# Thrombin Receptor Antagonists and Other New Oral Antiplatelets Drugs

David J. Moliterno, MD
Professor and Chairman
Department of Internal Medicine

The University of Kentucky
Linda and Jack Gill Heart Institute

# Thrombin Receptor Antagonists and Other New Oral Antiplatelets Drugs—or maybe new approaches with our current drugs

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# Conflict of Interest Statement

*"Thrombin Receptor Antagonists and Other New Oral Antiplatelet Drugs—or maybe…"*

David J. Moliterno, MD

DSMB: Janssen Pharmaceuticals (GEMINI Study)

Research Grant: Merck (Steering Committee: TRACER and TRA2P)

Astra Zeneca (Steering Committee: TWILIGHT Study)

# Options to Improve Antithrombotic Rx

- Increase the strength (dose) of current Rx
- Use more potent agent(s)
- Add additional, hopefully safer, agents (eg, polypharmacy)
- Use polypharmacy but remove the least effective agent of the group
- Tailor therapy to each patient (eg, personalized medicine)

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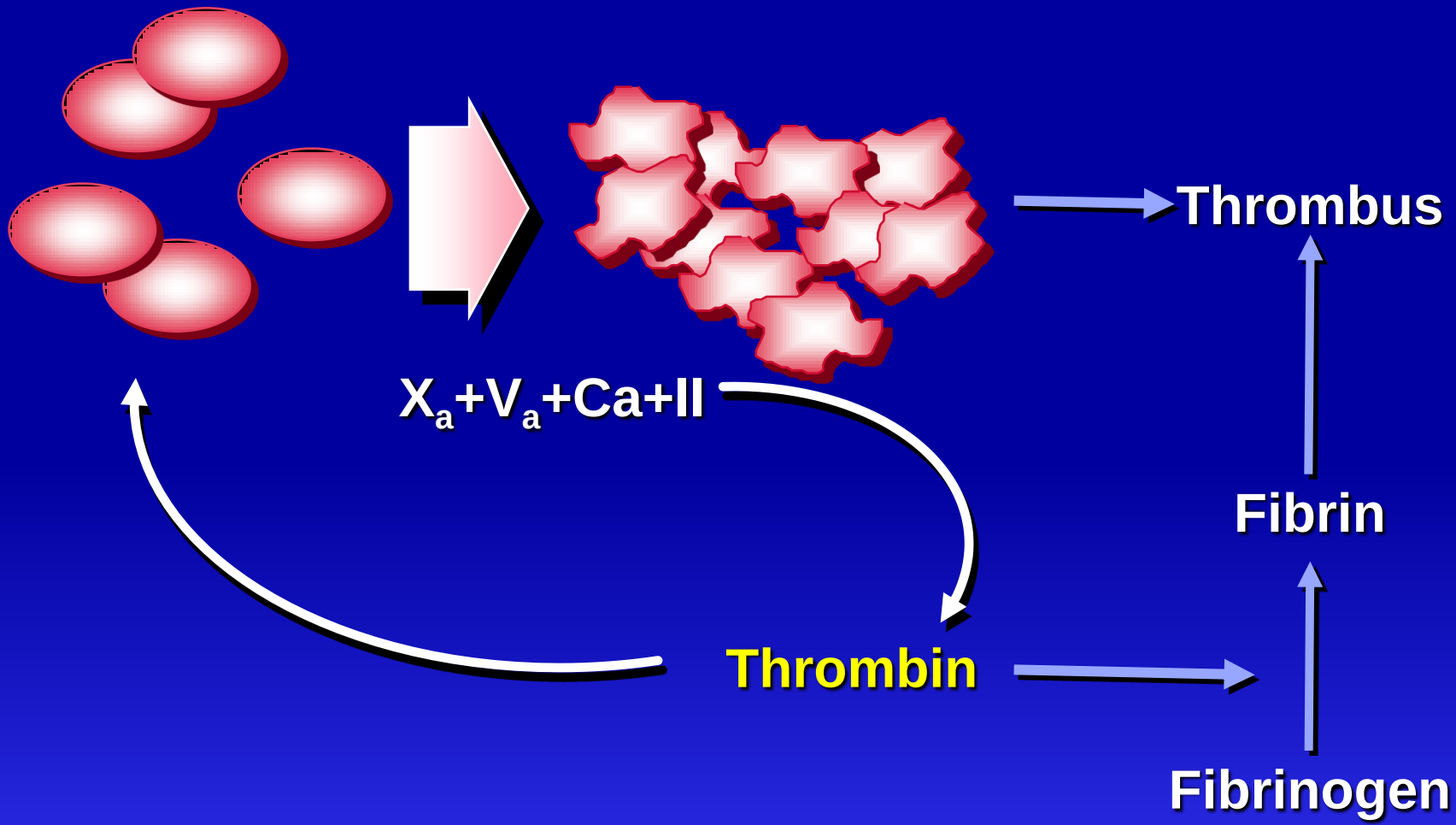
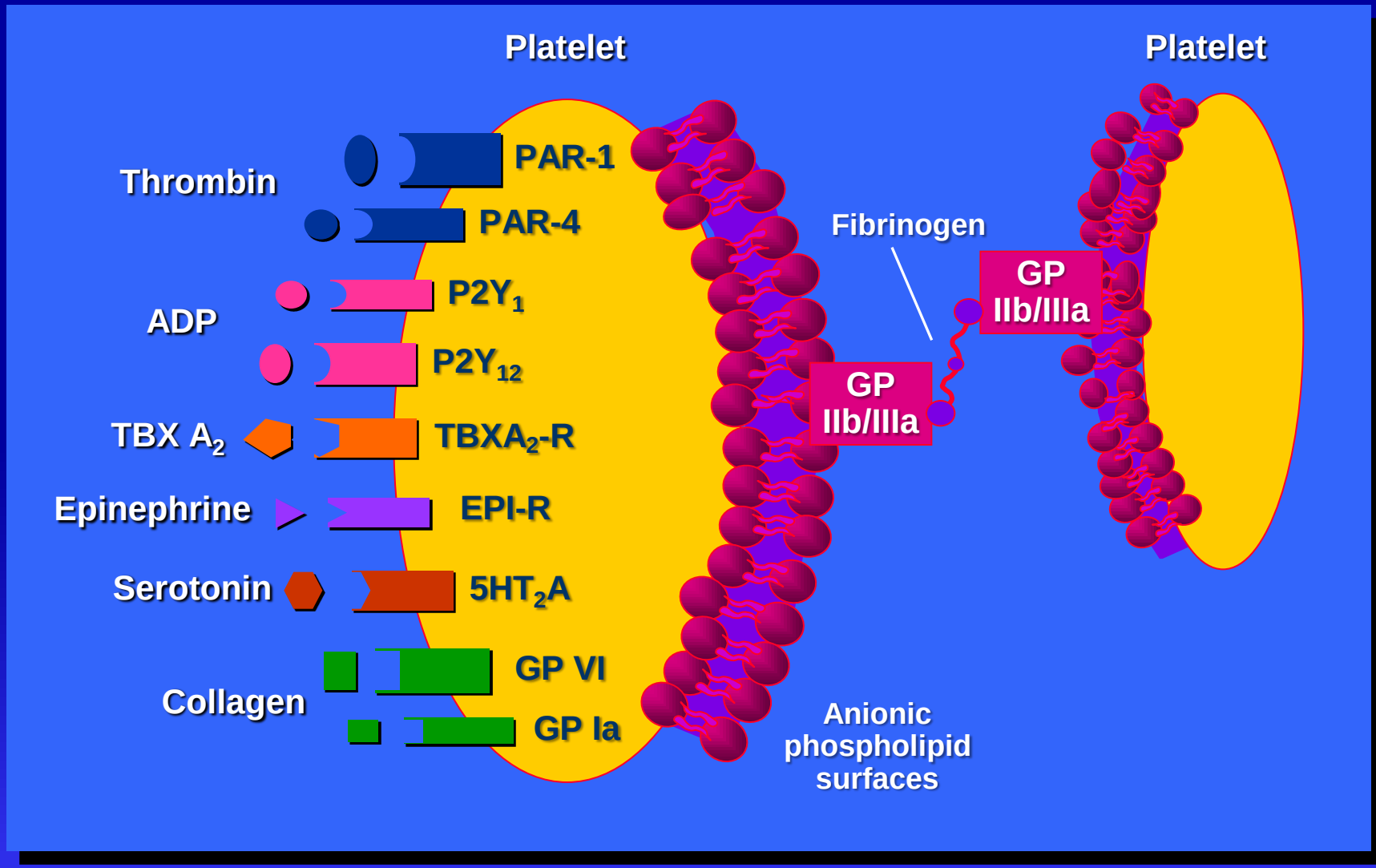
# Platelet-Thrombin Interaction

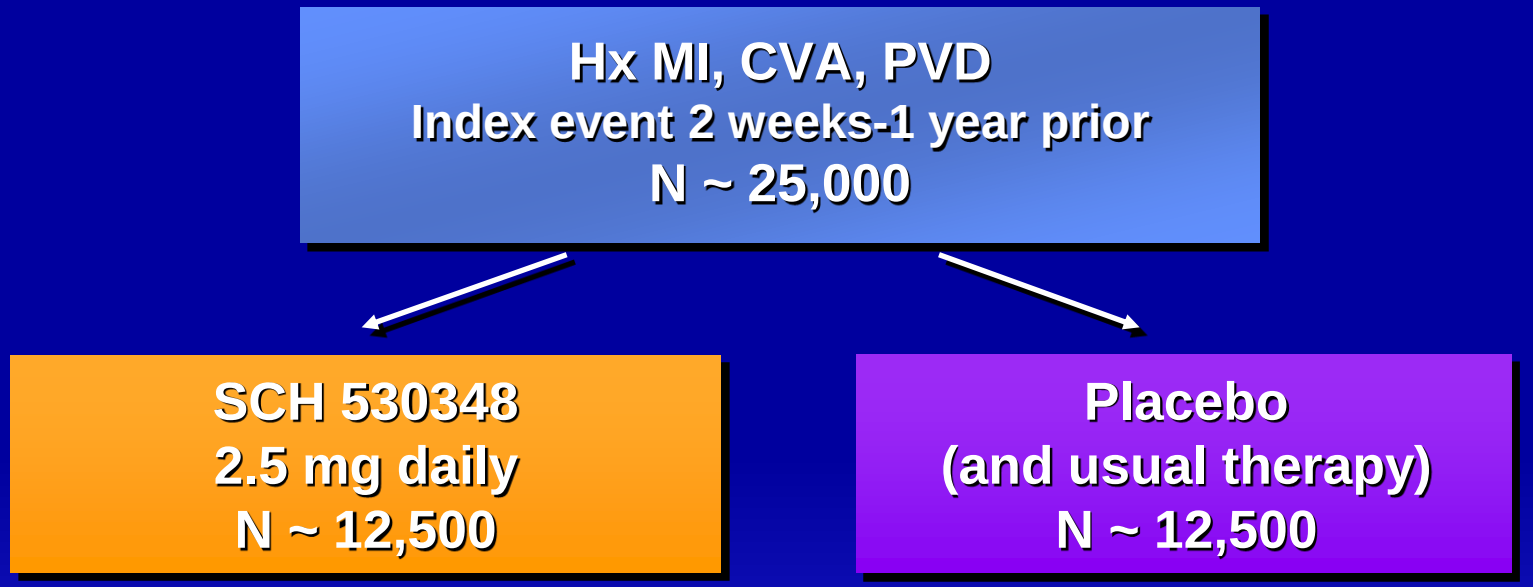


# Thrombin PAR Receptor



# TRA·2P

## *Thrombin Receptor Antagonist for 2º Prevention*



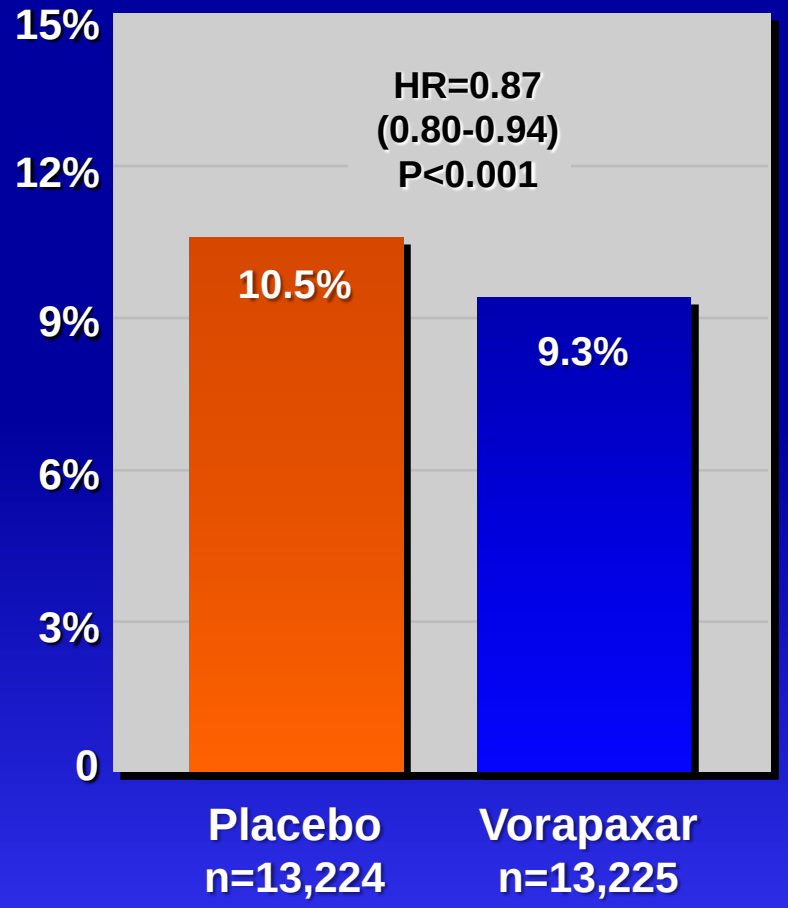

• 1-Year Cardiovascular Death, MI, Stroke, or Urgent Coronary Revascularization (2279 events) •

www.clinicaltrials.gov

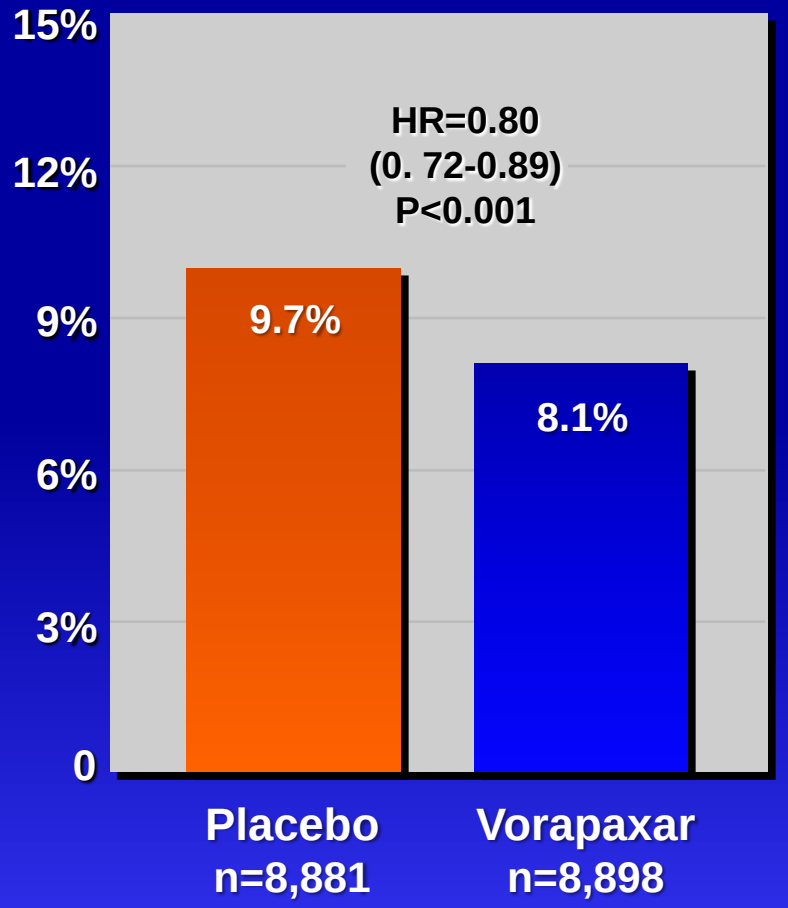
TRA 2°P TIMI 50

# TRA·2P

## All Groups Death, MI, CVA



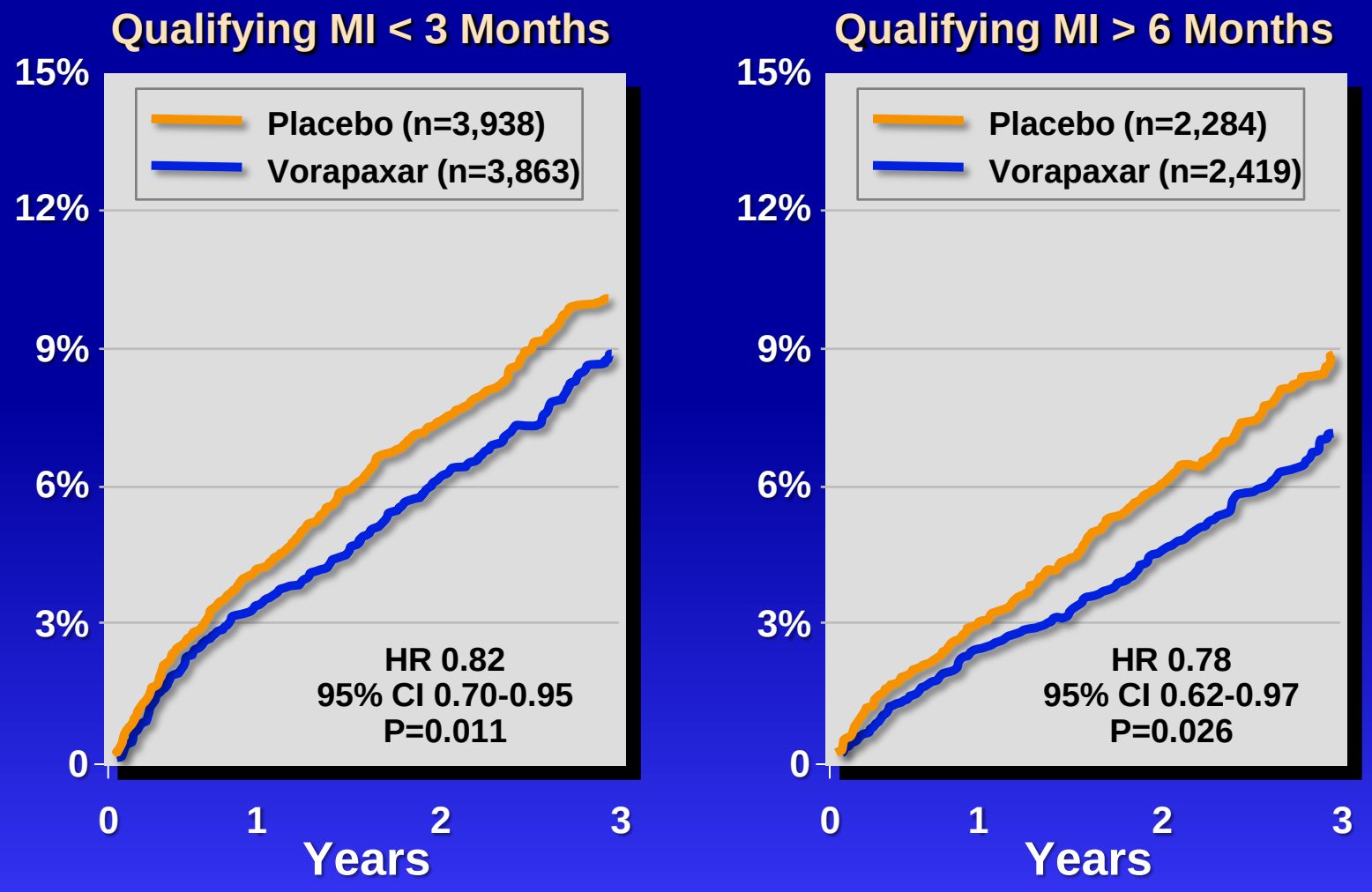

## MI Cohort Death, MI, CVA




Morrow DA et al. N Engl J Med 2012:366;1404-1413

# TRA·2P

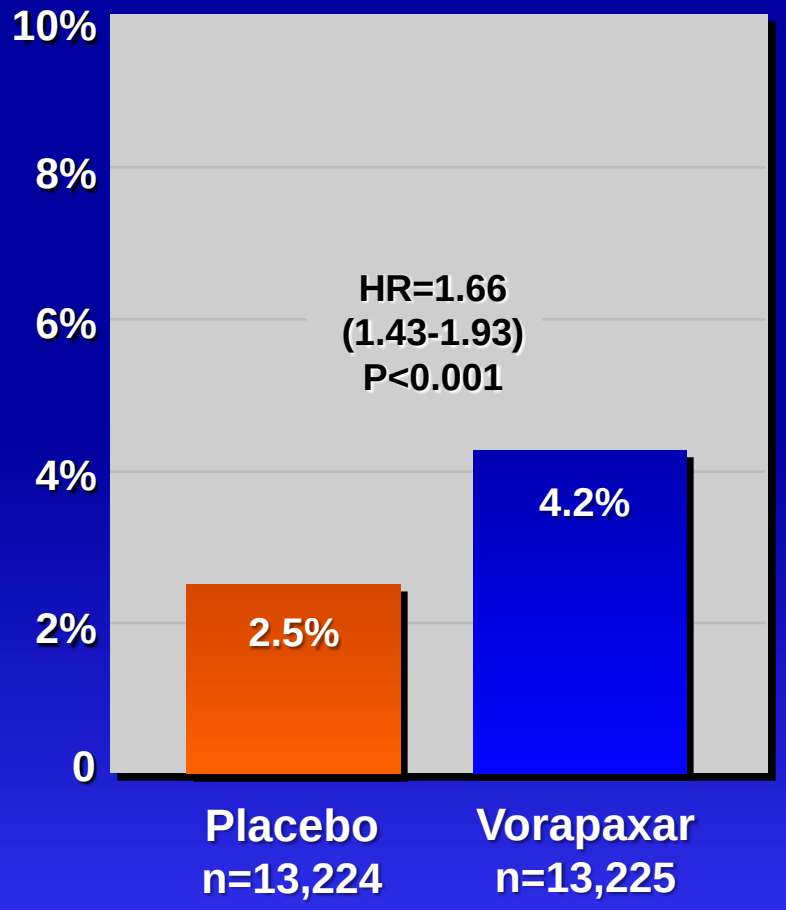
## Death, MI, CVA



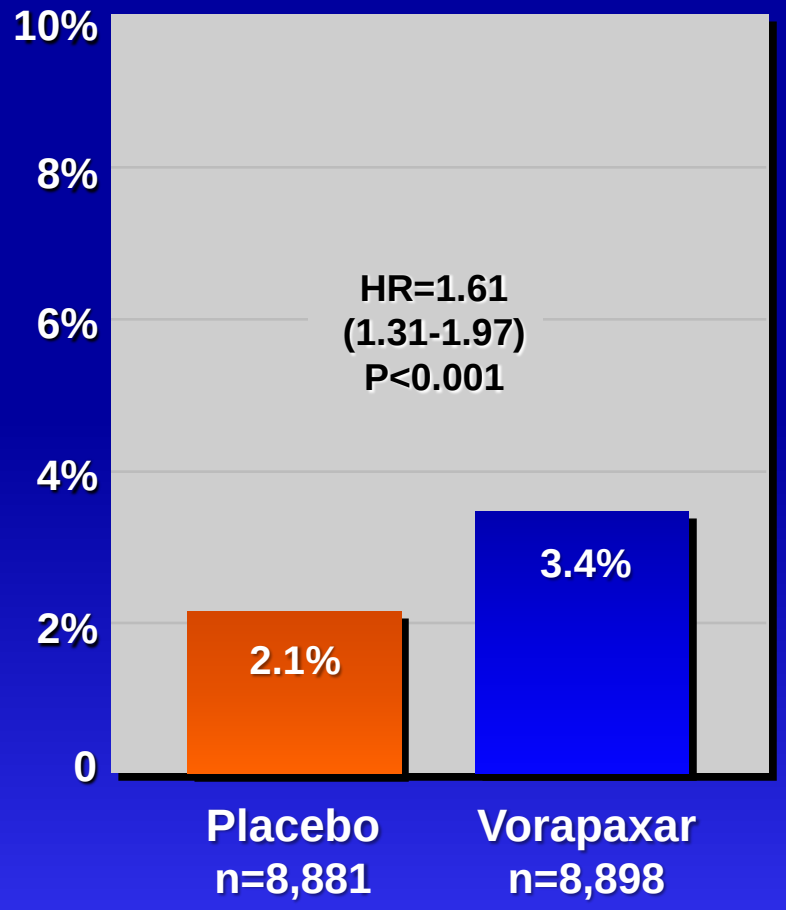

Scirica B et al. Lancet 2012;380:1317-24

# TRA·2P

## Overall GUSTO Mod/Sev Bleeding




## MI Cohort GUSTO Mod/Sev Bleeding




Morrow DA et al. N Engl J Med 2012:366;1404-1413

# Summary

- **PAR-1 receptor antagonists are novel compounds uncoupling platelet function from thrombin activity**
- **Vorapaxar was effective in TRA-2P for patients enrolled with MI (3 yr K-M)**
  - **Efficacy: 20% RRR; 1.6% ARR; NNT 62**
  - **Safety: 61% RRI; 1.3% ARI; NNH 76**
- **Vorapaxar benefit occurred irrespective of timing of prior MI, whether patients were receiving DAPT, and among all subgroups tested.**

# Danish Registry

**Bleeding After Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention**

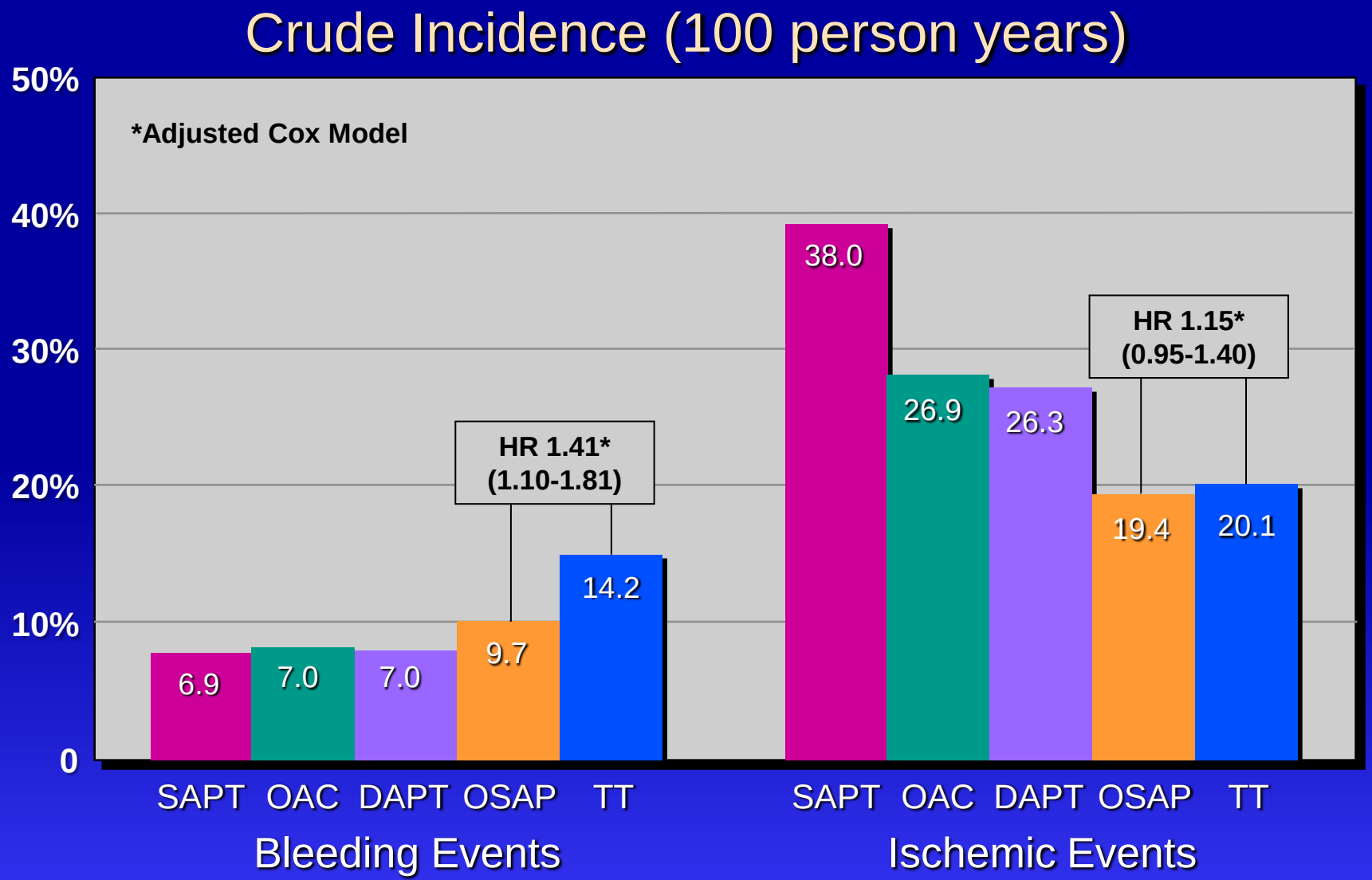
**A Nationwide Cohort Study**

Morten Lamberts, MD; Jonas Bjerring Olesen, MD; Martin Huth Ruwald, MD; Carolina Malta Hansen, MD; Deniz Karasoy, MD; Søren Lund Kristensen, MD; Lars Køber, MD, DMSc; Christian Torp-Pedersen, MD, DMSc; Gunnar Hilmar Gislason, MD, PhD; Morten Lock Hansen, MD, PhD

- Danish National Registry 2000-2009
- 11,480 subjects with AF and new MI or PCI
- Categorized as single, double, triple therapies
- Reviewed early and late (1 year) hospitalizations for bleeding and ischemic events

**Lamberts M et al. Circulation 2012;126:1185-1193**

# Danish Registry




Lamberts M et al. Circulation 2012;126:1185-1193

# WOEST

What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing

PCI
OAC required ≥1 year: AF, mechanical valve
N = 573

OAC + clopidogrel 75 mg daily

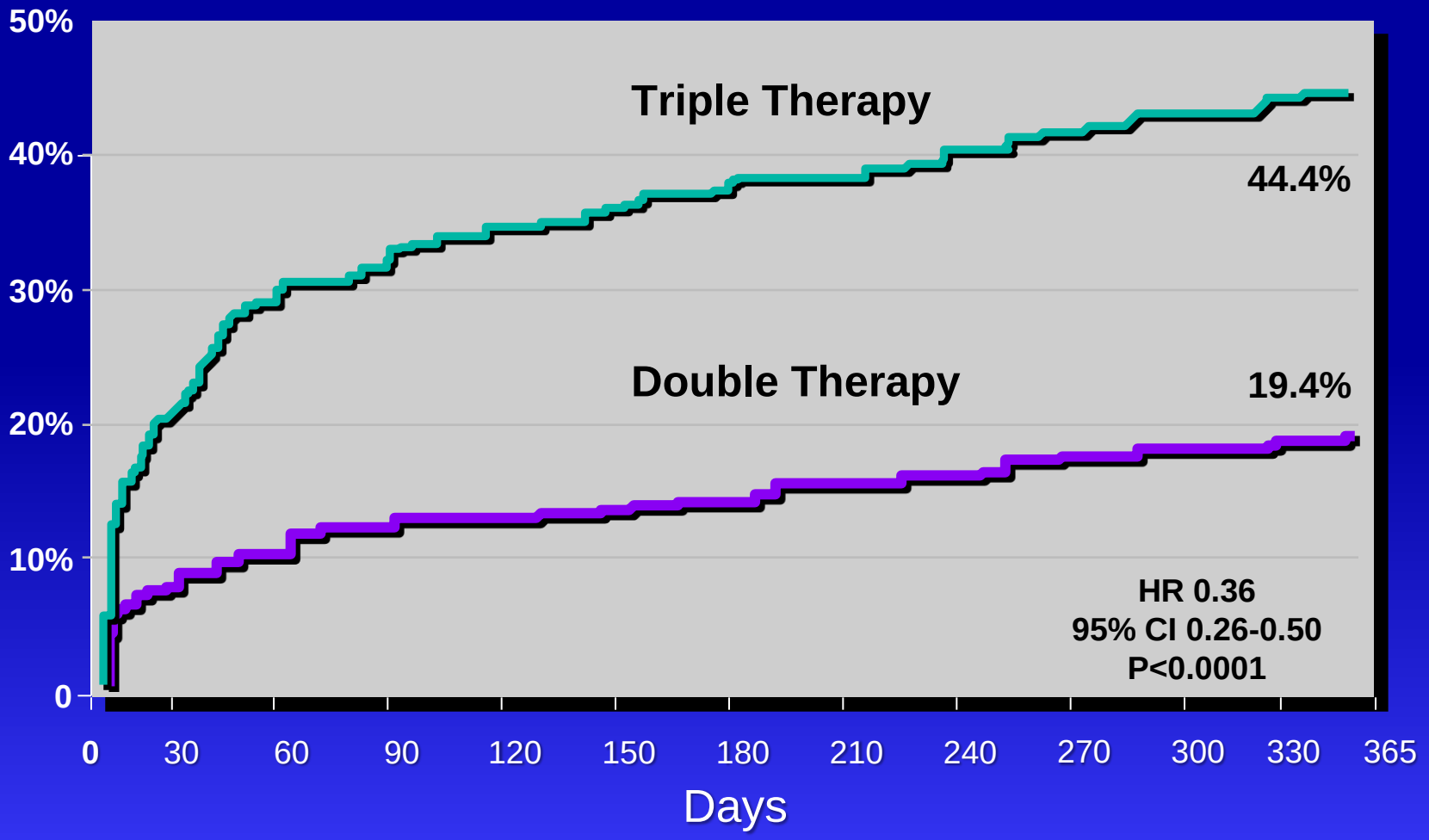
OAC + clopidogrel 75 mg + ASA 81 mg daily

• 1-Year Any TIMI Bleeding •

**Dewilde et al. Lancet 2013:381:1107-1115**

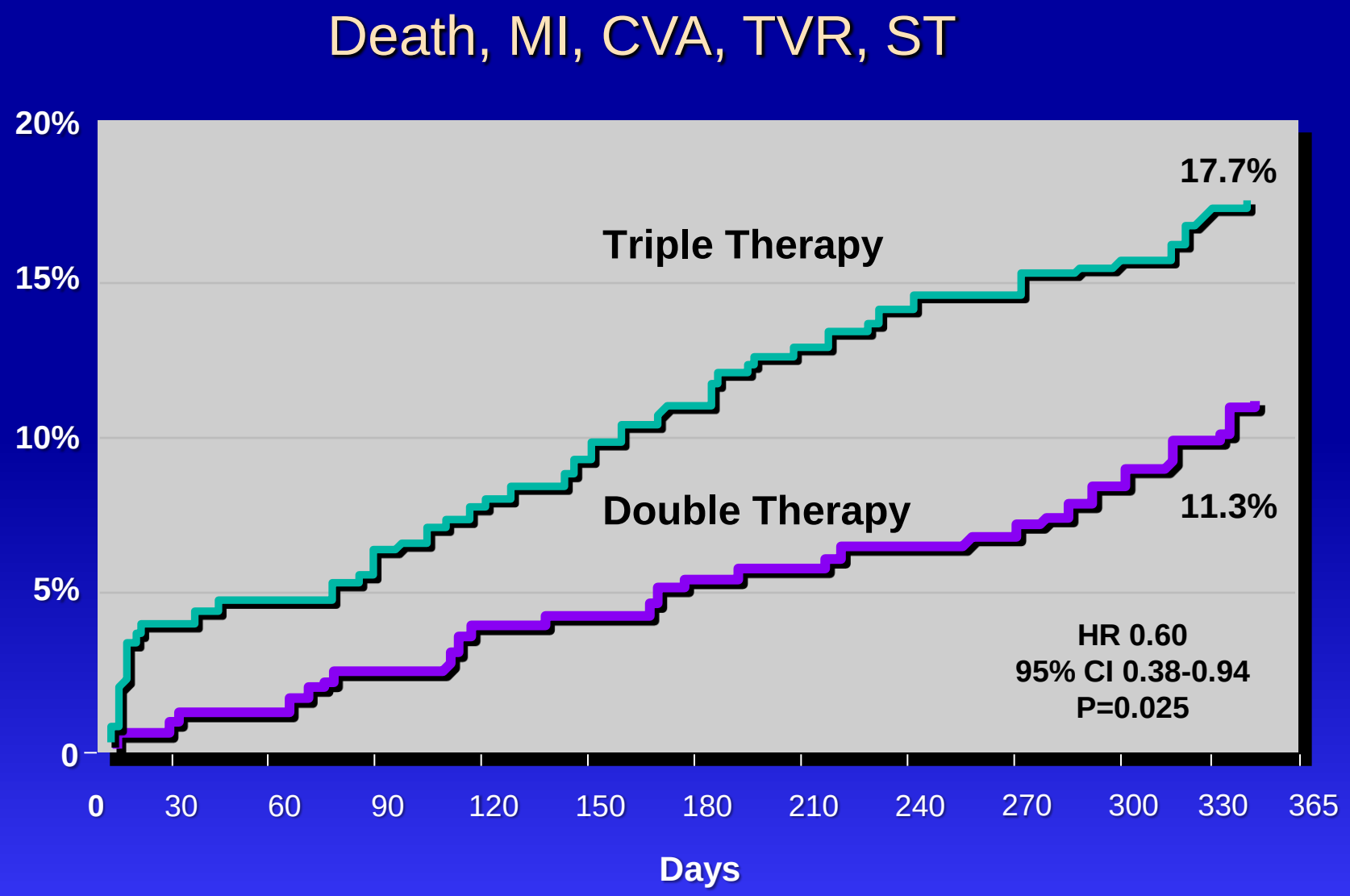
# WOEST

## Primary Outcome: Any TIMI Bleeding




Dewilde et al. Lancet 2013:381:1107-1115

# WOEST




Dewilde et al. Lancet 2013:381:1107-1115

# TWILIGHT

High-risk PCI (>65 yo, DM, CKD, or recent ACS)
3 months of DAPT (ticagrelor + ASA)
N = 9,000

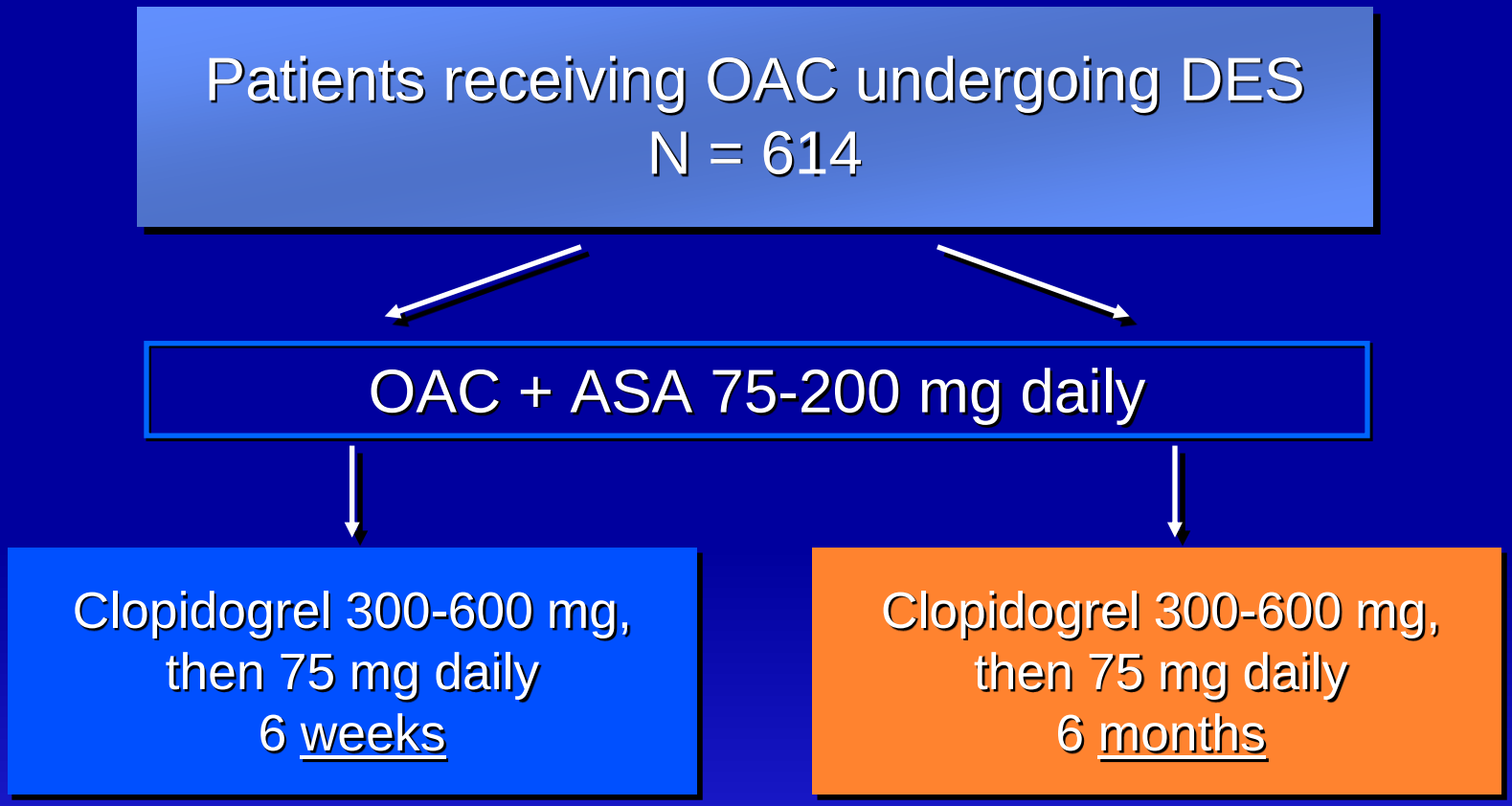
Ticagrelor 90 mg BID
+ ASA 81 mg daily

Ticagrelor 90 mg BID
+ Placebo daily

• 1-Year Cardiovascular Death, MI, Stroke •

www.clinicaltrials.gov

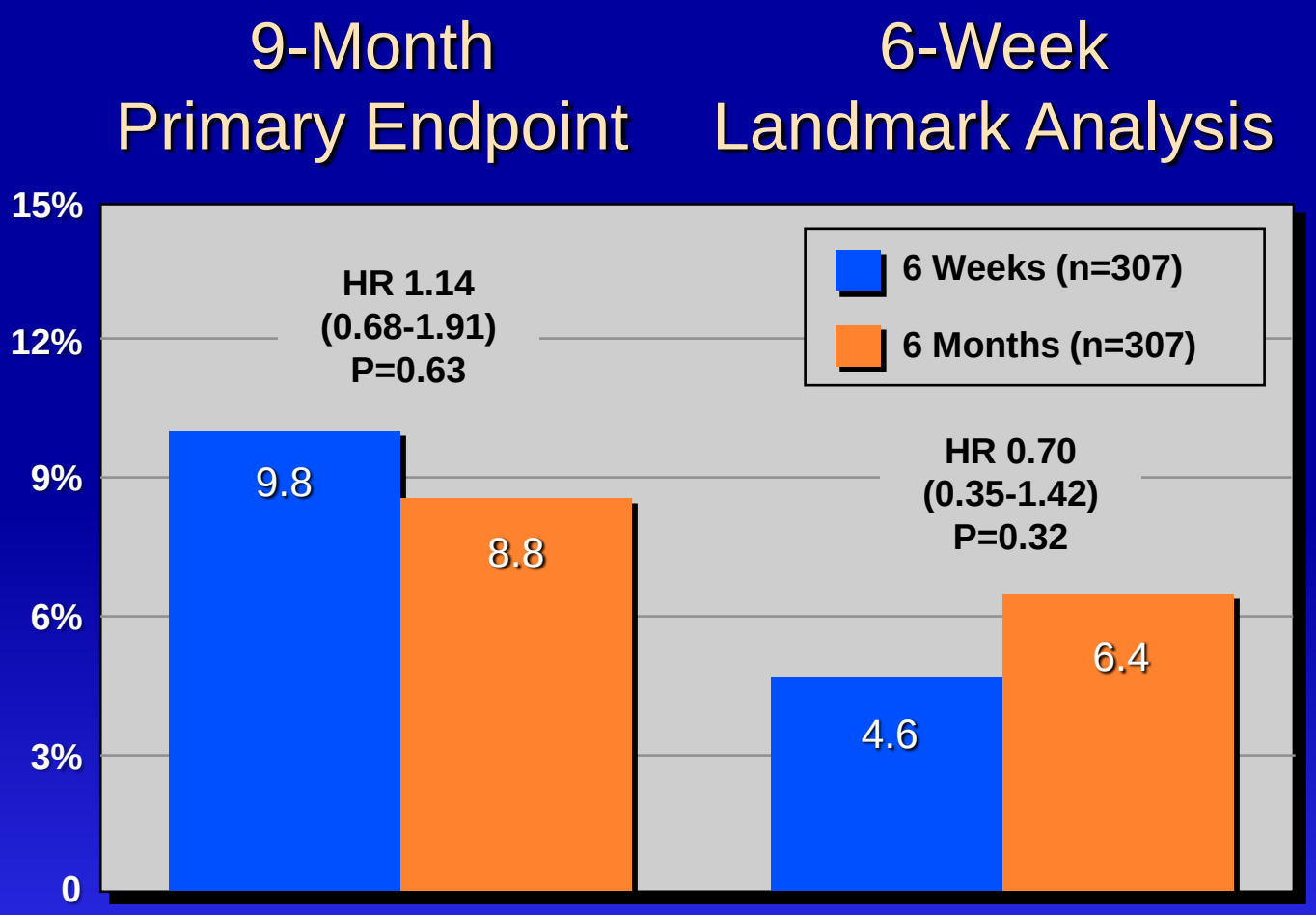
# ISAR-TRIPLE




• 9-Month Death, MI, CVA, ST, TIMI Major Bleeding •

Fiedler KA et al. J Am Coll Cardiol 2015:65:1619-1629

# ISAR-TRIPLE

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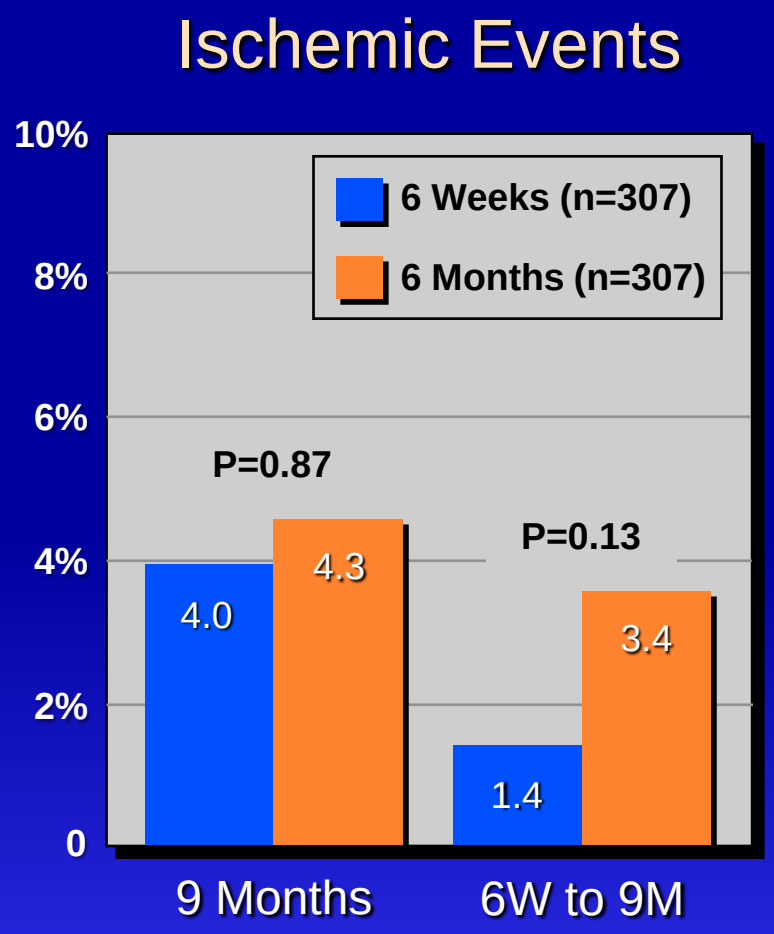
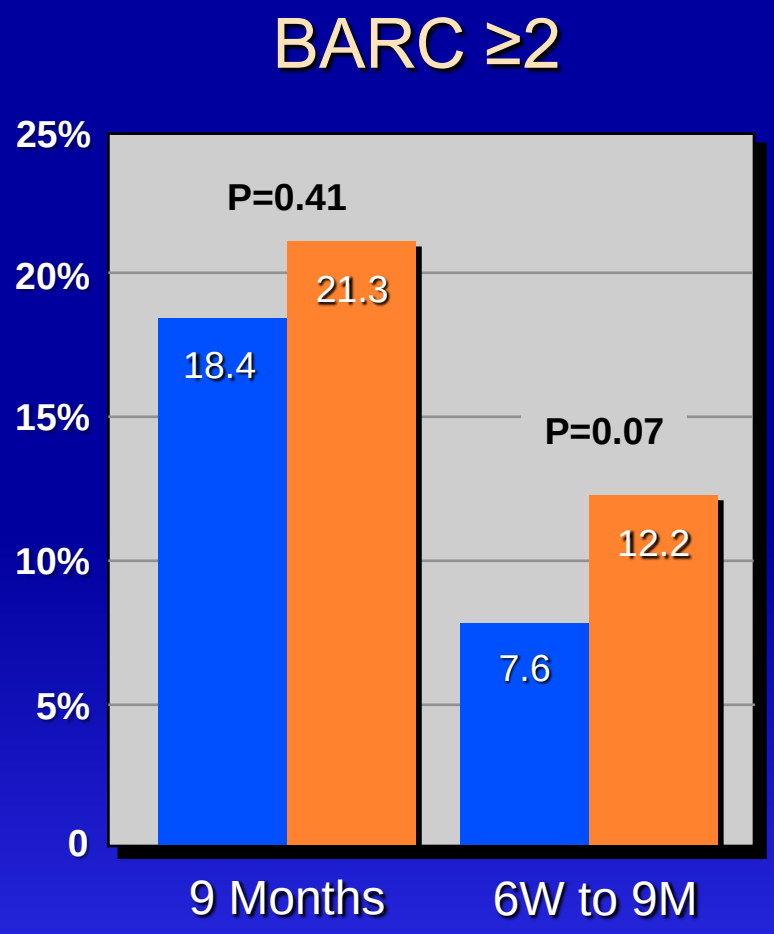



Fiedler KA et al. J Am Coll Cardiol 2015:65:1619-1629

Special Report

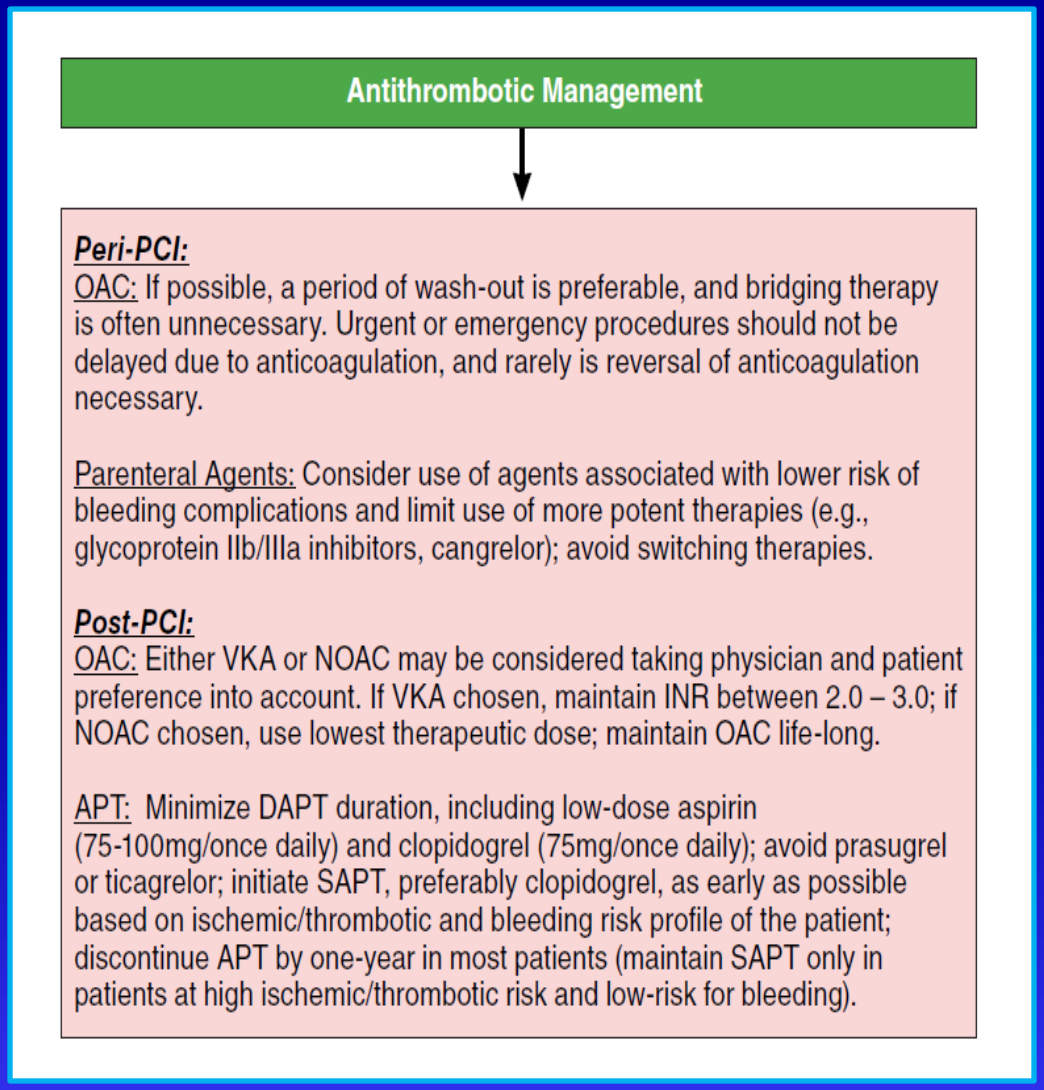
# Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

## A North American Perspective—2016 Update

Dominick J. Angiolillo, MD, PhD; Shaun G. Goodman, MD; Deepak L. Bhatt, MD, MPH; John W. Eikelboom, MD; Matthew J. Price, MD; David J. Moliterno, MD; Christopher P. Cannon, MD; Jean-Francois Tanguay, MD; Christopher B. Granger, MD; Laura Mauri, MD; David R. Holmes, MD; C. Michael Gibson, MD; David P. Faxon, MD

Angiolillo et al. Circ Cardiovasc Intv 2016

# Algorithm for AF-PCI Considerations



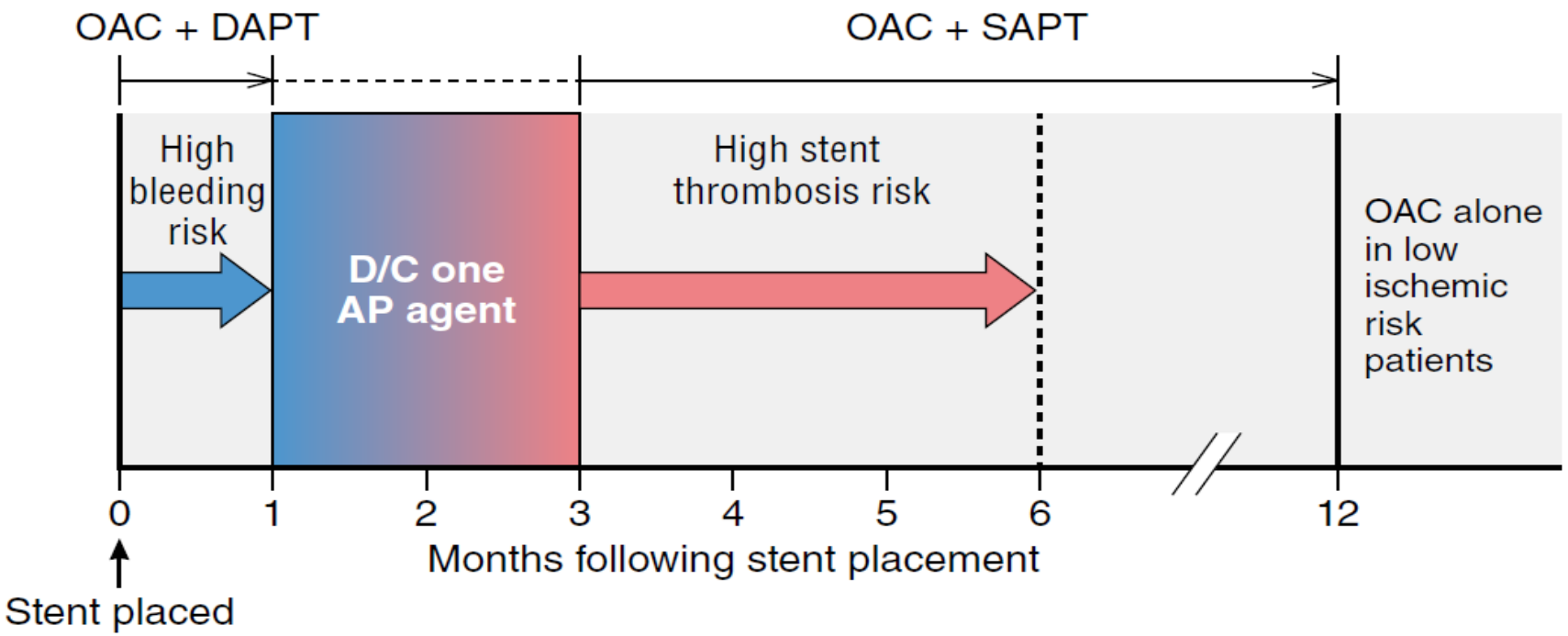

- Washout OAC
- INR ≤ 2.0 for radial
- INR ≤ 1.5 for femoral
- Withhold NOAC 24 hours (longer if SRI)
- Avoid polypharmacy anticoagulation (GPI)

- Low-dose ASA
- Lower INR target
- Shortened-course DAPT
- Lifelong OAC (± SAPT)

**Angiolillo et al. Circ Cardiovasc Intv 2016**

# Antithrombotic Management

## Recommended Algorithm

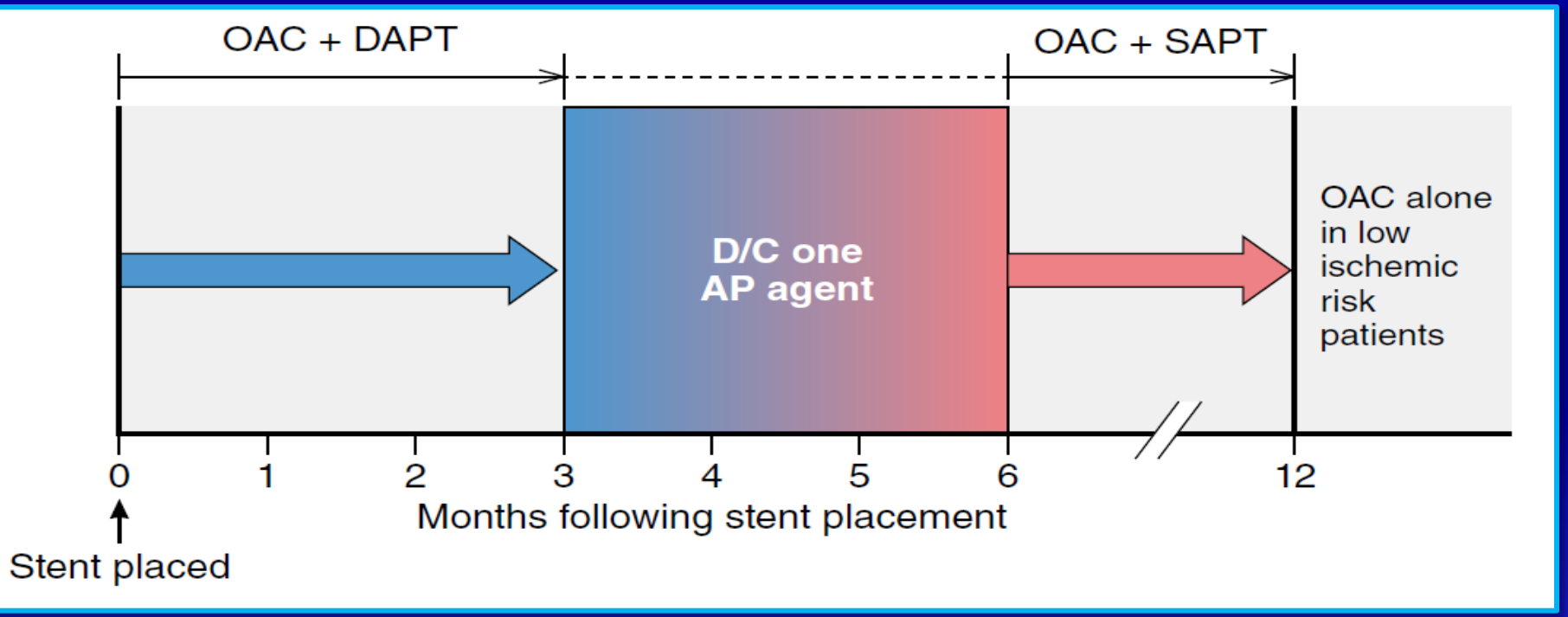



**Discontinuation of one antiplatelet agent should be considered 1-3 months after PCI, this may occur sooner (including immediately after PCI) or later (but not beyond 6 months) according to the ischemic/thrombotic and bleeding risk profiles of the patient.**

**Angiolillo et al. Circ Cardiovasc Intv 2016**

# Antithrombotic Management

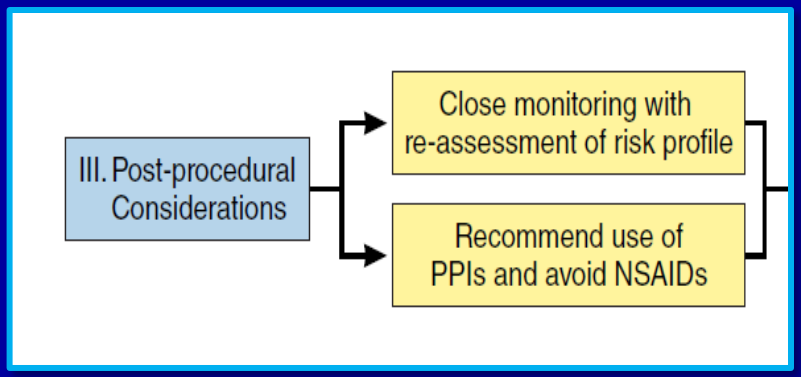
## High Thrombotic / Low Bleeding Risk




**Shorter (e.g., 3 month) and longer (e.g., 6 months) DAPT duration should be considered in patients treated with BMS and DES, respectively.**

**Angiolillo et al. Circ Cardiovasc Intv 2016**

# Algorithm for AF-PCI Considerations



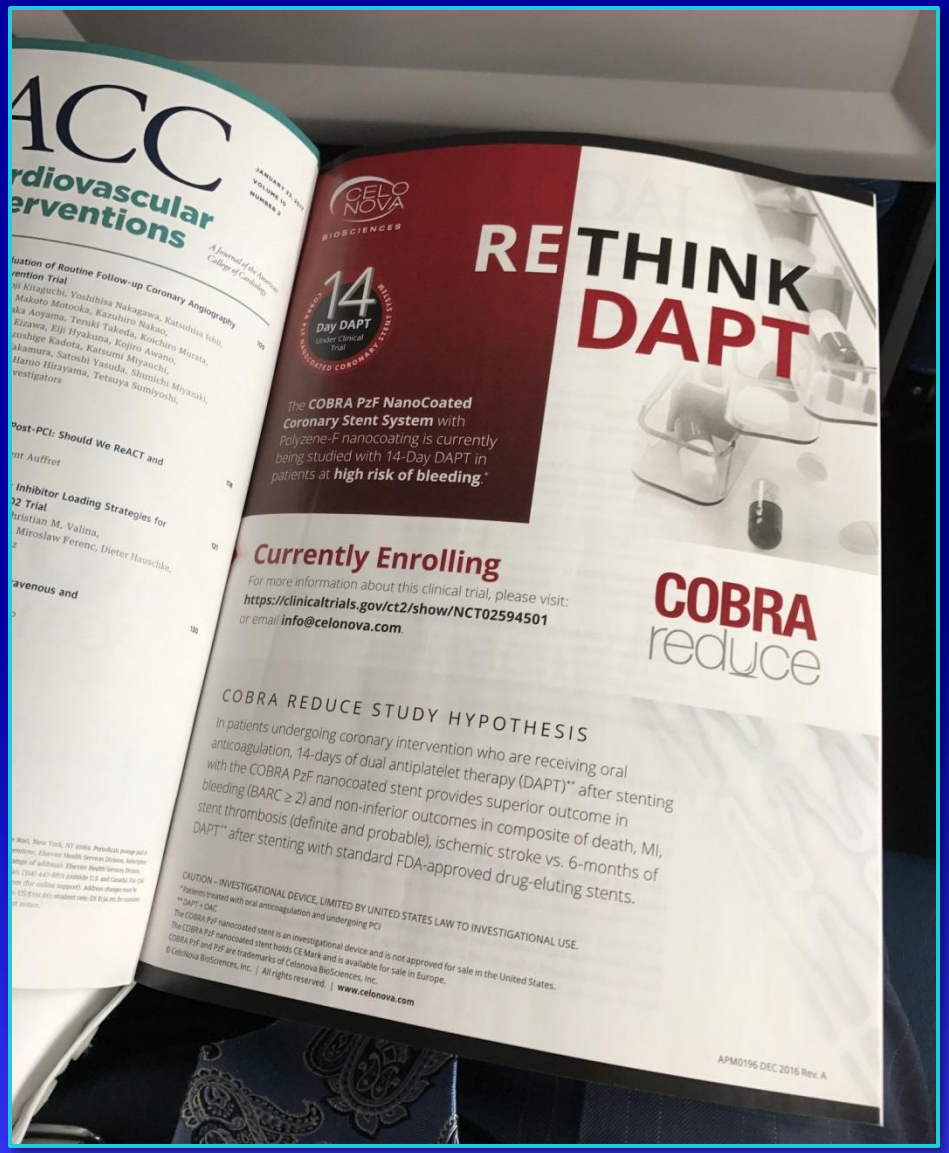

- More frequent follow-up than AF alone or ACS alone or PCI alone
- Specific guidance for patient and PCP
- Choice, extent, duration of antithrombotic therapy may change for patient or guidelines
- At 6-12 months post-PCI need to reconsider antiplatelet risk-benefit

**Angiolillo et al. Circ Cardiovasc Intv 2016**

# Ongoing Clinical Trials

| | PIONEER AF-PCI | REDUAL-PCI | AUGUSTUS | ENTRUST AF-PCI |
|---|---|---|---|---|
| NOAC | Rivaroxaban | Dabigatran | Apixaban | Edoxaban |
| Clinicaltrials.gov identifier | NCT01830543 | NCT02164864 | NCT02415400 | NCT02866175 |
| Trial status | Enrollment completed | Enrolling | Enrolling | Planning |
| Study type | Open-label, randomized | Open-label, randomized | Open-label (apixaban vs warfarin) and blinded (aspirin vs placebo), randomized | Open-label, randomized |
| Patients | 2169 patients with AF who undergo a PCI with stenting | 2500 patients with AF undergoing PCI with stenting (elective or post ACS) | 4600 patients with AF undergoing PCI with stenting or an ACS | 1500 patients with AF after successful PCI with stenting (elective or post ACS) |

# NanoCoated Stents




*** Not approved for sale in the USA. Investigational only.**

**Clinicaltrials.gov/NCT02594501**

# COBRA

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VOL. 10, NO. 2, 2017

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http://dx.doi.org/10.1016/j.jcin.2016.10.037

## 9-Month Clinical and Angiographic Outcomes of the COBRA Polyzene-F NanoCoated Coronary Stent System

Donald E. Cutlip, MD,[a] Kirk N. Garratt, MD,[b] Victor Novack, MD, PhD,[c] Mark Barakat, MD,[d] Perwaiz Meraj, MD,[e] Luc Maillard, MD, PhD,[f] Andrejs Erglis, MD,[g] Rajiv Jauhar, MD,[e] Jeffrey J. Popma, MD,[a] Robert Stoler, MD,[h] Sigmund Silber, MD,[i] for the PzF SHIELD Trial Investigators

Clinicaltrials.gov/NCT02594501

# Summary

- Over the first year, stent-associated thrombosis occurs in 1-2% of patients depending on stent and clinical acuity
- More potent or polypharmacy has reduced the incidence of stent-associated thrombosis by 1%
- Over the first year, stent-associated major bleeding occurs in 2-3% of patients
- More potent or polypharmacy has increased the incidence of stent-associated bleeding by 1%

# Summary

- ~5% of ACS patients have “pre-existing” AF
- ACS patients are at risk for AF because of shared risk factors and changes associated with AMI
- Triple therapy is associated with a 40% increased risk of clinically significant bleeding
- Small RCT suggest Dual Therapy with OAC and SAPT (clopidogrel) at least as effective and safer
- Many ongoing or planned RCT to better understand polypharmacy best practices and how NOACs and newer $P2Y_{12}$ agents fit in
- For longer-term care, monotherapy vs “safer” dual