FACTOR Xa AND PAR-1 BLOCKER
: ATLAS-2, APPRAISE-2 & TRACER TRIALS

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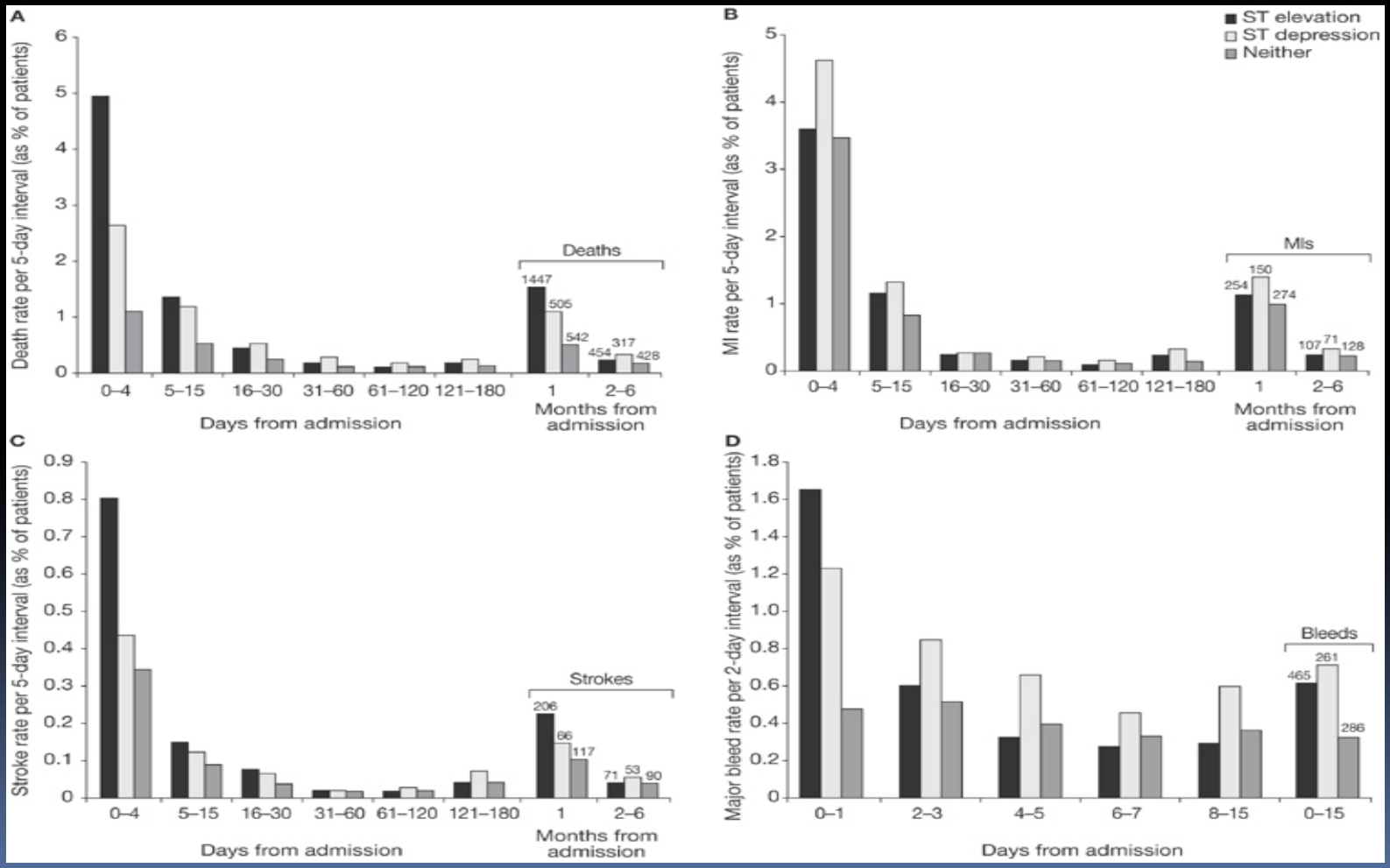
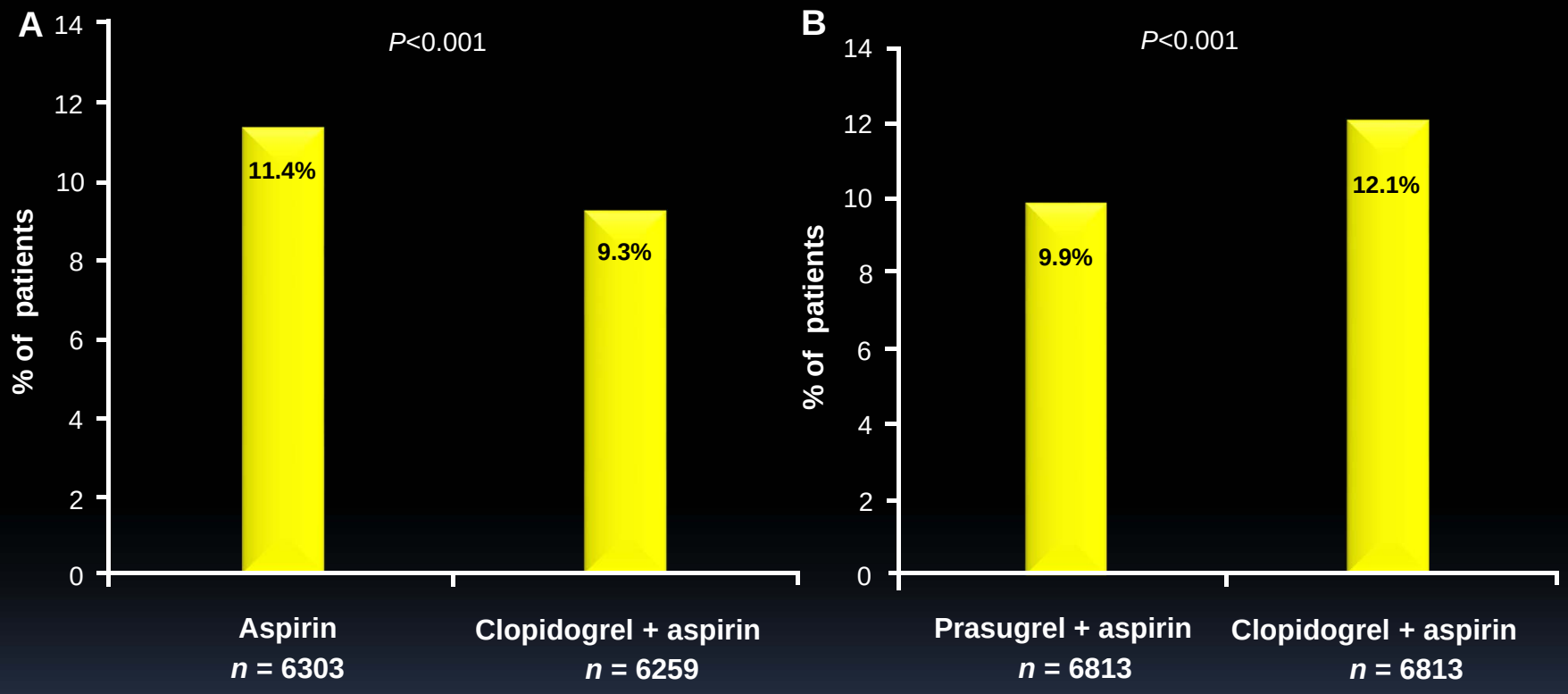
Introduction

- After acute coronary syndrome, patients remain at risk for recurrent ischemic events, despite revascularization and contemporary evidence based care



Nature Clinical Practice Cardiovascular Medicine (2008) 5, 580-589

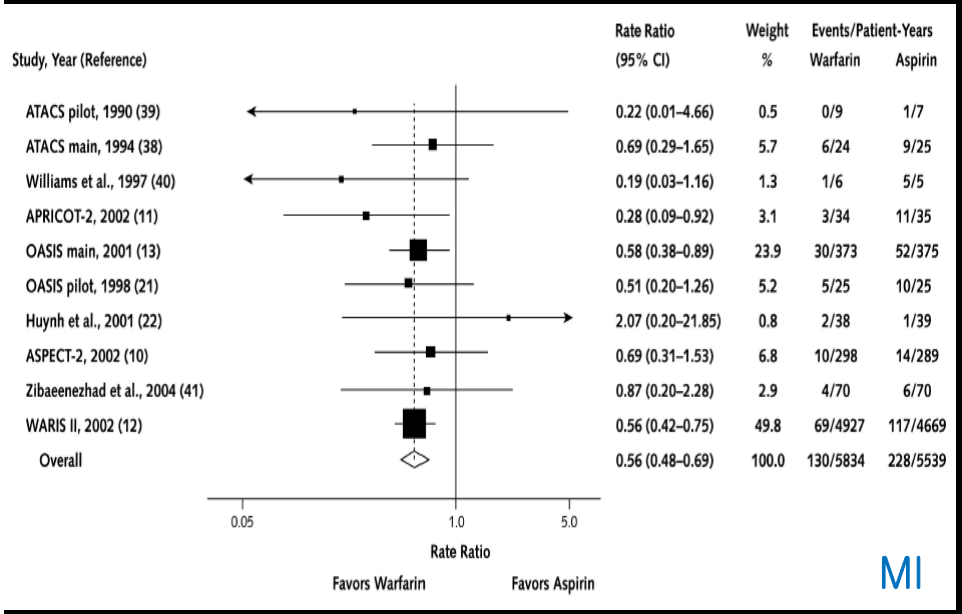
Dual Antiplatelets Therapy In ACS



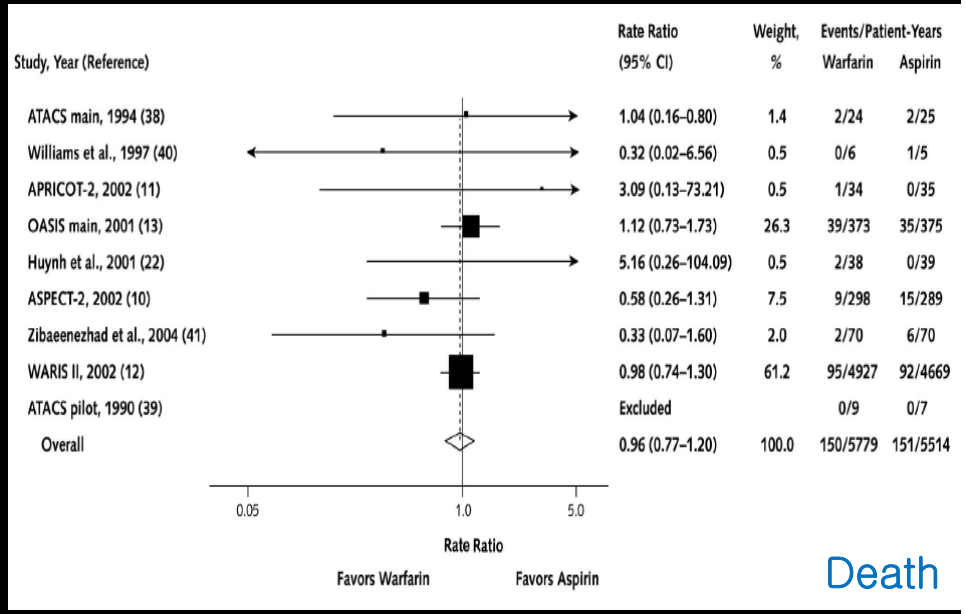
(A) Incidence of primary outcome (non-fatal myocardial infarction, stroke, or death from cardiovascular causes) in the CURE trial over 12 months. (B) Incidence of primary endpoint (death from cardiovascular causes, non-fatal MI, or non-fatal stroke) at 15 months in the TRITON trial.

European Heart Journal (2009) 30, 1695–1702

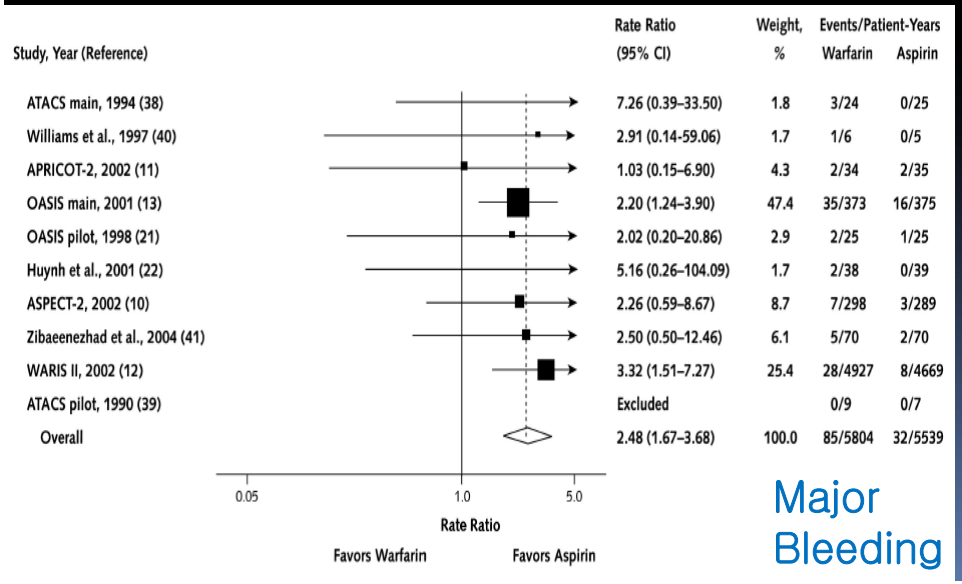
Warfarin Plus Aspirin After ACS : Meta-analysis



MI



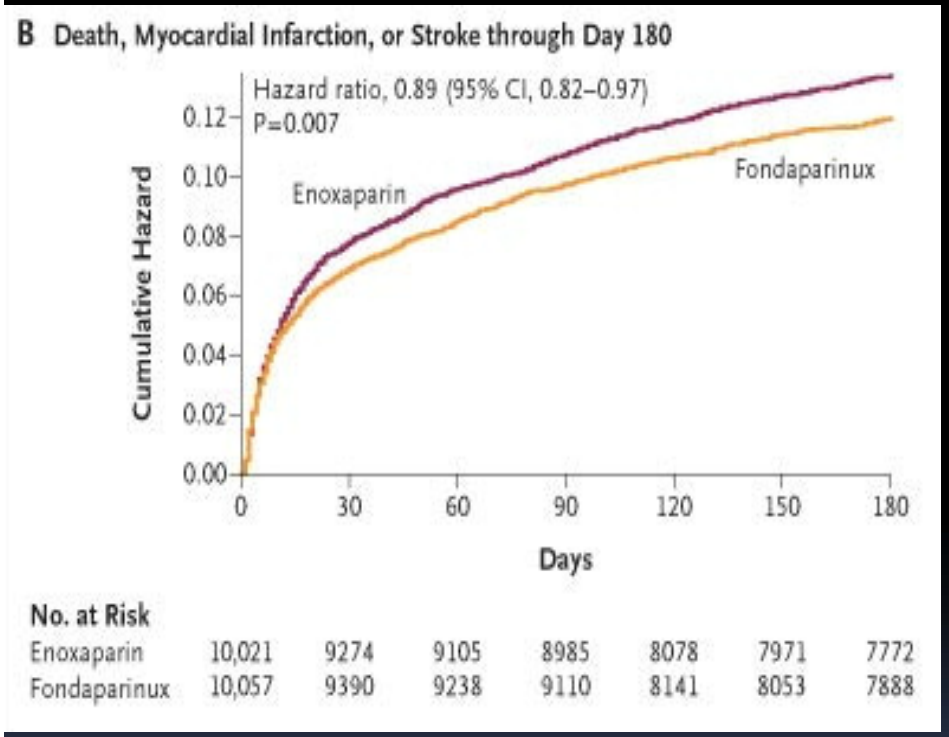
Death

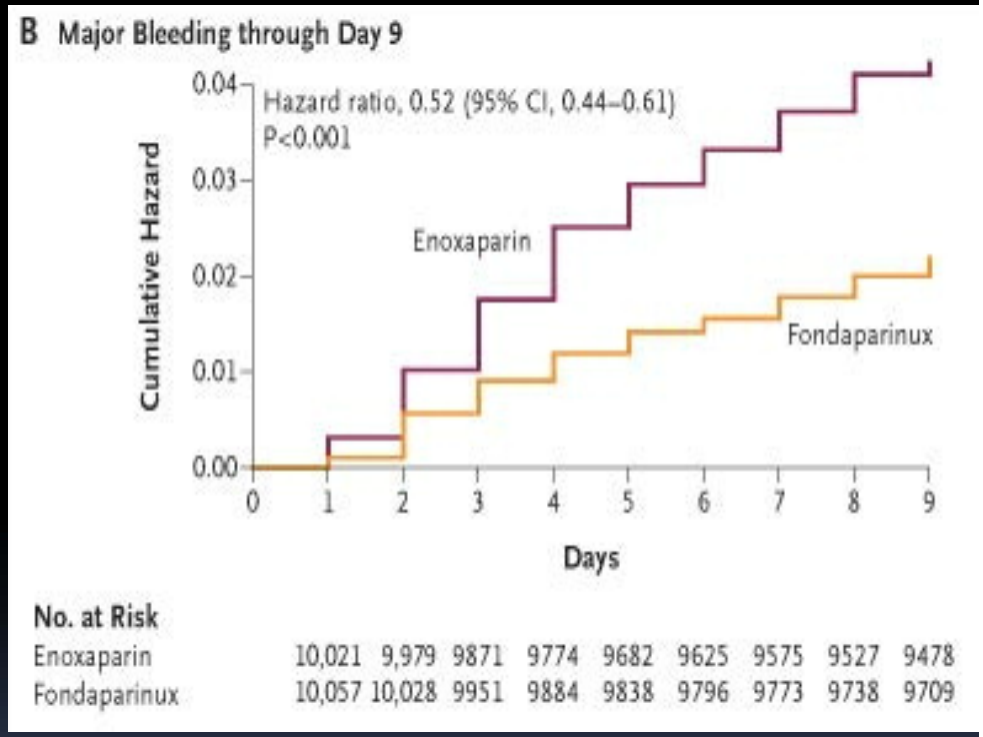


Major Bleeding

Ann Intern Med. 2005;143:241-250

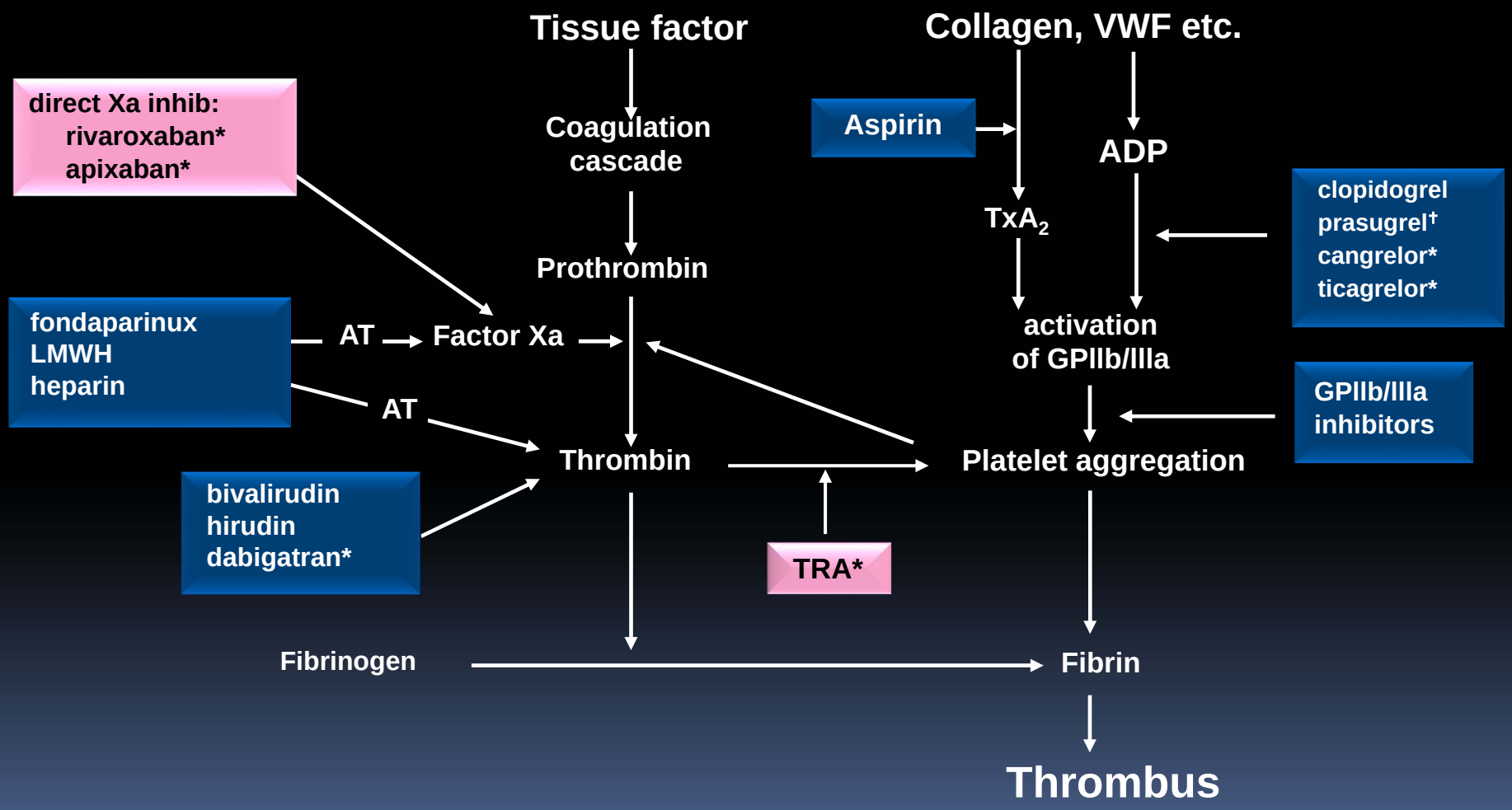
Fondaparinux In Acute Coronary Syndrome : OASIS-5



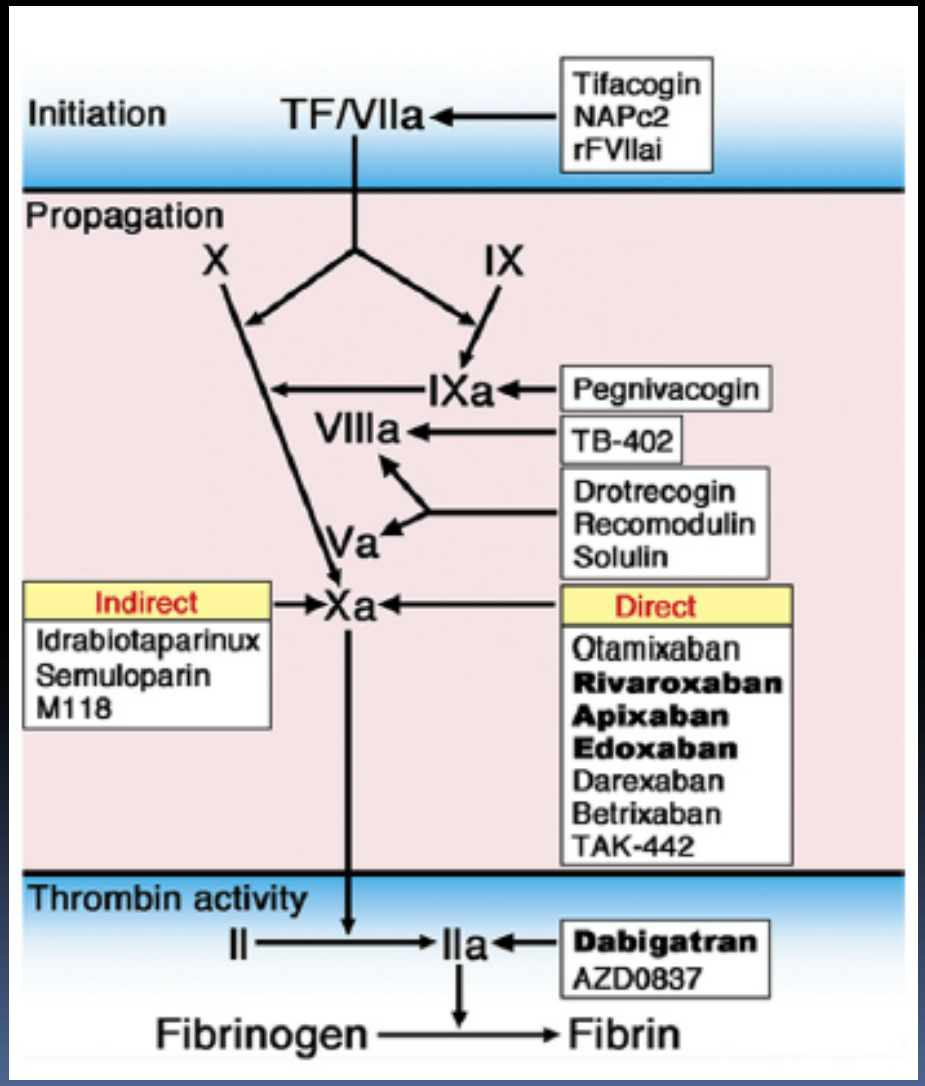


N Engl J Med 2006; 354:1464-1476

Coagulation Cascade, Platelet Activation Pathways, And Targets Of Antithrombotic Agents



Targets of Novel Anticoagulants for Long-Term Use



J Am Coll Cardiol 2012;59:1413–25

Targeting Factor Xa In ACS

- Cellular effect of factor Xa
  - Tissue factor expression
  - Release of plasminogen activator inhibitor 1
  - Expression of E-selectin, intercellular adhesion molecule 1, vascular cell adhesion protein
  - Release of several inflammatory cytokines : IL 6,8

- ➢ Factor Xa might be more attractive target for inhibition than thrombin
  - functioning at the confluence of early coagulation steps on both Tf-bearing cells and platelets
  - more thrombogenic than thrombin on molar basis
  - By contrast with thrombin inhibitors, factor Xa inhibitors decrease endogenous thrombin potential and allow small amounts of thrombin generation activating protein C

Rivaroxaban

- Pharmacokinetics
  - Oral anticoagulant that directly and selectively inhibits factor Xa
  - Oral bioavailability is 80% to 100%, negligible interaction with food
  - Dual mode of elimination
    - 2/3 metabolized by liver
    - 1/3 excreted in urine by kidney
  - Metabolized by cytochrome p450 (CYP450)
  - Average half-life 7 to 11 hours
- Clinical development
  - RECORD trial
    - Venous thromboembolism prophylaxis after total hip and knee arthroplasty
    - Rivaroxaban was superior to a once day dose of enoxaparin for prevention for VTE and all-cause mortality
  - ROCKET AF trial
    - Rivaroxaban was not inferior to dose adjusted warfarin in stroke prevention and clinical bleeding

ATLAS ACS2 TIMI 51 trial

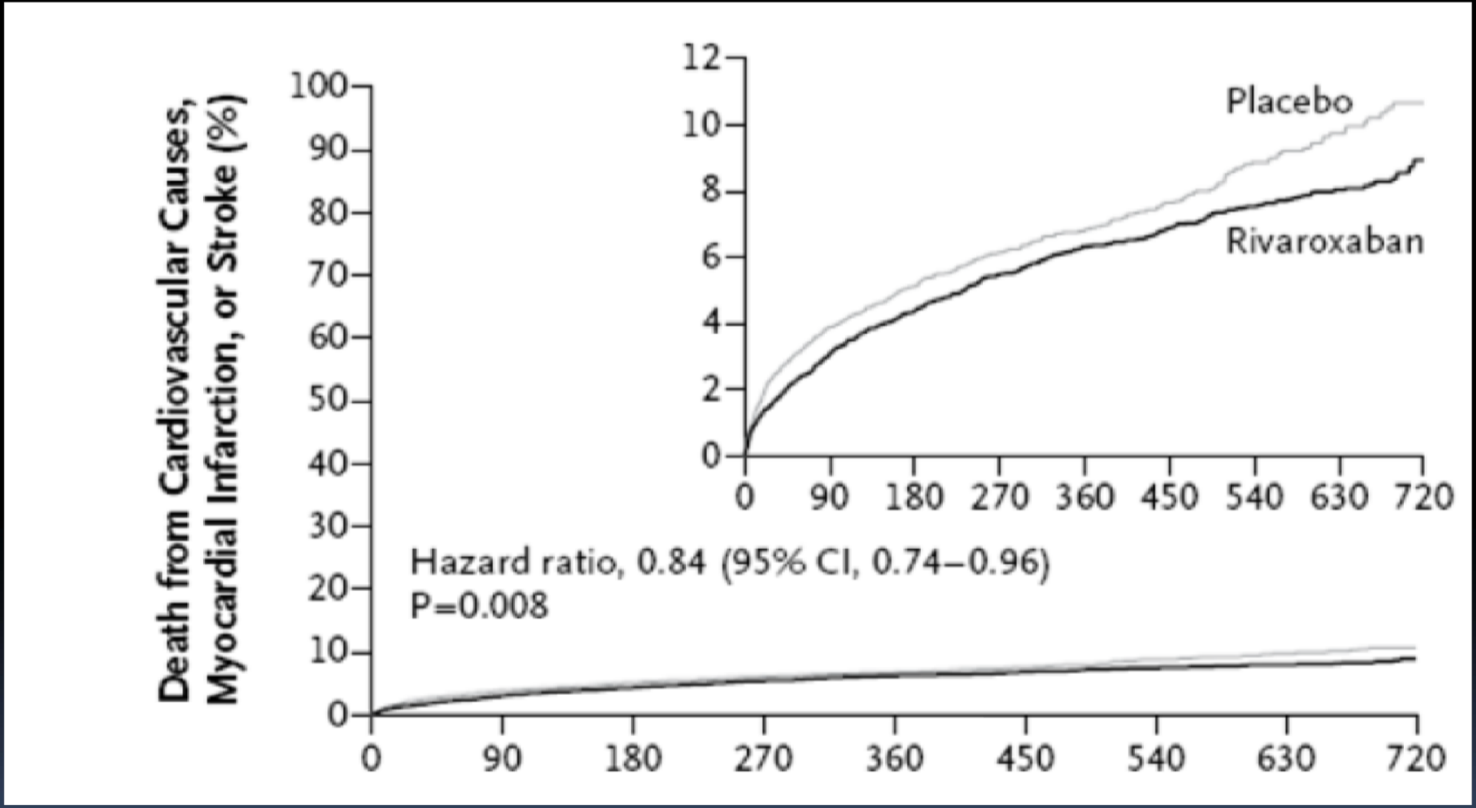
- Rivaroxaban in patients with a recent acute coronary syndrome

- Previous phase II trial ATLAS ACS- TIMI 46 trial
  - Rivaroxaban was tested at total daily doses ranging from 5 to 20mg
  - Reduced death, myocardial infarction, stroke
  - Dose-dependent increase in bleeding events

- In this phase III trial
  - Evaluate twice-daily rivaroxaban at doses of 2.5mg or 5mg as adjunctive therapy in patients with a recent ACS
  - Study population
    - Acute coronary syndrome
      - ST elevation myocardial infarction, non-ST elevation myocardial infarction. Unstable angina in past 7 days
      - Exclusion criteria
        - Low platelet (< 90,000/mL), low hemoglobin (<10g/dL)
        - Low creatinine clearance (30ml/min)
        - Clinically significant GI bleeding
        - Previous intracranial hemorrhage

Result

- Primary efficacy end point
  - CV death, MI, stroke



10.7%

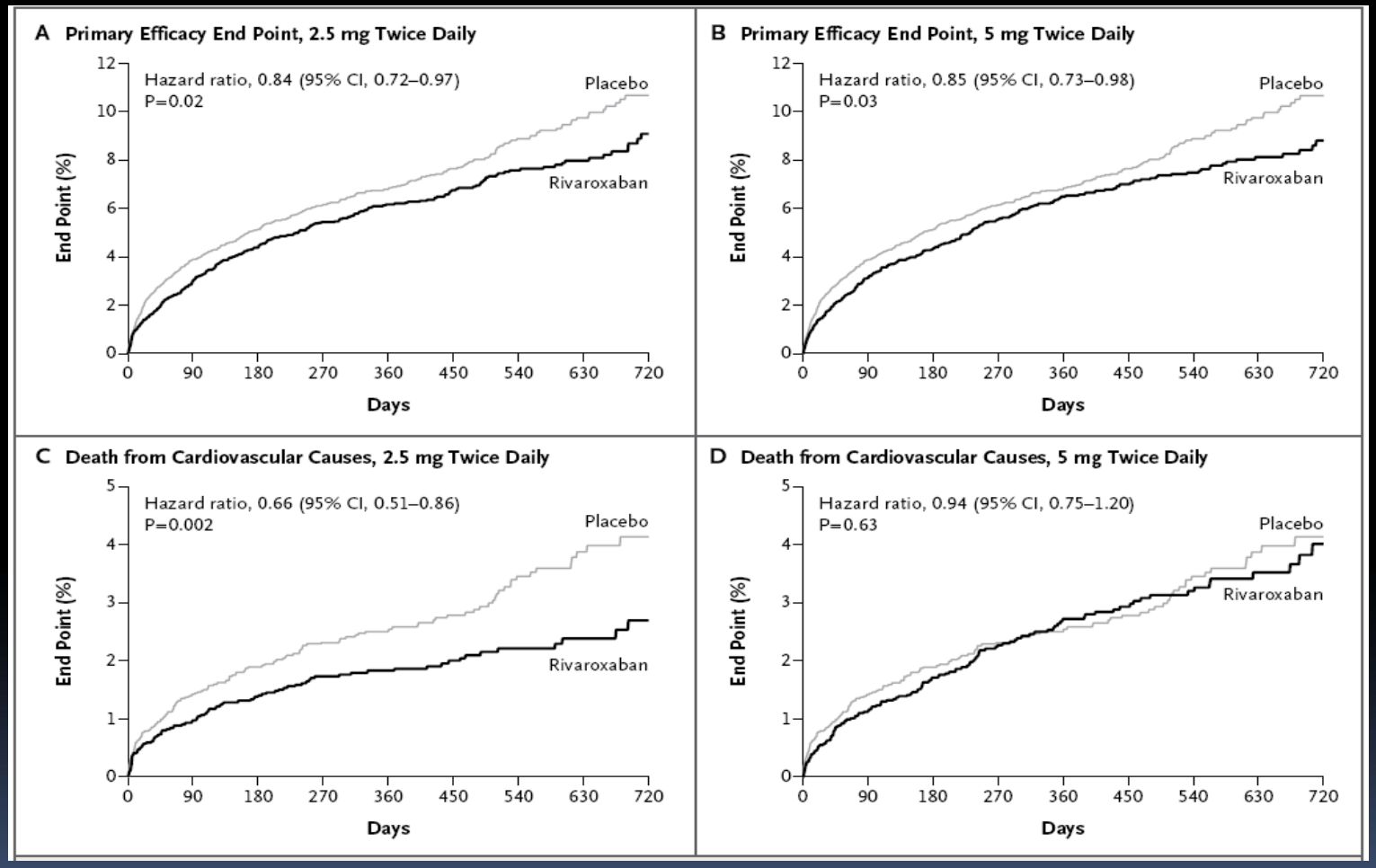
8.9%

Rivaroxaban significantly reduced the primary efficacy end point compared with placebo with rates of 8.9% vs. 10.7% (HR 0.84, 95% CI 0.74 to 0.96 : p=0.008)

N Engl J Med 2012;366:9-19

Result

- Primary end points according dose



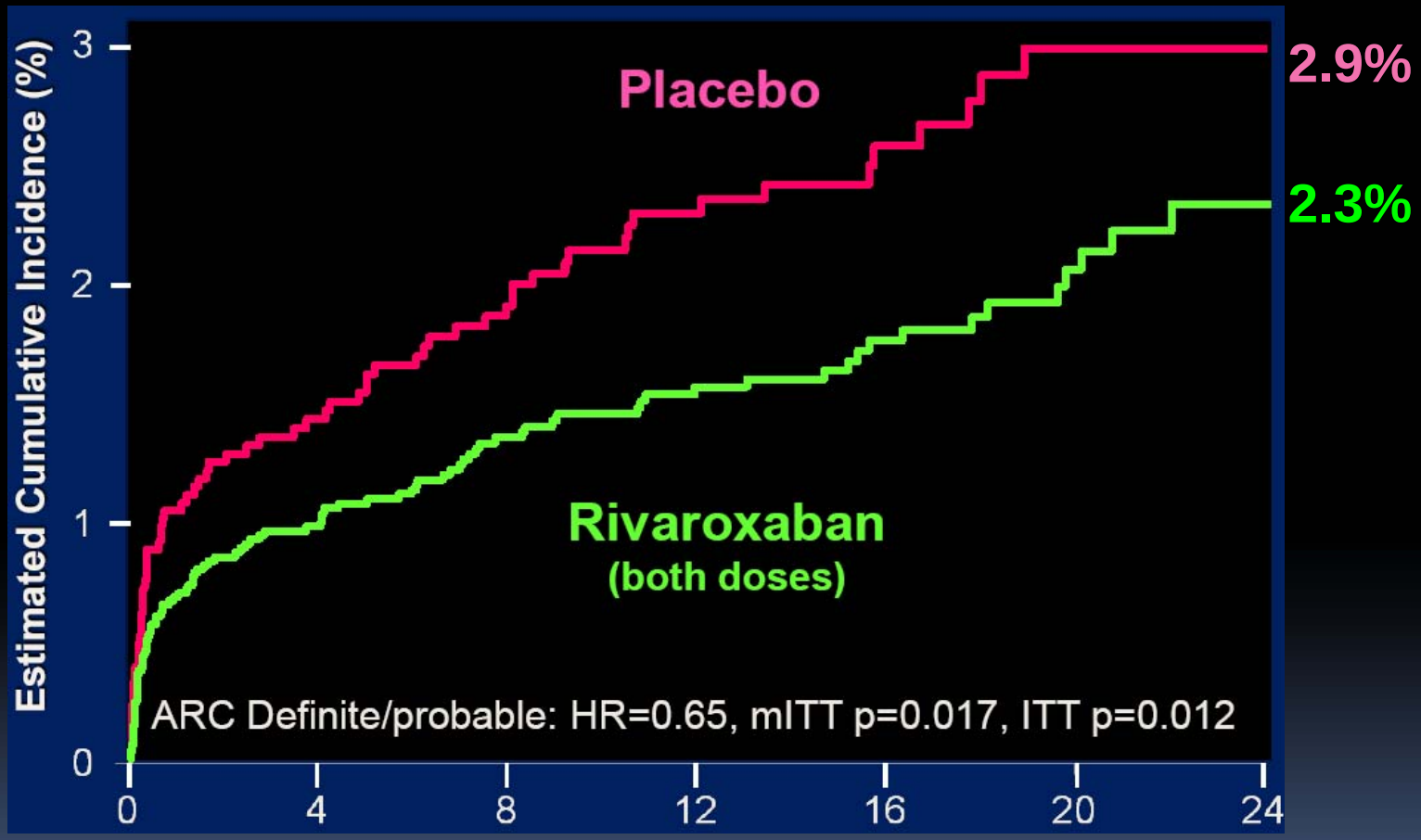
Each doses of rivaroxaban reduced the primary efficacy end point

2.5mg dose 9.1% vs.10.7% **5mg dose 8.8% vs.10.7%**

N Engl J Med 2012;366:9-19

Results

- Stent thrombosis



Rivaroxaban reduced the risk of stent thrombosis compared with placebo 2.3% vs.2.9% (HR 0.65, 95% CI 0.74 to 0.95; p=0.02)

N Engl J Med 2012;366:9-19

Results

- Safety endpoint

	Rivaroxaban			Placebo
Safety	2.5mg Twice daily (N=5114)	5mg Twice daily (N=5115)	Combined (N=20,229)	(N=5113)
TIMI major bleeding not associated with CABG	65(1.8)	82 (2.4)	**147(2.1)**	**19(0.6)**
TIMI minor bleeding	32(0.9)	49(1.6)	81(1.3)	20(0.5)
TIMI bleeding requiring medical attention	492(12.9)	637(16.2)	1129(14.5)	282(7.5)
Intracranial hemorrhage	14(0.4)	18(0.7)	**32(0.6)**	**5(0.2)**
Fatal bleeding	6(0.1)	15(0.4)	**21(0.3)**	**9(0.2)**

Rivaroxaban significantly increased the rate of bleeding, but no significant difference in the rate of fatal bleeding (0.3% vs.0.2%,p=0.66)

Apixaban

- Pharmacokinetics
  - Oral direct factor Xa inhibitor selectively and reversibly inhibits factor Xa
  - Oral bioavailability is approximately 50%
  - Peak concentrate 3 hours after oral administration
  - Half life around 12 hours
  - Renal excretion was one of the significant routes of elimination
  - Metabolized by CYP3A4 system
- Clinical development
  - ADVANCE trial
    - Apixaban was a convenient alternative for VTE prophylaxis after total hip and knee replacement without increasing bleeding
  - ARISTOTLE trial
    - In patients with atrial fibrillation
    - Apixaban is superior to warfarin at preventing stroke or systemic embolism, causes less bleeding and results in lower mortality

APPRAISE-2 trial

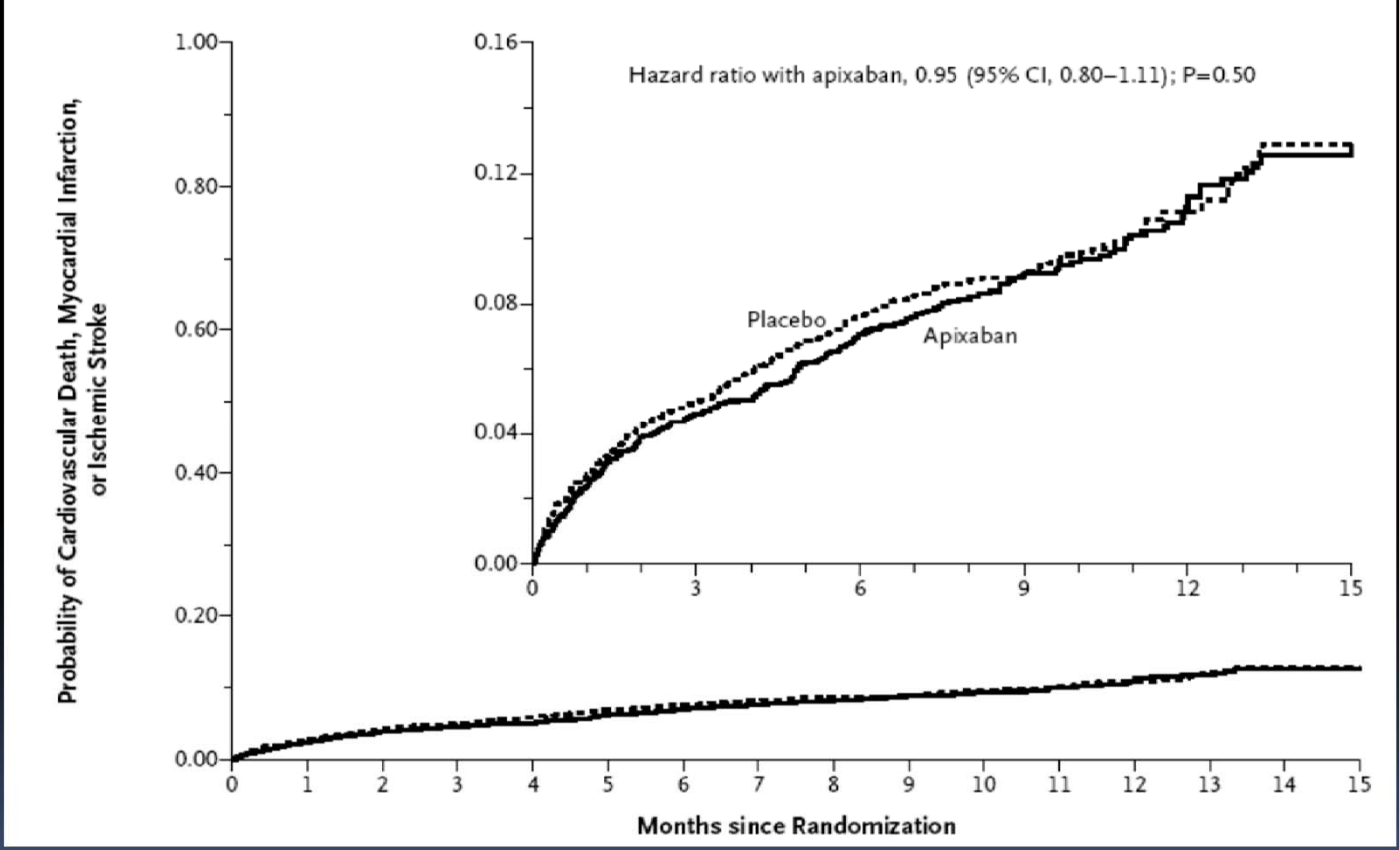
: Apixaban with antiplatelet therapy after acute coronary syndrome

- In APPRISE -1 trial
  - Apixaban showed reduction in ischemic events with the addition of antiplatelet therapy in patients with ACS

- Study design
  - Double blind placebo controlled randomized clinical trial
  - Study population
    - ACS within the pervious 7 days
    - Two or more of following high risk characteristics
      - Age at least 65 years
      - Diabetes mellitus
      - Myocardial infarction within the previous 5 years
      - Cerebrovascular disease
      - Peripheral vascular disease
      - Clinical heart failure or left ventricular EF < 40%
      - Calculated creatinine clearance < 60m/min

Results

- Primary efficacy
  - Cardiovascular death, myocardial infarction, ischemic stroke

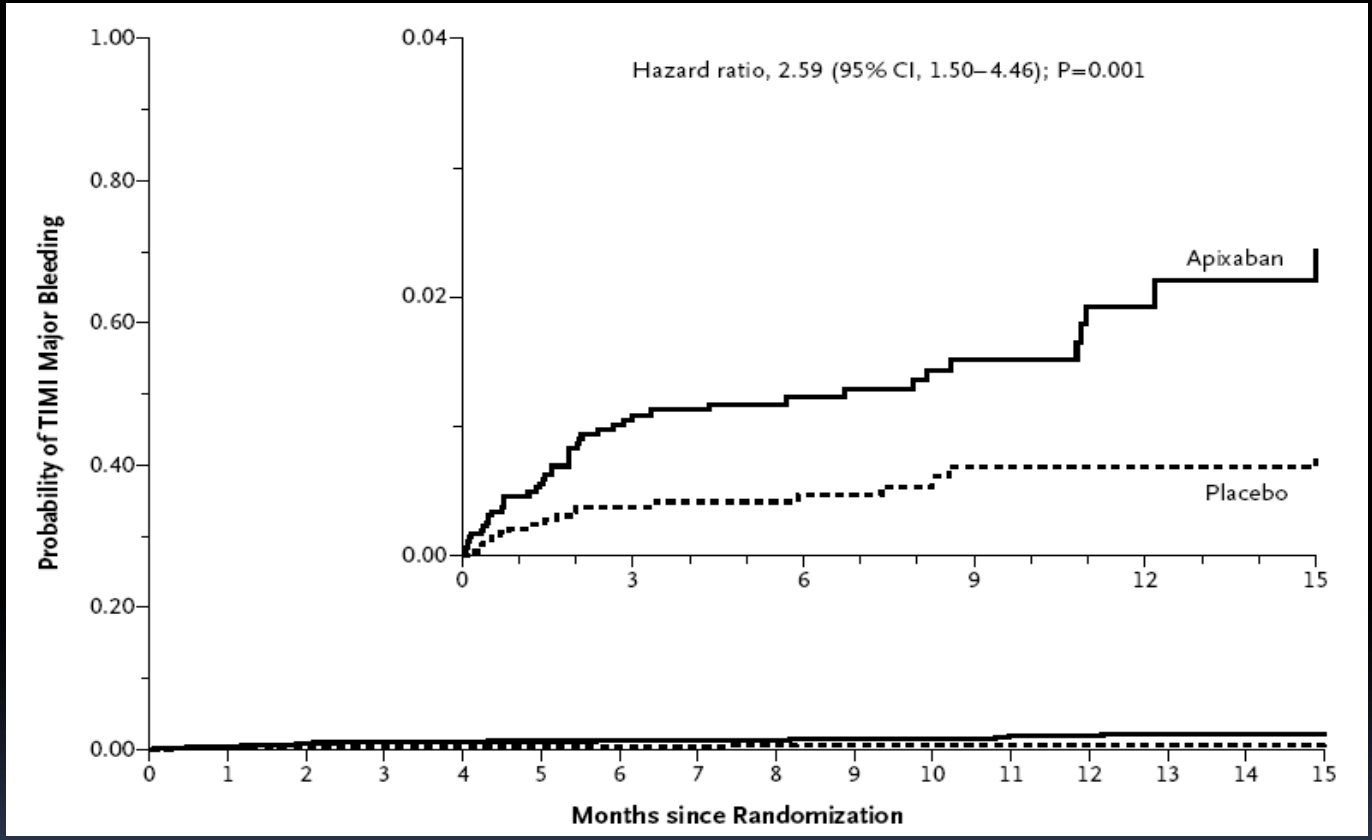


There were no significant difference between the apixaban and placebo groups
Apixaban vs. placebo 7.5% vs. 7.9% (HR 0.95, 95% CI 0.80 to 1.11; p=0.51)

N Engl J Med 2011;365:699-708

Results

- Primary safety outcomes



In apixaban group, significant increase in bleeding events including increases in events of fatal and intracranial bleeding

Fatal bleeding (5 vs. 0), intracranial bleeding (12 vs.3) total bleeding (679 vs.305)

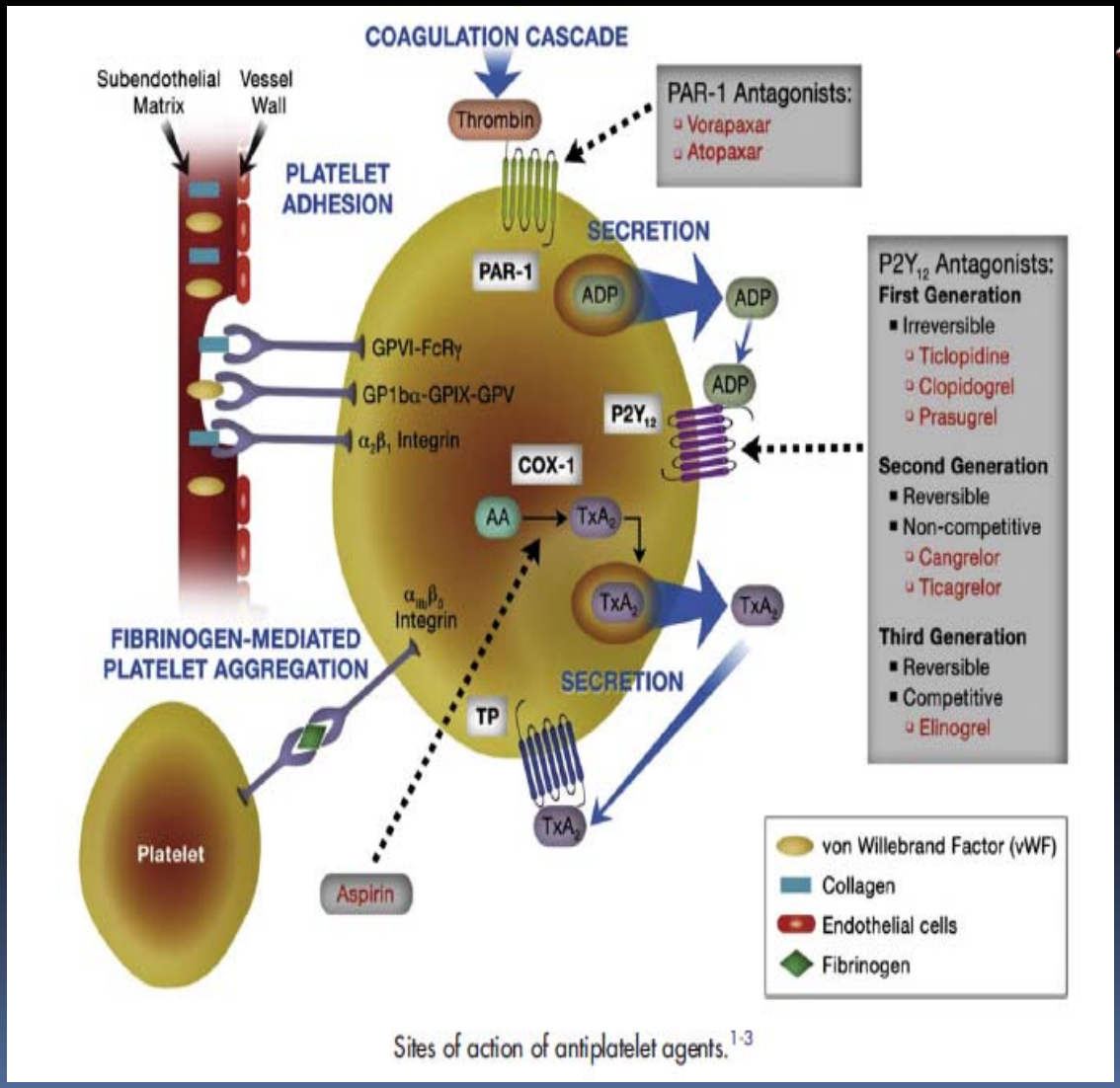
N Engl J Med 2011;365:699-708

APPRAISE-2 vs. ATLAS ACS2

- The 2 trials of oral factor Xa inhibitor show lack of consistency in efficacy

- The reason of discrepancy
  - Difference in the inclusion criteria
    - APPRAISE-2 population
      - Older, more diabetes, renal dysfunction, previous stroke
      - More frequent heart failure and moderate to severe LV dysfunction
      - → Less related to thrombotic events and less responsive to anticoagulation treatment
  - Difference of factor Xa inhibition potency
    - In APPRAISE -2 trial
      - 5mg BID apixaban (same dose of atrial fibrillation test- ARISTOTLE trial)
    - In ATLAS-2 trial
      - 2.5mg or 5mg BID rivaroxaban (1/4 dose of atrial fibrillation test- ROCKET trial)
      - → Better efficacy and lower bleeding rate
  - APPRAISE-2 trial was prematurely terminated
    - Mean treatment duration
      - 13.1 months vs. 8 months

Vorapaxar : PAR-1 Inhibitor
Nobel Oral Antiplatelet Agent



Sites of action of antiplatelet agents.[1-3]

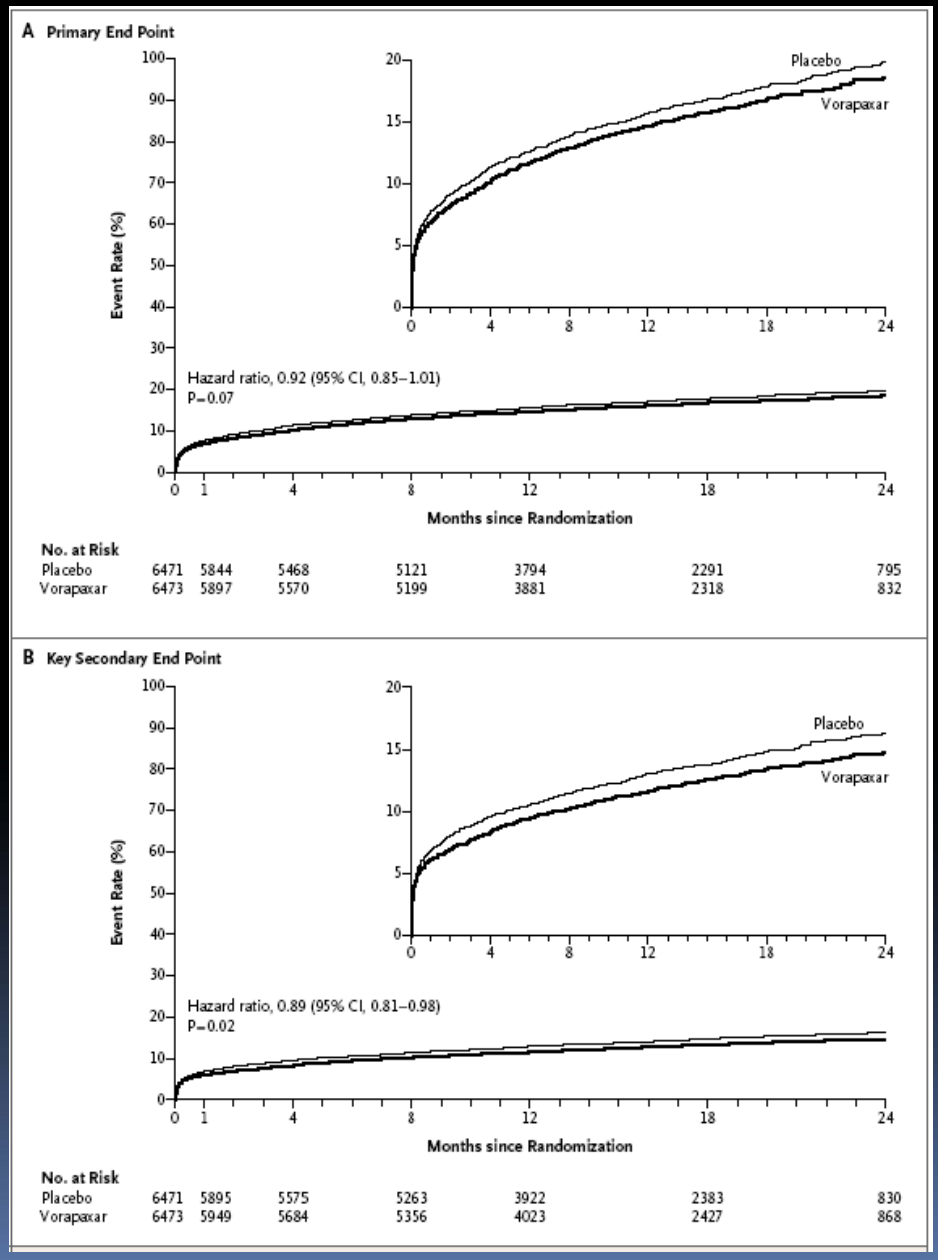
- Pharmacokinetics
  - Oral competitive protease-activated receptors (PAR) antagonist
    →Inhibit thrombin-induced platelet aggregation
  - Completely absorbed via GI tract
  - Peak effects are seen within 1~2 hours after oral loading
  - Metabolized by CYP 3A4
  - Major route of elimination is feces with minor renal excretion

TRACER trial

: Thrombin-receptor antagonist vorapaxar in acute coronary syndrome

- Study population
  - Patients with ACS within 24 hrs
  - : One of the followings
  - Age at least 55 years
  - Previous myocardial infarction, PCI or CABG
  - Diabetes mellitus
  - Peripheral vascular disease
- Study procedures
  - 1:1 ratio randomly assigned vorapaxar and placebo
    - Loading dose 40mg and maintenance dose of 2.5mg

Result



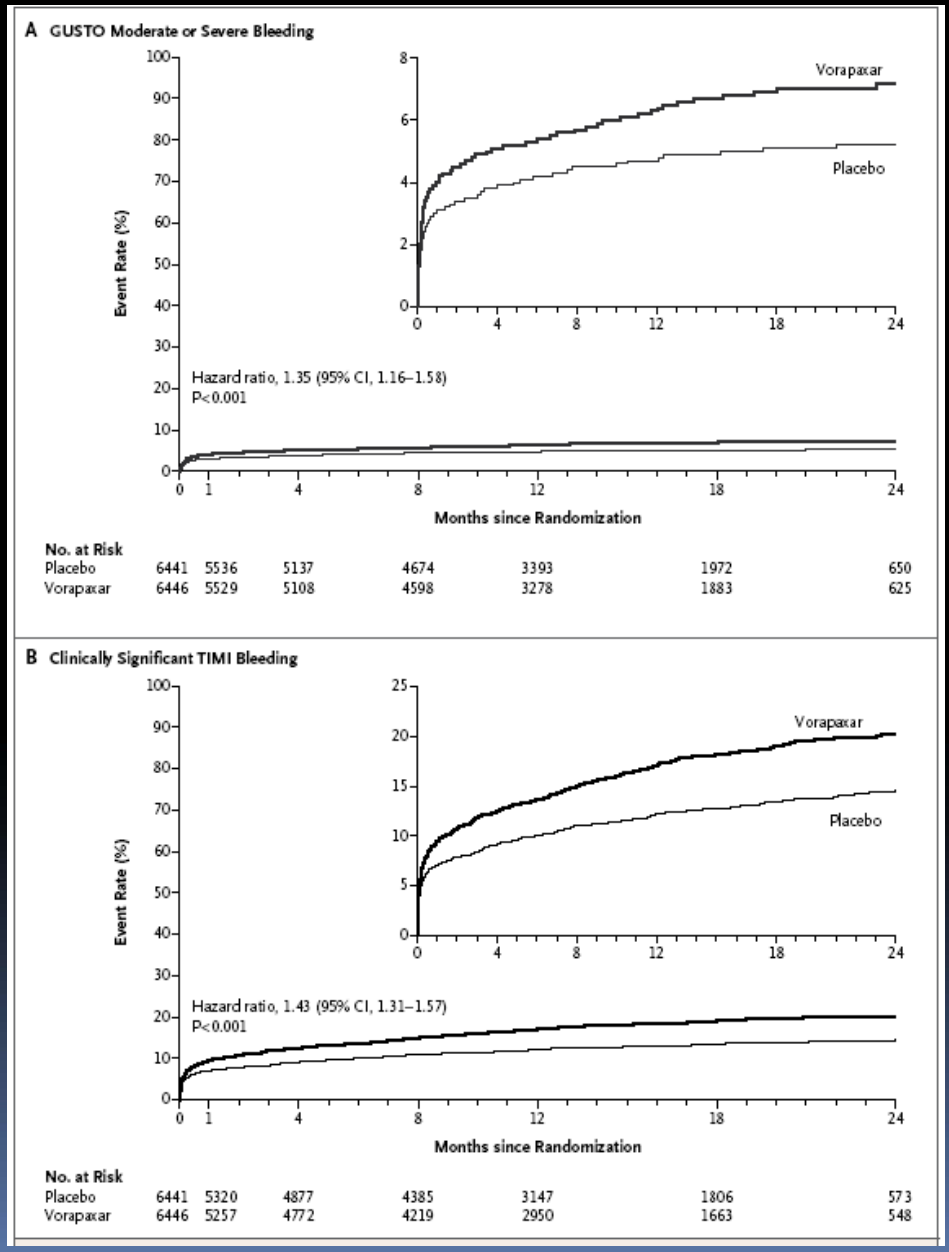
- **Primary end point**
  - Death from cardiovascular cause, myocardial infarction, stroke, recurrent ischemia with rehospitalization or urgent coronary revascularization

- In addition of PAR-1 inhibition with vorapaxar to standard therapy resulted in a nonsignificant relative reduction of 8% in primary end point

Vorapaxar group vs. placebo group
18.5% vs. 19.9%
(HR 0.92, 95% CI 0.85 to 1.01 p=0.07)

N Engl J Med 2012;366:20-33

Result



- **Risk of bleeding**

Vorapaxar increase the rate of GUSTO moderate to severe bleeding
7.2% vs. 5.2%
(HR 1.35, 95% CI 1.16 to 1.58, p< 0.001)

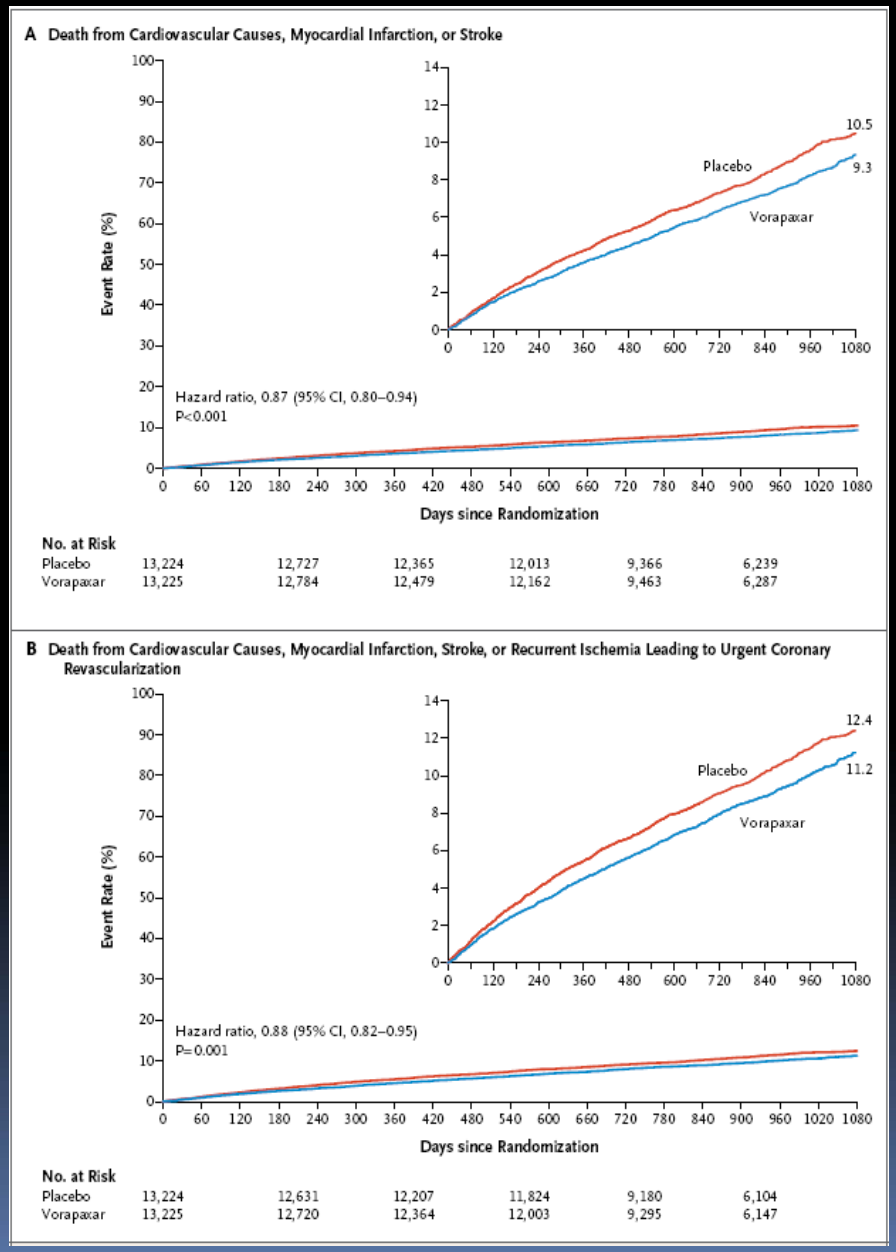
N Engl J Med 2012;366:20-33

Vorapaxar In Patients With Stable Atherosclerosis : TRA 2P-TIMI 50 Trial

- TRA 2P-TIMI 50 trial
  - Evaluate the efficacy and safety of vorapaxar in reducing atherothrombotic events in patients with established atherosclerosis
  - Patients
    - MI, ischemic stroke or peripheral arterial disease
    - Exclusion
      - Planning to undergoing revascularization procedure
      - Bleeding diathesis
  - Randomization
    - Vorapaxar 2.5mg : placebo - 1:1

Vorapaxar In Patients With Stable Atherosclerosis

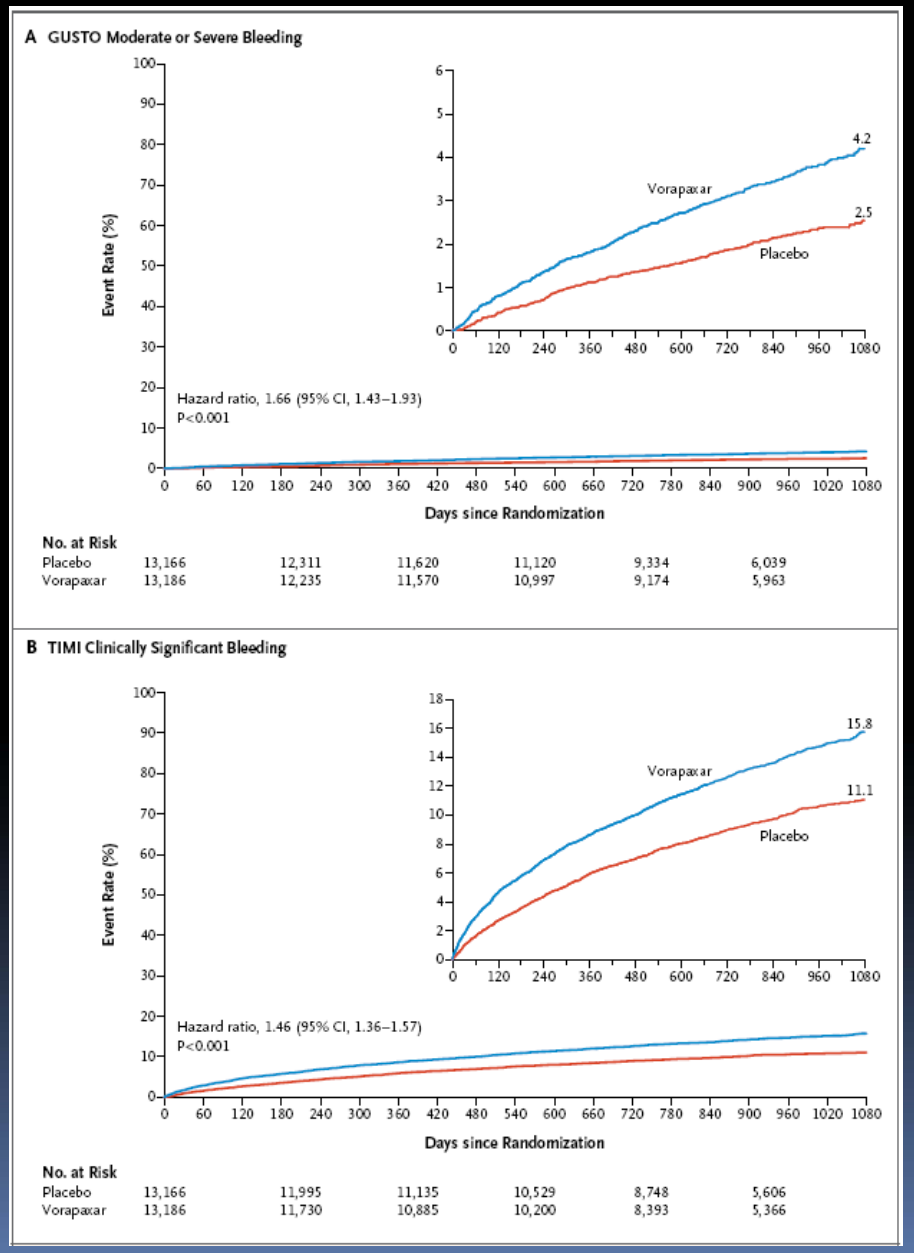
- Result
  - Primary end point
    - Cardiovascular death, MI, stroke
    - **9.3% vs. 10.5%** (p <0.001)
  - Secondary end point
    - Cardiovascular death, MI, stroke urgent coronary revascularization
    - **11.2% vs. 12.4%** (p=0.001)



N Engl J Med 2012;366:1404-13

Vorapaxar In Patients With Stable Atherosclerosis

- Results
  - Moderate to severe bleeding
    - 4.2% vs. 2.5% (p<0.001)
  - TIMI major bleeding
    - 15.8% vs. 11.1% (p<0.001)
  - Intracranial bleeding
    - 1.0% vs. 0.5% (p<0.001)



N Engl J Med 2012;366:1404-13

Conclusion

- Novel anticoagulants or antiplatelets are potentially beneficial treatment option for patients with recent ACS
  - But, increase in bleeding is clear
- New era of secondary prevention after ACS will be characterized by need to balance ischemic versus bleeding risk
- Existing agents need to be tested in combination with novel antiplatelets regimens, such as prasugrel or ticagrelor in addition to aspirin
- Rivaroxaban seems to represent novel addition to DAPT

  after ACS event (vorapaxar in ACS? or prior MI), but its place in clinical practice, if approved for this indication, will depend on very careful consideration of all available treatment options, risk-benefit relationships, patients-specific needs, and the cost

Warfarin
50 year old our car
prone to breakdown
We know how to fix it

New agent
Make sure before we know where the emergency brake is