



**High quality, Prospective Registry  
Design: Statistical  
Recommendations, Issues and  
Answers for TREAT**  
**INDUSTRY PERSPECTIVE**

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# Potential benefits of well-designed study leading to class labeling of anticoagulation in transradial PCI

- Safety
- Use
- Costs Healthcare

# What are key study design issues for observational data?

- **Confounding and Bias**
  - Variations in degree of use of anticoagulants due to pre-existing patterns specific to US
  - Variations in drug administration and monitoring (potentially affect bleeding and ischemic outcomes)
  - Confounding by indication, both for drug and route PCI
  - Variations in center/operator by procedural volume, radial experience, geographic region, population size

# What are key study design issues for observational data?

- Sample size
  - Adequate to help adjust for above issues of confounding
  - Adequate to represent less used anticoagulants in US
  - Feasibility—barriers to industry participation
    - Risk of misinterpretation of data as superiority of one anticoagulant over another
    - Risks of supporting a study of off-label use of their drug
    - Can study design adequately support uniform class labeling of anticoagulants, including theirs, in transradial PCI
- Endpoints and definitions

# What would be the best basis for specific drug bleeding evaluation?

- Possible pitfalls--Power
  - Low usage patterns in US of certain anticoagulants
    - ability to precisely evaluate safety of low use drugs (wide CI around estimate of bleed)
    - ability to adequately compare transfemoral and transradial PCI bleeding risks of low use drugs
  - Interaction or effect modification between drug type, PCI route, and bleeding

## Opportunities for imbedded studies or pre-specified data collections

- enrich for subpopulations to improve power?
  - specific subpopulations at higher risk for bleeding
  - specific anticoagulants (?utility and/or feasibility)
- non-bleeding safety questions?
- use of platelet aggregation indices/devices, other novel markers of drug effect?

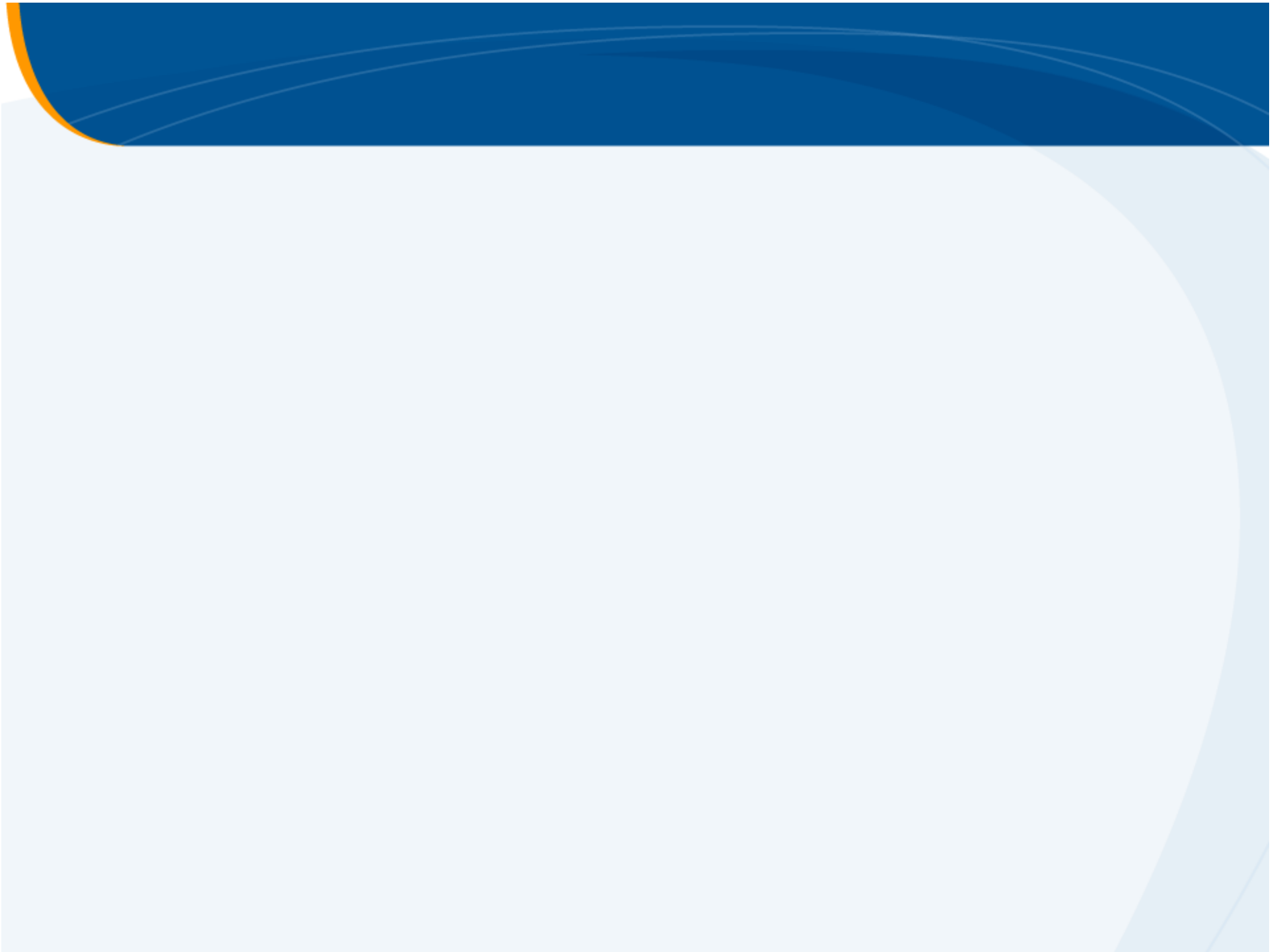
# What are optimal comparators for bleeding safety and TRI?

- Site limited
  - bleeding creating vascular compromise
  - access site bleeds
- Systemic

## OPC: can we pool data from other studies to add information?

- Large scale observational registry (pre-existing data)
- Bleeding data in randomized controlled antithrombotic therapy trials which have some percentage of transradial PCI





# Hemorrhagic endpoints and incidence in a stable to low risk ACS population

**Table 4. Hemorrhagic End Points\***

Variables	Heparin Plus Glycoprotein IIb/IIIa	Bivalirudin	P Value
Major bleeding	123/3008 (4.1)	71/2993 (2.4)	<.001
Intracranial	2/3008 (0.1)	1/2993 (0)	>.99
Retroperitoneal	16/3008 (0.5)	7/2993 (0.2)	.06
Vascular access puncture	74/3008 (2.5)	25/2993 (0.8)	<.001
Gastrointestinal	18/3008 (0.6)	4/2993 (0.1)	.003
Genitourinary	6/3008 (0.2)	1/2993 (0)	.13
Related to cardiac surgery	18/3008 (0.6)	17/2993 (0.6)	.88
Minor bleeding	772/3008 (25.7)	400/2993 (13.4)	<.001
TIMI bleeding criteria†			
Major bleeding	26/3008 (0.9)	19/2993 (0.6)	.30
Minor bleeding	91/3008 (3.0)	39/2993 (1.3)	<.001
Any transfusion	76/3008 (2.5)	50/2993 (1.7)	.02
Transfusion ≥2 U	58/3008 (1.9)	39/2993 (1.3)	.06
Red blood cell	57/3008 (1.9)	43/2993 (1.4)	.17
Whole blood	4/3008 (0.1)	1/2993 (0)	.38
Platelets	18/3008 (0.6)	10/2993 (0.3)	.13
Thrombocytopenia			
Platelets <100 ×10 <sup>3</sup> /μL	50/2863 (1.7)	20/2868 (0.7)	<.001
Platelets <50 ×10 <sup>3</sup> /μL	19/2863 (0.7)	8/2868 (0.3)	.03

Abbreviation: TIMI, Thrombolysis in Myocardial Infarction trial.<sup>10</sup>

\*Values are expressed as number/total (percentage). Denominators are corrected for missing values.

†TIMI major and minor bleeding are mutually exclusive classifications.

## ● Evolution of bleeding definitions

- TIMI major and minor bleed
- Bivalirudin studies change previous research accepted bleeding definitions
- Argue this is more updated and thus clinically relevant
- Increases statistical power (higher event rate) and difference between anticoagulants
- ACUIITY definition major bleed used in new composite 'quadruple' endpoint
  - Major bleeding was defined as the cumulative occurrence within 25 to 35 days after randomization of intracranial or intraocular bleeding, hemorrhage at the access site requiring intervention, hematoma with a diameter of at least 5 cm, a reduction in hemoglobin levels of at least 4 g per deciliter without an overt bleeding source or at least 3 g per deciliter with such a source, reoperation for bleeding, or transfusion of a blood product.
- Is time to hemostasis, or CABG related bleeding relevant?