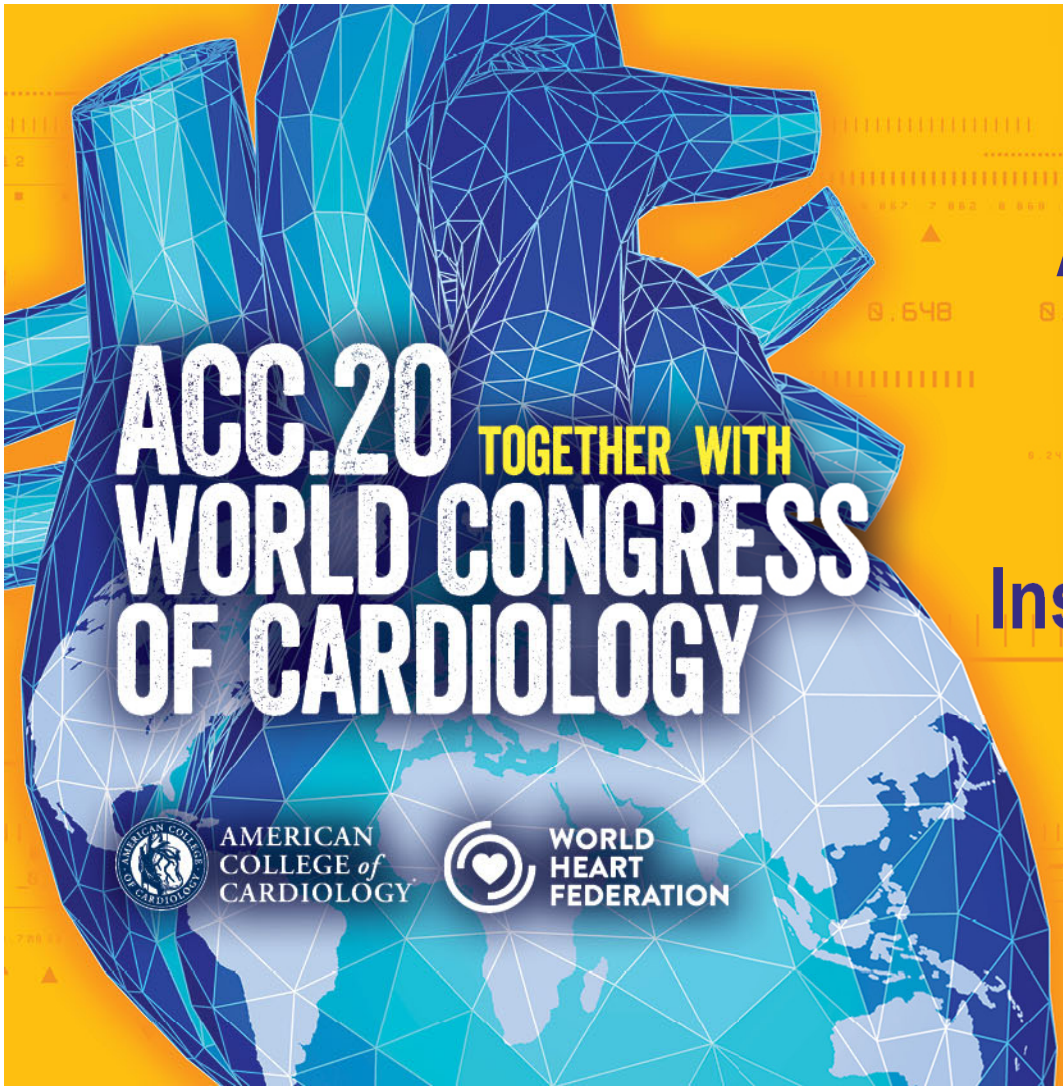

How Long To Continue Aspirin After ACS/PCI In Patients With Atrial Fibrillation?

Insights From AUGUSTUS

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On Behalf of the AUGUSTUS Investigators

Disclosures

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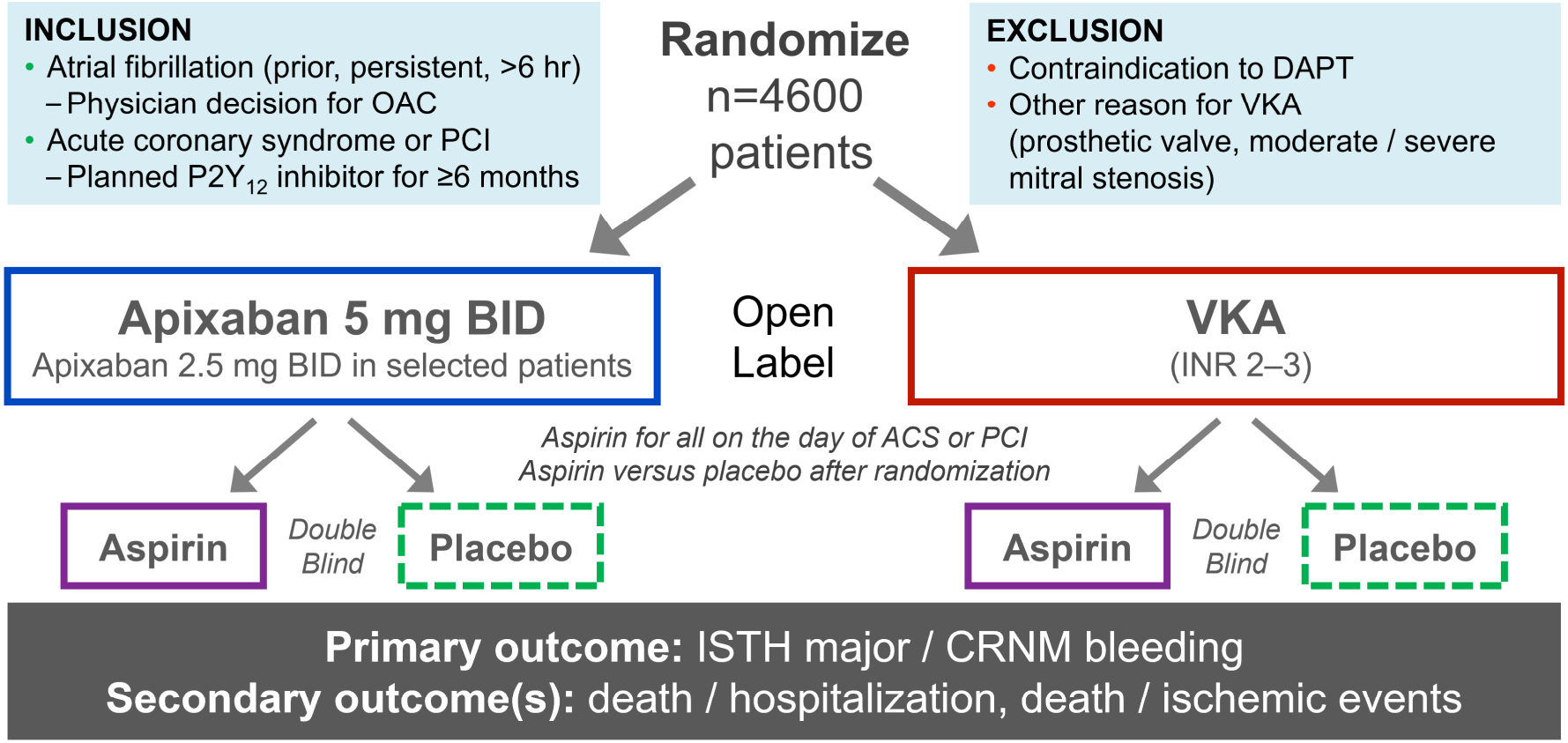
Conflict-of-interest disclosures available at
http://www.dcri.duke.edu/research/coi

AUGUSTUS Trial Design



Lopes RD, et al. Am Heart J. 2018;200:17-23.

Background

- AUGUSTUS demonstrated that, in patients with atrial fibrillation and recent ACS or PCI on a $P2Y_{12}$ inhibitor and oral anticoagulant (apixaban or warfarin), placebo resulted in significantly less bleeding than aspirin
- There was no significant difference between patients assigned aspirin and placebo in the secondary outcomes of the composites of…
  - death or hospitalization
  - ischemic events [death, stroke, myocardial infarction, stent thrombosis (definite or probable), or urgent revascularization]

Lopes RD, et al. N Engl J Med 2019;380:1509-24

Ischemic Events With Placebo vs. Aspirin

- Though not statistically significant, there were numerically more of some ischemic events in patients assigned placebo than aspirin:

	Aspirin	Placebo
– Death	72 (3.1%) vs.	79 (3.4%)
– Cardiovascular Death	53 (2.3%) vs.	58 (2.5%)
– Stroke	20 (0.9%) vs.	19 (0.8%)
– Stent thrombosis (definite or probable)	11 (0.5%) vs.	21 (0.9%)
– Myocardial infarction	68 (2.9%) vs.	84 (3.6%)
– Urgent revascularization	37 (1.6%) vs.	47 (2.0%)

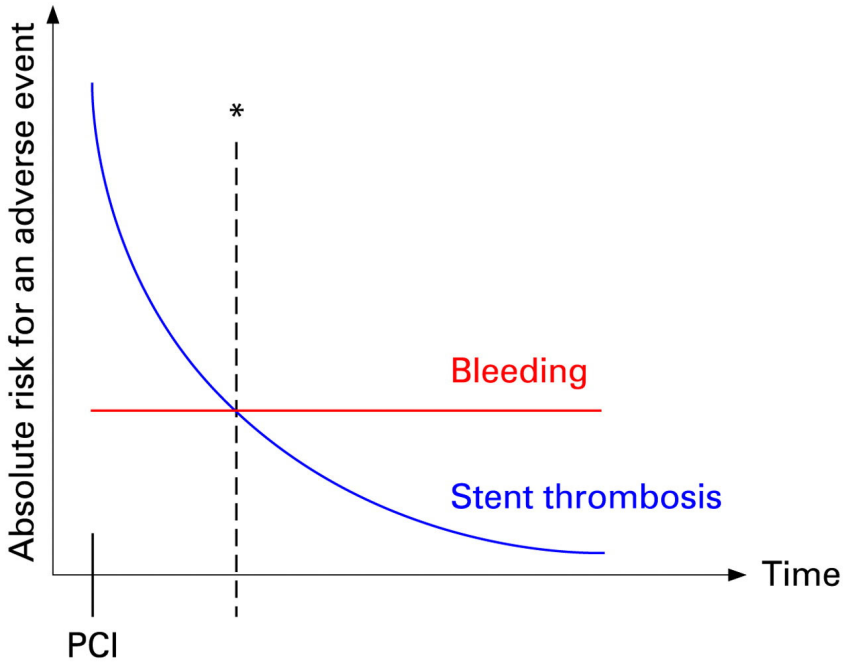
- Analysis of the stent thrombosis events suggested that most of the increased risk was early, within 30 days of randomization

Lopes RD, et al. N Engl J Med 2019;380:1509-24
Lopes RD, et al. Circulation 2020; 141:781-783

Tradeoff Between Bleeding and Ischemic Events

There is a temporal component to the balance of bleeding and ischemic risk

- Recurrent ischemic events (specifically stent thrombosis) tend to occur early after ACS/PCI
- Bleeding risk is cumulative and is higher with long-term, potent antithrombotic therapy



Schomig A, et al. Heart 2009;95:1280–1285

Objective

Assuming that there might be a risk/benefit trade off that changes over time...

To explore the balance of risk (bleeding) and benefit (ischemic events) between randomization and 30 days and between 30 days and 6 months, with aspirin and placebo, among patients enrolled in AUGUSTUS

Composite Clinical Outcomes

The AUGUSTUS primary bleeding (ISTH major or CRNM bleeding) and secondary ischemic event outcome (death, stroke, myocardial infarction, stent thrombosis, or urgent revascularization) are not of comparable severity

	Bleeding	Ischemic Event
Severe	Fatal, intracranial, ISTH major	CV death, stent thrombosis, MI, stroke
Intermediate	Fatal, intracranial, ISTH major, bleeding hospitalization	CV death, stent thrombosis, MI, stroke, urgent revascularization
Broad	Fatal, intracranial, ISTH major, bleeding hospitalization, CRNM	CV death, stent thrombosis, MI, stroke, urgent revascularization, CV hospitalization

Statistical Analysis

- Kaplan-Meier method used to estimate event probabilities for each composite bleeding and ischemic outcome from randomization to 30 days and from 30 days to 6 months
- Absolute differences in bleeding and ischemic events between aspirin and placebo were compared
- All analyses were done using intention-to-treat principle and included all randomized patients and all events

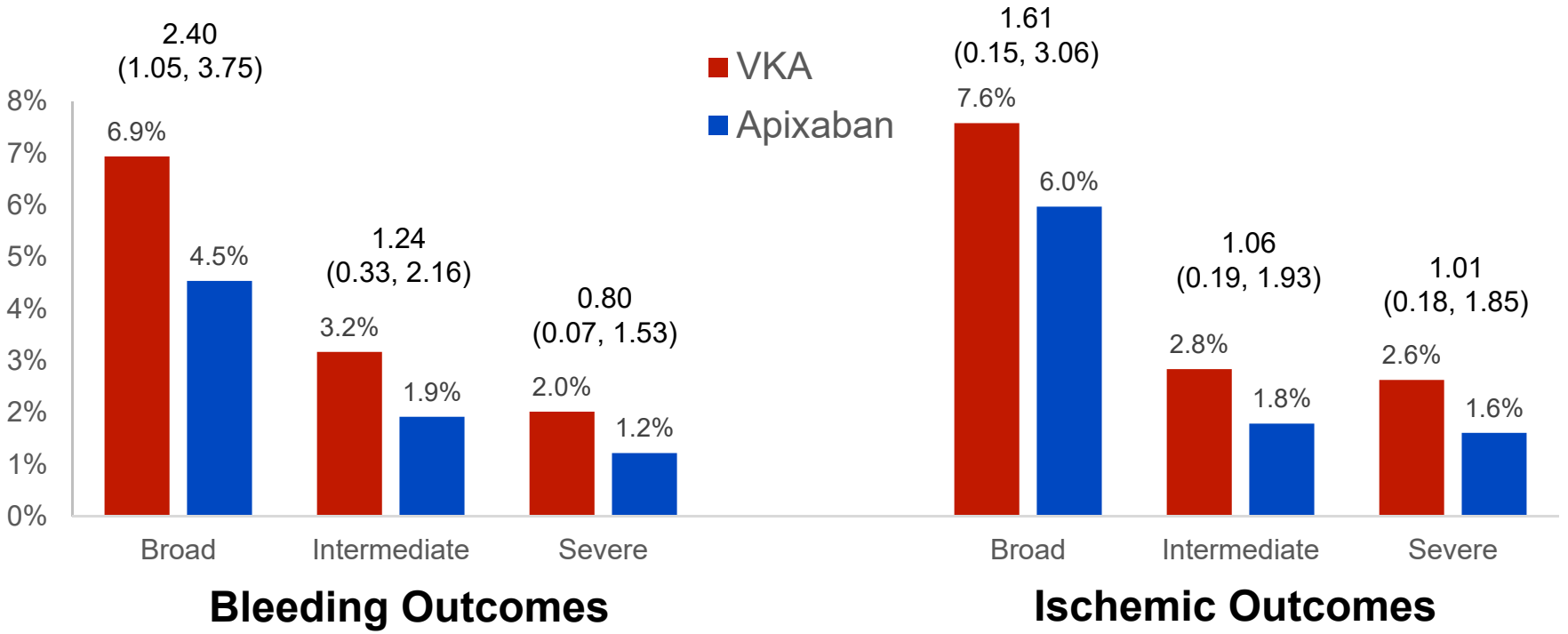
Baseline Characteristics (n=4614)

• Age (yrs)	71 (64, 77)	• Prior OAC	49%
• Weight (kg)	83 (74, 95)	• P2Y12 inhibitor	
• CHA_2DS_2-VASc	4 (3, 5)	– Clopidogrel	93%
• HAS-BLED	3 (2, 3)	– Prasugrel	1%
• Female	29%	– Ticagrelor	6%
• Cr >1.5 mg/dl	8%	• Enrolling indication	
• Hypertension	88%	– ACS + PCI	37%
• Heart Failure	43%	– ACS + Med	24%
• Diabetes	36%	– Elective PCI	39%
• Stroke/TIA	4%	• Time Event to Rand (d)	6 (3, 10)

*Median (25^{th}, 75^{th})

Bleeding and Ischemic Outcomes: Apixaban vs. VKA

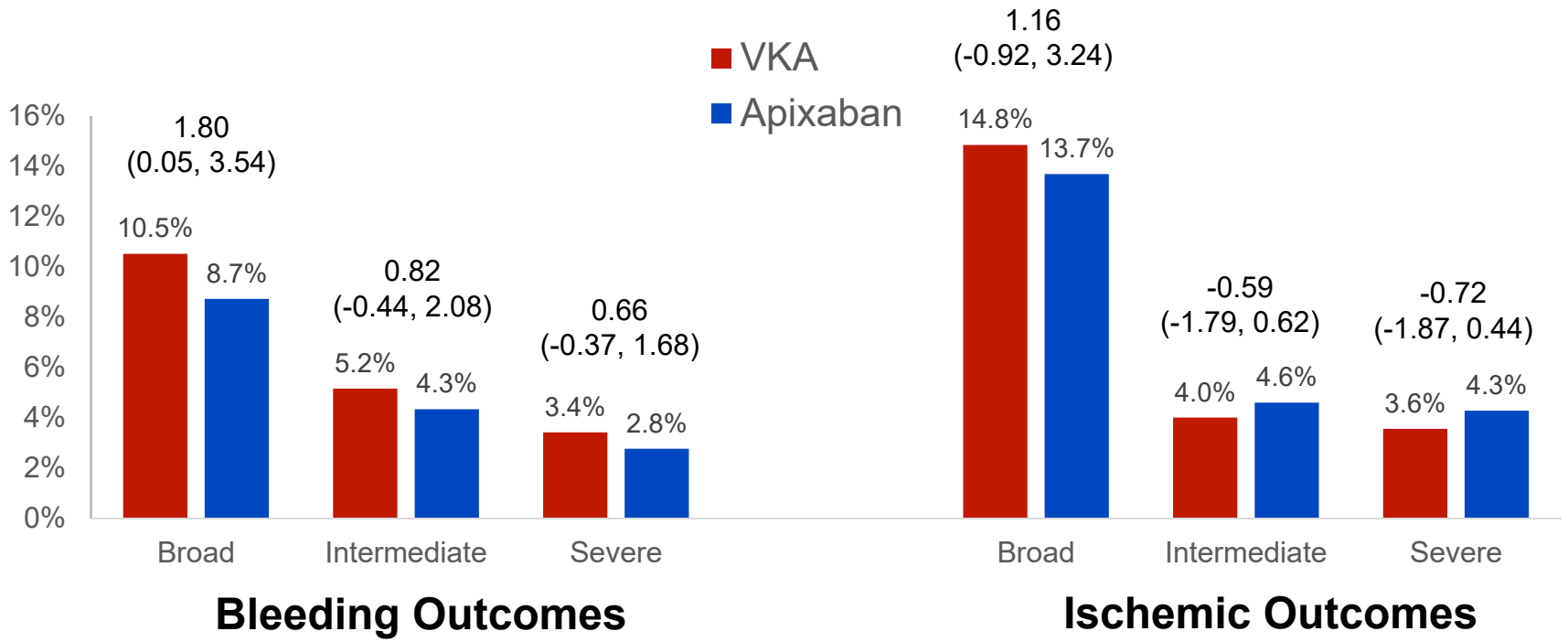
Randomization to 30 Days



Numbers are **absolute** risk differences (95% confidence intervals) for VKA - apixaban

Bleeding and Ischemic Outcomes: Apixaban vs. VKA

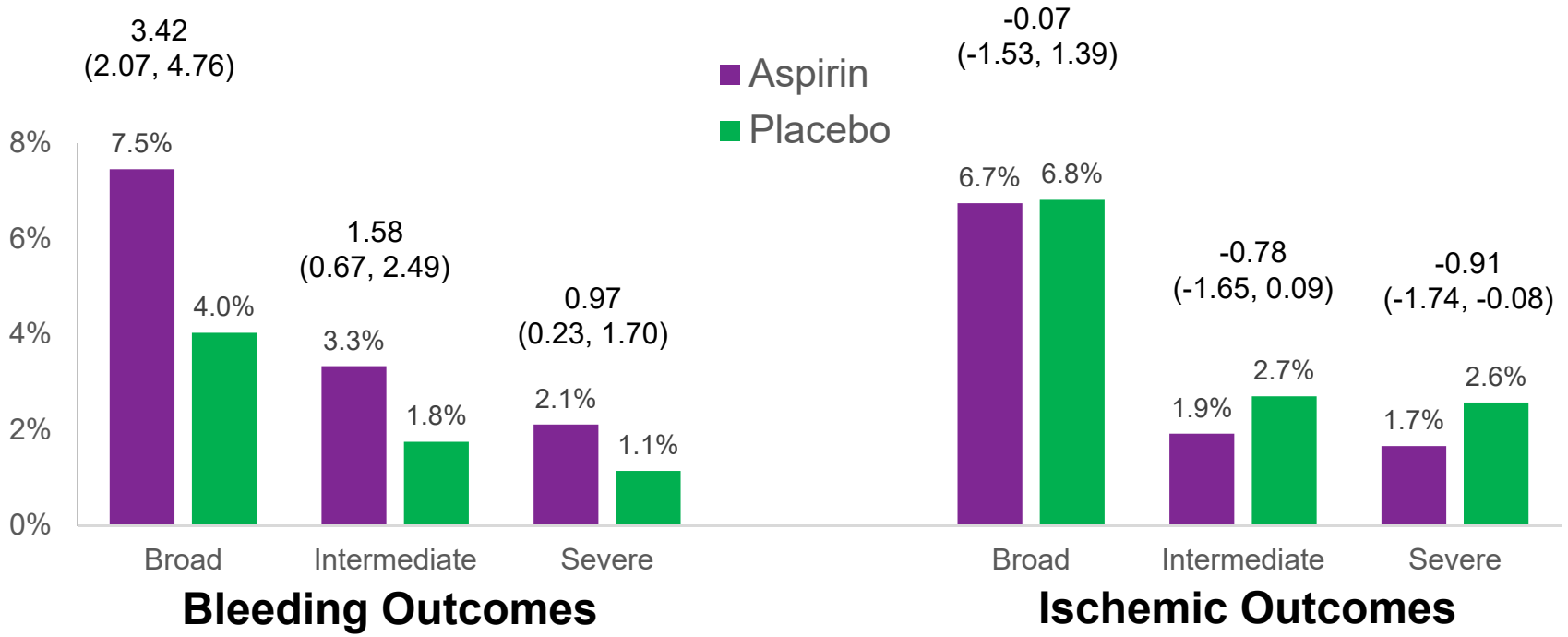
30 Days to 6 Months



Numbers are **absolute** risk differences (95% confidence intervals) for VKA - apixaban

Bleeding and Ischemic Outcomes: Aspirin vs. Placebo

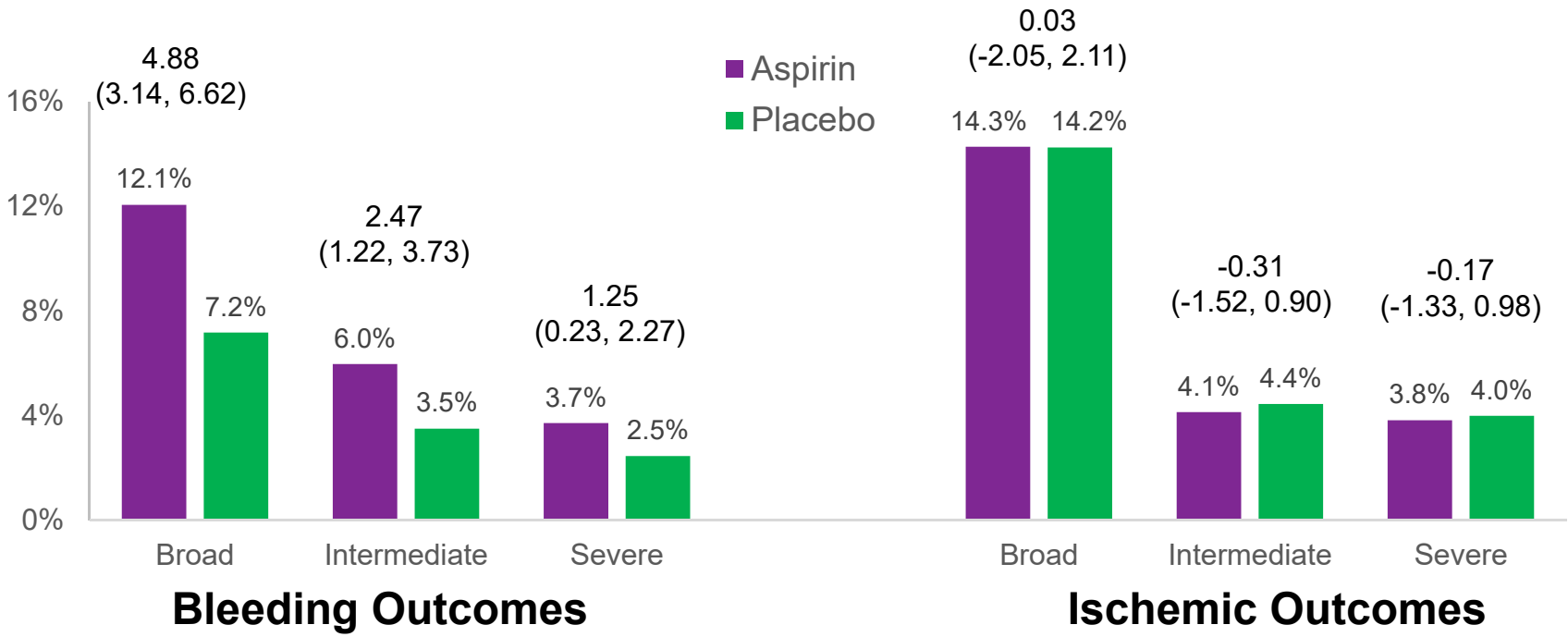
Randomization to 30 Days



Numbers are **absolute** risk differences (95% confidence intervals) for aspirin - placebo

Bleeding and Ischemic Outcomes: Aspirin vs. Placebo

30 Days to 6 Months

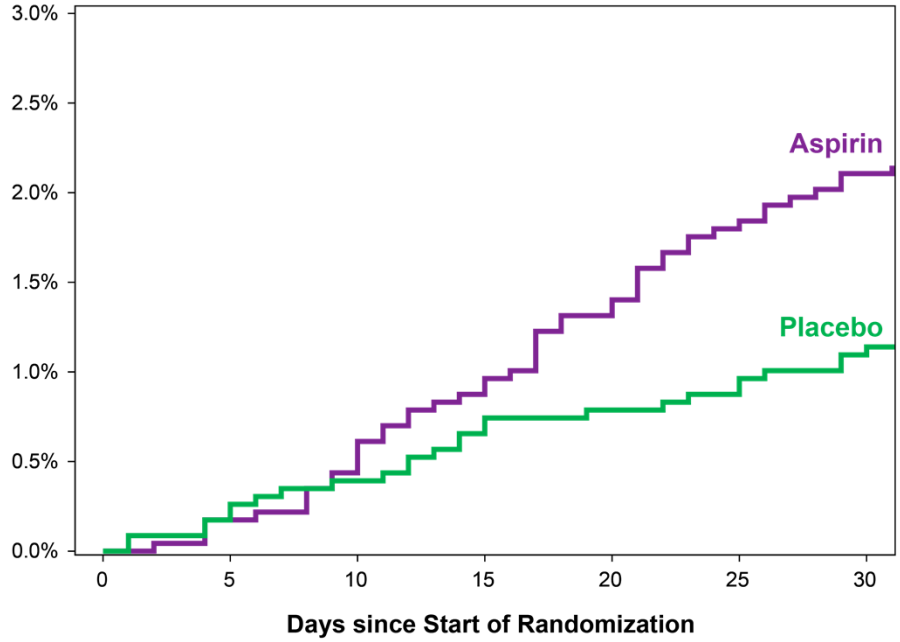


Numbers are **absolute** risk differences (95% confidence intervals) for aspirin - placebo

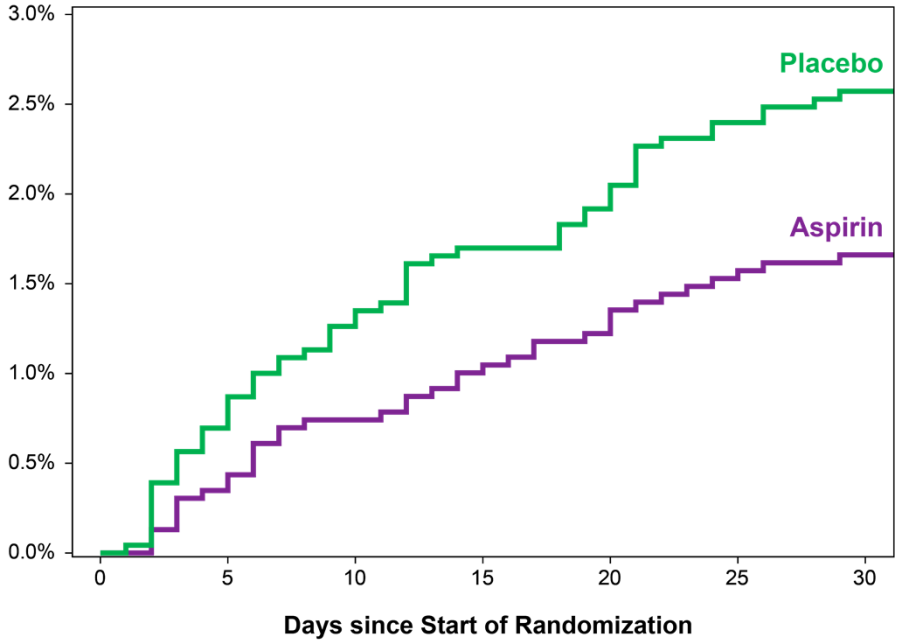
Severe Bleeding and Ischemic Outcomes

Randomization to 30 Days

Fatal, ICH, Major Bleeding



CV Death, Stroke, MI, Stent Thrombosis



Severe Bleeding and Ischemic Outcomes

30 Days to 6 Months

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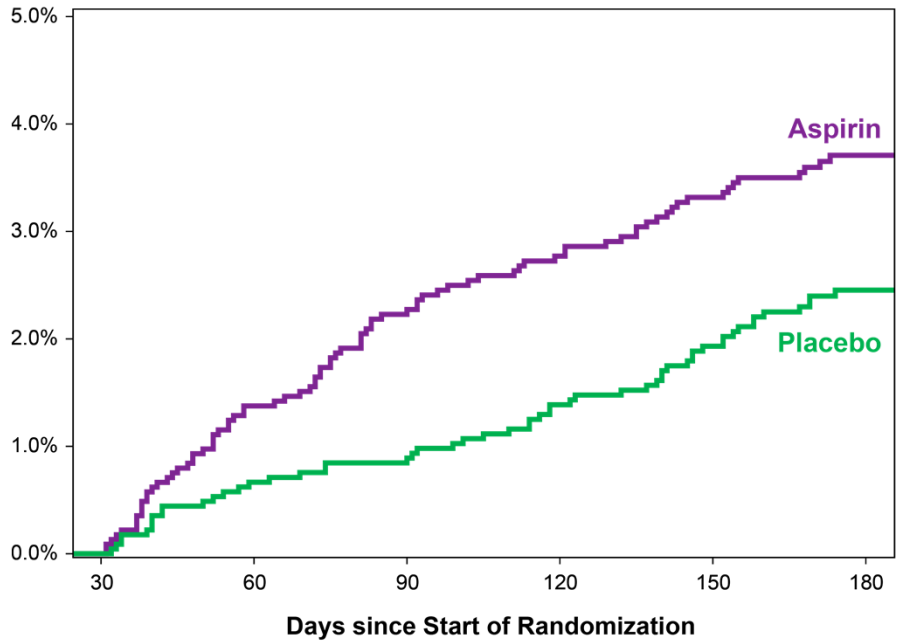
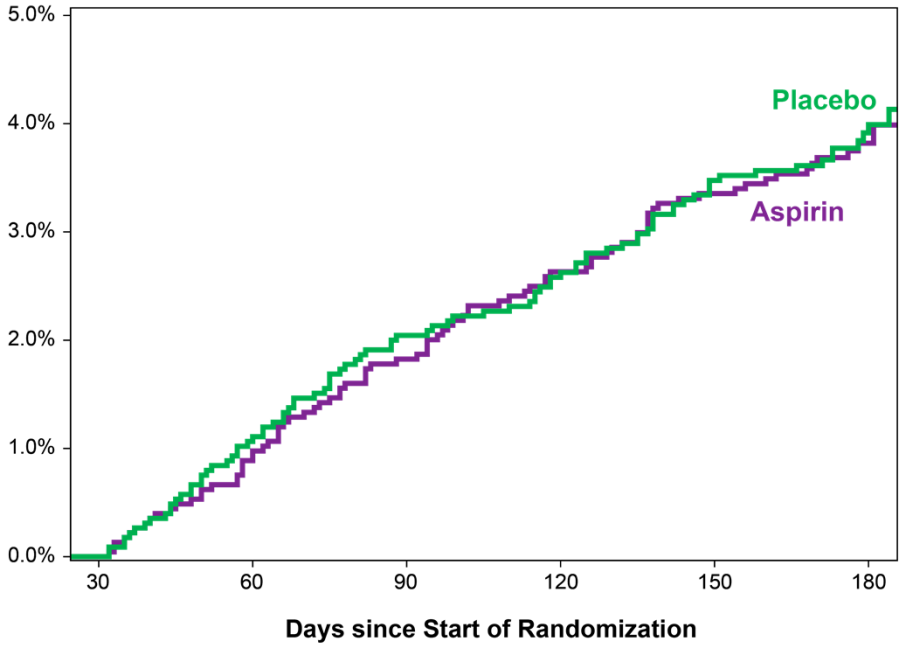


CV Death, Stroke, MI, Stent Thrombosis



Limitations

- Patients received aspirin prior to randomization (median 6 days) in both arms and this could have influenced subsequent bleeding or ischemic outcomes
- The severe, intermediate, and broad composite bleeding and ischemic event outcomes may not be of completely comparable severity
- This is a post-hoc secondary analysis and the analysis plan, composite outcomes, and time windows (randomization to 30 days and 30 day to 6 months) were developed after seeing the initial AUGUSTUS results
- The number of events is small, particularly for the more severe outcomes and when subdivided by time window, creating the potential for type II error

Conclusions

- Among patients with atrial fibrillation and a recent ACS or PCI receiving a $P2Y_{12}$ inhibitor and oral anticoagulation with apixaban or warfarin…
  - The use of aspirin acutely and for up to approximately 30 days results in an equal increase in severe bleeding and reduction in severe ischemic events
  - After 30 days, aspirin continues to increase bleeding without significantly reducing ischemic events
- These results should inform patient-centric, shared decision making regarding the ideal duration of aspirin after an ACS or PCI in patients with atrial fibrillation receiving oral anticoagulation

Circulation

The Risk / Benefit Tradeoff of Antithrombotic Therapy in Patients with Atrial Fibrillation Early and Late After an Acute Coronary Syndrome or Percutaneous Coronary Intervention: Insights from AUGUSTUS

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