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

$X_a + V_a + Ca + II \rightarrow \text{Thrombin}$

$\rightarrow \text{Thrombus}$

$\rightarrow \text{Fibrin}$

$\rightarrow \text{Fibrinogen}$
Thrombin PAR Receptor

- Thrombin PAR-1
- Thrombin PAR-4
- ADP
- P2Y₁
- P2Y₁₂
- TBX A₂
- TBX A₂-R
- Epinephrine
- EPI-R
- Serotonin
- 5HT₂A
- Collagen
- GP VI
- GP la
- GP IIb/IIIa
- Anionic phospholipid surfaces
- Fibrinogen

Platelet

Thrombin PAR Receptor
**Thrombin Receptor Antagonist for 2º Prevention**

Hx MI, CVA, PVD  
Index event 2 weeks-1 year prior  
N ~ 25,000

- SCH 530348  
  2.5 mg daily  
  N ~ 12,500

- Placebo  
  (and usual therapy)  
  N ~ 12,500

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

www.clinicaltrials.gov
TRAP-2P

All Groups
Death, MI, CVA

HR=0.87
(0.80-0.94)
P<0.001

Placebo 10.5%
n=13,224
Vorapaxar 9.3%
n=13,225

MI Cohort
Death, MI, CVA

HR=0.80
(0.72-0.89)
P<0.001

Placebo 9.7%
n=8,881
Vorapaxar 8.1%
n=8,898

Death, MI, CVA

Qualifying MI < 3 Months

- Placebo (n=3,938)
- Vorapaxar (n=3,863)

HR 0.82
95% CI 0.70-0.95
P=0.011

Qualifying MI > 6 Months

- Placebo (n=2,284)
- Vorapaxar (n=2,419)

HR 0.78
95% CI 0.62-0.97
P=0.026

**Overall GUSTO Mod/Sev Bleeding**

- **Placebo**: n=13,224, 2.5% (P<0.001)
- **Vorapaxar**: n=13,225, 4.2%

**HR=1.66 (1.43-1.93)**

**MI Cohort GUSTO Mod/Sev Bleeding**

- **Placebo**: n=8,881, 2.1%
- **Vorapaxar**: n=8,898, 3.4%

**HR=1.61 (1.31-1.97)**

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)

*Adjusted Cox Model

Bleeding Events

- SAPT: 6.9%
- OAC: 7.0%
- DAPT: 7.0%
- OSAP: 9.7%
- TT: 14.2%

Ischemic Events

- SAPT: 38.0%
- OAC: 26.9%
- DAPT: 26.3%
- OSAP: 19.4%
- TT: 20.1%

HR 1.41* (1.10-1.81)

HR 1.15* (0.95-1.40)

Lamberts M et al. Circulation 2012;126:1185-1193
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
Primary Outcome: Any TIMI Bleeding

Dewilde et al. Lancet 2013:381:1107-1115
Death, MI, CVA, TVR, ST

Dewilde et al. Lancet 2013:381:1107-1115
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 •
Patients receiving OAC undergoing DES
N = 614

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 •
9-Month Primary Endpoint

HR 1.14 (0.68-1.91)  
P=0.63

6-Week Landmark Analysis

HR 0.70 (0.35-1.42)  
P=0.32

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

- 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)

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).

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

<table>
<thead>
<tr>
<th></th>
<th>PIONEER AF-PCI</th>
<th>REDUAL-PCI</th>
<th>AUGUSTUS</th>
<th>ENTRUST AF-PCI</th>
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<tbody>
<tr>
<td><strong>NOAC</strong></td>
<td>Rivaroxaban</td>
<td>Dabigatran</td>
<td>Apixaban</td>
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<td><strong>Clinical trials.gov identifier</strong></td>
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<td>Enrolling</td>
<td>Planning</td>
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<tr>
<td><strong>Study type</strong></td>
<td>Open-label, randomized</td>
<td>Open-label, randomized</td>
<td>Open-label (apixaban vs warfarin) and blinded (aspirin vs placebo), randomized</td>
<td>Open-label, randomized</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>2169 patients with AF who undergo a PCI with stenting</td>
<td>2500 patients with AF undergoing PCI with stenting (elective or post ACS)</td>
<td>4600 patients with AF undergoing PCI with stenting or an ACS</td>
<td>1500 patients with AF after successful PCI with stenting (elective or post ACS)</td>
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NanoCoated Stents

Clinicaltrials.gov/NCT02594501

* Not approved for sale in the USA. Investigational only.
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, b Sigmund Silber, MD, f 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\textsubscript{12} agents fit in
- For longer-term care, monotherapy vs “safer” dual