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Professor Medicine/Cardiology
Duke University Medical Center
Director, Cardiovascular Devices Unit
Co-Director, Cardiac Safety Research Consortium
Duke Clinical Research Institute
Cardiac Safety: *Rare but catastrophic events*

2004

**Innovation**

**Stagnation**

Challenge and Opportunity on the Critical Path to New Medical Products

U.S. Department of Health and Human Services
Food and Drug Administration
March 2004
Our Core Values

- Nurture a collaborative pre-competitive environment
- Bring manufacturers, regulators & clinical thought-leaders together
- Examine key cardiac safety research issues
- Improve knowledge, enhance innovation & public health
Member Companies 2018

- Abbott
- AbbVie
- AliveCor
- Amgen
- AMPS
- Astra Zeneca
- AlCor
- Bayer
- Bioclinica
- Biomedical Systems
- Boehringer Ingelheim
- Cardiocore
- CardioNet
- Celerion
- Chiesi Pharma
- CytoVas
- Dabi, Ltd
- Daiichi
- Duck Flats Pharma
- Eli Lilly
- Epidemico
- Gilead Sciences
- G.E. Health Care
- Global Instrumentation
- GlaxoSmithKline
- InVivo Sciences
- Johnson & Johnson
- Medifacts
- Medpace
- Medtronic
- Merck
- Monebo
- Mortara Instrument
- Merck
- Nabios GmbH
- OBS Medical
- Perspective Informatics
- Pfizer, Inc
- Portola
- Quintiles
- Roche
- Salix
- Sanofi Aventis
- Takeda
- Taylor Microtech
- Vince & Associates
Partnering Organizations

- DIA
- HESI
- ACC-NCDR
- ICOS
- NIH
- AHA
- FDA
- Health Canada
- PMDA Japan
Key Initiatives

**Think Tanks**
- Cardiac Safety Signals in Oncology Studies
- Sudden Cardiac Death in the Young
- Endpoint Adjudication in Medical Device Trials
- The Proarrhythmic Assessment of New Chemical Entities
- Social Listening for Cardiac Safety
- Improve Efficiencies in Phase 3 Development

**White Papers**
- Long-term ECG Safety Monitoring
- Efficiencies in Phase 3 Development
- NOAC monitoring, reversal agents, and post-approval safety and effectiveness evaluation
- Evolution of strategies to improve preclinical cardiac safety testing
- Effects of anti-diabetes drugs on cardiac ventricular repolarization

**Research Projects**
- National Cardiac Screening Warehouse Pilot Study
- Enhancing Cardiac Safety though Social Media
- National Health Care Resource Pediatric Warehouse
- Pediatric Screening Tools
- Restricted Mean Survival Time (RMST) statistical analysis approach for analyzing diabetes
- Cardiovascular Outcomes Trials
# Obligatory Drug-Device Safety Interactions

**DES & Extended Dual Antiplatelet Therapy:**

*February 2007, April 2007, September 2007*

## Regulatory
- **FDA:**
  - CDER
  - CDRH
  - Off Comm
- **E.U.:**
  - Austria
  - U.K.
  - Sweden
- **Japan:**
  - MHLW
  - PMDA

## Academia
- Duke
- Harvard
- Cleveland Clinic
- Columbia
- U of NM
- Wash Hrt Ctr
- London School of Hyg & Trop Med
- CVPath

## Societies
- ACC
- SCAI
- ESC
- NIH
- AHRQ

## Industry
- Abbott
- Medtronic
- BSCI
- Cordis/J&J
- Biosensors
- OrbusNeich
- Eli Lilly (Daichi)
- Sanofi
- BMS

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*Source: Duke Clinical Research Institute*

*Image: Cardiac Safety Research Consortium*
Dual Antiplatelet Therapy (DAPT) RCT

Initial Procedure – Enrollment

Randomization (All Eligible Subjects)

End of Treatment
End of Follow Up

0  12 m  30 m  33 m

DES n = 15,245
BMS n = 5,400

Open label DAPT

R

DES n = 12,196
BMS n = 4,320

30 m DAPT arm

Obs

Double Blind Placebo Controlled RCT

– 12 vs 30m randomization in subjects clear and on treatment at 12m
– Stratified by lesion and clinical complexity
– Co primary endpoints: ST and MACCE,
– Safety endpoint: Major bleed
– 33 months follow up, to include 3 month “rebound period”
– Simultaneous RCT of 12 vs 30m DAPT in BMS
– Both clopidogrel and prasugrel

12 m DAPT arm

Obs
The DAPT Study 2014

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Herrlinger, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massaro, Ph.D., for the DAPT Study Investigators

**ABSTRACT**

9961 Underwent randomization at 12 mo

5020 Were assigned to receive aspirin plus thienopyridine
237 Were excluded
132 Withdrew consent
88 Were lost to follow-up
17 Were not available for follow-up
225 Were excluded
116 Withdrew consent
91 Were lost to follow-up
18 Were not available for follow-up
4732 (94.3%) Were included in clinical follow-up at 33 mo
4716 (95.4%) Were included in clinical follow-up at 30 mo
51 Were excluded
9 Withdrew consent
34 Were lost to follow-up
8 Were not available for follow-up
4658 (94.3%) Were included in clinical follow-up at 33 mo

**Key Points:**
- DES: 9,961 pts
- SES, PES, ZES, EES
- BMS: 2,816 pts
- Inclusion: “1 year clear”
- RCT: >1 yr placebo vs. thienopyridine
  - Clopidogrel, Prasugrel
- Co-1º Endpoint: 12-30 mos:
  - ARC Def/Prob ST
  - MACE (Death, MI, Stroke)
- 1º Safety: 12-30 mos GUSTO bleeding

Mauri L et al, NEJM 2014
The TREAT Initiative

Cardiac Safety & Bleeding Risk in Women

2010

Shifting the Balance of Potency and Bleeding Risk for Anti-Coagulant and Anti-Platelet Agents Through Radial Arteriotomy:
An Obligatory Drug-Device Safety Interaction Cardiac Safety Critical Path Thinktank/Incubator

23 June 2010
Washington, D.C.
FDA Headquarters

A broad range of anti-coagulant and anti-platelet agents and combinations are widely used in acute coronary syndromes and percutaneous coronary intervention. In all cases, benefits from potent agents are balanced against characterization of safety, defined primarily by bleeding. As more than the majority of bleeding reported with such agents originates from femoral arteriotomy sites, changing device technique to radial arteriotomy could support reconsideration of the safety/benefit balance, sufficient to warrant revision of current product labelling.
The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D’Agostino, Sr., Ph.D.

Embedding a randomized clinical trial into an ongoing registry infrastructure: Unique opportunities for efficiency in design of the Study of Access site For Enhancement of Percutaneous Coronary Intervention for Women (SAFE-PCI for Women)

Connie N. Hess, MD, MHS, a Sunil V. Rao, MD, a David F. Kong, MD, a Laura H. Aberle, BSPh, a Kevin J. Anstrom, PhD, a C. Michael Gibson, MD, b Ian C. Gilchrist, MD, Alice K. Jacobs, MD, c Sanjit S. Jolly, MD, c Roxana Mehran, MD, c, John C. Messenger, MD, d L. Kristin Newby, MD, MHS, e Ron Waksman, MD, f and Mitchell W. Krucoff, MD

The NEW ENGLAND JOURNAL of MEDICINE

September 2013

A Registry-Based Randomized Trial Comparing Radial and Femoral Approaches in Women Undergoing Percutaneous Coronary Intervention

The SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) Trial

Sunil V. Rao, MD, a Connie N. Hess, MD, MHS, a Britt Barham, BA, a Laura H. Aberle, BSPh, a Kevin J. Anstrom, PhD, a Tejan B. Patel, MD, a Jesse P. Jorgensen, MD, a Ernest L. Mazzafferi Jr, MD, c Sanjit S. Jolly, MD, c Alice Jacobs, MD, c L. Kristin Newby, MD, c C. Michael Gibson, MD, c David F. Kong, MD, c Roxana Mehran, MD, c Ron Waksman, MD, f Ian C. Gilchrist, MD, f Brian J. McCourt, a John C. Messenger, MD, f Eric D. Peterson, MD, MPH, c Robert A. Harrington, MD, f Mitchell W. Krucoff, MD

Lauer M et al, NEJM 2013

Hess C et al, Am Heart J 2013

Rao S et al JACC Cardiovascular Int 7(8)2014
Thinktank on Cardiogenic Shock
Anatomy of a CSRC Thinktank

- **No lectures:** everyone in the room is an expert

- **Pragmatic perspectives:**
  - Clinician, manufacturer, regulator, trialist, statistician
  - BRIEF presentations: emphasis on discussion
  - Syntax: what works; what is broken; near term priorities; long term priorities
  - *Emphasis on spontaneous discussion* and dialogue

- **Objectives of the process today:**
  - Illuminate 1,000 unsolvable barriers
  - Identify 1 or 2 that together we can actually address (low hanging fruit)