IV Congresso

Novas Fronteiras em Cardiologia

Doença coronária: para além da angioplastia

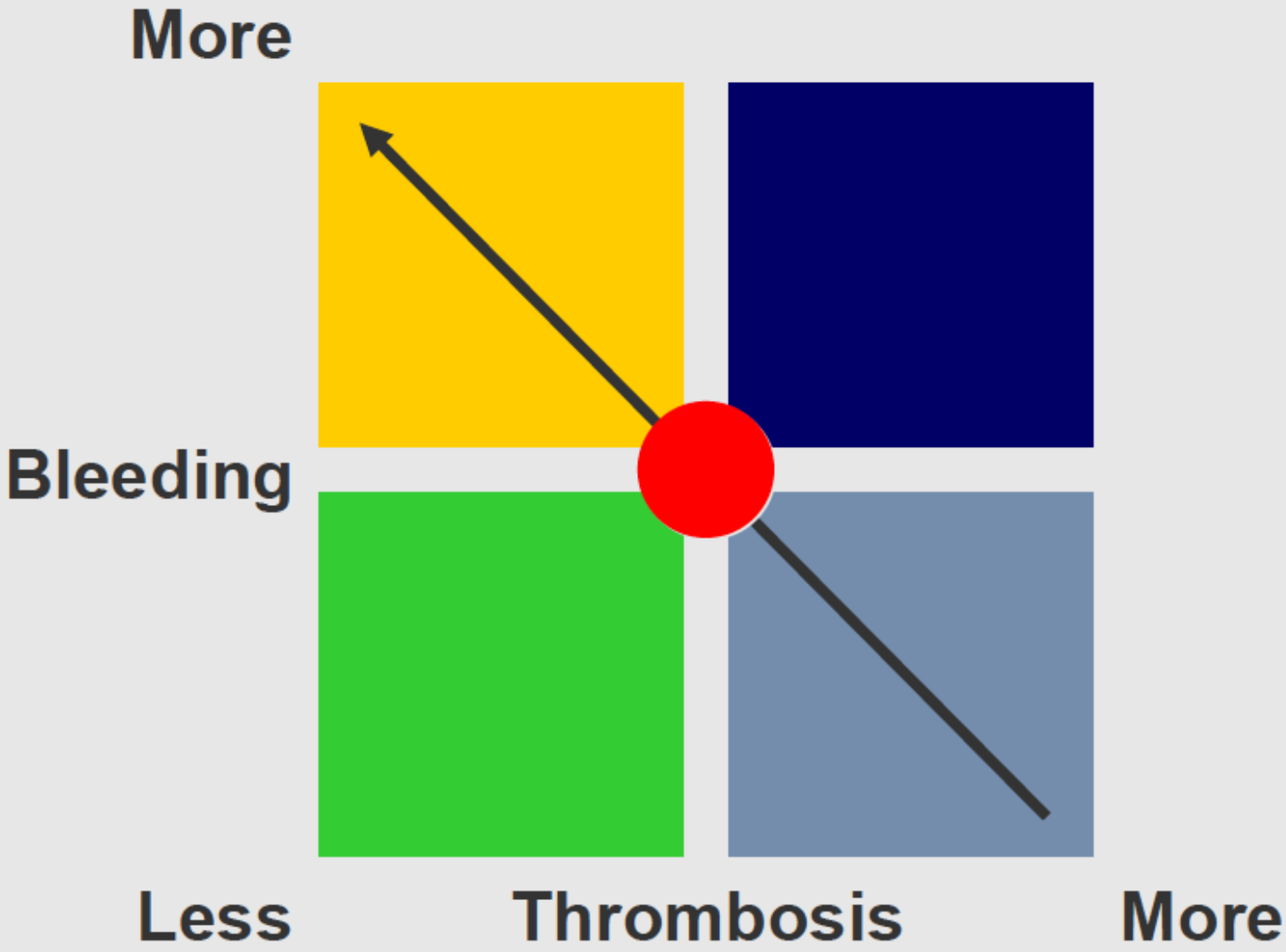
REG1

7 a 9 de Fevereiro 2014

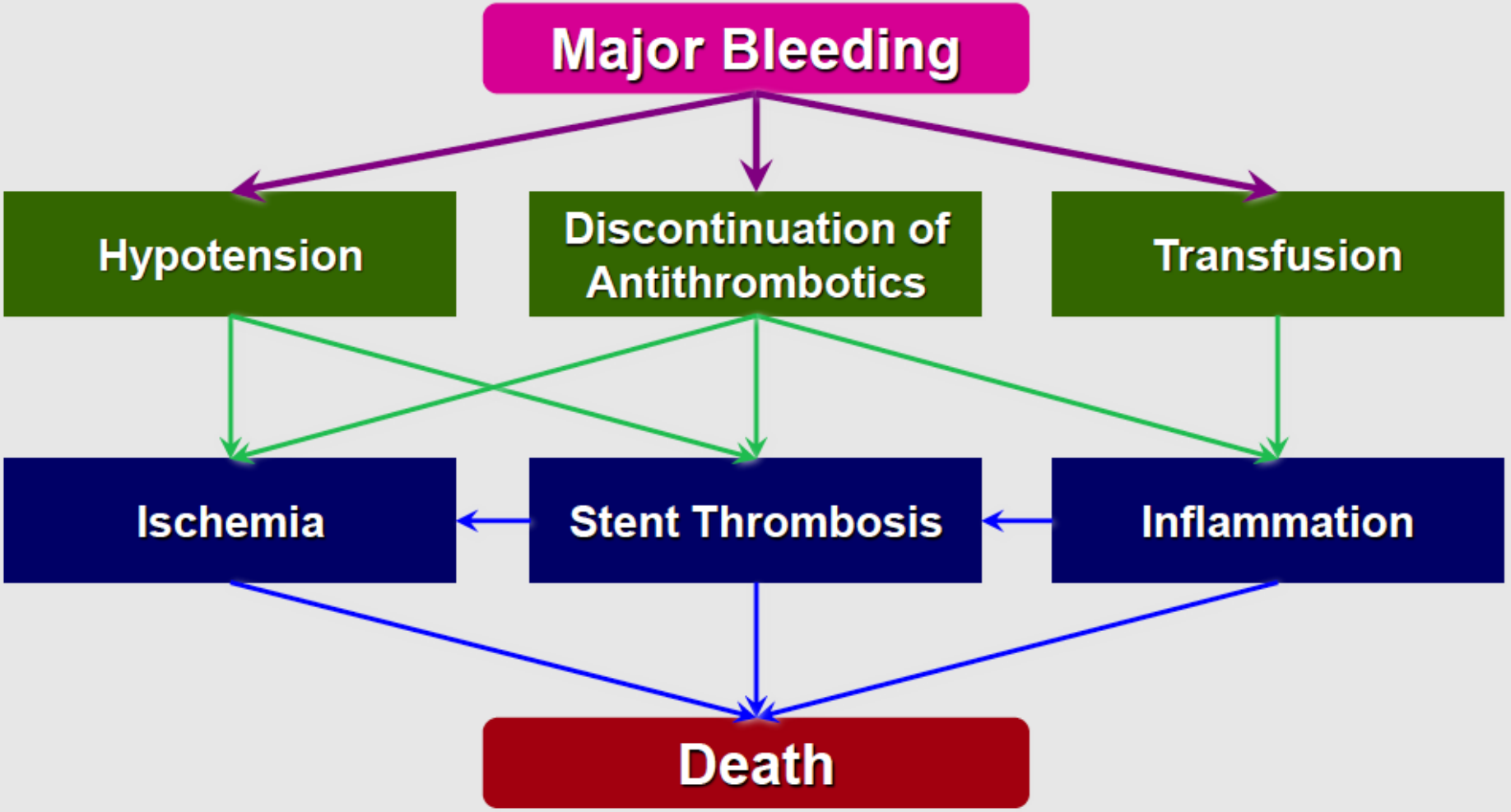
Hotel Vila Galé Ericeira

Cláudia Jorge
Hospital de Santa Maria

Paradigm for Antithrombotic Drugs



Bleeding and Mortality – Potential Relationships



Bhatt DL et al. In Braunwald: Harrison's Online 2005.

The Ideal Anticoagulant

REGULATE-PCI

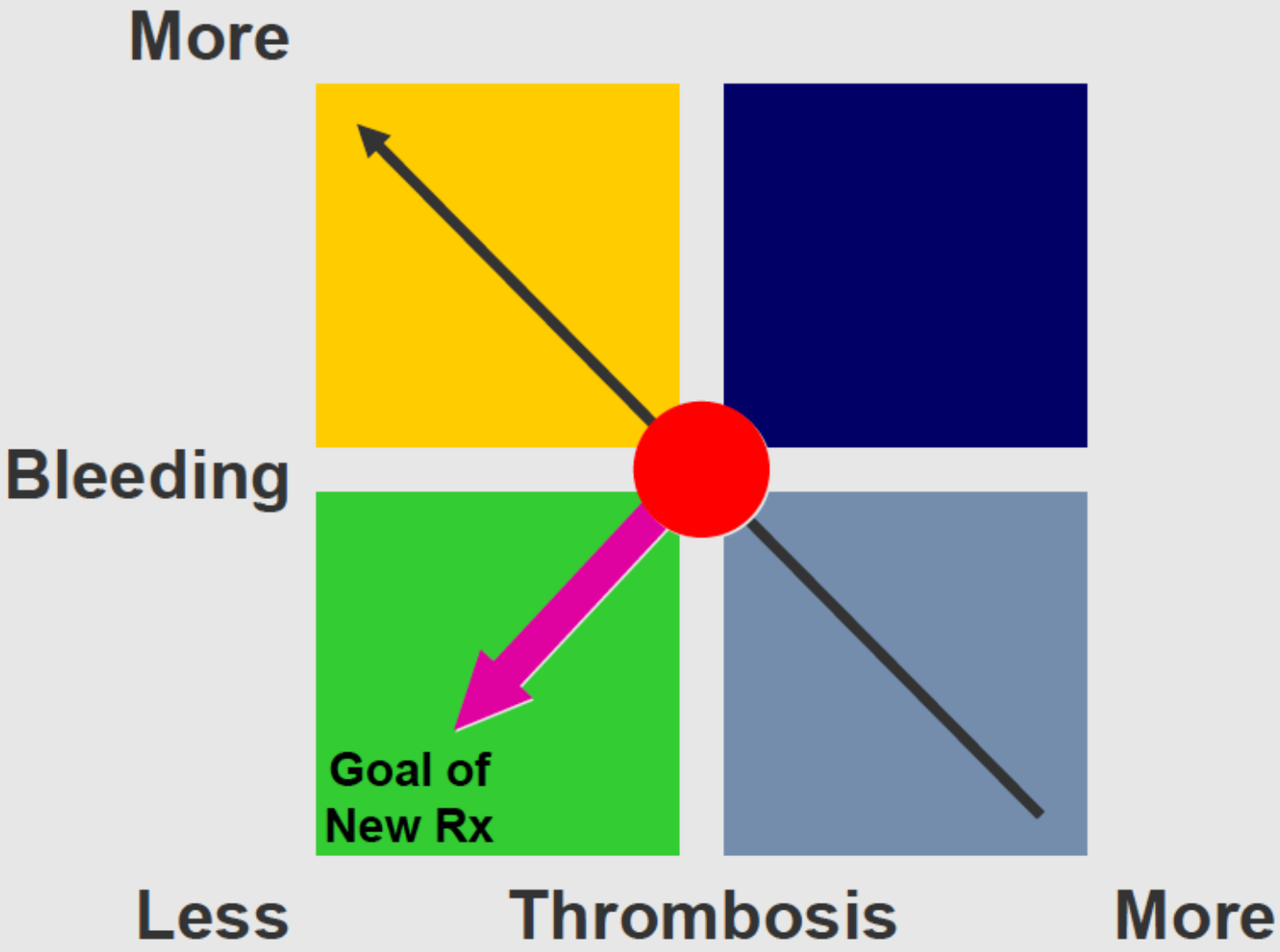
Characteristics

- Improved clinical outcome
  - Antithrombotic efficacy
  - Safety (bleeding)

  } can these be uncoupled?
- Predictable dose response - no monitoring
- Parenteral or oral administration
- Rapid onset of action
- Availability of a safe antidote
- Free of non-anticoagulant side effects
- Minimal interaction with other drugs

Adapted from Hirsh J, O' Donnell, Weitz. Blood 2005;105:453.

Paradigm for Antithrombotic Drugs



Aptamers: Unique protein target binding properties

Protein

the same but different

Oligonucleotide
(e.g. anti-sense, siRNA)

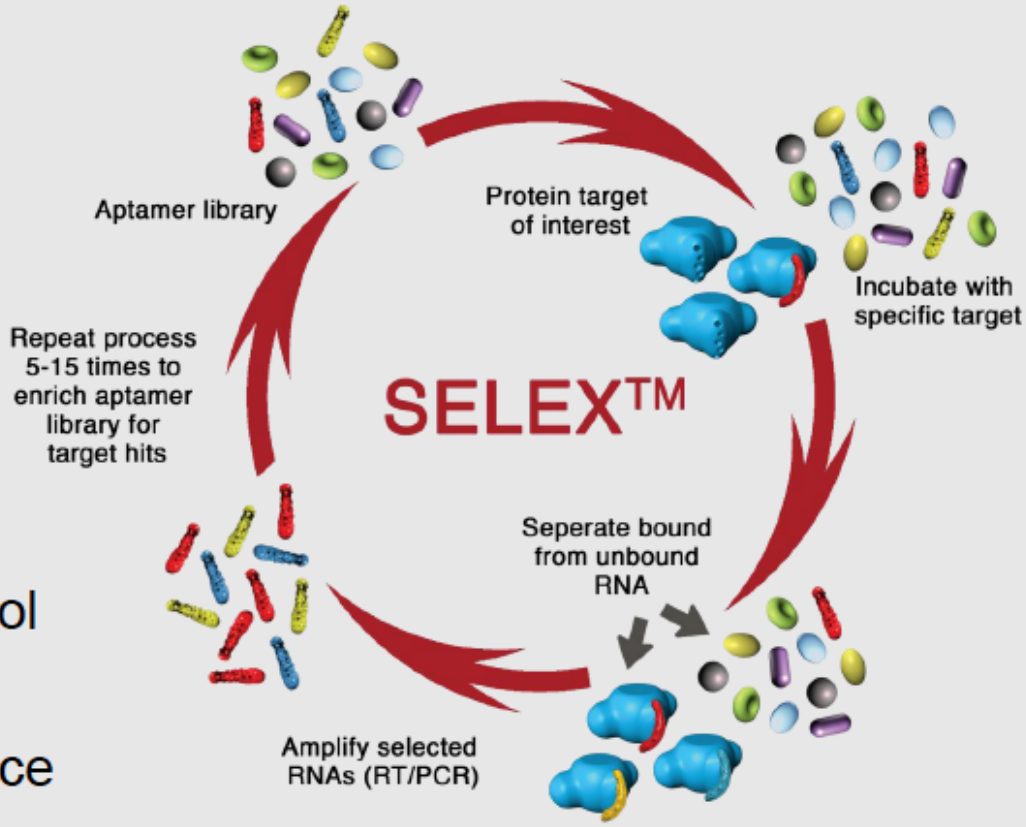
Nucleic acid structure
Blocks gene expression

Aptamer

Nucleic acid structure
Blocks protein function

Aptamer identification

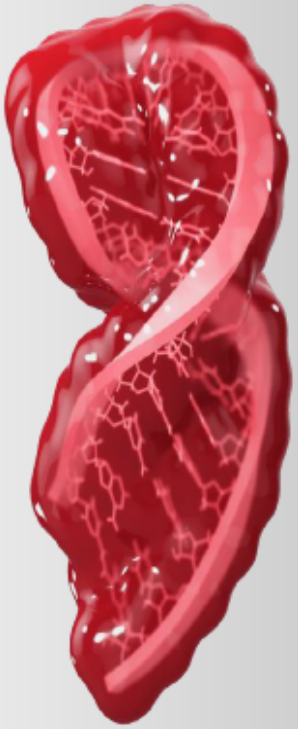
- Single-stranded nucleic acids that adopt a defined shape
- Unique MOA's for robust blocking of protein-protein interactions
- Minimal toxicity
- Low/no immunogenicity
- IV or subcutaneous injection
- Effects can be modulated by administration of specific control agents
- Non-renal, non-hepatic clearance
- Tunable pharmacokinetics
  - Polyethylene glycol (PEG)



REG1: A two component, actively controllable aptamer anticoagulant system

REGULATE PCI

ANTICOAGULANT



Synthetic with low cost of goods

Convenient weight based IV bolus administration with **no dose adjustment in the renally or hepatically impaired**

No active metabolites, protein binding or tissue accumulation

Pegnivacogin (RB006)

SPECIFIC AFFINITY FOR FACTOR IXA

31 nucleotides + 40 kDa PEG | $t_{½}$ ~100hr | t_{max} < 5 min

ACTIVE CONTROL AGENT

Anivamersen (RB007)

SPECIFIC AFFINITY FOR PEGNIVACOGIN

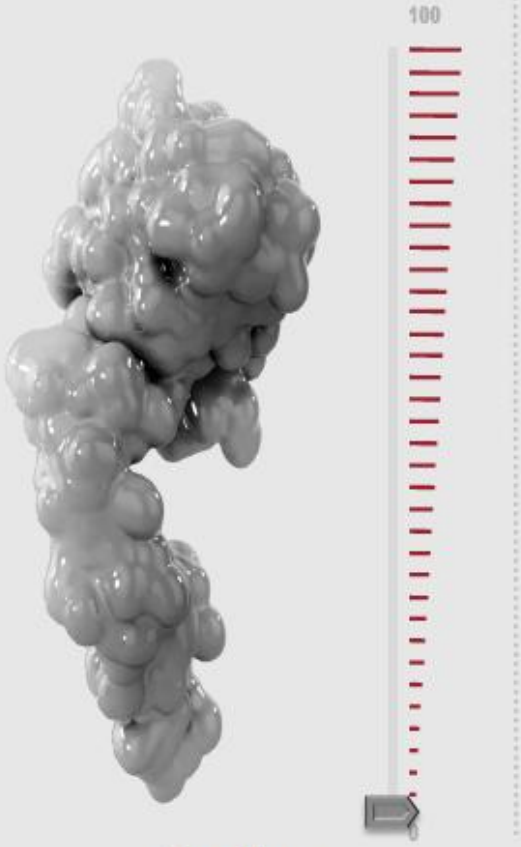
No Other Known Activity

15 nucleotides | $t_{½}$ < 5 min | t_{max} ~ immediate

REG1 Mechanism of Action

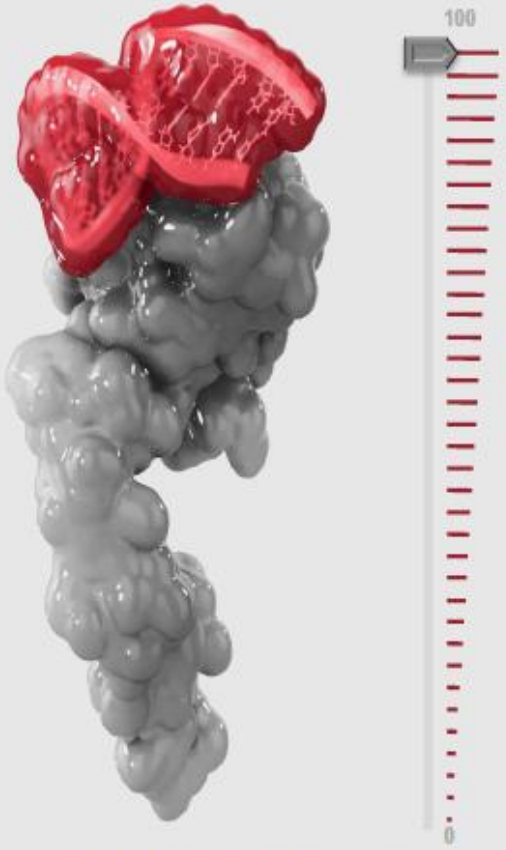
REGULATE-PCI

Coagulation proceeds unimpeded and clots form



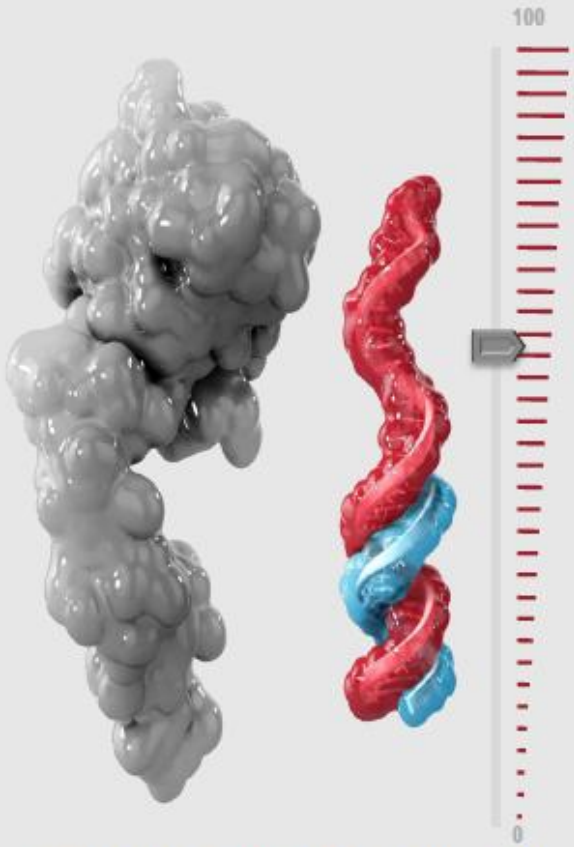
Baseline

Pegnivacogin selectively inhibits Factor IXa and clotting cannot proceed



Fully anticoagulated

Anivamersen binds to **Pegnivacogin**; the resulting complex is inert and the clotting cascade resumes



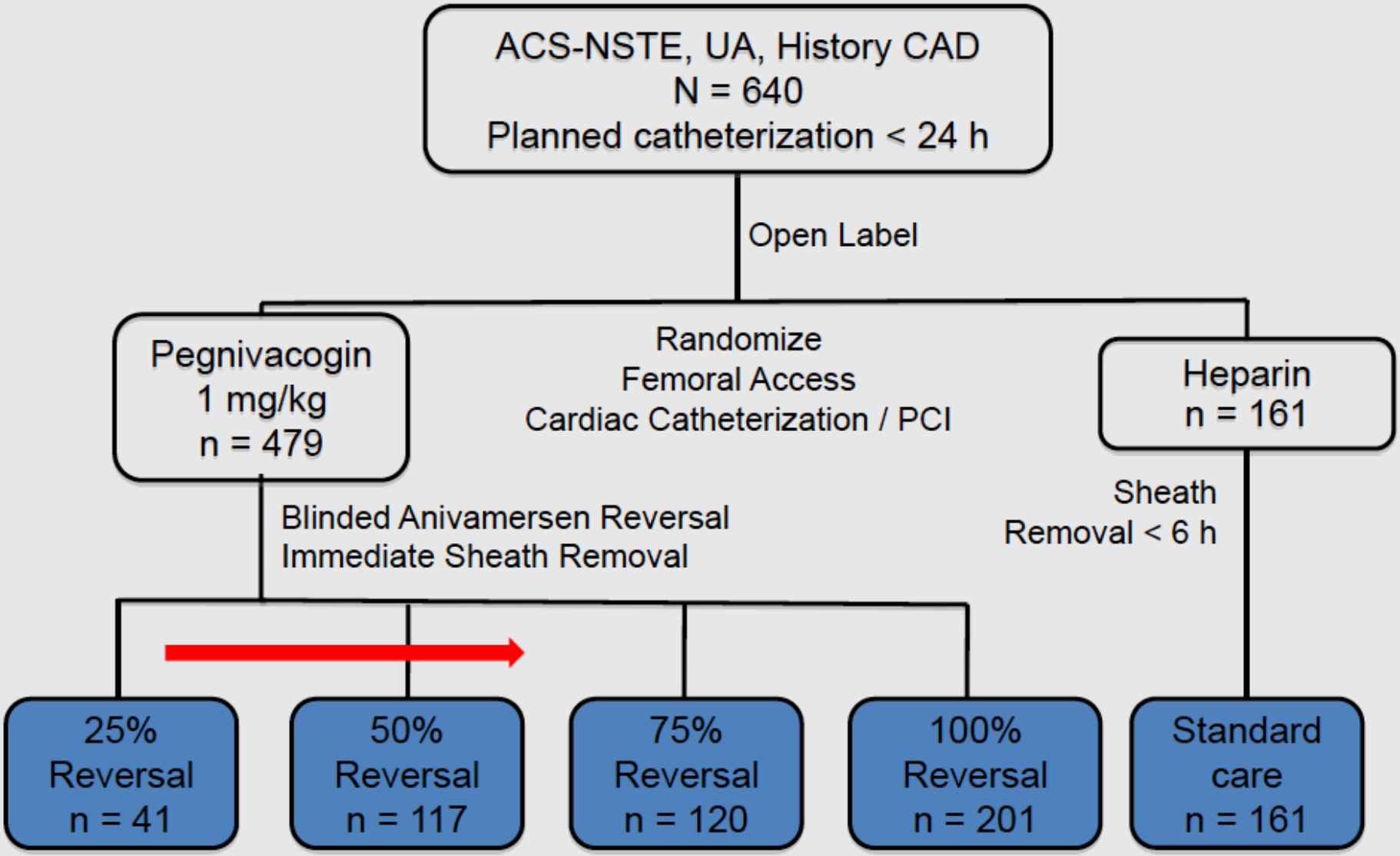
Partial or complete reversal

Rationale for Targeting FIXa

REGULATE-PCI

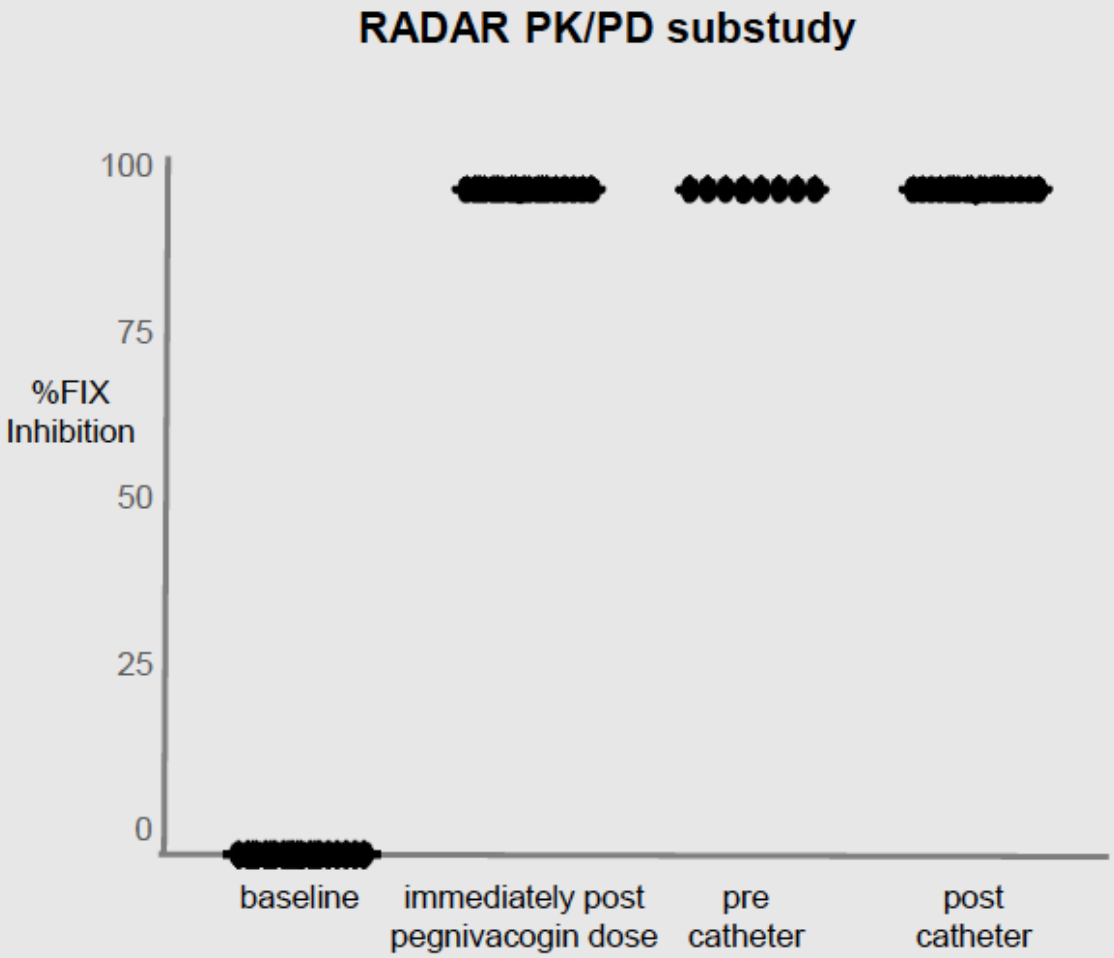
- Proximal driver of clot propagation
- More thrombogenic than Factor Xa and thrombin
- FIXa activation of FX is rate limiting to thrombin generation
- High levels of target inhibition achievable
- High Factor IX levels are associated with ACS and VTE
- Patients w/ hemophilia B have well characterized coagulopathy
  - FIX replacement restores normal clotting
  - Patients w/ hemophilia B trait have a lower incidence of ACS

RADAR Enrollment



Pegnivacogin (1 mg/kg) provides near complete inhibition of Factor IXa

REGULATE PCI

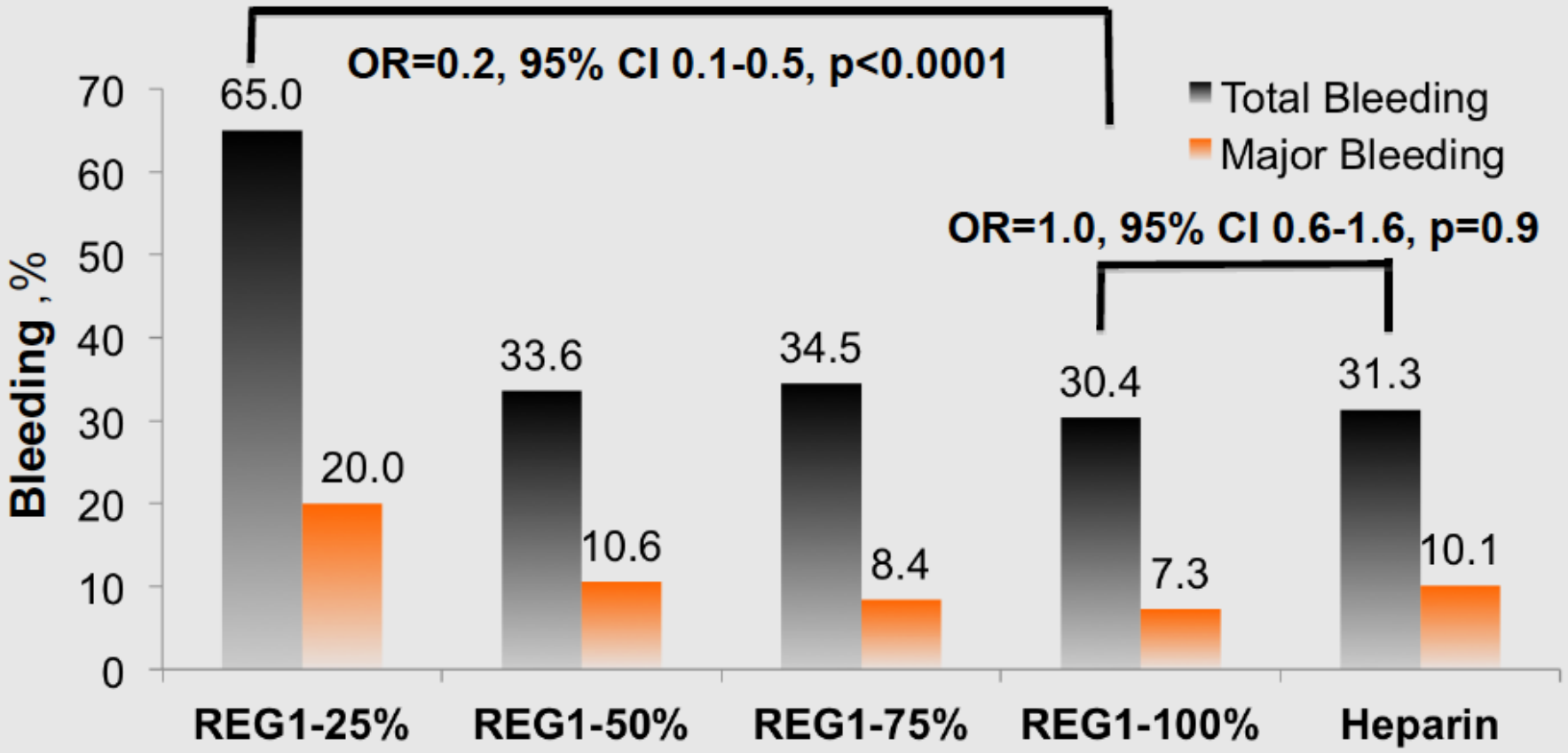


PK/PD in ACS patients is consistent with that in stable CAD patients and healthy volunteers

Timing
Post dose – 10 to 20 minutes
Pre-catheter – 45 mins to 18 hrs
Post-catheter – 2 hrs to ~20 hrs

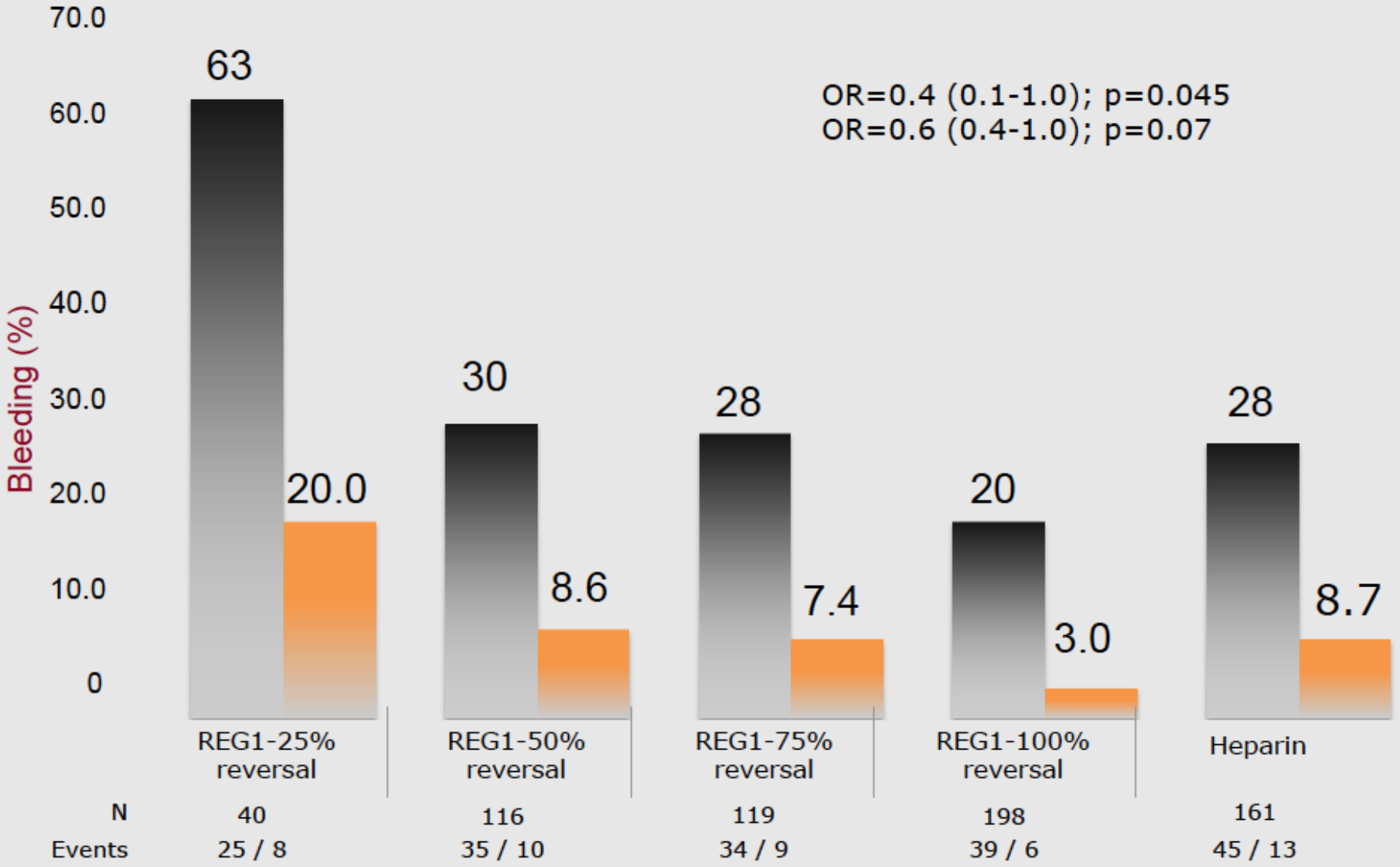
Povsic, European Heart Journal, June 30, 2011

ACUITY Bleeding Through 30 Days

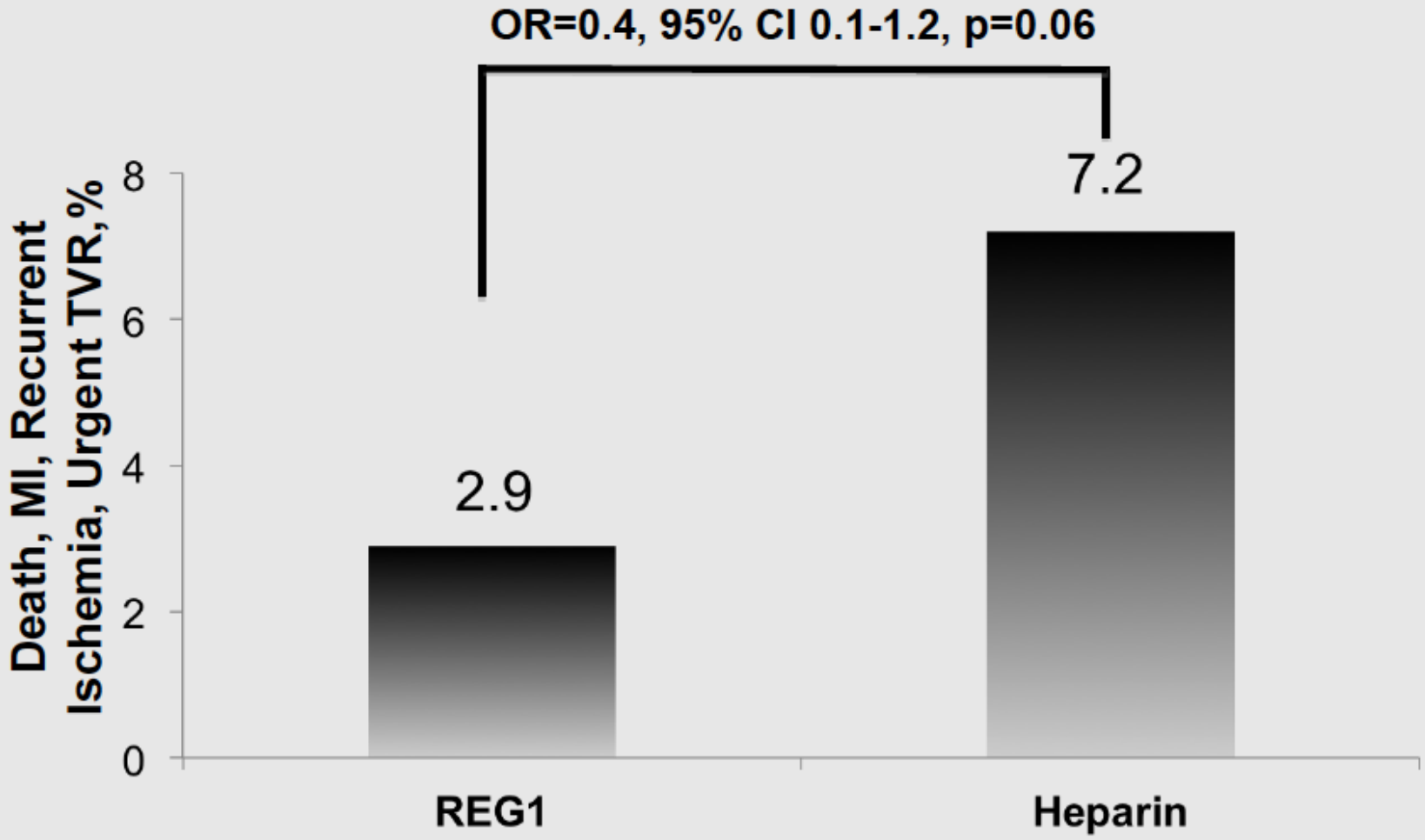


	REG1-25%	REG1-50%	REG1-75%	REG1-100%	Heparin
N	40	113	119	194	160
Events	26 / 8	38 / 12	41 / 10	59 / 14	50 / 16
Open Reversal	12 (30.8%)	6 (5.3%)	6 (5.1%)	9 (4.6%)	NA

RADAR Bleeding Results Through 48 Hours

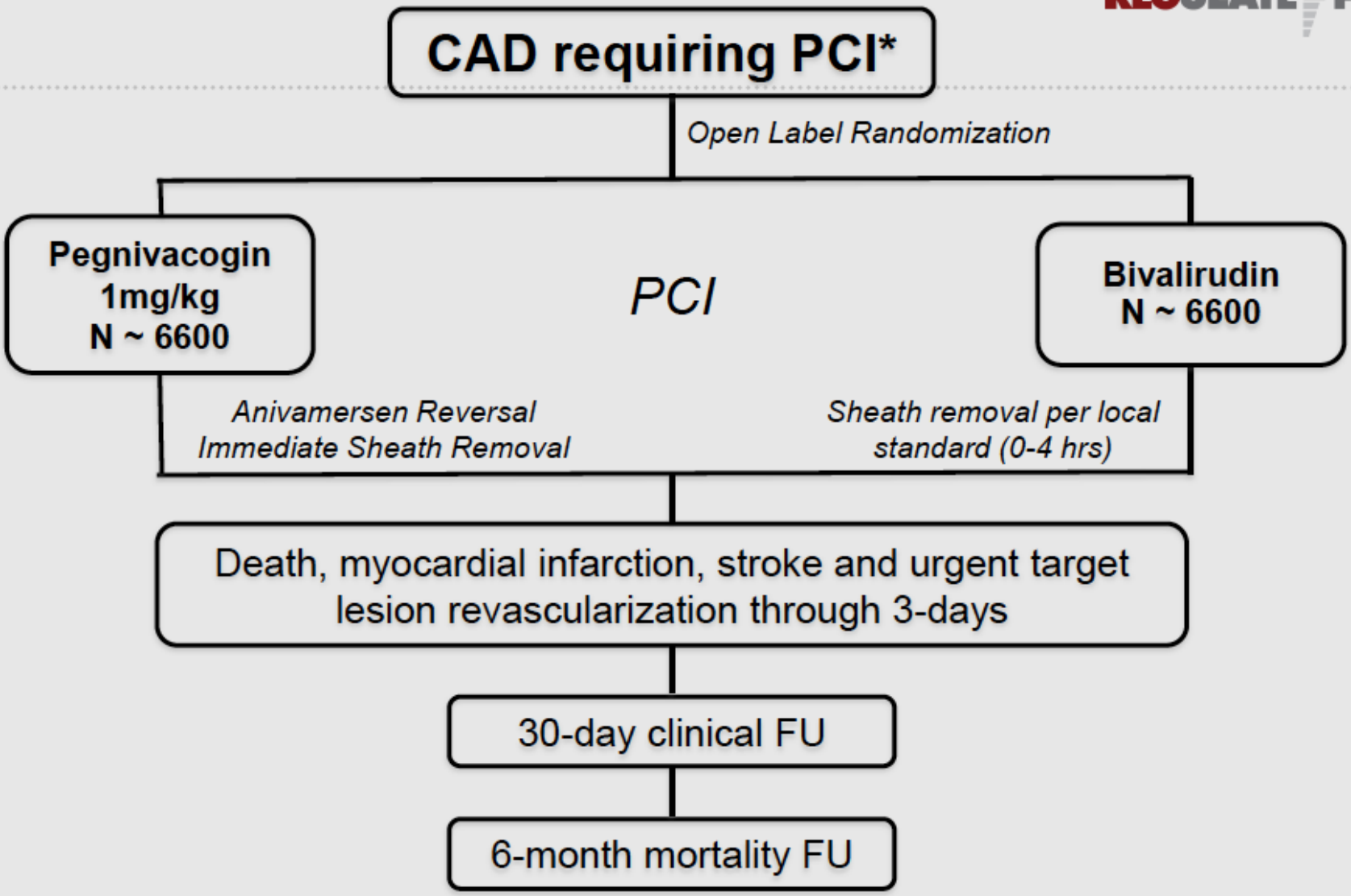


Ischemic Events through Discharge: PCI Cohort



REGULATE-PCI

A Randomized, Open-label, Multi-Center, Active-Controlled, Parallel Group Study To Determine The Efficacy And Safety Of The REG1 Anticoagulation System Compared To Bivalirudin In Patients Undergoing Percutaneous Coronary Intervention



*At least 6600 patients with recent NSTEMI, excludes STEMI undergoing primary PCI

Inclusion Criteria

REGULATE PCI

- Patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)
- Male or female age 18 or greater

Subgroup Stratification

REGULATE-PCI

Subgroup A: Ischemic symptoms at rest and positive cardiac markers (Tn T or I or CKMB) from an acute coronary syndrome within 7 days

Subgroup B: Not meeting criteria for Subgroup A with at least one of the following:

- Remote acute coronary syndrome (>7 days) with positive cardiac markers
- Unstable angina (ACS without positive cardiac enzymes)
- Age >70 years
- Diabetes
- Chronic kidney disease (estimated CrCl < 60 mL/min)
- Planned multivessel PCI
- Prior CABG surgery
- Peripheral vascular disease

Subgroup C: All other patients undergoing PCI not meeting criteria for Subgroup A or B

Key Exclusion Criteria

REGULATE PCI

1. Acute ST-segment elevation myocardial infarction within 48 hours of randomization
2. Evidence of a contraindication to anticoagulation or increased risk of bleeding such as thrombocytosis, or trauma/surgery, GI/GU bleed within 3 months or planned surgery within 3 months
3. Planned PCI (<3 d) or CABG (<30 d)
4. Hgb < 9 or Plt < 100k
5. Unable to be treated with Bivalirudin per local label including due to impaired renal function
6. Unable to take ASA + P2Y12 inhibitor for 30 days
7. Use of:
   - Fibrinolytic agents within 48 hours
   - GP IIb/IIIa inhibitors within 24 hours
   - Bivalirudin within 24 hours

Outcomes

REGULATE PCI

Primary Outcome

- Composite of death, nonfatal myocardial infarction, nonfatal stroke, urgent target lesion revascularization through day 3

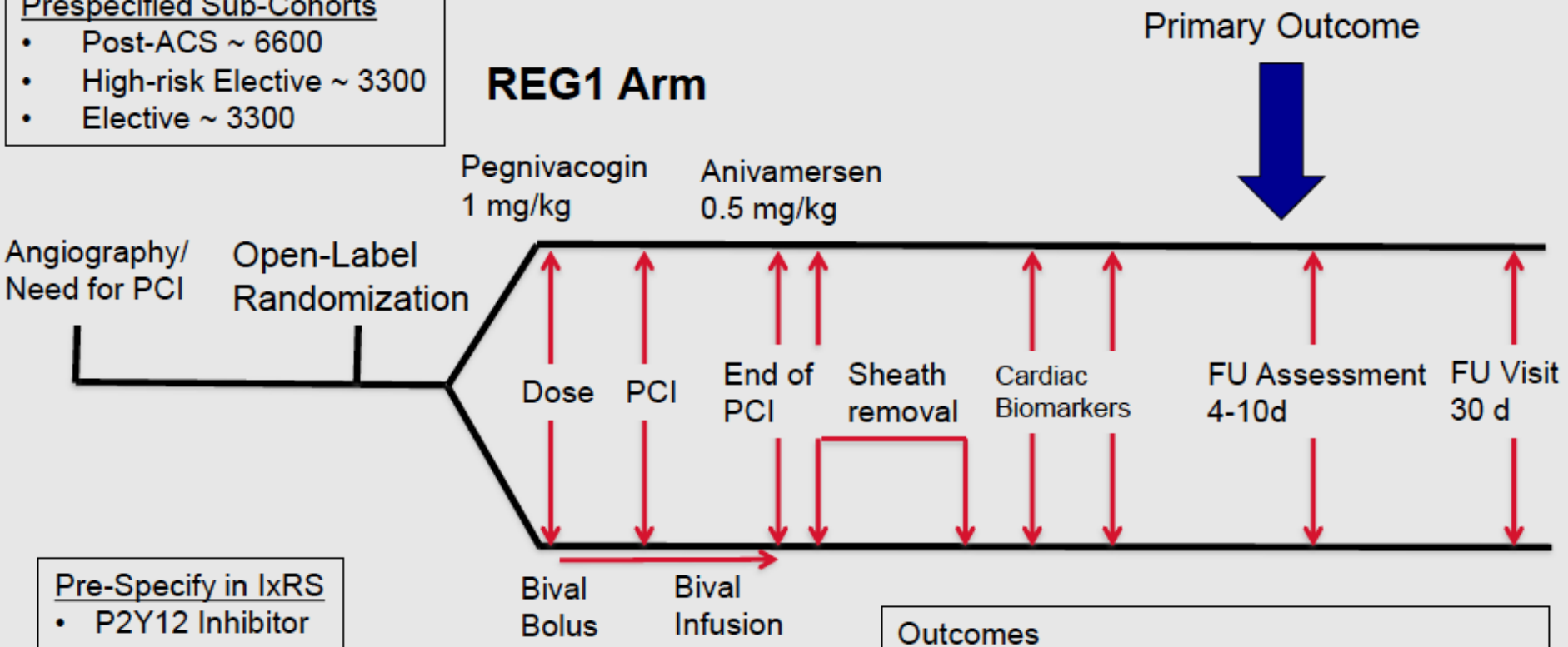
Secondary Outcomes

- Composite of death, nonfatal myocardial infarction, nonfatal stroke, urgent target lesion revascularization and intraprocedural and post-procedural stent thrombosis through day 3
- Bleeding complications through day 3 and 30 (BARC)
- Composite ischemic events through 30 days
    - Overall
    - Biomarker (+) patients (Group A)
    - Biomarker (-) patients (Group B/C)

Study Design

REGULATE-PCI

Prespecified Sub-Cohorts
- Post-ACS ~ 6600
- High-risk Elective ~ 3300
- Elective ~ 3300



Pre-Specify in IxRS
- P2Y12 Inhibitor
- Vessels Treated
- Access Site
- VCD Use

Outcomes
- 1^0 Death, MI, Stroke, Urgent TLR (day 3)
- Bleeding (BARC)
- Intraprocedural Thrombotic Complications
- Allergic Reactions

Pre-PCI Planned Treatment

REGULATE PCI

- Open Label Trial = concern that randomized group will impact concomitant treatment
- Indicate **planned** treatment **prior** to randomization:
    - ADP/P2Y12 inhibitor (i.e.., clopidogrel, prasugrel, or ticagrelor). If already given, indicate administered ADP/P2Y12 inhibitor
    - Procedural access (femoral or radial). If sheath is already placed, indicate actual access site
    - Planned VCD use (yes/no)
    - Planned target vessel(s) (number and vessels)

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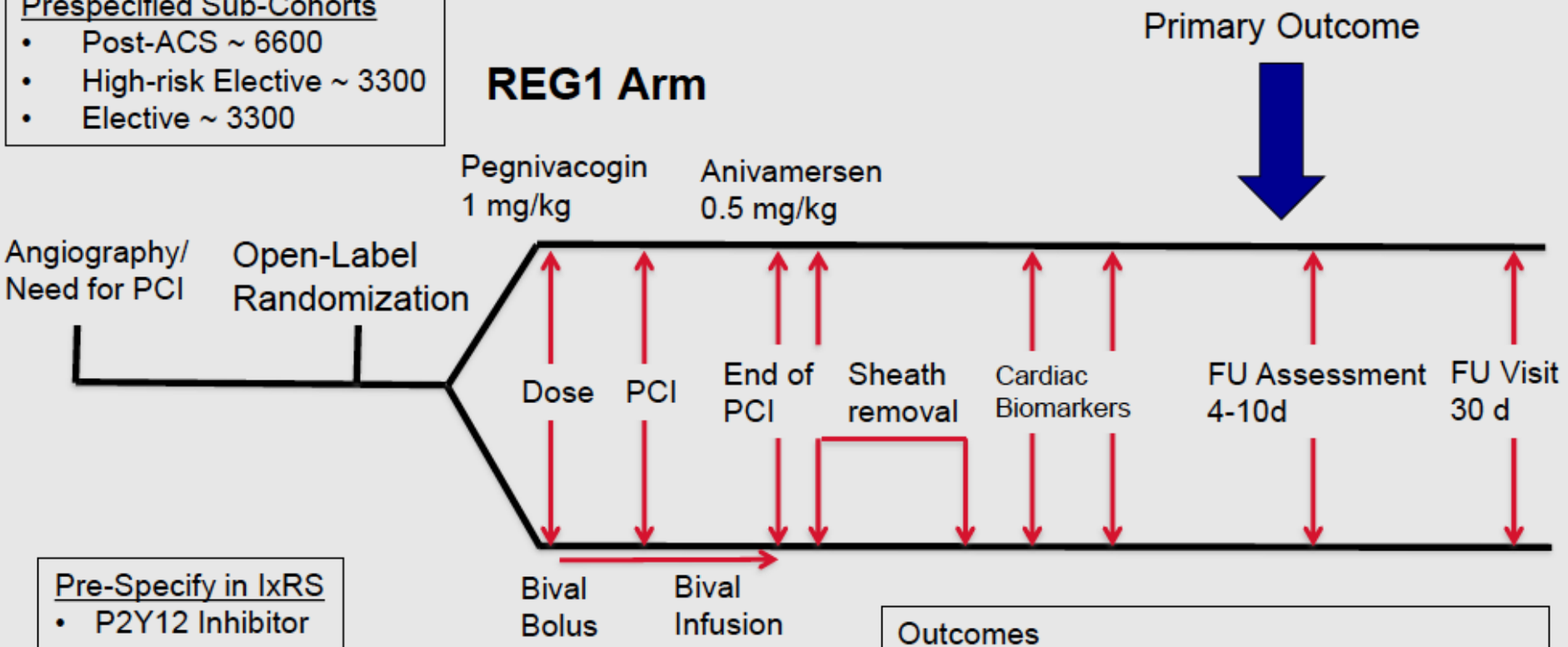

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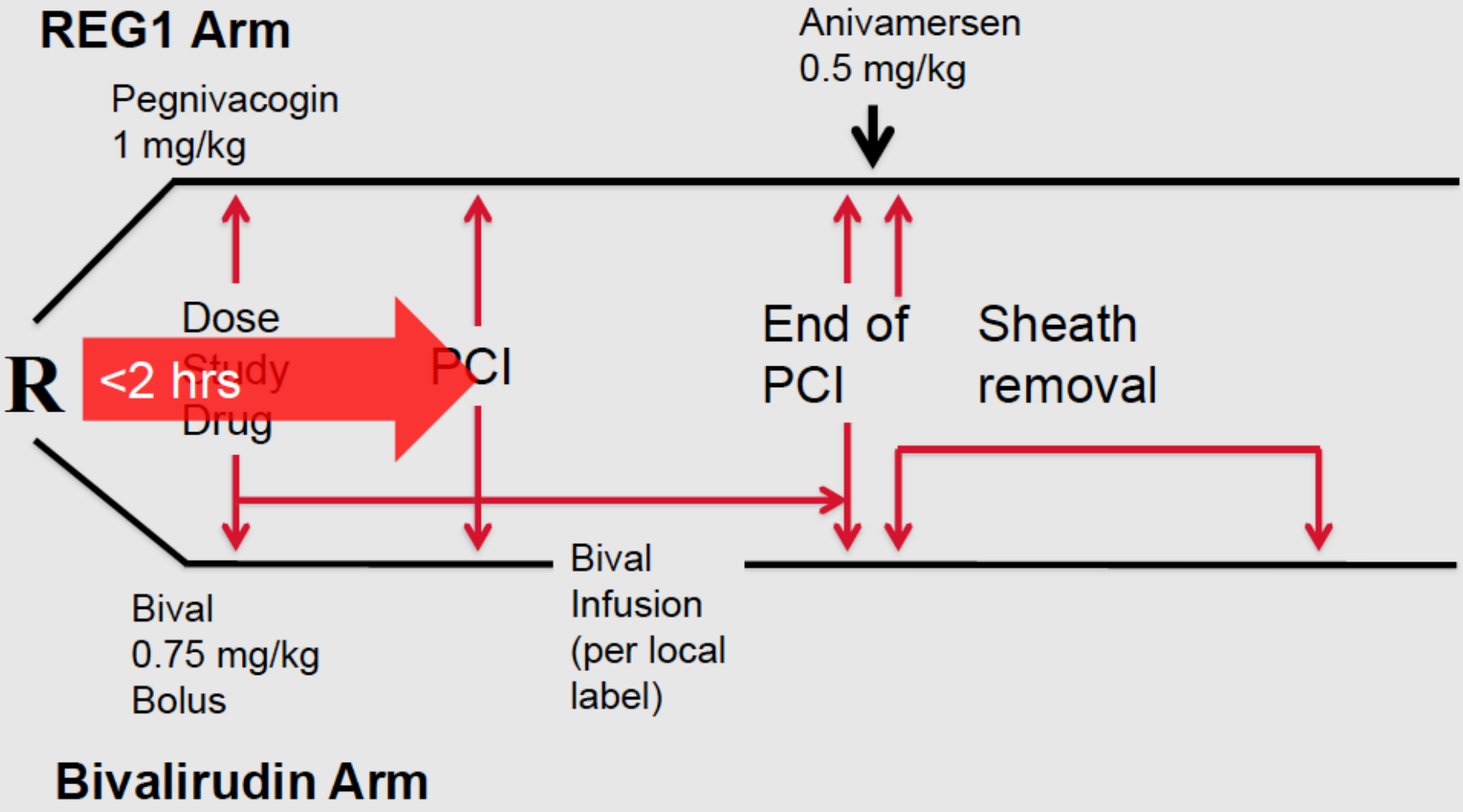
Study Scheme: PCI/Sheath Removal



Sheath Removal

REGULATE PCI

REG1 Anticoagulation System

Sheath is removed approximately 2-10 minutes after anivamersen is administered

Bivalirudin

Sheath removal per:

- Femoral access without VCD: approximately 2-4 hours from the completion of PCI procedure
- Femoral access with VCD: at the completion of the PCI procedure
- Radial access: at the completion of the PCI procedure

Study Design

REGULATE-PCI

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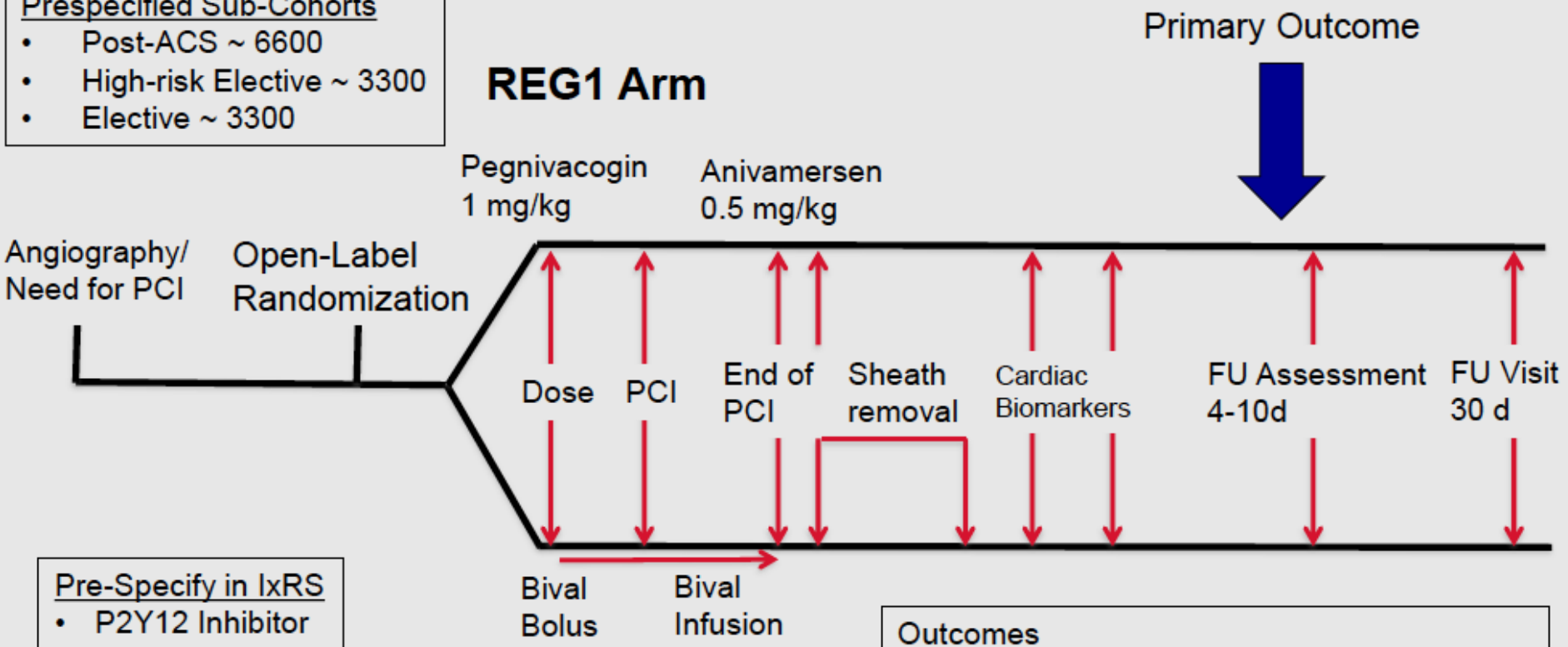

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Post Randomization Central Lab Work

REGULATE-PCI

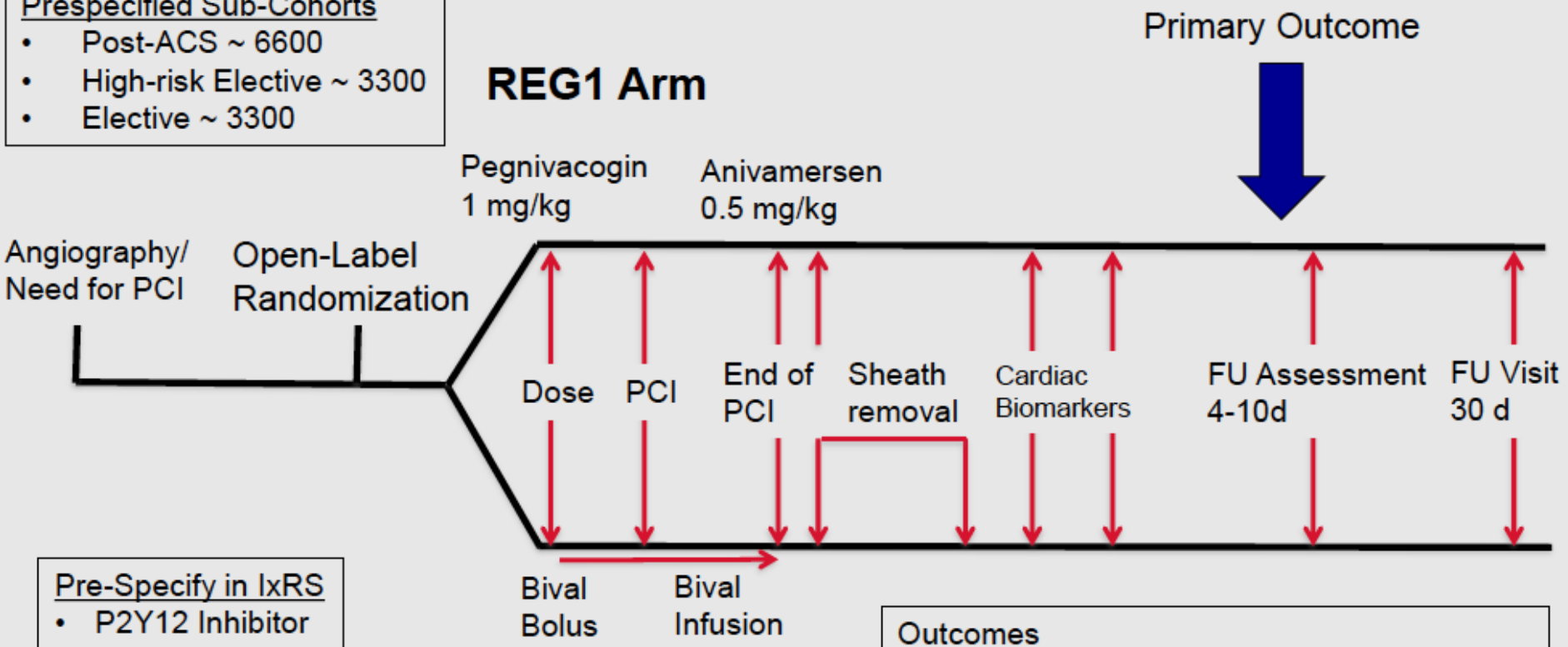
Central lab work	90 ± 30 Minutes Post Dose	8 ± 2 Hours Post Dose	20 ± 4 Hours Post Dose *
Hemoglobin			X
Cardiac Biomarker	X	X	X
Immunology	X		X

* Patients must be available for 20 ± 4 hours for all study related Central Labs

Study Design

REGULATE-PCI

Prespecified Sub-Cohorts
- Post-ACS ~ 6600
- High-risk Elective ~ 3300
- Elective ~ 3300



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- Allergic Reactions

Follow-up (Day 3) Assessment

REGULATE PCI

If hospital discharge occurs on or before Day 3:

- All assessments will be performed
  - At Discharge **AND**
  - via telephone between 4-10 days from randomization*

If discharge after day 3:

- Perform assessments day 4-10 before discharge

The following will be performed:

- Primary efficacy and safety endpoints (death, nonfatal myocardial infarction, nonfatal stroke, urgent target lesion revascularization, bleeding)
- Select concomitant medications
- AEs (through day 3)

*If a patient happens to return for a visit within this timeframe for another reason, this information can be obtained at that time (in lieu of the phone call).

Follow-up Day 30 (+5 days)

At 30 days post-dose (+ 5 days), an End of Study follow-up evaluation will be conducted via telephone (office visit is also acceptable).

The evaluation will assess the following:

- The primary efficacy endpoint (death, nonfatal myocardial infarction, nonfatal stroke, urgent target lesion revascularization)
- Any patient-reported bleeding (only clinically significant bleeding that required medical treatment will be documented in the eCRF)
- Any other SAE that occurred since discharge
- Targeted concomitant medications

6 Month Vital Status (+/-14 days)

At 6 months post-dose follow-up to determine vital status (Alive or Dead) of the patient. The patient or family does not necessarily have to be contacted. Medical records and other methods are acceptable to determine the following:

- Vital status (alive or deceased)
- If deceased, cause of death (cardiac or non-cardiac)
- If vital status is unknown, date in which patient was last known alive

Rationale for Unblinded Study

REGULATE-PCI

- PROBE study design proposed to allow immediate removal of arterial sheaths at end of PCI for REG1 patients
- Early sheath removal in comparator group not clinically feasible due to increased risk of bleeding
  - Timing of arterial sheath removal after PCI dependent upon reversal of anticoagulant effect of therapies during PCI (bivalirudin) usually 2-4 hours after completion of study
- Reflects how pegnivacogin/anivamersen will be used in clinical practice
- Sheath removal at end of PCI avoids unnecessary exposure to prolonged high levels of anticoagulation
  - High levels of pegnivacogin anticoagulation would have to be continued if blinded to allow for sheath removal based on comparator
  - Leaving sheath in place for prolonged time exposes patient to sheath related complications

Participating Countries

REGULATE PCI

*Austria 5

*Belgium 5

Canada 20

Czech Republic 12

Estonia 3

*France 17

*Germany 45

Hungary 12

*Israel 15

*Italy 19

Netherlands 7

Poland 31

Portugal 9

*Russia 23

Slovakia 5

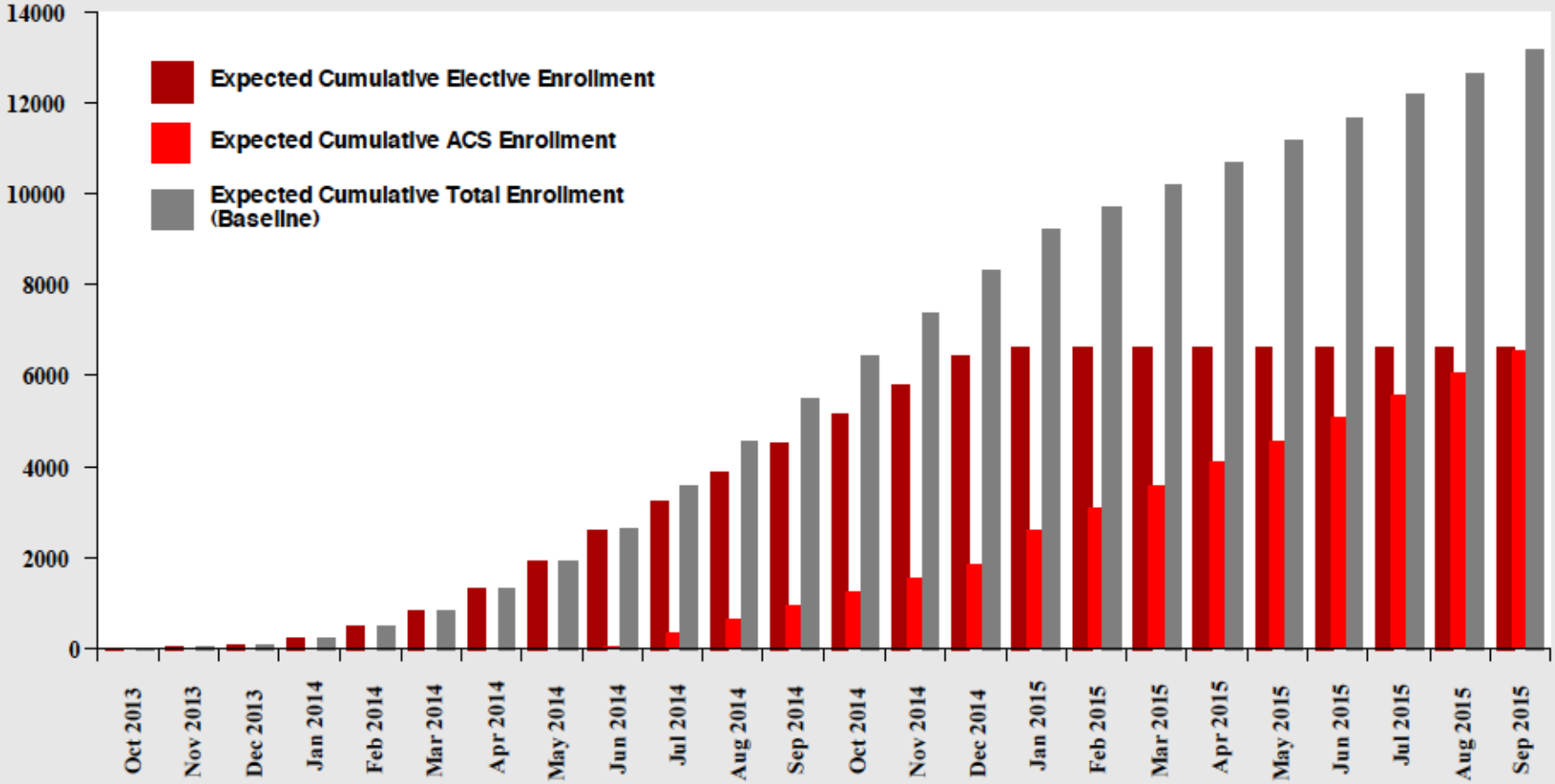
Spain 23

United Kingdom 8

United States 200

* Countries that Regulatory approval

Enrollment Projections



"It is a good thing that we live in a time when medicine has made such progress."

Lucius Annaeus Seneca (ca. 4 BC - AD 65)

Study Update
January 16, 2014; 4:15pm

REGULATE-PCI

- 75 sites activated (463 targeted, probably fewer)
  - United States 67
  - Canada 4
  - Estonia 1
  - Hungary 2
  - Netherlands 1
- 34 sites enrolling
- 323 patients enrolled
  - United States (Jeffrey Tauth = 84 in 2 months!) 255
  - Canada (Warren Cantor = 43) 54
  - Estonia (Toomas Marandi = 11) 11
  - Hungary 3

Study Update

REGULATE PCI

- Subgroup
  - 250 Subgroup B
  - 73 Subgroup C
- P2Y12 Antagonist
  - 44 Prasugrel
  - 28 Ticagrelor
  - 251 Clopidogrel
- Access
  - 139 Radial
  - 184 Femoral
- Planned Target Vessel
  - Bypass Graft – 15
  - Multiple Lesions – 54