# Quoi de neuf avec les anticoagulants ?

Hôpital Pitié-Salpêtrière AP-HP

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ACTION Group

SORBONNE UNIVERSITÉ

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CARDIO RUN 2024

16ème CONGRÈS DE PATHOLOGIE CARDIO-VASCULAIRE

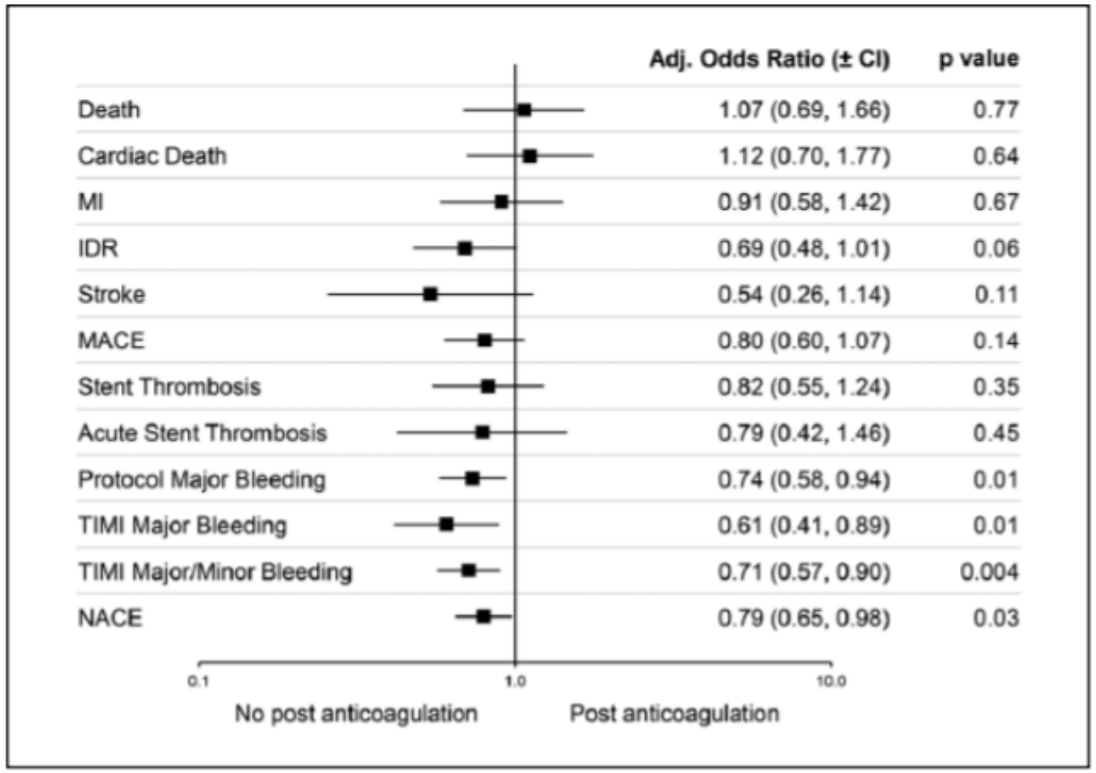
18-19-20 SEPTEMBRE 2024

Hôtel Saint Alexis ILE DE LA RÉUNION France

# Primary PCI anticoagulation

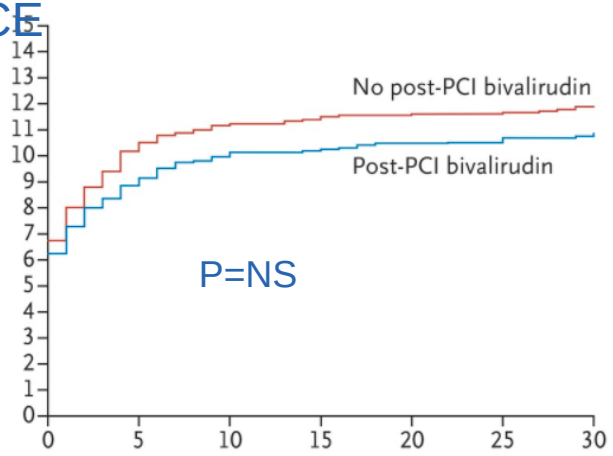
# Pooled EUROMAX and HORIZON MI n=5239

➔ L'anticoagulation **post-primary PCI** augmente les bleeding sans diminuer les évènements ischémiques

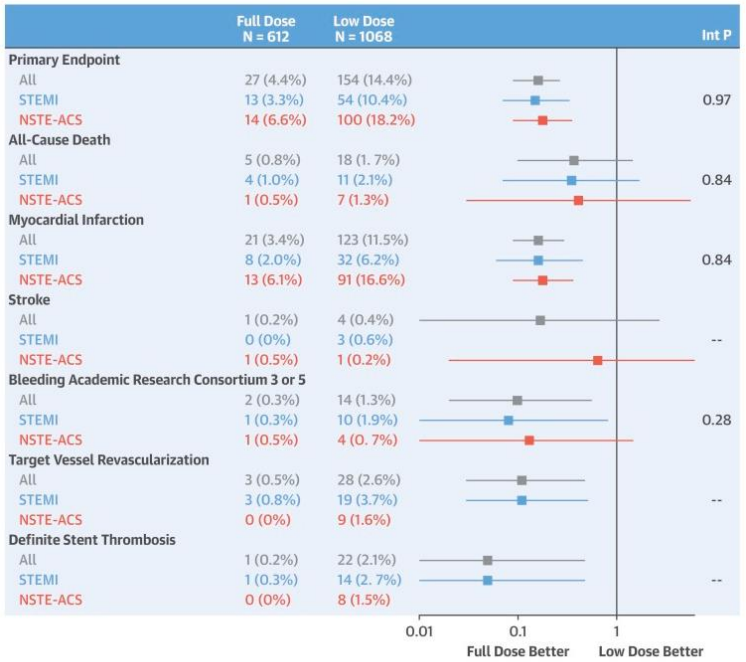



# MATRIX trial Bivalirudine versus HNF

➔ L'infusion de Bivalirudine **post-PCI** ne réduit pas les MACE




➔ Mais l'infusion forte dose > faible dose …




Gargiulo, G. et al. J Am Coll Cardiol. 2019;73(7):758-74.

# ATOLL : primary PCI

Randomization as *early* as possible
*Real life* population (shock, cardiac arrest included)
***No anticoagulation before*** Rx
***Similar antiplatelet*** therapy in both groups

**STEMI → Primary PCI**

| ENOXAPARIN IV | UFH IV |
|---|---|
| 0.5 mg/kg | 50-70 IU with GP IIbIIIa |
| with or without GPIIbIIIa | 70-100IU without GP IIbIIIa |
| | (Dose ACT-adjusted) |

**Primary PCI**

| ENOXAPARIN SC | UFH IV or SC |
|---|---|

**30 days**

***1° EP:*** **Death, Complication of MI, Procedure Failure, Major Bleeding**

***Main 2° EP:*** **Death, recurrent MI/ACS, Urgent Revascularization**

Montalescot G, et al. *Lancet*. 2011;378:693-703

*Montalescot G, et al. Lancet. 2011;378:693-703*

**The primary endpoint occurred in 126 (28%) patients after anticoagulation with enoxaparin versus 155 (34%) patients on unfractionated heparin**

**Relative risk [RR] 0·83, 95% CI 0·68–1·01, p=0·06**

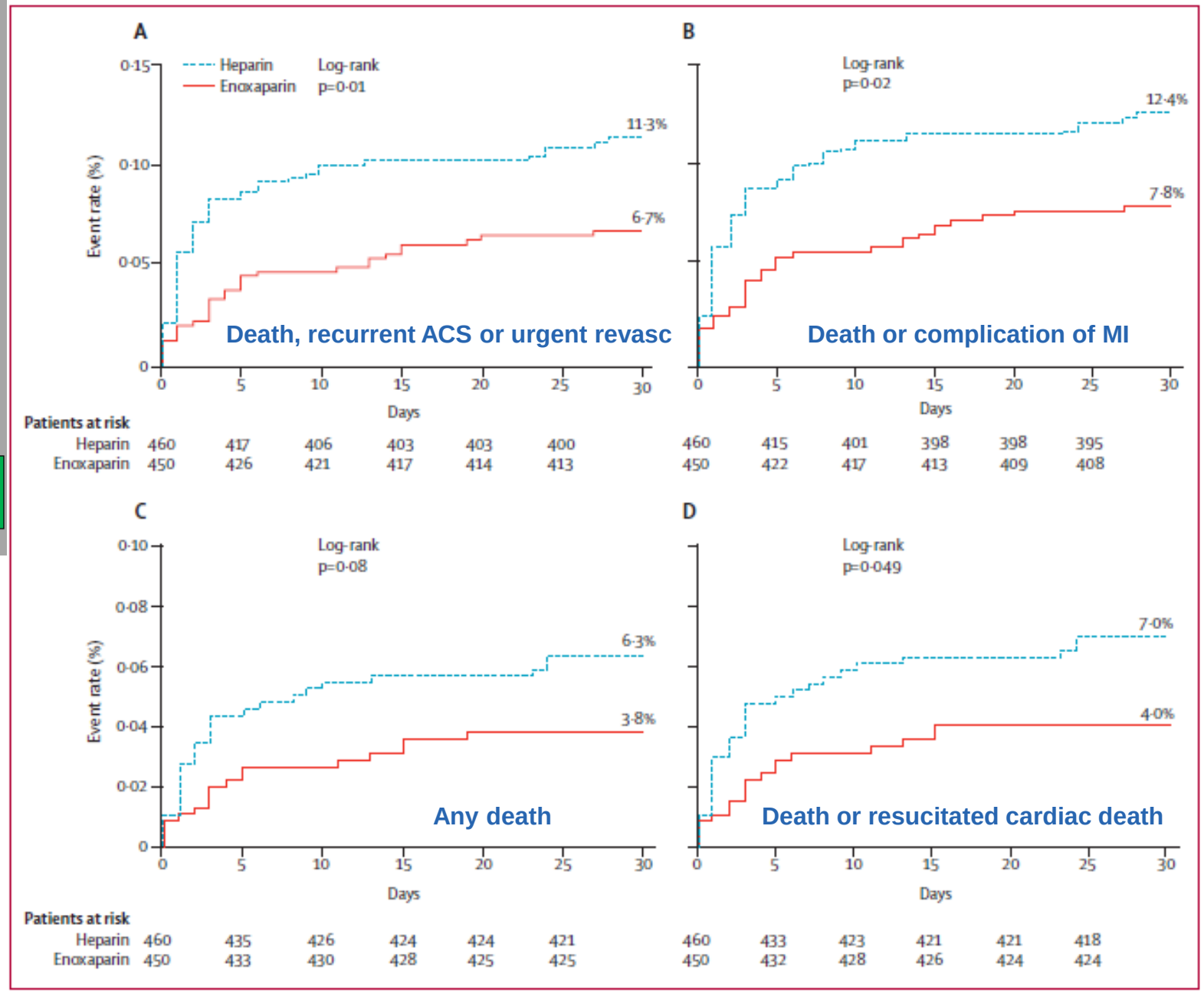
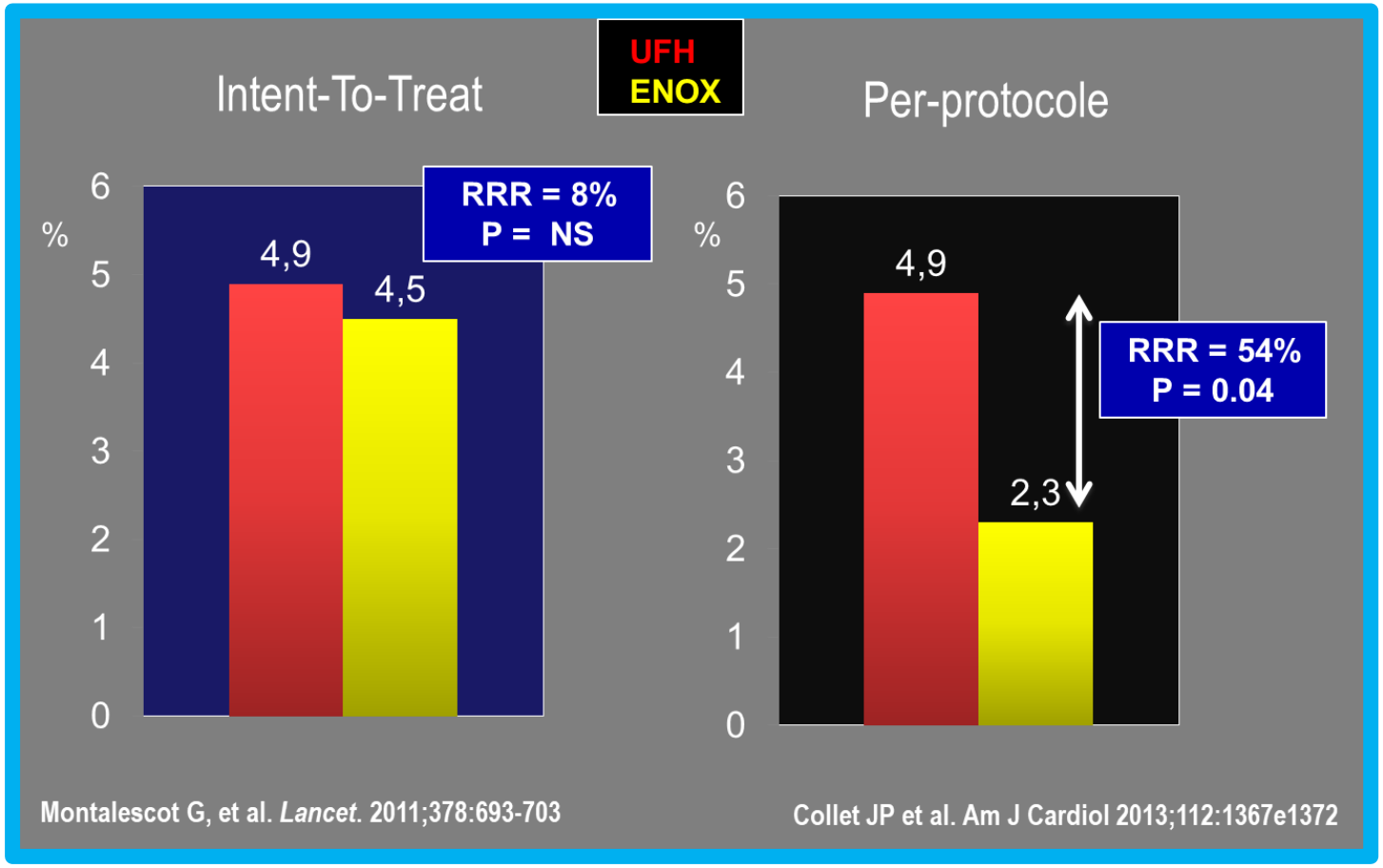
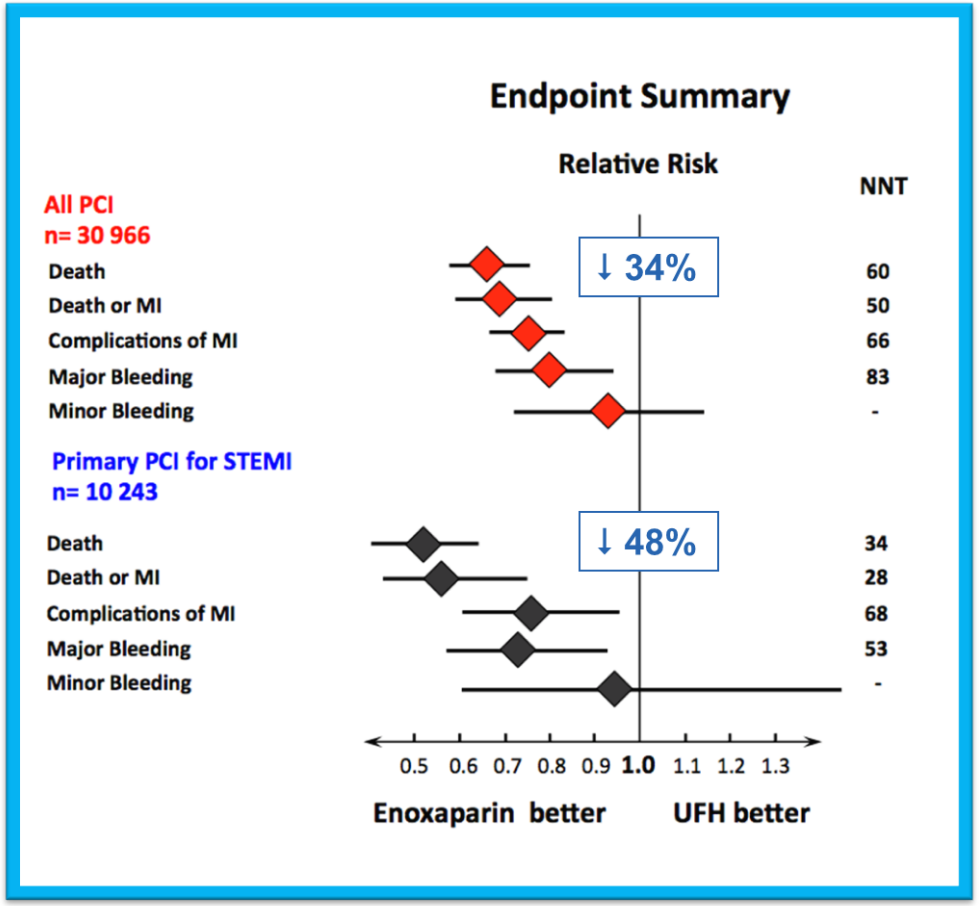



***Figure 2:*** **Clinical outcomes at 30 days in patients on enoxaparin or unfractionated heparin**
Time-to-event curves through 30 days are shown for (A) the main secondary endpoint of death, recurrent acute coronary syndrome, or urgent revascularisation, (B) death or complication of myocardial infarction, (C) any death, and (D) death or resuscitated cardiac death. All these endpoints were prespecified.

# ATOLL, per-protocole



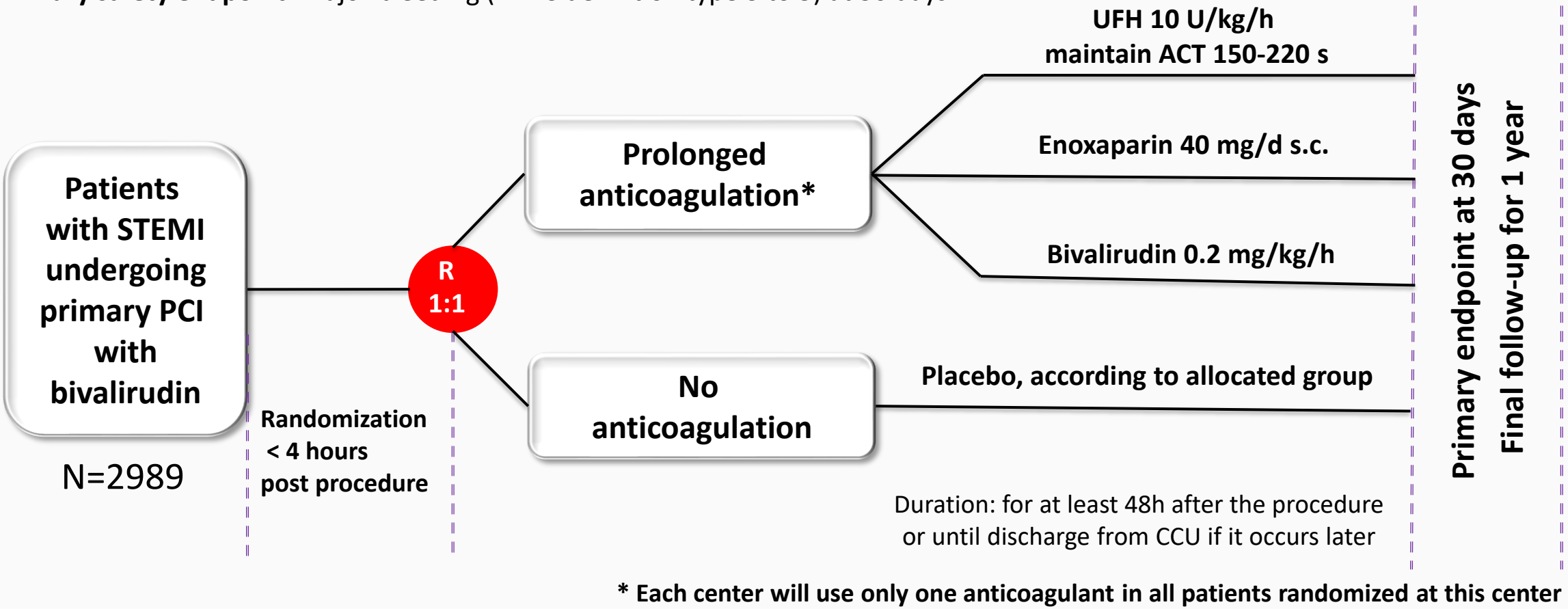

# ATOLL → Metaanalysis




J. Silvain et al. BMJ 2012

# RIGHT Trial Design

- **Investigator-initiated, multicentre, randomised, double-blind**, placebo-controlled trial at 53 sites in China
- **Primary efficacy endpoint：** composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, stent thrombosis (definite) or urgent revascularization (any vessel) at 30 days
- **Primary safety endpoint:** major bleeding (BARC definition type 3 to 5) at 30 days




*** Each center will use only one anticoagulant in all patients randomized at this center**

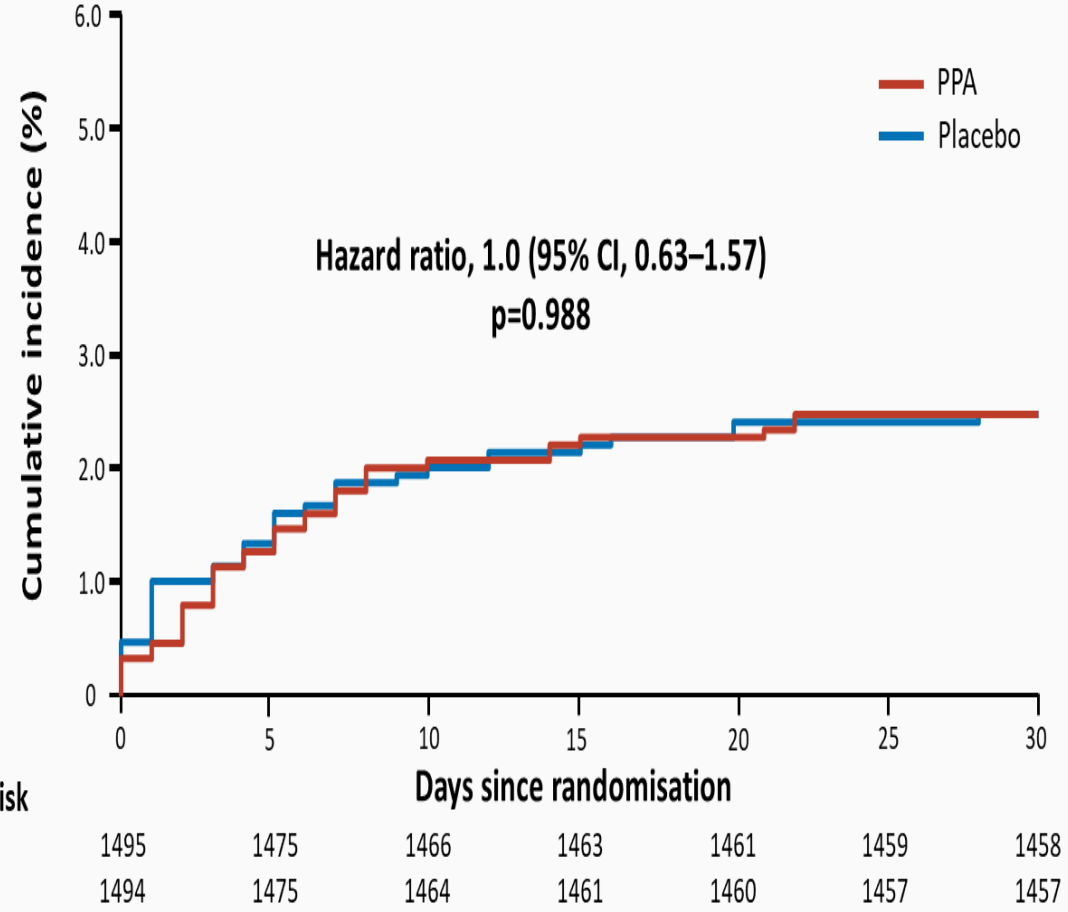


Am Heart J 2020;227:19-30; RIGHT ClinicalTrials.gov number, NCT 03664180

# Primary Outcomes at 30 Days

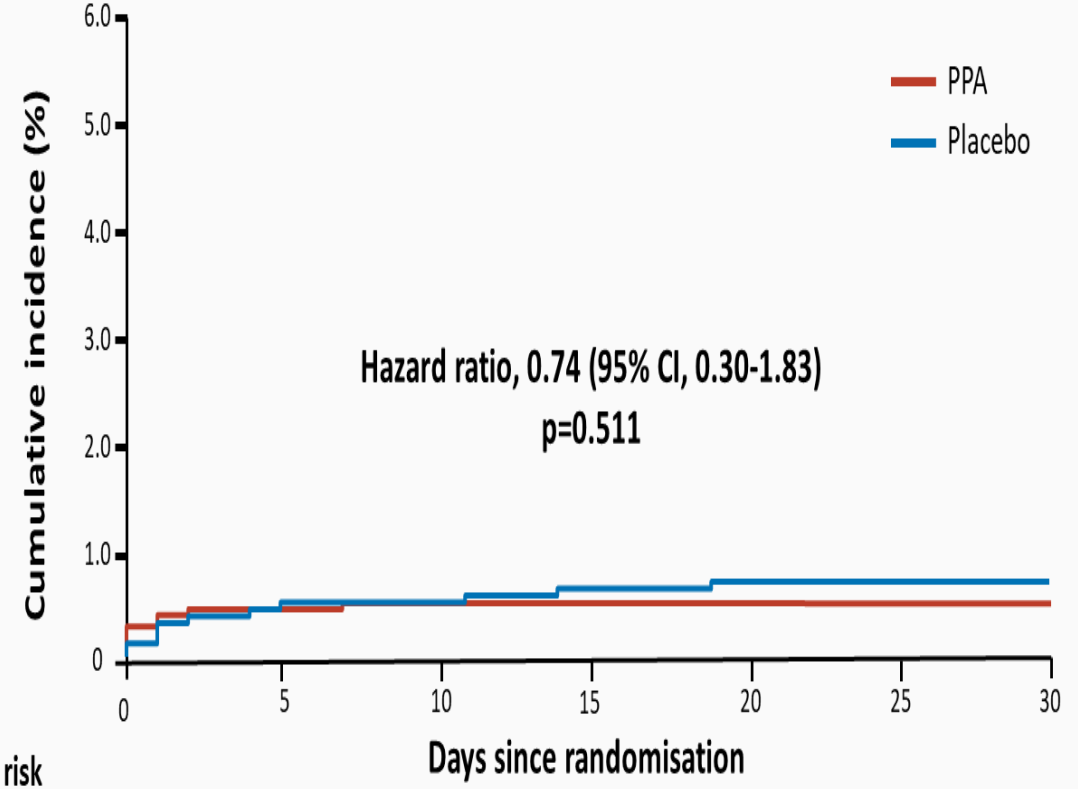
RIGHT

- **MACE**




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 1495 | 1475 | 1466 | 1463 | 1461 | 1459 | 1458 |
| PPA | 1494 | 1475 | 1464 | 1461 | 1460 | 1457 | 1457 |

- **Major bleeding**




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 1488 | 1470 | 1462 | 1458 | 1457 | 1456 | 1456 |
| PPA | 1468 | 1448 | 1440 | 1438 | 1437 | 1435 | 1435 |

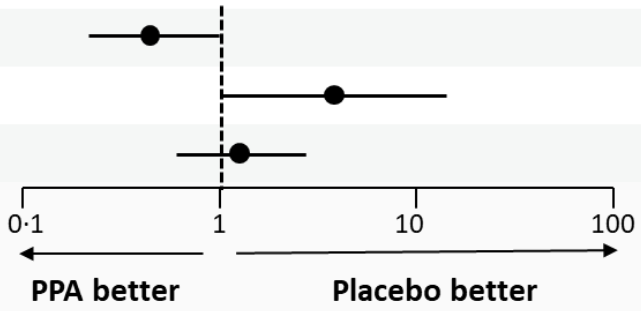



Circulation. 2024;149(16):1258-1267

# Secondary Exploratory Findings at 30 Days

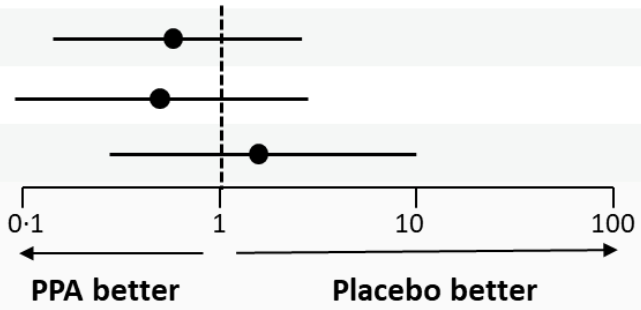
**A** Primary efficacy outcome in three anticoagulation regimen groups

| Subgroup | PPA | Placebo | Hazard ratio (95%CI) | *p for interaction 0·015* |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| Enoxaparin | 10/474 (2·1) | 21/471 (4.5) | | 0·46 (0·22-0·98) |
| UFH | 11/510 (2·2) | 3/512 (0·6) | | 3·71 (1·03-13·28) |
| Bivalirudin | 16/510 (3·1) | 13/512 (2·5) | | 1·24 (0·60-2·59) |




**B** Primary safety outcome in three anticoagulation regimen groups

| Subgroup | PPA | Placebo | Hazard ratio (95%CI) | *p for interaction 0·679* |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| Enoxaparin | 3/466 (0·6) | 5/470 (1·1) | | 0·60 (0·14-2·52) |
| UFH | 2/503 (0·4) | 4/508 (0·8) | | 0·50 (0·09-2·75) |
| Bivalirudin | 3/499 (0·6) | 2/510 (0·4) | | 1·54 (0·26-9·24) |

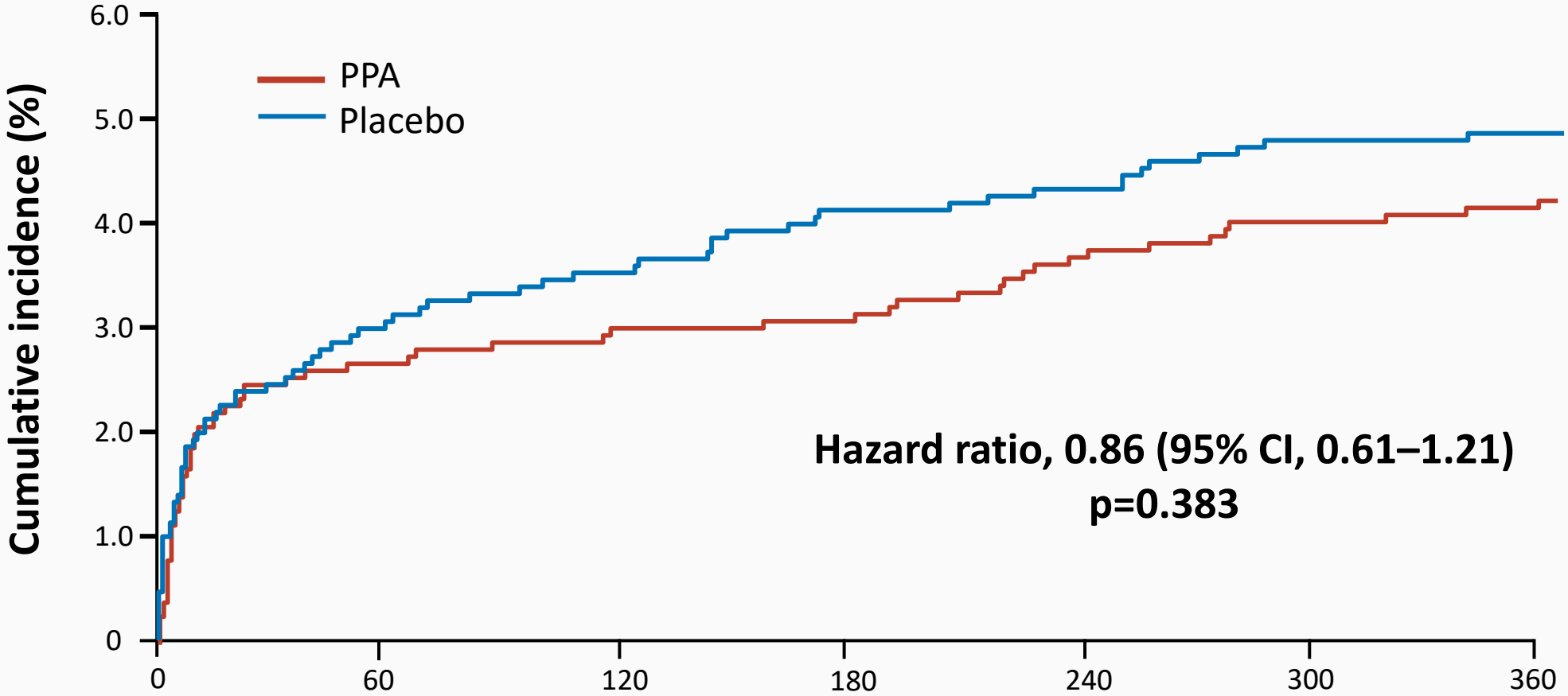





Circulation. 2024;149(16):1258-1267

# MACE at 1 Year

RIGHT




**No. at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 1495 | 1437 | 1430 | 1421 | 1418 | 1411 | 1410 |
| PPA | 1494 | 1441 | 1436 | 1435 | 1426 | 1421 | 1419 |

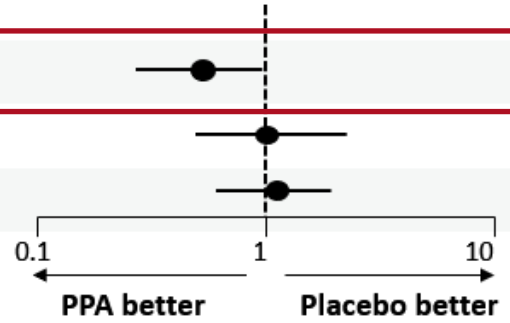


MACE: Death, MI, stroke, stent thrombosis or urgent revascularization

# Secondary Exploratory Findings at 1 Year

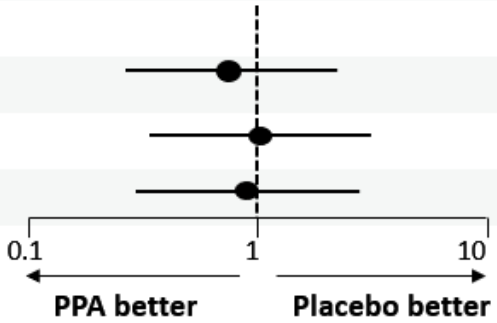
**A** MACE in three anticoagulation regimen groups

| Subgroup | PPA | Placebo | Hazard ratio (95%CI) | *P for interaction 0.134* |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| Enoxaparin | 17/474 (3.6) | 31/471 (6.6) | | 0.53 (0.30-0.97) |
| UFH | 16/510 (3.1) | 15/512 (2.9) | | 1.08 (0.53-2.18) |
| Bivalirudin | 30/510 (5.9) | 27/512 (5.3) | | 1.12 (0.66-1.88) |




**B** BARC 3 to 5 in three anticoagulation regimen groups

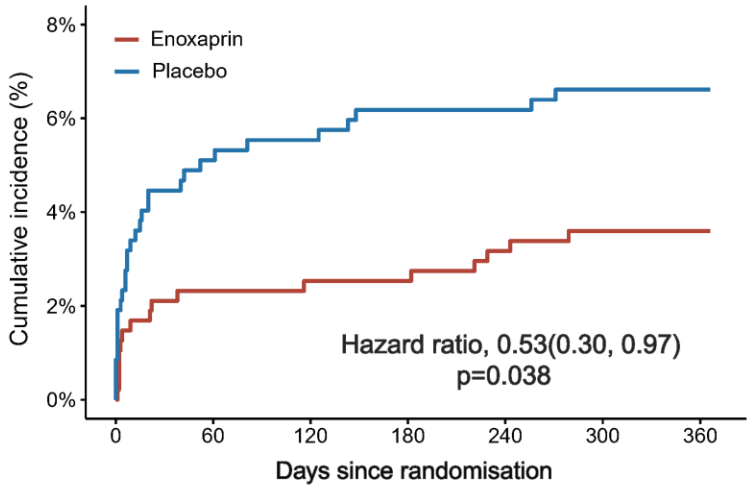
| Subgroup | PPA | Placebo | Hazard ratio (95%CI) | *p for interaction 0.924* |
|---|---|---|---|---|
| | *no./total no. (%)* | | | |
| Enoxaparin | 6/466 (1.3) | 8/470 (1.7) | | 0.75 (0.26-2.16) |
| UFH | 7/503 (1.4) | 7/508 (1.4) | | 1.01 (0.36-2.89) |
| Bivalirudin | 6/499 (1.2) | 7/510 (1.4) | | 0.88 (0.30-2.62) |



# Secondary Exploratory Findings at 1 Year

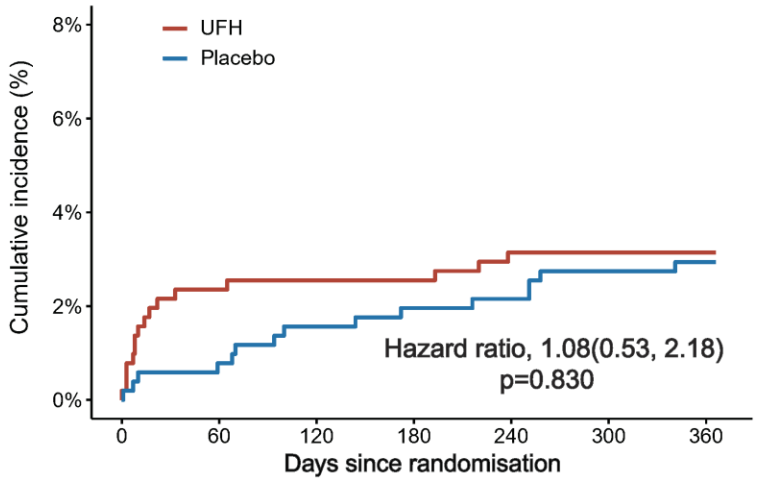
RIGHT

## 1-year MACE in three anticoagulation regimen groups



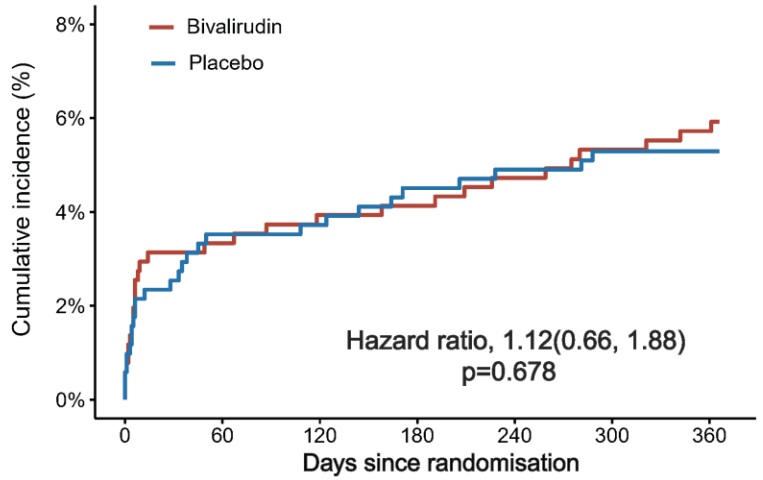

No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Enoxaprin | 474 | 460 | 459 | 459 | 456 | 454 | 454 |
| Placebo | 471 | 441 | 439 | 436 | 436 | 434 | 434 |




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| UFH | 510 | 495 | 494 | 494 | 491 | 491 | 491 |
| Placebo | 512 | 506 | 502 | 500 | 499 | 496 | 495 |




No. at risk

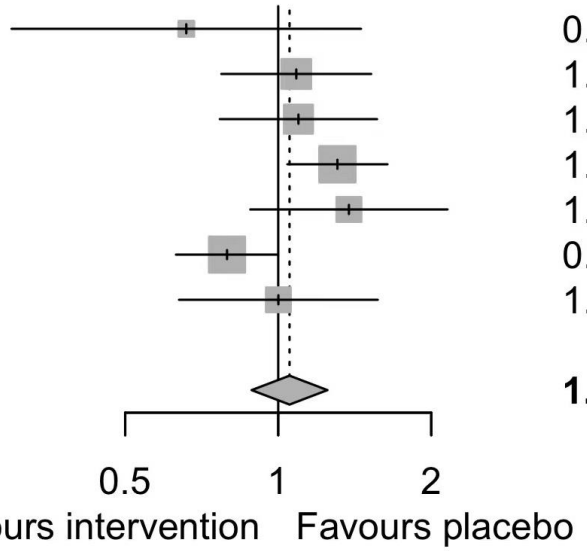
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Bivalirudin | 510 | 486 | 483 | 482 | 479 | 476 | 474 |
| Placebo | 512 | 490 | 489 | 485 | 483 | 481 | 481 |

- **Enoxaparin**
- **UFH**
- **Bivalirudin**

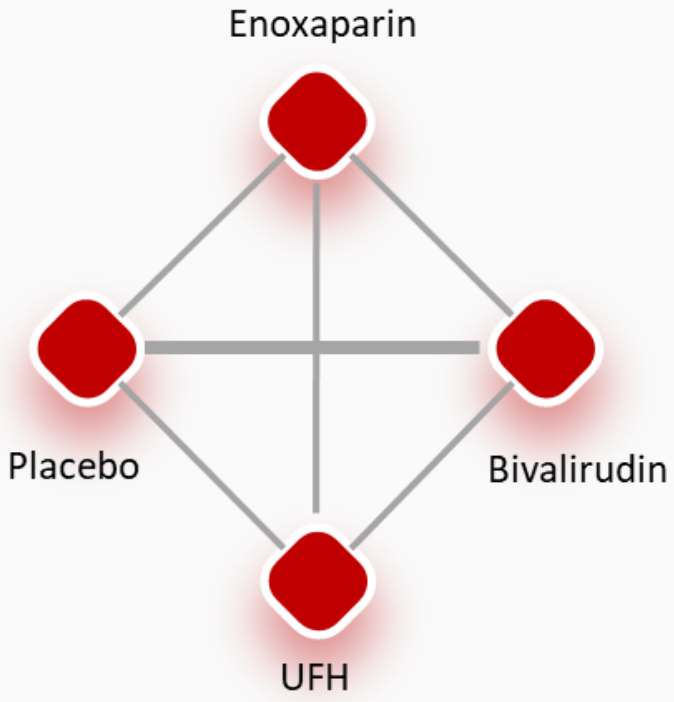
# MA: PPA vs. no PPA on MACE at 30 Days

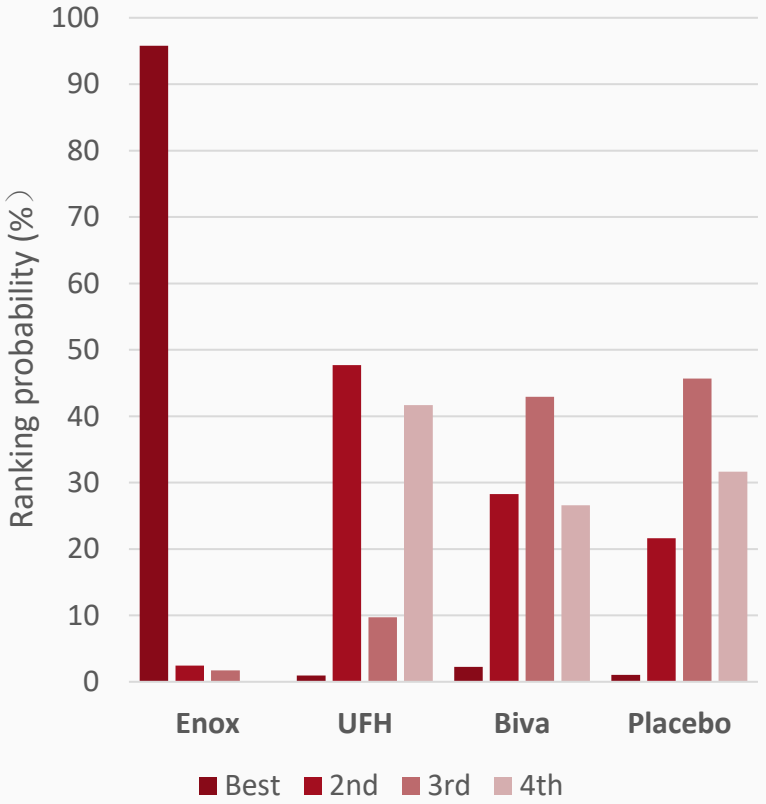
| Study | Experimental Events | Experimental Total | Control Events | Control Total | RR | 95%-CI | Weight |
|---|---|---|---|---|---|---|---|
| ATLAST (2001) | 10 | 555 | 15 | 549 | 0.66 | [0.30; 1.46] | 4.2% |
| EUROMAX (2013) | 65 | 1089 | 61 | 1109 | 1.09 | [0.77; 1.52] | 15.2% |
| MATRIX (2015) | 57 | 918 | 57 | 1006 | 1.10 | [0.77; 1.56] | 14.4% |
| EUROMAX and HORIZONS-AMI (2017) | 135 | 2153 | 148 | 3086 | 1.31 | [1.04; 1.64] | 22.7% |
| GLOBAL LEADERS Study (2020) | 51 | 1038 | 29 | 813 | 1.38 | [0.88; 2.15] | 10.6% |
| BRIGHT-4 (2022) | 123 | 3009 | 155 | 3007 | 0.79 | [0.63; 1.00] | 22.4% |
| RIGHT (2024) | 37 | 1494 | 37 | 1495 | 1.00 | [0.64; 1.57] | 10.5% |
| **Random effects model** | | **10256** | | **11065** | **1.05** | **[0.89; 1.25]** | **100.0%** |

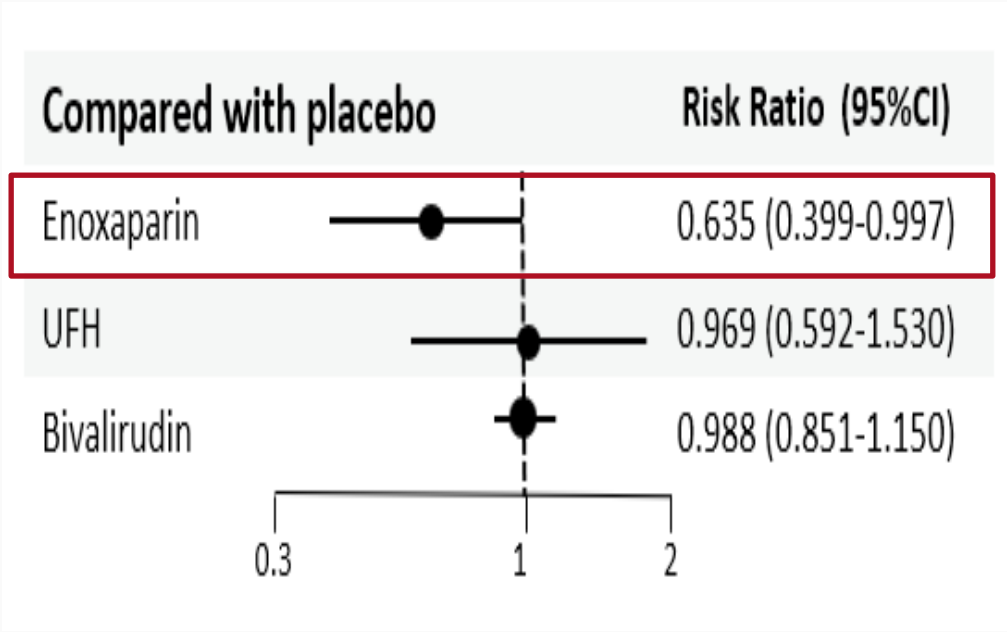
Heterogeneity: $I^2$ = 51%, $\tau^2$ = 0.0204, $p$ = 0.06



# Network Analysis: Heterogeneity of Anticoagulants on MACE at 30 Days



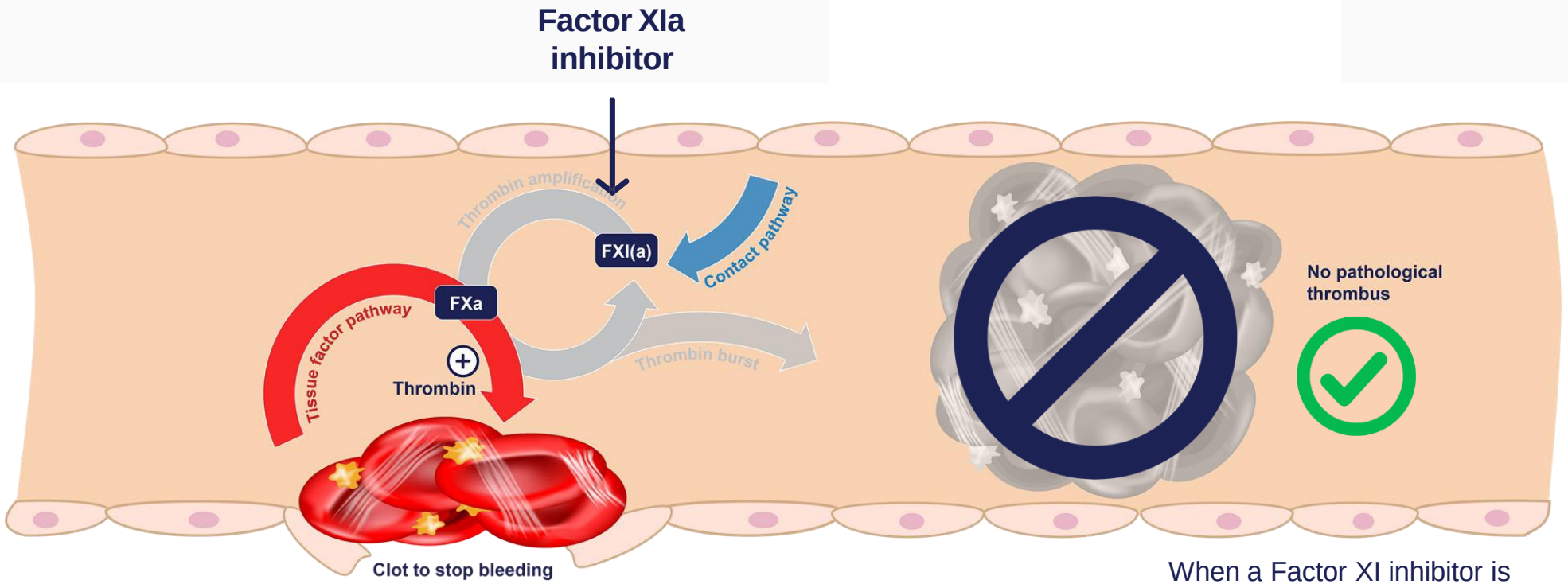




- **Network plot**
- **Ranking plot**
- **Forest plot**

# Anti-XI et FA

# Factor XIa inhibitor

## Hypothesis: Uncoupling Hemostasis from Thrombosis




AND the tissue factor pathway still produces thrombin, which allows beneficial blood clots to form.

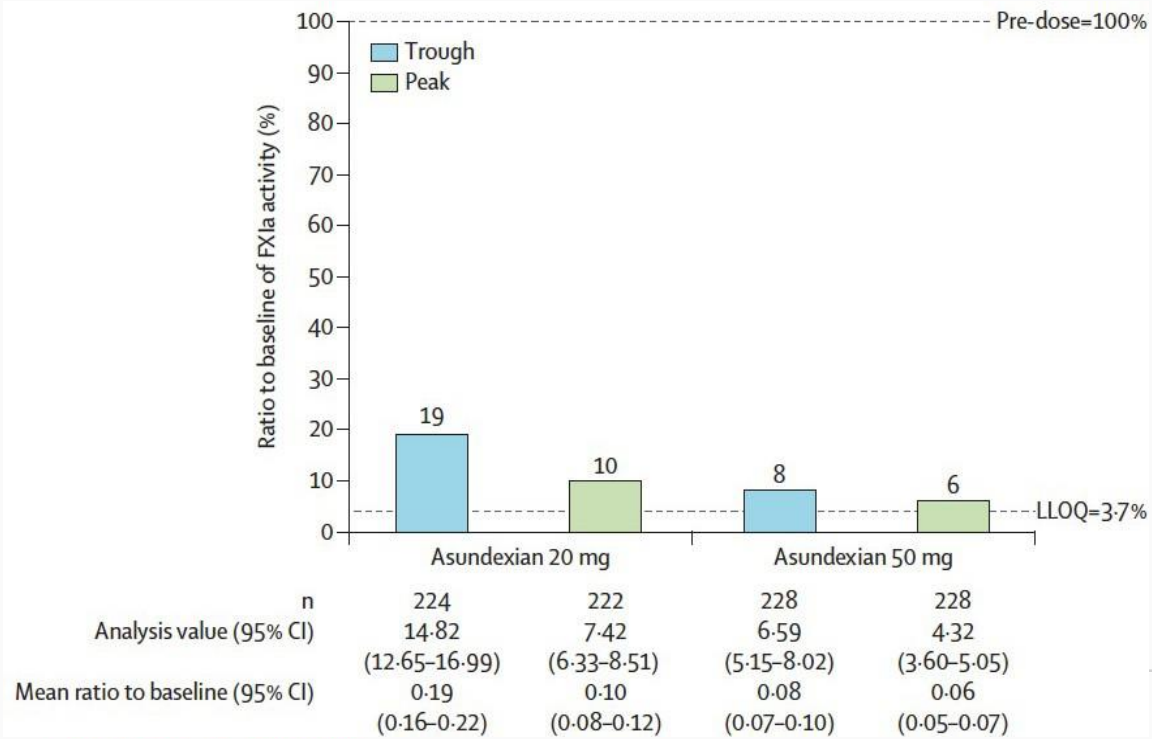
When a Factor XI inhibitor is used, thrombin amplification is inhibited, which prevents pathological thrombi—

# Phase 2, PACIFIC-AF

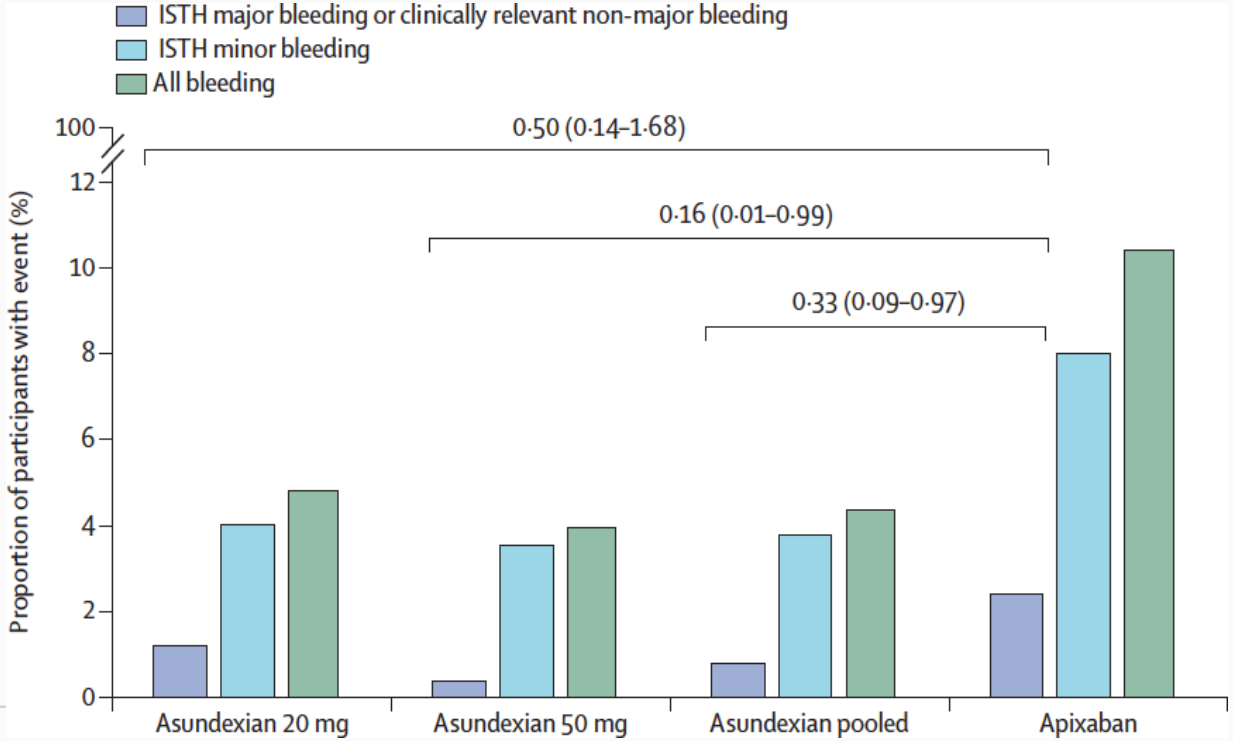
## Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

*Jonathan P Piccini, Valeria Caso, Stuart J Connolly, Keith A A Fox, Jonas Oldgren, W Schuyler Jones, Diana A Gorog, Václav Durdil, Thomas Viethen, Christoph Neumann, Hardi Mundl, Manesh R Patel, on behalf of the PACIFIC-AF Investigators**

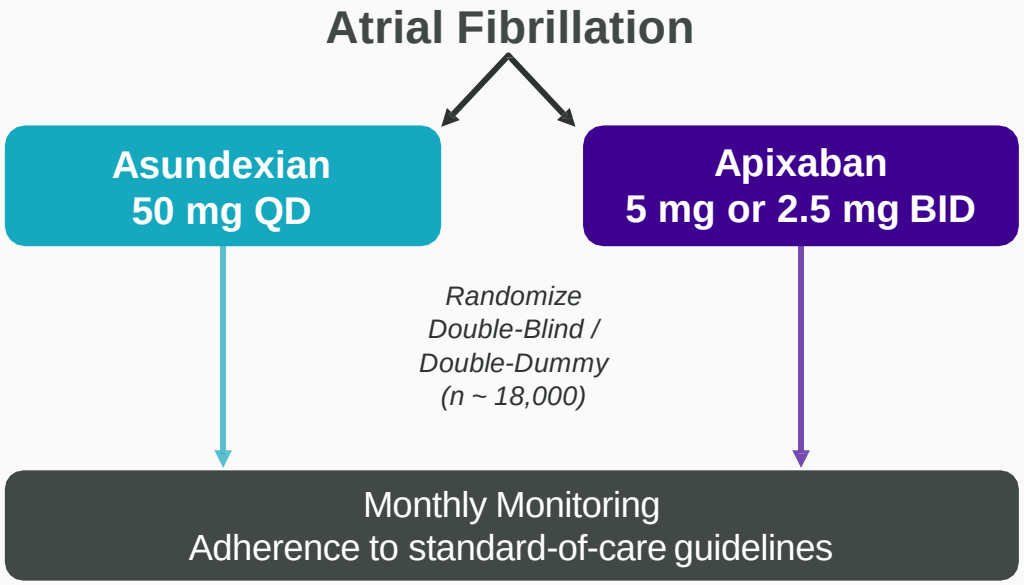
### FXIa Activity — Inhibition Data




### Primary Safety Outcome (ISTH bleeding classification)

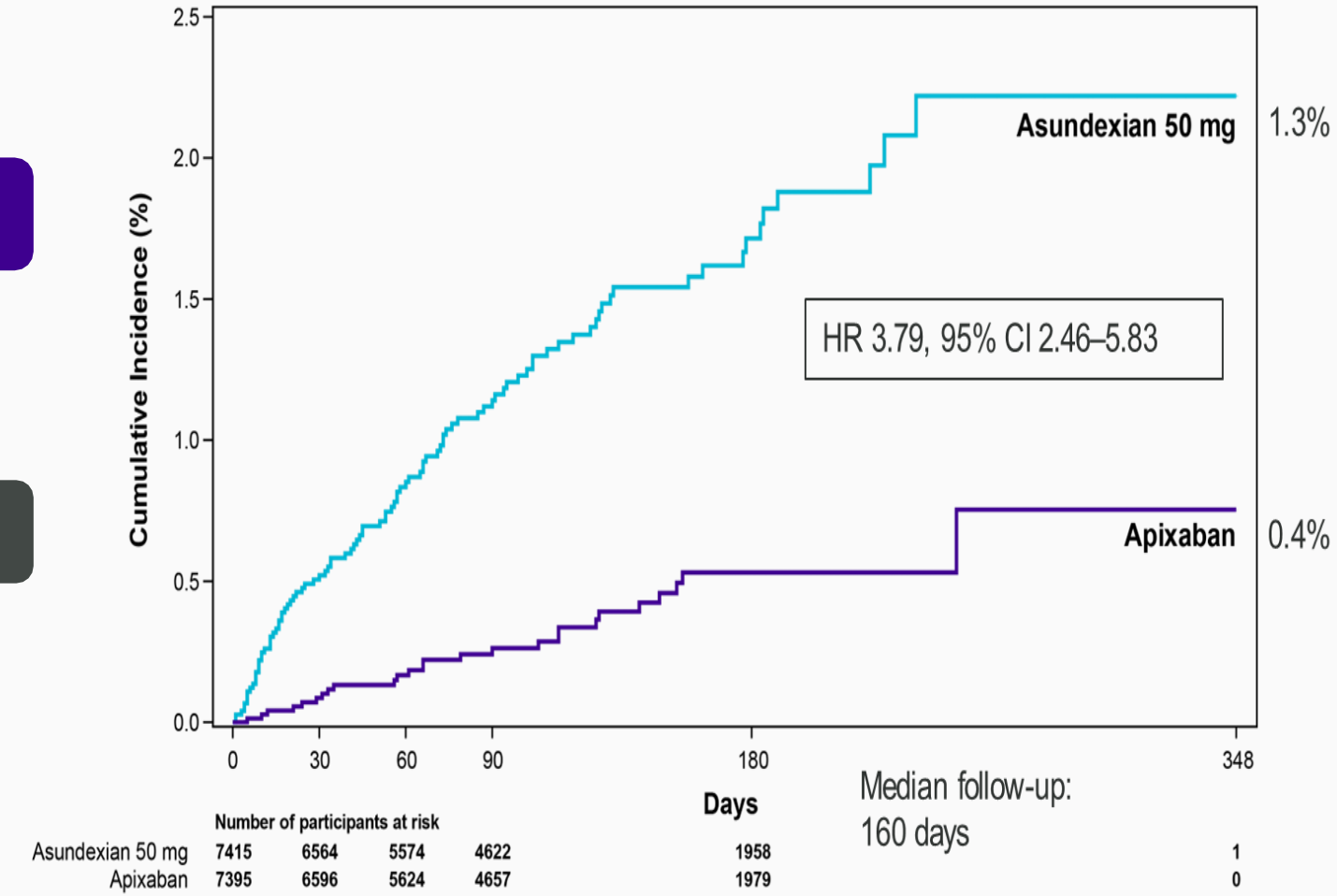


# Phase 3 (OCEANIC-AF), 1° outcome




**Primary Efficacy Endpoint:** Stroke or Systemic Embolism

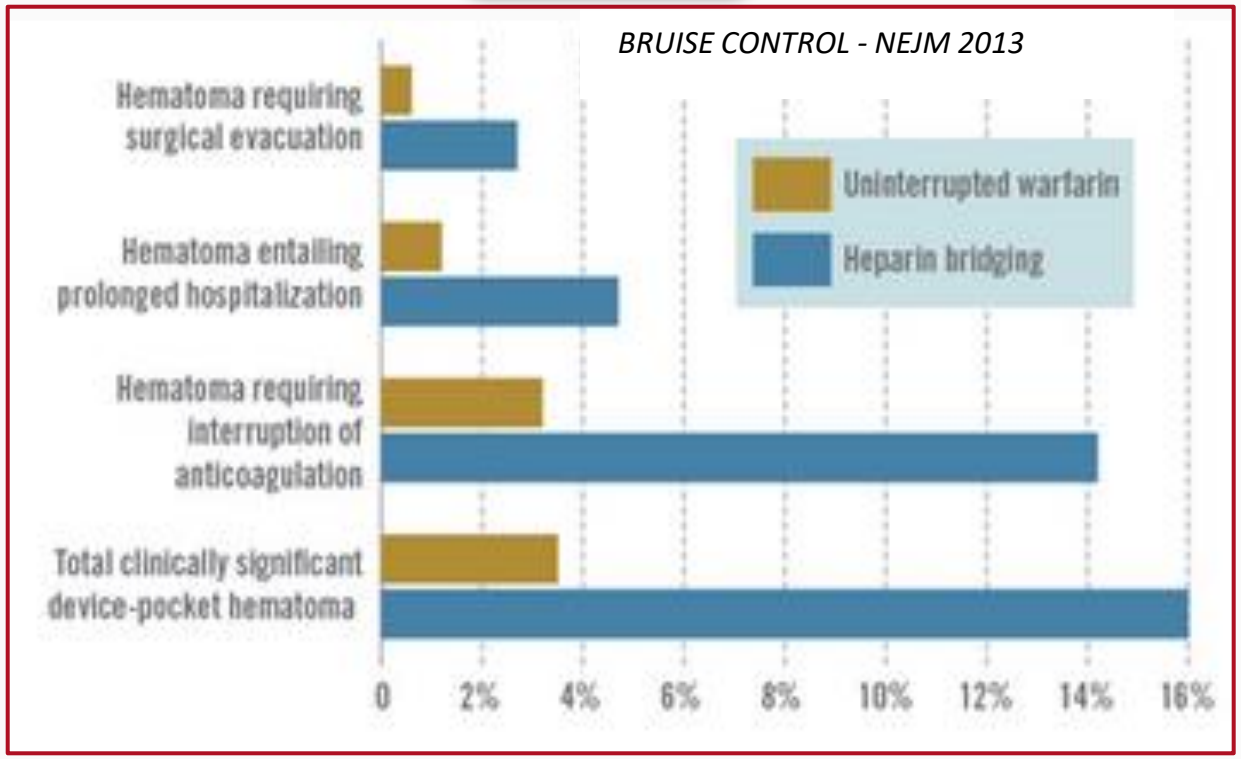
**Primary Safety Endpoint:** ISTH Major Bleeding

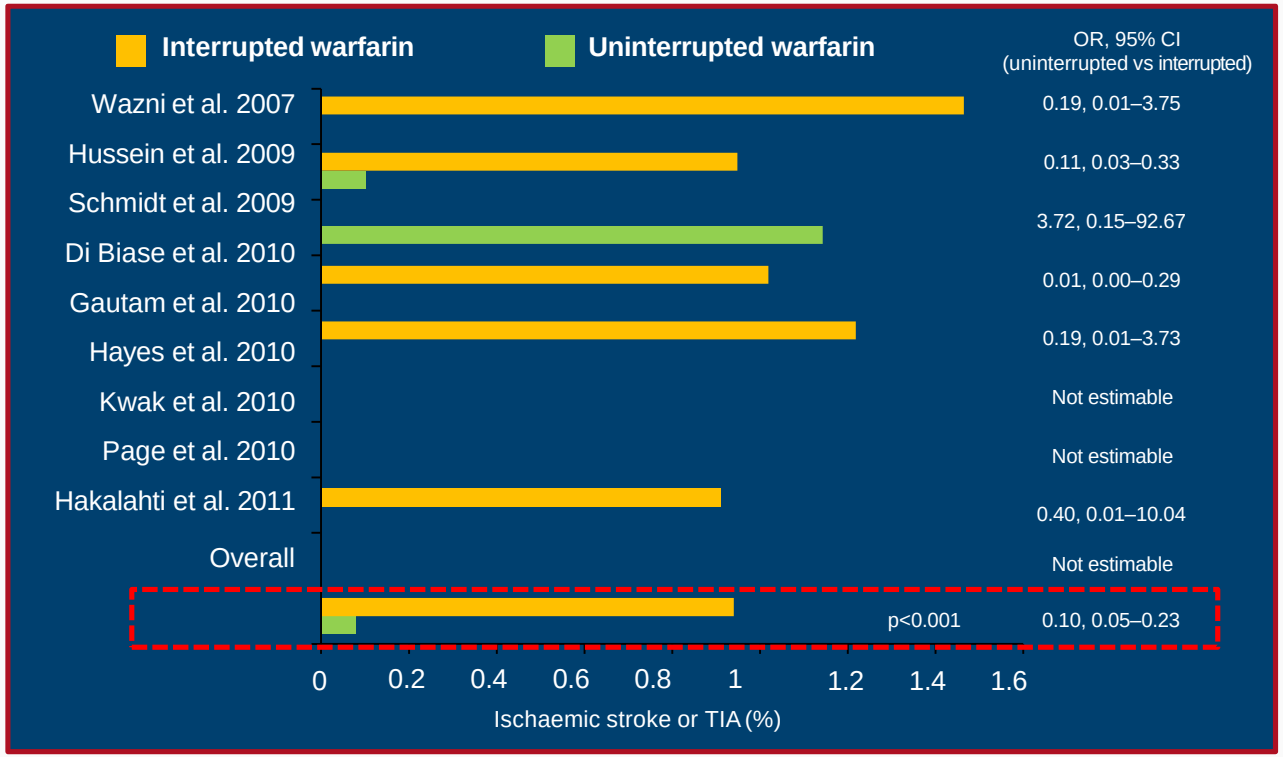



| | | | |
|---|---|---|---|
| ISTH major bleeding | 17 (0.2%) | 53 (0.7%) | 0.32 (0.18–0.55) |

# Anticoagulation interruption before cath

# Interruption with bridging << Continuation

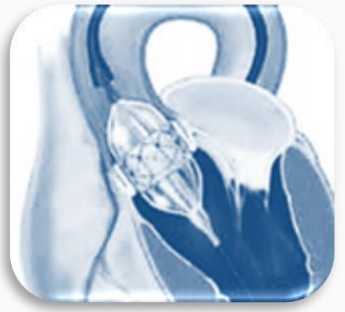


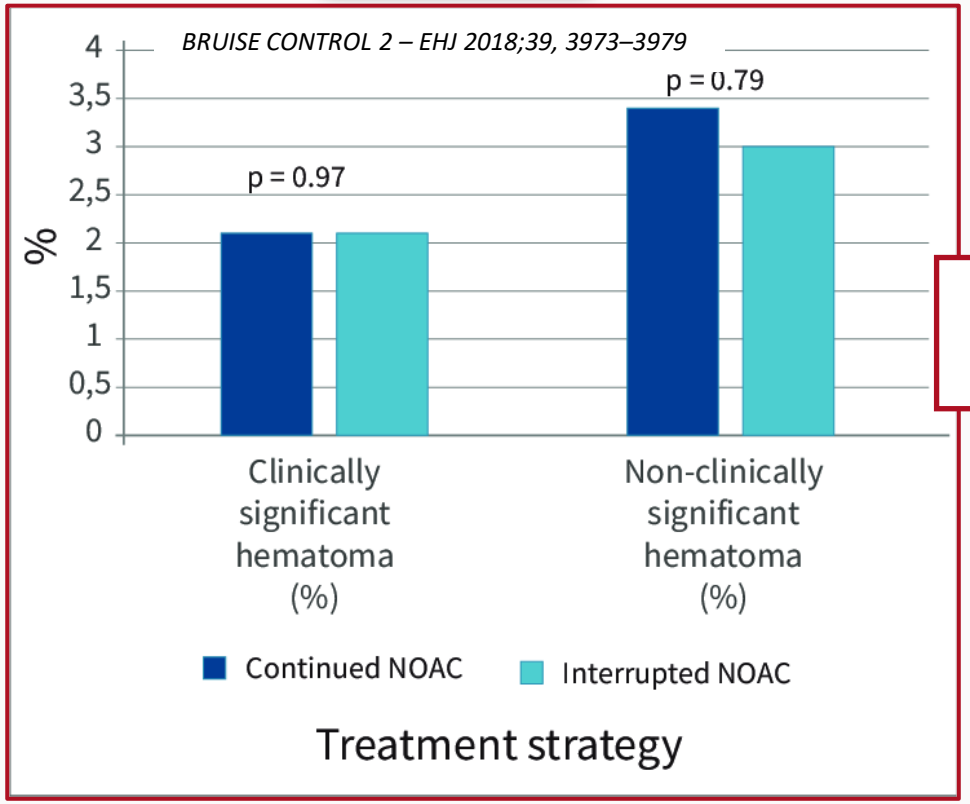




Santangeli P, et al. Circ Arrhthm Electrophysiol 2012;5:302–11.

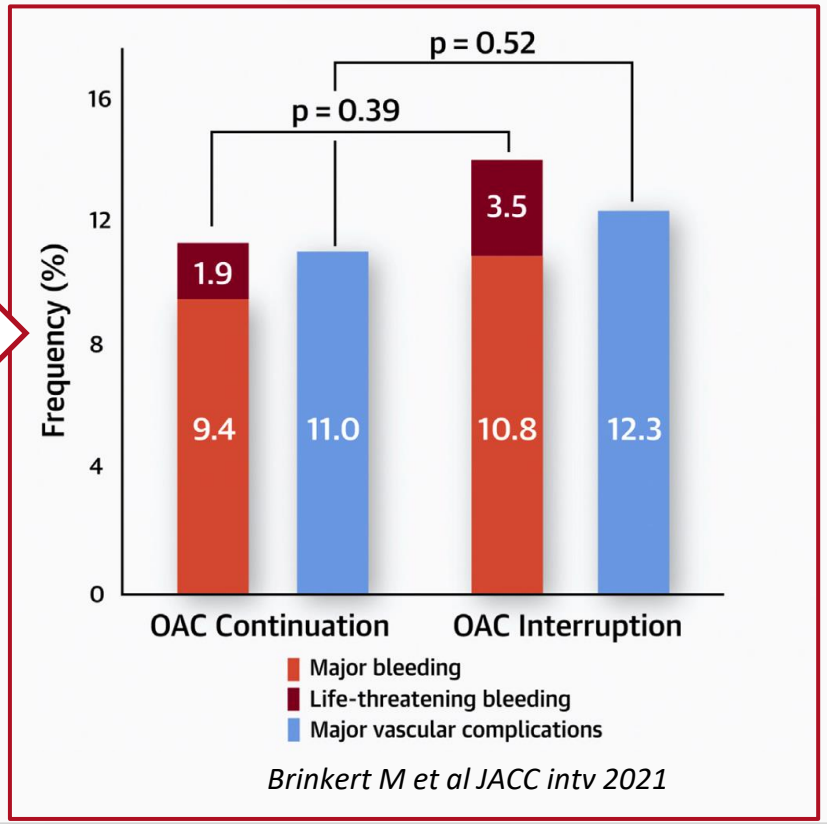
# Interruption = Continuation

# Do the lessons learnt on the venous side apply to TAVI?



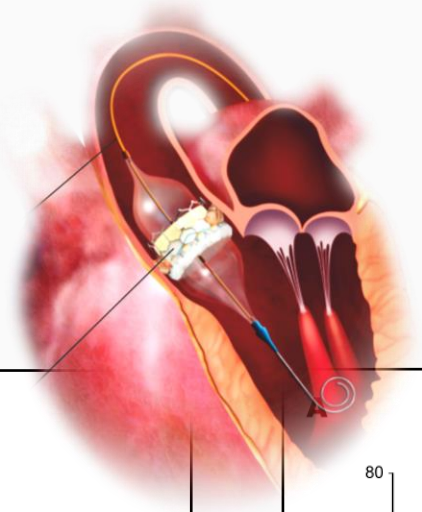



?

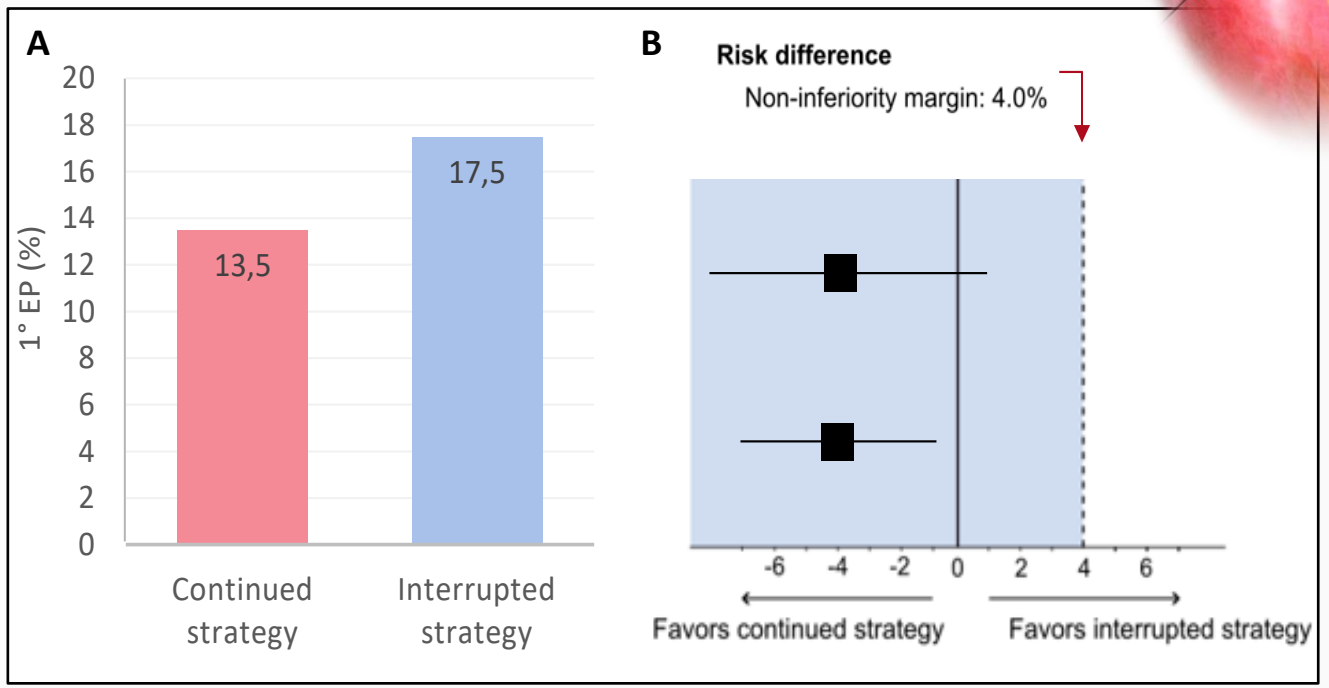



*Brinkert M et al JACC intv 2021*

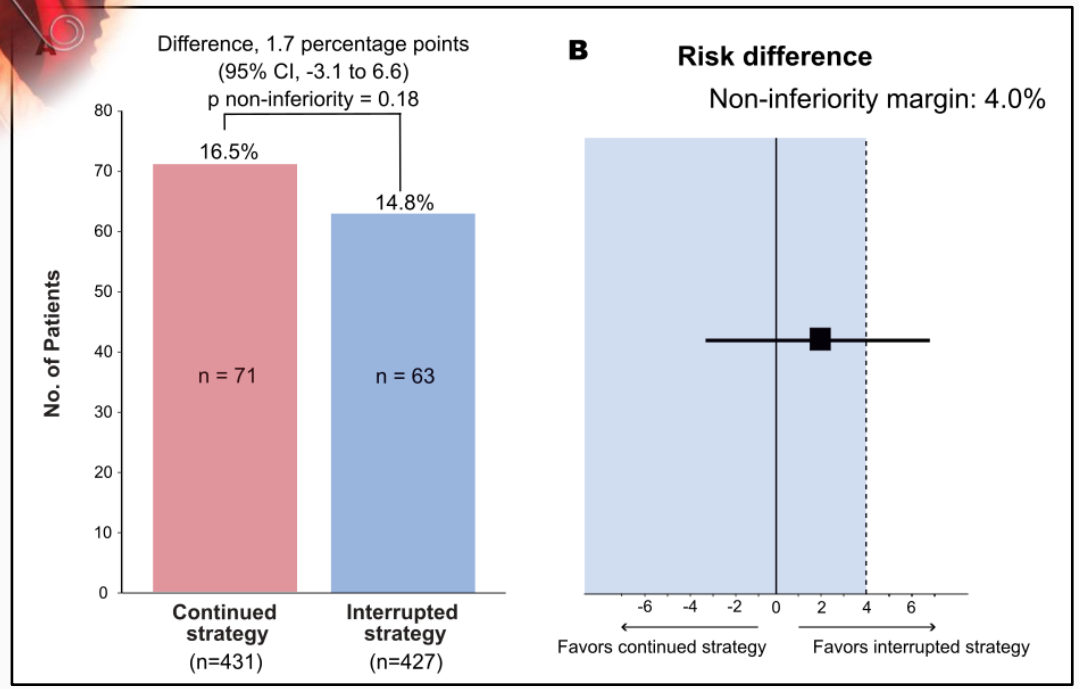
# Non-Inferiority Hypothesis of POPULAR-PAUSE TAVI



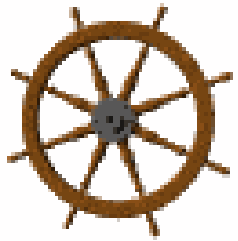
## HYPOTHESIS




## RESULT



*Merci!*



*action-groupe.org*

Pitié-Salpêtrière