The DCB Dose Difference: A Comparison of Drug in Tissue of Different .018 DCBs

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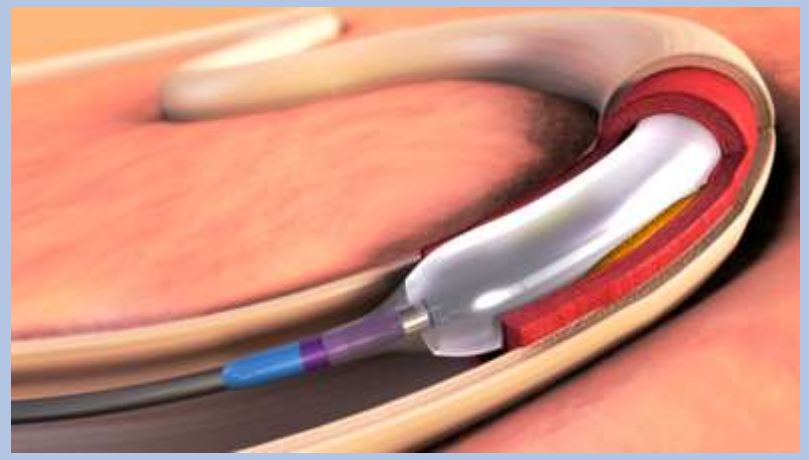
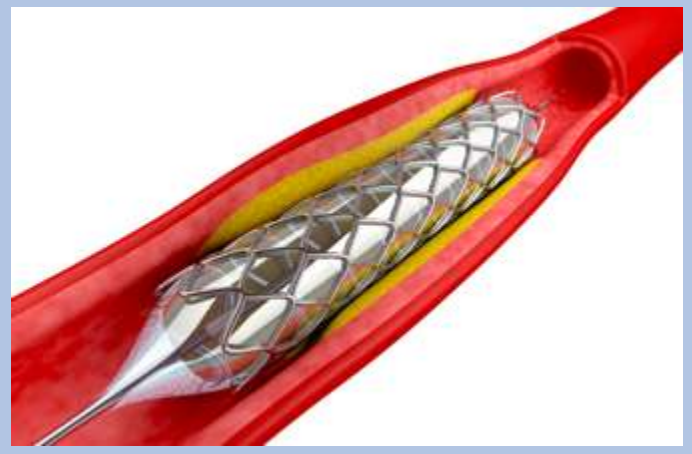
Disclosures: Dr. Andrew Holden

- Dr. Holden is a Medical Advisory Board Member for Medtronic, Boston Scientific, and Gore
- Dr. Holden is a Clinical Investigator for Medtronic, Boston Scientific, Gore, Abbott, Cagent, Endologix, Intact Vascular, Shockwave, Bard, Cook, Endospan, Intervene, Spectranetics, TriReme, Merit, Reflow, Terumo, Surmodics
- No other relevant disclosures

Background

- Peripheral vascular interventions (including angioplasty, atherectomy, and stenting) may restore luminal flow; however, they also incite local injury.
- Vascular wall injury initiates inflammatory, migratory, proliferative and extracellular matrix deposition processes which can lead to neointimal hyperplasia and restenosis.

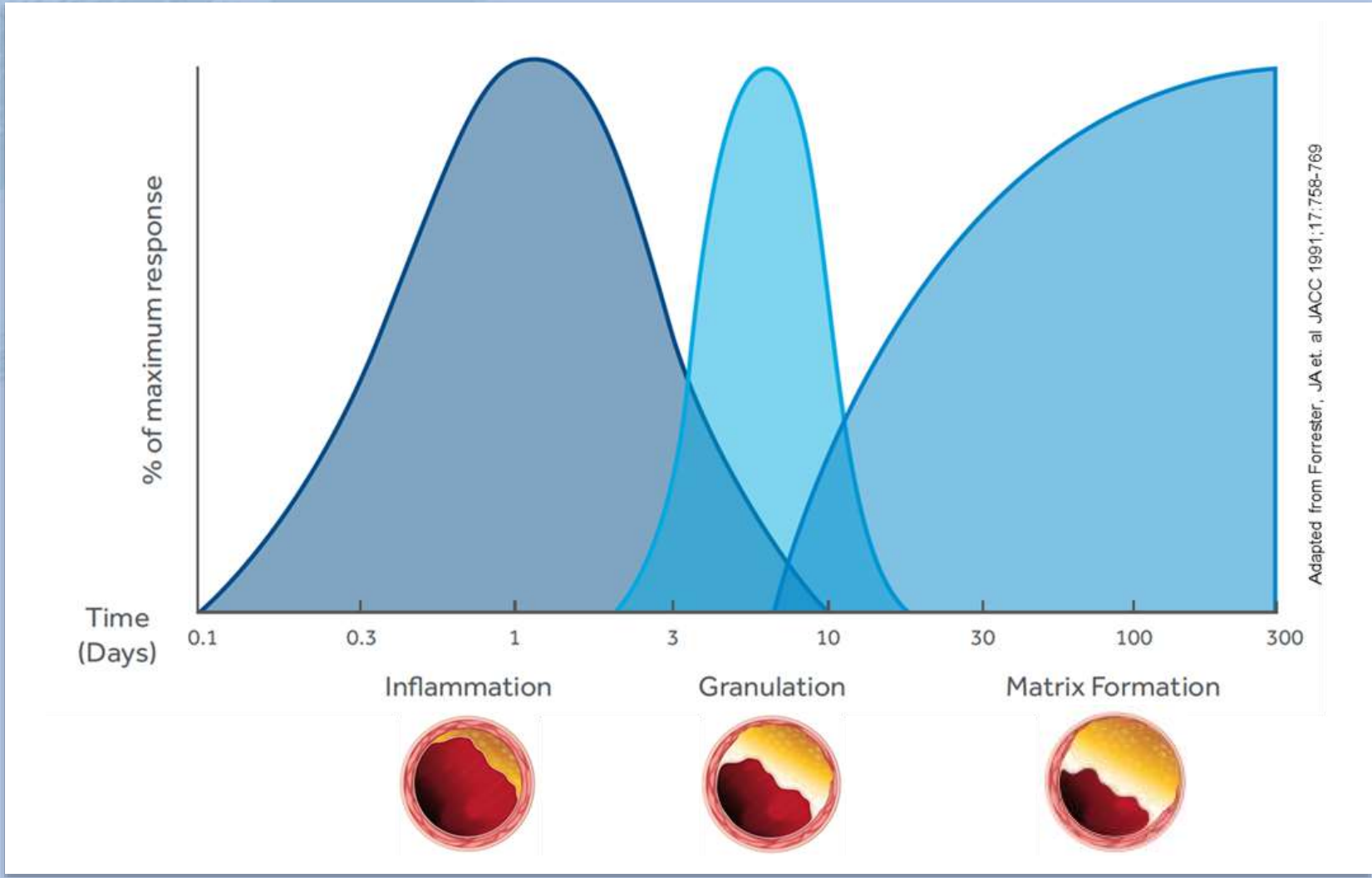




Klink M et al Atherosclerosis 1996;12:17-31

Biology of Restenosis Cascade in Arteries

Inflammation, Granulation & Extracellular Matrix Formation



Anti-restenotic Drugs in Endovascular Intervention

- Although there is clear evidence of improved patency using anti-restenotic drugs combined with angioplasty balloons and stents[1,2], much remains unknown about mechanism of action
- Effects of anti-restenotic drug dose, coatings, and excipient choices to optimally prevent restenosis should be further evaluated

1. Laird, et al, Circulation: Cardiovascular Interventions. 2019;12:e007702.
2. Dake et al., Circulation. 2016;133(15):1472-83.

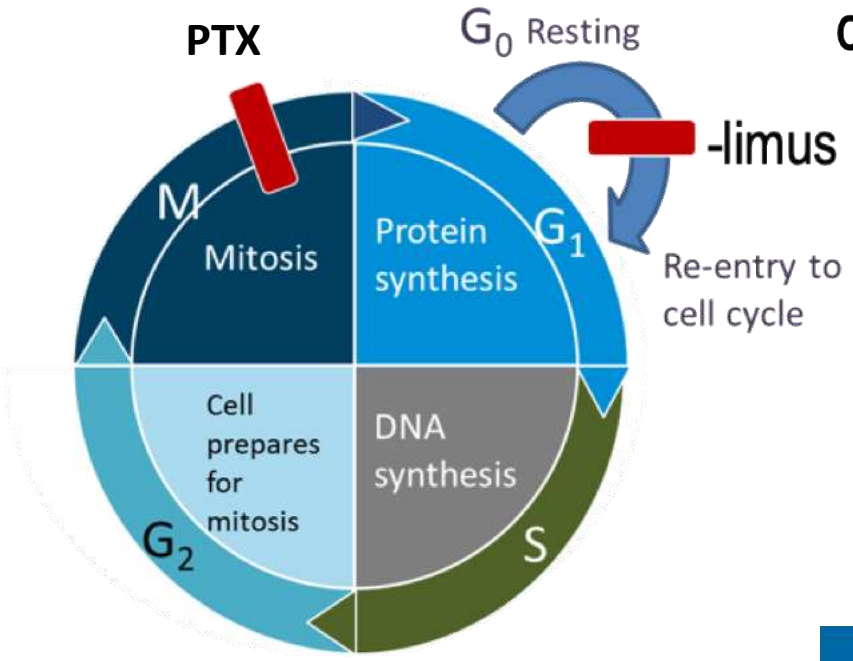
Mechanisms of Action
Conventional Knowledge

Paclitaxel (Cytotoxic)
Interferes with cell division

Cytotoxic drugs halt cell division, inducing apoptosis

Rapid transfer (via excipient) allows <u>acute</u> delivery, especially beneficial if no artificial reservoir is present

➡ DCB



Limus (Cytostatic)
Interferes with cell growth

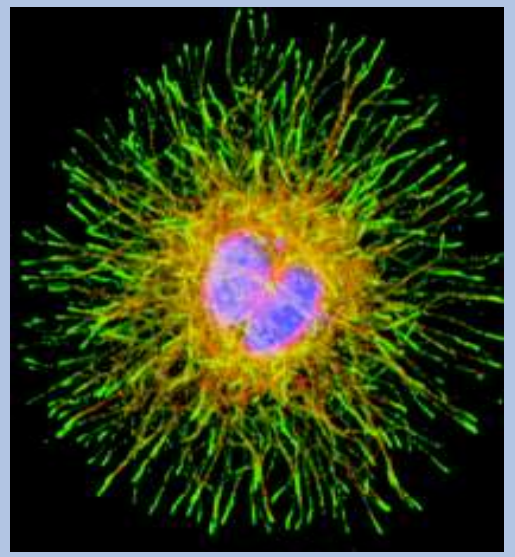
Cytostatic drugs hold a cell in G_0 phase, arresting growth

Prolonged elution (via polymeric 'reservoir') allows <u>sustained</u> delivery, especially beneficial when stent is present

➡ Coronary DES

Mechanisms of Action
Additional Effects of Paclitaxel

- Paclitaxel inhibits microtubule function and is cytotoxic if it acts on the cell during mitosis = apoptosis[1,2]
- However, only 10% of cells are dividing at any point in time
- In the remaining surviving cells, microtubules are involved in:[1,2,3]
  - » Cell Motility & Migration
  - » Protein Transport
  - » **Protein Secretion/Extracellular Matrix (ECM)**
  - » Angiogenesis



1. Microtubules: From understanding their dynamics to using them as potential therapeutic targets. Ilan Y. J Cell Physiol. 2019 Jun;234(6):7923-7937.
2. Microtubules: structure, chemistry, and function. Stephens RE, Edds KT. Physiol Rev. 1976 Oct;56(4):709-77.
3. Picture: Giulian V. M Dec. 26, 2012 https://www.anti-agingfirewalls.com/2012/12/26/microtubules-the-intra-cellular-transport-system-health-and-longevity/

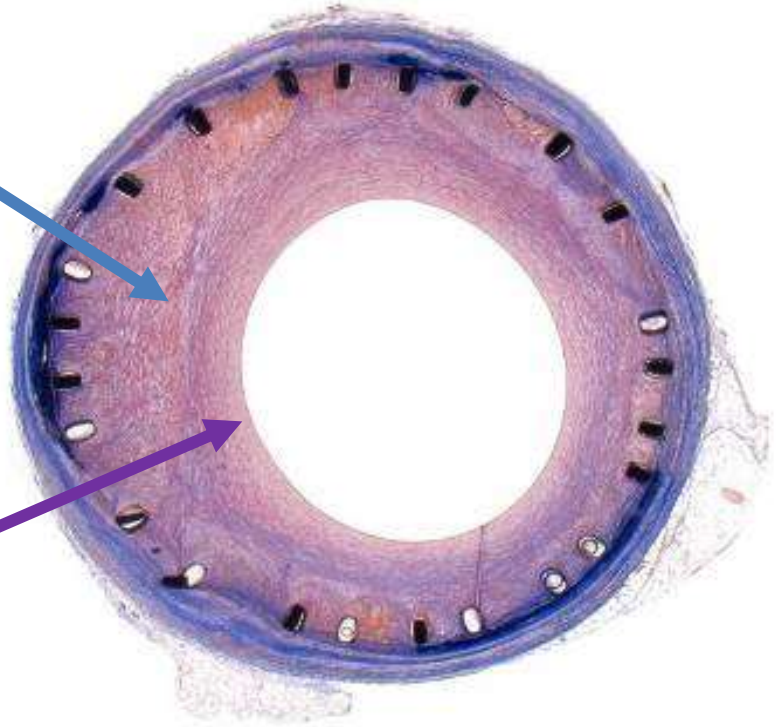
Vessel Response to Stent Injury

Paclitaxel Modulates Healing

Uninhibited Healing

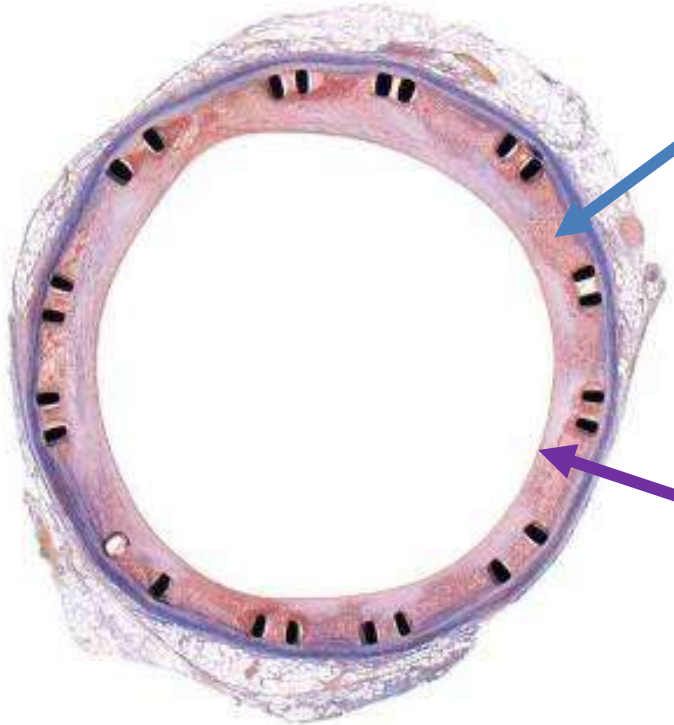
Secretory SMCs + ECM layers are thick

Healthy contractile SMCs



Non-coated Balloon

Paclitaxel Modulated Healing



Secretory SMCs + ECM layers are thin

Healthy contractile SMCs

DCB

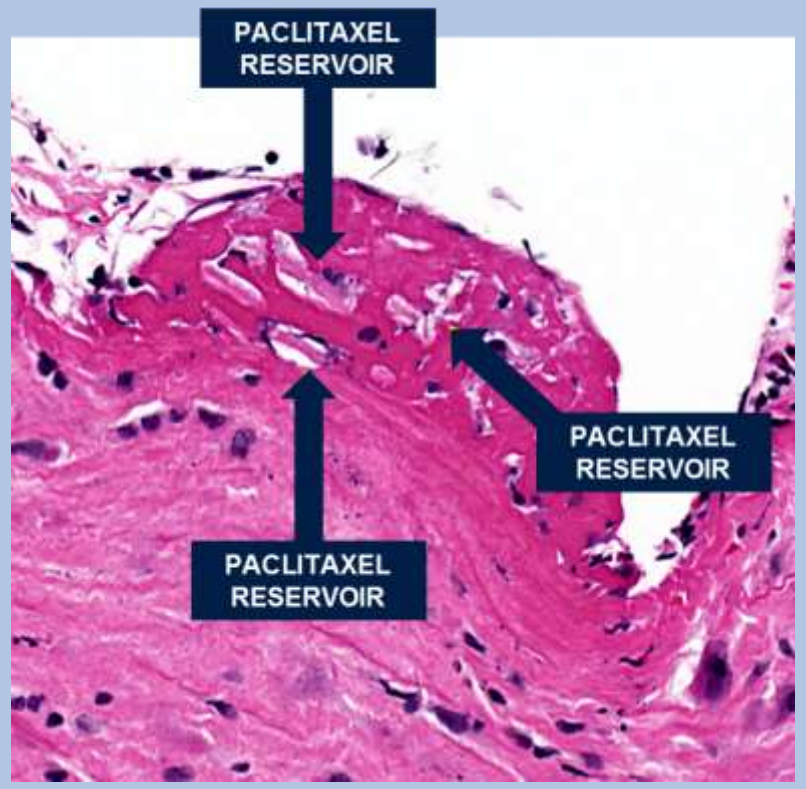
Medtronic data on file

Factors for Successful Revascularization

- Acute lumen gain with restoration of normal flow
- Durable result by combating the restenosis cascade (drug elution)
- Modulate the healing response – facilitate smooth muscle cells to produce mature competent tissue
- Mature competent tissue will prevent recurrence of atherosclerosis

Drug Elution to Achieve Mature Competent Tissue

1. **Right drug** (lipophilic, fast diffusion and tissue uptake, broad mechanism of action)
2. **Right amount of drug** (dose)
3. **Effective drug transfer** (balloon, coating, and excipient)
4. **Right drug formulation** (crystalline drug reservoirs, amorphous dissolvable)
5. **Right duration of drug in the vessel** to modulate the healing response



How can we confirm drug efficacy?

In-stent Restenosis (ISR) Porcine Model Study

Purpose: To compare suppression of ISR between two 0.018” Drug-coated Balloons (DCB): the IN.PACT Pacific DCB and the Ranger DCB

Model: Yucatan mini swine model of ISR

Device Specifications:

	Ranger DCB	IN.PACT Pacific DCB
Drug	Paclitaxel	Paclitaxel
Dose	2µg/mm^2	3.5µg/mm^2
Excipient	Citrate Ester	Urea
Uncoated PTA	Sterling PTA	Pacific Extreme
Balloon Platform	0.018”	0.018”

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Dose	2µg/mm^2	3.5µg/mm^2	3.5µg/mm^2
Excipient	Citrate Ester	Urea	Urea
Uncoated PTA	Sterling PTA	Pacific Extreme	Admiral Extreme
Balloon Platform	0.018”	0.018”	0.035”

ISR Porcine Model Study: Methodology & Analysis

Methodology

Create ISR model in swine peripheral vasculature by injuring the target artery with angioplasty followed by a stent implantation

↓

Day 0 (after 28 days maturation): Treat the stented sites with DCB; Perform angiographic imaging

↓

Day 90 (IPP/Ranger): Perform interim angiographic imaging; Measure suppression of restenosis as compared to Day 0

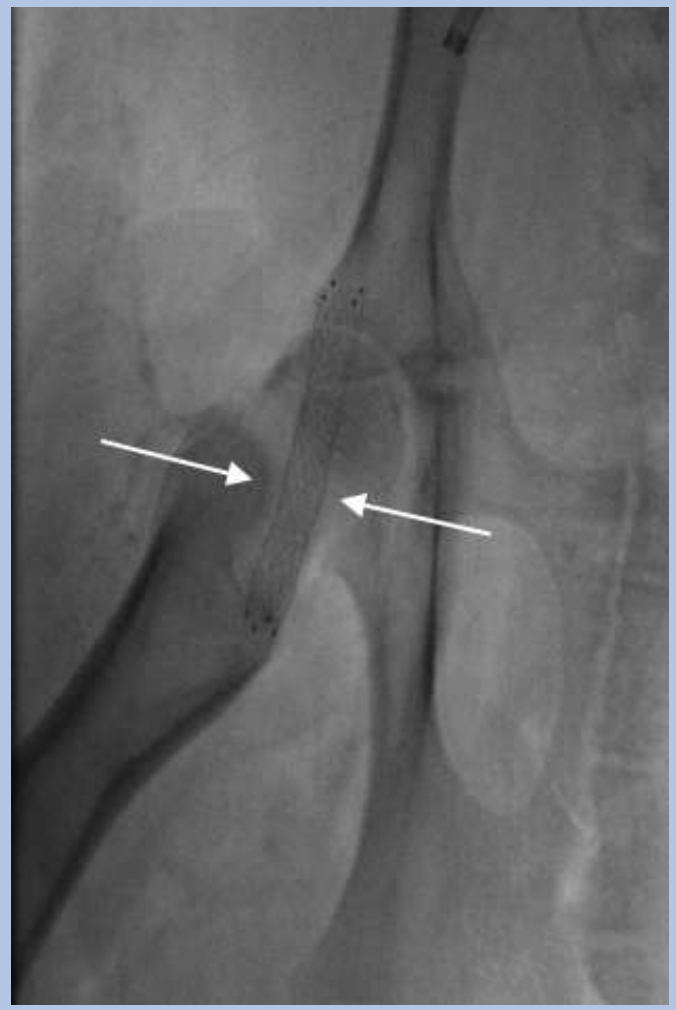
↓

Day 120 (IPP/Ranger): Perform terminal angiographic imaging; Measure suppression of restenosis as compared to Day 0; Obtain sample tissues for drug content analysis

Restenosis Analysis

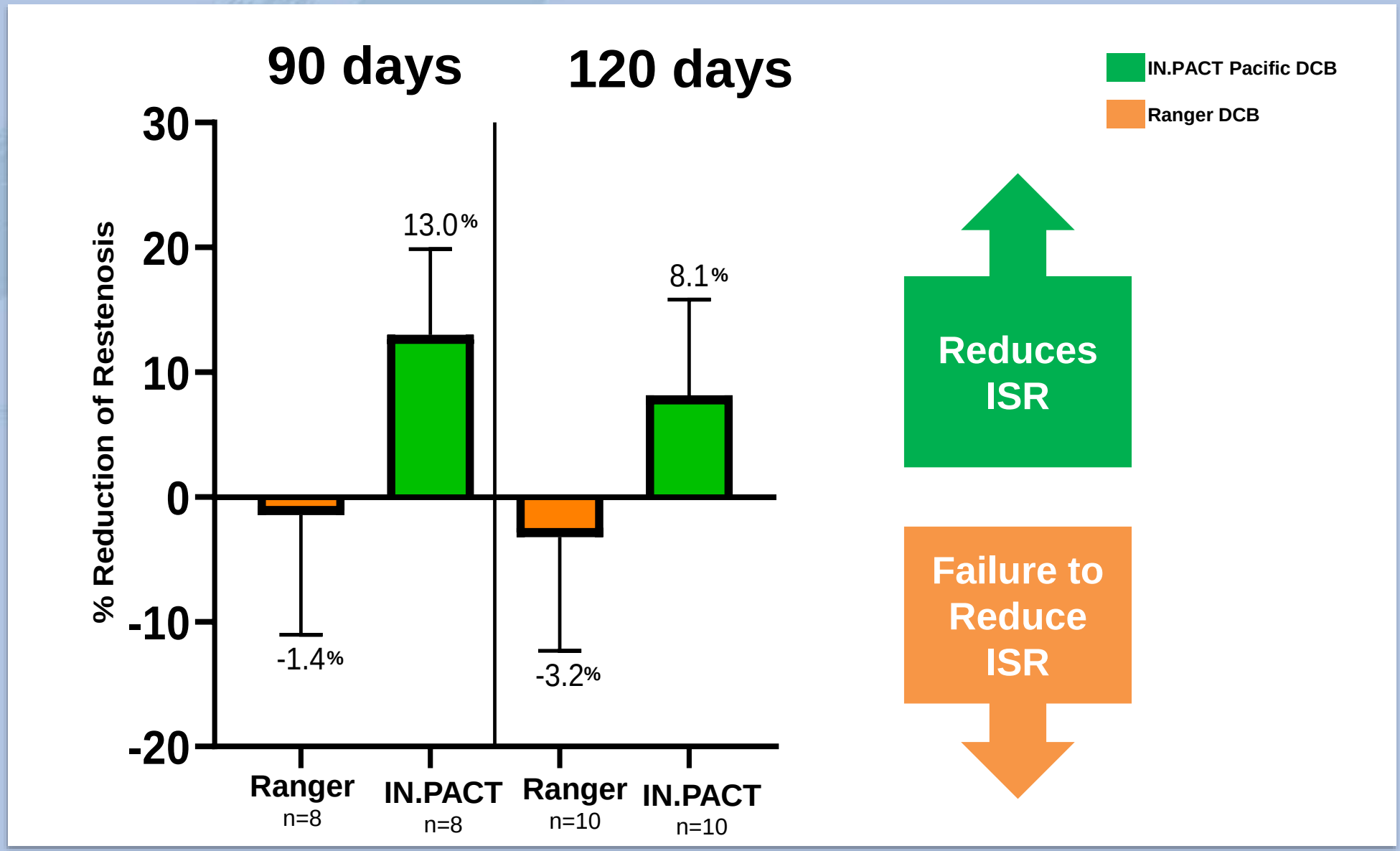
Determine % Reduction of Restenosis as compared to baseline (Day 0)

$$\%\ \text{Reduction of Restenosis} = \frac{(\text{Day 0 Restenosis} - \text{Day x Restenosis})}{\text{Day 0 Restenosis} \times 100}$$



Medtronic data on file

Outcomes: In-stent Restenosis Through 120 days



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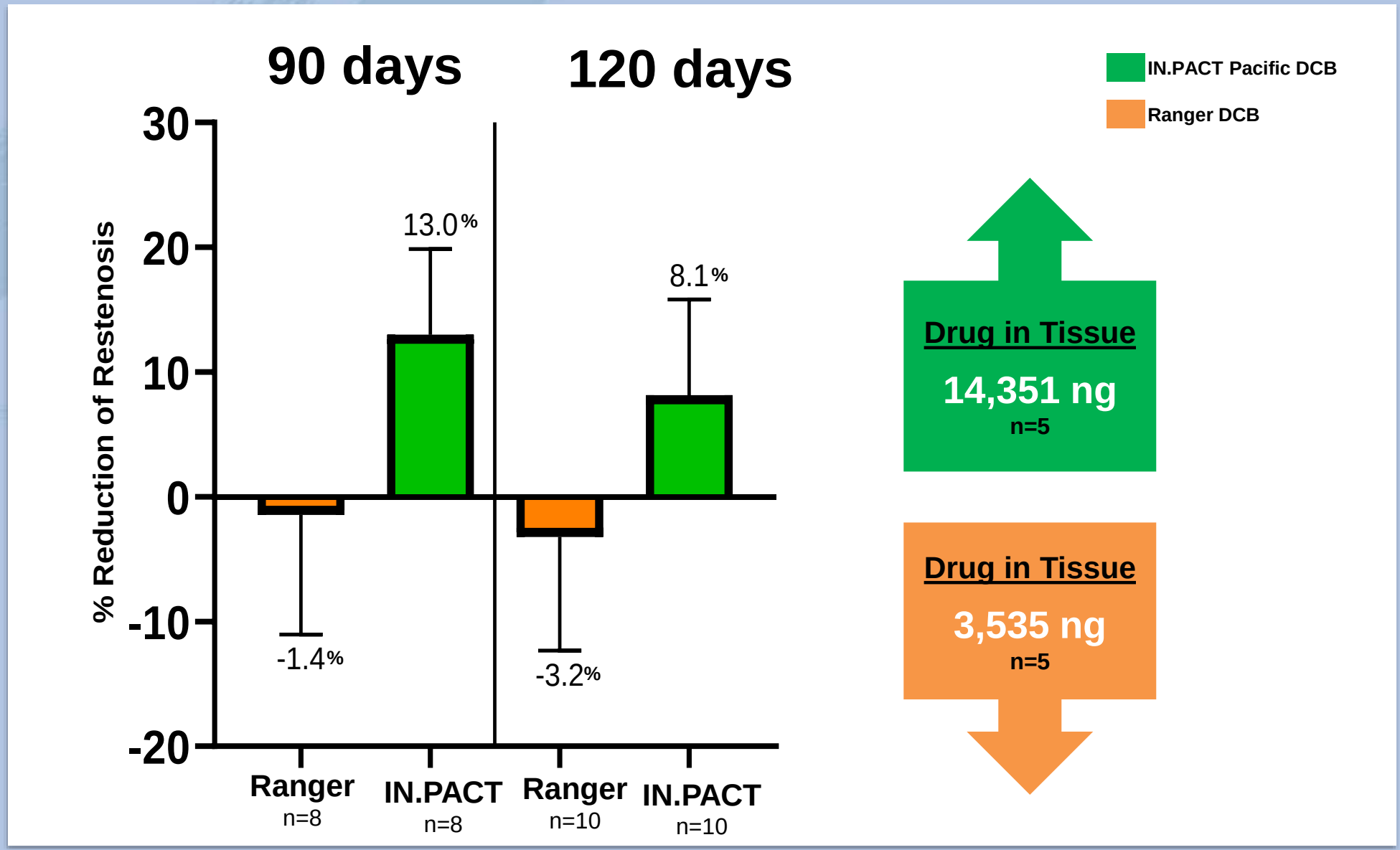

Summary

- The IN.PACT DCB platform offers a unique formulation (drug/dose/excipient) that effectively inhibits in-stent restenosis through 120 days in an animal model as compared to the Ranger DCB
  - IN.PACT DCB demonstrated an 8.1% **reduction of ISR** through 120 days
  - Ranger DCB demonstrated a 3.2% **increase of ISR** through 120 days
- This study demonstrates the mechanisms behind DCB drug formulation (including input dose) driving long term effectiveness
- Also explains the superior long-term patient outcomes seen in IN.PACT DCB studies
- Further study of inhibitory/healing mechanisms are needed and each DCB must be considered on its own merit

Acknowledgments

- Dr Juan Granada, Executive Director and Chief Scientific Officer
  CRF-Skirball Center for Cardiovascular Research
  Columbia University Medical Center, New York

- Dr Bob Melder, Senior R&D Director, Medtronic Cardiovascular Medtronic

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