

Protecting Patients Through Informed Consent and Appropriate Therapy

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Circulatory Systems Device Panel

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Financial Disclosure

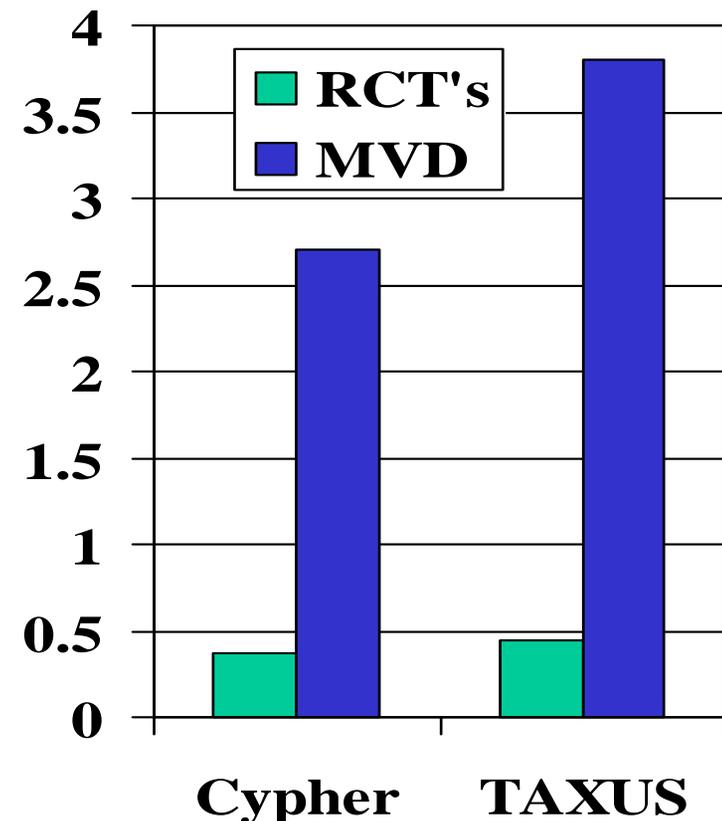
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Why Was This Panel Convened ?

Stent Thrombosis IS a real problem in off-label DES for MVD

12 mo. Stent Thrombosis – Single DeNovo lesions vs. MVD

- Stent thrombosis may be rare in the selected patients in the RCT's of on-label use BUT
- ***Stent thrombosis is >7 times higher in off-label DES use in MVD***



Data from FDA presentation 12/7/06: RCT's presented to FDA vs post-market registries from companies

What is the Magnitude of the Problem ?

- There are 3,600 excessive deaths/year in patients with MVD who receive DES instead of CABG despite proven long term survival of CABG (P. Smith)
- There are 2,200 additional deaths/year from stent thrombosis (S. Kaul)
- We now face an \$7 Billion additional annual cost and potential morbidity and mortality of antiplatelet therapy to treat an iatrogenic disease caused by DES (G.Stone)

How Did We Get Here ?

- Approval of DES based on comparison trials with a “strawman” (BMS) instead of CABG
- Highly selected patient enrollment in RCT’s (~ 4% of patients screened)
- Pivotal trials were inadequately powered for patient benefit endpoints, using instead surrogate endpoints and were of short duration
- The results in these select few are generalized to the population as a whole
- Greater than 60% of DES use is off label, and growing

Informed Consent

- Patients do not receive adequate informed consent after the diagnostic and before the interventional procedure
- Misrepresentation of current CABG results (as we heard yesterday)
- Inadequate opportunity for other caregivers (surgeon, non-interventional cardiologist, PCP) to render opinion regarding each therapy especially regarding long term survival and benefit

Common Problems in Patients with DES

- Postponement of surgery due to clopidogrel usage
- Excessive intraoperative bleeding resulting in increased blood transfusion in urgent cardiac, general, orthopedic and neurosurgical procedures
- Additional complexity of CABG after DES due to decreased LV function and lack of target vessels (full metal jacket)
- 6 of the last 50 patients (12%) receiving cardiac transplant at Duke had stent thrombosis of DES

STS and ACC Have Database Experience

- STS Database has over 3 million patients from 80% of U.S. cardiac surgical centers
- Preliminary discussions of joint database usage to track outcomes of cardiovascular interventions have occurred between the leadership of the ACC and STS

The New York Times

U.S.

WORLD

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BUSINESS

TECHNOLOGY

SCIENCE

HEALTH

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WASHINGTON

EDUCATION

FDA: Heart Stents Don't Up Risk of Death

By THE ASSOCIATED PRESS

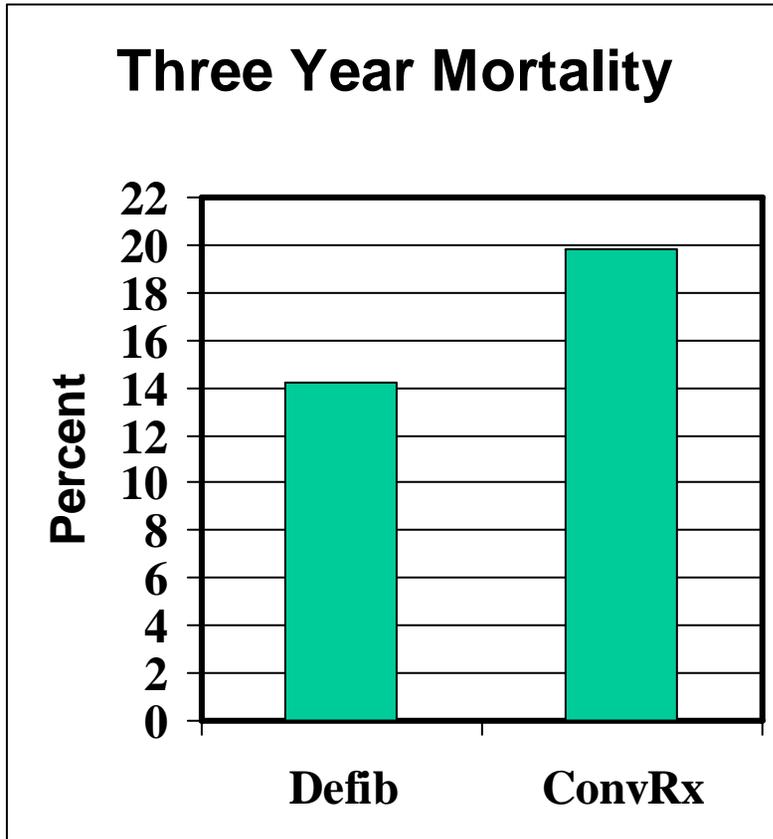
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- This headline appears to be substantively correct in the context of single vessel stenting as demonstrated in the pivotal trials
- However, off label use of DES, particularly in multivessel disease, is a major public health problem causing unnecessary deaths
- We seek to help solve this problem by offering the following recommendations

Recommendations

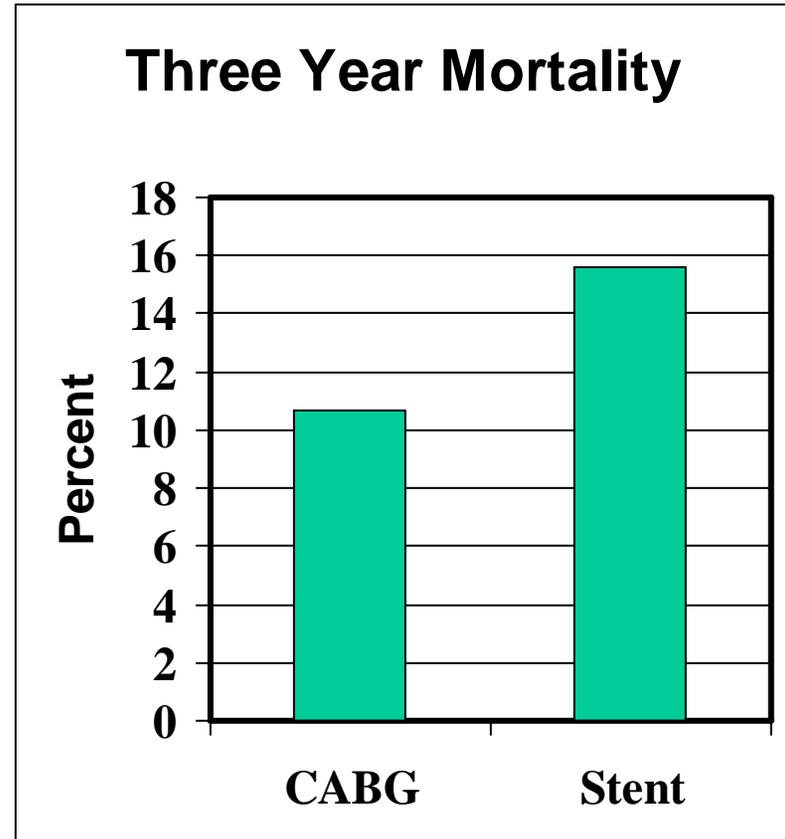
- A labeling change for DES to reflect the fact that the safety and effectiveness of stenting in multivessel disease has not been established
- Adequate informed consent of patients of all treatment options by a multidisciplinary team before intervention in multivessel disease
- Use of robust, comprehensive databases to assist the FDA, clinicians and industry to determine appropriate therapy in various subsets of patients with coronary artery disease
- A stronger FDA/Specialty Society partnership utilizing the combined strengths of the FDA, the STS, the ACC, and the medical device industry

Defibrillator Rx, MADIT II



*Conventional Rx 39%
higher than Defib*

NY State Registries – 3VD w prox LAD



*Stent Rx 46% higher
than CABG*

Absolute and Relative Mortality Differences for CABG Vs Stent in MVD Similar to Mortality Differences That Drive Other Decisions in Cardiovascular Medicine

	Absolute Mort Diff	Relative Mort Diff
PCI vs. Thrombolytics for STEMI (30 d) (ACC/AHA)	2%	29%
Simvastatin for 2° Prevention (4S trial) (6 yr)	3.7%	30%
CABG vs. Stents for 3VD (NY State) (3 yr)	4.8%	31%
Defibrillators for low EF after MI (MADIT II) (20 mo)	5.6%	29%

Another fact often not disclosed to patients – MVD PCI causes myocardial injury

- 37% of patients undergoing MVD PCI have troponin elevation
- 28% of these patients with troponin elevation have MRI defined mean loss of 6g of LV muscle (~ 5% of LV mass)
- => 10% of MVD PCI's result in significant myocardial injury

Selvanygam et al Circ 2005

- Randomized clinical trials of DES resulting in labeling were performed in patients with single lesion stenting
- Although these trials are underpowered to detect a difference in stent thrombosis, concerns remain that there may be an increase with DES especially without antiplatelet therapy

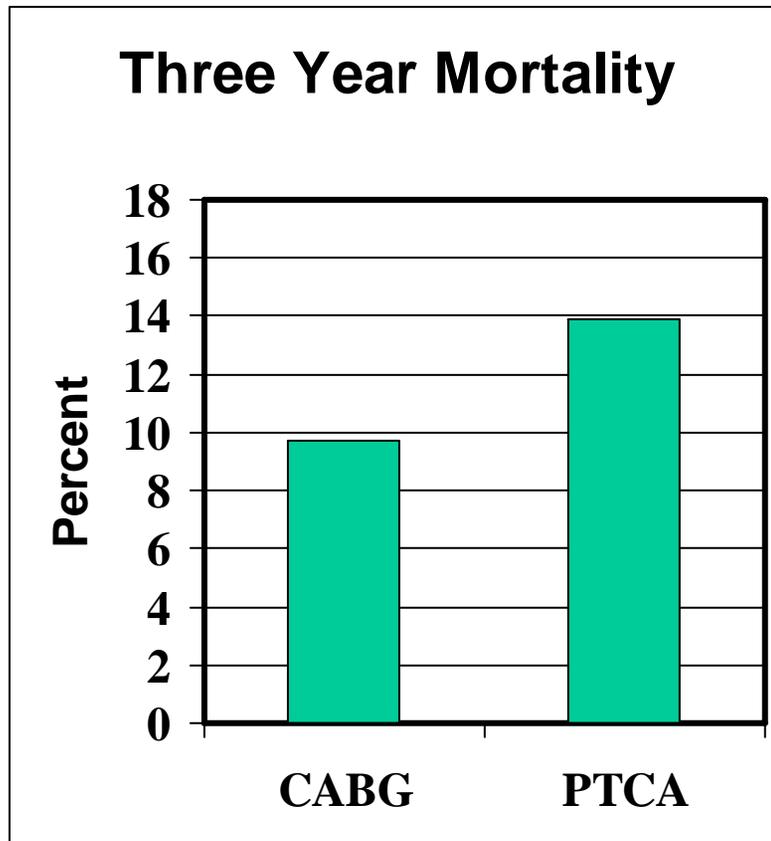
- From clinical experience, stent thrombosis is a problem
- ST appears to increase as off label use of DES increases in patients with multivessel disease (MVD)
- All RCT's to date have compared DES with BMS
- The gold standard of treatment of MVD is CABG

Focus Must Not Be On Procedure Success, But On Patient Benefit

- Dr. Baim, 12/7/06, proclaimed the dramatic progress in PCI in the treatment of coronary lesions: Acute occlusion almost eliminated, Emergency CABG now rare, Procedure success in 97% range.
- BUT – Has progress been made in PATIENT BENEFIT as stenting has been applied in the real world – answer in comprehensive robust database:

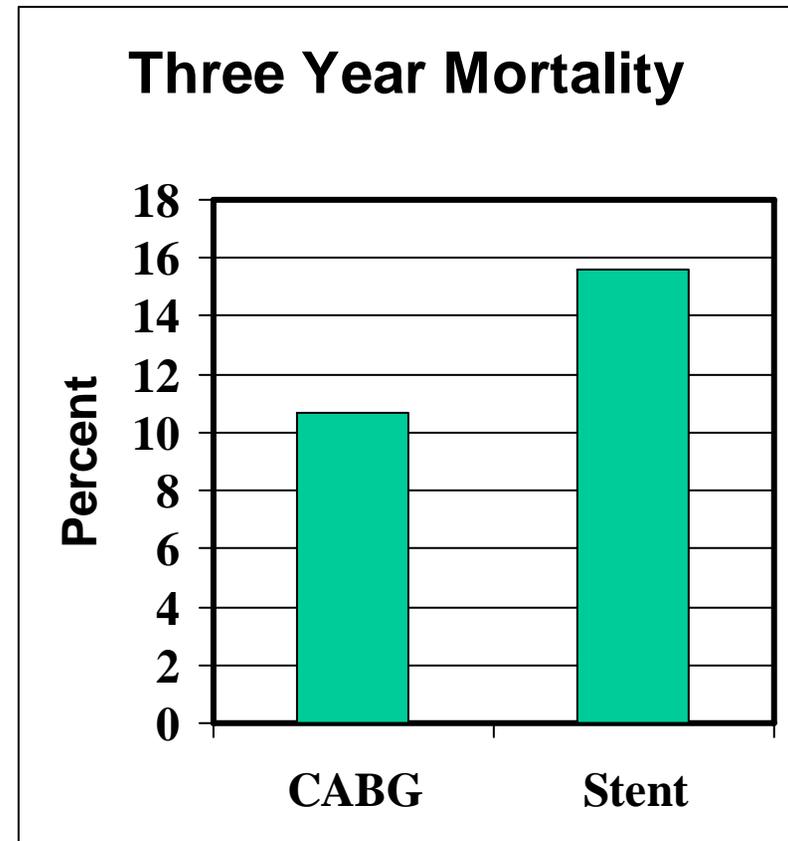
NY State Registries - 3 VD w prox LAD

Pre Stent JACC 2000



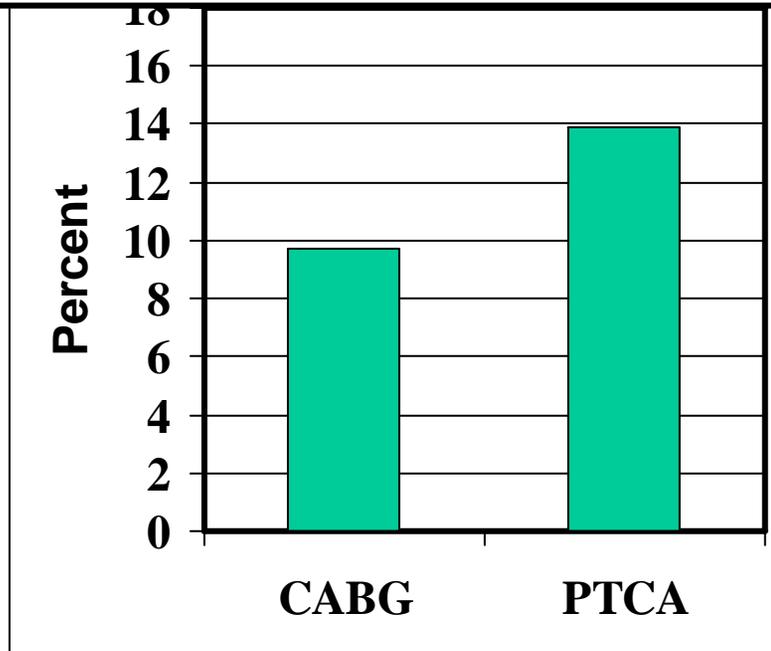
PTCA 43% higher than CABG

Stenting NEJM 2005

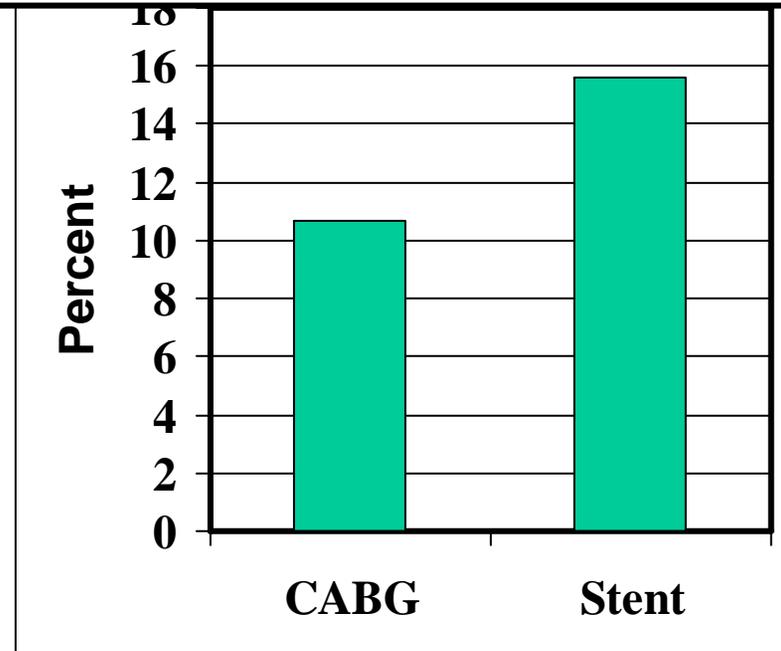


Stent 46% higher than CABG

No progress has been made in the treatment of multivessel disease relative to CABG as PCI has evolved to include stenting. This lack of progress, despite improved procedural success, is very likely related to excessive, off-label use in more complex patients



PTCA 43% higher than CABG



Stent 46% higher than CABG

Key Point – Improvement in Peri-stent Restenosis does not equal equivalent improvement in need for subsequent revascularization

- Much of need for revascularization (more than half) is related to lesions in other vessels or new lesions elsewhere in the stented vessel.
- Even IF “In-Lesion” restenosis is ZERO, about half of the subsequent revascularization associated with PCI will still occur.
- NHLBI registry of PCI – one year rate of need for revascularization – 12% with BMS, 9% with DES

COST EFFECTIVENESS ANALYSIS

From Great Britain:

National Health Service R&D

Health Technology Assessment Programme

- Health Technology Assessment 2004 Vol 8
- Coronary Artery Stents: A Rapid Systematic Review and Economic Evaluation
- An evaluation of Coronary Stents vs CABG, including Drug Eluting Stents.

Health Technology Assessment Programme

- Modeling done with projections of benefits extending beyond the short follow-up of published studies.
- Mortality for CABG and stenting –
 - Stenting minimally superior until 18 months (accumulated extension of life 3 days)
 - After 18 months, CABG progressively more beneficial. By ten years, accumulated extension of life by CABG was 6 months compared to Stents

Health Technology Assessment Programme

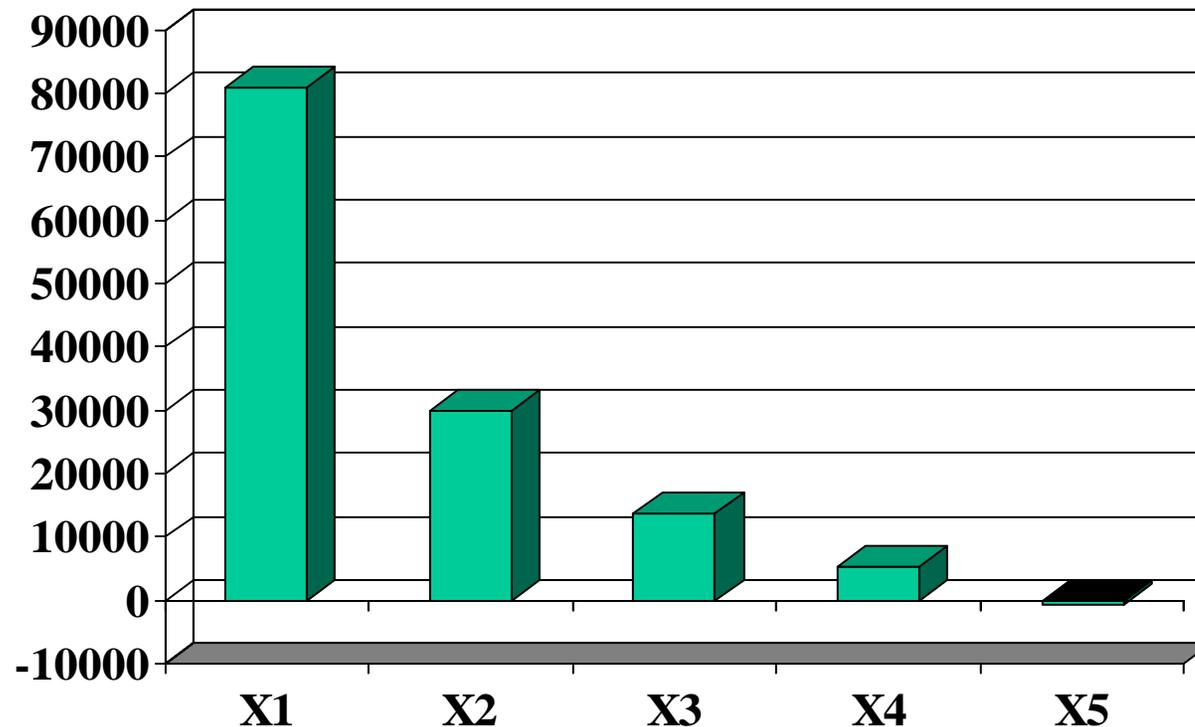
- Detailed model constructed for a low risk patient with 2 vessel disease, since ~ 90% of SVD treated by PCI and ~90% of 3VD treated by CABG in Great Britain.
- Corrected for bias created by delay in Rx
- Costs – Stenting with BMS's was ~ \$7000 less expensive than CABG at 1 year, ~\$6000 less expensive at 5 years. (DES cost difference ~\$5500 at 1 year, ~\$4500 at 5 yrs)

Health Technology Assessment Programme

- Because of progressive benefits of CABG, by 5 years, CABG had C-E of L 69,619/LY compared to BMS and L 52,411/LY compared to DES. C-E for CABG will continue to improve for subsequent years.
- Modeling was then done for multivessel disease with higher risk patients (e.g. poor LV, more than 2 vessels diseased, diabetic, etc.)

CABG very cost-effective vs BMS for all MVD except the simplest 2VD

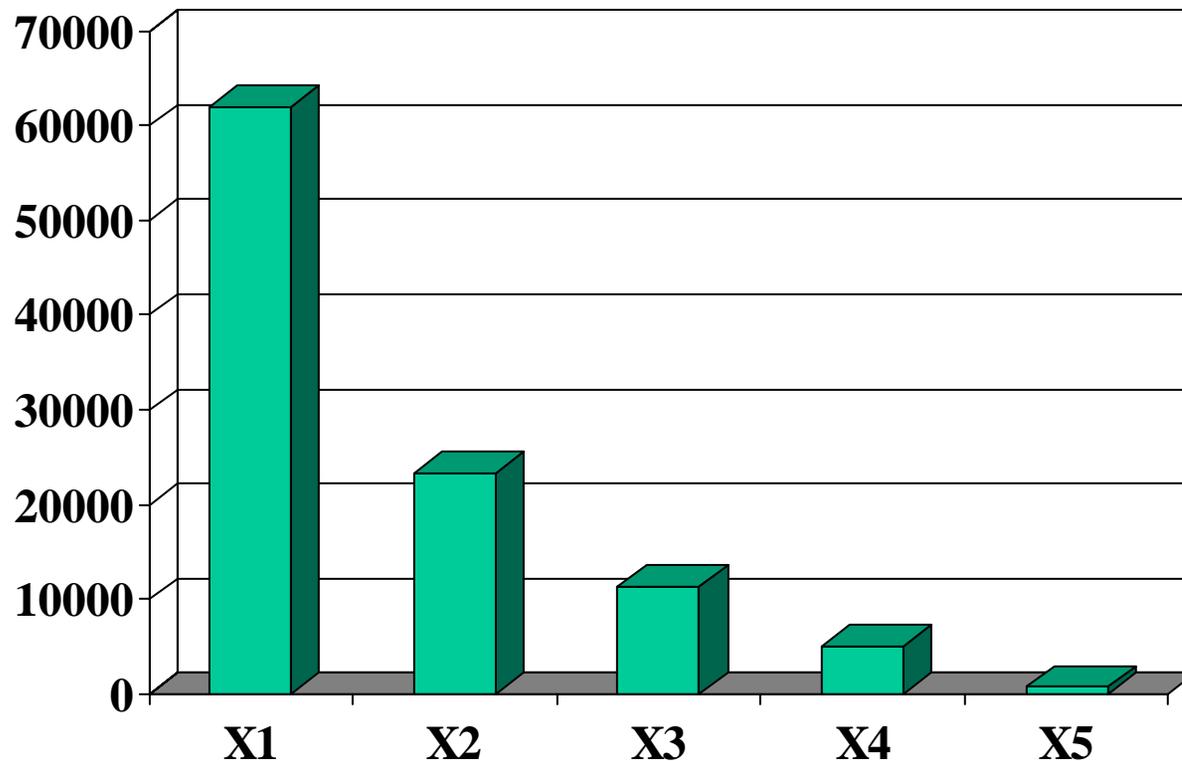
C-E of incremental Rx with CABG vs BMS at five years (L/QALY)



Increasing risk compared to baseline low risk 2VD patient

Similar cost-effectiveness benefit of CABG vs DES

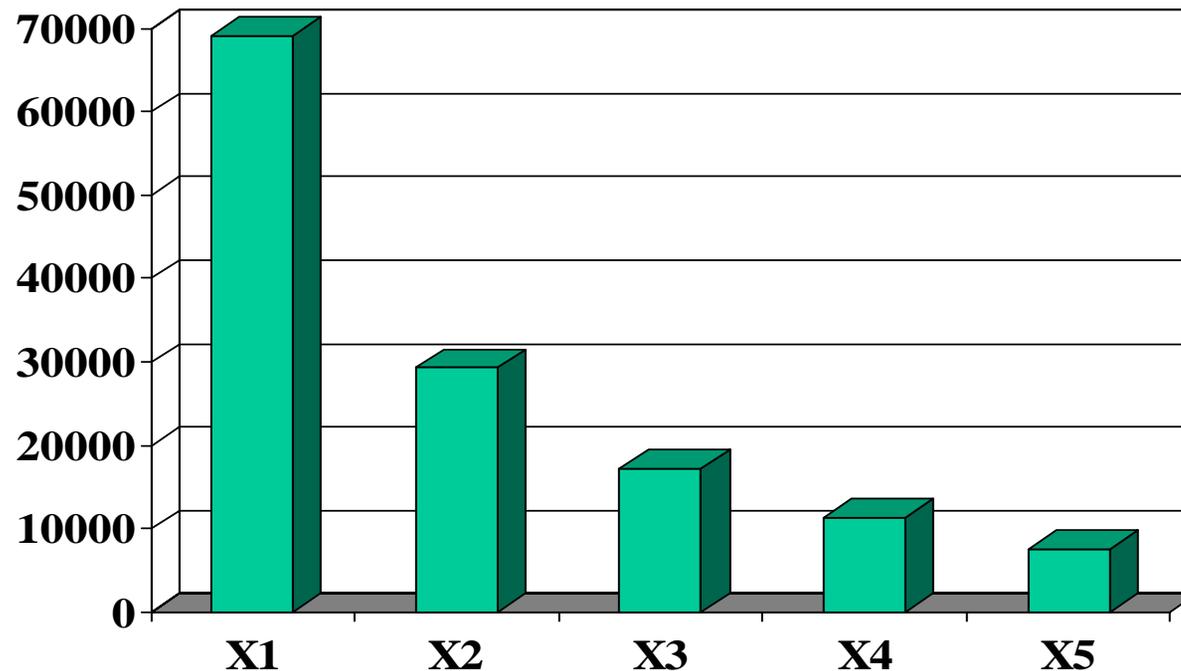
C-E of incremental Rx with CABG vs DES at five years (L/QALY), assuming 30% reduction in reinterventions.



Increasing risk compared to baseline low risk 2VD patient

Benefit Persists Even If Modeling Done Assuming NO Restenosis

C-E of incremental Rx with CABG vs DES at five year
(L/QALY), assuming 75% reduction in reinterventions
(= NO restenosis of stented vessel and most favorable estimate
of effect of restenosis on reinterventions)



Increasing risk compared to baseline low risk 2VD patient

Health Technology Assessment Programme - Conclusion

- “In the case of MVD the accumulated trial evidence comparing CABG with PTCA with BMS is sufficient to project over five years an important and substantial survival advantage for CABG over PTCA with BMS...
- “It is difficult to justify substitution by a less effective treatment simply on the grounds that it is cheaper...

Health Technology Assessment Programme - Conclusion

- “This argument remains valid also in the case of DES, since the the apparent additional benefits from fewer interventions and consequent QoL gains are balanced by the extra costs of the new stents.
- “Hence we find no grounds for the substitution of CABG by DES in multiple vessel disease.
- “Indeed we find that higher risk individuals gain greater relative benefit from CABG, not less.”

Cost-Effectiveness of CABG vs Stenting in MVD

Yock...Hlatky, Am J Med. 2003;115:382-9 (Stanford)

- Modeling to compare life-time C-E of two procedures by updating and extending the results of BARI.
- Updated for the effect of stents on PCI results.

Cost-Effectiveness of CABG vs Stenting in MVD

Yock...Hlatky, Am J Med. 2003;115:382-9 (Stanford)

- Model predicted a life-time survival benefit of CABG over PCI with stenting of 0.83 years.
- Initial CABG was DOMINANT compared to initial stenting with a LOWER life-time cost (-\$8400) and a HIGHER effectiveness (+0.31 QALY) compared to initial stenting

Cost-Effectiveness of CABG vs Stenting in MVD

Yock...Hlatky, Am J Med. 2003;115:382-9 (Stanford)

- Sensitivity analysis done to examine the *effect of complete elimination of restenosis* after stenting in the model.
- CABG still DOMINANT compared to stenting in this situation. The lifetime cost difference was less: -\$150, and the clinical benefit remained: + 0.27 QALY.

Cost-Effectiveness of CABG vs Stenting in MVD

Yock...Hlatky, Am J Med. 2003;115:382-9 (Stanford)

CONCLUSION

- ...although elimination of target lesion restenosis does improve the short-term outcomes of catheter-based interventions...
- “These improvements are not enough to make primary stenting less costly and more effective than CABG for relieving angina in patients with multivessel disease.”

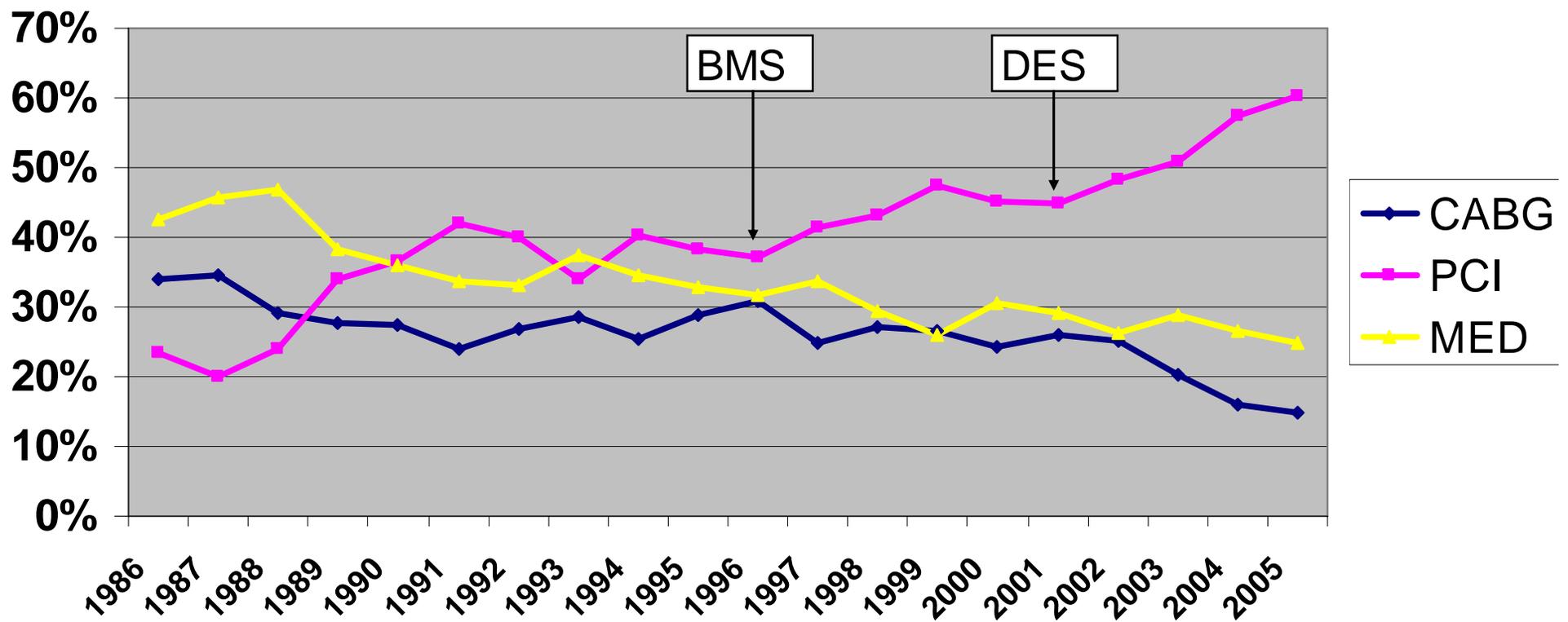
CABG IS Cost-Effective Relative to Stenting in MVD

If prolonged Plavix use is now to be a part of DES use, then the increased cost of \$1460/year makes the lifetime cost-effectiveness benefit of CABG relative to DES overwhelming.

- Why are we spending \$8 Billion to treat an iatrogenic disease created by off label use of drug eluting stents ?

Trends in Treatment Selection

Duke Initial Treatment Selection All Significant CAD N=26,318



Trends in Treatment Selection for Multivessel CAD

**Duke Initial Treatment Selection
High Severity CAD N=6,226**

