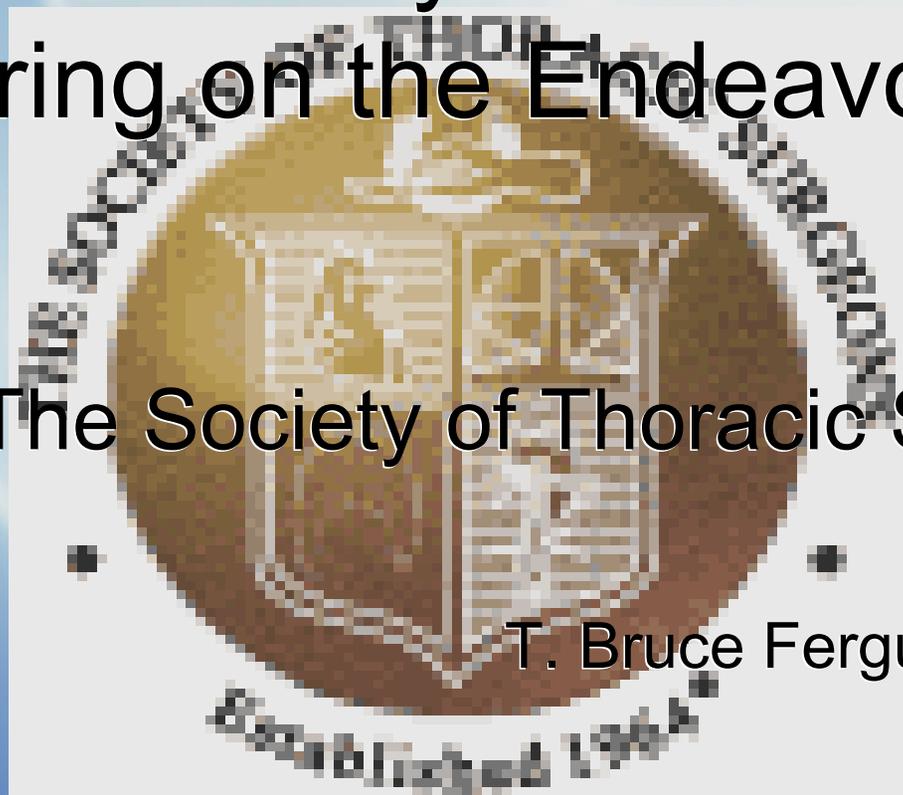


# Testimony to the FDA CSD Hearing on the Endeavor Stent

The Society of Thoracic Surgeons



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# The Society of Thoracic Surgeons

- Perspective:
  - Not simply that of a cardiac surgeon
  - Not simply that of a competing technology (CABG)
- Perspective that a framework for evaluation of CV Technology from the broad vantage point of clinical IHD therapy is necessary
  - 18-year experience with observational National Adult Cardiac Database, linked to outcomes research and analysis
  - 7-year experience with CQI in Medicine, funded by AHRQ



# RCTs in FDA Device Pre-Market Approval Process

- Directed to assess device efficacy
- Characteristics of Trials raises questions:
  - *Inferiority design* of CV device trials
    - Can it compound prior trial conclusion shortcomings (strawman phenomenon)?
  - Design without adequate *control group(s)*
    - Does this further distance the trial results from applicability and relevance in the “real world”?
  - Use of *composite end points* in CV trials
    - End points of least importance to patients typically contribute the most events in CVD composite metric
    - Interpretation of data from composite end points may be misleading to patients and physicians (*Ferreira-Gonzalez, BMJ 2007; 334:786-*)



# ‘Interpolation’ Between CV Device Trial Results

- Short cycle development of technology means that validation of RCT results in “real world” is difficult
- RCTs provide inadequate information to provide guidance for population subsets outside of the trial design (‘indication expansion’)
- Pre-market evaluation and approval process (design, endpoints, review criteria) can limit importance for many patients across the CVD spectrum
- Information given to patients usually limited to latest trial results, without multidisciplinary approach to care



# Caution in Interpretation

- On the pre-market side, the STS advocates caution in the use of pivotal RCT data as the only criteria for evaluation of new technology in CVD
- The FDA labeling language should reflect the parameters and conditions defined in the Trial design, including the lack of overall clinical context of the trial data
- To address ‘indication expansion,’ this labeling language should also reflect the knowledge limitation about the anticipated post-market, real-world context of device use



# The Importance of the Post-Market Domain

- Safety and Effectiveness of CV Devices should relate directly to patient safety and clinical benefit
  - Not addressed in these pre-market pivotal trials
- Current criteria, mechanisms, and funding to evaluate safety and effectiveness are insufficient
  - The pre-market evaluation process cannot ignore these considerations, because of the impact on patient safety
- Post-market evaluation would allow for:
  - testing in population subsets beyond trial populations
  - Evaluation of individual component end points from composite metrics of trials



# FDA - STS Partnership

- The STS and the FDA have partnered to create the mechanism for post-market evaluation of device therapy in cardiac surgery ('Purchase Order')
  - Based upon the STS National Adult Database, and linkage to Medicare dataset for long-term follow-up data
- A first step in the new patient-centered, multi-disciplinary post-market system that evaluates new CVD technologies in the context of clinical disease and in comparison with existing alternative treatments
  - Ischemic heart disease therapies
  - Percutaneous valve therapies
  - Heart failure device therapies



# Consequences of Current System Liabilities within CV Device Domain

- New information will *always* be forthcoming
  - Short cycle development of newer technologies doesn't always solve clinical problems related to this new information, from a patient safety and effectiveness view
- Current System liabilities result in consequences that are destined to be unfavorable for patients because the overall process of device evaluation is not patient-centered:
  - Inherent difference between Trial and the 'real world' use of the technology, relative to clinical context of IHD
  - Lack of post-market information or documentation of safety and effectiveness of therapy (until too late)
  - Design factors are device, and not patient, focused:
    - MVD, L Main, CTOs: CABG as Control, not BMS



# Consequences of Current System Liabilities within CV Device Domain

- Early Mortality outcomes are of greatest importance to patients
  - mortality is *least frequent* event in composite outcome metric in CVD trials
- Late Mortality can't be determined in RCTs
  - For most patients, mortality is the *most important* safety and effectiveness metric following CVD intervention
  - Can only be determined through long term, observational analyses



# MVD PCI vs. CABG: Late Mortality

Observational studies have compared long-term mortality in patients with significant multi-vessel CAD undergoing either PCI or CABG.

Four studies (Duke<sup>1</sup>, Cleveland Clinic<sup>2</sup>, NY State Registry<sup>3</sup> and NNE<sup>4</sup>) used independent, sophisticated statistical methods to correct for baseline characteristics and propensity (total 32, 237 pts).

Duration of Follow-up	Excess PCI Mortality	Weighted-Average Mortality Difference (%)	Excess Deaths w/ PCI vs. CABG per 100 treated
1 Year	Yes	2.3%	2.3 pts / 100 treated
2 Years	Yes	4.3%	4.3 pts / 100 treated
3 Years	Yes	5.1%	5.1 pts / 100 treated
4 Years	Yes	6.3%	6.3 pts / 100 treated

1. Smith, *Ann Thorac Surg* 2006; 82:1420-9. 2. Brenner, *Circulation* 2004; 109:2290-5.  
3. Hannan, *NEJM* 2005; 352:2174-83. 4. Malenka, *Circulation* 2005; 112:371-6.



# Summary

- STS Recommends:
  - On the Pre-Market side:
    - Caution in relying just on pivotal RCTs for data
    - Strong labeling language to adequately address the findings of the pre-market evaluation, but which also addresses ‘indication expansion’
  - On the Post-Market side:
    - Aggressive development of observational database resources to evaluate safety and effectiveness of translating these FDA recommendations into ‘real world’ use
    - Significant industry investment in these observational database resources, for development and sustainable implementation
  - More optimal communication of risks and benefits to patients on both sides of the process