

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)

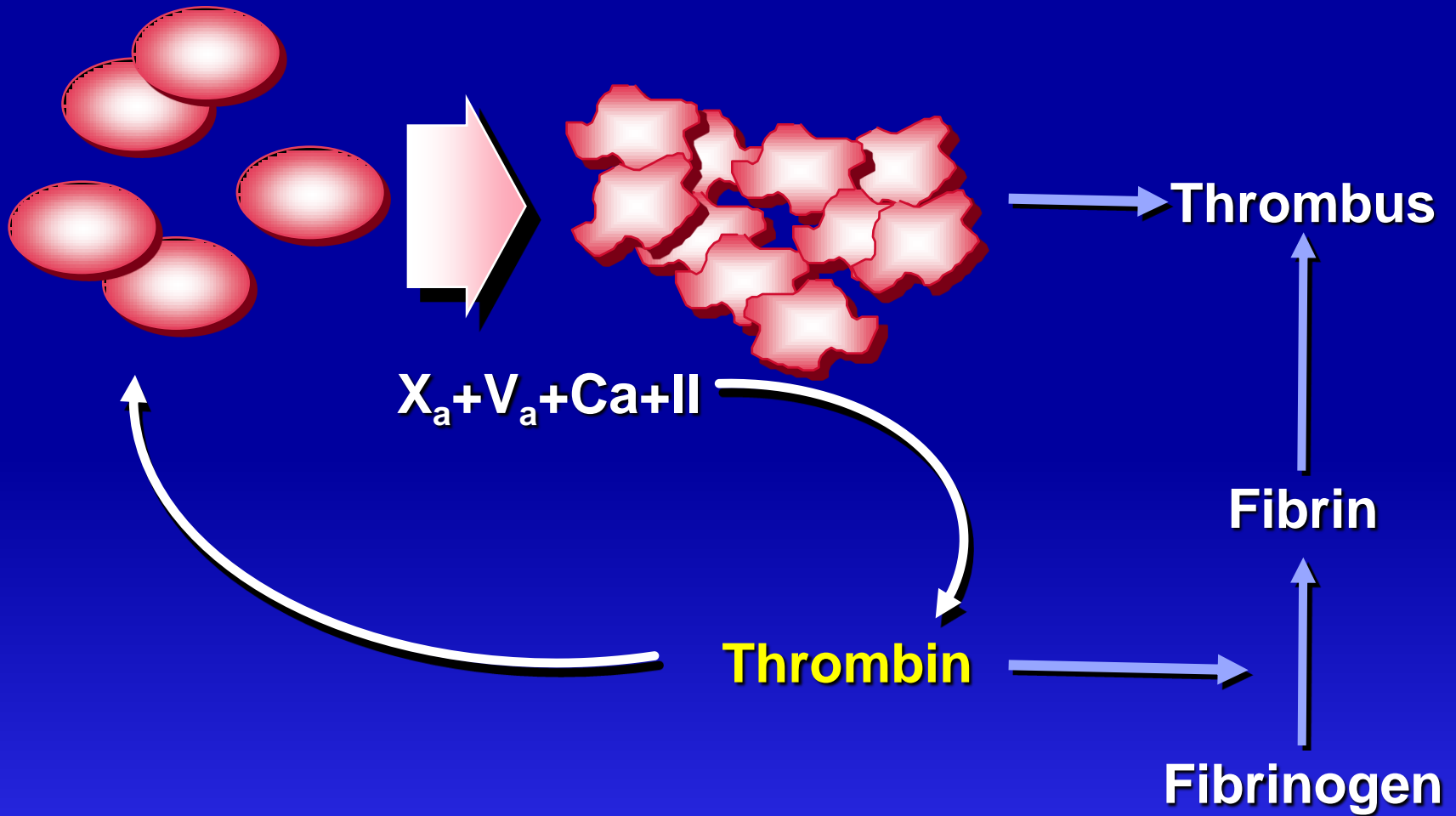
Options to Improve Antithrombotic Rx

- 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)

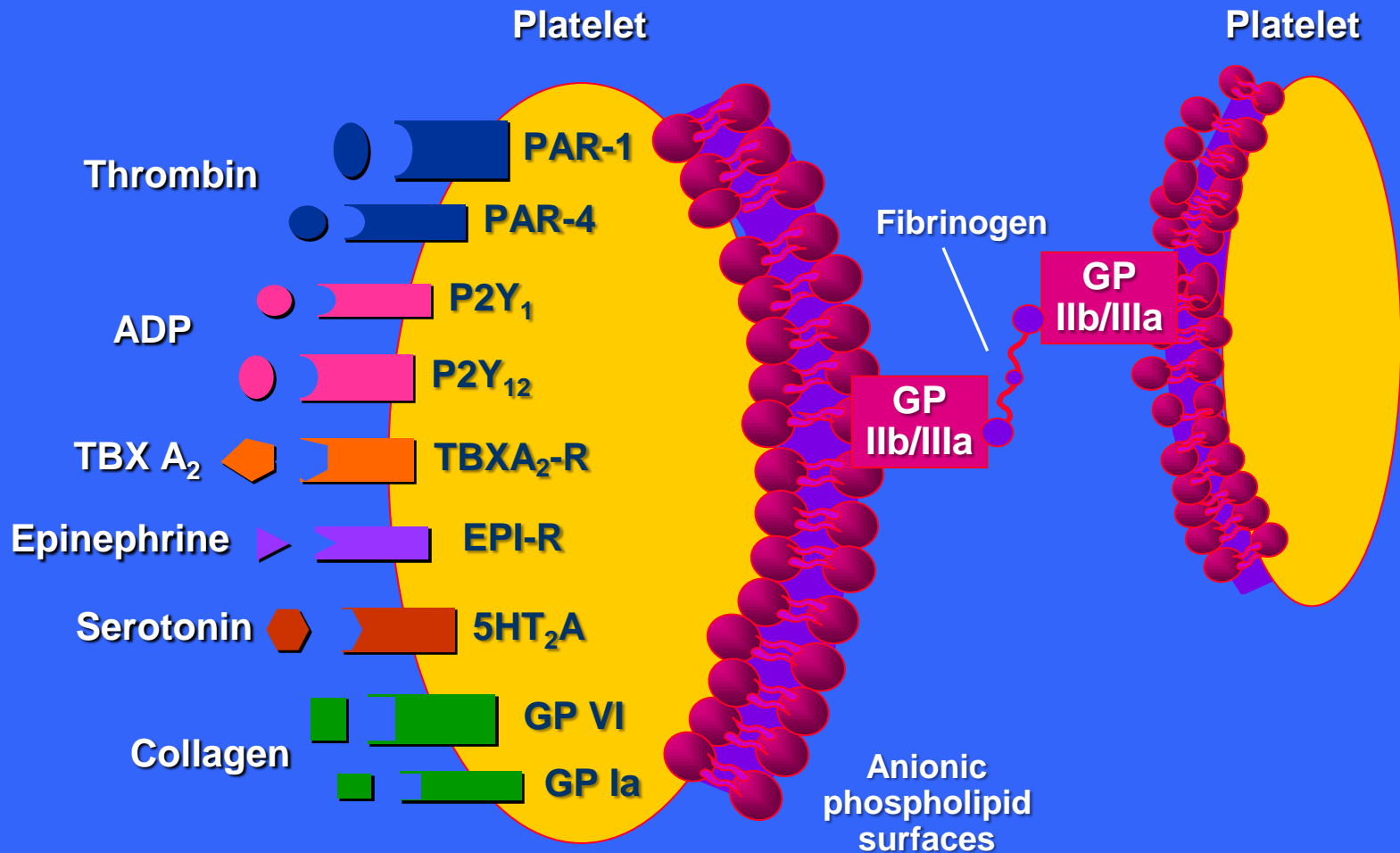
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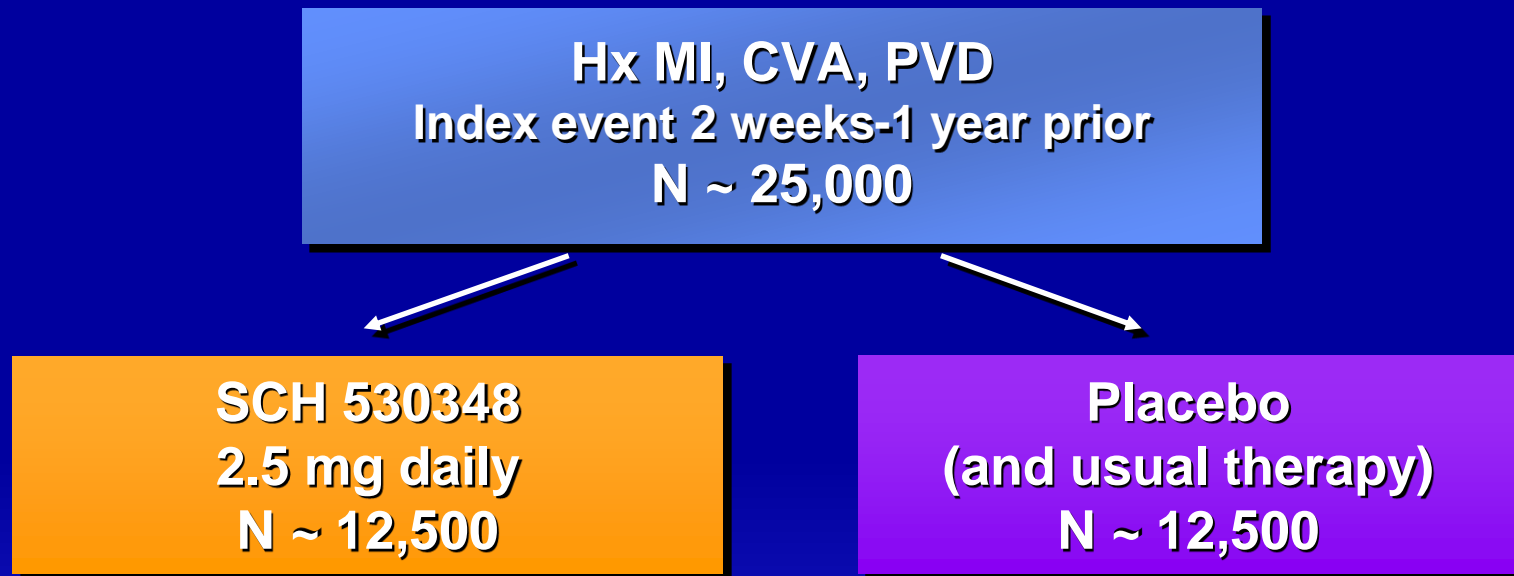
Platelet-Thrombin Interaction



Thrombin PAR Receptor



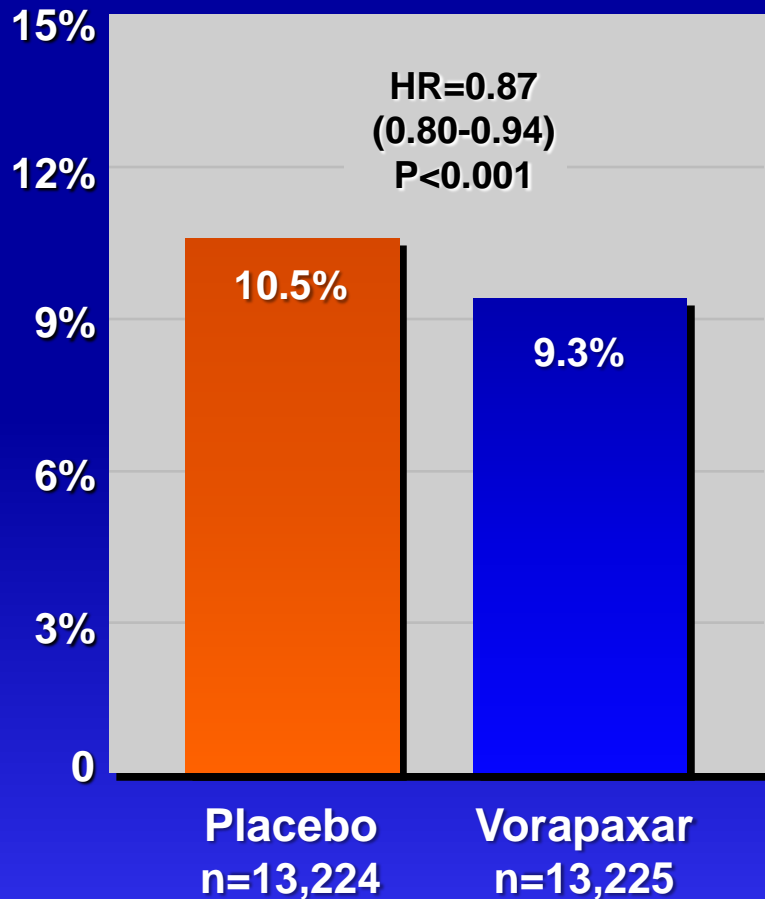
Thrombin Receptor Antagonist for 2^o Prevention



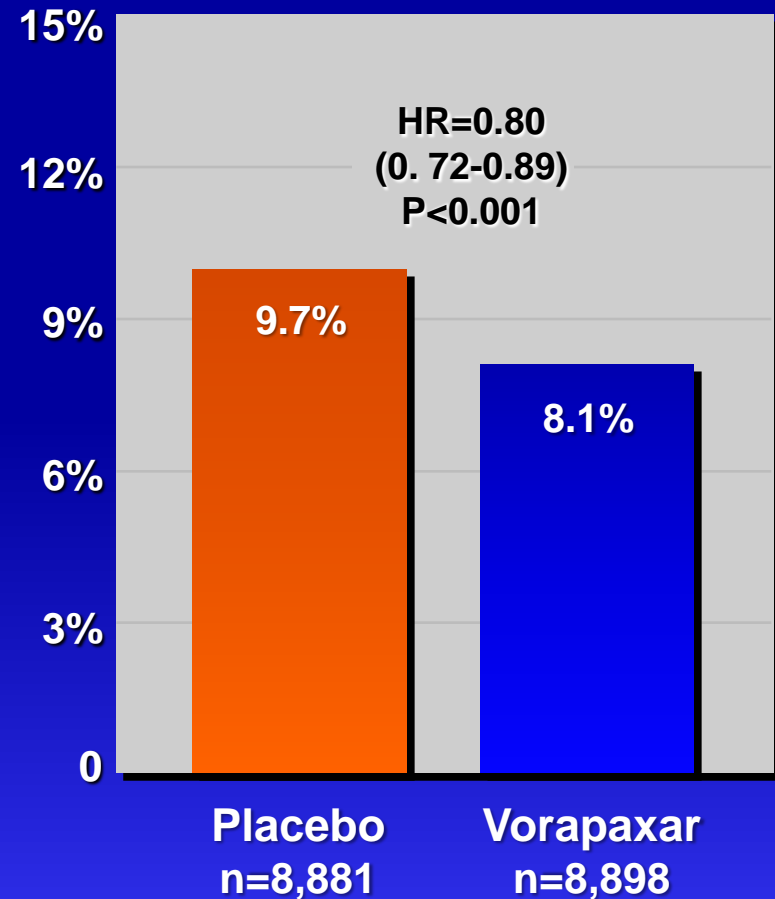
• 1-Year Cardiovascular Death, MI, Stroke, or Urgent Coronary Revascularization (2279 events) •

TRA·2P

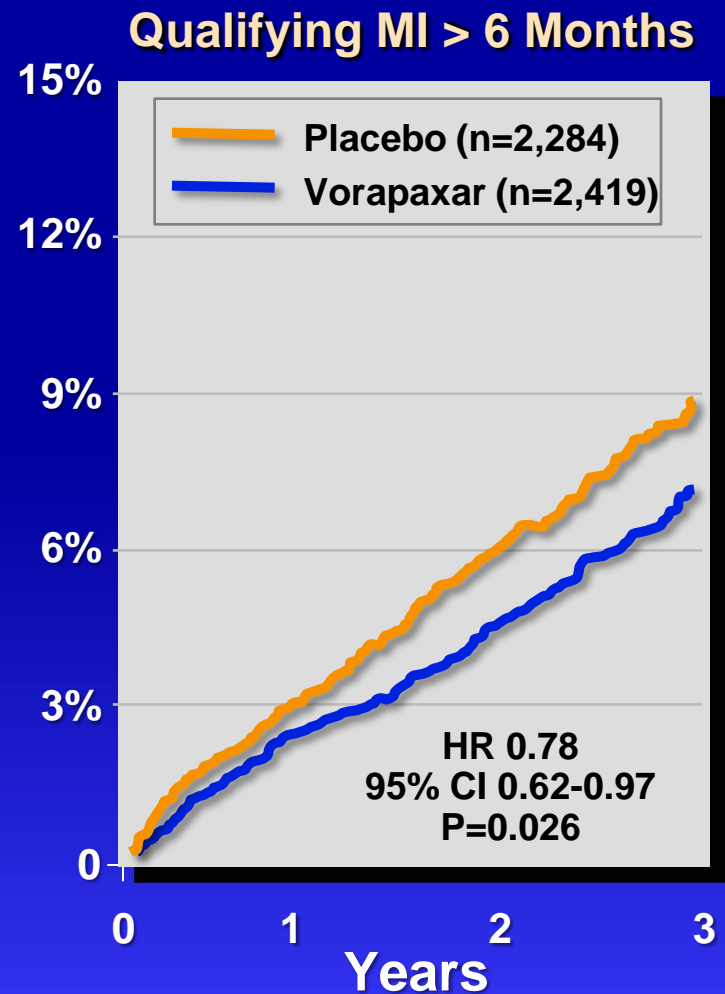
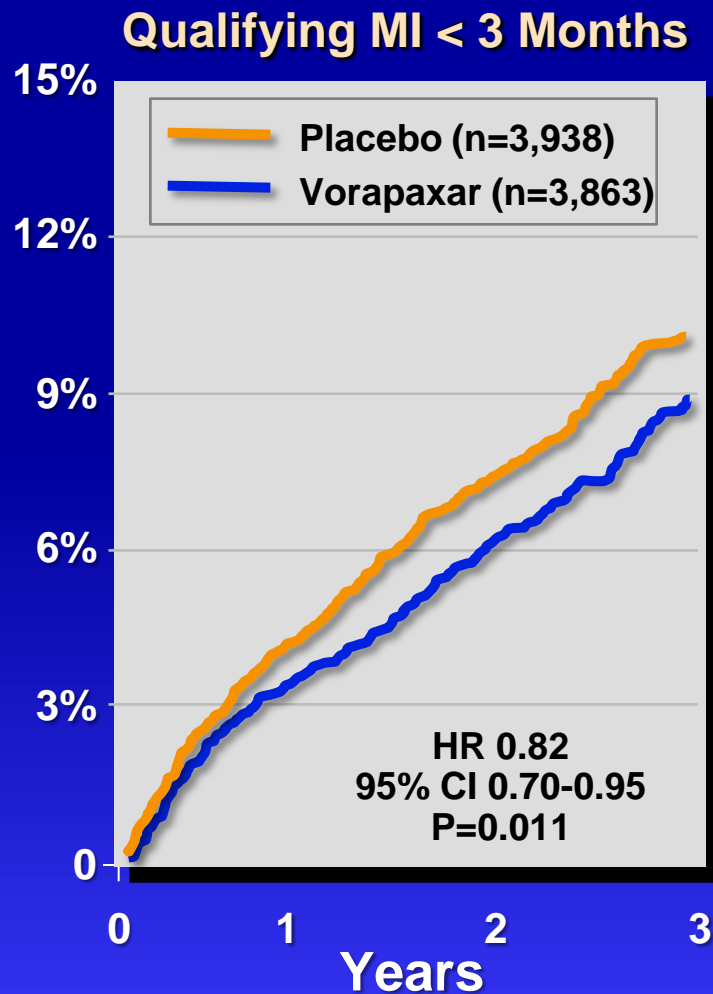
All Groups Death, MI, CVA



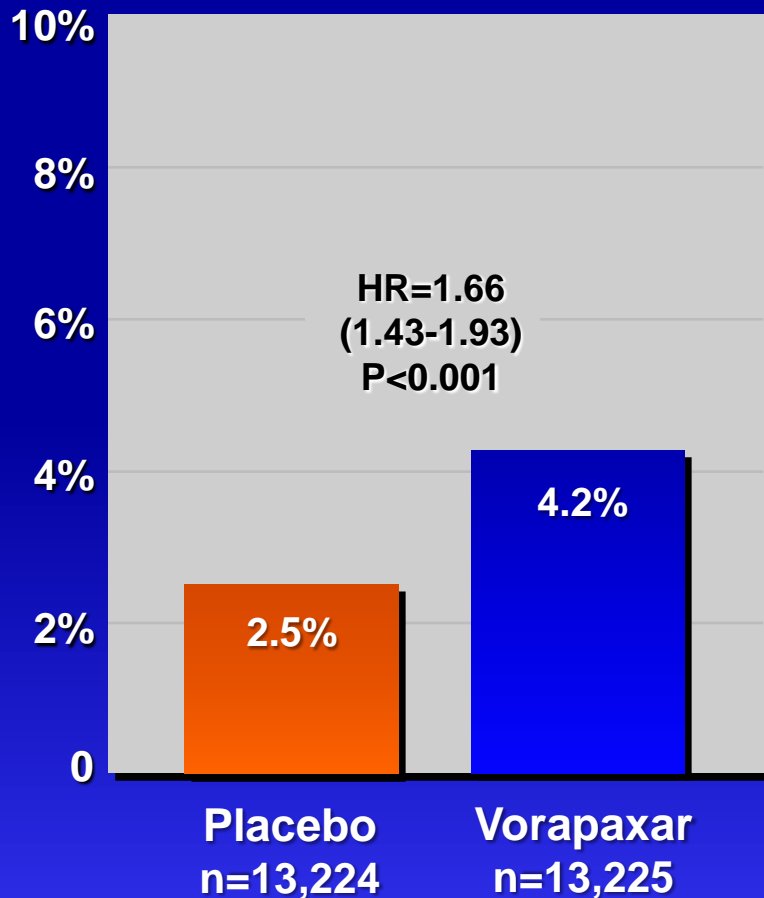
MI Cohort Death, MI, CVA



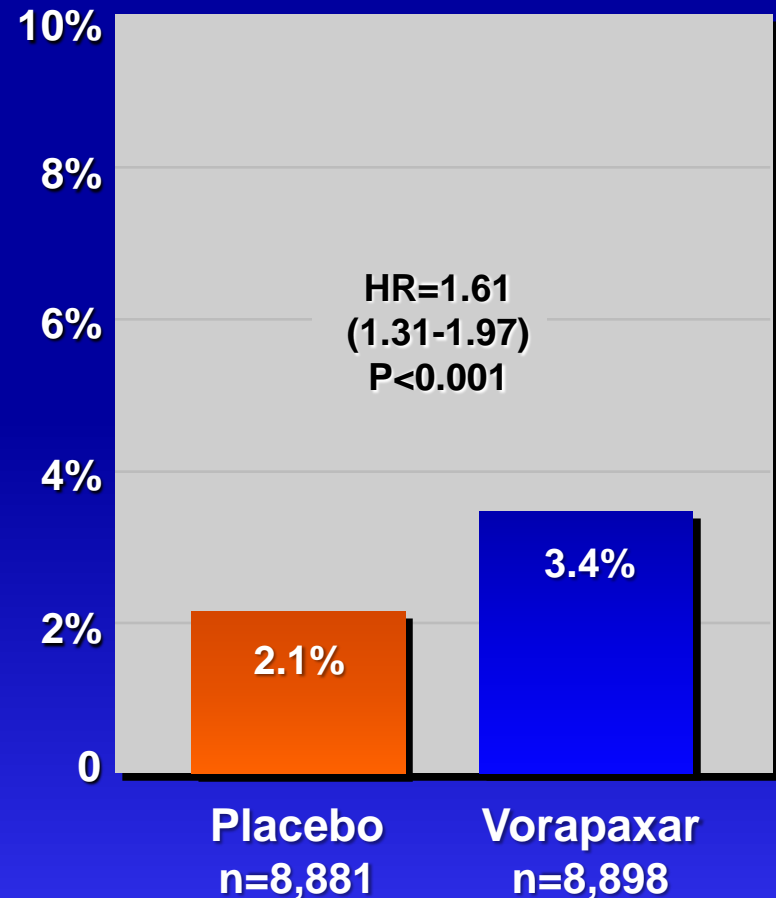
Death, MI, CVA



Overall GUSTO Mod/Sev Bleeding



MI Cohort GUSTO Mod/Sev Bleeding



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

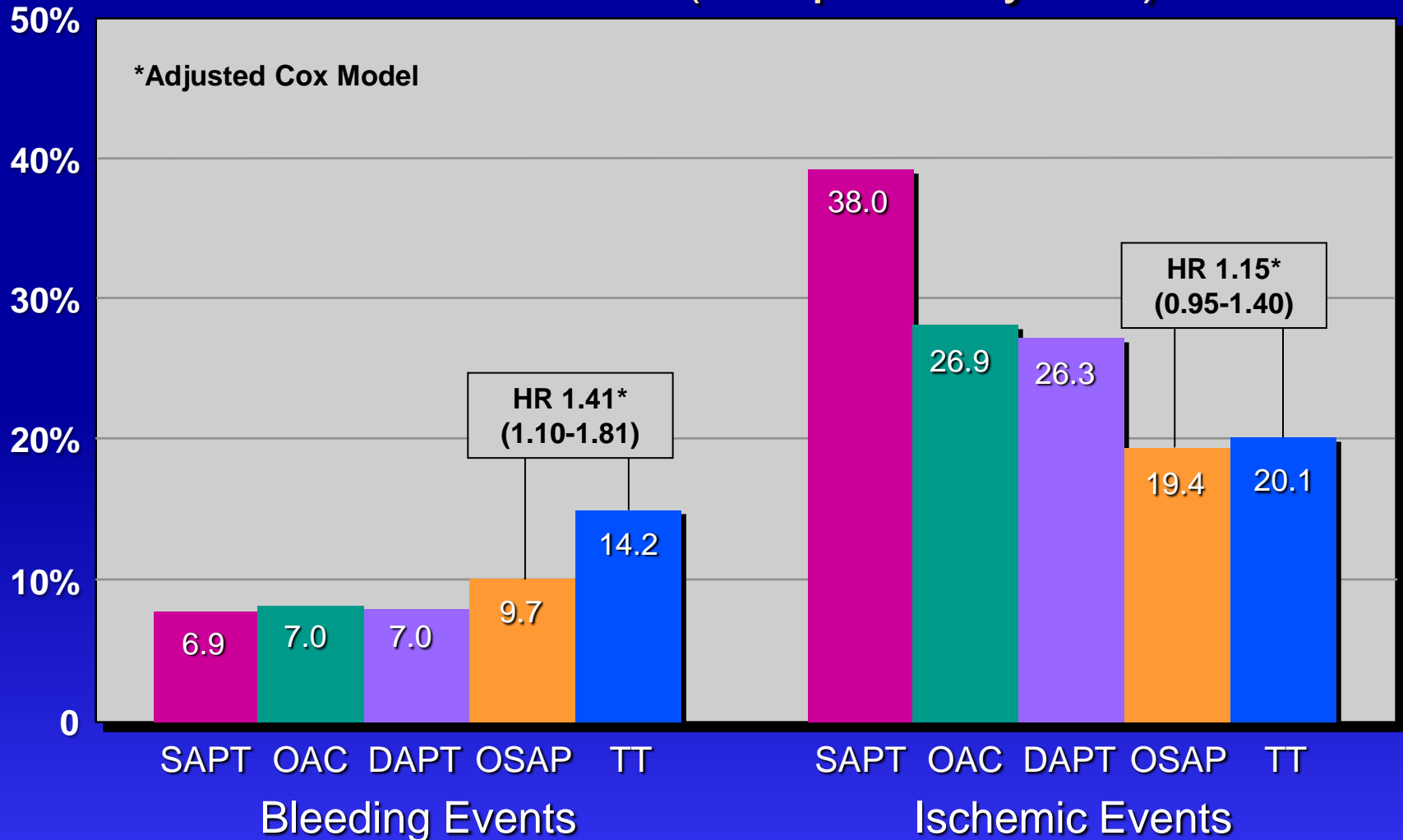
Bleeding After Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention A Nationwide Cohort Study

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

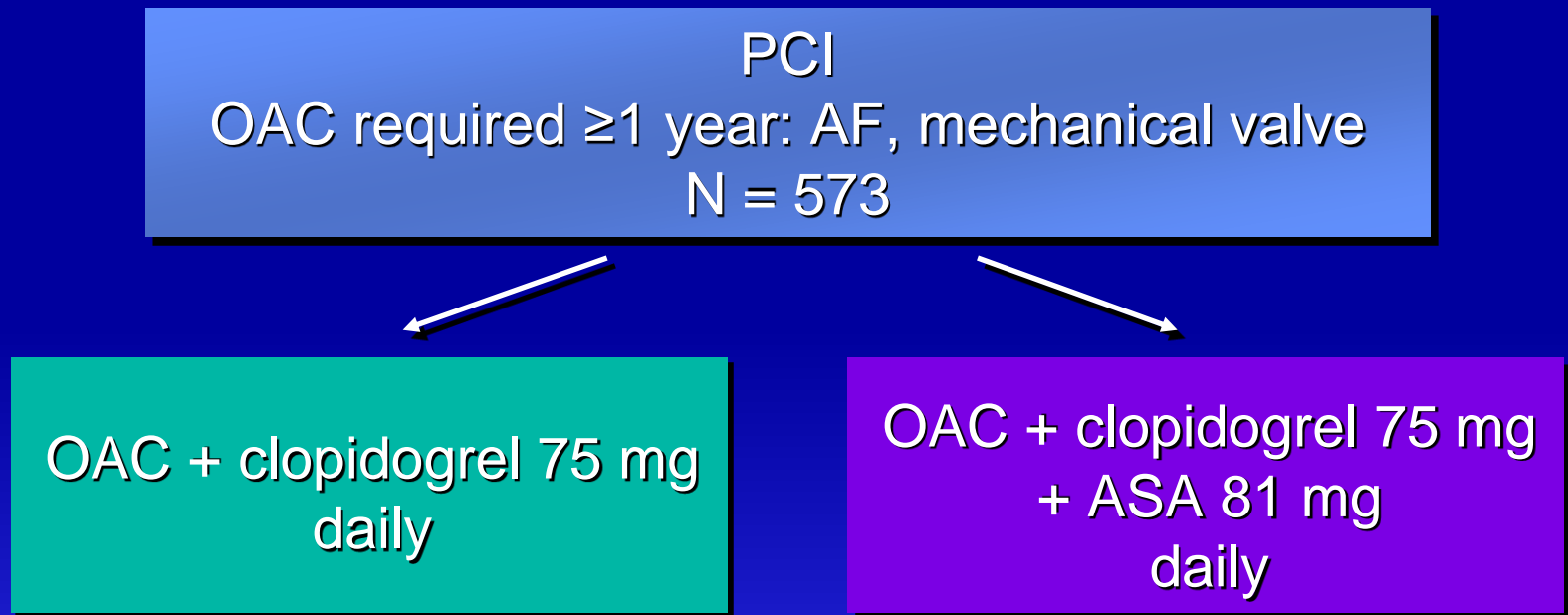
Danish Registry

Crude Incidence (100 person years)



WOEST

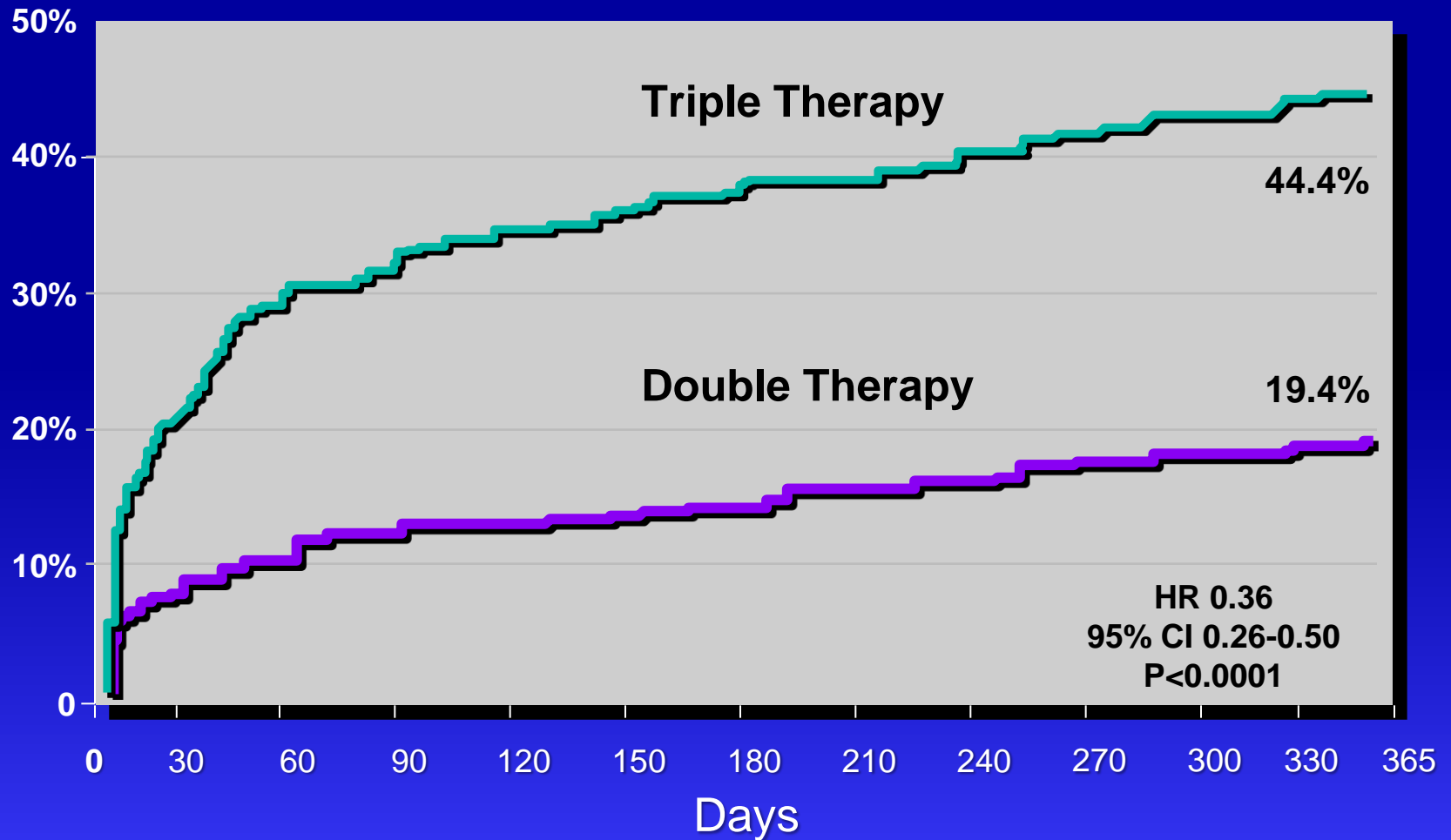
What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting



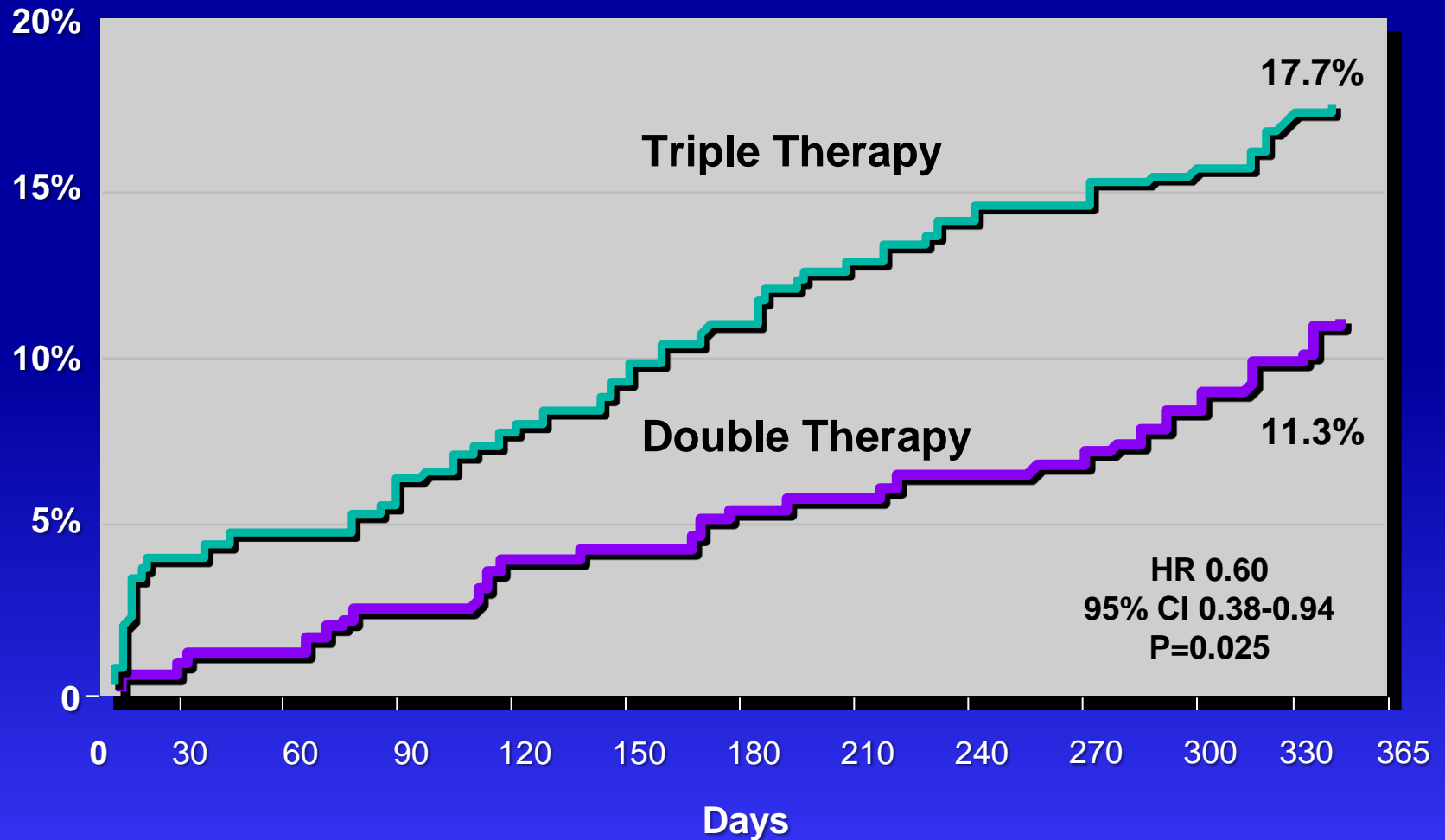
• 1-Year Any TIMI Bleeding •

WOEST

Primary Outcome: Any TIMI Bleeding



Death, MI, CVA, TVR, ST



TWILIGHT

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

```
graph TD; A[High-risk PCI (>65 yo, DM, CKD, or recent ACS)  
3 months of DAPT (ticagrelor + ASA)  
N = 9,000] --> B[Ticagrelor 90 mg BID  
+ ASA 81 mg daily]; A --> C[Ticagrelor 90 mg BID  
+ Placebo daily];
```

Ticagrelor 90 mg BID
+ ASA 81 mg daily

Ticagrelor 90 mg BID
+ Placebo daily

• 1-Year Cardiovascular Death, MI, Stroke •

ISAR-TRIPLE

Patients receiving OAC undergoing DES
N = 614

```
graph TD; A[Patients receiving OAC undergoing DES  
N = 614] --> B[OAC + ASA 75-200 mg daily]; B --> C[Clopidogrel 300-600 mg,  
then 75 mg daily  
6 weeks]; B --> D[Clopidogrel 300-600 mg,  
then 75 mg daily  
6 months]; C --> E[• 9-Month Death, MI, CVA, ST, TIMI Major Bleeding •]; D --> E;
```

OAC + ASA 75-200 mg daily

Clopidogrel 300-600 mg,
then 75 mg daily
6 weeks

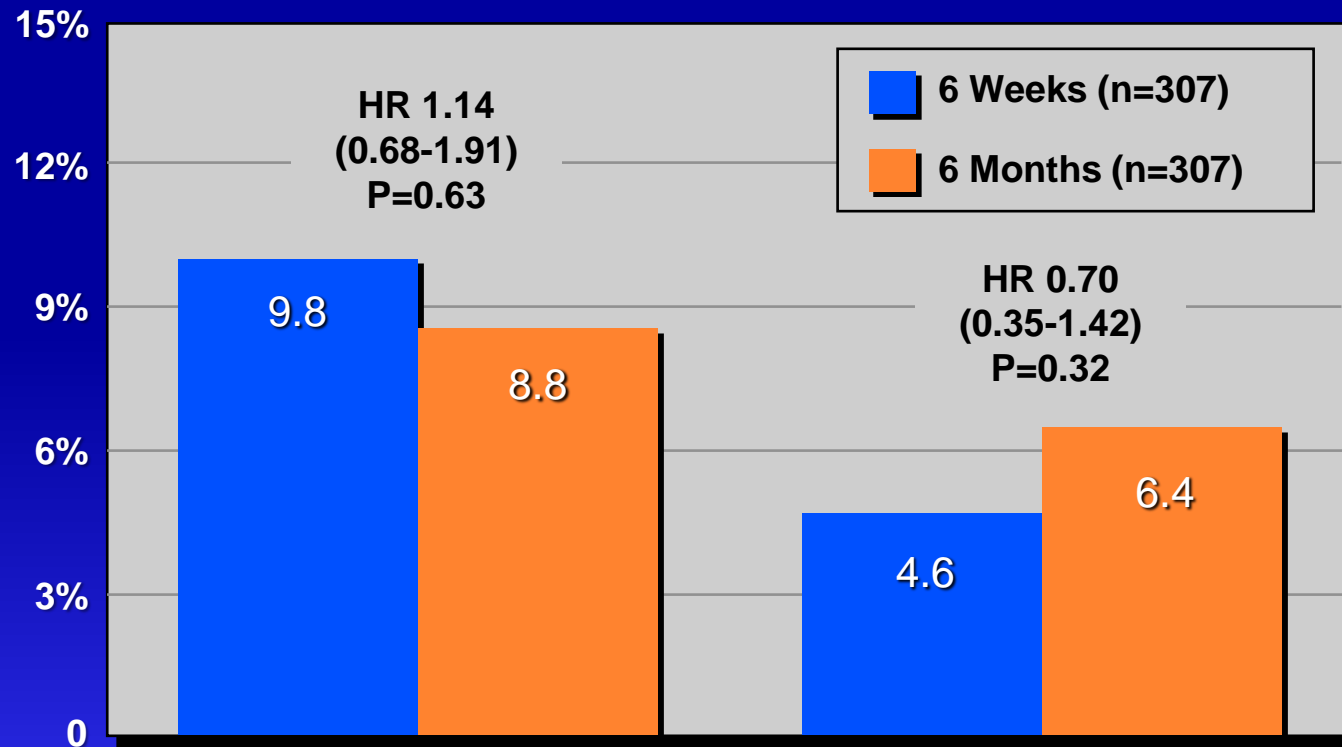
Clopidogrel 300-600 mg,
then 75 mg daily
6 months

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

ISAR-TRIPLE

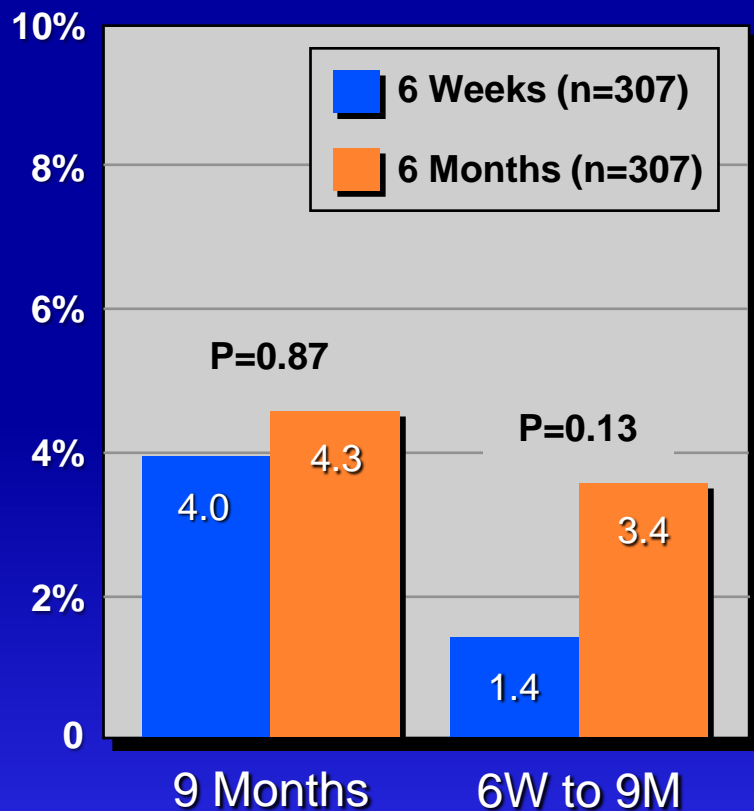
9-Month
Primary Endpoint

6-Week
Landmark Analysis

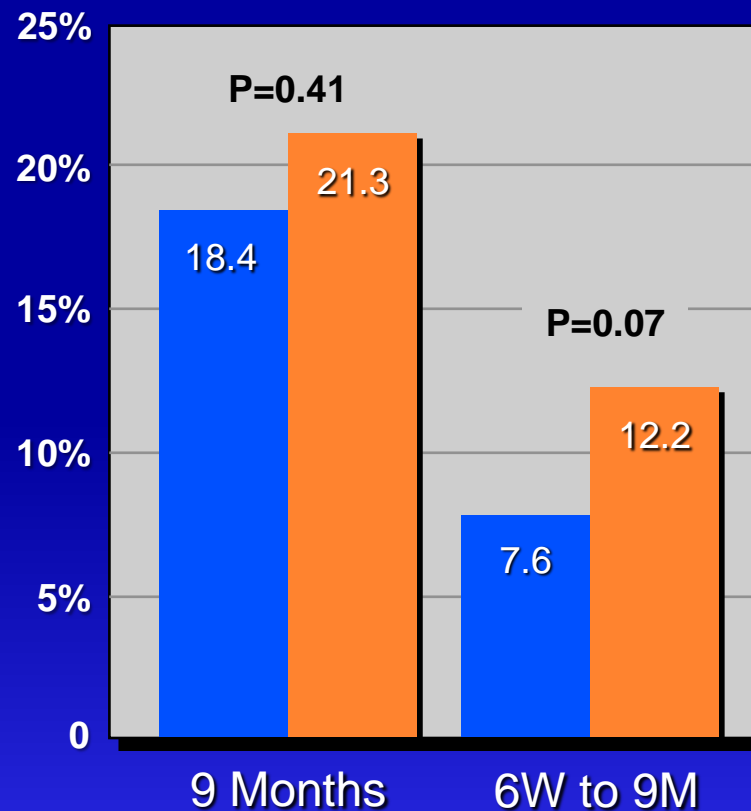


ISAR-TRIPLE

Ischemic Events



BARC ≥ 2



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

Algorithm for AF-PCI Considerations

Antithrombotic Management

Peri-PCI:

OAC: If possible, a period of wash-out is preferable, and bridging therapy is often unnecessary. Urgent or emergency procedures should not be delayed due to anticoagulation, and rarely is reversal of anticoagulation necessary.

Parenteral Agents: Consider use of agents associated with lower risk of bleeding complications and limit use of more potent therapies (e.g., glycoprotein IIb/IIIa inhibitors, cangrelor); avoid switching therapies.

Post-PCI:

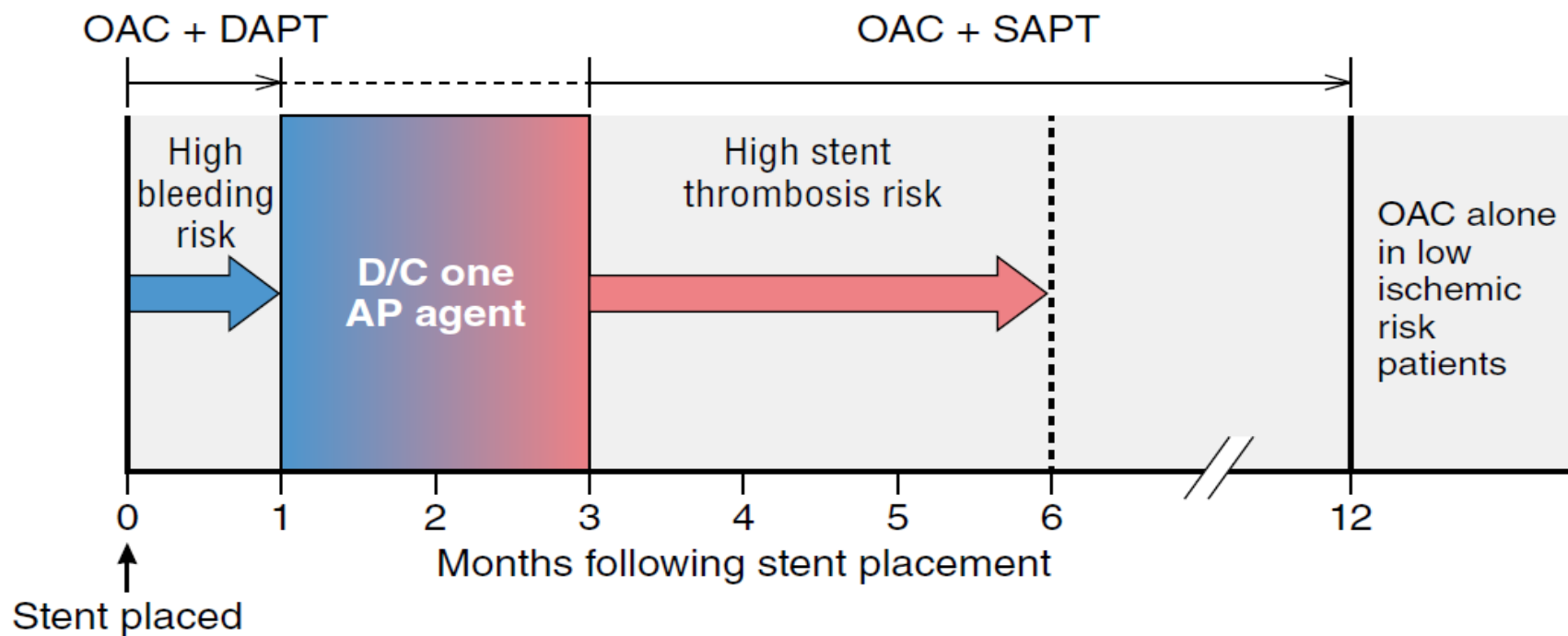
OAC: Either VKA or NOAC may be considered taking physician and patient preference into account. If VKA chosen, maintain INR between 2.0 – 3.0; if NOAC chosen, use lowest therapeutic dose; maintain OAC life-long.

APT: Minimize DAPT duration, including low-dose aspirin (75-100mg/once daily) and clopidogrel (75mg/once daily); avoid prasugrel or ticagrelor; initiate SAPT, preferably clopidogrel, as early as possible based on ischemic/thrombotic and bleeding risk profile of the patient; discontinue APT by one-year in most patients (maintain SAPT only in patients at high ischemic/thrombotic risk and low-risk for bleeding).

- Washout OAC
- INR \leq 2.0 for radial
- INR \leq 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 (\pm SAPT)

Antithrombotic Management

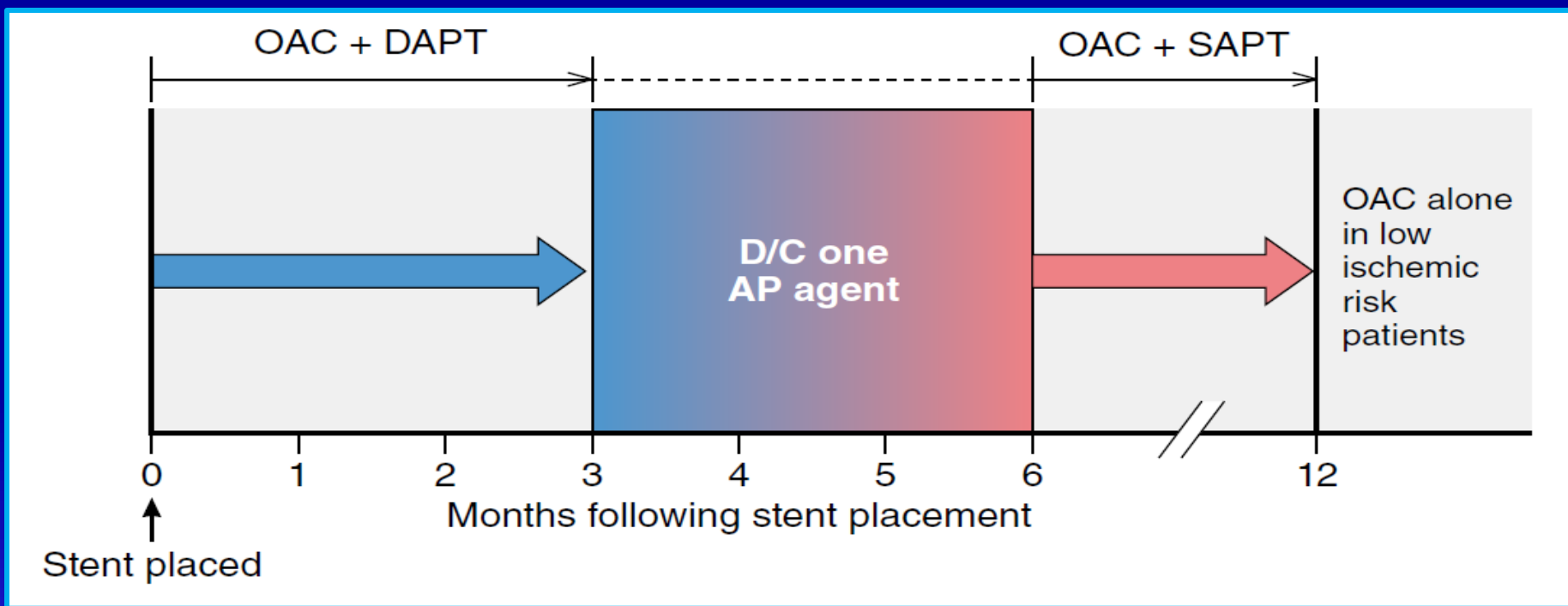
Recommended Algorithm



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.

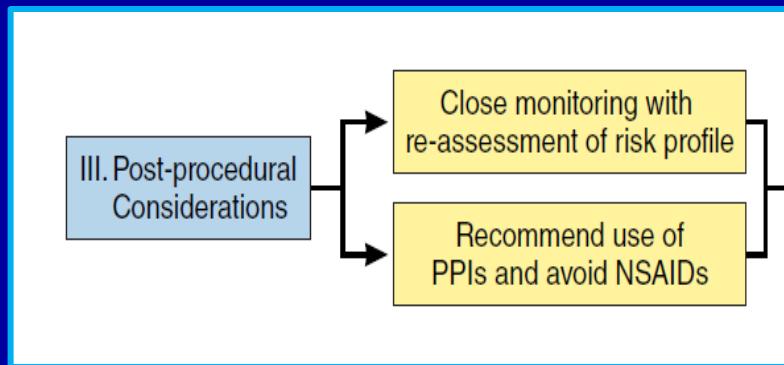
Antithrombotic Management

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.

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

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

ACC
Cardiovascular Interventions
A Journal of the American College of Cardiology
JANUARY 26, 2016
VOLUME 12
NUMBER 1

RETHINK DAPT

14
Day DAPT
INVESTIGATIONAL CORONARY STENT

The **COBRA PzF NanoCoated Coronary Stent System** with Polyene-F nanocoating is currently being studied with 14-Day DAPT in patients at **high risk of bleeding**.*

Currently Enrolling
For more information about this clinical trial, please visit:
<https://clinicaltrials.gov/ct2/show/NCT02594501>
or email info@celonova.com

COBRA reduce

COBRA REDUCE STUDY HYPOTHESIS
In patients undergoing coronary intervention who are receiving oral anticoagulation, 14-days of dual antiplatelet therapy (DAPT)** after stenting with the COBRA PzF nanocoated stent provides superior outcome in bleeding (BARC ≥ 2) and non-inferior outcomes in composite of death, MI, stent thrombosis (definite and probable), ischemic stroke vs. 6-months of DAPT** after stenting with standard FDA-approved drug-eluting stents.

CAUTION - INVESTIGATIONAL DEVICE, LIMITED BY UNITED STATES LAW TO INVESTIGATIONAL USE.
*Patients treated with oral anticoagulation and undergoing PCI
**DAPT + DAC
The COBRA PzF nanocoated stent is an investigational device and is not approved for sale in the United States.
COBRA PzF and PzF are trademarks of Celonova Biosciences, Inc.
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APM0196 DEC 2016 Rev. A

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

[Clinicaltrials.gov/NCT02594501](https://clinicaltrials.gov/NCT02594501)

JACC: CARDIOVASCULAR INTERVENTIONS

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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

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 P2Y₁₂ agents fit in
- For longer-term care, monotherapy vs “safer” dual