Clinical Use of Direct Oral Anticoagulants (DOACs) in Acute Coronary Syndromes (ACS)

Evidence-Based Management and Therapeutic Strategies

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Outlines

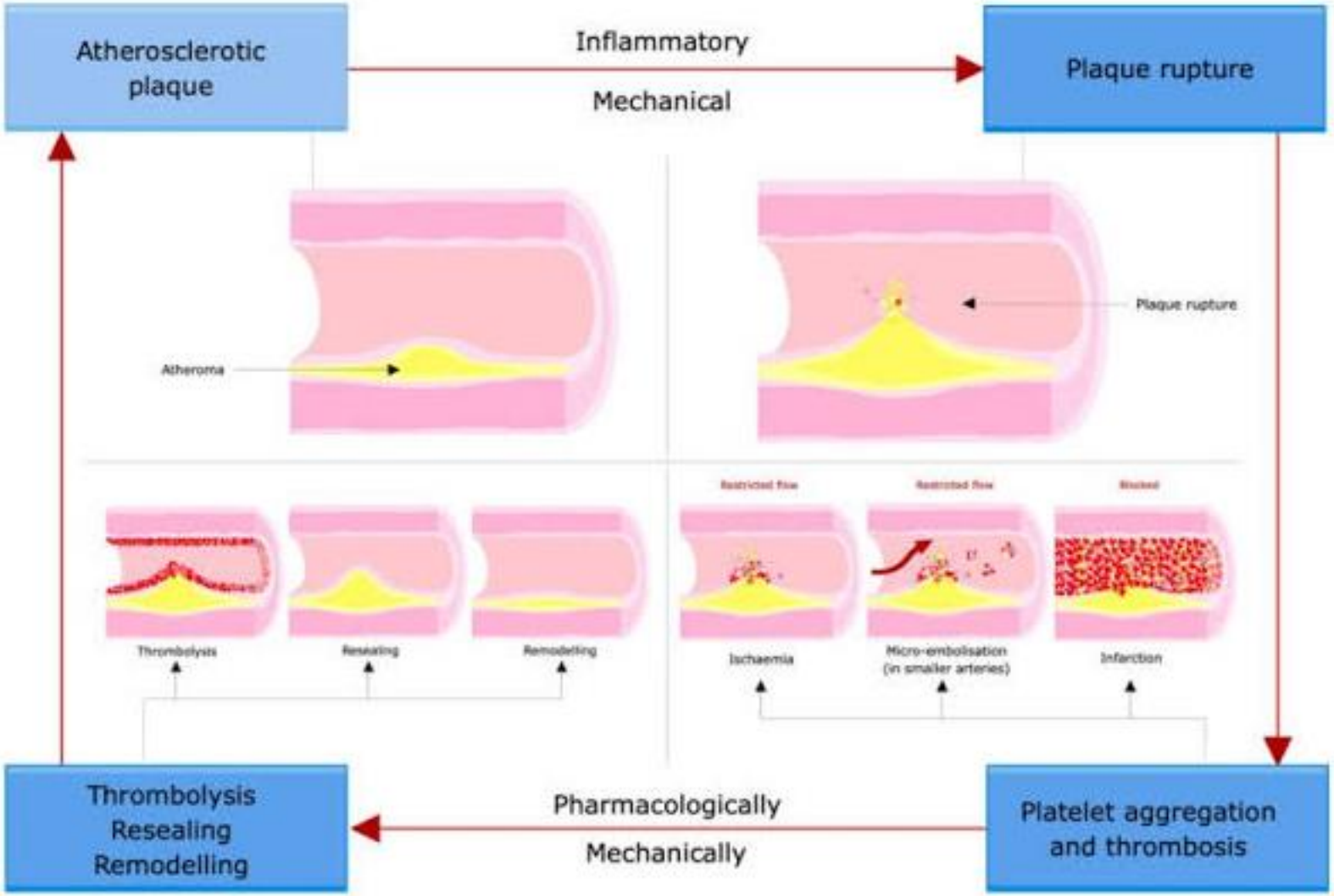
- The Thrombotic Challenges in ACS
- Key Trials for DOAC
- Guideline Recommendations
- DOAC Dosing and Drug Interactions
- Safety Profile and Reversal Agents
- Future Directions and Unanswered Questions
- Summary and Key Takeaways

The Thrombotic Challenges in ACS

- Pathophysiology of ACS
- Current Standard of Care
- Residual Ischemic Risk
- The Rationale for DOACs

The Thrombotic Challenge in ACS *

Pathophysiology of ACS:



The Thrombotic Challenge in ACS

Current Standard of Care:

- Dual Antiplatelet Therapy (DAPT: Aspirin + P2Y12 Inhibitor) ± Parenteral Anticoagulation (in the acute phase).

Key Components of Antithrombotic Therapy

Antiplatelet (COX-1 Inhibitor)	Aspirin	The cornerstone of therapy; administered as a loading dose and continued lifelong for secondary prevention.
Antiplatelet (P2Y12 Inhibitor)	Ticagrelor, Prasugrel, Clopidogrel	Used in combination with aspirin (DAPT). Prasugrel or ticagrelor are generally preferred over clopidogrel due to superior efficacy, particularly in patients undergoing percutaneous coronary intervention (PCI).
Anticoagulant (Parenteral)	Unfractionated Heparin (UFH), Enoxaparin, Fondaparinux, Bivalirudin	Used in the acute phase to prevent clot formation, especially around the time of an invasive procedure (PCI).
Anticoagulant (Oral, long-term adjunct)	Rivaroxaban (low dose)	May be considered for long-term secondary prevention in patients at high ischemic risk and low bleeding risk, added to aspirin and clopidogrel after the initial period.

The Thrombotic Challenge in ACS

Residual Ischemic Risk:

- Despite optimal DAPT, patients with ACS (especially high-risk) remain vulnerable to recurrent ischemic events (heart attack, stroke, or cardiovascular death)

Key factors contributing to residual ischemic risk include:

- Clinical Risk Factors **-** Prior Medical History (previous MI, HF, DM, or AF)

  Polyvascular Disease: (e.g., coronary, peripheral, and cerebrovascular arteries.)

  Older Age

  Renal Impairment

  Incomplete Revascularization

- Biomolecular and Lifestyle Factors- Inflammation, Lipid Imbalances, Thrombotic Activity, Lifestyle Factors, Psychosocial Factors

The Thrombotic Challenge in ACS*

The Rationale for DOACs:

- The primary rationale for **DOACs for ACS** is
  - to reduce the persistent high risk of recurrent ischemic events and all-cause mortality, which remains elevated despite standard antiplatelet therapy, by targeting the coagulation cascade (Factor Xa or Thrombin)

Key rationales include:

- Persistent Thrombin Generation in ACS
- Dual Pathway Inhibition
- Superiority over Warfarin
- Improved Efficacy/Safety Balance

Key Trials for DOAC

ACS without AF

1. ATLAS ACS 2–TIMI 51 (Rivaroxaban)
2. APPRAISE-2 (Apixaban)
3. GEMINI-ACS-1 (Rivaroxaban)
4. COMPASS (Rivaroxaban)

ACS with AF

1. PIONEER AF-PCI (Rivaroxaban)
2. RE-DUAL PCI (Dabigatran)
3. AUGUSTUS (Apixaban)
4. ENTRUST-AF PCI (Edoxaban)

Key Trials for DOAC for ACS without AF

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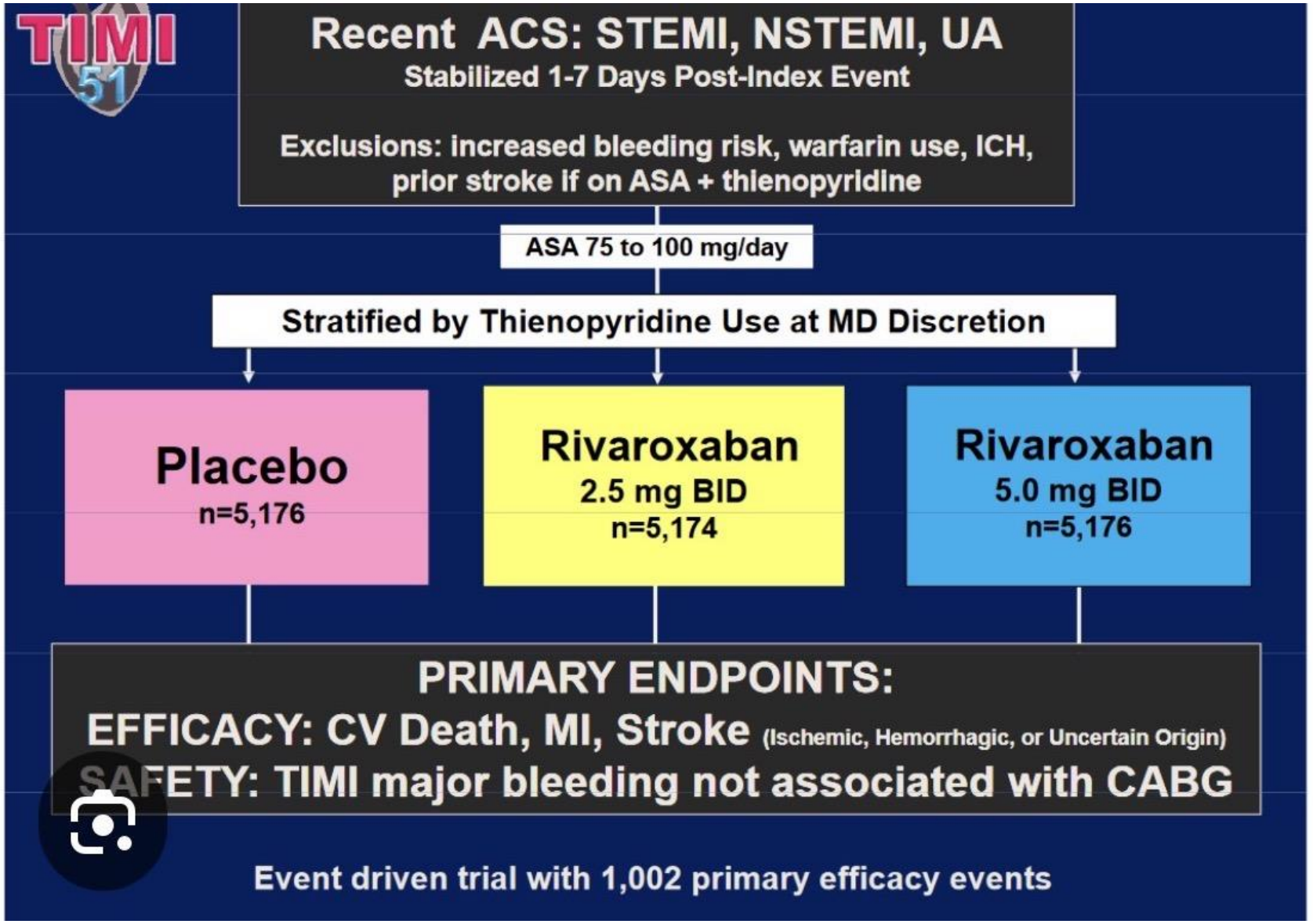
1. ATLAS ACS 2–TIMI 51 (Rivaroxaban)*



1. ATLAS ACS 2–TIMI 51 (Rivaroxaban)

- **Design:** 15,526 patients with recent ACS were randomized to
  - placebo, or
  - rivaroxaban 2.5 mg BID, or
  - rivaroxaban 5.0 mg BID,

  on top of DAPT (aspirin + clopidogrel).
- **Key Finding:** The **2.5 mg BID** dose significantly reduced the composite of CV death, MI, or stroke compared to placebo (8.9% vs. 10.7%).
- **Mortality:** Notably, the 2.5 mg dose showed a reduction in **all-cause mortality**.
- **Safety:** There was a significant increase in major bleeding and intracranial hemorrhage, though not in fatal bleeding.
- **Clinical Impact:** This led to the approval of the "vascular dose" (2.5 mg BID) for ACS in many regions, though uptake remains selective due to bleeding concerns.

2. APPRAISE-2 (Apixaban)

- This trial investigated apixaban in high-risk ACS patients already receiving antiplatelet therapy.

- **Design:** 7,392 patients received apixaban 5 mg BID or placebo plus DAPT.

- **Key Finding:** The trial was **terminated early** due to a significant increase in major bleeding without a corresponding reduction in ischemic events.

- **Conclusion:** Standard "stroke-prevention" doses of apixaban (5 mg BID) are too high when combined with DAPT in the post-ACS setting.

3. GEMINI-ACS-1 (Rivaroxaban)

- This was a Phase II safety trial exploring a "drop the aspirin" strategy, similar to what is done in AF patients.

- **Design:** Compared rivaroxaban (2.5 mg BID) + P2Y12 inhibitor vs. standard DAPT (aspirin + P2Y12 inhibitor).

- **Key Finding:** Bleeding rates were similar between the two groups.

- **Conclusion:** It suggested that replacing aspirin with low-dose rivaroxaban is safe, but it was not powered to prove it was more effective at preventing heart attacks.

4. COMPASS (Rivaroxaban)

- While COMPASS focused on **stable** coronary or peripheral artery disease (CAD/PAD), it is relevant because many participants had a history of ACS.

- **Design:** Rivaroxaban 2.5 mg BID + Aspirin vs. Aspirin alone.

- **Key Finding:** Significant reduction in MACE and mortality.

- **Clinical Impact:** It reinforced the "Dual Pathway" concept for long-term secondary prevention after the initial ACS stabilization phase.

Summary Table of 4 Key Trials about DOAC in ACS without AF

Trial	Drug	Regimen	Primary Result
ATLAS ACS 2	Rivaroxaban	2.5mg BID + DAPT	**Positive:** Reduced MACE & CV death; increased bleeding.
APPRAISE-2	Apixaban	5mg BID + DAPT	**Negative:** Terminated early due to excess bleeding.
GEMINI-ACS-1	Rivaroxaban	2.5mg BID + P2Y12	**Neutral/Safety:** Similar bleeding to standard DAPT.
COMPASS	Rivaroxaban	2.5mg BID + ASA	**Positive:** Benefit in stable CAD/PAD with prior MI.

- **Bottom Line:** Currently, only low-dose rivaroxaban (2.5 mg BID) is used in select high-ischemic-risk ACS patients without AF

- not "routine" for everyone because the bleeding risk often offsets the benefit.

Key Trials for DOAC for ACS with AF

1. PIONEER AF-PCI (Rivaroxaban)

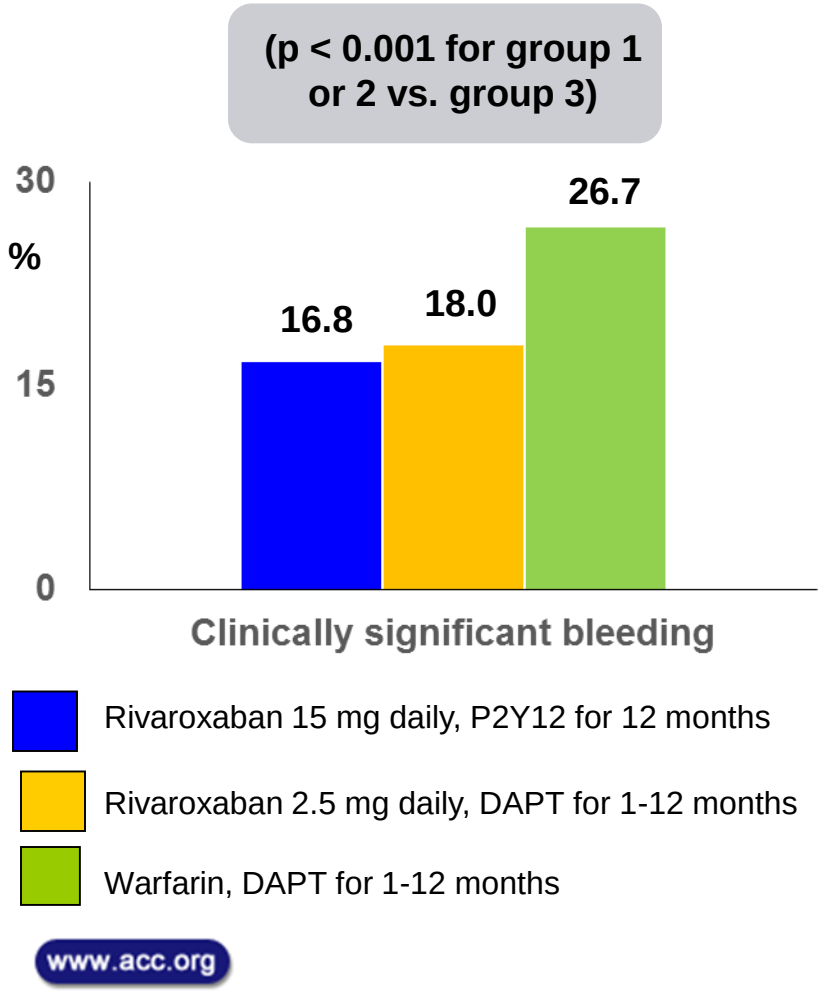
2. RE-DUAL PCI (Dabigatran)

3. AUGUSTUS (Apixaban)

4. ENTRUST-AF PCI (Edoxaban)

1. PIONEER AF-PCI Trial*

Trial design: Patients with AF and PCI randomized to: **Group 1**: Rivaroxaban 15 mg daily plus P2Y12 inhibitor for 12 months (n = 709). **Group 2**: Rivaroxaban 2.5 mg twice daily plus DAPT for 1-12 months (n = 709). **Group 3**: warfarin plus DAPT for 1-12 months (n = 706).



Results

- Clinically significant bleeding: **16.8% in group 1** vs. **18.0% in group 2** vs. **26.7% in group 3** (HR 0.59, p < 0.001 for group 1 vs. 3); (HR 0.63, p < 0.001 for group 2 vs. 3)
- **Stent thrombosis**: **0.8% in group 1** vs. **0.9% in group 2** vs. **0.7% in group 3** (HR 1.20, p = 0.79 for group 1 vs. 3; HR 1.44, p = 0.57 for group 2 vs. 3)

Conclusions

- Among patients with nonvalvular AF who underwent PCI, a rivaroxaban-based strategy was associated with a **lower frequency of clinically significant bleeding** compared with a warfarin/DAPT strategy
- Stent thrombosis appeared to be similar between the three groups (**not statistically significant**)

Gibson CM, et al. N Engl J Med 2016;375:2423-34

1. PIONEER AF-PCI (Rivaroxaban)

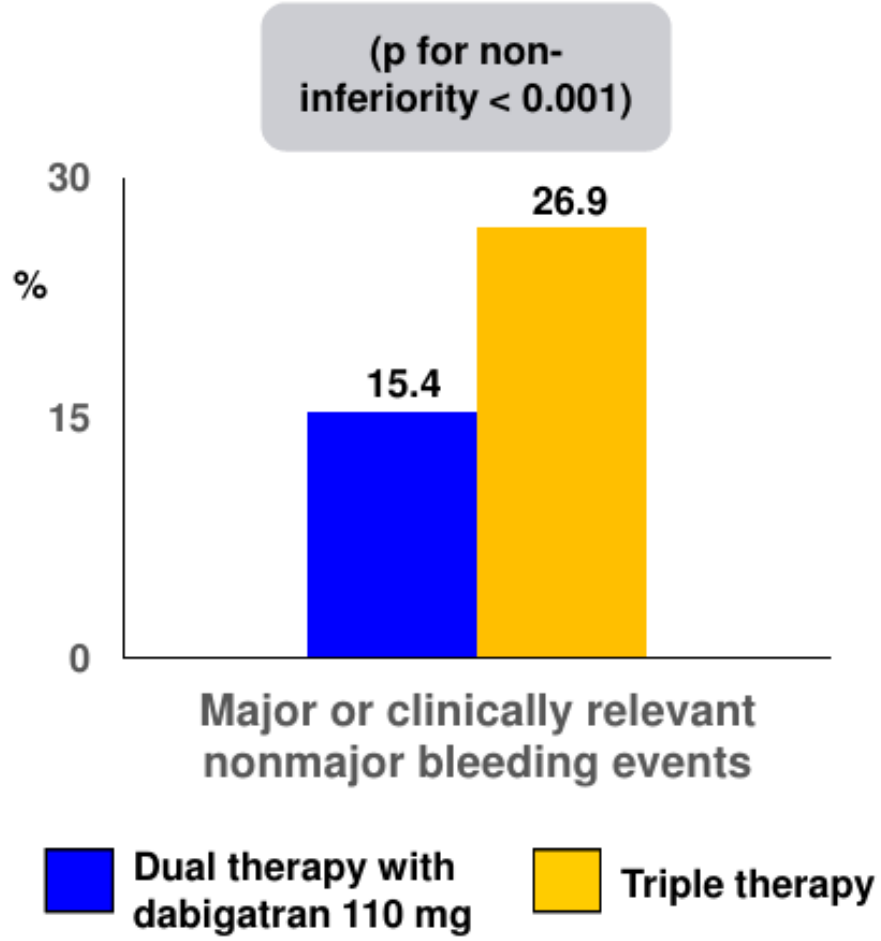
- The first major trial to challenge the standard of care.
- **Design:** 2,124 patients were randomized to:
  - Rivaroxaban **15 mg QD** + P2Y12 inhibitor.
  - Rivaroxaban **2.5 mg BID** + DAPT (Aspirin + P2Y12).
  - Traditional Triple Therapy (VKA + DAPT).

- **Key Finding:** Both rivaroxaban arms significantly reduced clinically significant bleeding compared to VKA triple therapy.

- **Takeaway:** Established that a reduced dose of rivaroxaban (15 mg) combined with a P2Y12 inhibitor is safer than warfarin-based triple therapy.

2. RE-DUAL PCI

Trial design: Patients with atrial fibrillation undergoing coronary revascularization were randomized to dual therapy with dabigatran at a dose of 110 mg (n = 981) vs. dual therapy with dabigatran at a dose of 150 mg (n = 763) vs. triple therapy with warfarin (n = 981).



Results

- Major or clinically relevant nonmajor bleeding events: 15.4% of the dual therapy with dabigatran 110 mg group vs. 26.9% of the triple therapy group (p for noninferiority < 0.001, p for superiority < 0.001)
- Major or clinically relevant nonmajor bleeding events: 20.2% of the dual therapy with dabigatran 150 mg group vs. 25.7% of the corresponding triple therapy group (excluding elderly participants outside the United States) (p for noninferiority < 0.001)

Conclusions

- Among patients with atrial fibrillation undergoing coronary revascularization, dual therapy compared with triple therapy was effective at reducing bleeding events

Cannon CP, et al. N Engl J Med 2017;Aug 27:[Epub]

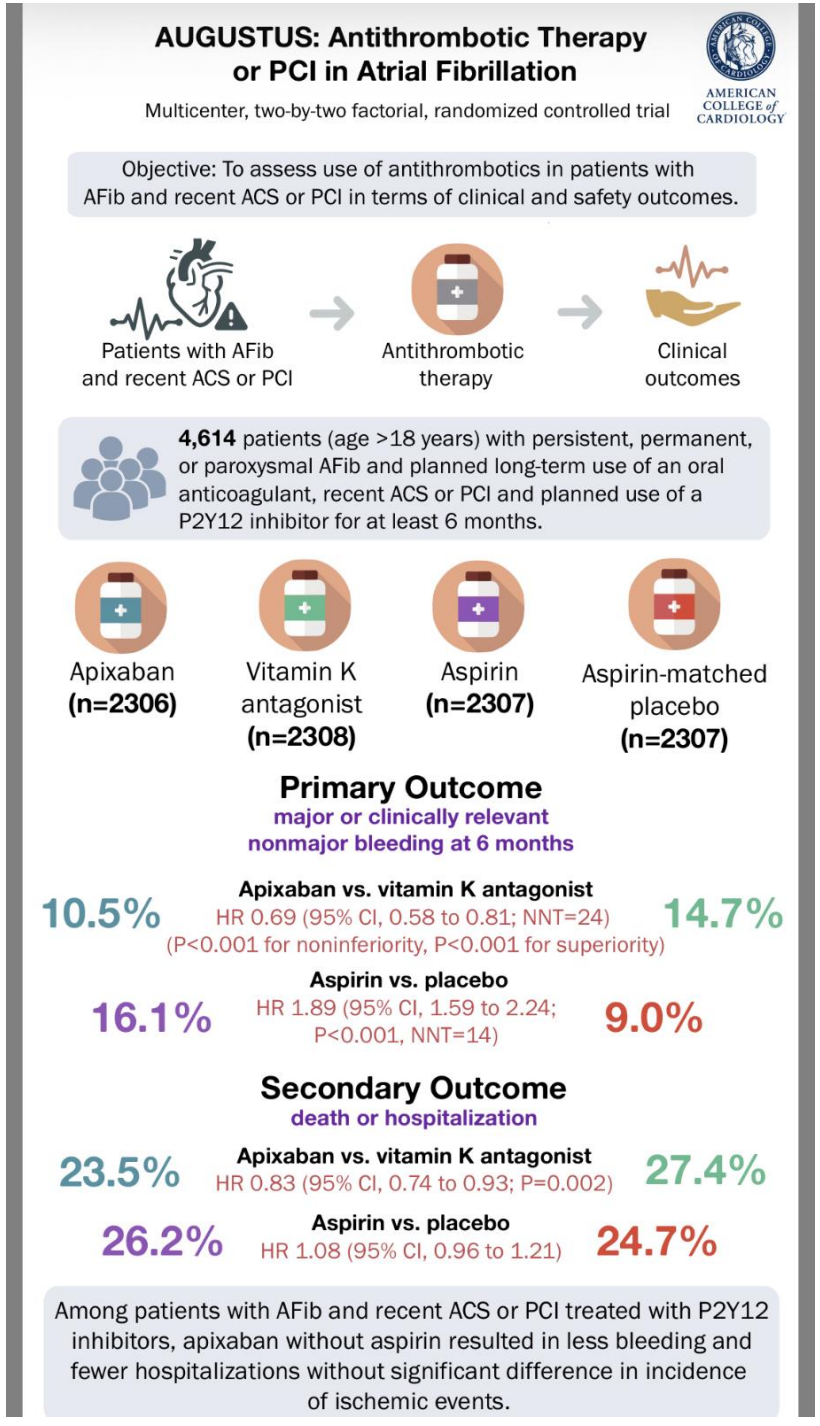
2. RE-DUAL PCI (Dabigatran)

- **Design:** 2,725 patients randomized to:
  - Dabigatran **110 mg BID** + P2Y12 inhibitor.
  - Dabigatran **150 mg BID** + P2Y12 inhibitor.
  - Triple Therapy (VKA + DAPT).

- **Key Finding:** Both dabigatran DAT regimens were superior to VKA triple therapy regarding bleeding.

- **Takeaway:** Ischemic events (MI/Stroke) were similar across groups, though a numerical increase in stent thrombosis was noted in the 110 mg group, leading many to prefer the 150 mg dose for high-ischemic-risk patients.

3. AUGUSTUS (Apixaban)



3. AUGUSTUS (Apixaban) – The "Gold Standard"

- The most robust trial due to its **2x2 factorial design**, which separately tested the DOAC vs. VKA and Aspirin vs. Placebo.
- **Design:** 4,614 patients randomized to:
  - **Anticoagulant:** Apixaban (5 mg BID) vs. VKA.
  - **Antiplatelet:** Aspirin vs. Placebo.
  - *All patients received a P2Y12 inhibitor (mostly clopidogrel).*

- **Key Finding:** Apixaban was safer than VKA, and **omitting aspirin** (Placebo arm) significantly reduced bleeding without increasing ischemic events.

- **Takeaway:** This trial solidified the strategy of **Apixaban + Clopidogrel** as a preferred regimen for most patients.

4. ENTRUST-AF PCI (Edoxaban)

- **Design:** 1,506 patients randomized to
  - Edoxaban **60 mg QD** + P2Y12 inhibitor vs.
  - VKA + DAPT.

- **Key Finding:** Edoxaban-based DAT was non-inferior to VKA triple therapy for major or clinically relevant non-major bleeding.

- **Takeaway:** Further supported the class-wide safety of DOAC-based dual therapy over warfarin-based triple therapy.

Summary of Modern Management (ACS with AF)

Feature	Contemporary Strategy
Choice of Anticoagulant	**DOAC** is preferred over VKA (Warfarin).
Regimen Structure	**Dual Therapy** (DOAC + P2Y12) is the default after the first week.
Triple Therapy Duration	Limited to the **periprocedural period** (usually ≤ 1 week/at discharge).
Preferred P2Y12	**Clopidogrel** is the standard; Ticagrelor/Prasugrel are generally avoided in triple therapy due to high bleeding risk.

Long-Term Management (The AFIRE Trial)

- Once a patient is **12 months post-ACS/PCI**, the **AFIRE trial** showed that **DOAC monotherapy** is safer and even more effective than continuing an antiplatelet drug (DOAC + Aspirin/Clopidogrel).

Guideline Recommendations:Balancing Ischemia vs. Bleeding

Main Concept: Tailor the duration of Triple Therapy (OAC + DAPT) based on individual risk.

- **High Ischemic Risk / Low Bleeding Risk:**
  - Triple Therapy (OAC + Aspirin + P2Y12i) for **1 week** (max 1 month).
  - Followed by **Dual Therapy (OAC + P2Y12i)** for up to 6 or 12 months.
  - Finally, **OAC Monotherapy** long-term.

- **High Bleeding Risk / Low Ischemic Risk:**
  - Initiate **Dual Therapy (OAC + P2Y12i)** immediately post-hospital discharge (avoiding Aspirin entirely).
  - Followed by **OAC Monotherapy** after 6 months.

Guideline Recommendations: Balancing Ischemia vs. Bleeding

Preferred DOACs:

- Low-dose **Rivaroxaban (15mg QD)**,
- **Dabigatran (110mg BID)**, or
- **Apixaban (5mg BID)** are generally preferred over VKAs (Warfarin) in this setting due to favorable bleeding profiles with DAT.

DOAC Dosing and Drug Interactions

- **Rivaroxaban Dosing:**
  - **Secondary Prevention Post-ACS (ATLAS):** 2.5 mg BID (with Aspirin ± Clopidogrel).
  - **AF + PCI (PIONEER):** 15 mg once daily (with P2Y12i).

- **Apixaban Dosing (AF + PCI, AUGUSTUS):** 5 mg BID, or 2.5 mg BID if ≥ 2 of:
  - age ≥ 80 years,
  - body weight ≤ 60 kg, or
  - serum creatinine ≥ 1.5 mg/dL.

DOAC Dosing and Drug Interactions contd.

- **Renal Function:** All DOACs require dose adjustments based on creatinine clearance (CrCl).
  - CrCl must be calculated before initiation and monitored during treatment.
  - *Caution:* DOACs are generally contraindicated in severe renal impairment (CrCl < 15 ml/min) or for patients on dialysis.

- **Drug Interactions:** Be aware of strong CYP3A4 and P-glycoprotein inhibitors/inducers, which can significantly alter DOAC levels (e.g., Clarithromycin, Ketoconazole).

Safety Profile and Reversal Agents

Safety: Bleeding Risk and Reversal Strategies

- **The Primary Concern:** Combining DOACs with potent antiplatelet agents (DAPT) significantly increases the risk of bleeding.

- **Reduction Strategies:**
  - Use lower doses of the DOAC (e.g., Rivaroxaban 2.5mg BID).
  - Limit the duration of triple therapy to the minimum necessary.
  - Prefer **Clopidogrel** over Ticagrelor or Prasugrel for the P2Y12 inhibitor component of DAT, especially in high-bleeding-risk patients.
  - Use a **Proton Pump Inhibitor (PPI)** in all patients on triple therapy.

Safety Profile and Reversal Agents Contd.

Reversal Agents:

- **Dabigatran (Direct Thrombin Inhibitor):** Idarucizumab (specific reversal agent).
- **Rivaroxaban/Apixaban/Edoxaban (Factor Xa Inhibitors):** Andexanet alfa (specific reversal agent) or Activated prothrombin complex concentrate (aPCC) for urgent reversal.

Future Directions and Unanswered Questions

Unanswered Questions:

- The role of DOACs (Apixaban, Dabigatran) for secondary prevention in patients *without* AF (analogous to ATLAS ACS 2-TIMI 51).

- Optimal management of patients presenting with ACS who are already on a DOAC for another indication (e.g., DVT/PE).
  - *Current strategy: Hold DOAC, use parenteral anticoagulant (e.g., Heparin/LMWH) per protocol, and decide on readministration after PCI.*

- Optimal duration and choice of P2Y12 inhibitor in DAT (Clopidogrel is the standard, but Ticagrelor/Prasugrel use is an evolving area).

Future Directions and Unanswered Questions Contd.

Future Trends

- More focused research on individualized risk stratification tools to precisely identify patients who will benefit from DOAC-based dual pathway inhibition while minimizing bleeding.

Summary and Key Takeaways

1. **Post-ACS Secondary Prevention (No AF):** Very low-dose **Rivaroxaban 2.5 mg BID** is the only DOAC approved in some regions to reduce recurrent ischemic events in high-risk patients (Evidence: **ATLAS ACS 2-TIMI 51**).

2. **ACS/PCI + Atrial Fibrillation (AF): Dual Antithrombotic Therapy (DAT)** (DOAC + P2Y12i) is preferred over Warfarin-based Triple Therapy.

3. **Preferred DAT Regimen:** DOAC at AF dose + **Clopidogrel** (without Aspirin) significantly reduces bleeding (Evidence: **PIONEER, RE-DUAL PCI, AUGUSTUS**).

4. **Duration:** Limit Triple Therapy duration to **≤ 1 week** (max 1 month) in most patients, then transition to DAT.

5. **Safety:** Bleeding risk is the primary concern; use PPI and adhere to guideline-recommended, reduced-intensity regimens.

Thank you for your attention.