



ACC Latin America Conference 2016

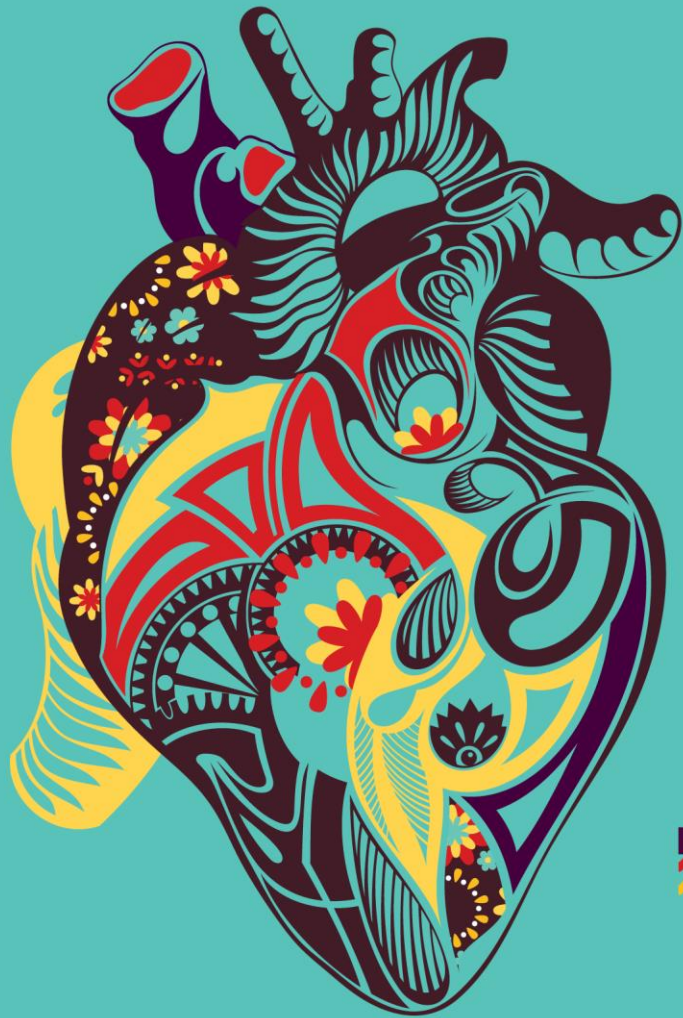
MEXICO CITY

OCTOBER 7 – 8, 2016

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UNIQUE EDUCATIONAL EXPERIENCE
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ÚNICA EXPERIENCIA
EDUCACIONAL EN TU ÁREA

Practical Guidance on Anti-thrombotics

SESSION DAY/TIME: Friday, October 7, 5:15pm-6:00pm

Roy M. John, MD. PhD

Cardiac Arrhythmia Service

Brigham and Women's Hospital

Boston, MA

Disclosures:

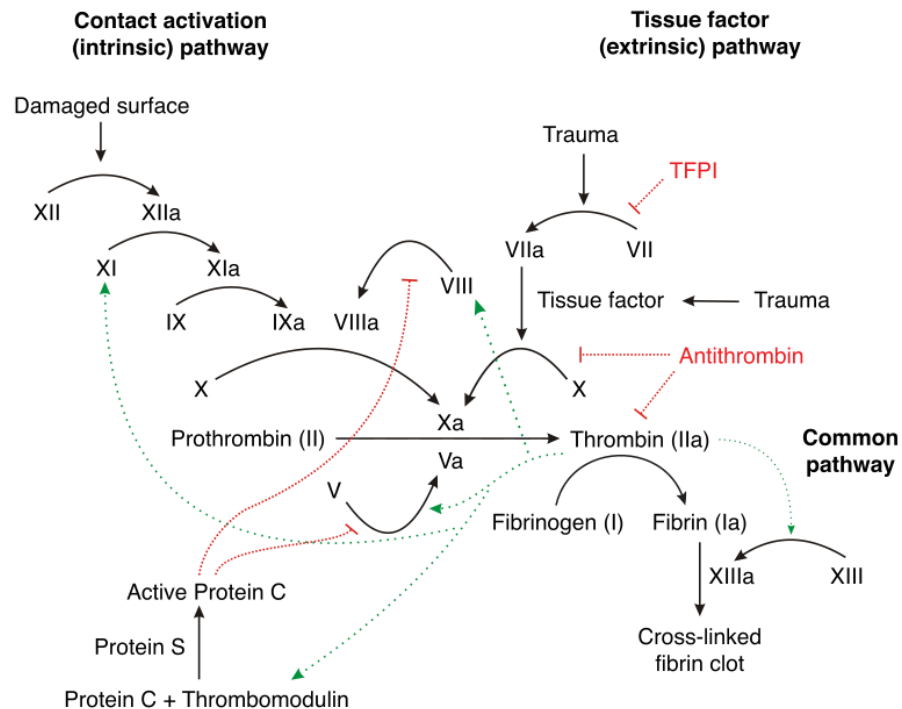
Research Support St Jude Medical Inc., Biosense Webster, Inc.



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Oral Anticoagulants Approved for Stroke Prevention in AF

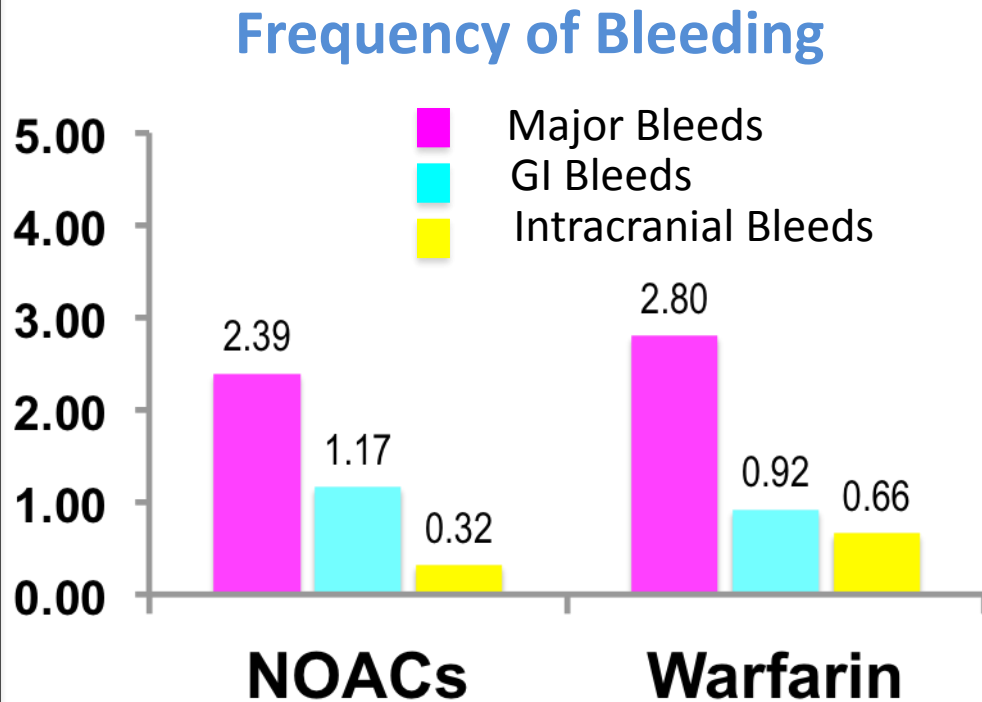
- Vitamin K Antagonist:
 - Warfarin
- Direct Thrombin Inhibitor:
 - Dabigatran etexilate (Pradaxa)
- Direct Factor Xa Inhibitor:
 - Apixaban (Eliquis)
 - Rivaroxaban (Xarelto)
 - Edoxaban (Savaysa)



Meta-analysis of NOAGs compared with Warfarin in AF

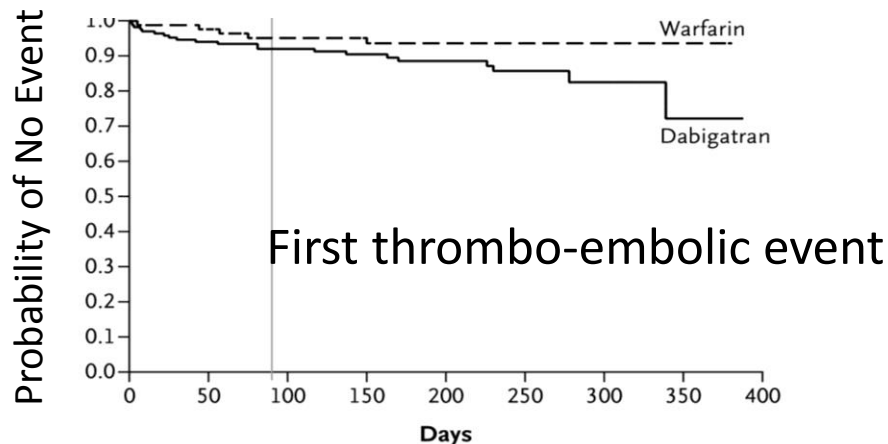
- N = 71,683 (4 Phase III NOAG Trials)
- Reduction in:
 - Stroke or systemic embolism by 19%
 - Major bleeds by 14%
 - Intracranial bleed by 52%

ADVANTAGES: Rapid onset of action,
no food interaction and less
interaction with drugs



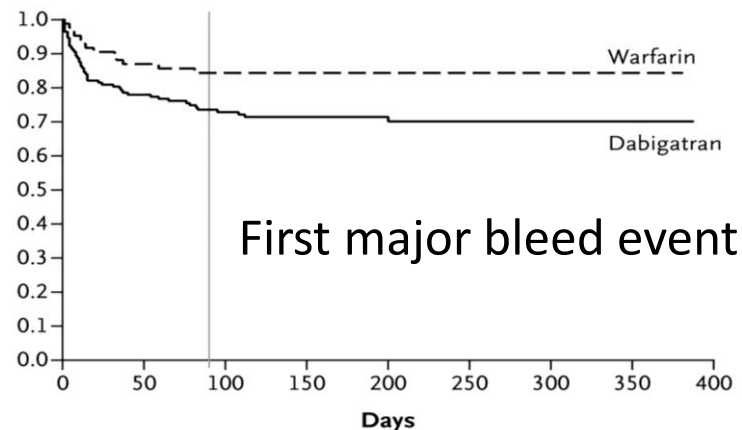
Dabigatran vs Warfarin in Mechanical Heart Valves

Dabigatran was associated with higher rates of ischemic stroke (5%, vs. 0% with warfarin) and major bleeding (4% vs. 2%)



No. at Risk

| | | | | | | | | |
|------------|-----|-----|-----|-----|----|----|----|---|
| Dabigatran | 168 | 156 | 126 | 108 | 73 | 44 | 15 | 7 |
| Warfarin | 84 | 82 | 66 | 55 | 40 | 22 | 9 | 4 |

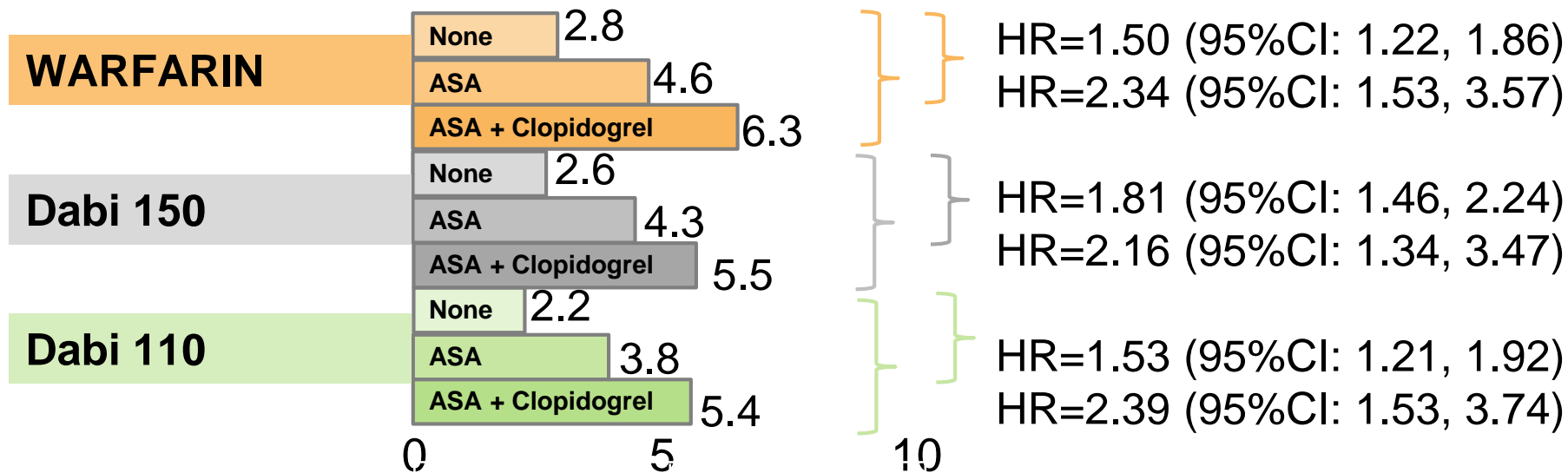


| | | | | | | | |
|-----|-----|-----|----|----|----|----|---|
| 168 | 129 | 103 | 86 | 58 | 32 | 11 | 6 |
| 84 | 73 | 56 | 50 | 38 | 22 | 11 | 4 |



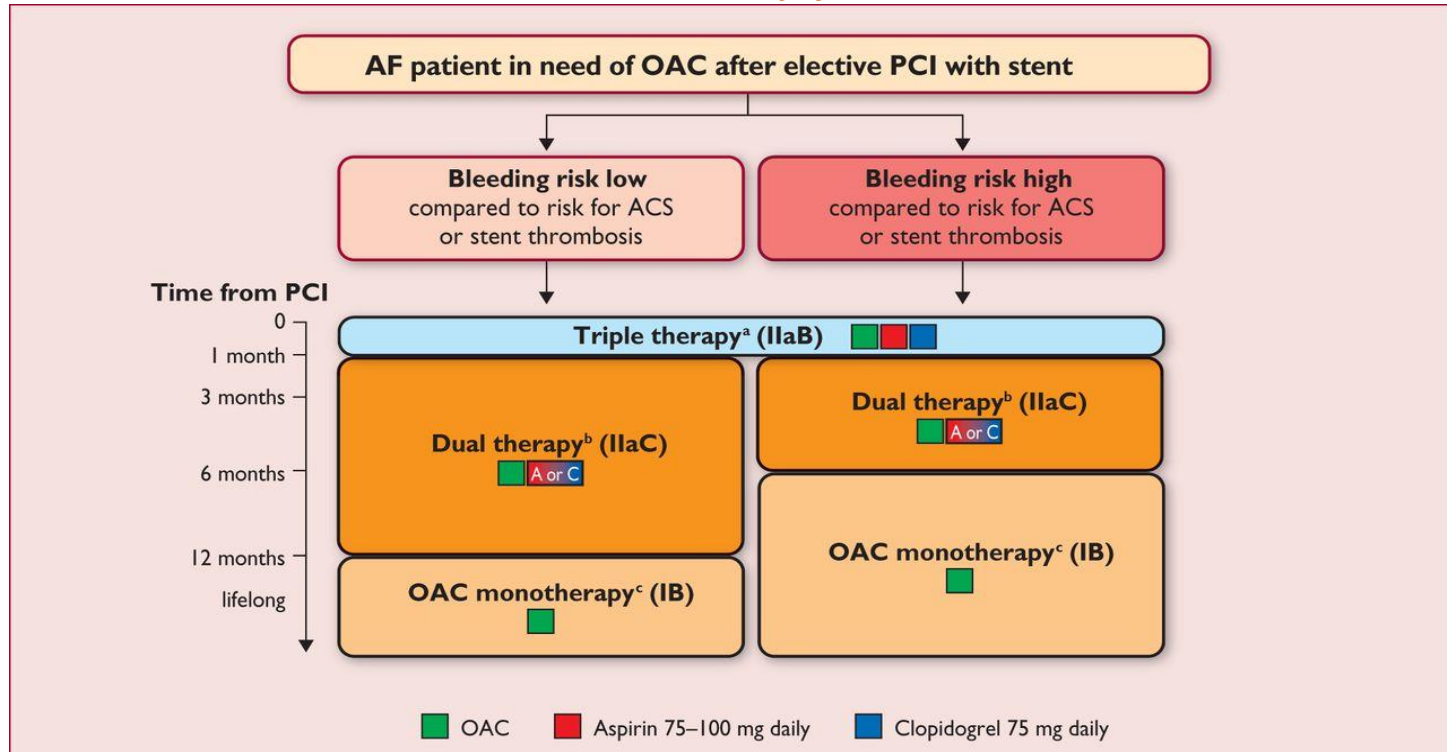
RE-LY Study: Bleeding with Antiplatelet Therapy

Major Bleeding*



*Adjusted for age, gender, warfarin experience, SBP, CAD, CHF, TIA, HTN, DM, CrCl, Statins

How to Approach Combination Antithrombotic Therapy- Elective PCI



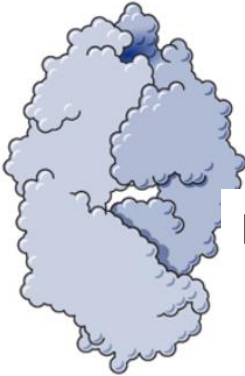

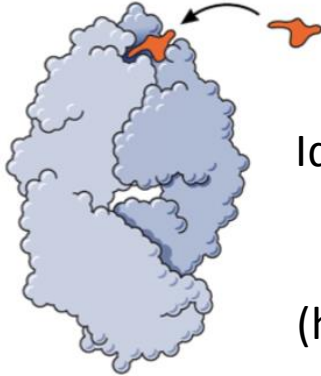

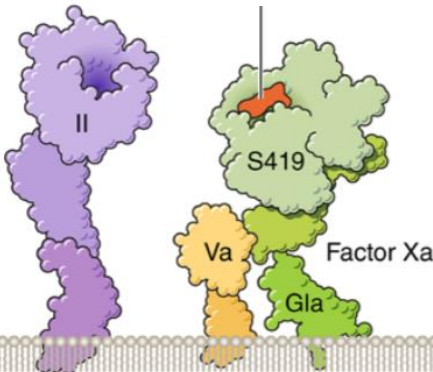
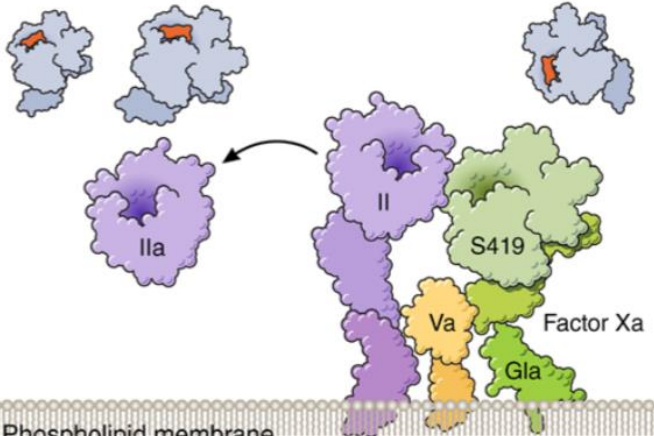
Non-Specific Reversal Agents

After Discontinuation of drug and Supportive Care (fluids / transfusions)

| Agent | Clotting Factors Replaced | Dose |
|--------------|---------------------------|----------------|
| 4 Factor-PCC | Factors II, VII, IX, X | 25-50 units/kg |
| 3 Factor-PCC | Factors II, IX, X | 25-50 units/kg |
| aPCC | Factors II, VIIa, IX, X | 80 units/kg |
| rFVIIa | FVIIa | 90 ug/kg |



Specific NOAG Reversal Agents

| NOAC reversal agent | Target | Mechanism |
|--|--|--|
|  <p>Idarucizumab</p> |  <p>Dabigatran</p> |  <p>Idarucizumab binds Dabigatran (high affinity)</p> |
|  <p>Andexanet alpha</p> | <p>Xa Inhibitors</p>  |  <p>Phospholipid membrane</p> |

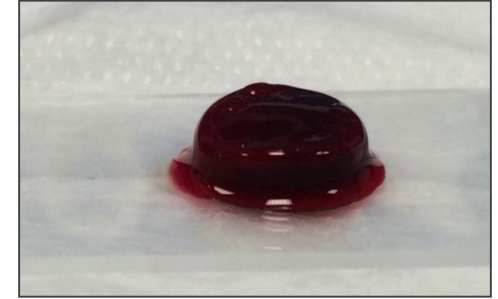
Ciraparantag



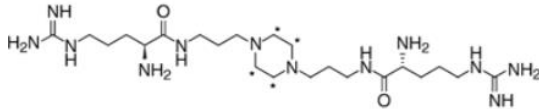
BASELINE
(Pre-edoxaban)



ANTICOAGULATED
(Pre-PER977, 2.75 hrs
60 mg edoxaban p.o.)

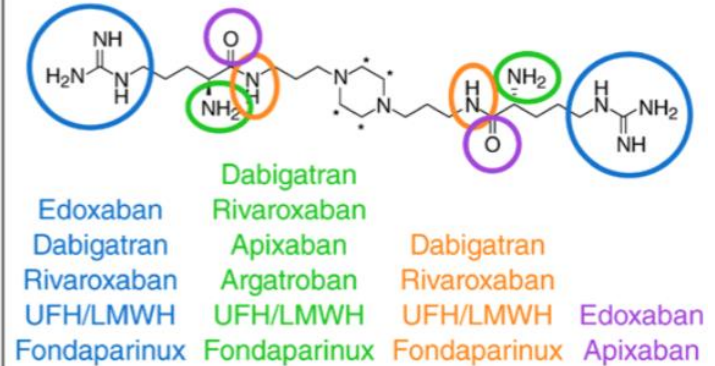


REVERSED
(1 hr post 100 mg i.v. bolus
PER977)



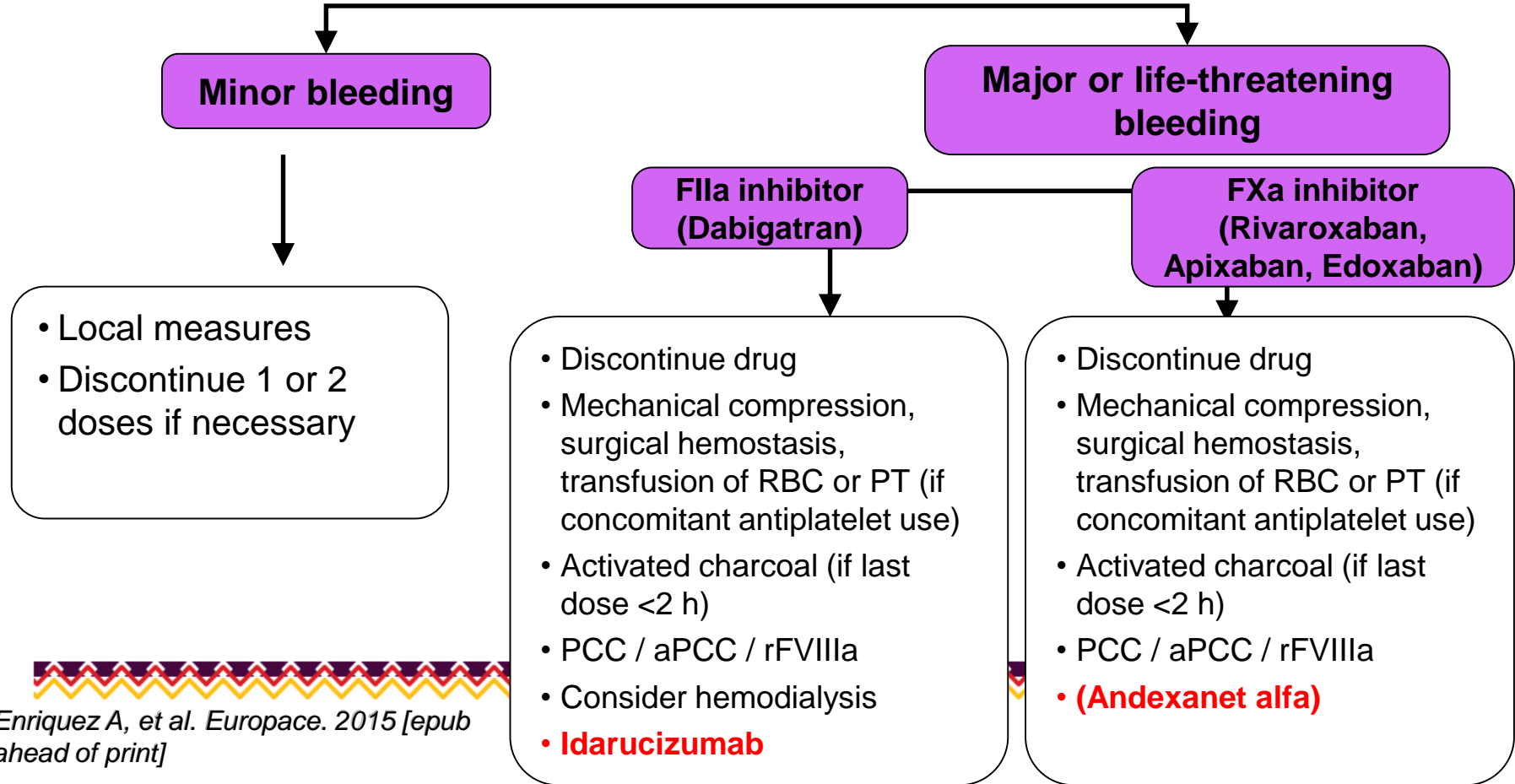
Ciraparantag (PER977)

Apixaban
Argatroban
Edoxaban
Dabigatran
Rivaroxaban
UFH
LMWH
Fondaparinux



Computer-aided energy minimization modeling predicts 8 non-covalent binding sites on ciraparantag for NOACs or heparins

NOAC Bleeding Management Algorithm



Restarting Anticoagulation After GI Bleed

442 Patients with GI Bleed on Warfarin: Outcomes 90 days

| Event | Resumed Warfarin (N=260) | Did Not Resume Warfarin (N=182) | HR (95% CI) | P-value |
|-----------------------|-----------------------------|------------------------------------|------------------|---------|
| Thrombosis | 0.4% | 6% | 0.05 (0.01-0.58) | <0.001 |
| Recurrent GI Bleed | 10% | 6% | 1.32 (0.50-3.57) | 0.09 |
| Death | 6% | 20% | 0.31 (0.15-0.62) | <0.001 |

Restarting anticoagulation is associated with:

Significant 95% reduction in thrombotic events

Significant 69% reduction in death

Non-significant increase in recurrent GI bleed

Summary (NOAGs and Bleeding)

- Serious bleeding is *uncommon* with NOACs
50% less compared to warfarin
- Many bleeds are preventable
Stop unnecessary antiplatelet agents and NSAIDs
- For most bleeds: *temporarily stopping anticoagulation and supportive measures* are all that is needed
- Laboratory coagulation tests have limited utility
- PCCs are the preferred non-specific reversal agent
- Specific antidotes *available for dabigatran and likely soon to be available for Fxa inhibitors*: trauma, urgent surgery, stroke requiring lysis
- Anticoagulation should be *restarted in the majority of patients* who experience a bleed once stabilized

