

# Drug Eluting Stents: Balancing Risks and Benefits

Sanjay Kaul, MD; George A. Diamond, MD

Division of Cardiology

Cedars-Sinai Medical Center

Los Angeles, California



# Drug-Eluting Stents

## What We Know

- Quantum leap in interventional cardiology
- Reduces angiographic and clinical restenosis
- Does not confer benefits in hard clinical outcomes in chronic stable CAD
- May predispose to stent thrombosis, a rare but potentially life-threatening outcome

# Drug-Eluting Stents

## What We Don't Know

- Uncertainty regarding benefit (restenosis, TLR)
  - Is the benefit in “real-world” clinical practice similar to that observed in “idealized” clinical trials ?  
*(diabetes, complex lesions, unprotected left main and multi-vessel disease, vein grafts, renal failure, ACS, CTO)*
  - Do DES prevent or “forestall” restenosis?
  - What about late complications such as aneurysms?
  - What is the clinical relevance of “late loss”?

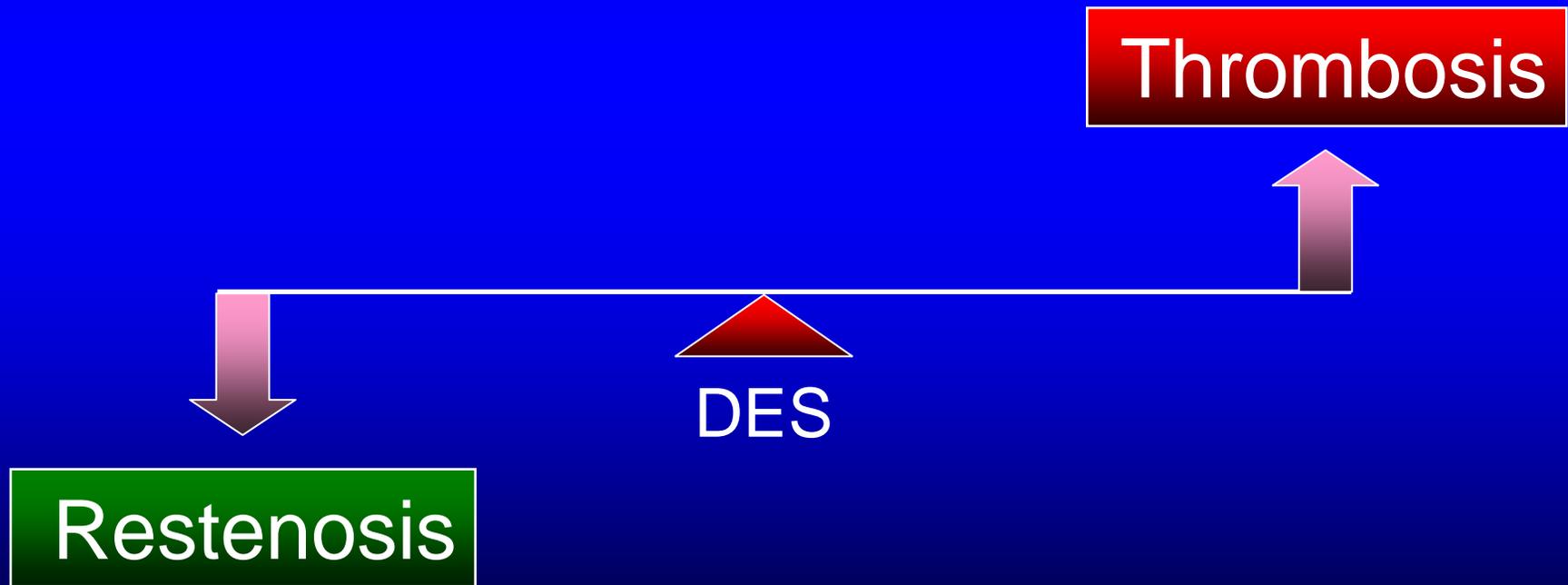
# Drug-Eluting Stents

## What We Don't Know

- Uncertainty regarding risk (stent thrombosis)
  - What is the magnitude of the problem in “real-world”?
  - What is the duration of risk?
  - What is the exact mechanism(s)?
  - Who is most at risk?
  - What are the safe and effective ways to mitigate risk?

# Drug-Eluting Stents

## Balancing Risk and Benefit



# Balancing Risk and Benefit

## Mitigate Risk and Accentuate Benefit

- Mitigate risk at “acceptable” benefit
  - Avoid DES in patients unable or unlikely to take dual antiplatelet therapy or in need of non-cardiac procedures
  - ? Extend antiplatelet therapy beyond 6-12 month  
(perhaps indefinitely in patients at low bleeding risk)
- Accentuate benefit at “acceptable” risk
  - Judicious, selective, evidence-based use ideally reserved for patients at highest risk for restenosis  
(longer lesions >15-20mm, smaller vessels <3.0mm)

# Drug-Eluting Stents

## Limitations of Current Antiplatelet Therapy

- Risk of bleeding (moderate and severe)
- Monetary cost (\$1000-\$1400 per year)
- Optimal duration unknown (0 RCT, 1 nonrandomized)
- Moderate to low compliance (and affordability)
- Off-label use for non-emergency stenting

**Risk-benefit-cost of dual antiplatelet therapy not clear enough to warrant “definitive” recommendations**

# Balancing Risk and Benefit

## The Science of Medicine

### TLR @ 4y

Cypher<sup>®</sup> = 23.6% vs 7.8%;  $P < 0.001$

TAXUS<sup>®</sup> = 20% vs 10.1%;  $P < 0.001$

Thrombosis



Restenosis

DES

### Late stent thrombosis (1- 4y)

Cypher<sup>®</sup> = 0.0% vs 0.6%;  $P < 0.025$

TAXUS<sup>®</sup> = 0.2% vs 0.7%;  $P < 0.036$

HR 4.54 (0.98, 21.03)

### Death or Q-MI @ 4y

Cypher<sup>®</sup> = 6.4% vs 8.2%;  $P = 0.14$

HR 1.30 (0.91, 1.86)

TAXUS<sup>®</sup> = 7.5% vs 7.3%;  $P = 0.93$

HR 0.99 (0.76, 1.29)

$\beta_{\text{error}} = 0.6-0.7$

Sample size

Stent thrombosis = 6,000-8,000

Death or Q-MI = 20,000-25,000

# Balancing Risk and Benefit

## The Science of Medicine

TLR @ 4y

Cypher<sup>®</sup> = 23.6% vs 7.8%;  $P < 0.001$

TAXUS<sup>®</sup> = 20% vs 10.1%;  $P < 0.001$

Thrombosis



Restenosis

DES

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Death or Q-MI @ 4y

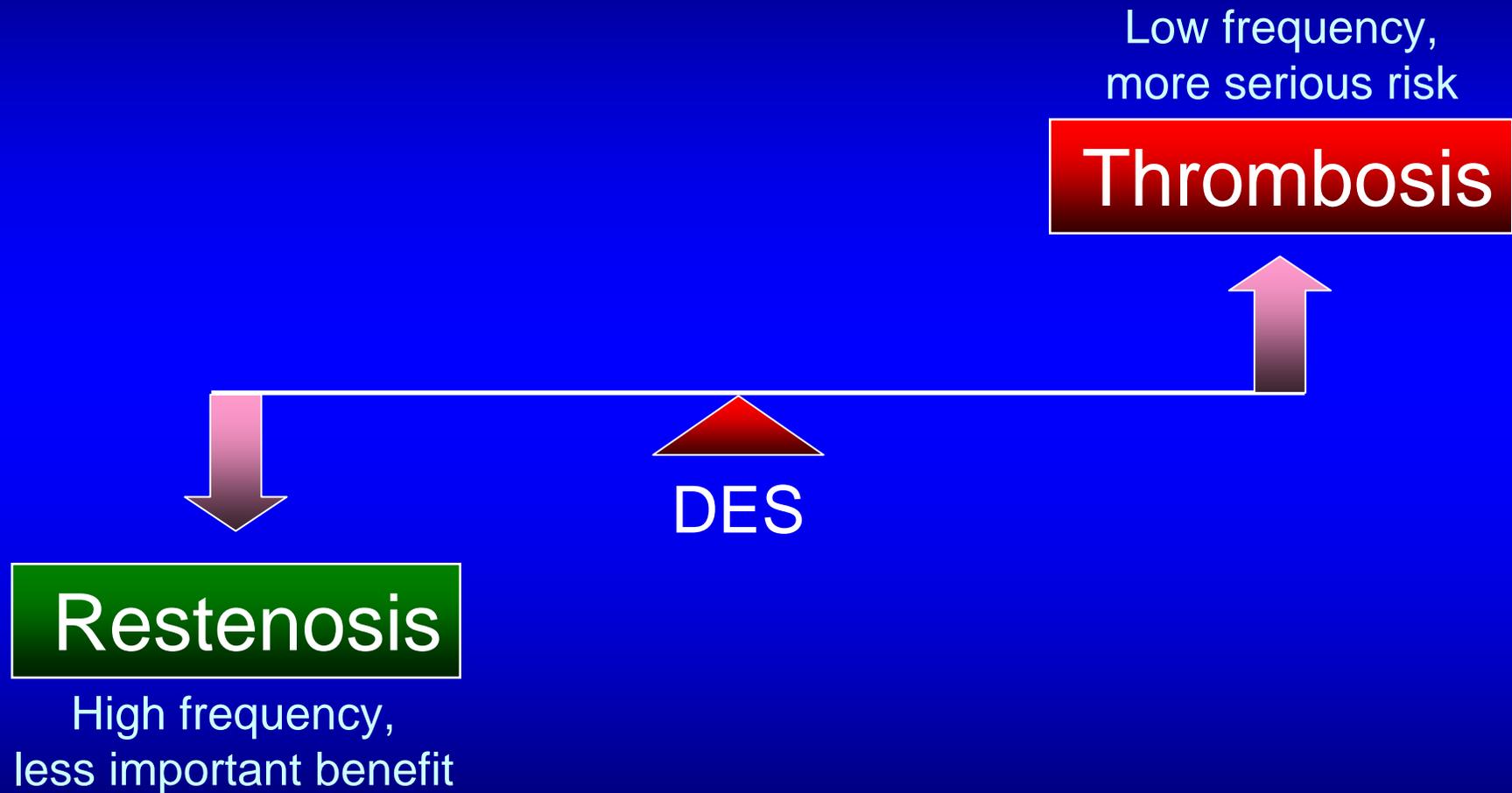
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Robust scientific inference to guide clinical practice  
not possible based on “inconclusive” information

# Balancing Risk and Benefit

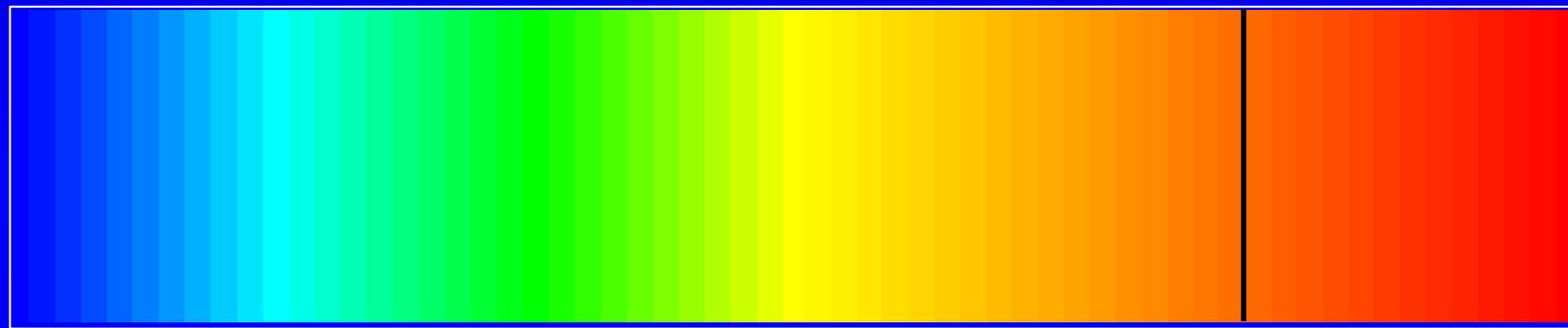
## The Art of Medicine



Is this an “acceptable” trade-off?

# Balancing Risk and Benefit

## Current DES Utilization



0%  
use

100%  
use

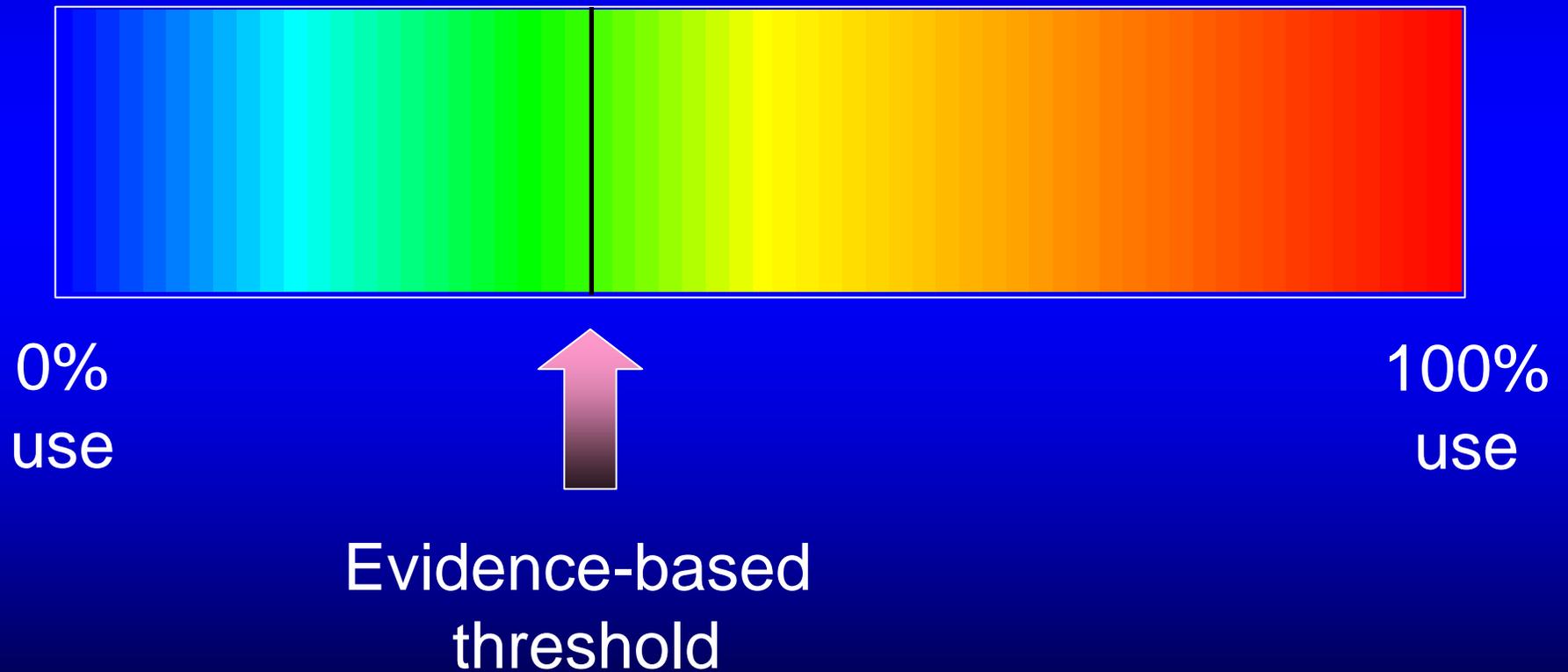


Current practice  
~60% "off-label"

(TAXUS ARRIVE 1, BASKET-LATE)  
(↑ stent thrombosis = 2-3%)

# Balancing Risk and Benefit

## “Optimal” DES Utilization



# “Optimal” DES Utilization

## Recommended Regulatory Solutions

- Approval
- Operational
- Administrative
- Additional targets

# Recommended Regulatory Solutions

## Approval

- Larger and longer pre-approval RCTs
- Broad spectrum of patients
- Hard clinical endpoints (all cause death or Q-MI)
- Adequately powered to address death or Q-MI (N=20-30K)
- Post-approval device registries with extended follow-up and greater and timely public access to data

Approval process likely to benefit from greater rigor than the current standard of “**least burdensome pathway**” for devices (FDAMA, 1997)

# Recommended Regulatory Solutions

## Operational

- Explicit standards of evidence
  - Robust trial design and statistical methodology
  - Emphasis on **clinical importance** >> **statistical significance**
- Universal criteria adopted by principal stakeholders
  - Sponsors, investigators, regulators, reimbursers/payors, professional/technical societies, guideline committees

# Recommended Regulatory Solutions

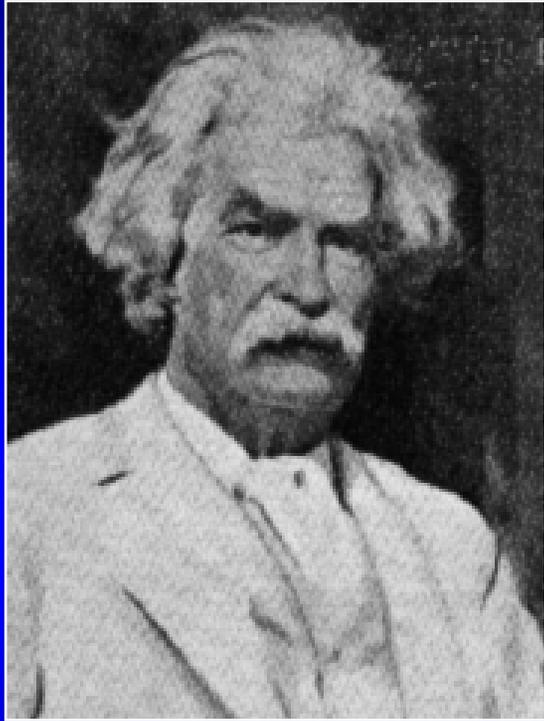
## Administrative

- Comprehensive post-marketing surveillance
  - Accurate, user-friendly, point-of-care, easily trackable, electronic
  - Resultant labeling changes (if warranted)
- Balancing private versus public interests
  - Encourage innovation without compromising public safety
- Incentives to encourage compliance and education
- Consistent public policy
  - “Off-label” use of drug (clopidogrel) to optimize “on-label” use of DES
  - “Spinach versus stents”

# Recommended Regulatory Solutions

## Additional Targets

- Therapeutic reform
  - Medical versus revascularization strategy for stable CAD  
(“root cause” – overutilization of revascularization)
- Tort reform
  - Change the current standard of evidence from the “community” to “evidence-based, best clinical practice” standard
- Fiscal reform
  - Reimbursement incentives to encourage optimal utilization
  - Reward evidence-based best clinical practice



MARK TWAIN

Will power lasts  
about two weeks,  
and is soluble in  
alcohol.

# Balancing Risk and Benefit

## Trading Thrombosis for Restenosis

We should not allow inflated expectations of benefit to preclude objectivity or the need for vigilance against unanticipated harm

# Balancing Risk and Benefit

## Gartner's Hype Cycle



*Technology Trigger*   *Peak of Inflated Expectations*   *Trough of Disillusionment*   *Slope of Enlightenment*   *Plateau of Productivity*

“A sequence of events experienced by an overly-hyped product or technology, including a peak of unrealistic expectations followed by a valley of disappointment when those expectations aren't met”