



**Effect of REG1 Anticoagulation System versus
Bivalirudin on Cardiovascular Outcomes Following PCI:**

The REGULATE-PCI Randomized Clinical Trial

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on the Behalf of the REGULATE-PCI Investigators

The trial was sponsored by Regado Biosciences

Conflicts of Interest: R Mehran

Consulting:

- AstraZeneca; Bayer; CSL Behring; Janssen Pharmaceuticals, Inc.; Merck & Co., Inc.; Osprey Medical Inc.; Regado Biosciences, Inc.; The Medicines Company; Watermark Consulting

Scientific Advisory Board:

- Abbott Laboratories; AstraZeneca; Boston Scientific Corporation; Covidien; Janssen Pharmaceuticals, Inc.; Merck & Co., Inc.; The Medicines Company; sanofi-aventis
- Please visit websites <https://www.mountsinai.org>, <https://www.dcri.org>, <https://www.my.clevelandclinic.org> for comprehensive disclosures for the institutions and investigators

Trial Organization

Academic Leadership

Executive Committee

- John Alexander (co-PI)
- Michael Lincoff (co-PI)
- Roxana Mehran (co-PI)
- Paul Armstrong
- Gabriel Steg
- Christoph Bode
- Steve Zelenkofske (Regado)

Steering Committee:

K. Huber (Austria), P.R. Sinnaeve (Belgium), Chris Buller (Canada), M. Aschermann (Czech Republic), P. Laanmets (Estonia), B. Merkely (Hungary), V. Guetta (Israel), M. Valgimigli (Italy), J.H. Cornel (Netherlands), J.D. Kasprzak (Poland), J. Morais (Portugal), B. Alekryan (Russia), V. Fridrich (Slovakia), J. Lopez/Sendon (Spain), R. Stables (UK), M.G. Cohen (USA), T. Povsic (USA), A. Levinson (USA), R. Becker (USA), V. Hasselblad (USA).

Operations

Project Management: DCRI, C5R, Regado, PAREXEL

US Site Management: DCRI, C5R

CN Site Management: CVC

ROW Site Management: PAREXEL

Data Management: DCRI

Statistics: DCRI

Safety: DCRI

Clinical Event Committee: DCRI

IXRS: ClinPhone Perceptive Informatics)

Study Drug: Catalent / PAREXEL

DSMB: Stanford U. – Robert Harrington (chair)



BACKGROUND

- Refinements in antithrombotic therapies have considerably enhanced the efficacy and safety of percutaneous coronary intervention (PCI), although no optimal strategy yet exists.
- Platelet glycoprotein IIb/IIIa receptor antagonists reduce ischemic complications,¹ but are accompanied by increased bleeding with associated mortality, morbidity and medical resource cost.²
- Bivalirudin reduces the risk of bleeding compared to heparin and glycoprotein IIb/IIIa inhibition, but is associated with higher rates of stent thrombosis and trends to more periprocedural myocardial infarction.³

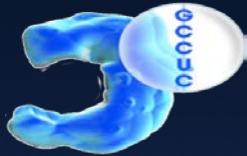
What would be an ideal antithrombotic Regimen for PCI?

- Rapid Onset of Action
- Predictable Dose-Response
- High Anti-Thrombotic Efficacy
- Quick Reversibility or Titratability

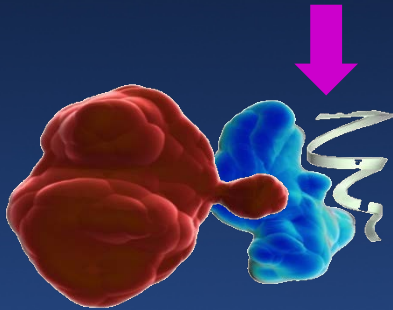
The REG1 Anti-Coagulation System



Factor IXa



pegnivacogin
(RB006)



pegnivacogin
Anticoagulant aptamer

- Specific affinity for Factor IXa

+



anivamersen
(RB007)

anivamersen
Active control agent

- Specific affinity for pegnivacogin with no other activity

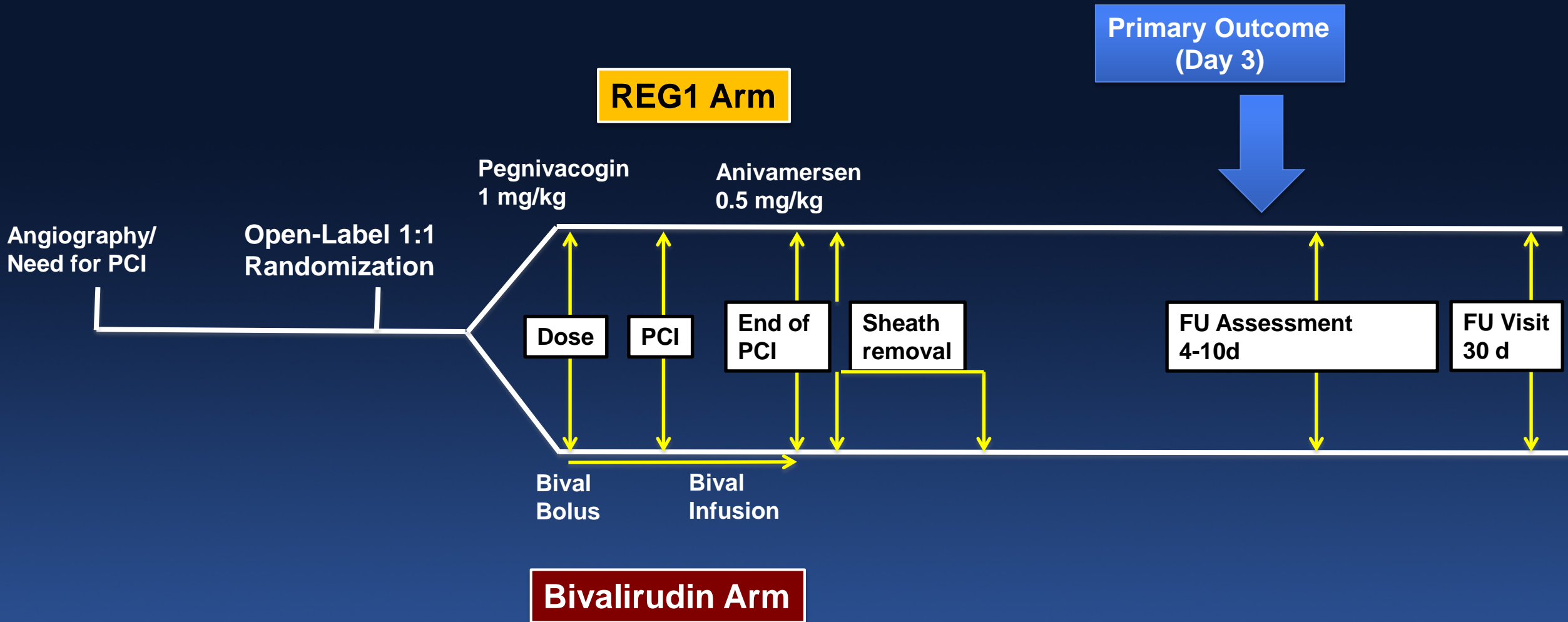
REG1 In the RADAR Trial

- **The phase 2, randomized, active-controlled RADAR trial showed that with a least 50% reversal of pegnivacogin by anivamersen, early vascular sheath removal was feasible and bleeding rates similar to heparin.**
- **The composite of 30-day death, non-fatal MI, urgent target vessel revascularization, or recurrent ischemia in the target vessel was numerically lower in patients assigned to REG1 than Heparin (OR: 0.5; 95% CI: 0.2 – 1.4; p = 0.1). The majority of ischemic events were non-fatal periprocedural MIs.**
- **In the RADAR study, 3 patients had allergic-like reactions shortly after pegnivacogin administration, of which 2 of these reactions were serious.**

The REGULATE-PCI Randomized Clinical Trial

- Randomized, open-label, active-controlled, superiority, phase 3 trial to test the *hypothesis that near complete FXa inhibition with Pegnivacogin during PCI would provide a greater reduction in ischemic events than bivalirudin without increased bleeding* as a result of anticoagulant reversal with Anivamersen.

Study Scheme



Inclusion Criteria

- Patients with CAD undergoing PCI stratified by 3 key subgroups:
 - **Subgroup A:** Patients with MI within prior 7 days - ischemic symptoms at rest and **positive cardiac biomarkers**
 - **Subgroup B:** Patients with **at least one of the following risk factors:** ACS with positive cardiac biomarkers > 7 days prior to randomization; unstable angina (without positive cardiac biomarkers); age > 70 years; diabetes; chronic kidney disease (estimated CrCl < 60 mL/min); planned multivessel PCI; prior CABG surgery; peripheral vascular disease;
 - **Subgroup C:** Patients with **negative cardiac biomarkers and no risk factor**, thereby not meeting criteria for Subgroup A or B.
- Enrollment began with approximately 1000 patients from Subgroups B and C, with expansion to include the Subgroup A only after the safety of REG1 in lower-risk patients had been established.

ENDPOINTS

(Assessed at 3 and 30 Days)

Primary Efficacy Endpoint

- Composite of death, non-fatal MI, non-fatal stroke and urgent TLR through Day 3.

Primary Safety Endpoint

- Incidence of bleeding (BARC 3 or 5; not related to CABG) through Day 3;

Secondary Endpoints

- Components of the primary endpoint through day 3
- Composite of death, non-fatal MI, non-fatal stroke and urgent TLR through day 30
- Bleeding endpoints through day 30
- Incidence and severity of allergic adverse events.

STATISTICAL ANALYSIS

- Efficacy analyses were based upon the **intention-to-treat population**, with the test of the null hypothesis based on the odds ratio and two-sided 95% CI from the Cochran-Mantel-Haenszel test with risk subgroup (Subgroup A, B, or C) as the stratification factor.
- **Superiority Trial Design** with an expected **risk reduction of 20%** for the primary efficacy endpoint.
 - Anticipated 830 adjudicated events, providing an 90% power for a two-sided alpha less than or equal to 0.049 with one planned interim efficacy review at 50% enrollment.
- **Endpoint Estimations:**
 - Primary endpoint event rate of 7.0% in the Bivalirudin arm (8% in Subgroup A, 6% in Subgroups B and C)
 - Primary endpoint event rate of 5.6% in the REG1 arm.
- **Estimated sample size of 13,200 patients**, of whom at least 6600 were to be enrolled from Subgroup A. Secondary endpoints were to be evaluated using a hierarchical closed testing procedure to preserve overall Type I error.

REGULATE PCI Enrollment

September 13, 2013

- Initial recruitment in the trial

April 2, 2014

- Enrollment expanded to include patients in Subgroup A after review of safety among the first approximately 1000 patients.

June 29, 2014

- Ongoing evaluation of reports of severe allergic reactions
- Sponsor and executive committee suspended enrollment
- A total of 3232 of the planned 13,200 patients had been enrolled at 225 hospitals in North America and Europe.

August 21, 2014

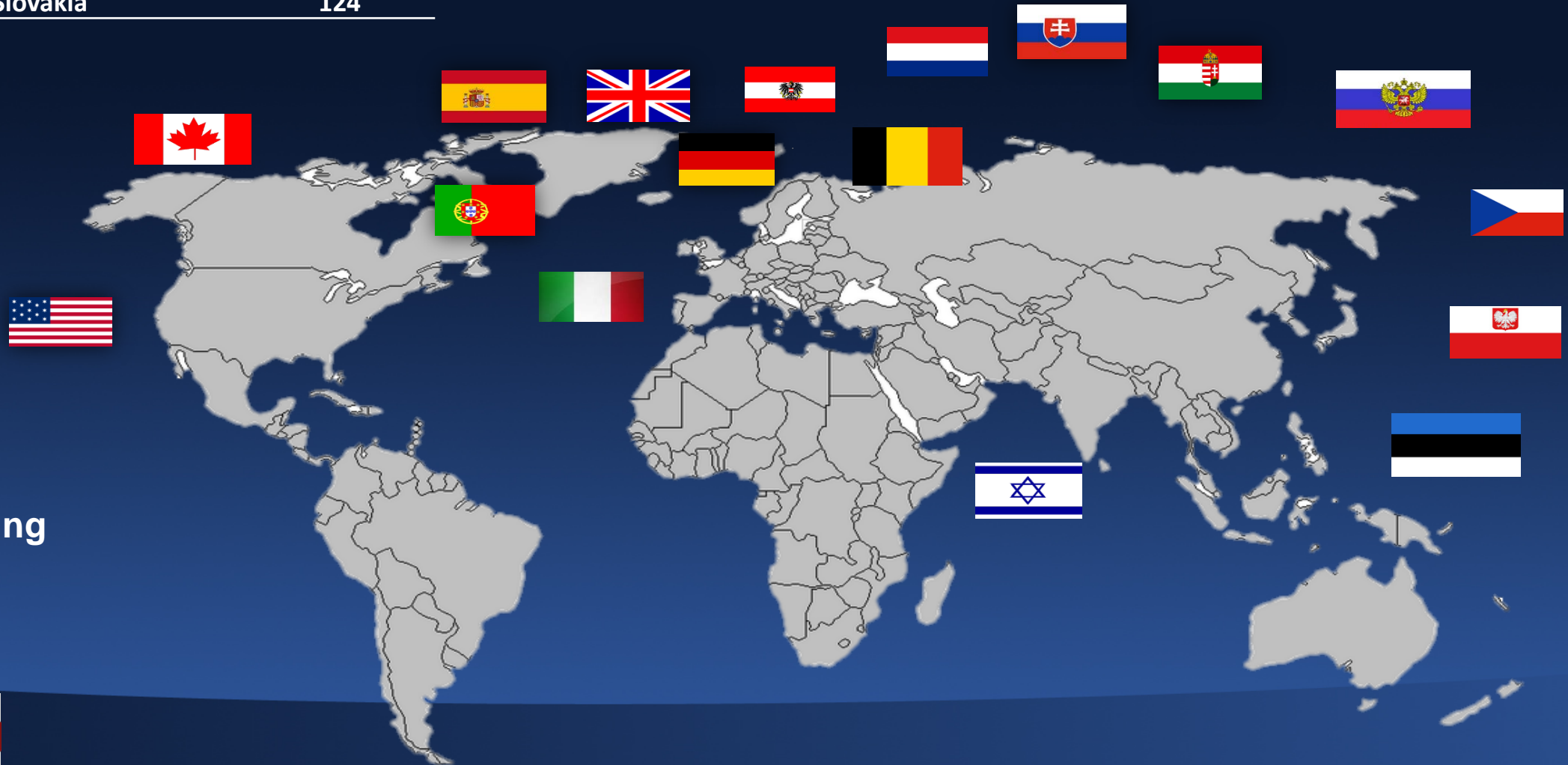
- DSMB recommended permanent termination of the trial based on findings of excess rates of allergic reactions with REG1 without evidence of offsetting benefit.

Top 5 Enroller Countries

	Country	N. Of Patients
1	United States	1965
2	Canada	288
3	Estonia	174
4	Italy	131
5	Slovakia	124

Participating Countries

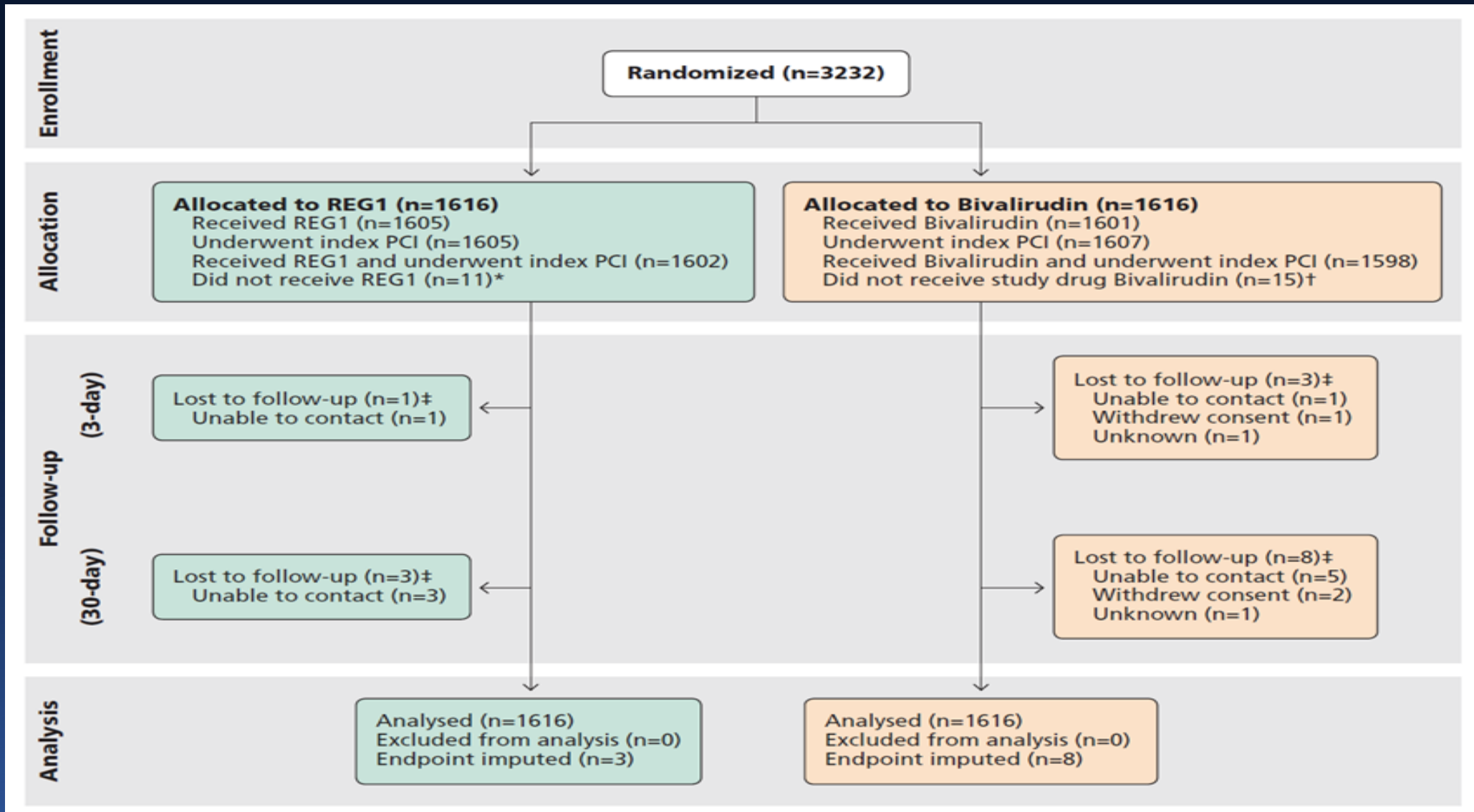
17 Participating
Countries



Top 5 Enroller Centers

	Country	Investigator	Center	N. Of Patients
1	United States	J .Tauth	HS Cardiology Associate (Hot Springs National Park, AR)	304
2	United States	G. Soliman	Heart Center, Inc. (Huntsville, AL)	148
3	Estonia	T. Marandi	University of Tartu (Tartumaa, Eesti)	134
4	Canada	W. Cantor	Southlake Regional Health Centre, (Newmarket, ON)	123
5	Slovakia	M. Hranai	Národný, Oddelenie Intervenčnej Kardiológie	123

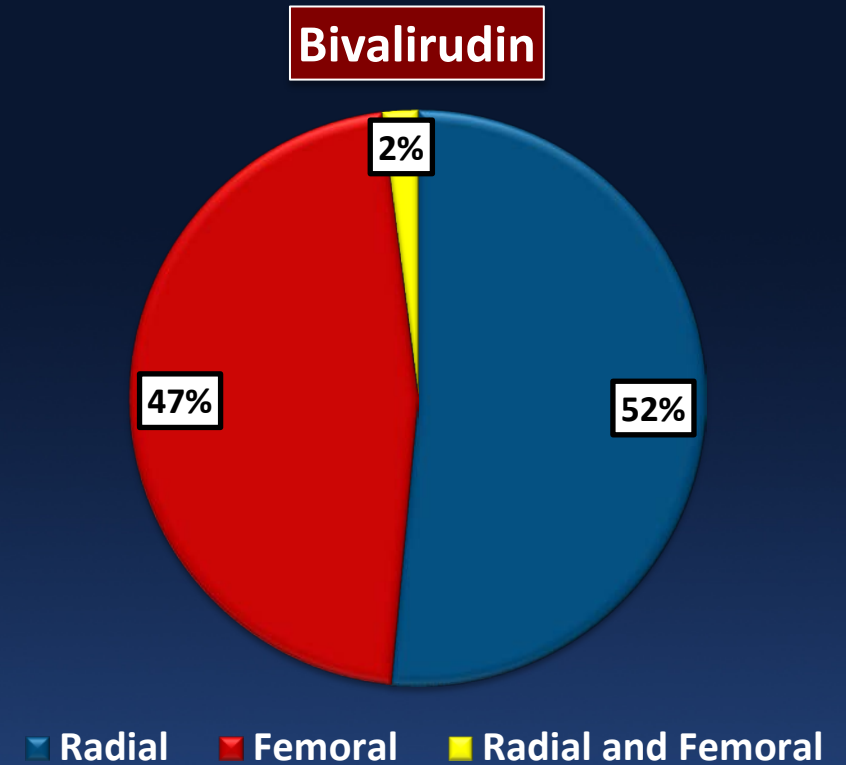
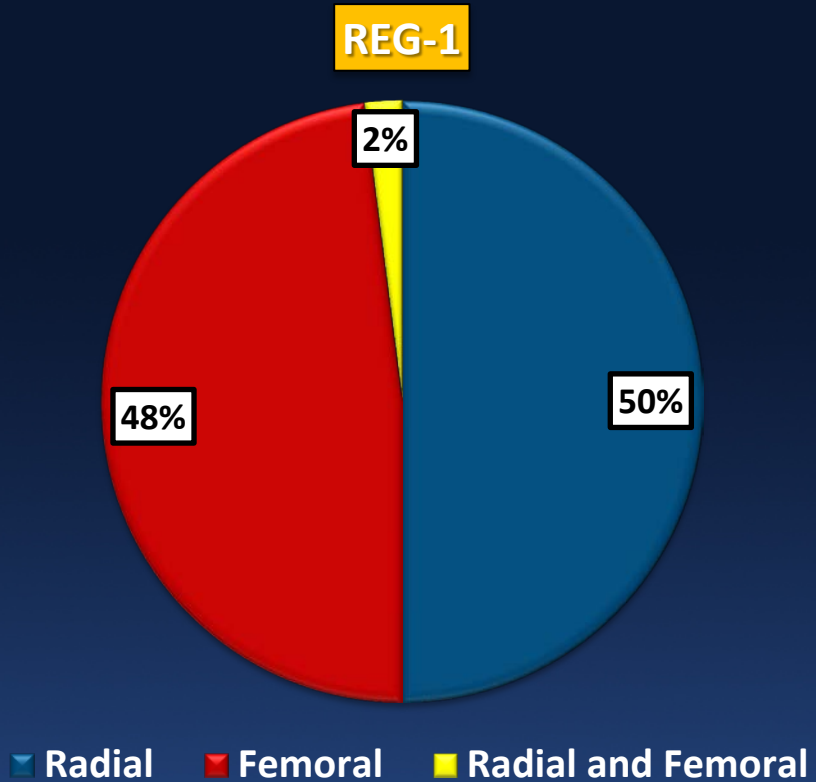
STUDY CONSORT DIAGRAM



BASELINE CHARACTERISTICS

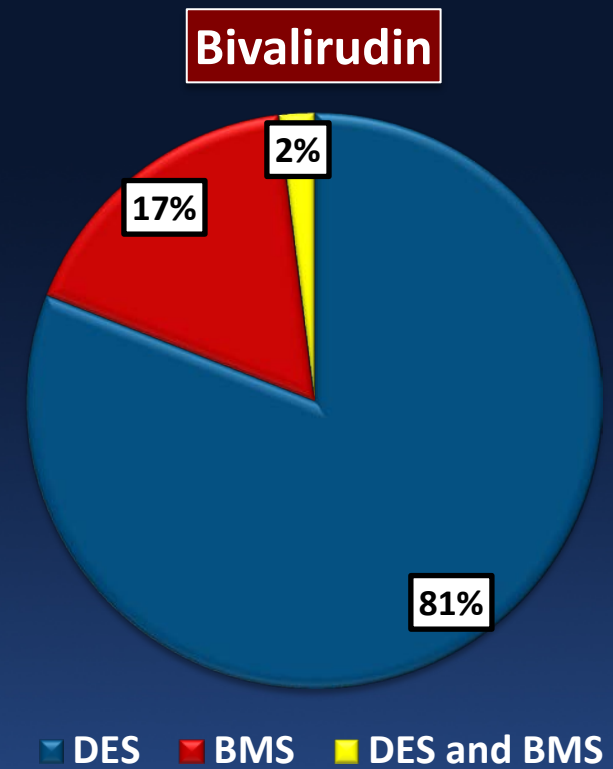
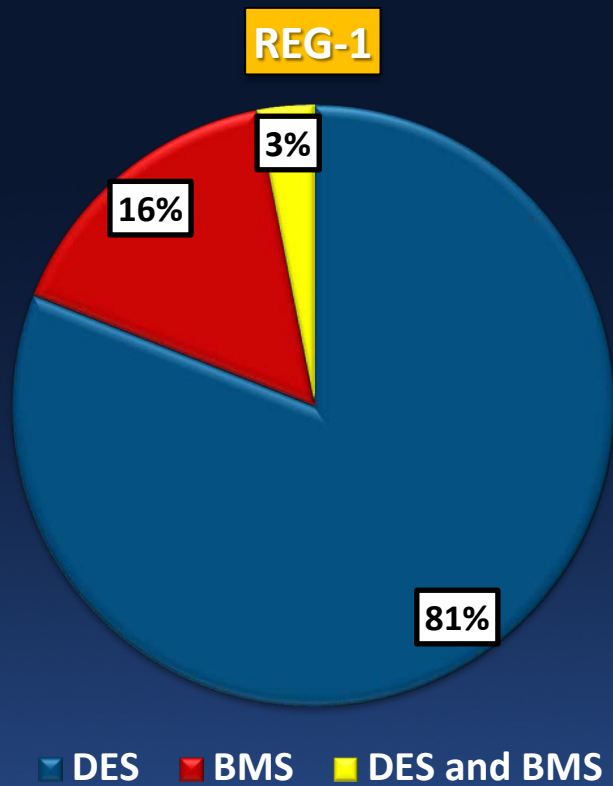
Characteristic	REG1 (N = 1616)	Bivalirudin (N = 1616)
Age - mean, years	65 +/- 11	65 +/- 11
Male sex – no. (%)	1215 (75)	1184 (73)
Diabetes mellitus – no. (%)	571 (35)	553 (34)
Body mass index – mean, kg/m2	30 +/- 6	30 +/- 6
Prior myocardial infarction – no. (%)	576 (36)	582 (36)
Prior PCI – no. (%)	818 (51)	850 (53)
Prior coronary bypass surgery – no. (%)	278 (17)	265 (16)
Prior stroke – no. (%)	67 (4)	68 (4)
Left ventricular dysfunction (EF <55%) – no. (%)	553 (38)	594 (41)
Current tobacco use – no. (%)	348 (22)	322 (20)
History of any allergies – no. (%)	520 (32)	538 (33)
Randomization stratification subgroup		
Subgroup A	246 (15)	247 (15)
Subgroup B	1101 (68)	1100 (68)
Subgroup C	269 (17)	269 (17)

PCI ACCESS SITE

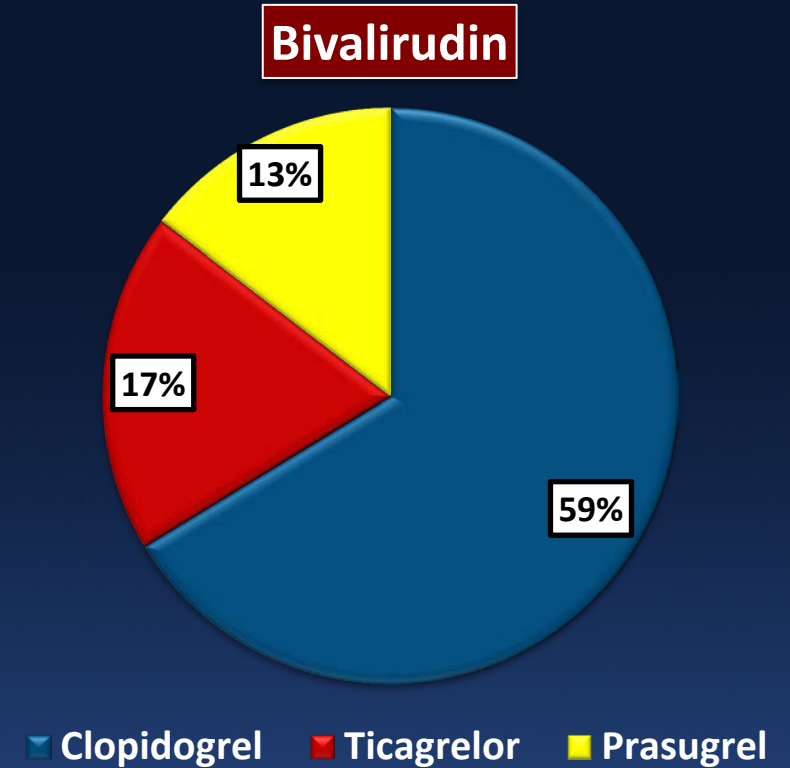
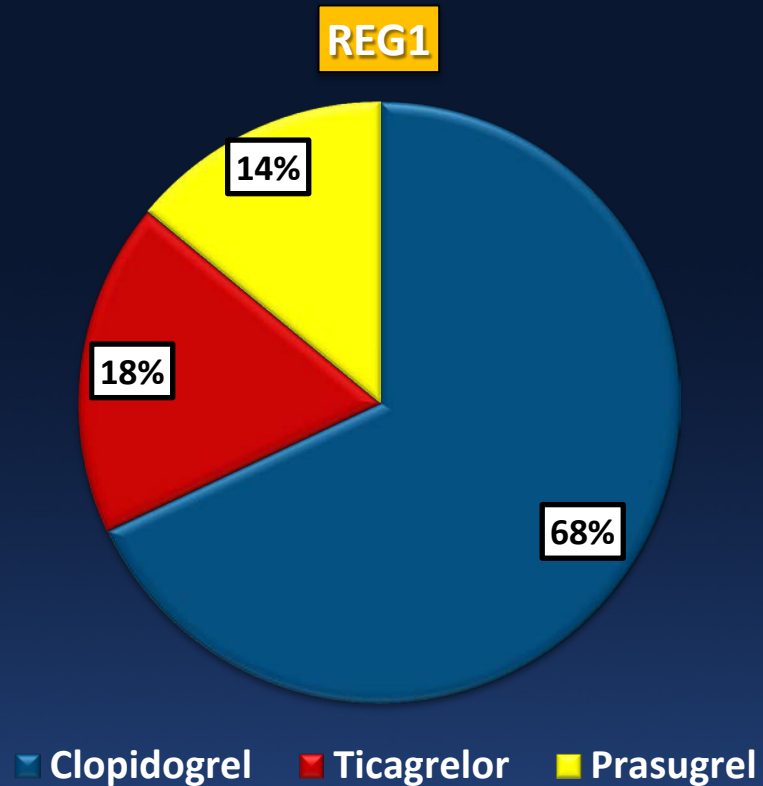


- Vascular closure devices used in $\approx 32\%$ of patients in both randomization arms

Stent Used During PCI



Platelet P2Y12 Antagonist Therapy After PCI



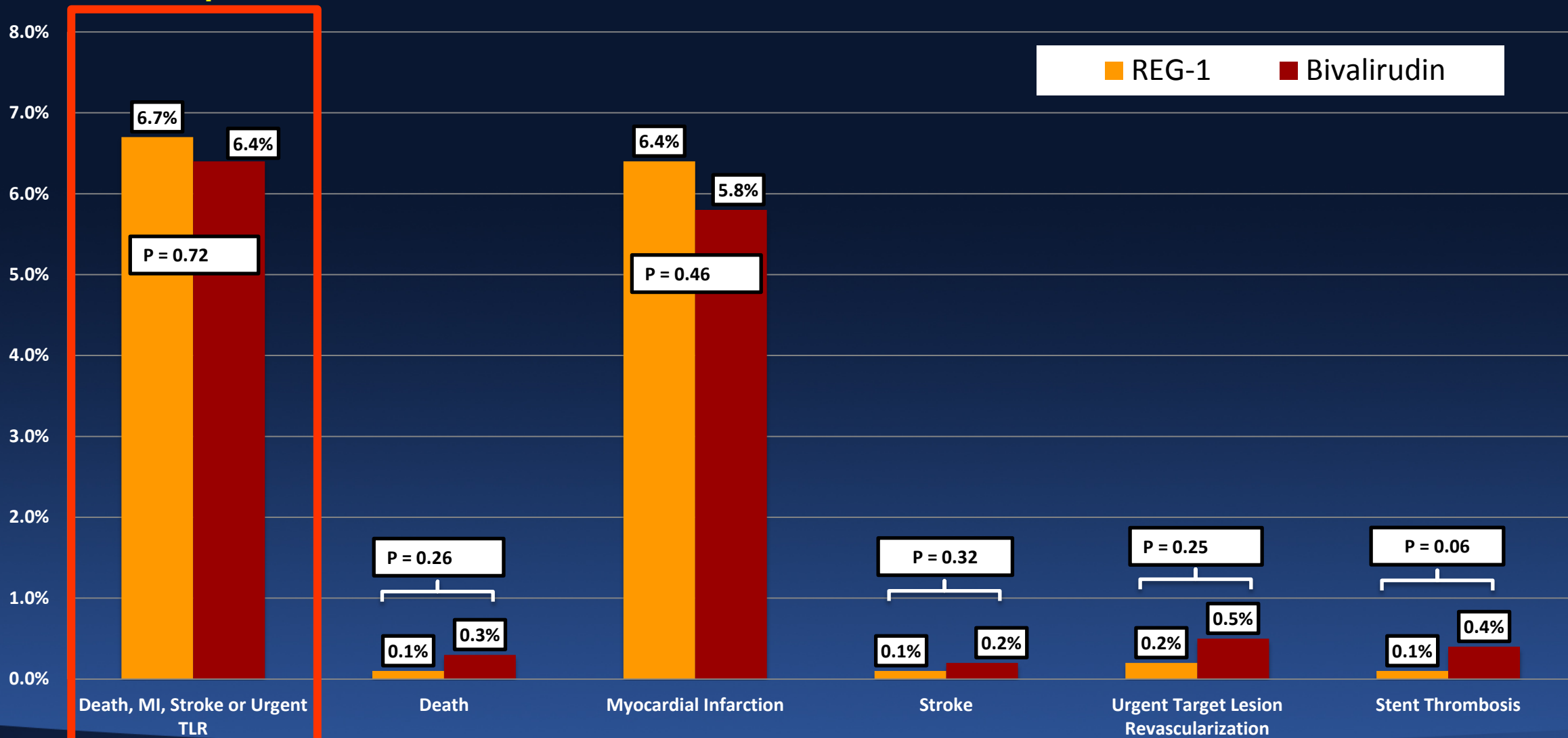
- 99% treated with Aspirin in both randomization arms

ALLERGIC EVENTS

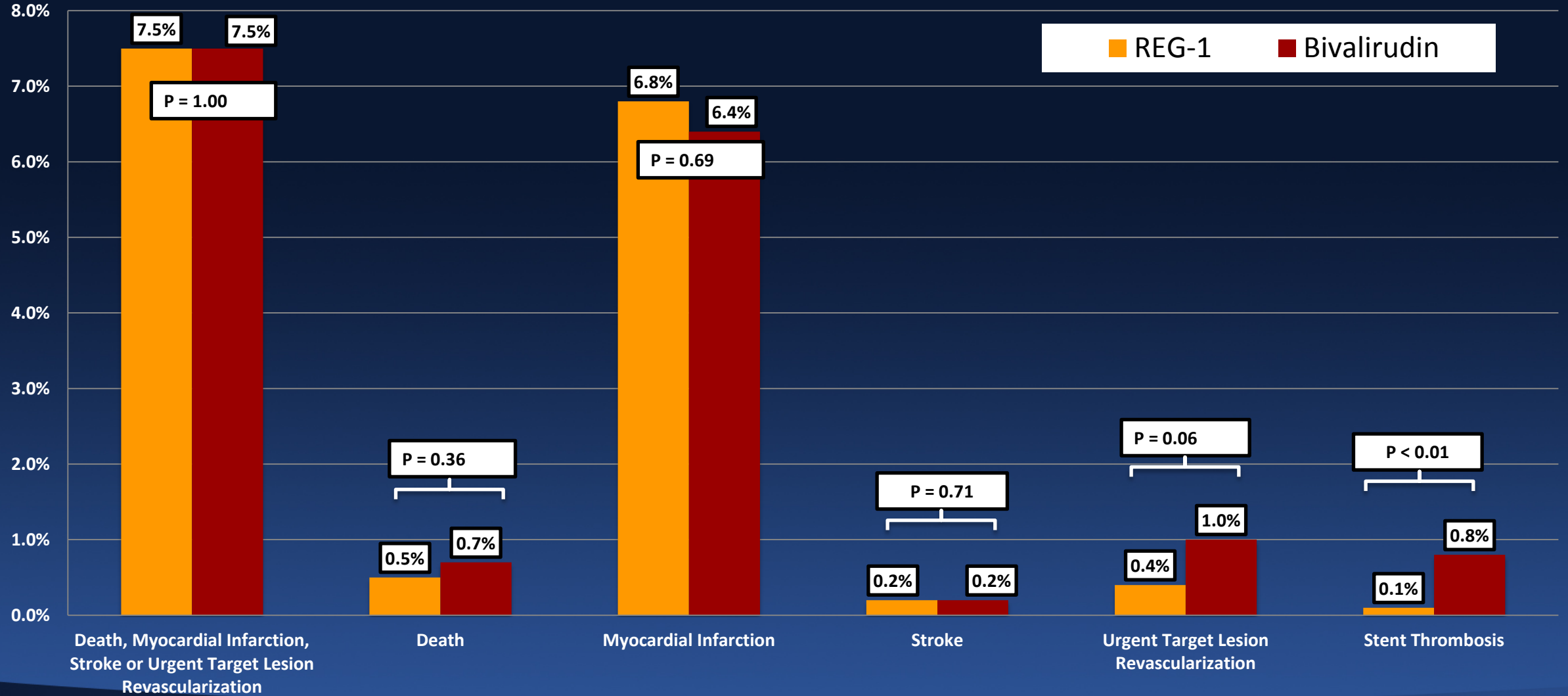
End Point by Day 3	REG1 (N = 1605)	Bivalirudin (N = 1601)
<u>Serious Allergic Events</u>	10 (0.6)	1 (< 0.1)
Fatal Event	1	0
Severe Event (Anaphylactic Reaction)	9	1
Organ System Involvement		
Mucocutaneous	9	1
Respiratory	8	1
Circulatory	6	1
GI or GU	4	0
<u>Non-Serious Allergic Events</u>	14 (0.9)	9 (0.5)
Severe Event (Anaphylactic Reaction)	8	3
Non-Severe Event	6	6

EFFICACY ENDPOINTS (Day 3)

1° Endpoint

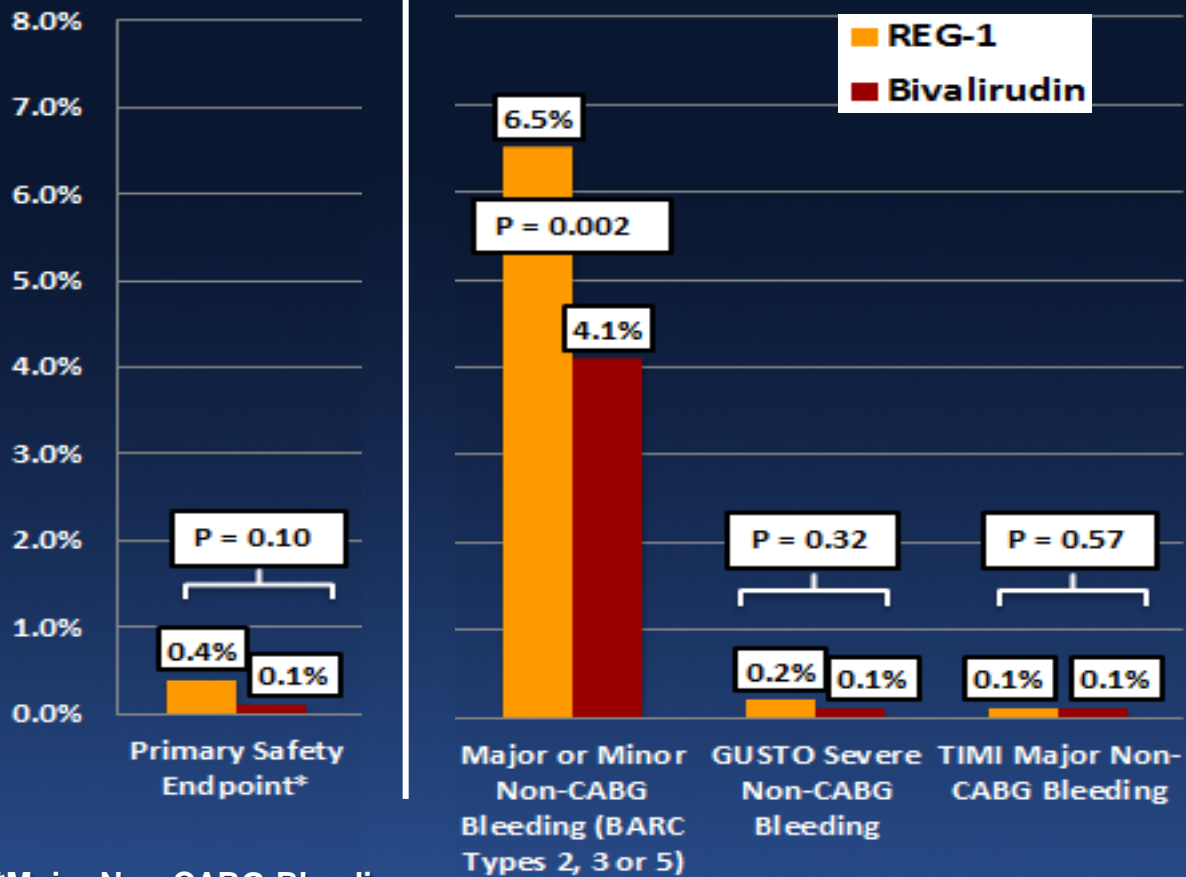


EFFICACY ENDPOINTS (Day 30)

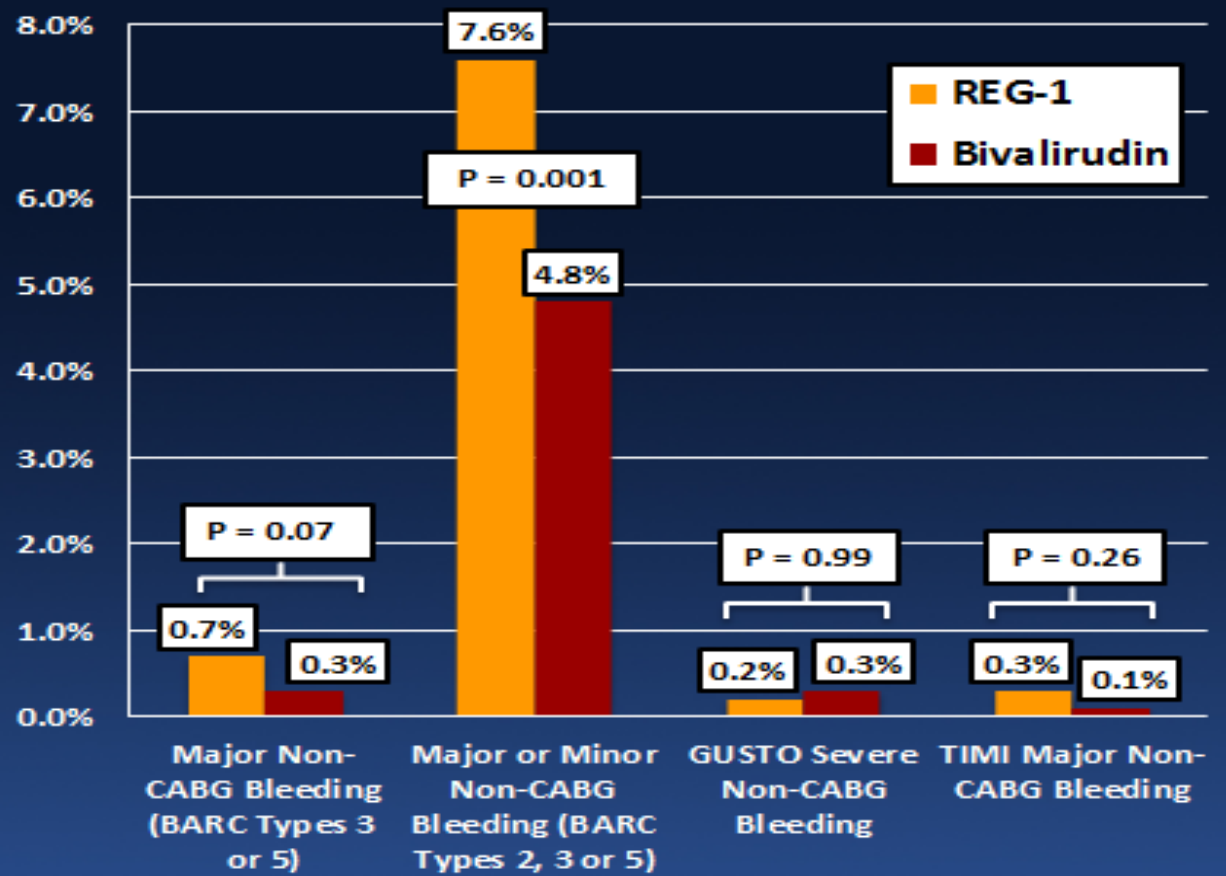


BLEEDING SAFETY ENDPOINTS

Bleeding Rates by Day 3



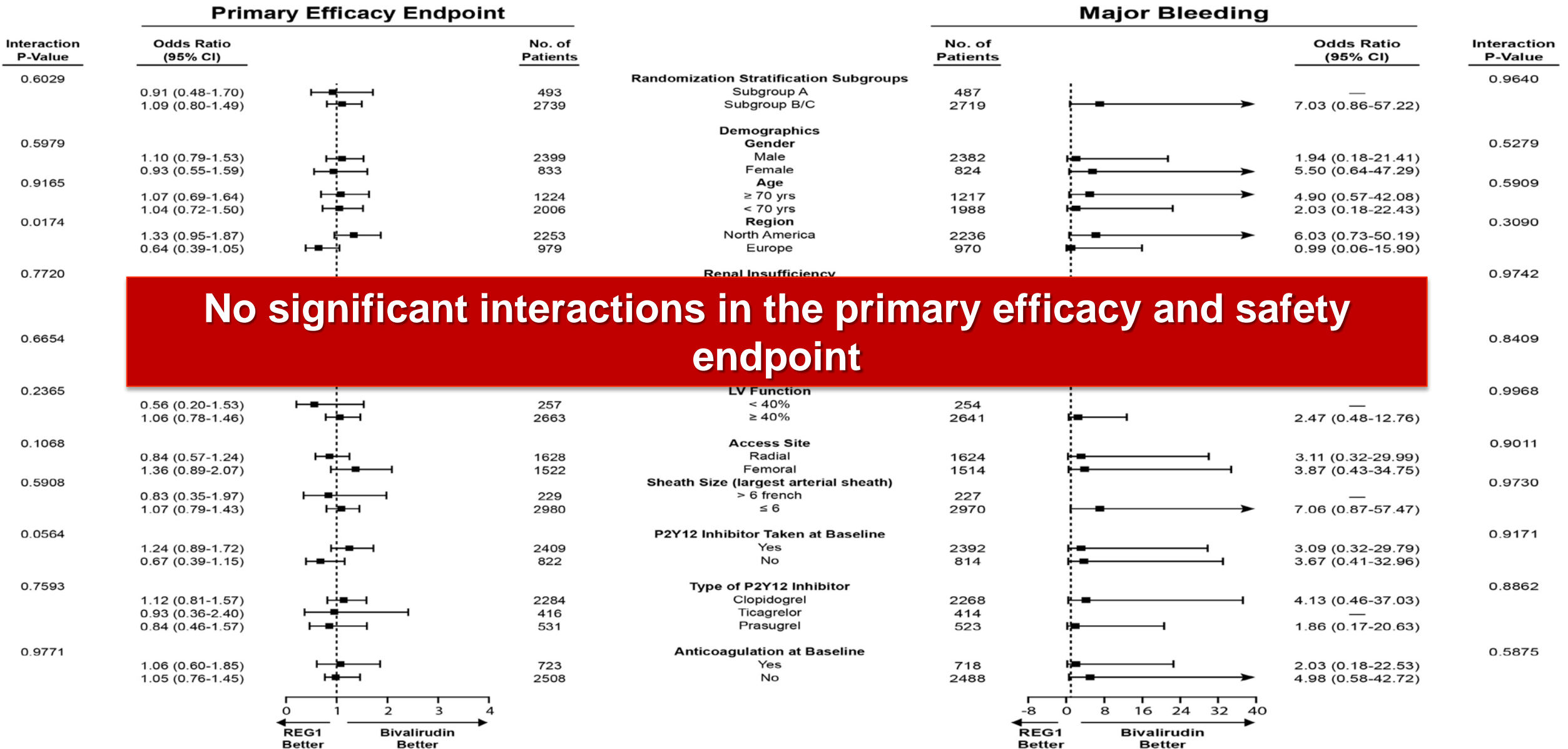
Bleeding Rates by Day 30



*Major Non-CABG Bleeding
(BARC Types 3 or 5)

Subgroup Analysis

Primary Efficacy Endpoint and Major Bleeding



LIMITATIONS

- **Given the early termination of the trial with only 211 of the planned 830 primary endpoint events accrued, any conclusion regarding the safety in bleeding and efficacy in ischemic events of REG1 compared with Bivalirudin has to be considered exploratory.**
- **Open label design- Independent CEC blinded to treatment allocation was put forth to minimize bias in endpoint adjudication.**

CONCLUSIONS

- In patients undergoing PCI, REG1 Anticoagulation System is associated with similar incidence ischemic events, but more moderate/severe (BARC 2,3,5) bleeding compared to Bivalirudin monotherapy
- The reversible factor IXa inhibitor REG1, as currently formulated, is associated with an infrequent but unacceptably high rate (0.6%) of severe allergic reactions.
- Future investigations are planned to identify the mechanism of allergic reactions associated with REG1 Anticoagulation System
- The concept of high-level aptamer-based anticoagulation with active reversal is promising, however its clinical role has yet to be defined and further improvements are needed in its safety profile.