The FDA Perspective on Thrombogenicity Testing of Coronary Interventional Devices:
Insights From the Large Animal Testing

Michael C. John, MPH
Circulatory Support Devices Branch
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices & Radiological Health
Outline

- Thrombogenicity Testing in the Canine Model
- Thrombosis Evaluation in Large Animal Testing
- Animal Models
- Study Design
- Case Study
- Clinical Relevance of the Canine Thrombo Model

Focus on Coronary Interventional Devices
Case Study – 4 hr Jugular Canine Data

0= No thrombus present
1= Minimal thrombus
2= Moderate
3= Severe
4= Extensive, ~75% of material length

- Grade 3 thrombus formation in both groups

- What does the large animal data show?
Canine Thrombogenicity Model

• Beagle or Mongrel Dogs
• Evaluation in the Jugular Vein
• 4 hour dwell time
• Non-heparinized animals
Challenges With the In vivo Canine Thrombogenicity Model

• Survey results indicate little confidence in the reliability of this model

• Thrombogenicity is already assessed during the large animal safety studies additional in vivo canine study may not be indicated

• The Three Rs – “Refine, Reduce Replace”
  – Replacement refers to the preferred use of non-animal methods over animal methods whenever it is possible to achieve the same scientific aim.
  – Reduction refers to methods that enable researchers to obtain comparable levels of information from fewer animals, or to obtain more information from the same number of animals.
  – Refinement refers to methods that alleviate or minimize potential pain, suffering or distress, and enhance animal welfare for the animals used.

Is this analysis clinically relevant?
Rationale for Animal Testing

- Primary goal of animal testing is to demonstrate safety with some expectation of effectiveness prior to clinical testing
- Characterize deployment/implantation characteristics and failure modes
- Provide FDA with an initial assessment of how the device interacts with the biological system
Selection of Large Animal Model

• Two most widely used models are pigs and sheep
• The juvenile domestic swine and the adult Yucatan miniature swine are generally accepted models because of similarity in biologic response to humans.
  – Yucatan or Sinclair adults are better for chronic evaluation because they tend not to outgrow their stents.
Sheep Models

• FDA is aware of the difficulties achieving appropriate anticoagulation in this model
  – Recommend cage-side ACT measurements and careful monitoring of dual anti-platelet therapy
  – Important to include descriptive narratives from the pathologist or veterinary pathologist describing all thrombotic events such that FDA can understand whether these were species-specific or device-related events.
  – Suitable for thrombogenicity testing as well
Overview of DES Study Design

- n=6-8 samples/group
- Acute and Chronic timepoints
- Control BMS (DES optional)
- Overlap and Max Dose Testing
- Bioabsorbable Stents – evaluation of materials until completely degraded

• Domestic Swine
  - 3-5 days
  - 30 days
  - 90 days
  - 180 days

• Mini-Swine

• Study duration

• Acute Toxicity & Thromboreistance

• Chronic Vascular Responses
  • (Safety and Effectiveness)

• Late chronic study timepoints should be chosen based on PK data (elution kinetics & degradation profile)

• Later depending on Polymer or coatings and materials
Acute vs Late Stent Thrombosis: *Not the same process*

**Acute Thrombosis**
- Soon after device implantation
- Stent and catheter
- Material properties
- Device design

**Late Thrombosis**
- Long-term reaction
- Stent only
- Additional factors: Endothelial recovery (strut coverage)
  Inflammation

In Vivo Canine Model

In Vivo Large Animal Model (Swine and Ovine)
Cascade of Events Following Stent Placement In Animal Arteries

- Platelet Deposition
- Leukocyte recruitment
- VSMC proliferation /migration
- Matrix deposition

Slide courtesy of R. Virmani
Safety Endpoints

MORPHOMETRIC ANALYSIS and HISTOLOGIC GRADING SYSTEMS FOR:

- Inflammation
  - WBC and Giant Cells
  - Granulomas
- Injury
  - Damage to IEL, EEL, Media and Adventitia
- Neointimal Response
  - Percent Stenosis
  - Neointimal area & thickness
  - Medial area & thickness
- Endothelialization
- Other
  - Hemorrhage
  - Thrombosis
  - Aneurysms
  - Fibrin Deposition
  - Calcification

John et al. JACC Interv. 2008;1:535-44
Scanning Electron Microscopy

• Provides en face visualization of the stented vessel
• Can identify exposed (de-endothelialized) areas of the stent surface, which are potentially pro-thrombogenic

Joner et al. JACC. 2008;52:333-42

Thrombogenicity Endpoints in Large Animal Studies

• Performance and handling evaluation
  – Gross evaluation of catheters

• 3-day acute study
  – Typically only applies to DES (coupled with acute tox testing)
  – Dynamic period of healing, challenging to interpret outcomes unless severe

• Mid to Long-term histology
• Clinical pathology
Case Study - Large Animal Data

- Swine SEM and histology data show typical healing responses
- The canine and large animal data therefore demonstrate conflicting results
- How do we interpret the thrombogenic potential of this device?

Nakazawa et al. AJC. 2007;100:36M-44M
Device Evaluation: The Big Picture

- Device evaluation is a multi-factorial process
- Animal testing data is one component of a comprehensive evaluation of the device
- FDA reviews the totality of the data when evaluating the safety and effectiveness of a device
Pros and Cons

• Canine model
  – Pros
    • Small (n=2/3), short (acute) & relatively inexpensive
    • Suitable for iterative changes to device materials/geometry
  – Cons
    • Non-heparinized
    • Long catheter dwell time
    • Mismatch of catheter sizing to treatment vessel
    • Non-orthotopic placement

• Large Animal models (sheep and pig)
  – Pros
    • Clinically similar if not identical device placement
    • Multifaceted assessment of all biological responses (incl. thrombogenicity)
  – Cons
    • Cost and time-intensive
Concluding Remarks

• The utility of the canine model remains a complex issue
• More clinically relevant and/or reliable methods of thromboresistance evaluation are needed
• The large animal testing should be leveraged whenever possible
• Optimized canine or other testing may be indicated when new implant materials are being proposed, or if making a claim about materials being more hemocompatible
• Sponsors are encouraged to utilize the pre-submission process to ensure that the thrombogenicity testing strategy is appropriate
Animal Studies Guidance

• Guidance for Industry and FDA Staff: General Considerations for Animal Studies for Cardiovascular Devices – http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm220760.htm
Thank You

Michael.John@fda.hhs.gov
301-796-6329