The Emerging Role of NOACs/DOACs in CAD

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Rationale for Thrombin Inhibition in CAD

- Despite aggressive secondary prevention, patients with atherosclerotic cardiovascular disease continue to experience recurrent events at a rate of 5-10%/year
- Previous studies have demonstrated that vitamin K antagonists, either alone or in combination with ASA can lead to modest further reductions in coronary event rates but with unacceptable increases in bleeding including ICH and fatal bleeding
- Recently, several direct acting oral anticoagulants have been introduced and have shown generally similar efficacy to warfarin for patients with thrombotic conditions (AF, DVT/PE) with an improved safety profile

NOACs in CAD

- NOACs in acute coronary syndromes
- NOACs in AF/PCI
- NOACs in stable CHD

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ATLAS-2 Trial (TIMI 51)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

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ABSTRACT

BACKGROUND

Acute coronary syndromes arise from coronary atherosclerosis with superimposed thrombosis. Since factor Xa plays a central role in thrombosis, the inhibition of factor Xa with low-dose rivaroxaban might improve cardiovascular outcomes in patients with a recent acute coronary syndrome.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 15,526 patients with a recent acute coronary syndrome to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke.

RESULTS

Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (hazard ratio in the rivaroxaban group, 0.84; 95% confidence interval [CI], 0.74 to 0.96; P=0.008), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs. 10.7%, P=0.02) and the twice-daily 5-mg dose (8.8% vs. 10.7%, P=0.03). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, P=0.002) and from any cause (2.9% vs. 4.5%, P=0.002), a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting (2.1% vs. 0.6%, P<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, P=0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%, P=0.66) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs. 0.4%, P=0.04).

CONCLUSIONS

In patients with a recent acute coronary syndrome, rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. (Funded by Johnson & Johnson and Bayer Healthcare; ATLAS ACS 2–TIMI 51 ClinicalTrials.gov number, NCT00809965.)

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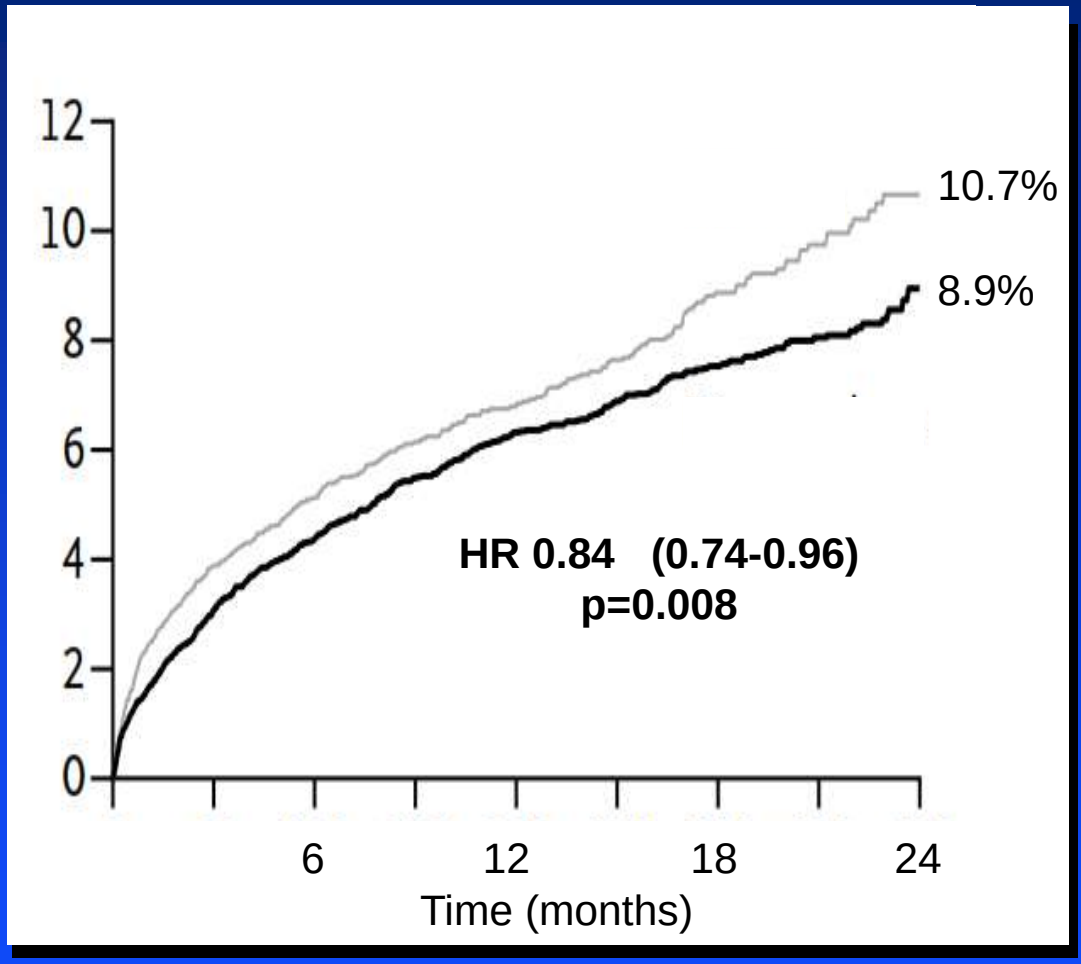
*Investigators in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1112277) was published on November 13, 2011, at NEJM.org.

N Engl J Med 2011.

- Randomized 15,526 pts with recent ACS to RIVA 2.5 bid, RIVA 5 bid, or placebo (93% also receiving DAPT)
- 50% STEMI, 26% NSTEMI, 24% unstable angina
- Median treatment duration 13 months
- Primary endpoint: composite of CV death/MI/Stroke

Primary Endpoint (CVD/MI/Stroke)

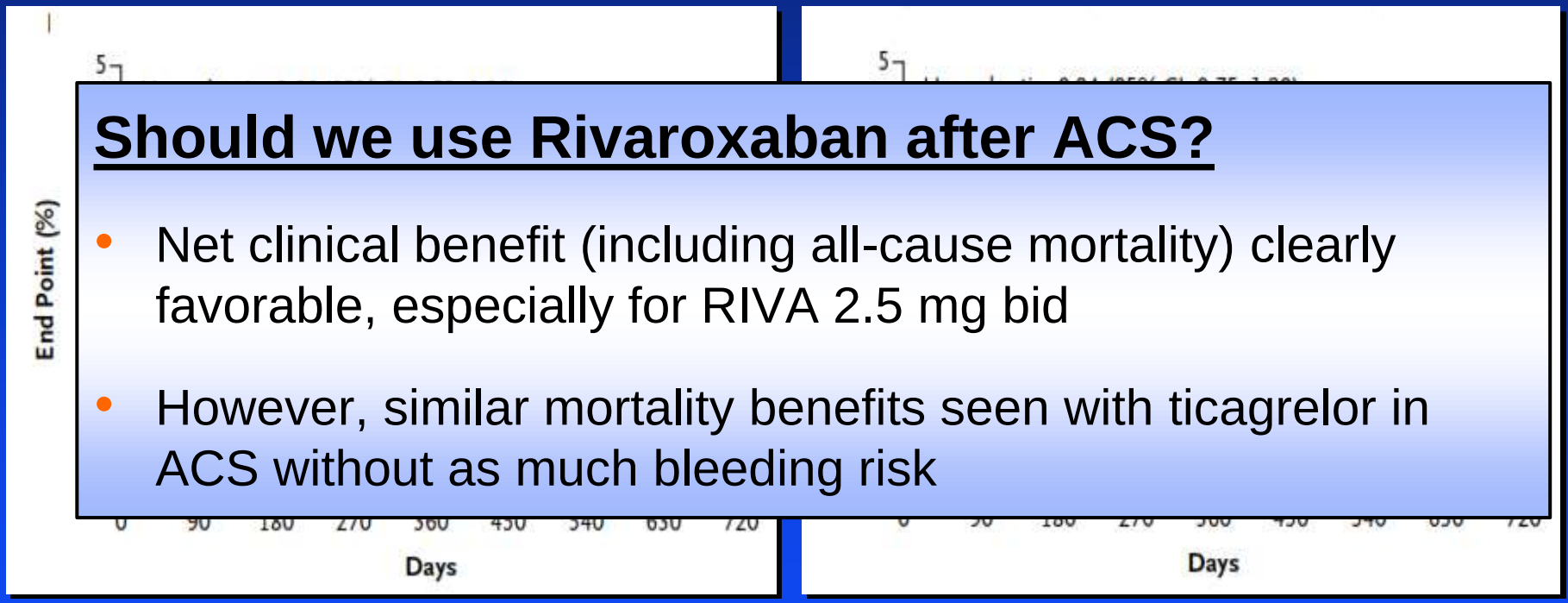


- Benefit driven by significant reductions in CVD (3.3% vs. 4.1%) and MI (5.5% vs. 6.6%)
- Stent thrombosis also reduced (2.3% vs. 2.9%)
- TIMI major bleeding ↑'d significantly (2.1% vs. 0.6%, p<0.001)

Dose Comparison: CV Death

RIVA 2.5 mg BID

RIVA 5 mg BID



Should we use Rivaroxaban after ACS?

- Net clinical benefit (including all-cause mortality) clearly favorable, especially for RIVA 2.5 mg bid
- However, similar mortality benefits seen with ticagrelor in ACS without as much bleeding risk

Difference in mortality at least partly explained by differences infatal bleeding between the 2 doses (0.1% vs. 0.4%)

Mega JL, et al. N Engl J Med 2012; 366:9-19

NOACs in CAD

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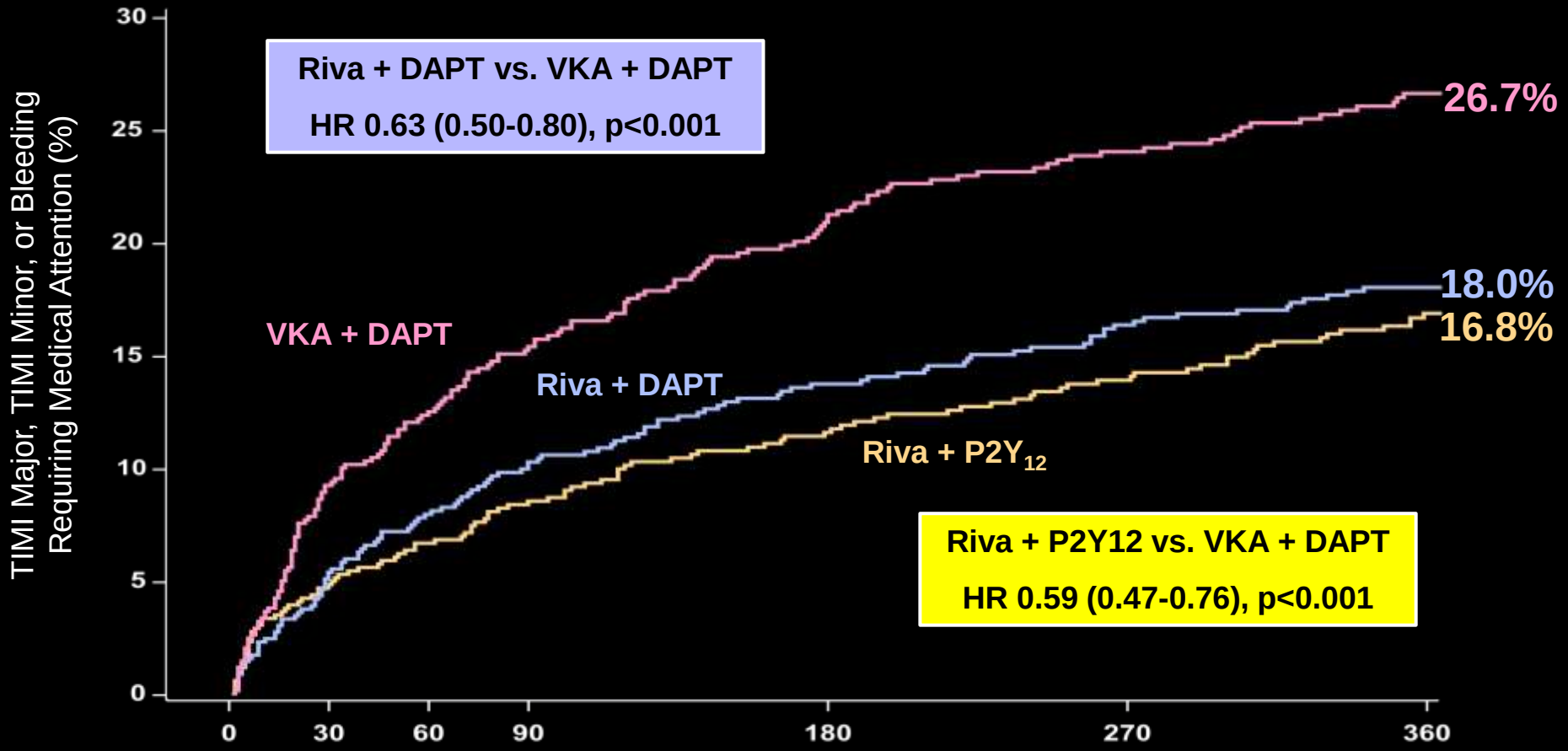
PIONEER-AF

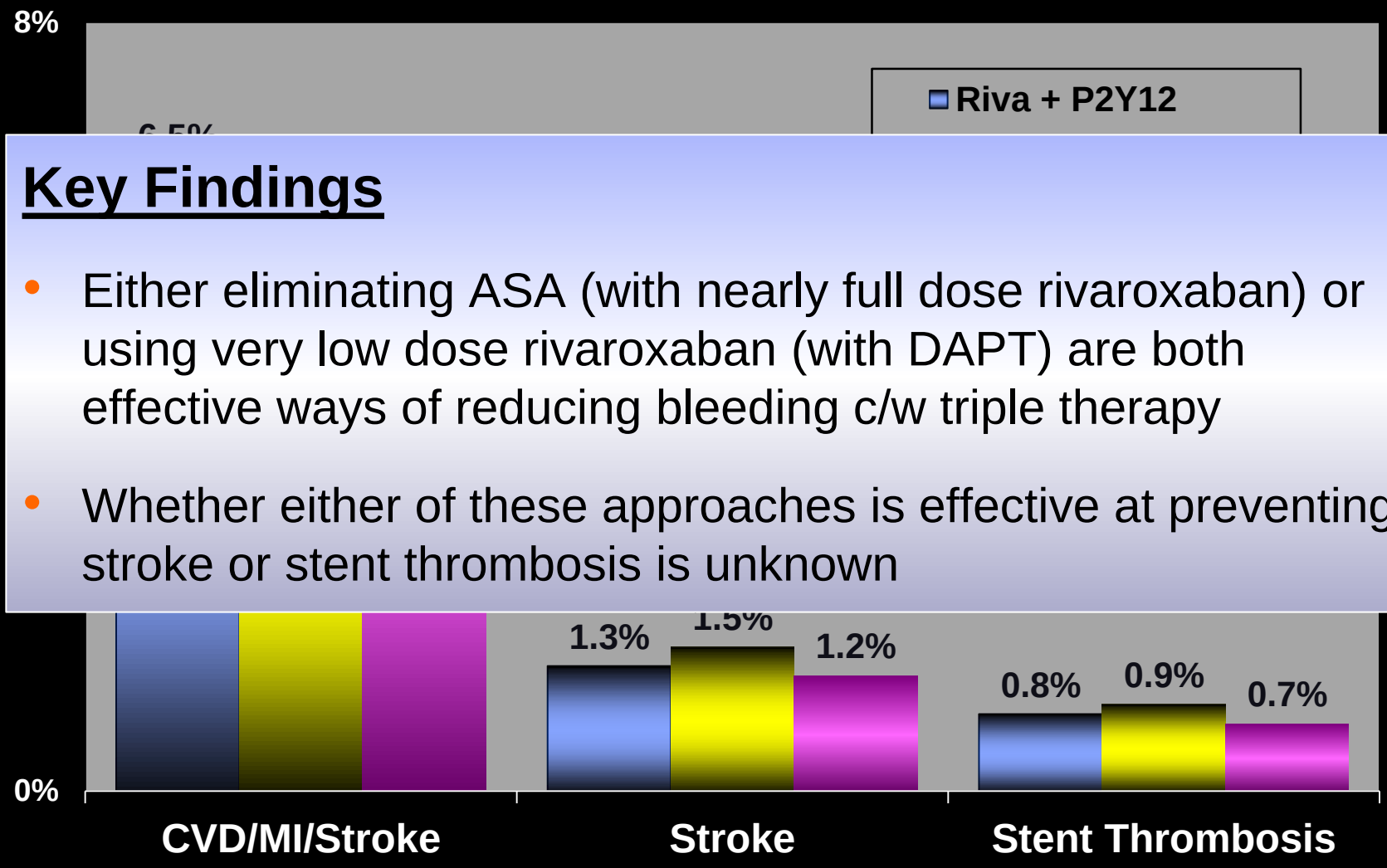
- 2124 patients with non-valvular AF and PCI randomized to 3 alternative antithrombotic regimens
  - *RIVA 2.5 mg bid + DAPT (ATLAS-like regimen)*
  - *RIVA 15 mg QD + P2Y12 alone (ROCKET-AF like regimen)*
  - *Warfarin + DAPT (standard regimen)*
- DAPT duration (1, 6, or 12 months) prespecified by treating clinician
- Primary endpoint: Clinically significant bleeding (TIMI major, TIMI minor, or bleeding requiring medical attention)
- Secondary endpoint: CVD/MI/stroke

Primary (Safety) Endpoint: Clinically-Significant Bleeding



Gibson CM, et al. N Engl J Med 2016; 375:2423-2434

Secondary (Efficacy) Endpoints



Key Findings

- Either eliminating ASA (with nearly full dose rivaroxaban) or using very low dose rivaroxaban (with DAPT) are both effective ways of reducing bleeding c/w triple therapy
- Whether either of these approaches is effective at preventing stroke or stent thrombosis is unknown

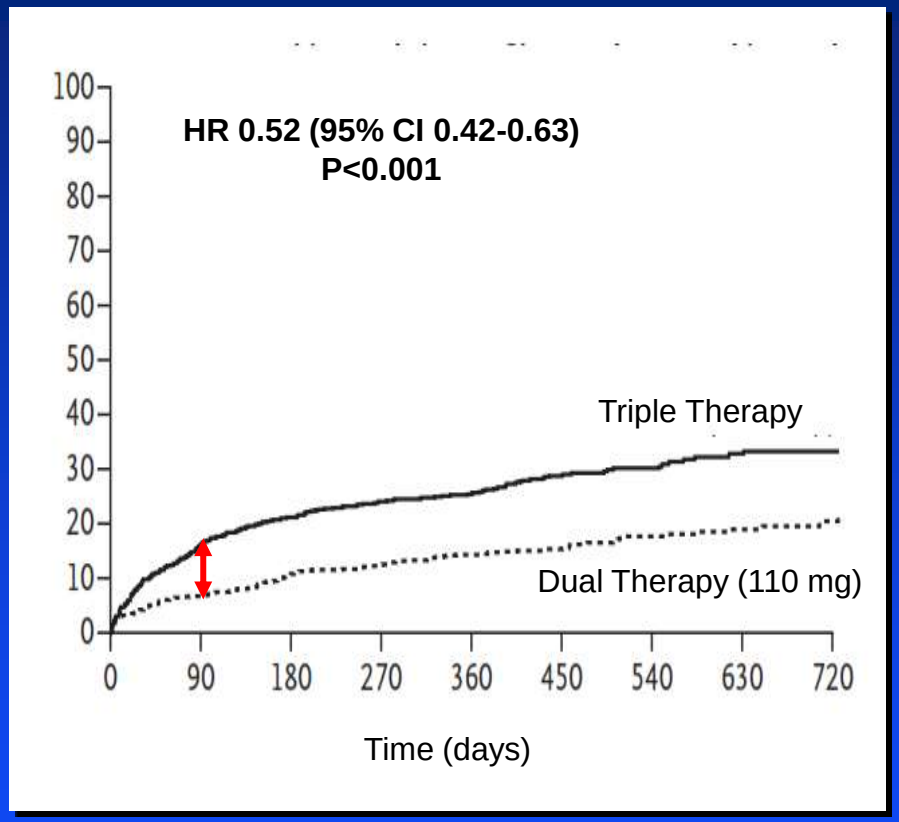
Gibson CM, et al. N Engl J Med 2016; 375:2423-2434

RE-DUAL PCI

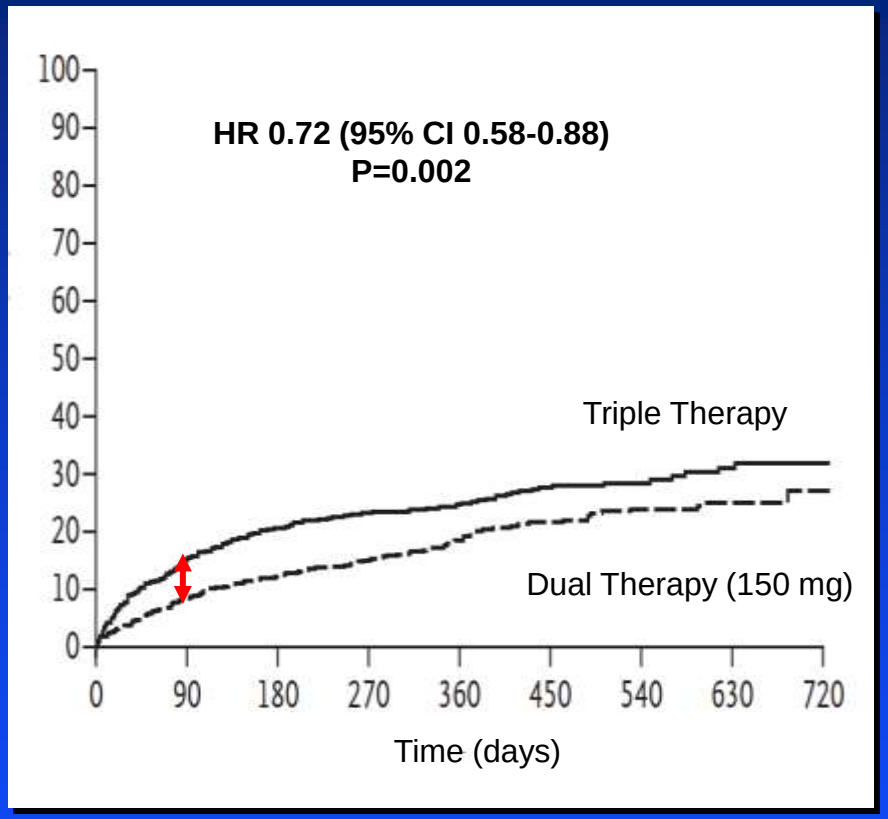
- 2725 patients with non-valvular AF and PCI randomized to 3 alternative antithrombotic regimens
  - *Dabigatran 150 mg bid + P2Y12*
  - *Dabigatran 110 mg bid + P2Y12*
  - *Warfarin + P2Y12 + ASA (triple therapy)*
- P2Y12 duration 12 months in all pts
- ASA duration in triple therapy group only 1-3 months

Clinically Significant Bleeding

Dabigatran 110 mg



Dabigatran 150 mg

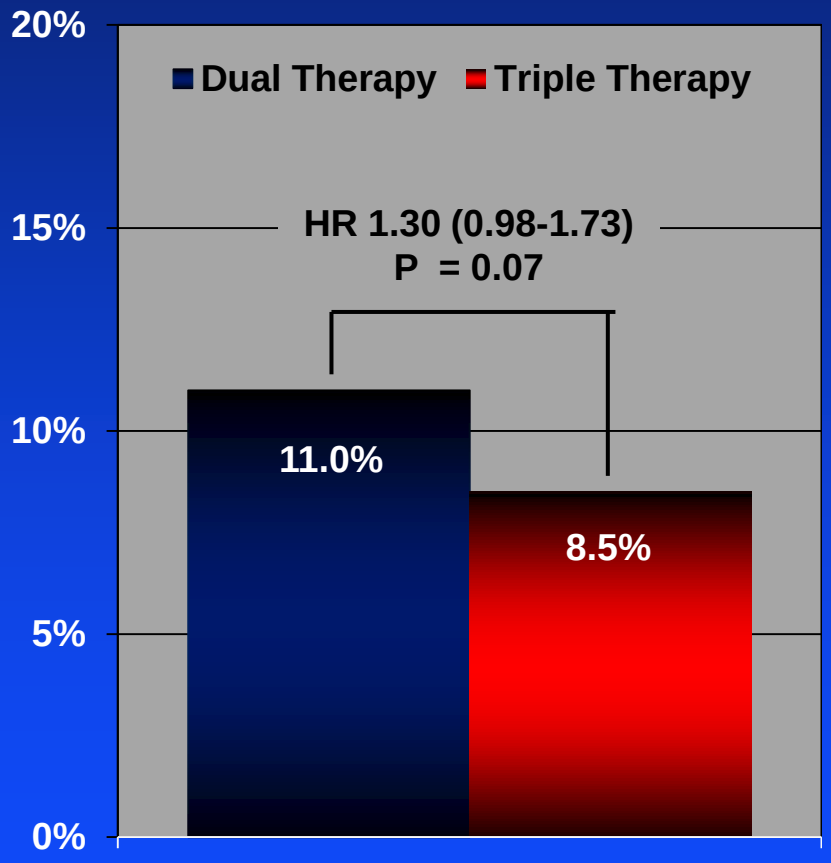


Bleeding reduction greater with low dose dabigatran
Virtually all the benefit is seen when triple therapy pts are receiving ASA

Cannon CP, et al. N Engl J Med 2017; 377:1513-1524

Death or Thromboembolic Events

Dabigatran 110 mg



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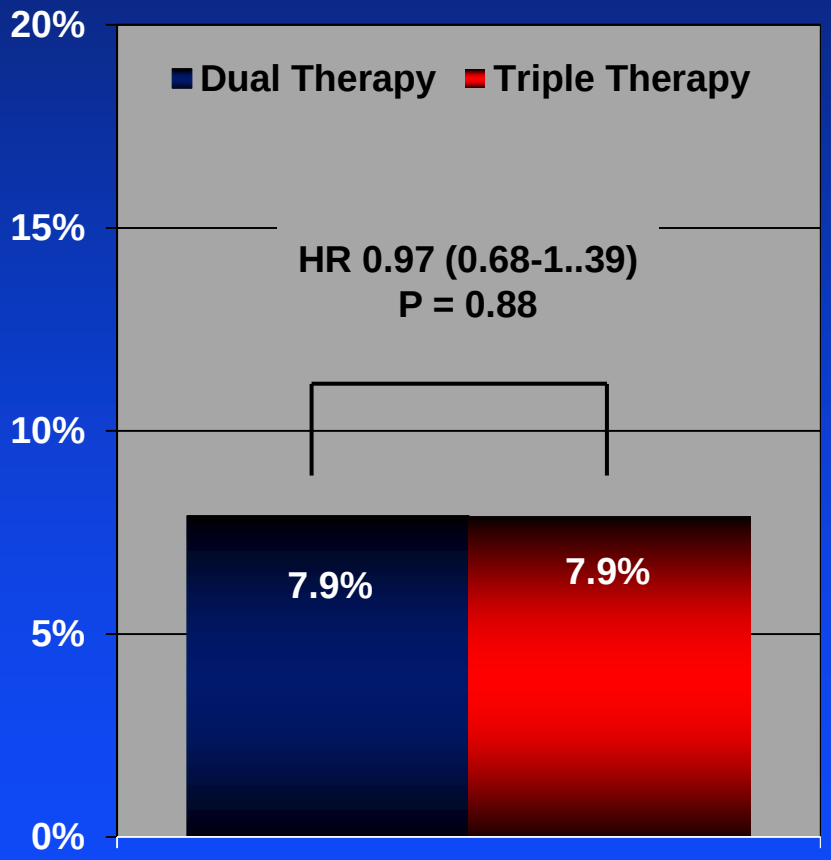

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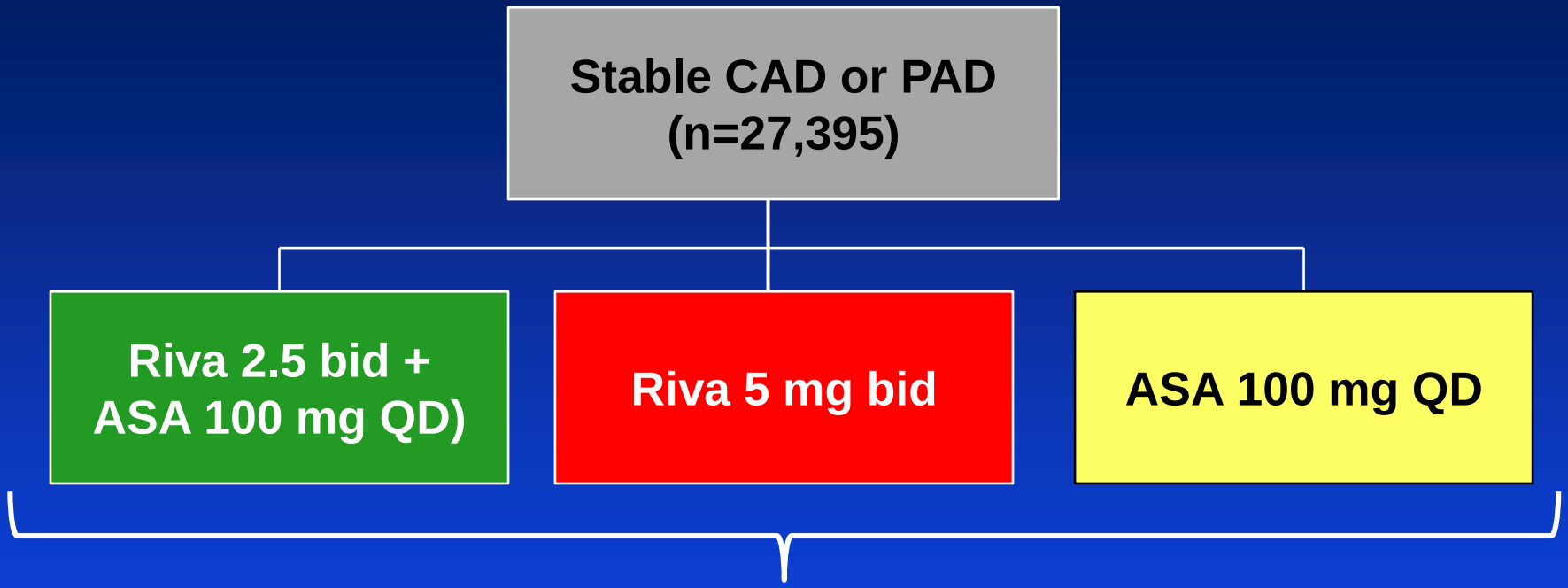
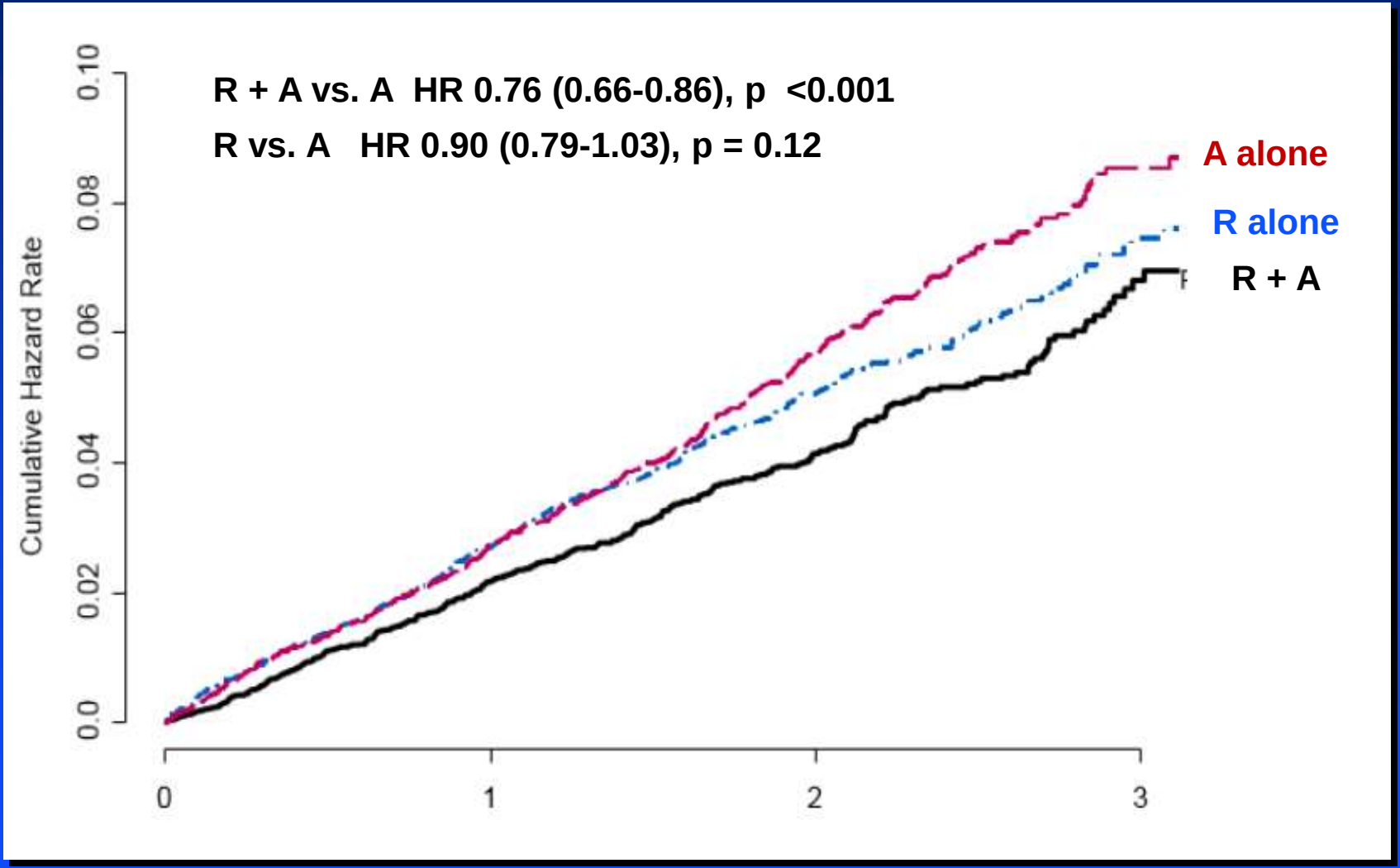
COMPASS Trial Design



Primary Endpoint: CV death, MI, or stroke

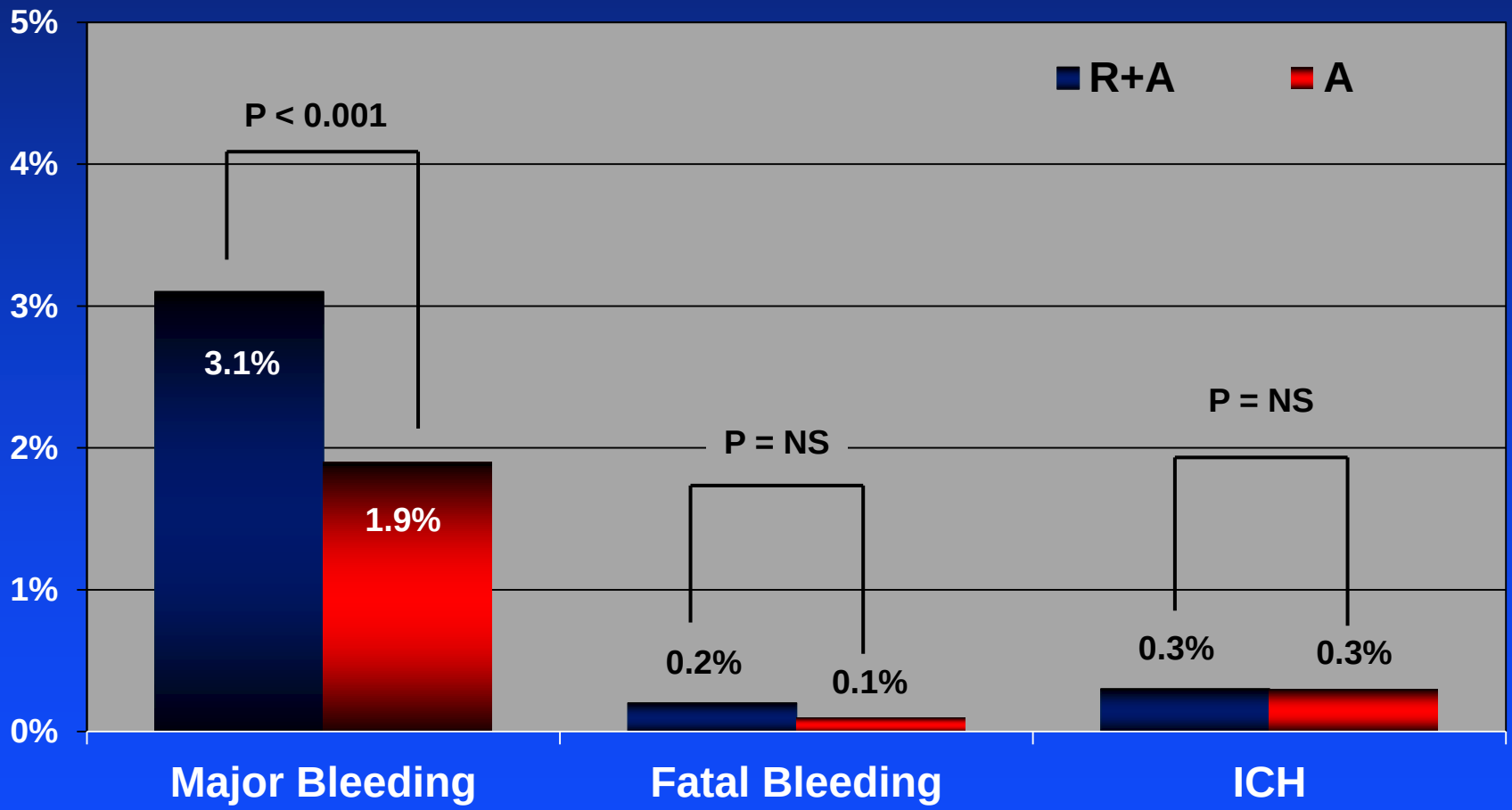
Safety Endpoint: ISTH major bleeding (similar to BARC 3)

Primary Endpoint: CV Death, MI, Stroke



Eikelboom JW, et al. NEJM 2017; 377: 1319-30

Safety Endpoints



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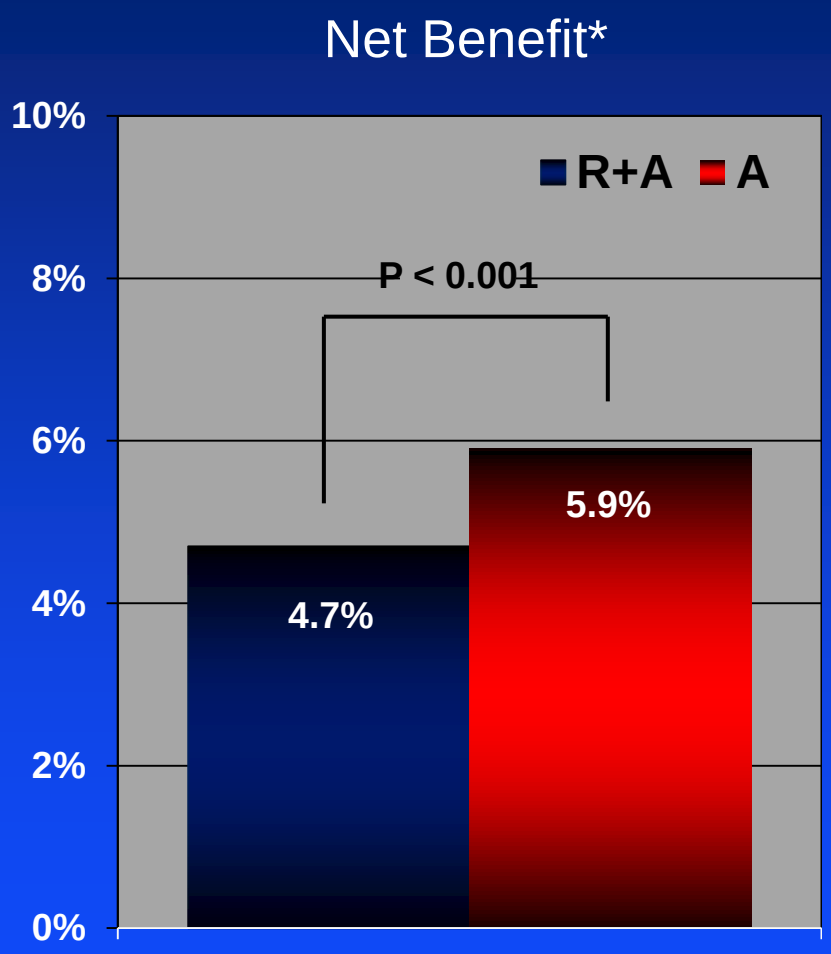
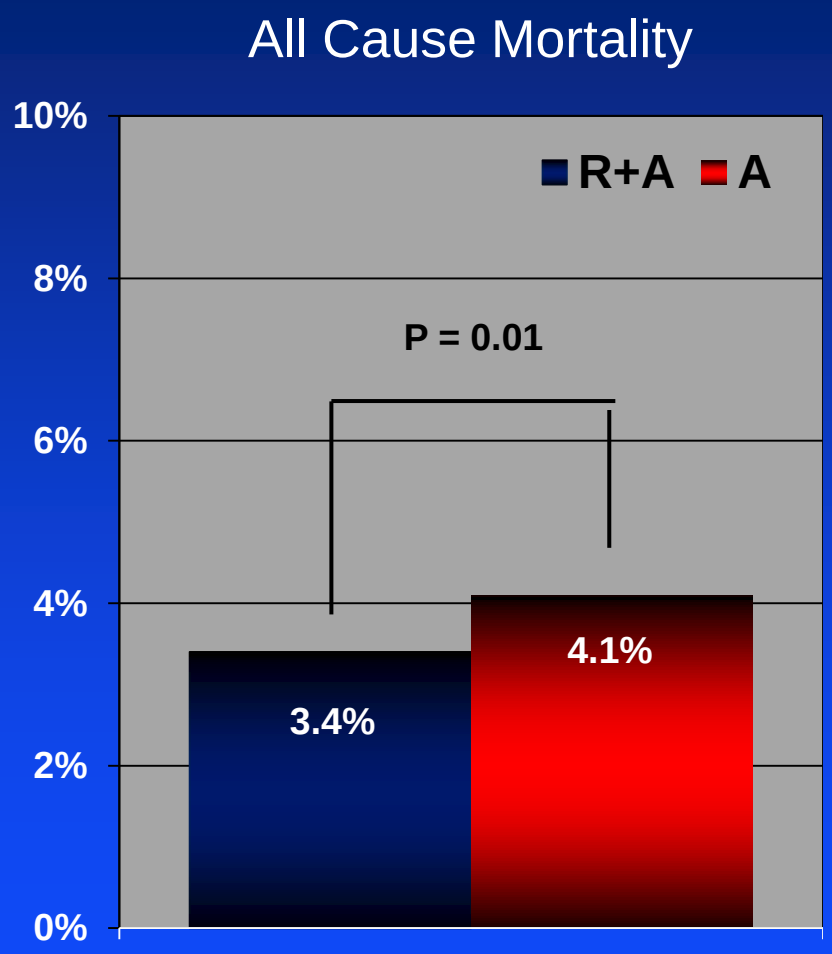
Balance of Safety/Efficacy





Net Benefit Endpoint: Composite of CV death, MI, stroke, fatal bleeding, or bleeding into critical organ

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Summary

Indication	Take Home Messages
ACS	Very low dose NOAC (i.e., riva 2.5 bid) is beneficial, but may be able to achieve similar benefits with less bleeding with ticagrelor

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AF + Stenting	NOAC + P2Y12 inhibitor generally safer than triple therapy. However, benefit seems largely due to ASA elimination. Await AUGUSTUS trial to see the true benefit of the NOAC
Stable CAD/PAD	Substantial benefit (including ↓'d mortality) of low dose rivaroxaban (2.5 bid) on top of standard therapies.