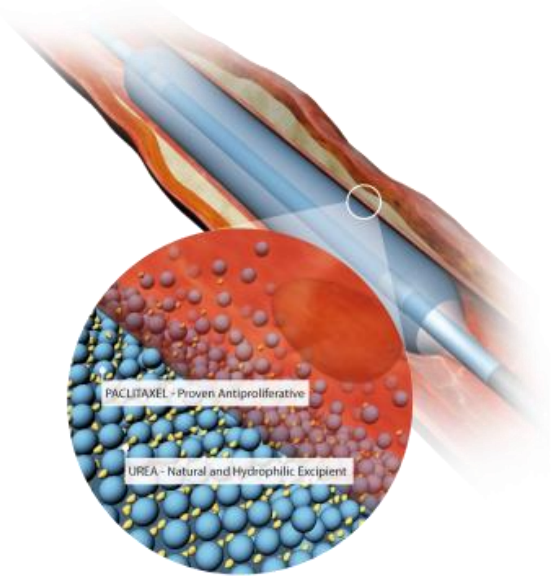
Procedural optimization for successful DCB treatment



Jeehoon Kang, MD

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ISR in the Contemporary DES Era

- **Development in 2nd generation DES have** markedly **reduced the rates of ISR**

- **However, ISR occurs even in the newer generation DES era** with considerable incidence **ranging from 3% to 20%** of patients

- **DES-ISR treatment continues to be challenging issue for interventional cardiologists**, because

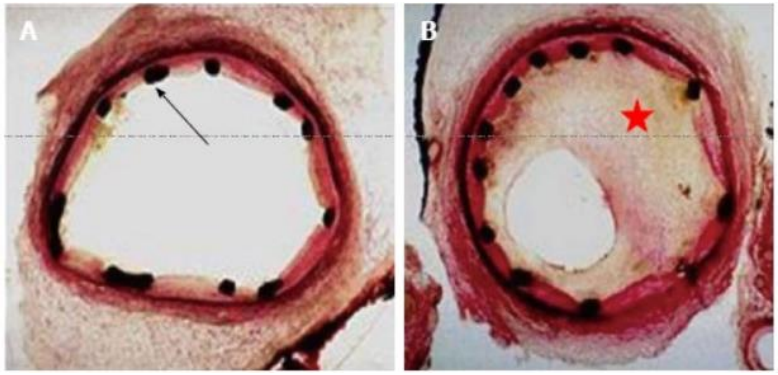
    1. More than **half of ISR patients present with acute coronary syndrome**

    2. ISR, compared to *de novo* lesion, **increases rates of future MACE**
        - even after successful treatment of ISR

Pathogenesis of ISR

- ✓ **Neointimal tissue proliferation** because of arterial wall damage
  - ✓ Intimal / medial damage → Proliferation and migration of VSMC, ECM → Activates the coagulation-fibrinolysis system

- ✓ Various phases
  - ✓ Early within days of stent deployment
    - ✓ **Elastic recoil** and **relocation of axially transmitted plaque**
  - ✓ Late (weeks to months) ISR
    - ✓ **Reorganization of thrombus, neointima formation and remodeling**
    - ✓ **Neoatherosclerosis**: accumulation of lipid-laden foamy macrophages within the neointima



How to Treat ISR? Still in Controversy

Restenosis		
DES are recommended for the treatment of in-stent restenosis of BMS or DES.[373,375,378,379]	I	A
Drug-coated balloons are recommended for the treatment of in-stent restenosis of BMS or DES.[373,375,378,379]	I	A
In patients with recurrent episodes of diffuse in-stent restenosis, CABG should be considered by the Heart Team over a new PCI attempt.	IIa	C
IVUS and/or OCT should be considered to detect stent-related mechanical problems leading to restenosis.	IIa	C

- **2018 ESC/EACTS guideline provide an equivalent recommendation**
  - **DES or DCB** for the treatment of ISR (Class I, LOE A)

- **Optimal treatment strategy for ISR is still under debate.**

2018 ESC/EACTS Guidelines on myocardial revascularization, Eur Heart J 2018

CE approved DCBs

Supplementary Table 8 **CE-approved drug-coated balloons (in alphabetical order)**

Device	Carrier	Drug	References
Agent	ATBC	Paclitaxel	
Angiosculpt	NDGA	Paclitaxel	–
Danubio	BTHC	Paclitaxel	–
Dior II	Shellac	Paclitaxel	34,35
Elutax	–	Paclitaxel	36
IN.PACT Falcon	Urea	Paclitaxel	37
MagicTouch	Phospholipid-based	Sirolimus	
Moxy	Polysorbate	Paclitaxel	38
Pantera Lux	BTHC	Paclitaxel	39
Protégé NC	BTHC	Paclitaxel	–
SeQuent Please	Iopromide	Paclitaxel	40–44

CE approved DCBs in Korea

Lux coating technology for rapid drug absorption

Drug Paclitaxel
- 3.0 µg Paclitaxel/mm² balloon surface
- Anti-proliferative

Excipient Butyryl-tri-hexyl citrate (BTHC)
- Degrades to citric acid and alcohol, rapidly metabolized
- Keeps Paclitaxel in microcrystalline structure

Lux coating technology
- For rapid drug absorption into the vessel wall[9]
- Improving bioavailability at the target site[9]

Lesion preparation

pre-dilation with

PTCA Balloon / Non Compliant Balloon / Scoring Balloon

Ratio balloon-vessel-diameter 0.8-1.0, Inflation pressure > nominal

Acceptable angiographic result
no dissection or only Typ A or B;
TIMI III; residual stenosis ≤ 30 %

Dissection Type C-F; TIMI < III;
residual stenosis > 30%

DCB-only with SeQuent® Please NEO
- DCB distal and proximal at least 2-3 mm longer as predilatated area
- ratio balloon-to-vessel diameter 0.8-1.0
- 8-10 atm, 30 sec. inflation time

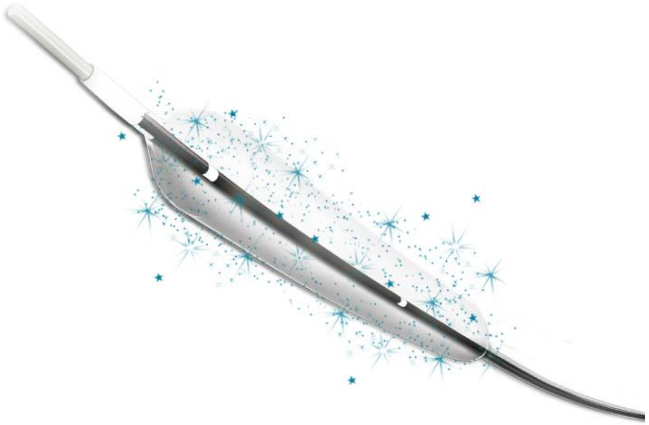
Stenting
DES implantation Coroflex® ISAR

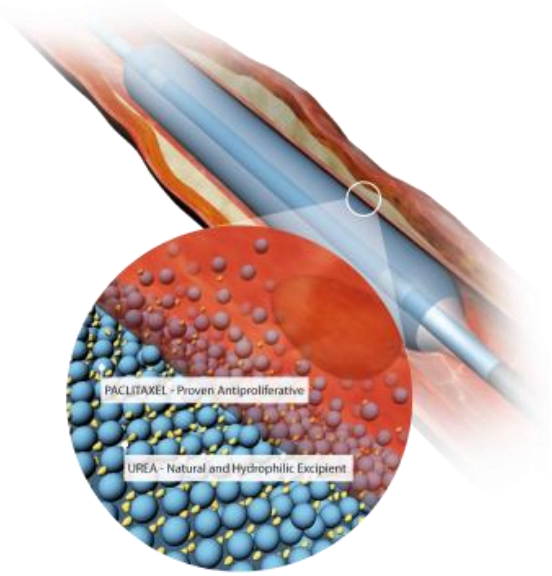
DAPT DEB only: 4 weeks
BMS-ISR: 4 weeks
DES-ISR: time defined by DES but at least 4 weeks
Spot-BMS + DEB: 3 months

DAPT according to current guideline

DCBs in USA

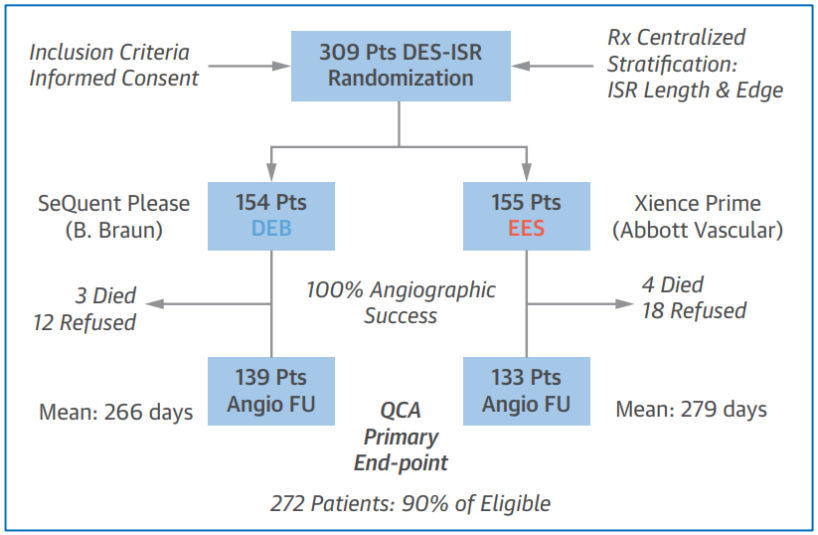
Drug Coated Balloons are not approved
for coronary use in the USA

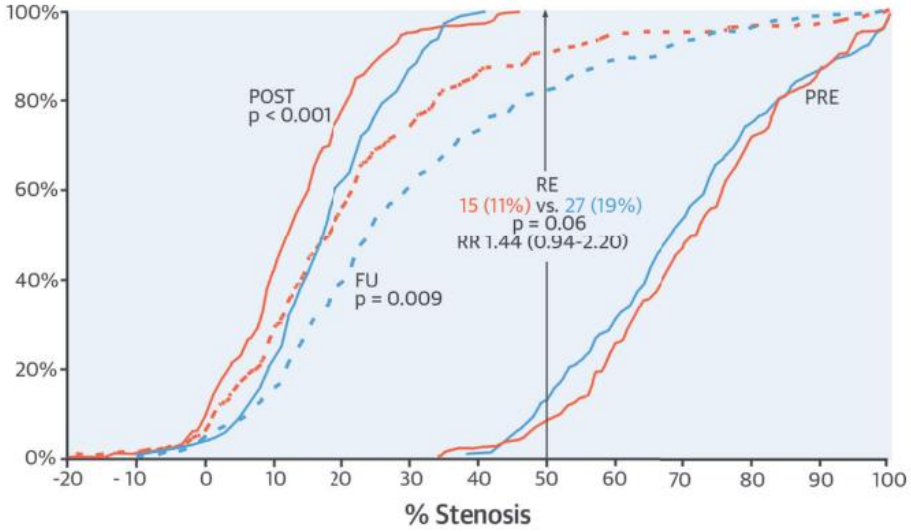


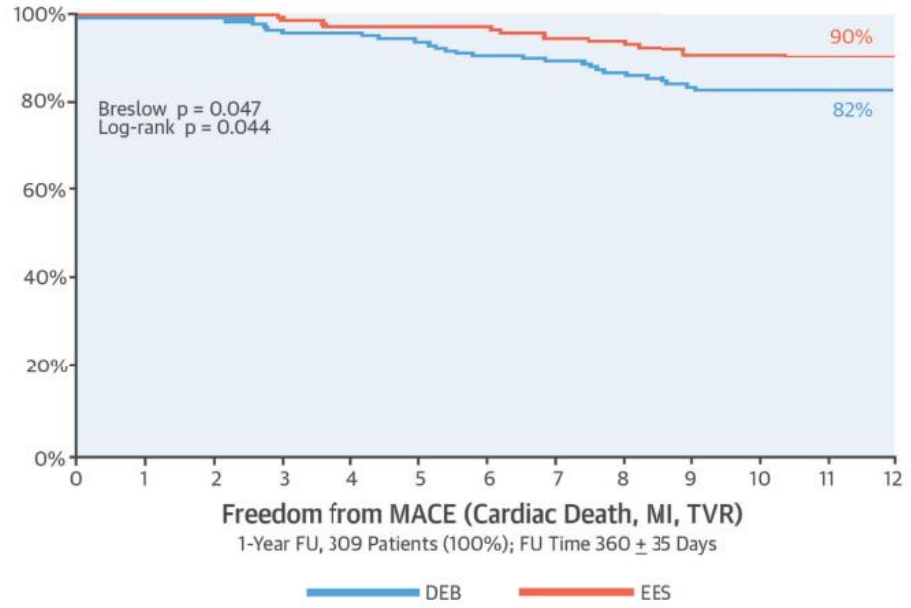


Clinical studies of DCBs

RIBS-IV RCT: DCB vs. 2nd Generation DES



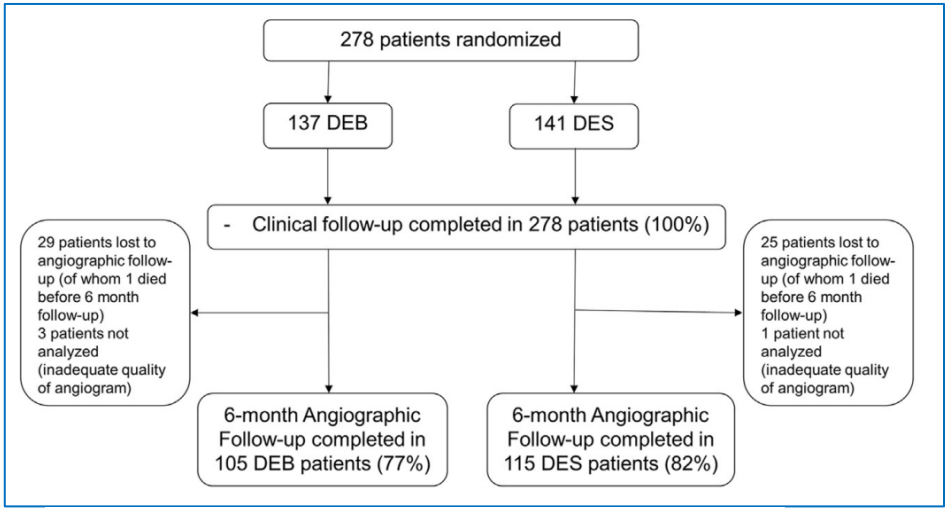




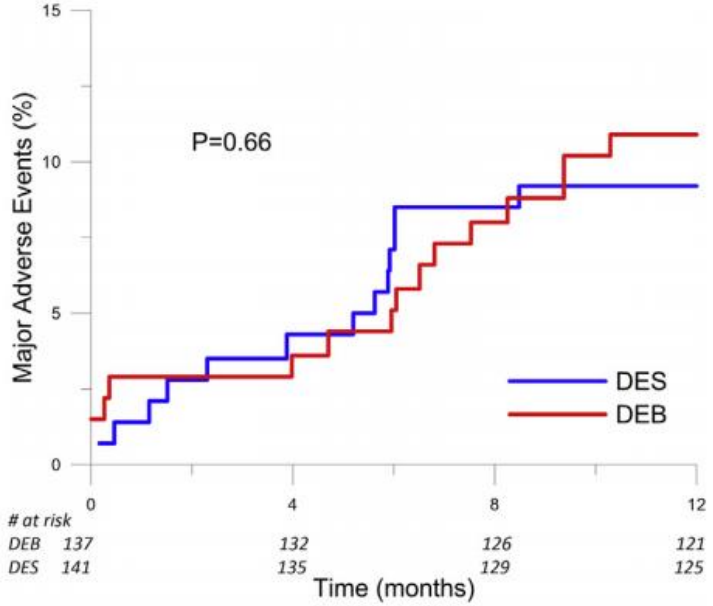
"In patients with DES-ISR, ***EES provided superior long-term clinical and angiographic results*** *compared with* ***DCB."***

J Am Coll Cardiol 2015;66:23–33.

DARE RCT: DCB vs. Any DES



	Drug-Eluting Balloon (n = 137)	Drug-Eluting Stent (n = 141)	p Value
Death	0.7 (1)	1.4 (2)	0.58
Cardiac death	0	0.7 (1)	0.32
Myocardial infarction	2.2 (3)	2.8 (4)	0.74
Target vessel-related myocardial infarction	1.4 (2)	0.7 (1)	0.54
Stent thrombosis	0	0	n/a
Stroke	0.7 (1)	1.4 (2)	0.58
Target vessel revascularization	8.8 (12)	7.1 (10)	0.65
TVR percutaneous coronary intervention	8.8 (12)	5.7 (8)	0.36
TVR coronary artery bypass graft surgery	0	1.4 (2)	0.16
Coronary artery bypass graft surgery all	0.7 (1)	4.3 (6)	0.06
Percutaneous coronary intervention all	13.9 (19)	11.3 (16)	0.58
Composite major adverse events*	10.9 (15)	9.2 (13)	0.66

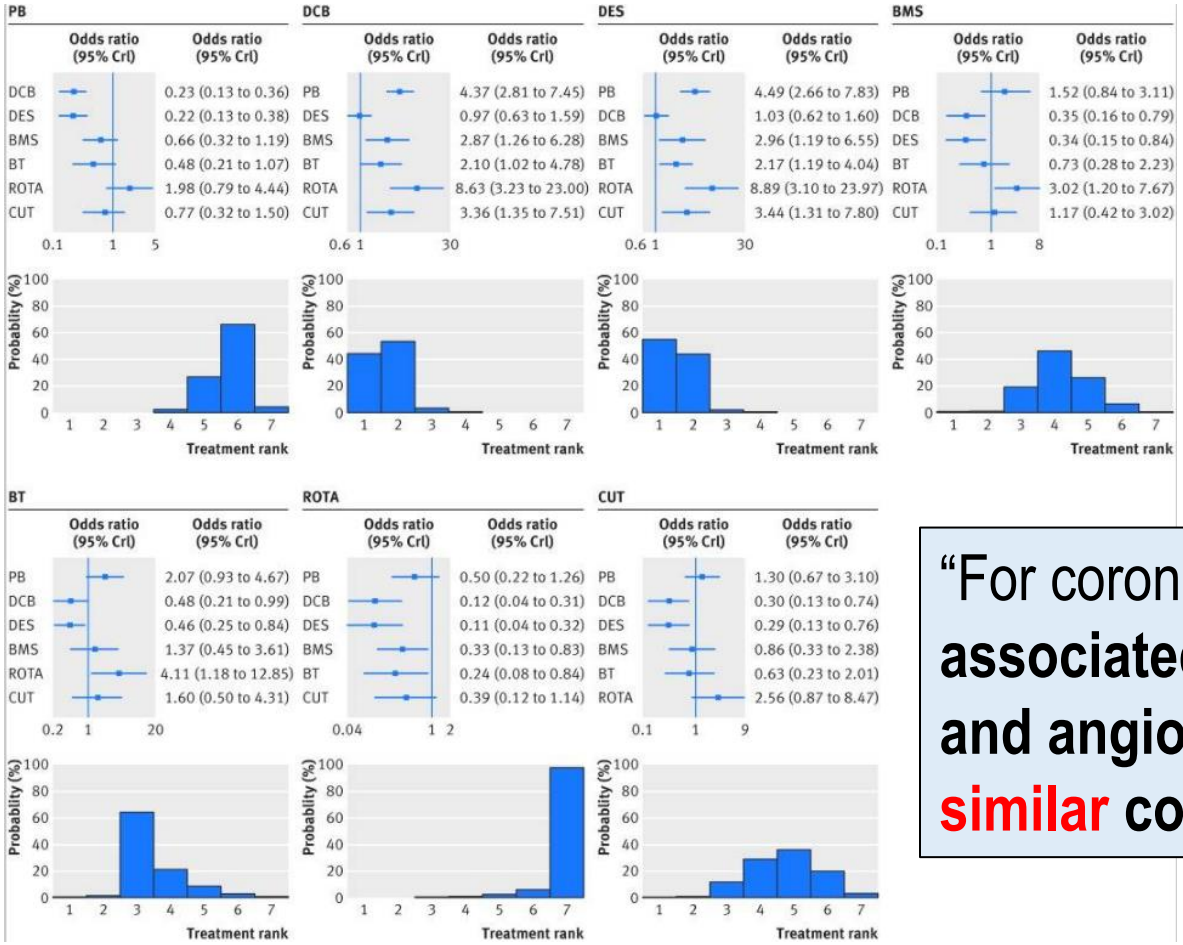


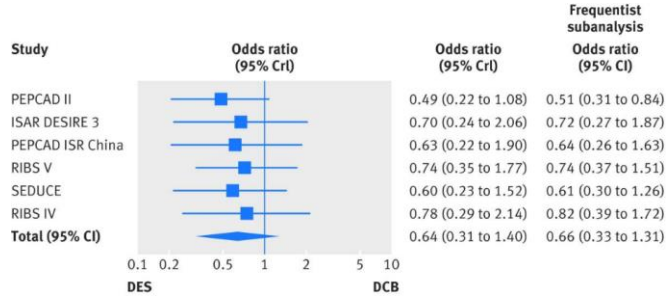
*"In patients with ISR, **treatment with DCB was non-inferior compared with DES** in terms of **6-month MLD**. There were **no differences in clinical endpoints**, including 12 month TVR."*

JACC Cardiovasc Interv. 2018;11(3):275-283

Systematic review & Bayesian network meta-analysis

- ✓ 24 trials (n=4880) and 7 interventional treatments (plain balloon, drug coated balloon, drug eluting stent, bare metal stent, brachytherapy, rotational atherectomy, and cutting balloon) were compared

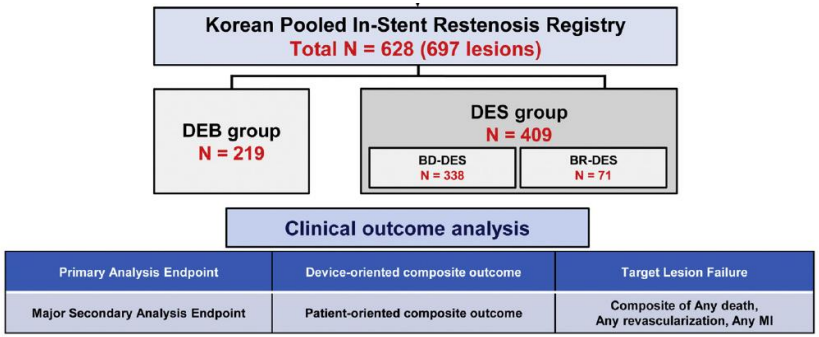




"For coronary ISR, **DCB and DES are associated with superior clinical and angiographic outcomes**, with a **similar comparative efficacy**."

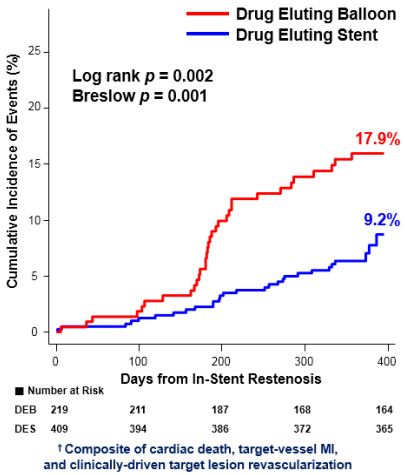
BMJ 2015;351:h5392

Korean Data: DCB vs. DES



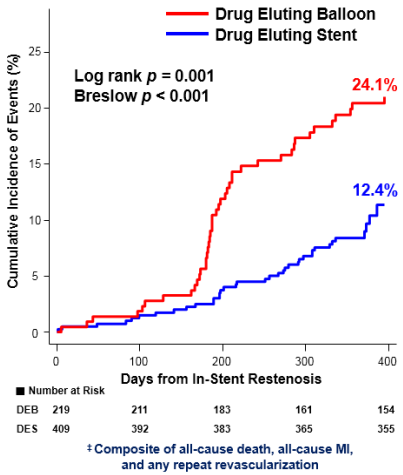
	DEB Patient N = 219 Lesion N = 265	DES Patient N = 409 Lesion N = 432	HR (95% CI)	Interaction *P* value
All patients	**17.9% (33/219)**	**9.2% (30/409)**	**0.47 (0.29 - 0.78)**	
Diabetes	20.0% (20/116)	12.1% (20/187)	0.54 (0.28 - 1.05)	**0.219**
No diabetes	15.4% (13/103)	7.0% (10/217)	0.29 (0.12 - 0.69)	
Chronic kidney disease	26.9% (13/58)	13.7% (14/120)	0.60 (0.27 - 1.33)	**0.247**
No CKD	14.8% (20/158)	7.4% (16/289)	0.31 (0.16 - 0.63)	
Acute coronary syndrome	15.8% (14/102)	10.9% (21/244)	0.62 (0.30 - 1.28)	**0.144**
No ACS	19.6% (19/117)	6.8% (9/164)	0.27 (0.11 - 0.63)	
Lesion length ≥ 28 mm	21.3% (6/35)	12.0% (17/161)	0.57 (0.20 - 1.60)	**0.371**
Lesion length < 28 mm	22.6% (45/230)	9.8% (20/271)	0.36 (0.19 - 0.67)	
Vessel diameter < 2.75 mm	31.5% (18/62)	16.7% (8/65)	0.32 (0.13 - 0.84)	**0.535**
Vessel diameter ≥ 2.75 mm	19.5% (33/203)	8.3% (25/359)	0.49 (0.26 - 0.90)	
Complex (Type B2 or C) lesion	31.2% (34/123)	11.3% (24/264)	0.29 (0.16 - 0.54)	**0.145**
No complex lesion	14.9% (17/142)	10.9% (12/138)	0.63 (0.25 - 1.59)	
Lesion with severe calcification	20.0% (2/10)	22.5% (5/23)	1.21 (0.24 - 6.06)	**0.166**
Lesion without severe calcification	22.5% (49/255)	10.0% (32/409)	0.38 (0.22 - 0.66)	
Intended follow-up angiography	21.2% (11/52)	12.5% (5/48)	0.47 (0.16 - 1.36)	**0.419**
No intended follow-up angiography	16.8% (22/167)	8.8% (25/361)	0.51 (0.29 - 0.90)	
BMS-ISR	0.0% (0/17)	5.9% (3/69)	**1.66 (0.05 - 50.8)**	**< 0.001**
DES-ISR	23.9% (51/248)	11.5% (34/363)	**0.43 (0.28 - 0.66)**	

(A) Target Lesion Failure†



† Composite of cardiac death, target-vessel MI, and clinically-driven target lesion revascularization

(B) Patient-Oriented Composite Outcomes‡



‡ Composite of all-cause death, all-cause MI, and any repeat revascularization

"In unselected patients of ISR, ***clinical outcome at one year was mainly dependent on difference in TLR*** *and found to be* ***better with contemporary DES than DCB****"*

Int J Cardiol. 2017 Mar 1;230:181-190

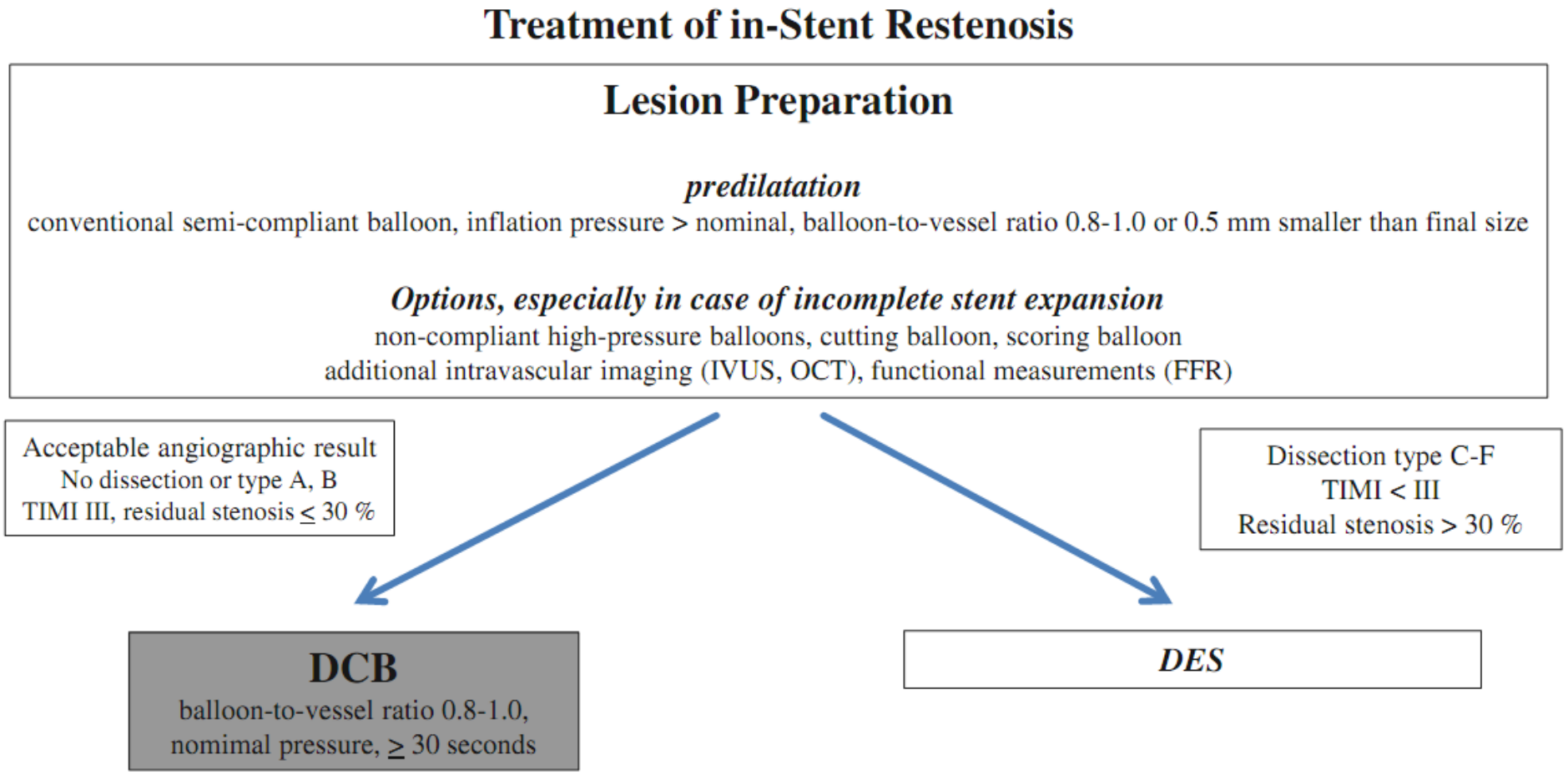
DES vs. DCB?

- ✓ **Shortcomings of the DES**
  - ✓ Metalic stents might induce sustained inflammation with increased neointimal proliferation.
  - ✓ Non-uniform tissue drug concentration in the stent area.
    - ✓ highest near to the stent struts, and lowest between the struts
  - ✓ Vulnerable factors may induce delayed and in-homogenous re-endothelization, late thrombosis and in-stent restenosis.

- ✓ **Proposed advantages of DCB**
  - ✓ Homogeneous drug delivery, immediate drug release without a polymer
  - ✓ Potential of reducing the intensity and DAPT,
  - ✓ Concept of “leaving no foreign object behind”

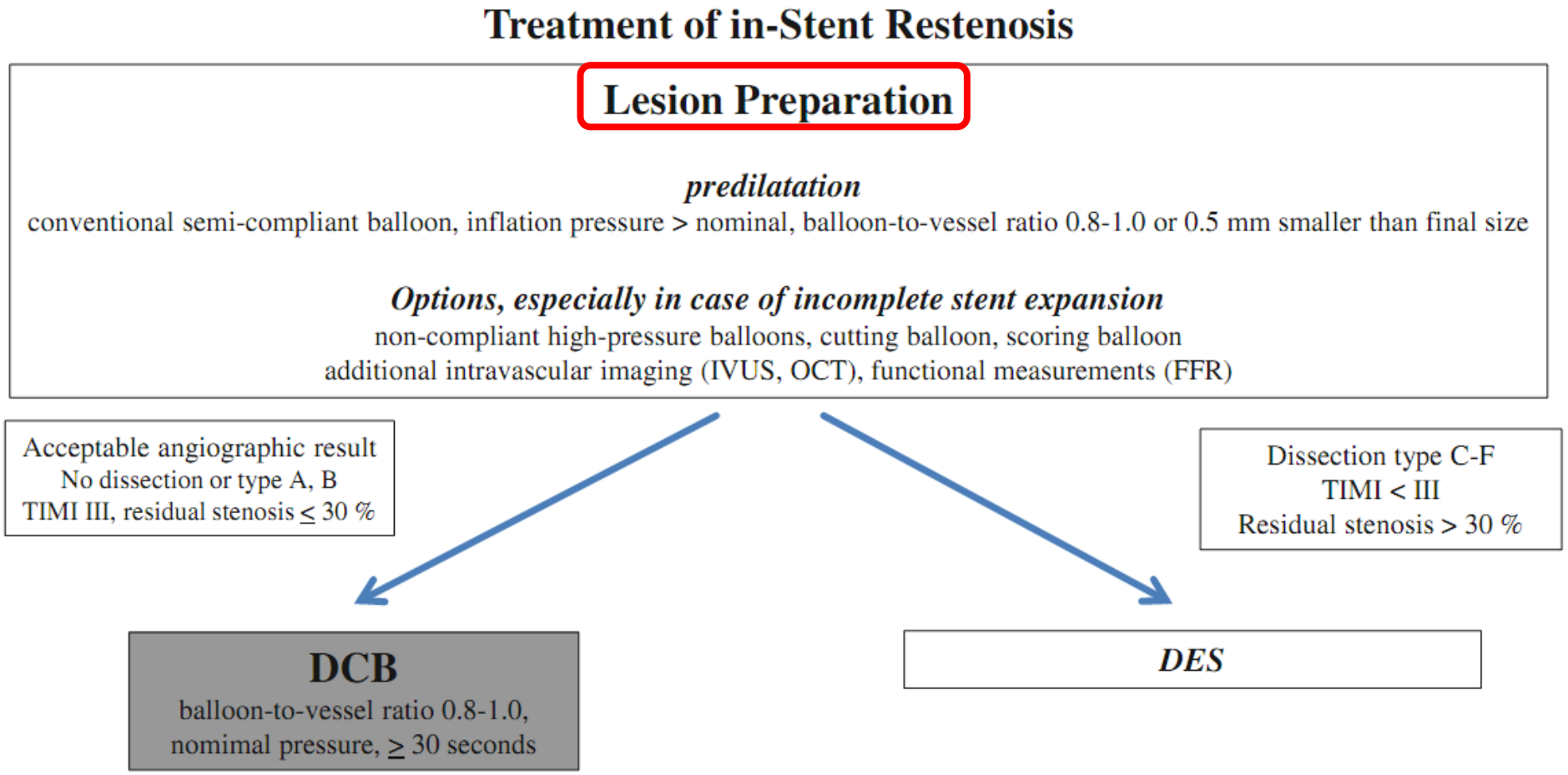
Beyond simple comparison of DES vs. DCB, ‘How and to whom’, may be more important for the DCB issue

Current Recommendation for DCB Procedure



Kleber FX et al. Clin Res Cardiol 2013

Current Recommendation for DCB Procedure



Kleber FX et al. Clin Res Cardiol 2013

ISAR-DESIRE 4 RCT: DCB with lesion prep.

	Scoring Balloon (n = 125)	Control (n = 127)
Target vessel		
Left anterior descending coronary artery	44 (35.2)	52 (41.0)
Left circumflex coronary artery	35 (28.0)	38 (29.9)
Right coronary artery	46 (36.8)	37 (29.1)
Restenosis morphology		
Focal margin	14 (11.2)	16 (12.6)
Focal body	70 (56.0)	71 (55.9)
Multifocal	12 (9.6)	9 (7.1)
Diffuse	23 (18.4)	28 (22.1)
Proliferative	2 (1.6)	1 (0.8)
Occlusive	4 (3.2)	2 (1.6)
Index stent type		
Bare metal	0 (0.0)	1 (0.8)
Biolimus eluting*	14 (11.2)	16 (12.6)
Everolimus eluting†	74 (59.2)	77 (60.6)
Sirolimus eluting‡	31 (24.8)	25 (19.7)
Zotarolimus eluting§	6 (4.8)	8 (6.3)
Bifurcation	36 (28.8)	34 (27.0)
Vessel size (mm)	2.96 ± 0.50	2.89 ± 0.48
Diameter stenosis, pre (%)	65.7 ± 14.1	67.2 ± 12.2
Minimal luminal diameter, pre (mm)	1.01 ± 0.46	0.94 ± 0.36
Procedures		
Treated as per protocol	119 (95.2)	120 (94.5)
Pre-dilation	120 (96.0)	122 (96.1)
Pre-dilation, balloon diameter, maximum (mm)	3.2 ± 0.48	3.2 ± 0.47
Balloon pressure, maximum (atm)	14.2 ± 3.7	14.2 ± 3.8
Minimal luminal diameter, post (mm)	2.37 ± 0.47	2.28 ± 0.40
Diameter stenosis, post (%)	21.6 ± 9.5	22.3 ± 9.9

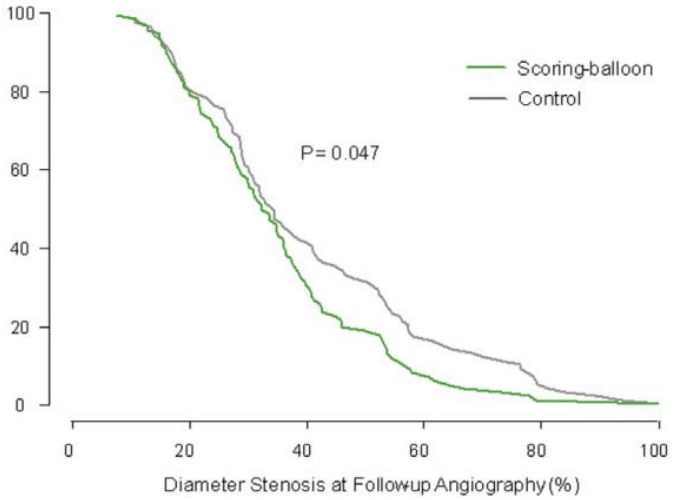


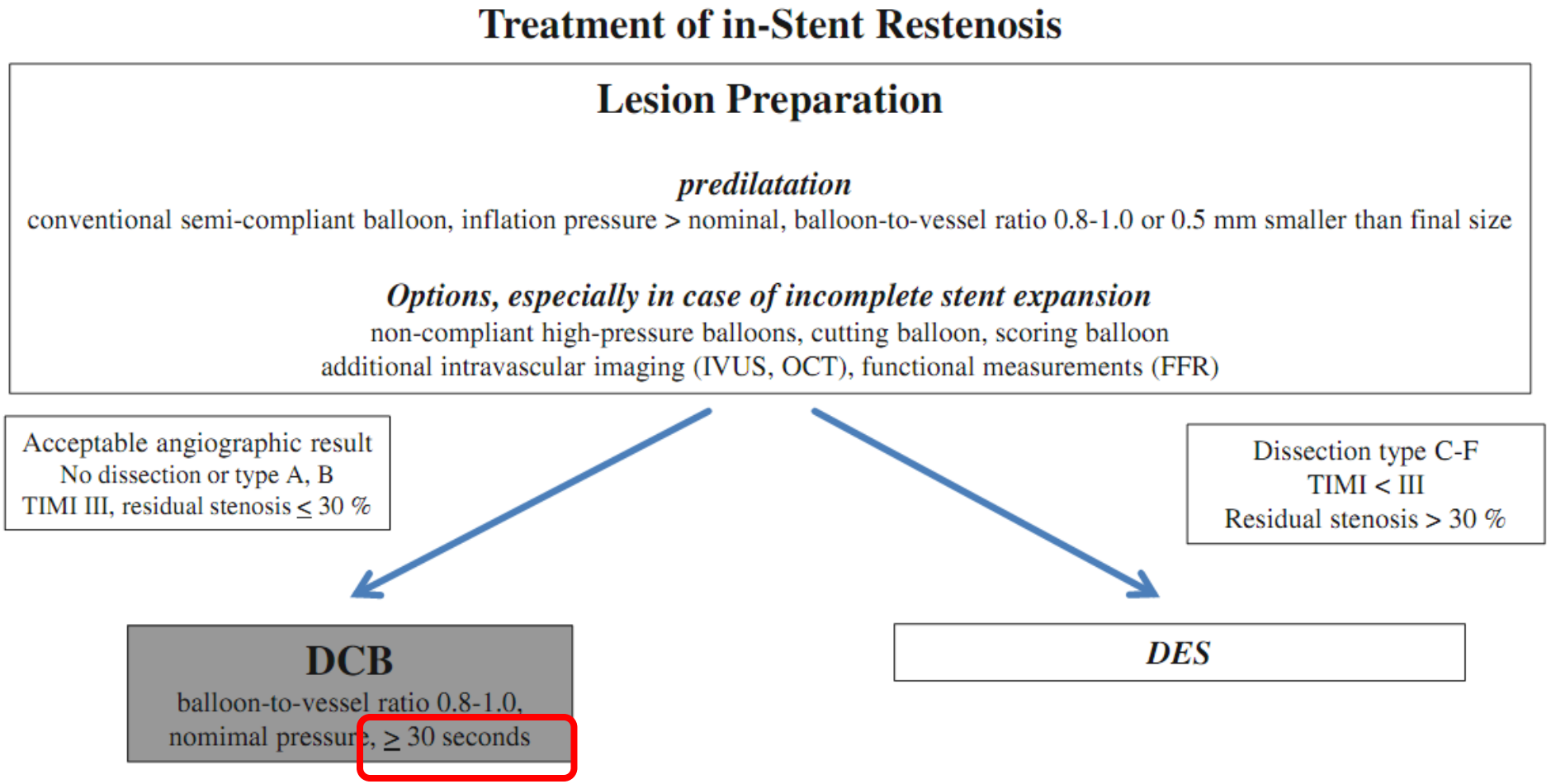
TABLE 4 Clinical Results at 1 Year According to Treatment Group

	Scoring Balloon (n = 125)	Control (n = 127)	p Value
Death	2 (1.6)	2 (1.7)	>0.99
Myocardial infarction	4 (3.2)	2 (1.6)	0.42
Death or myocardial infarction	5 (4.0)	4 (3.2)	0.73
Target lesion revascularization	20 (16.2)	27 (21.8)	0.26
Death, myocardial infarction, target lesion revascularization	23 (18.4)	29 (23.3)	0.35
Definite or probable target lesion thrombosis*	0 (0.0)	0 (0.0)	NA

"In patients with DES ISR, neointimal modification with scoring balloon improves the anti-restenotic efficacy of DCB therapy."

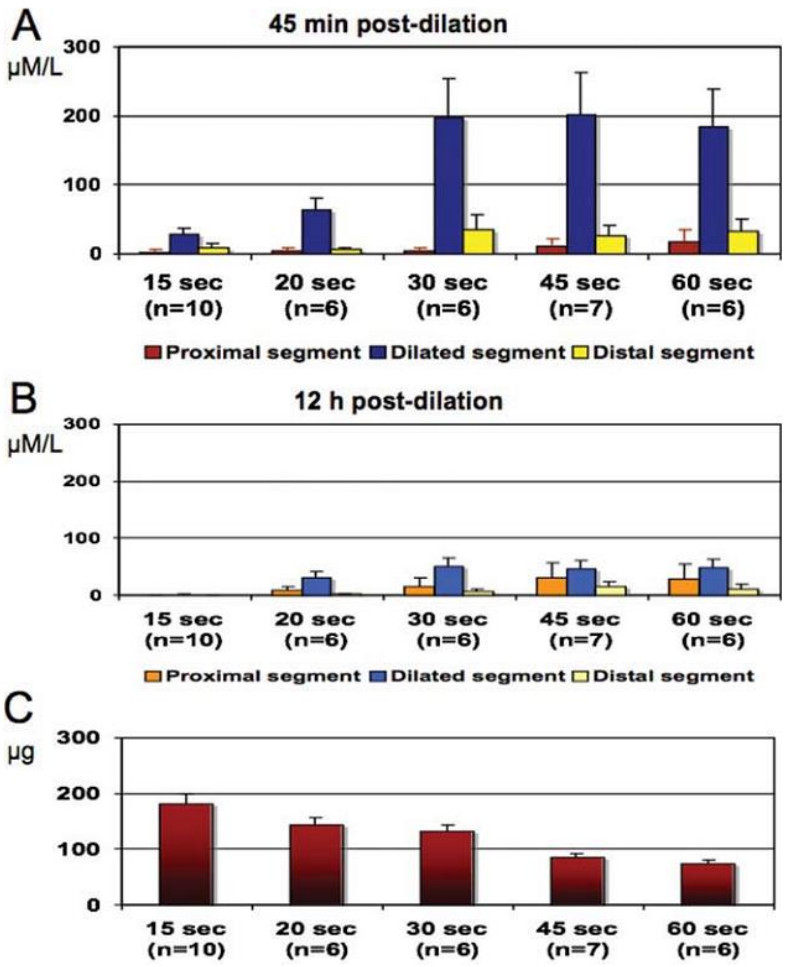
JACC Cardiovasc Interv. 2017;10:1332-40

Current Recommendation for DCB Procedure

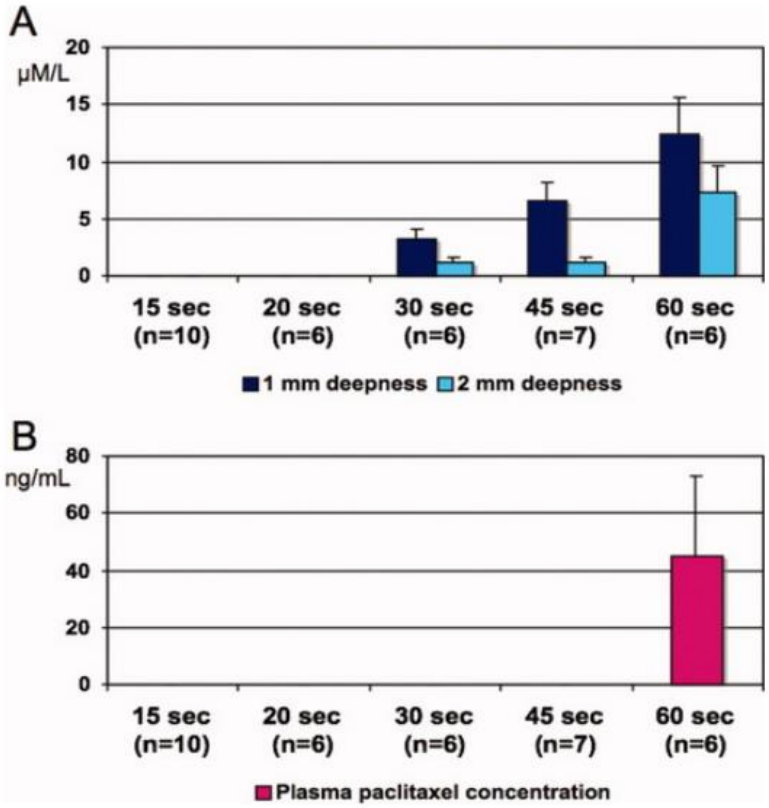


Kleber FX et al. Clin Res Cardiol 2013

DCB Procedural Factor : Background

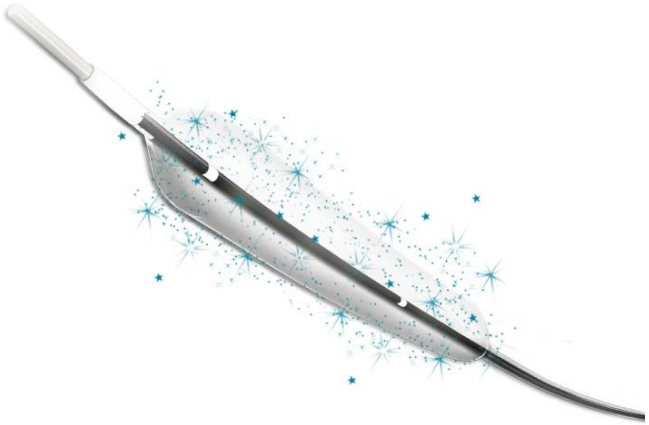


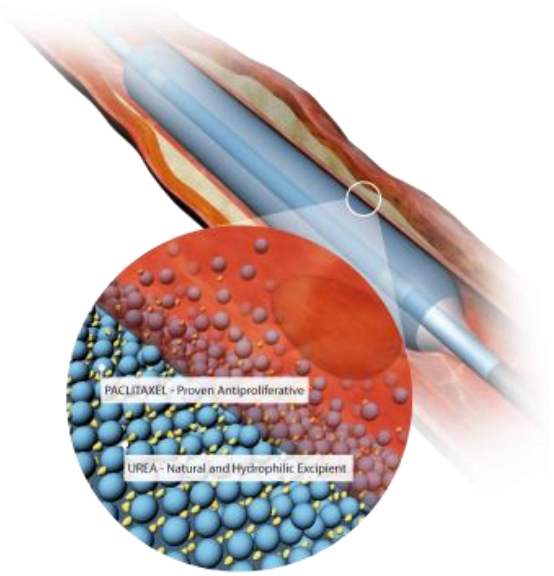
Inflation time-dependent tissue and balloon surface paclitaxel concentration



Inflation time-dependent tissue and plasma paclitaxel concentration

Posa A et al., Cath Cardiovasc Interv 2010





Procedural Optimization for DCB

- **Efficacy of DCB angioplasty is largely dependent on the amount of drug delivered and retained** on the wall of target lesion

"Major Routine Procedural Elements" Currently used to Enhance Clinical Outcomes after DCB in SNUH

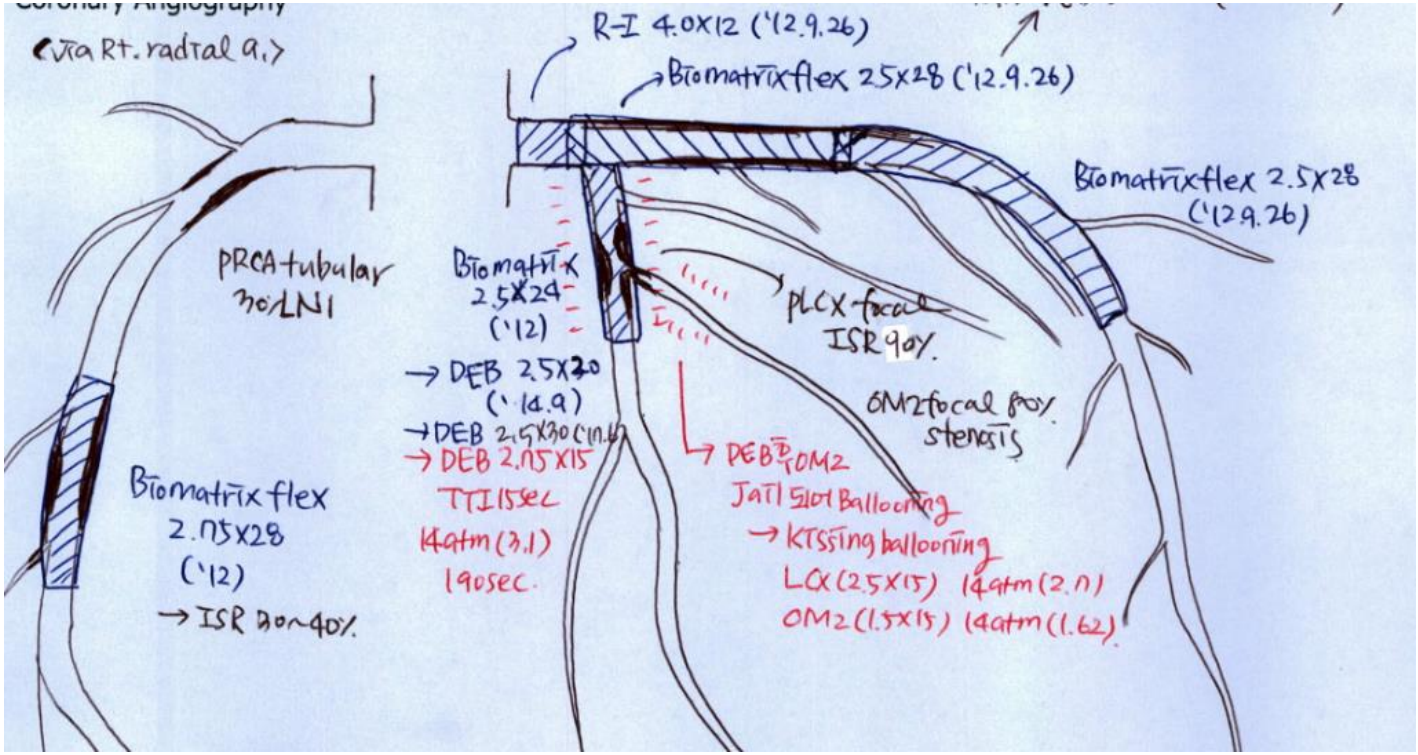
1) **Perfect lesion preparation**
   - Makes the lesion vulnerable, ready for drug uptake
   - Clean up the pathway to the target lesion

2) **Balloon-to-stent ratio**
   - Increases the contact area to maximize drug delivery

3) **Time to inflation of the DCB**
   - Minimizes the amount of drug lost during delivery

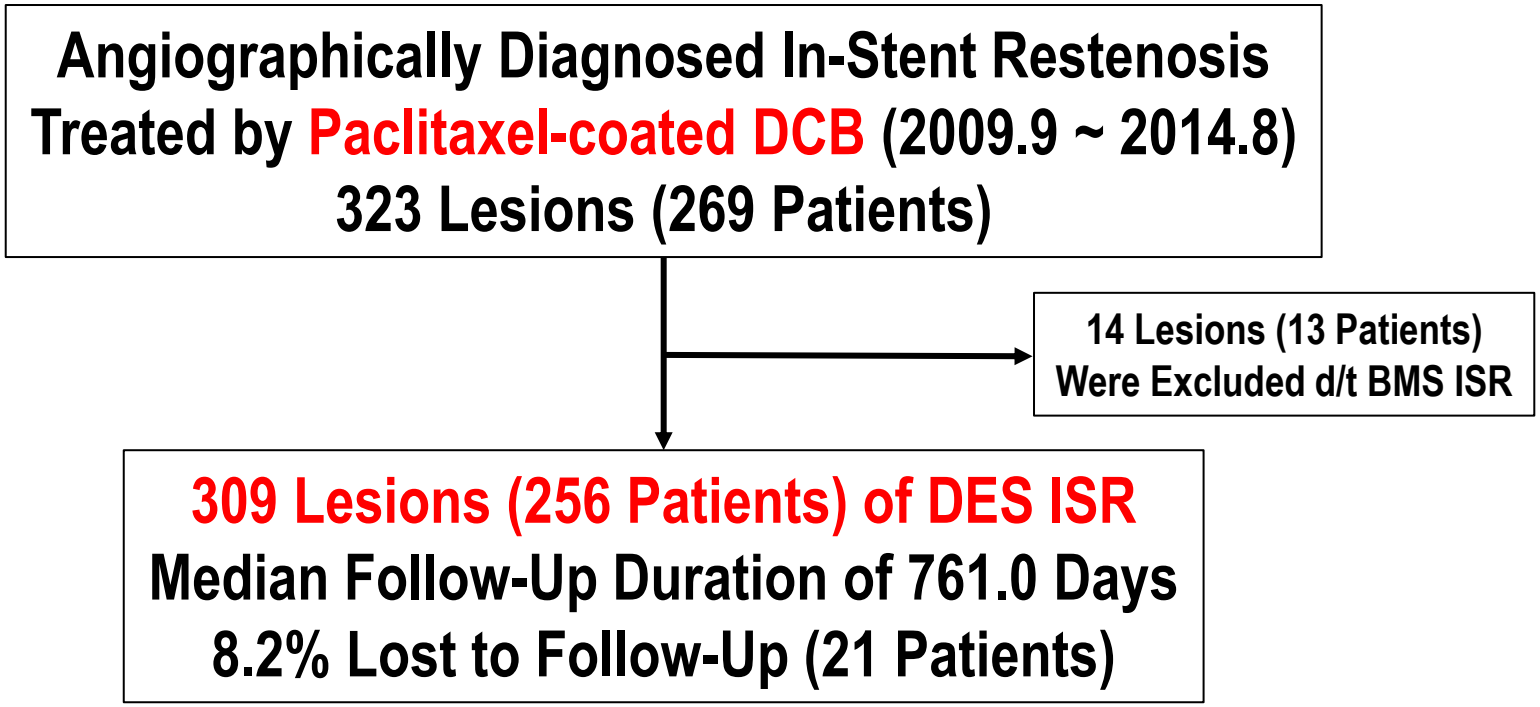
4) **Total Inflation Time of DCB**
   - Increases the contact time for drug to be delivered
   - (Needs the **ischemic preconditioning before DCB treatment)**

“Major Routine Procedural Elements” Currently used to Enhance Clinical Outcomes after DCB in SNUH



POBA to LCx with Centro 2.5x15, 9atm(2.5) ~ 18atm(2.86) 20sec x 2, 40sec
DCB ballooning to LCx with Sequent please 2.75x15, TTI 15sec, 14atm(3.1), IT 190sec
RS <10%, no dissection, TFG 3

Study Protocols



- **Angiographic follow-up at 6-month visit**
  - **Not routinely mandated** but depended on physician's discretion
- **Quantitative coronary analysis (QCA) of index DCB procedures**
  - Baseline and final images **+ Images after lesion preparation**

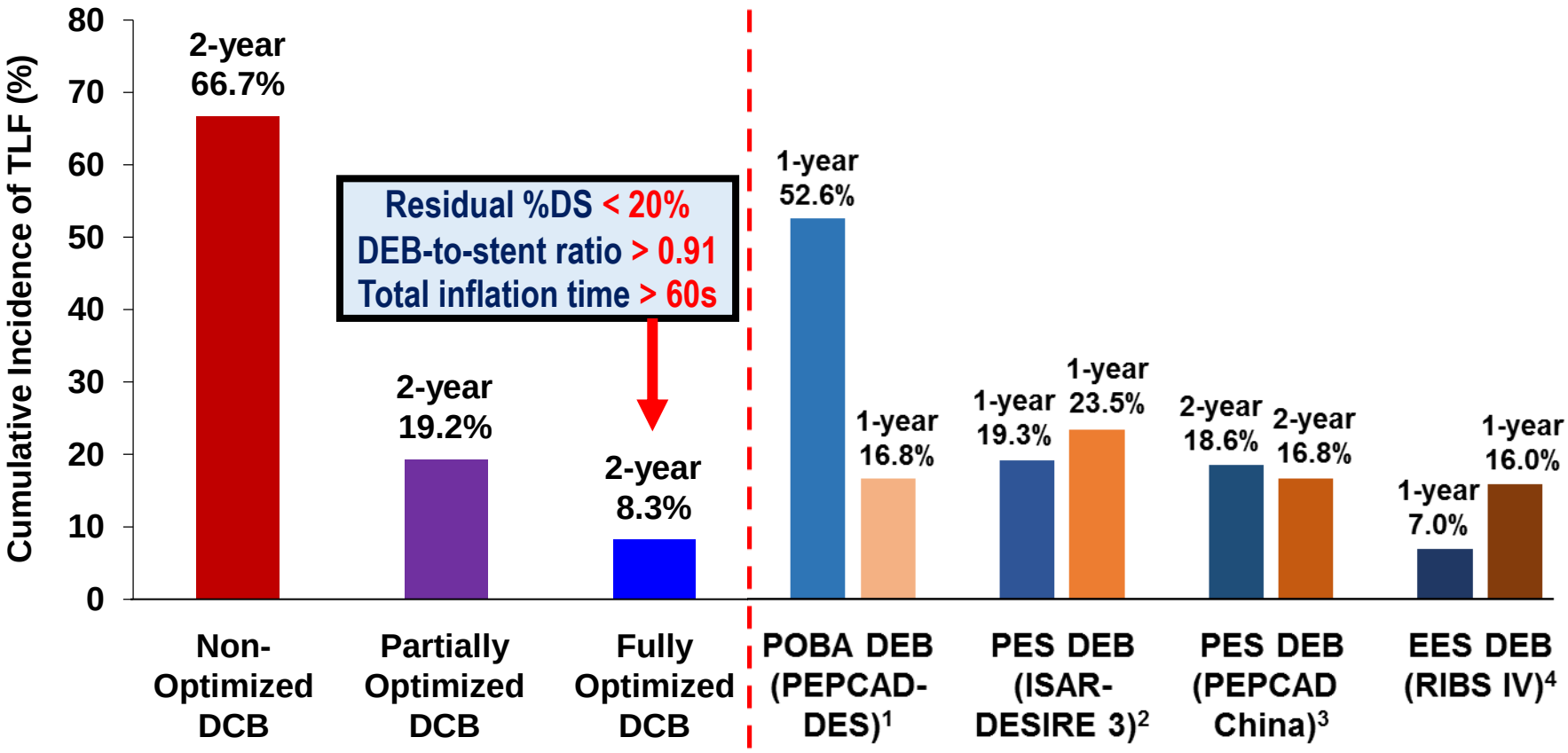
JACC Cardiovasc Interv. 2018;11(10):969-978.

Independent Predictors of Target Lesion Failure

	Hazard ratio	95% CI	*P*
Procedure-related factors			
Residual %DS after lesion preparation (per 1%↑)	**1.021**	1.014 – 1.028	< 0.001
DCB-to-stent ratio (per 0.1↓)	**1.288**	1.012 – 1.640	0.040
Total inflation time of DCB (per 10 seconds↓)	**1.078**	1.039 – 1.117	< 0.001
Patient-related factors			
Peripheral vascular disease	2.274	1.574 – 3.285	< 0.001
Diabetes mellitus	1.687	1.290 – 2.206	< 0.001
Prior history of myocardial infarction	1.226	1.052 – 1.429	0.009
Hypertension	1.184	1.012 – 1.385	0.035
Lesion-related factors			
Complex (type B2 or C) lesion	1.737	1.198 – 2.517	0.004
Long lesion (≥ 28 mm)	1.272	1.045 – 1.549	0.017

JACC Cardiovasc Interv. 2018;11(10):969-978.

Incidence of Target Lesion Failure by Combined Procedure-related Factors



2-year TLF rate in fully-optimized DCB group was 8.3%, Similar to or even better than 1st or 2nd generation DES groups in previous ISR trials

Conclusion

- Given the prognostic importance of DES ISR, efforts to improve outcomes after DCB angioplasty are crucial.

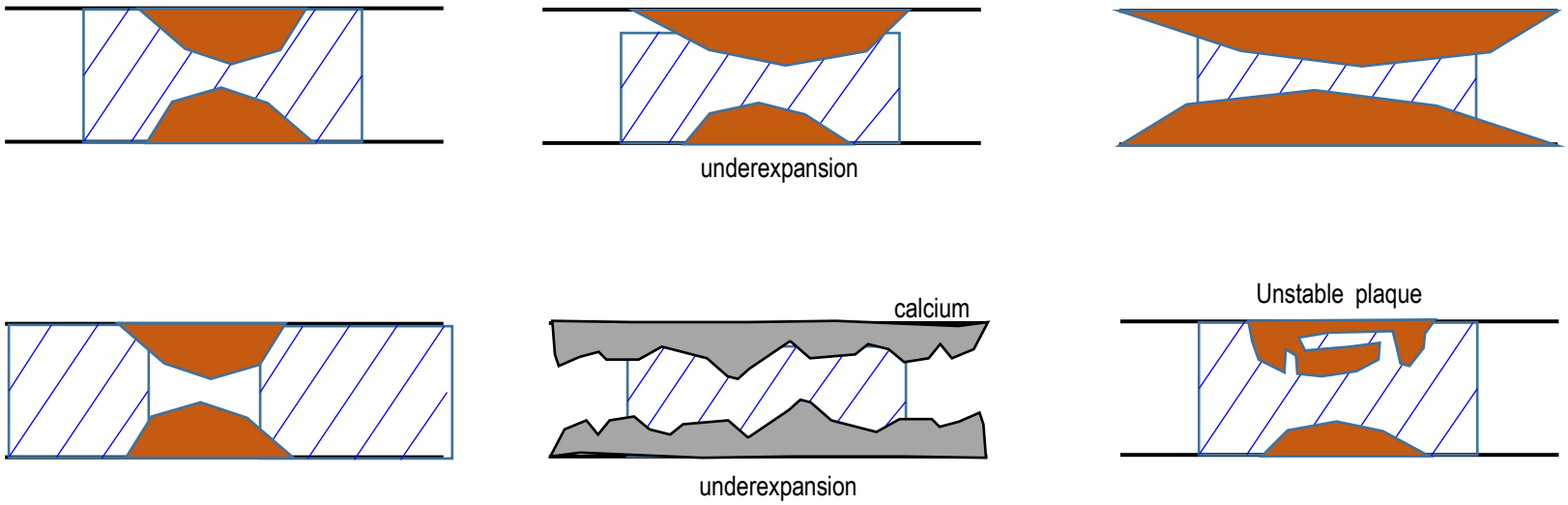
- There are important procedure-related factors that could independently predict future occurrence of TLF after DCB angioplasty for DES ISR

- Fully-optimized DCB angioplasty with
  [1] Proper lesion preparation until residual %DS < 20%,
  [2] Sufficient dilation with DEB-to-stent ratio > 0.91,
  [3] Prolonged inflation at least 60 sec,
  would improve clinical outcomes comparable to 2nd gen DES

JACC Cardiovasc Interv. 2018;11(10):969-978.

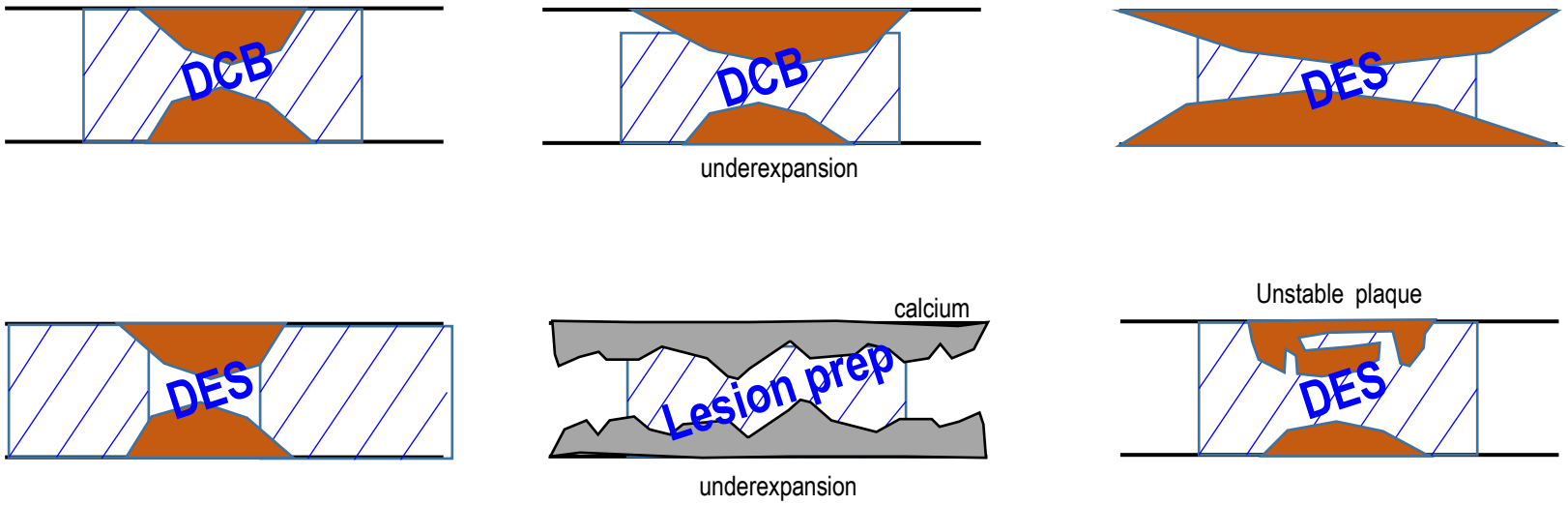
Directions of further studies

- ✓ In the aspect of personalized medicine, ***"Are all ISR lesions identical?"***
  - ✓ Focal neointimal hyperplasia in an otherwise well-expanded and apposed stent
  - ✓ Stent malapposition or underexpansion in a vessel without severe calcification
  - ✓ Diffuse neointimal hyperplasia
  - ✓ Stent fracture, stent gap, or stent edge restenosis
  - ✓ Stent underexpansion because of 360° calcification or nodule
  - ✓ Neoatherosclerosis with unstable plaque features.



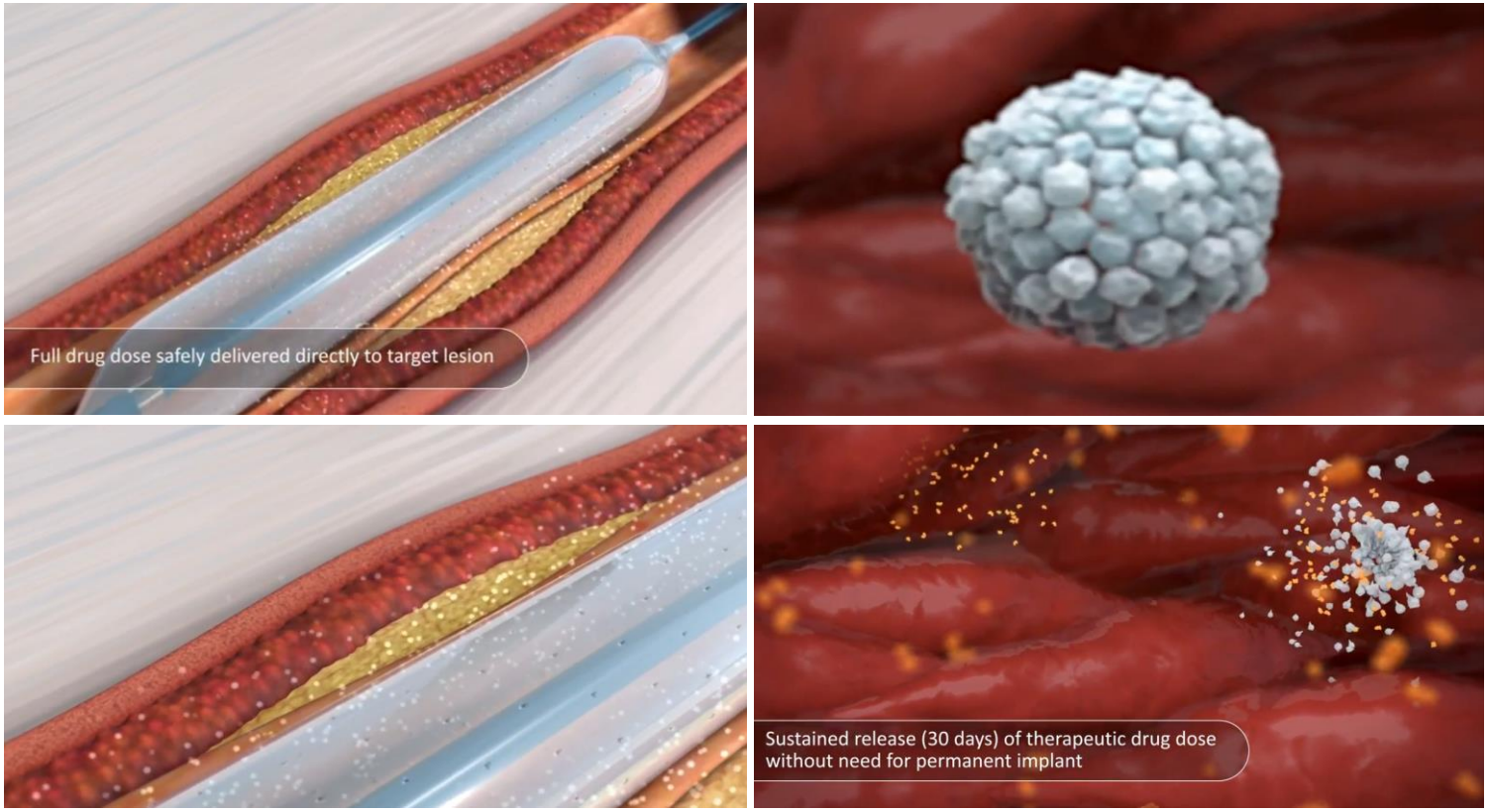
Directions of further studies

- ✓ In the aspect of personalized medicine, ***"Are all ISR lesions identical?"***
  - ✓ Focal neointimal hyperplasia in an otherwise well-expanded and apposed stent
  - ✓ Stent malapposition or underexpansion in a vessel without severe calcification
  - ✓ Diffuse neointimal hyperplasia
  - ✓ Stent fracture, stent gap, or stent edge restenosis
  - ✓ Stent underexpansion because of 360° calcification or nodule
  - ✓ Neoatherosclerosis with unstable plaque features.



Directions of further studies

- ✓ Any new technologies to overcome the procedural hurdles?
  - ✓ ***SABRE trial: new Sirolimus DCB***
  - ✓ New technique to pack labile drug molecules within particles AND overcome the flake off and undefined loss of the of DCB coating en route to the target lesion



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Thank You For Your Attention

Any comments, questions, contact

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