Bleeding, Procedural Outcomes and Other Key Endpoints/Variables – A Drug Industry View

Drug-Device Safety Interaction Cardiac Safety Critical Path Thinktank/Incubator

23 June, 2010

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Washington, D.C.

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What is the problem?

- **Multiple definitions of bleeding**
  - Each new trial is associated with a new bleeding definition (e.g. TIMI, GUSTO, ACUITY/HORIZONS, CURRENT, PLATO, etc)
  - Data collection tools are not standardized, often adjudicated with different algorithms, and does not allow other study definitions to be appropriately evaluated for a study
  - Difficult to understand similarities and differences across studies
- **Bleeding not adjusted by patient risk**
  - Several defined patients groups at increased risk (e.g. renal dysfunction, elderly, female)
  - Bleeding “risk scores” (e.g. CRUSADE, ACUITY/HORIZONS-AMI)
  - Overall patient risk (e.g. TIMI, Framingham, STS, EuroSCORE, etc)

What works?

- Many definitions are quantitative providing some objective evidence of risk
- Several studies attempt to evaluate results using other accepted bleeding definitions
- Remaining problems:
  - Difficult to understand different risk/benefit profiles
  - Labeling
  - Physician acceptance of what definition is important and which definition is not important
  - Some types of bleeding are not adequately captured by accepted definitions (e.g. CABG related, “nuisance”)
  - Different transfusion triggers –need clarity in protocols to use of blood products

What is needed? A short term view

- **Standardized definitions**
  - **Characterize and define periprocedural bleeding by procedure type and timing to administration of drug of interest**
    - **PeriPCI bleeding**
    - **PeriCABG bleeding—timing to CABG and urgent vs elective**
    - **Perisurgical bleeding (non-CABG)**
    - **Timing of events related to drug administration**
  - **Characterize bleeding using risk adjustment**
  - **Agreement to:**
    - **Risk following bleed**
    - **Meaning of a bleed**
      - What type of bleed is important
      - Is all bleeding the same or does the type of procedure change the meaning of a bleed

What is needed
A long term view

- Standardized definitions applied to non-periprocedural bleeds – especially when objective data not available
- Determine significance of a bleed
  - Large bleed leading to adverse event
  - Nuisance bleeding leading to drug discontinuation
- Bleeding risk versus length (and benefit) of therapy
- Events while off drug awaiting procedures

Appropriate concerns related to this meeting

- What is appropriate bleeding definition to determine procedural risk?
  - What data needed to be collected?
  - How long is the periprocedural period?
  - How is data adjudicated?
  - How is data interpreted?
- Will differences in bleeding due to technique and/or device determine whether a specific drug should be used, what dose, effects of risk adjustment?
- Will differences in bleeding due to technique and/or device really have any impact on a drug label?
- Will differences in drug risk profiles or procedural selection bias related to choice of patient make a difference in the labeling of a device?