

Drug Eluting Stents: Balancing Risks and Benefits

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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”?

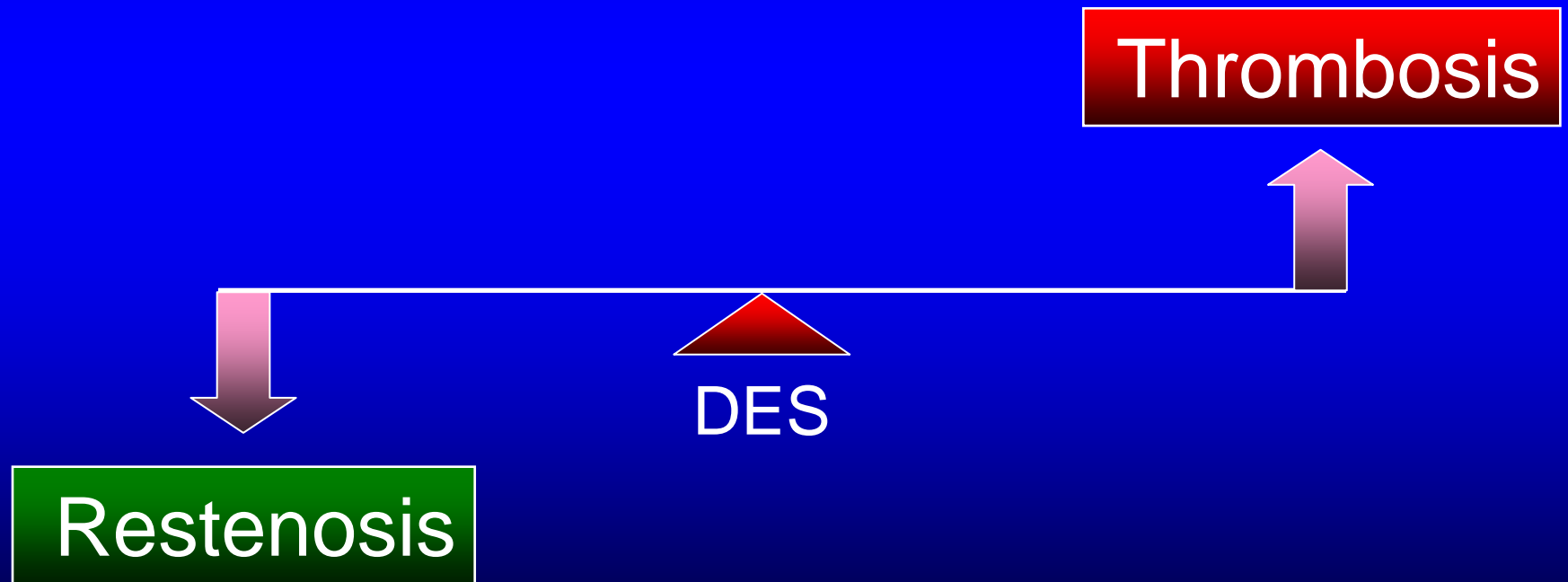
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What We Don't Know

- 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?

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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

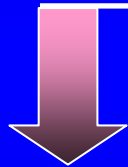
The Science of Medicine

TLR @ 4y

Cypher[®] = 23.6% vs 7.8%; $P < 0.001$

TAXUS[®] = 20% vs 10.1%; $P < 0.001$

Thrombosis



Restenosis

DES

Late stent thrombosis (1- 4y)

Cypher[®] = 0.0% vs 0.6%; $P < 0.025$

TAXUS[®] = 0.2% vs 0.7%; $P < 0.036$

HR 4.54 (0.98, 21.03)

Death or Q-MI @ 4y

Cypher[®] = 6.4% vs 8.2%; $P = 0.14$

HR 1.30 (0.91, 1.86)

TAXUS[®] = 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

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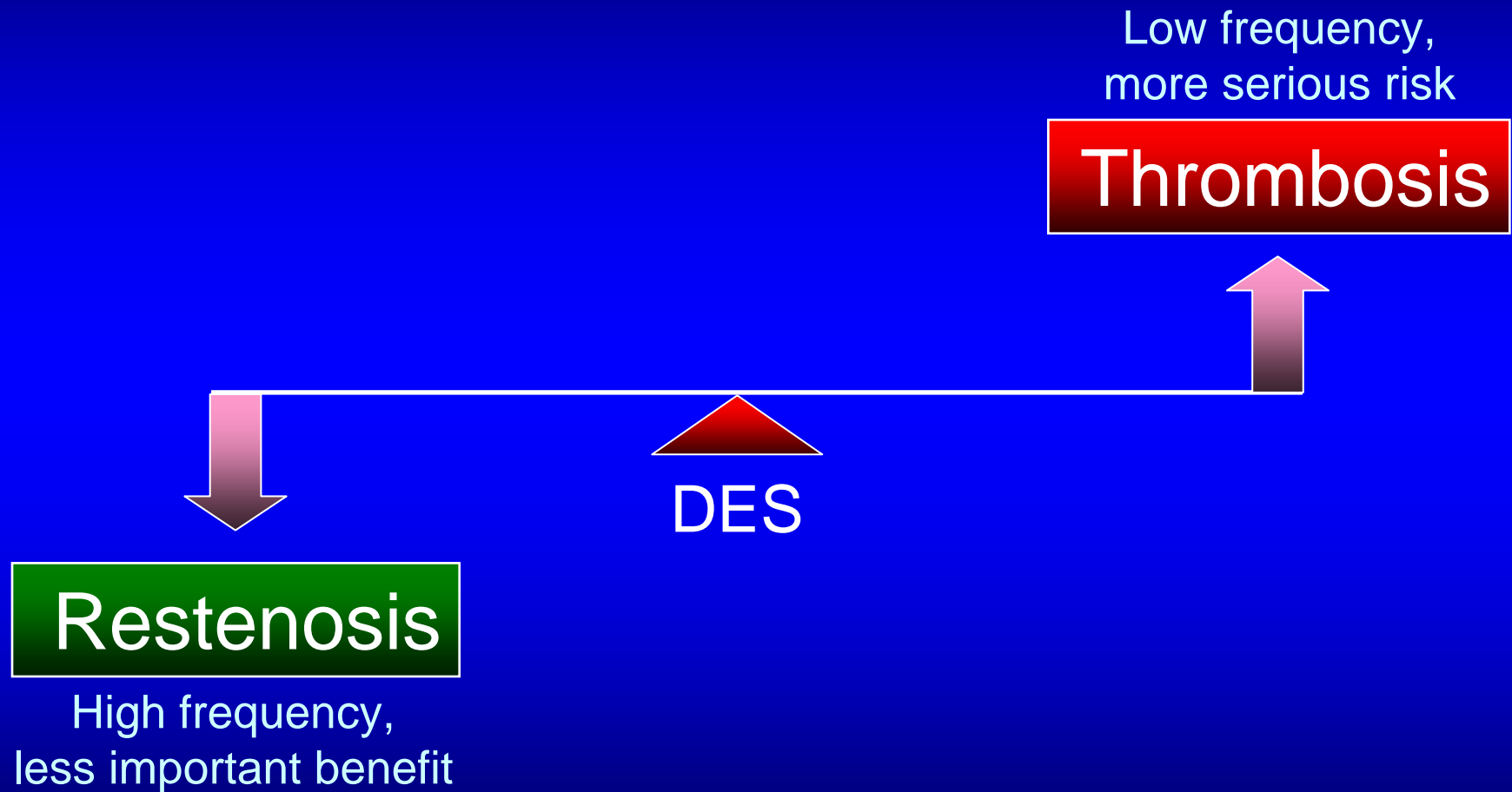
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Robust scientific inference to guide clinical practice
not possible based on “inconclusive” information

Balancing Risk and Benefit

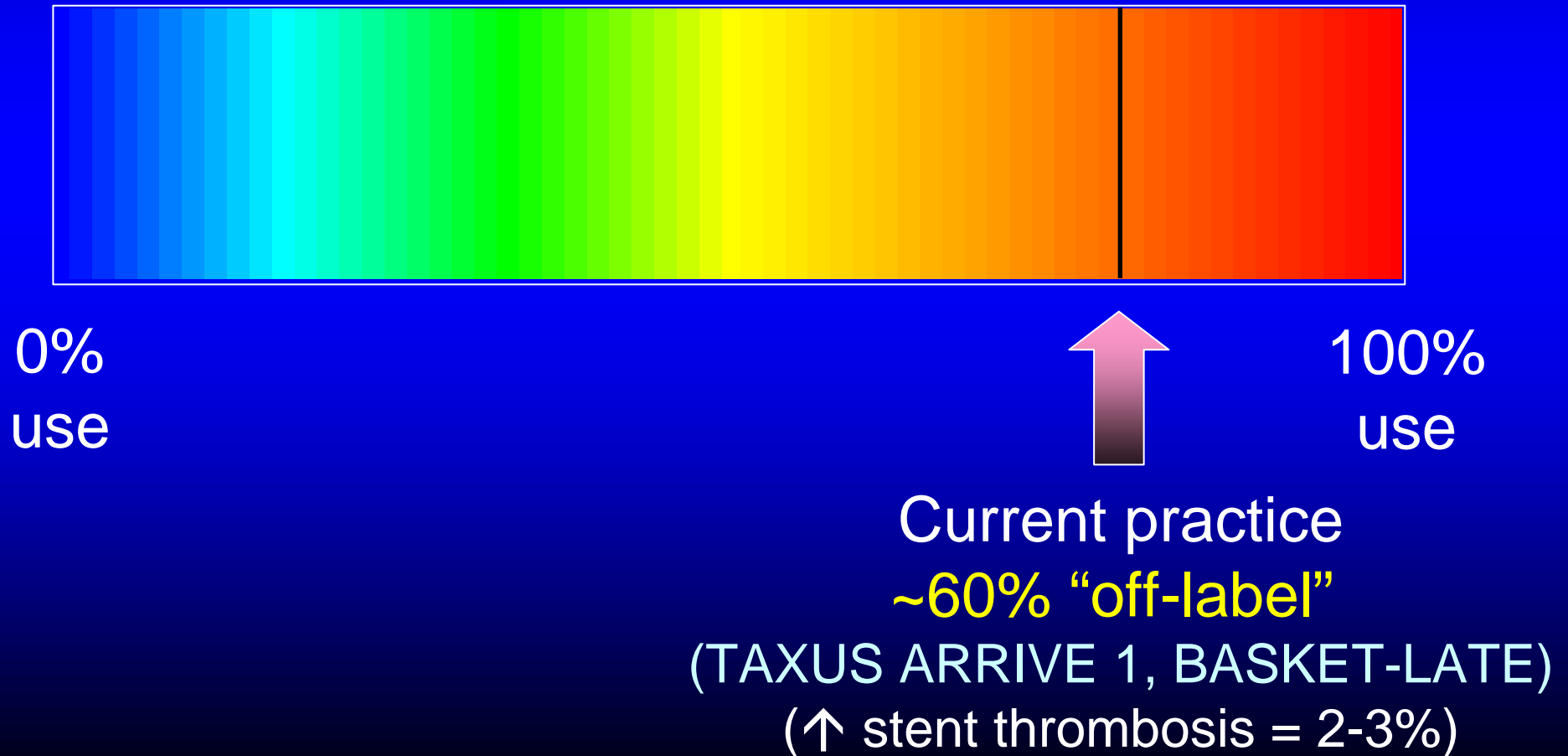
The Art of Medicine



Is this an “acceptable” trade-off?

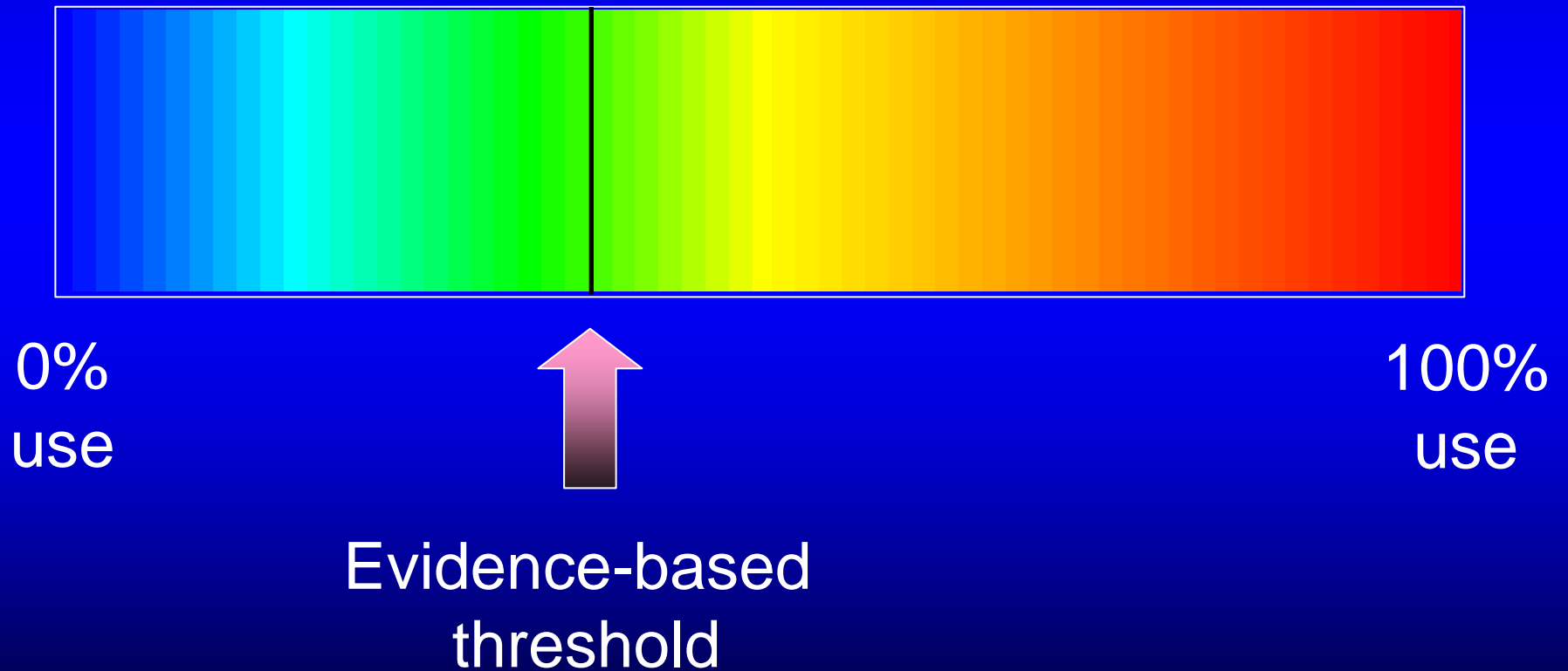
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Current DES Utilization



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

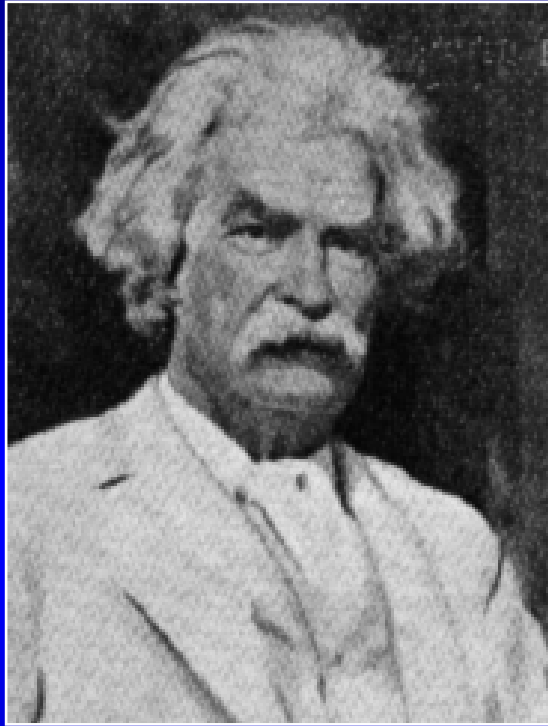
Administrative

- 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.

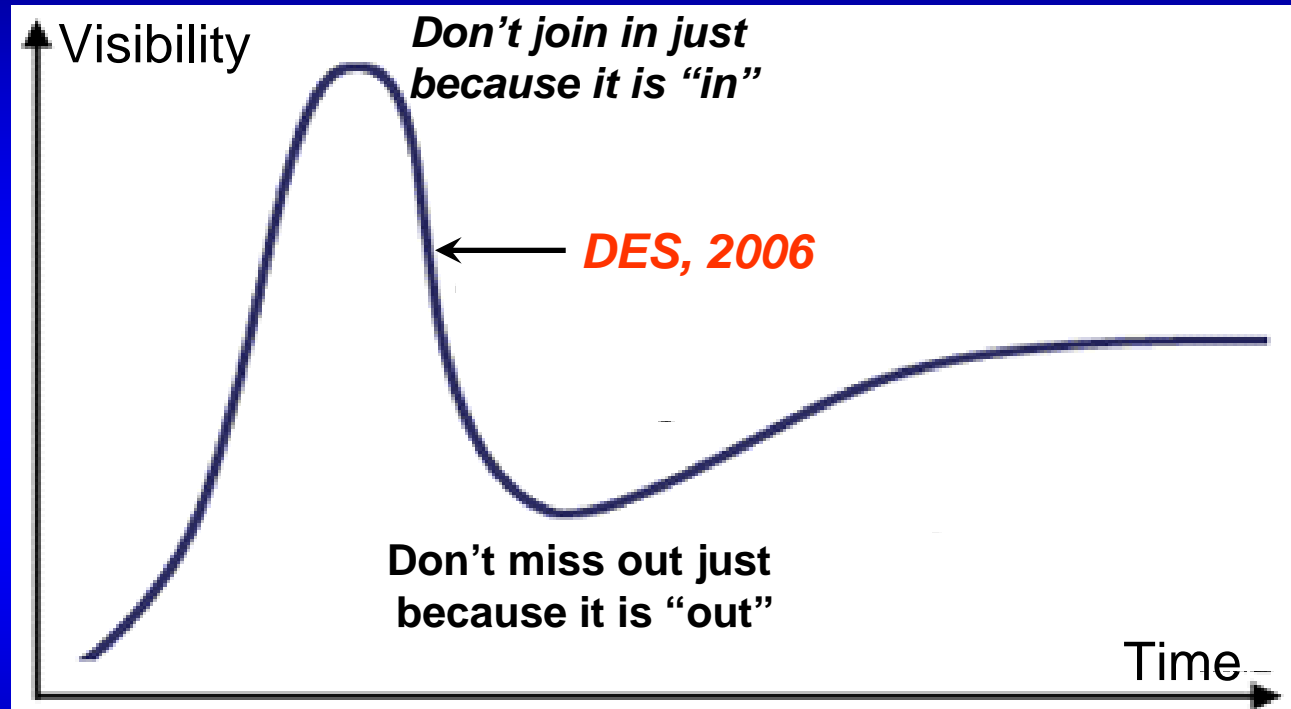
Balancing Risk and Benefit

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”