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Rationale and Likely Mechanism of Action of Paclitaxel-Coated Balloons

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Disclosure

Speaker name:

Ulrich Speck

I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a research company
- Owner of a healthcare company
- Coinventor of several balloon coating methods

- I do not have any potential conflict of interest

Paclitaxel on Coated Balloons

Facts

Paclitaxel is classified as cytostatic agent; however

- intravascular dose for tumor therapy is 300 mg/adult;
- single dose of 70 mg/adult* has no recognizable adverse effects;
- maximum dose on a balloon is 1 mg (coronary) to 10 mg (peripheral);
- cytostatic effect on microtubuli is unrelated to DNA.

*) Huizing MT et al. J Clin Oncol 1993;11:2127-2135; Margolis J et al. Clin Cardiol 2007;30:165-170

DCB: Where Does the Drug Go?

(Effective Products)

	mean [%]	range [%]
Balloon	100	---
Lost on the way to the lesion	10	5-30
<i>Transferred to the vessel wall</i>	10	5-20
Lost in the blood stream during inflation	70	40-70
Paclitaxel recovered from used balloons	10	0-30



Paclitaxel on Coated Balloons

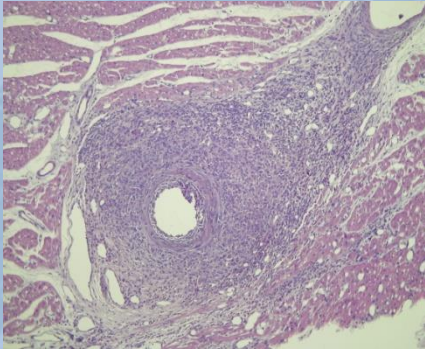
Facts

Mechanism

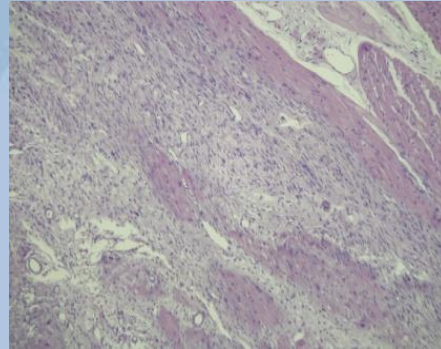
- action relies on the transfer of slowly dissolving particles into the vessel wall

Downstream Effects in Animal Experiments at High Dose

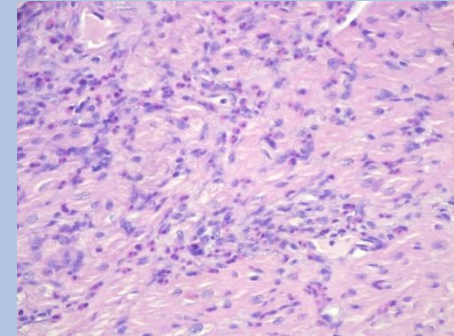
Detected in histological slices



50, S, vasculitis,
10x



40, L, scar, 10x



36, L, focal inflammation,
40x

...but no impact on myocardial function, e.g., left ventricular ejection fraction (EF) [%]

	3 $\mu\text{g}/\text{mm}^2$	2 x 5 $\mu\text{g}/\text{mm}^2$	Uncoated	p
Before treatment	42.0 \pm 8.3	40.1 \pm 4.4	45.4 \pm 9.9	0.573
At 28 days	39.5 \pm 6.5	34.7 \pm 4.3	39.0 \pm 6.2	0.375
Change	-2.5 \pm 8.1	-5.4 \pm 7.0	-6.4 \pm 4.2	0.642

Paclitaxel on Coated Balloons

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Potential particle-induced downstream effects?

- No perfusion or functional deficits in myocardium of swine in spite of multifold overdose in small hearts
- Experience with SeQuent Please in > 100 000 coronary patients: no increase in adverse effects compared to POBA or stenting

(2014 ESC/EACTS guidelines on myocardial revascularization, Windecker et al., European Heart Journal 2014)

- Use of SeQuent Please in intracranial vessels

(Vajda Z et al. Neurovascular in-stent stenoses: treatment with conventional and drug-eluting balloons. Am J Neuroradiol 2011; 32: 1942-1947)

- Particle burden due to DCB small compared to debris shed from atherosclerotic plaques

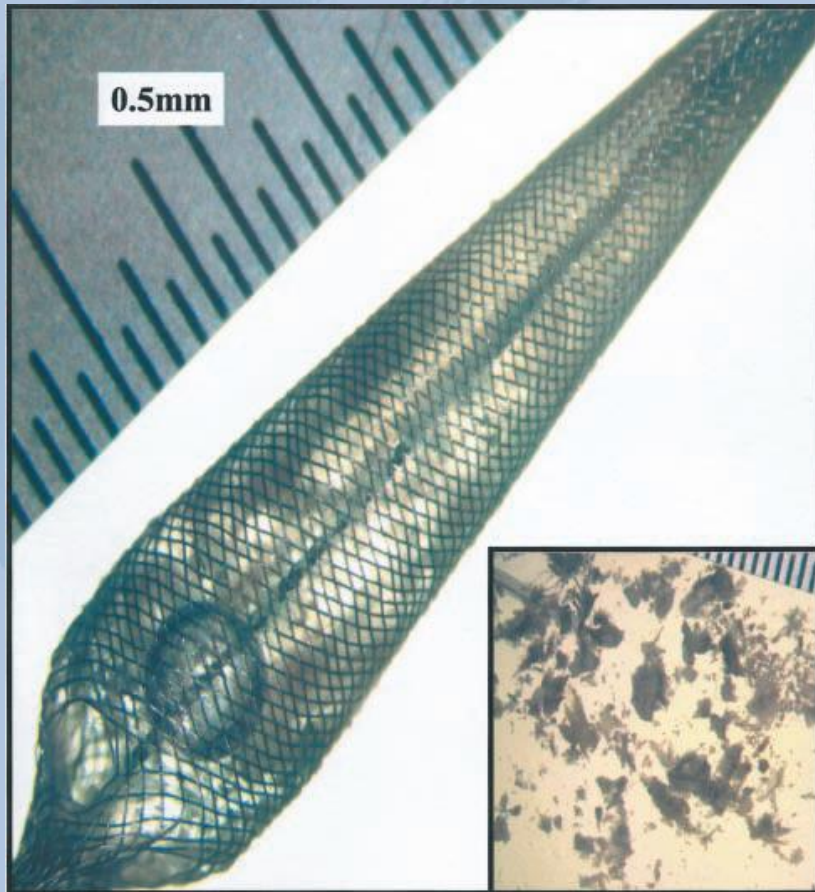
(Angelini A et al. Circulation 2001;104:2436-2441;Rogers C et al. Circulation 2004;109:1735-1740)

Paclitaxel on Coated Balloons

Facts

Comparison of particle burden due to plaque debris and coated balloons

Campbell Rogers, MD et al.
Circulation 2004;109:1735-1740



- Total embolic load per lesion for filters: mean $23 \pm 19 \text{ mm}^3$, range 2 - 83 mm^3
- 2 - 83 $\text{mm}^3 \sim 2 - 83 \text{ mg}$
- Total Ptx content of a PTCA balloon: up to approx. 1 mg

Distal Cerebral Protection Device Filled with Calcified Plaque Debris after Carotid Stenting

Velasco A and Mosimann PJ

JACC Cardiovasc Intervent 2013; 6: 22-23
Debris after stenting of a carotid artery



Conclusions from Current Experience

Study (examples)	Author, year	TLR rate 6 mths	TLR rate 12 mths	Coating-specific adverse events
ISR I + II	Scheller et al., 2008		2/54	none
Thunder	Tepe et al., 2008	2/48	5/48	none
In.Pact Deep	Zeller et al. 2014		18/196	1?/of several
SFA II	Tepe et al., 2014		5/207	none
Levant 2	Rosenfield et al., 2015		35/285	none
Conclusions		Efficacy not always optimal		Tolerance: no evidence of problems so far, remains to be observed

Paclitaxel on Coated Balloons

Conclusions

Mechanism of action

- relies on the transfer of slowly dissolving particles into the vessel wall

Resulting risks

- embolic risk negligible in view of plaque debris

Room for improvement

- restenosis inhibition in >95% of patients, difficult lesions, more vessel territories

Paclitaxel on Coated Balloons

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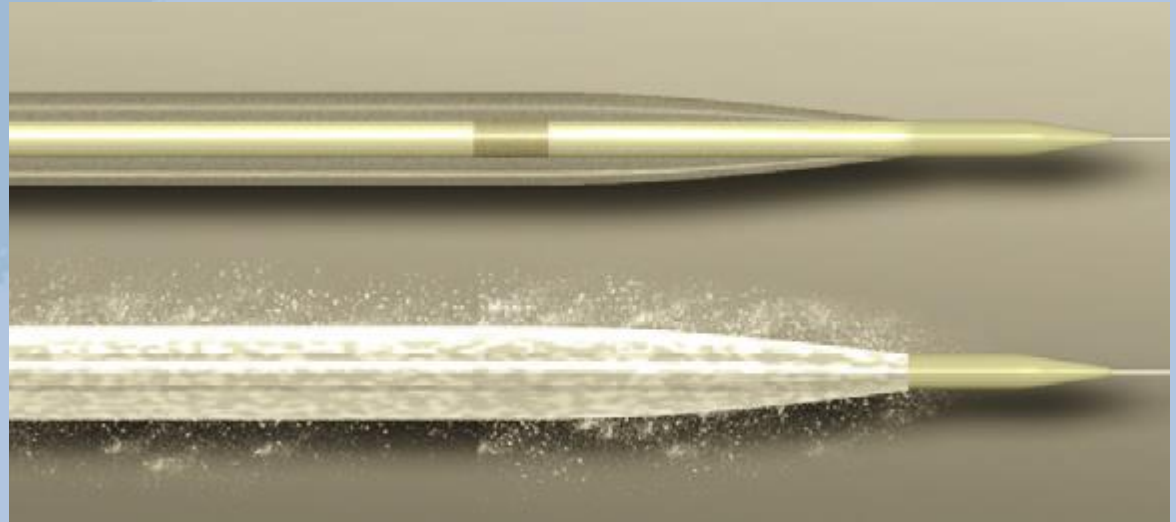
Comparison of Coronary Particle Burden due to Plaque Debris and Coated Balloons

	Atherosclerotic plaque material	DCB
Mass	2-83 mg	<< 1 mg
Size	0.015 to 20 mm ²	?
Material	Extracellular matrix, lipids	Paclitaxel

Conclusion: Since embolic protection is not routinely used in coronary interventions the risk due to particles seems to be accepted?

Advertisement (Photoshop)

1. „Stable“ DEB PTX coating technology



2. „Unstable“ DEB PTX coating with free PTX crystals on balloon surface

Reality



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