (France), Scot Garg (The Netherlands), Kurt Huber (Austria), Stefan James (Sweden), Juhani Knuuti (Finland), Jose Lopez-Sendon (Spain), Jean Marco (France), Lorenzo Menicanti (Italy), Miodrag Ostojic (Serbia), Massimo F. Piepoli (Italy), Charles Pirlet (Belgium), Jose L. Pomar (Spain), Nicolaus Reifart (Germany), Flavio L. Ribichini (Italy), Martin J. Schalij (The Netherlands), Paul Sergeant (Belgium), Patrick W. Serruys (The Netherlands), Sigmund Silber (Germany), Miguel Sousa Uva (Portugal), David Taggart (UK)

Procedural aspects of PCI

Specific PCI devices

	Class	Level
Manual catheter thrombus aspiration should be considered during PCI of the culprit lesion in STEMI.	Ila	A
For PCI of unstable lesions, intravenous abciximab should be considered for pharmacological treatment of no-reflow.	Ila	B
Drug-eluting balloons* should be considered for the treatment of in-stent restenosis after prior BMS.	Ila	B
Cutting or scoring balloons may be considered for dilatation of in-stent restenosis, to avoid slipping-induced vessel trauma of adjacent segments.	IIb	C

*Recommendations are only valid for specific devices with proven efficacy/safety profile, according to the respective lesion characteristics of the studies.

Some Clinical Data on the use of DEB for :

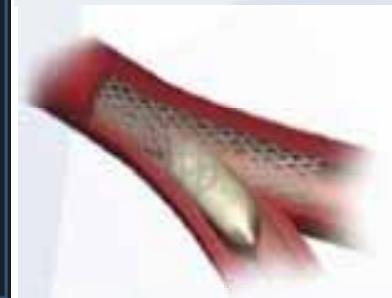
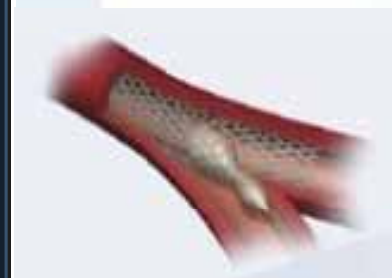
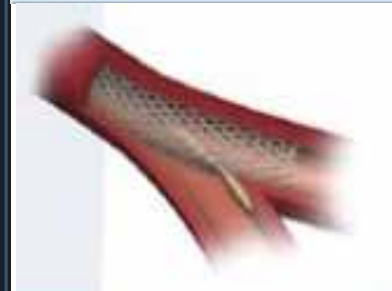
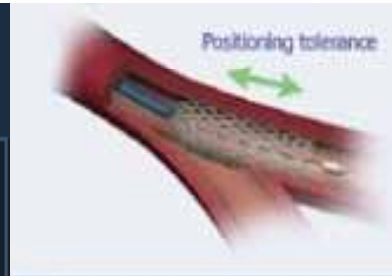
- ISR
- **Bifurcation**
- Small Vessels
- Native « De Novo » lesions

Simple Techniques

Provisional

When SB has minimal disease or only at the ostium AND when SB is suitable for stenting

- **6 Fr guiding catheter (7F if using Xience-Promus)**
 1. Wire both branches
 2. Dilate MB and SB if needed
 3. Stent MB leaving a wire in the SB
 4. Re-wire SB and then remove jailed wire
 5. Kissing balloon inflation
 6. Stent SB **only** if suboptimal result (TAP, reverse crush, culotte)

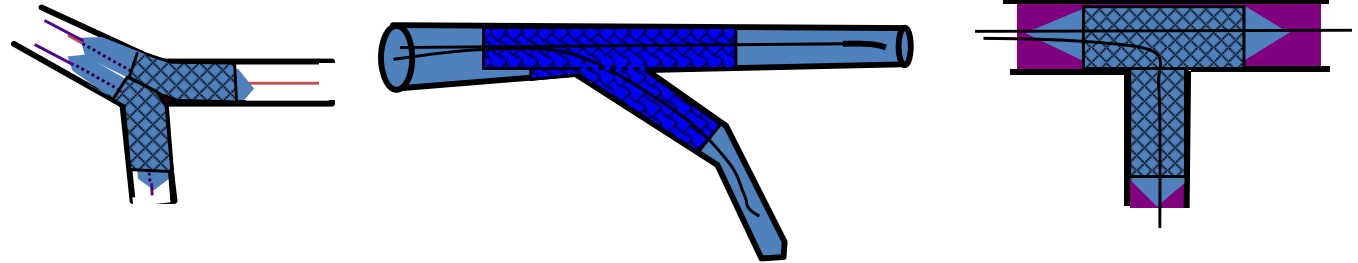


Can be performed in almost 80% of bifurcation lesions , but but with
high rate of restenosis and TLR

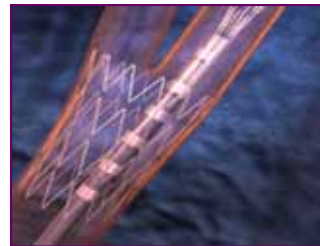
Complex Techniques

2-stent approaches

- T stenting
- Crush
- SKS
- Coulotte
- V Stenting



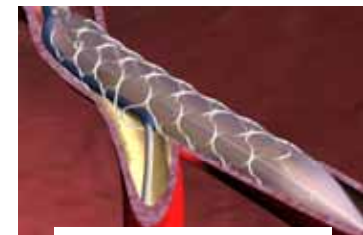
Dedicated Bifurcation Stents



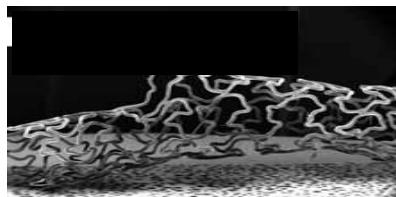
Biosensors (+ BA9)



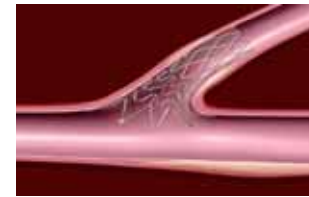
Guidant Frontier



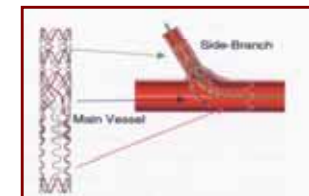
YMed Sidekick



Taxus Liberte + Petal



Tryton SB Stent



Cappella Sideguard

Associated with similar restenosis or TLR and higher MACCE rates and stent thrombosis as compared to provisional stenting

Meta-Analysis

EuroIntervention

Bifurcation stenting with drug-eluting stents: a systematic review and meta-analysis of randomised trials

Somjot S. Brar^{1,2*}, MD; William A. Gray^{1,2}, MD; George Dangas^{1,2}, MD, PhD; Martin B. Leon^{1,2}, MD; Vicken J. Aharonian³, MD; Simerjeet K. Brar³, BS; Jeffrey W. Moses^{1,2}, MD

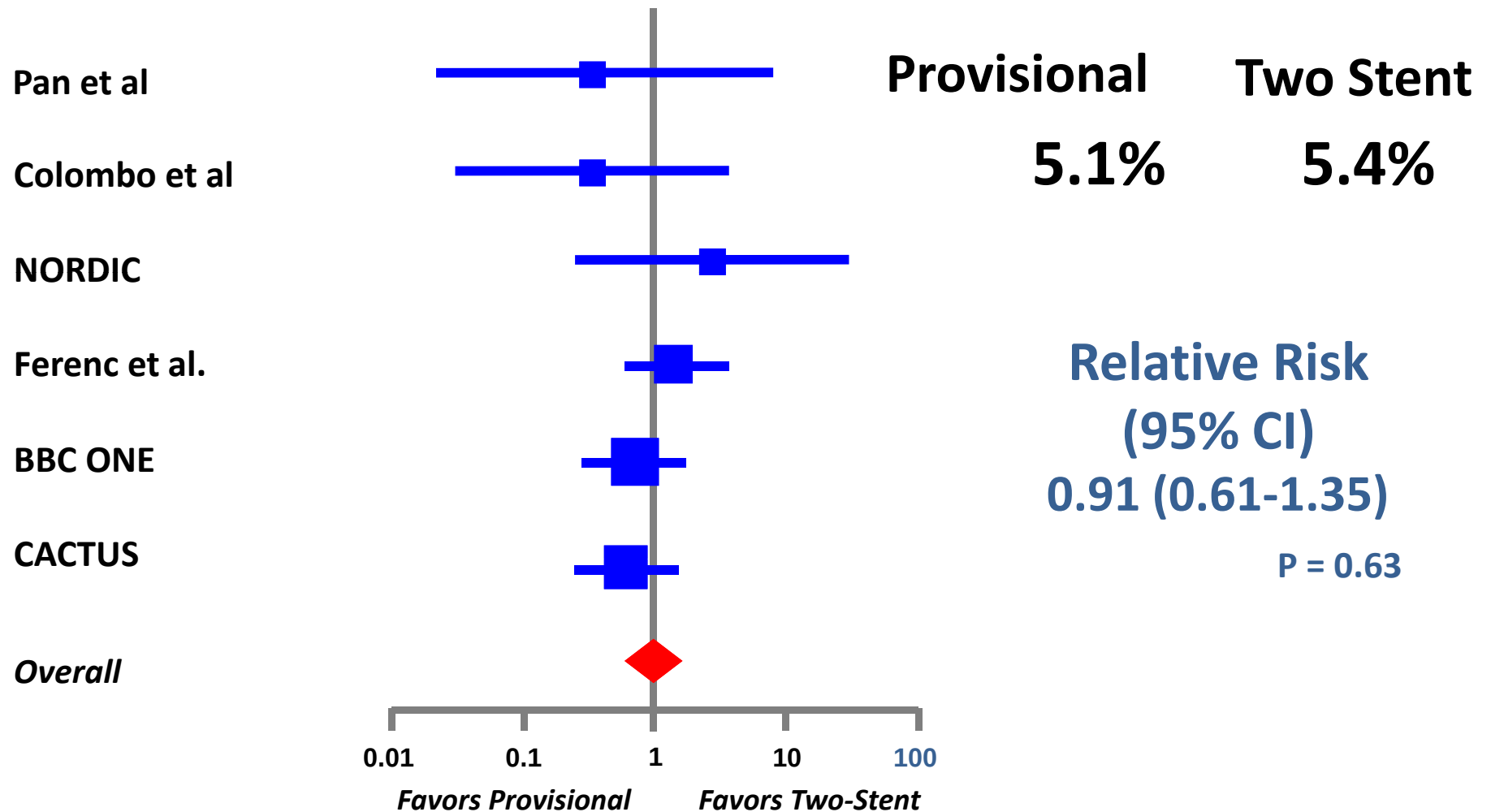
1. Center for Interventional Vascular Therapy, Columbia University Medical Center, New York, NY, USA; 2. Cardiovascular Research Foundation, New York, NY, USA; 3. Regional Cardiac Catheterisation Laboratory, Kaiser Permanente, Los Angeles, CA, USA

1 or 2 Stents: Randomized Trials

Study	No. Pat-ients	Two-stent Strategy	Type of DES	Thienopyridine duration, mo	Intention to Treat	Angio F/U (months)	Clinical F/U (months)
Pan et al	91	Any	SES	12	Yes	6	11
Colombo et al	85	Any	SES	3	No	6	6
NORDIC	413	Any	SES	6-12	Yes	8	6
Ferenc et al.	202	T-stenting	SES	6-12	Yes	9	12, 24
BBC ONE	500	Crush or Culotte	PES	9	Yes	–	9
CACTUS	350	Crush	SES	6	Yes	6	6, 12

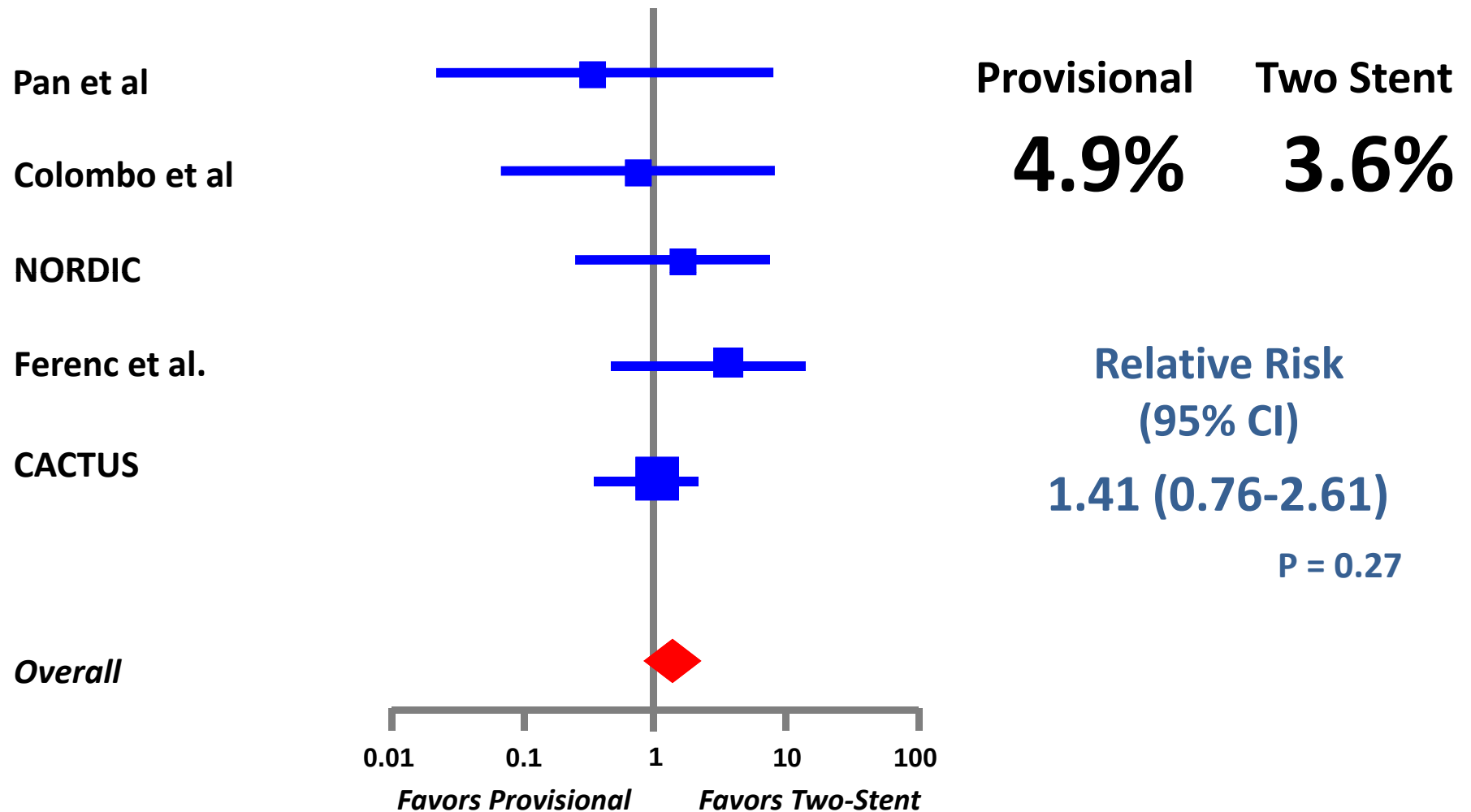
Bifurcation Stenting Meta-Analysis

Target Lesion Revascularization



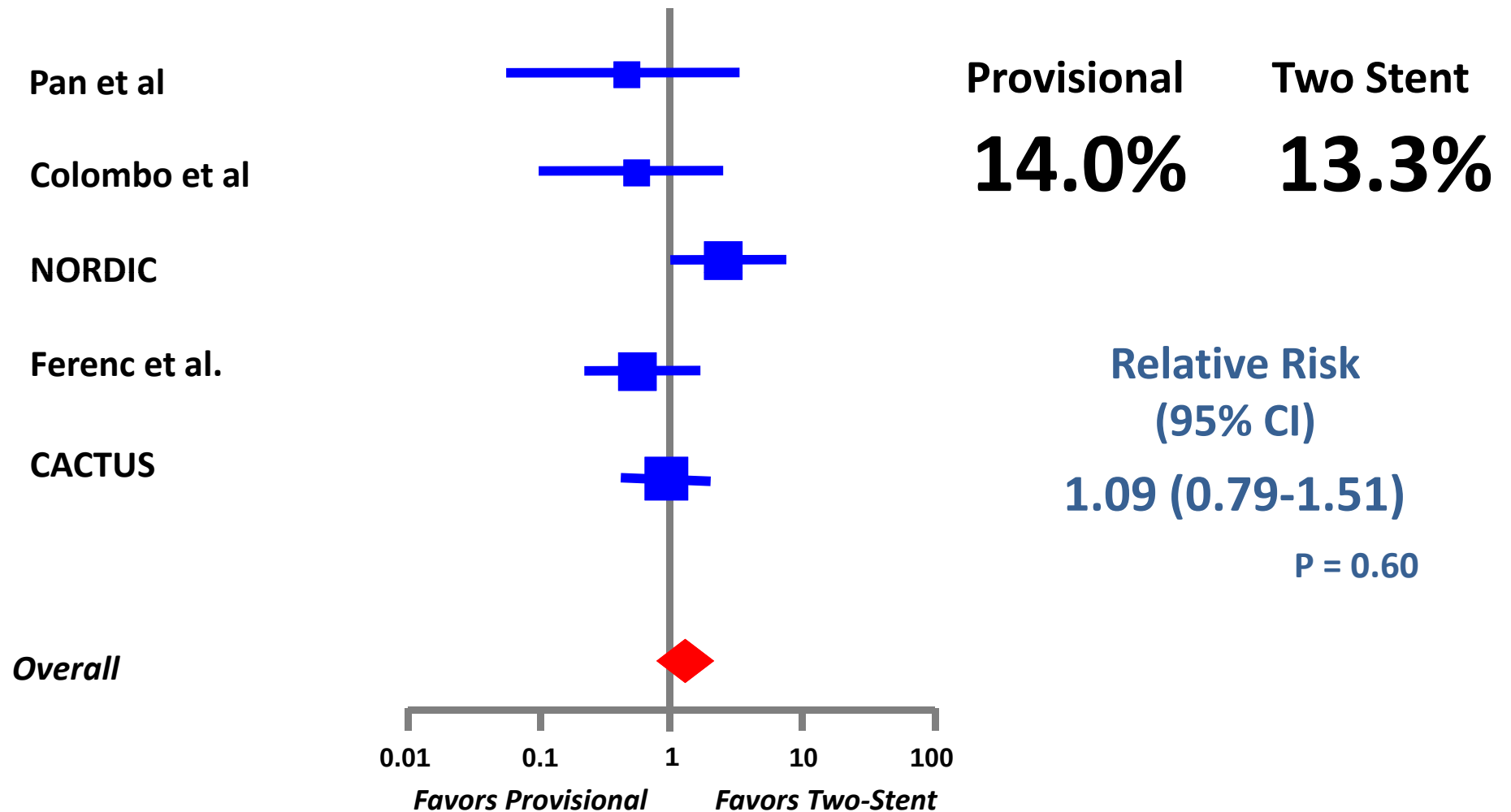
Bifurcation Stenting Meta-Analysis

Main Branch Stenosis



Bifurcation Stenting Meta-Analysis

Side Branch Stenosis

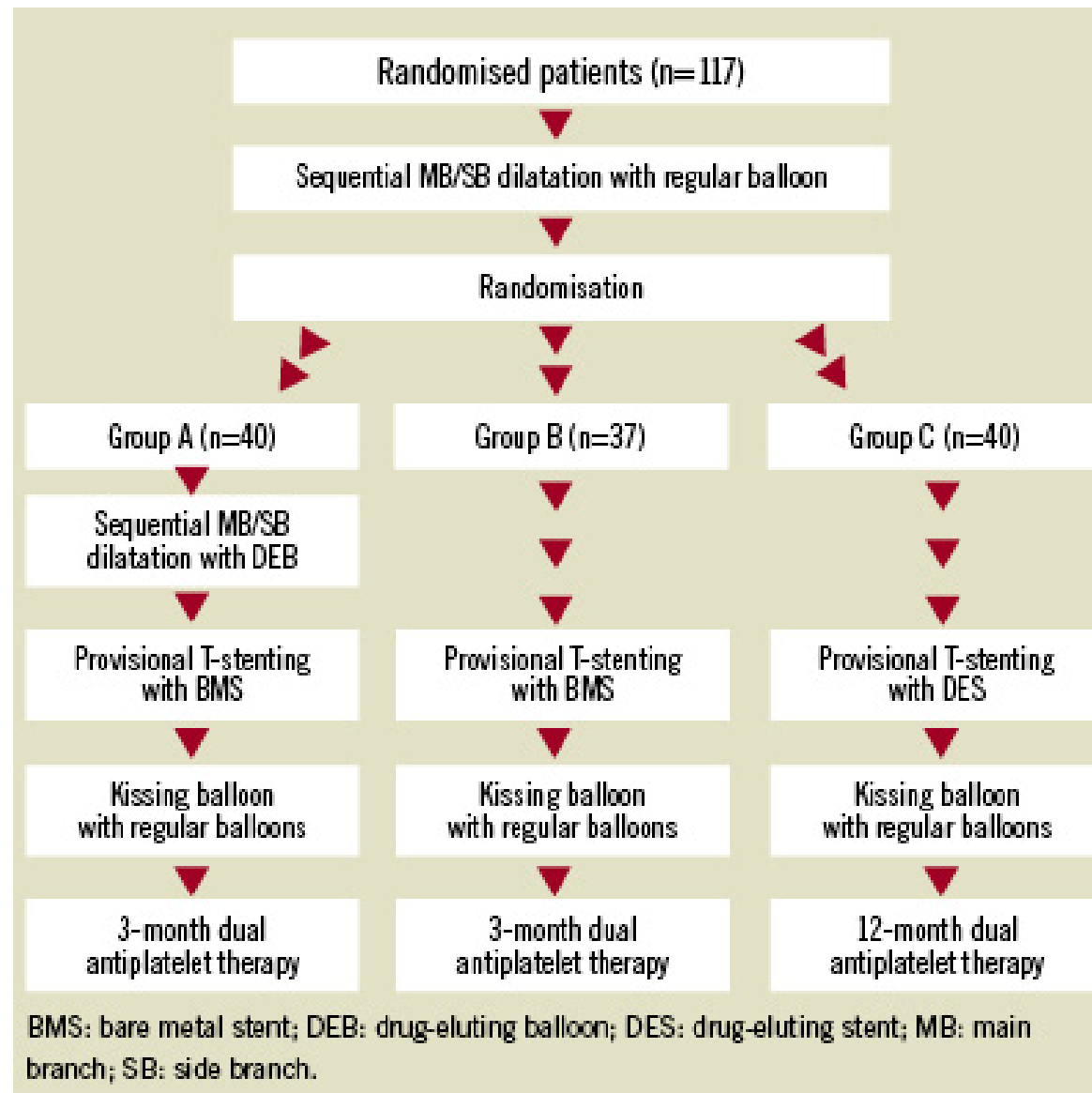


Proposed Employment Modalities of DEB in Bifurcation Lesion PCI

- **Sequential Predilatation with conventional Stenting DES in MB
Drug eluting balloon in SB or Final kissing
Conventional balloon in MB and DEB in SB)**
- **Sequential Predilatation with Conventional Balloons followed by conventional dilatation with DEB in MB and SB followed by BMS in MB and FKB with conventional balloons**
- **Predilatation with Conventional Balloons
Stenting BMS in Main Vessel followed by final kissing with two DEB (MB and SB)**

Coronary bifurcation lesions treated with the drug-eluting balloon: a preliminary insight from the DEBIUT study

Belkacemi A et al , *EuroIntervention* 2011;7: K66-K69.



DEBIUT randomized trial

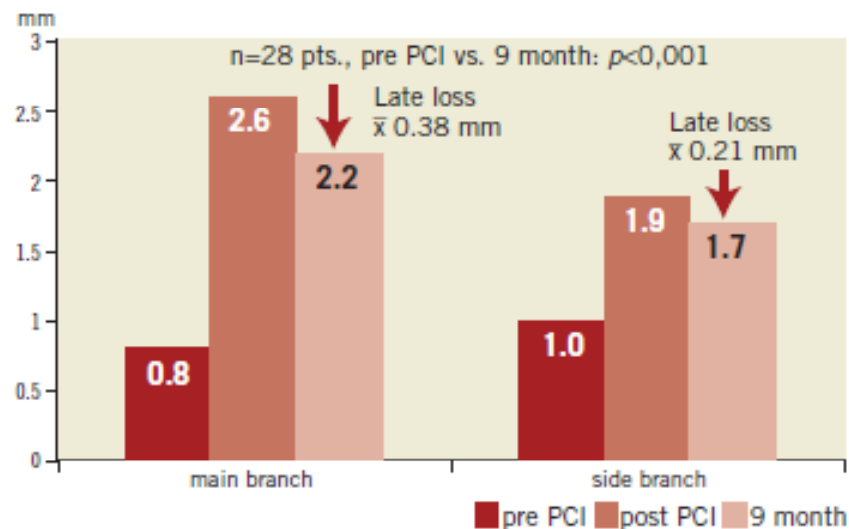
Results at 6 months

	DES Group		DEB Group	
	main branch	side branch	main branch	side branch
Ref. Diameter (mm):	2.8 / 2.3	2.3	2.8 / 2.7	2.6
Restenosis Rate (%): (in-segment)	5.4 / 13.5	2.7	0 / 9.4	6.3
TVR (%):	17.5		17.0	
Stent Thrombosis (%):	2.5		0.0	
Dual Antiplatelet Therapy (months):	12		3	

Treatment of bifurcation lesions with a drug-eluting balloon: the PEPCAD V (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) trial

Detlef G. Mathey^{1*}, MD; Imke Wendig¹, MD; Michael Boxberger², PhD; Klaus Bonaventura³, MD; Franz X. Kleber³, MD

Minimal Luminal Diameter of MB and SB pre-intervention , post intervention and at 9 month FU



Clinical Outcome

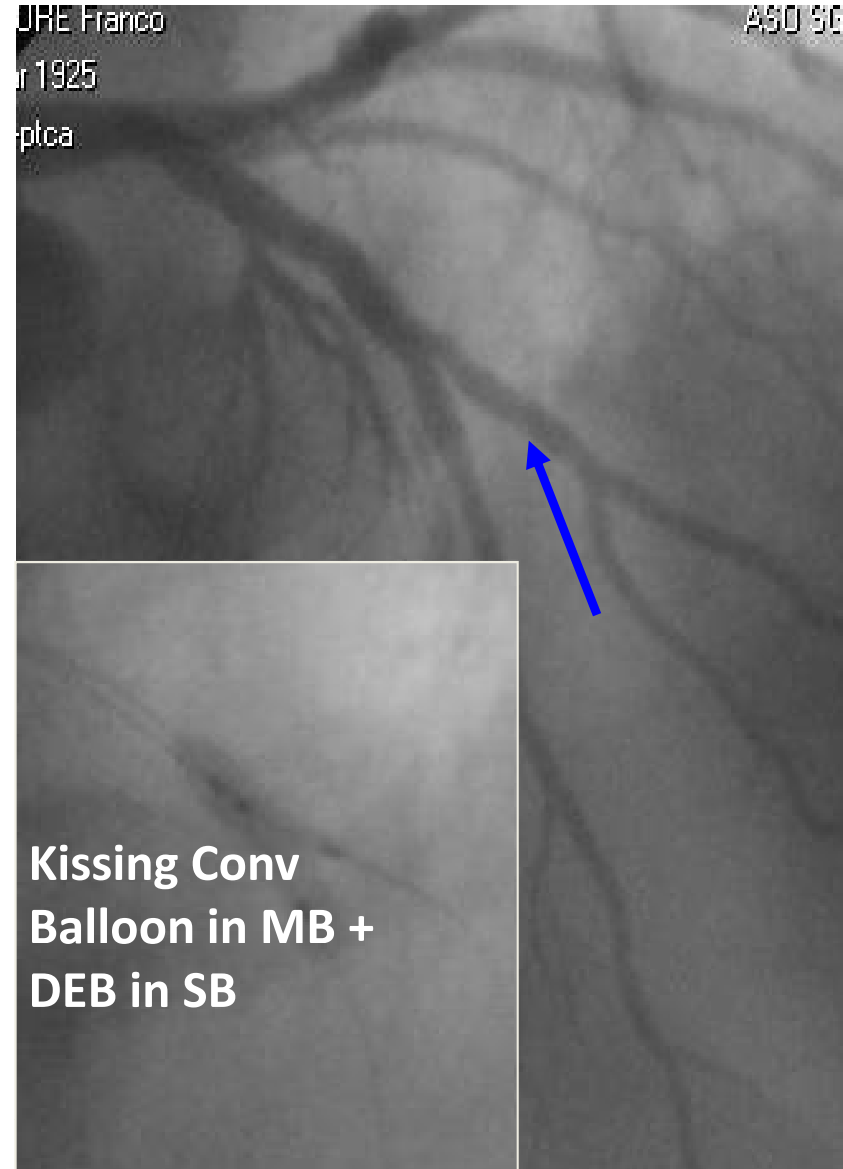
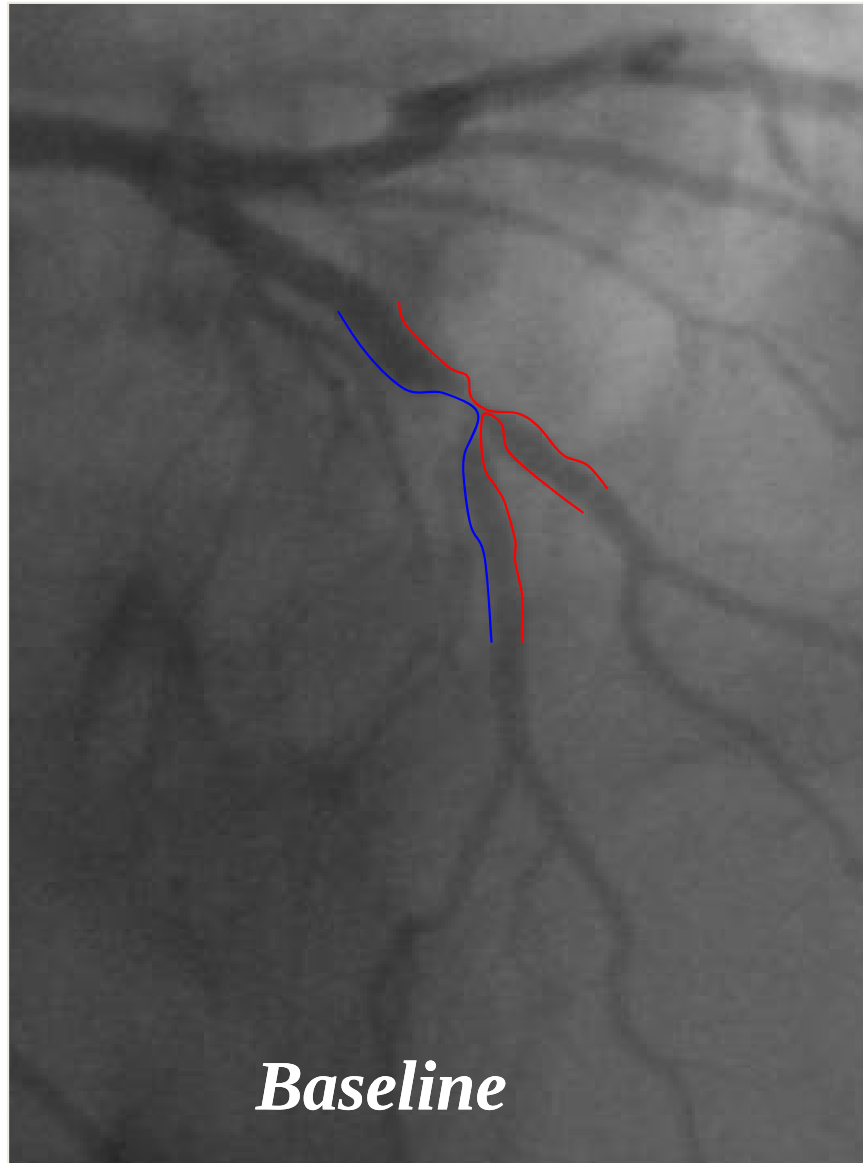
30 day follow up	
MACE	0/28 (0%)
9 month follow up	
Death	0/28 (0%)
Late Stent Thrombosis (1x definite, 1x probable)	2/28 (7,1%)
Restenosis with TLR	1/28 (3,6%)
Restenosis without TLR	2/28 (7,1%)

Published Studies of Bifurcation PCI with DEB

Reference	Number of patients	DEB	Follow-up	DAPT	Stent thrombosis
Fanggiday et al ²	20	DIOR	4 months	3 months	0
Mathey et al ³	28	SeQuent Please	9 months	3 months	2 (6 and 8 months)
Belkacemi et al ⁴	40	DIOR	12 months	3 months	0
Sgueglia et al ⁵	14	SeQuent Please, In.Pact Falcon, DIOR II, Pantera Lux	234±81 days	3 months	0
DAPT: dual antiplatelet therapy; DEB: drug-eluting balloon					

Treatment of Bifurcation : Provisional T with DEB

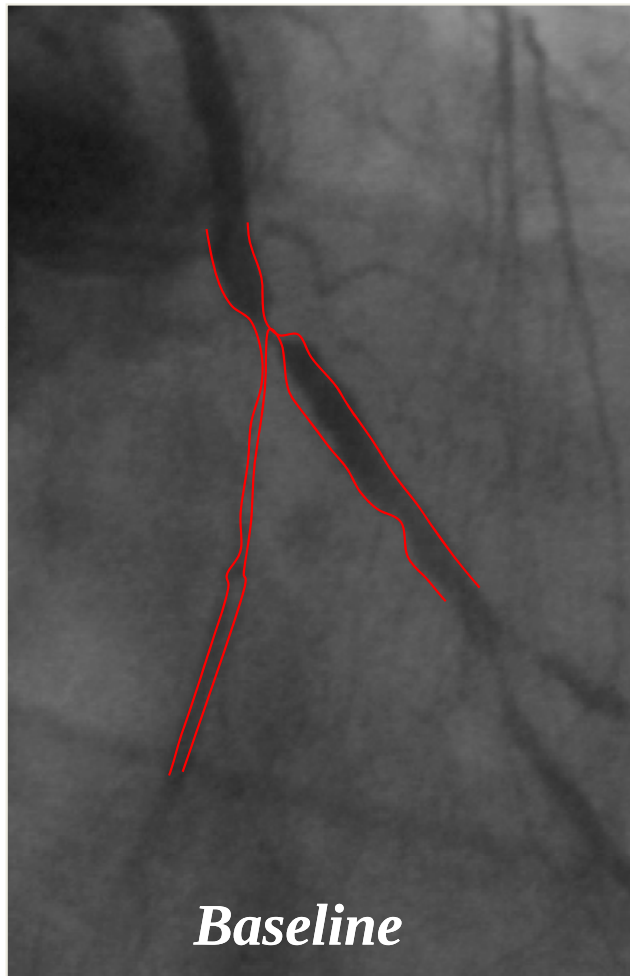
Medina 1,1,1 : Focal disease on SB (≥ 2.5 mm)



Stent in Main Vessel , PTCA in SB + Final kissing balloon with DEB in SB

Treatment of Bifurcation Lesion: DEB ?

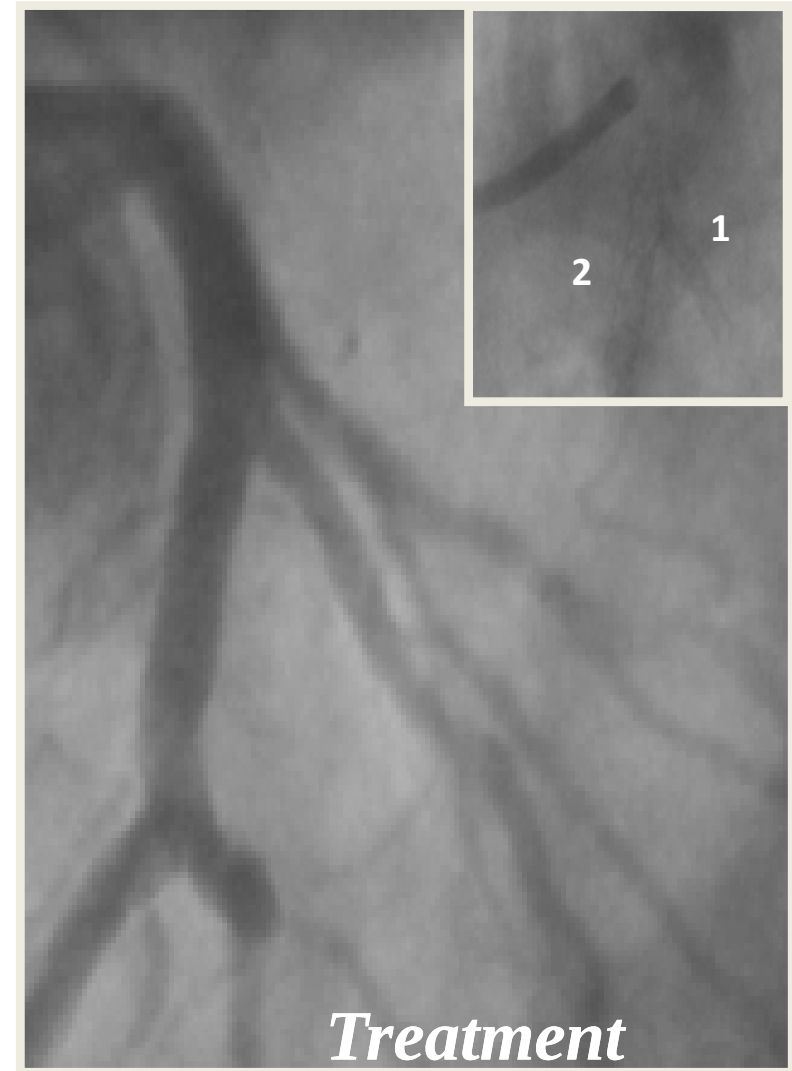
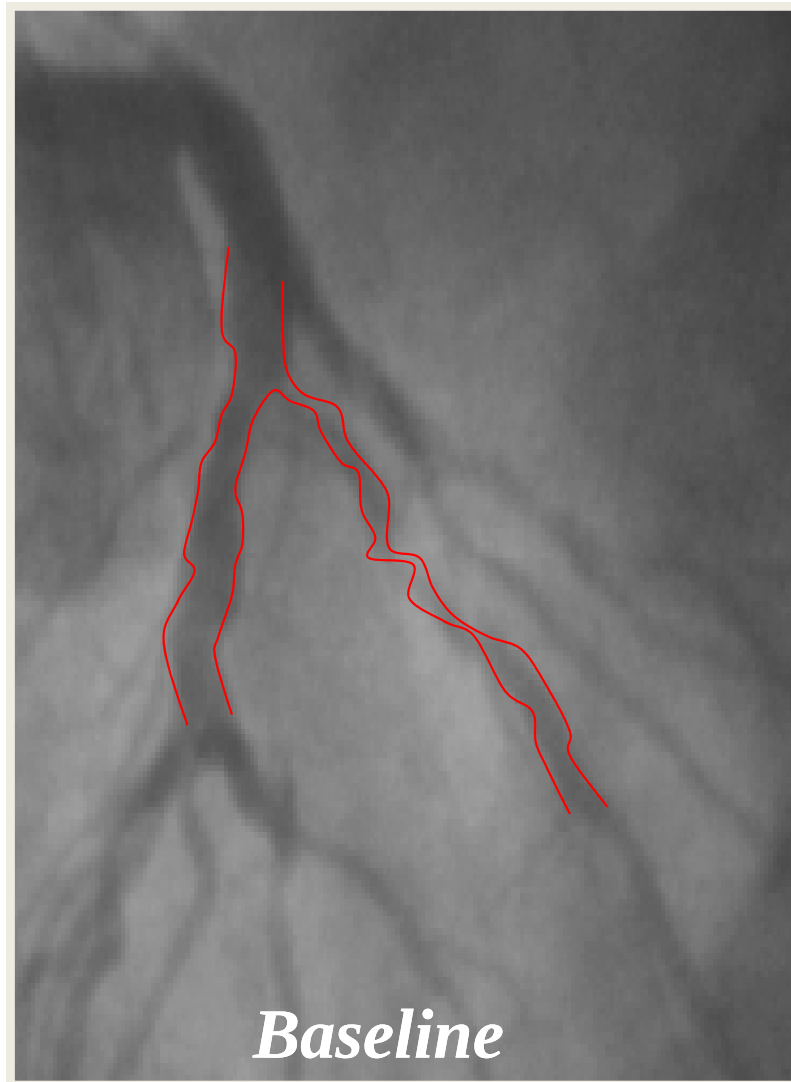
True bifurcation Medina 1,1,1 : Can you really use one stent ?



Elective 2 stents – MiniCrush + Final Kissing Balloon

Treatment of Bifurcation Lesion: DEB ?

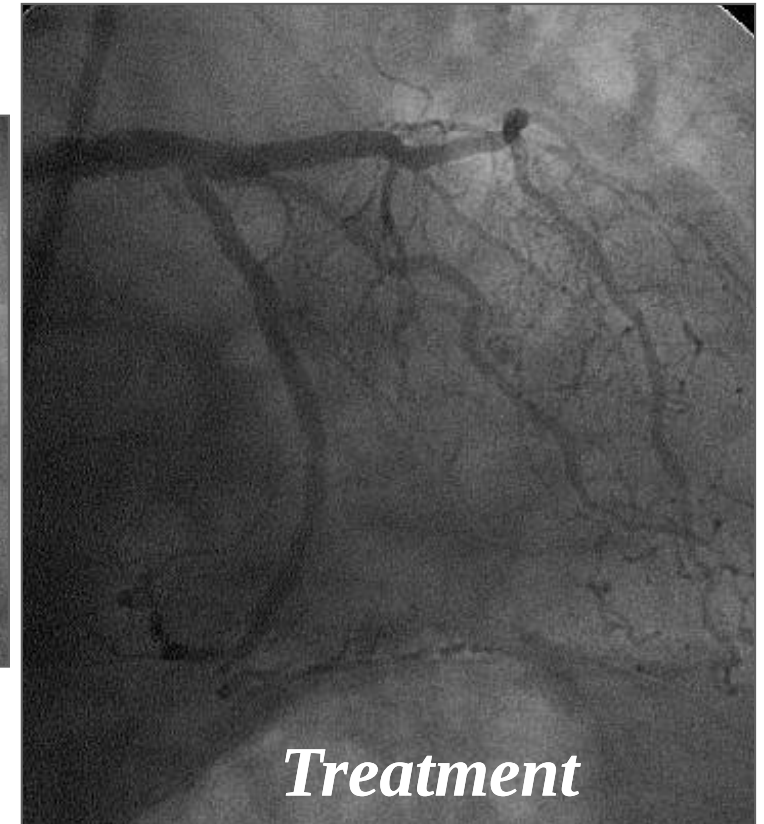
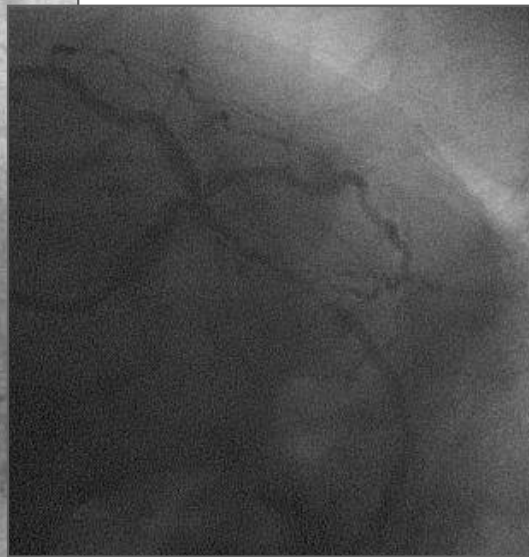
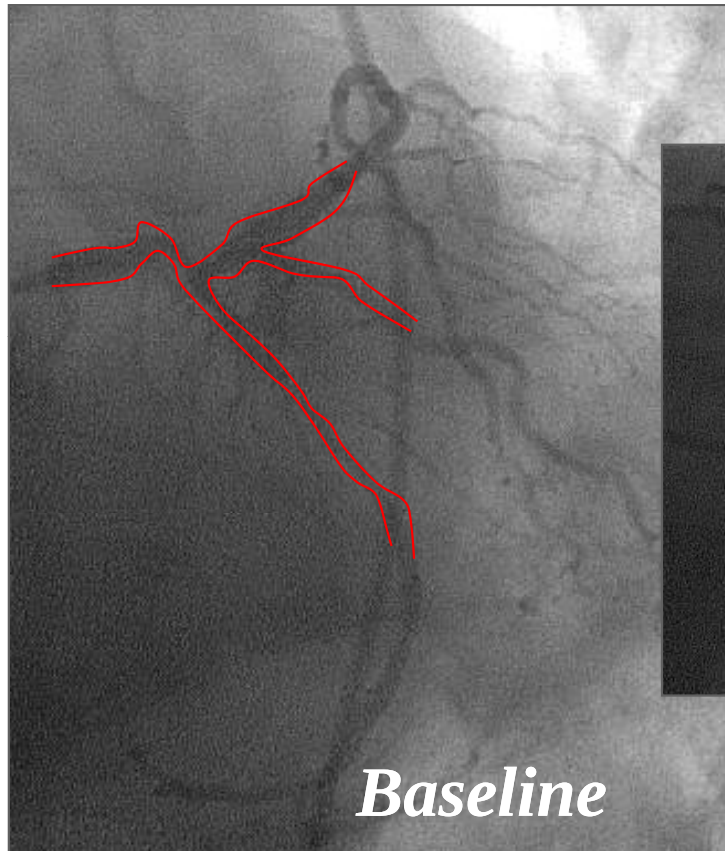
Medina 0,1,1 : Diffuse disease on SB (≥ 2.5 mm)



Elective 2 stents – MiniCrush + Final Kissing Balloon

Treatment of Bifurcation Lesion : DEB ?

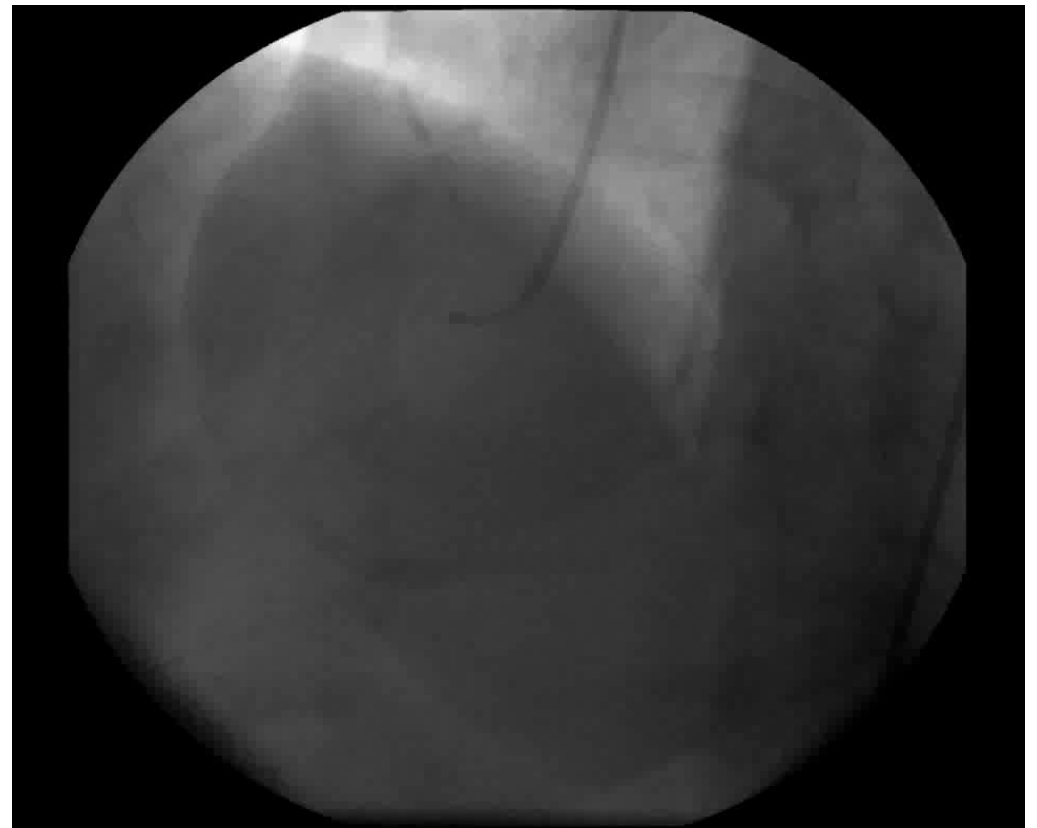
Medina 1,1,1 : Diffuse disease on LCX, Difficult access to LAD



Elective 2 stents – Modified T Stenting + Final Kissing Balloon

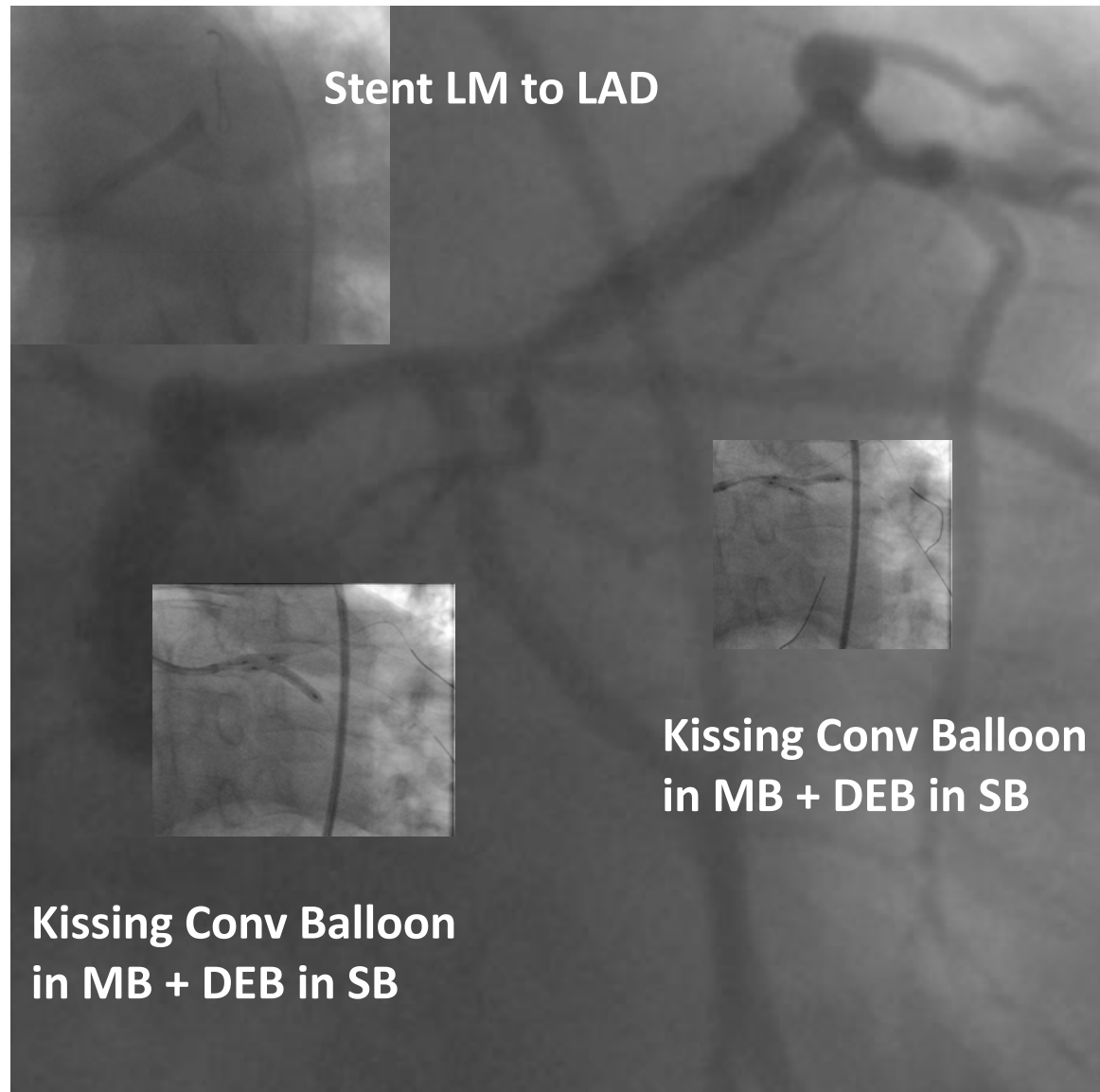
Is it good indication for DEB ?

G.L . ; 67 yrs , male



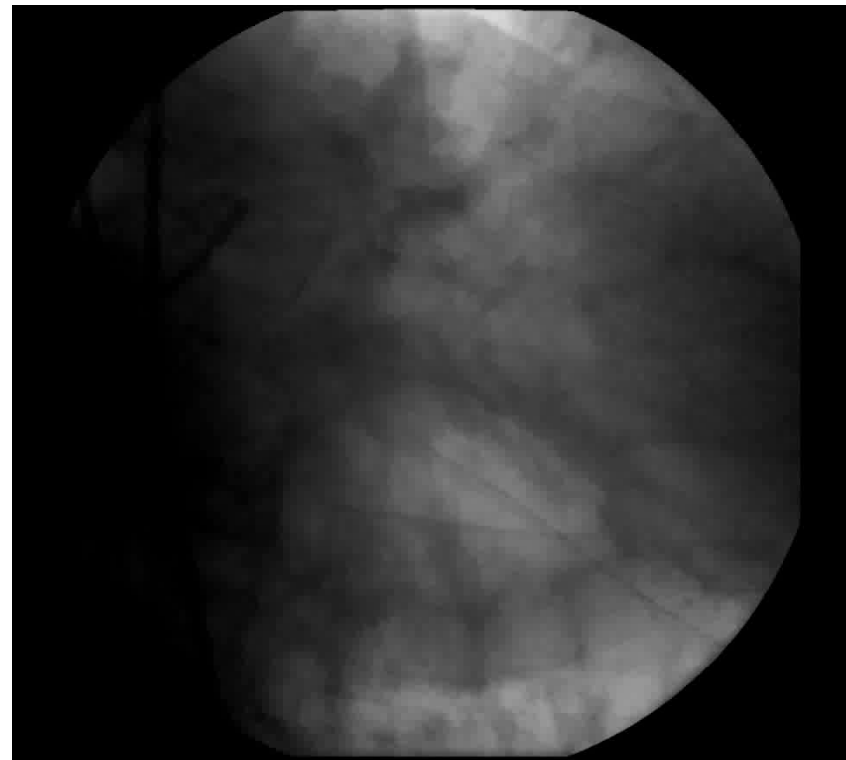
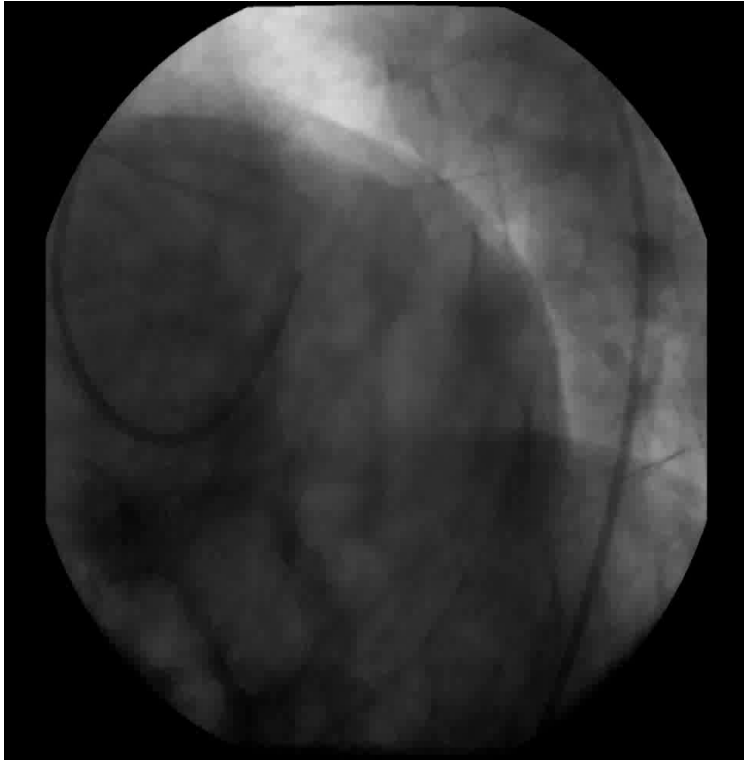
Baseline Angiography

Is it good indication for DEB ?



Is it good oindication for DEB ?

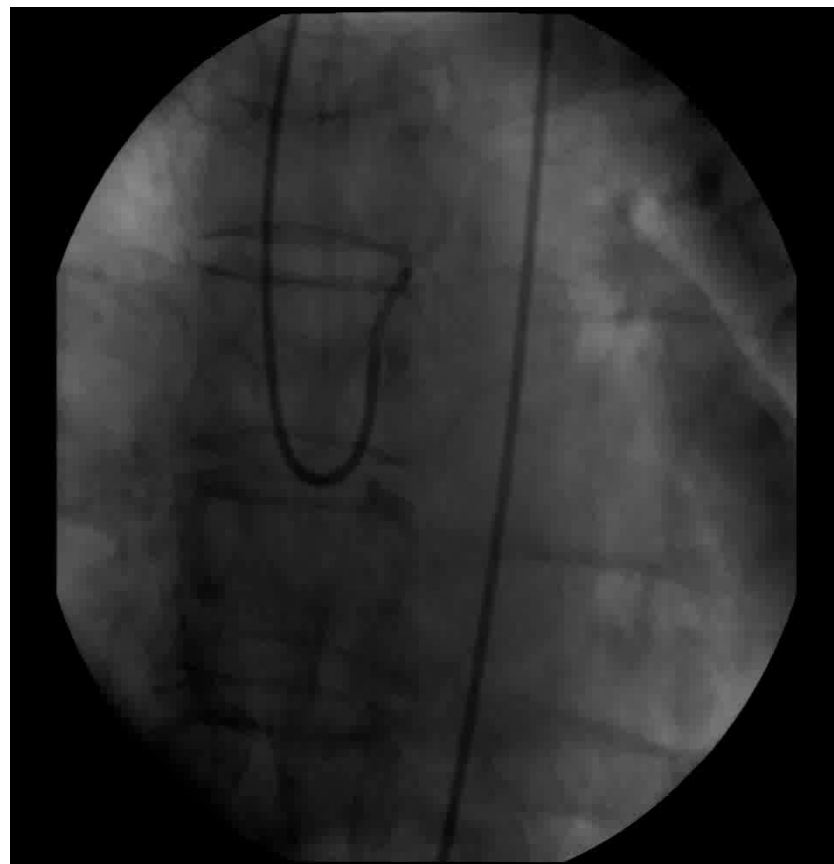
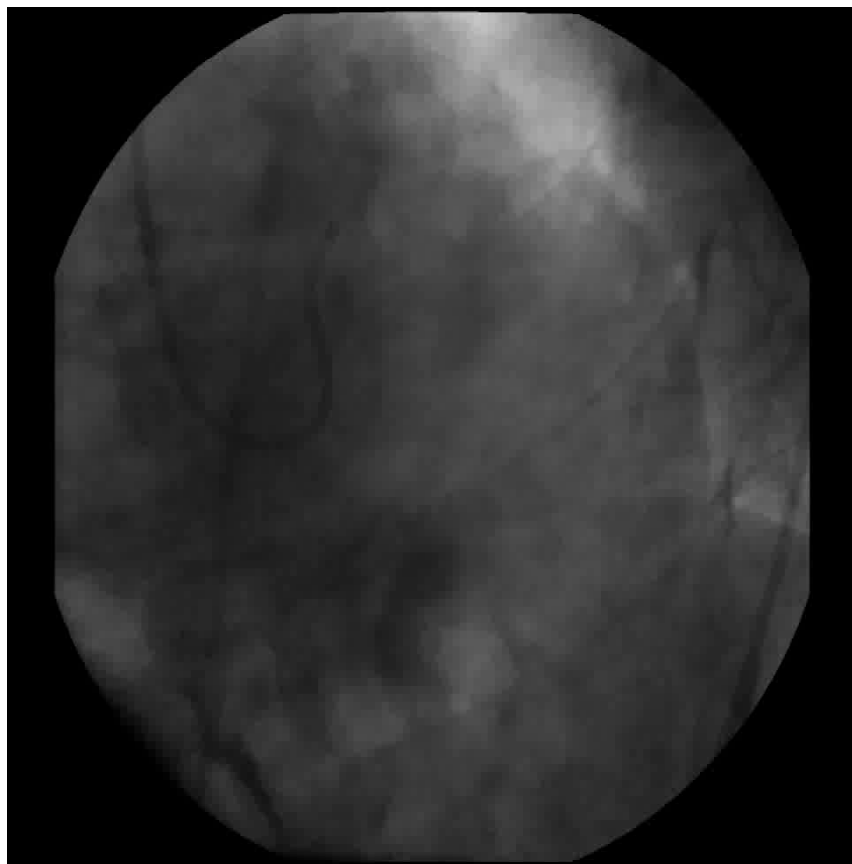
G.L . ; 67 yrs , male



Final Result

Is it good indication for DEB ?

G.L . ; 67 yrs , male



12 –month FU

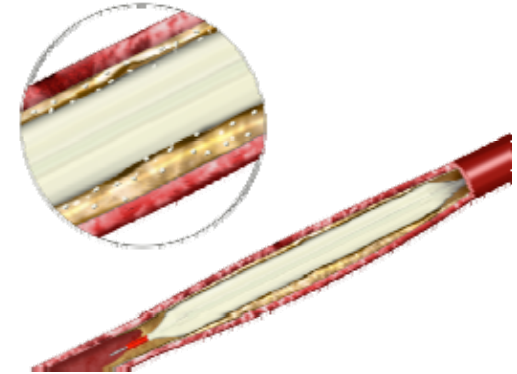
New Developments...

Mozec DEB™

Meril Life Sciences

Paclitaxel/**Sirolimus** Eluting Rx PTCA Balloon Dilatation Catheter

- A drug eluting balloon which allows for fast release of paclitaxel /sirolimus with sustained anti-proliferation effect over 3months.



Device Description

- Employs $3.0 \mu\text{g}/\text{mm}^2$ of Paclitaxel / Sirolimus timed to elute from a polymer **free solid lipid nano formulation in 45 secs.**
- Special formulation releases nano particles (50-500 nm) into the tissue. <10% drug is lost during transition.



Coated Balloon surface before Drug Release study



Balloon surface after Drug Release study

Magic Touch™

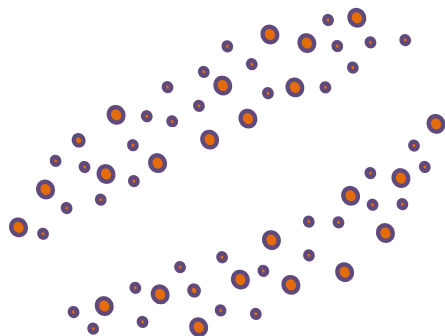
Sirolimus Coated Balloon



Concept Medical

- Drug carrier is a Lipid based component with proven safety profile
- Has Hydrophilic Head & **two Lipophilic tails which are used to encapsulate nano sized drug particle creating a nano carrier**
- Ensures higher tissue transfer
- Promotes healing in Arterial tissue

Magic Touch Drug Loading: 180 µgm on 3.0 x 15 mm



Take Home Message:

- ☐ Drug-eluting balloons represent an innovative device in interventional cardiology
- ☐ Four DEB have provided clinical data for ISR after BMS and DES with a significant decrease in TLR rates within the first 9 to 12 months after PCI of ISR.
- ☐ The ESC guidelines recommend DEB only for in-stent restenosis (ISR) of BMS.
- ☐ Promising data for additional indications have been reported in the treatment of side branches in bifurcation lesions, de-novo lesions in small vessels , AMI and de-novo lesions in peripheral PTA
- ☐ New DEB Sirolimus-coated with innovative coating approaches (Nanotechnology) are on arrival for clinical use and might add a further improvement in clinical outcome
- ☐ Available data on the role of DEB in Bifurcation treatment are still limited and undefined . Need for further targeted clinical trials