

# Anti-Thrombotic Therapy – Update 2017

Sophia-Antipolis (France), February 23-25 2017  
European Heart House

## SESSION 9: COEXISTING ATRIAL FIBRILLATION AND CAD

February 25 2017  
10:50-11:30

After an ACS

Raffaele De Caterina



“G. d’Annunzio” University – Chieti and  
“G. Monasterio” Foundation – Pisa, Italy

February 25, 2017 – 11:10-11:25 – 15 min. + 5 disc.

- ▶ Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
- ▶ Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI
- ▶ Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck

## 2 possible scenarios

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- ▶ Scenario 1: the patient with AF developing an ACS
- ▶ Scenario 2: the patient with a recent ACS (<1 year) who develops AF

AF=atrial fibrillation; ACS=acute coronary syndrome

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# Scenario 1: the patient with AF developing an ACS

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- ▶ In case the patient is treated with VKAs, the official suggestion is to perform PCI on uninterrupted VKAs, adding aspirin + clopidogrel – avoiding prasugrel or ticagrelor
- ▶ Then continue such «triple therapy» for the shortest possible time
- ▶ In this condition, for a variable time after the ACS, the patient needs DAPT, especially after stenting
- ▶ Since the duration of DAPT impacts bleeding, the «best possible stent», in terms of risk of stent thrombosis should be chosen

ORIGINAL ARTICLE

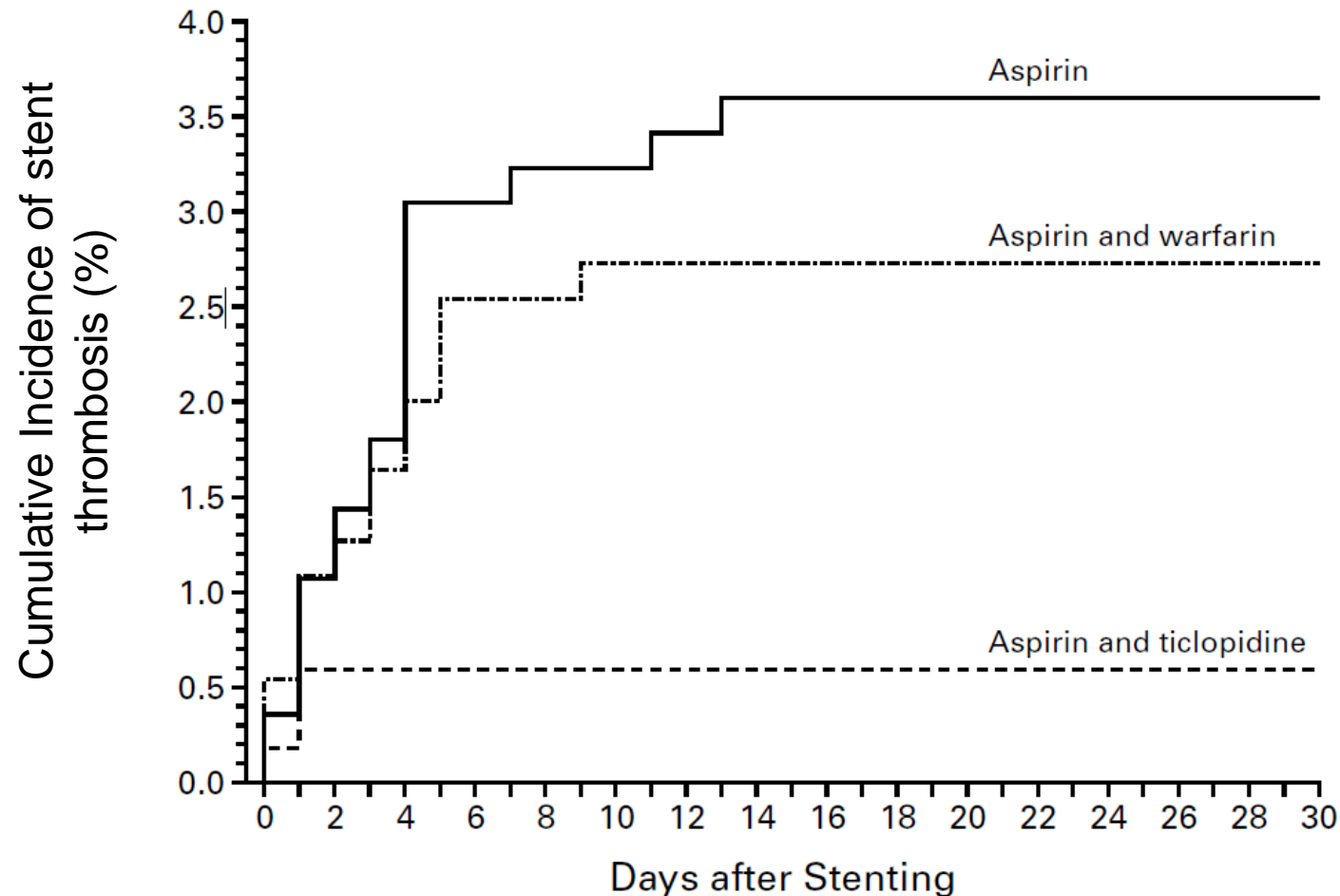
## Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk

Philip Urban, M.D., Ian T. Meredith, M.B., B.S., Ph.D.,  
Alexandre Abizaid, M.D., Ph.D., Stuart J. Pocock, Ph.D.,  
Didier Carrié, M.D., Ph.D., Christoph Naber, M.D., Ph.D.,  
Janusz Lipiecki, M.D., Ph.D., Gert Richardt, M.D., Andres Iñiguez, M.D., Ph.D.,  
Philippe Brunel, M.D., Mariano Valdes-Chavarri, M.D., Ph.D.,  
Philippe Garot, M.D., Suneel Talwar, M.B., B.S., M.D., Jacques Berland, M.D.,  
Mohamed Abdellaoui, M.D., Franz Eberli, M.D., Keith Oldroyd, M.B., Ch.B., M.D.,  
Robaayah Zambahari, M.B., B.S., M.D., John Gregson, Ph.D.,  
Samantha Greene, B.A., Hans-Peter Stoll, M.D., and Marie-Claude Morice, M.D.,  
for the LEADERS FREE Investigators\*

### CONCLUSIONS

Among patients at high risk for bleeding who underwent PCI, a polymer-free umirolimus-coated stent was superior to a bare-metal stent with respect to the primary safety and efficacy end points when used with a 1-month course of dual antiplatelet therapy. (Funded by Biosensors Europe; LEADERS FREE ClinicalTrials.gov number, NCT01623180.)

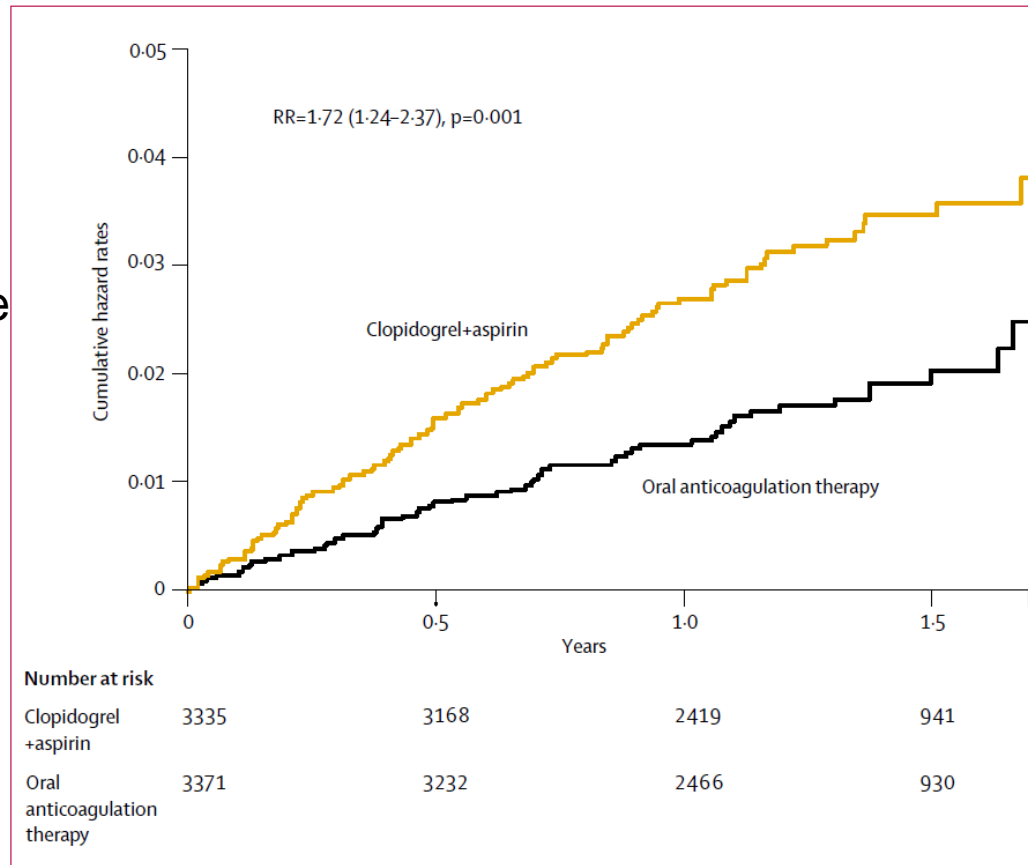
# Combination therapy with 2 antiplatelet agents reduces stent thrombosis more than aspirin alone or aspirin plus warfarin



# Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

The ACTIVE Writing Group on behalf of the ACTIVE Investigators\*

Cumulative  
risk  
of stroke



clopidogrel + aspirin

warfarin

Figure 3: Cumulative risk of stroke

# But what if the patient is already treated with a NOAC?

- ▶ Performing a PCI (scheduled or not) under NOAC is different than under VKA for many reasons:
  - ▶ Uncertainty about the last dose
  - ▶ uncertainty about adherence
  - ▶ Uncertainty about the extent of anticoagulation in the absence of mainstream tests, and hence
  - ▶ uncertainty about stacking or additional periprocedural anticoagulants
  - ▶ variability in renal function (especially when unknown in an acute setting)
  - ▶ singular anti-factor II or X blockade vs multifactor antagonism, etc.





For all these reasons, if the patient is already treated with a NOAC, the advice is

- ▶ temporary discontinuation of the short-acting NOAC
- ▶ safe initiation of antiplatelet therapy, and
- ▶ standard local anticoagulation practices peri-procedurally
- ▶ then restart the NOAC immediately discontinuing parenteral anticoagulation

# And then?

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- ▶ The dogma
- ▶ The heresy



# And then?

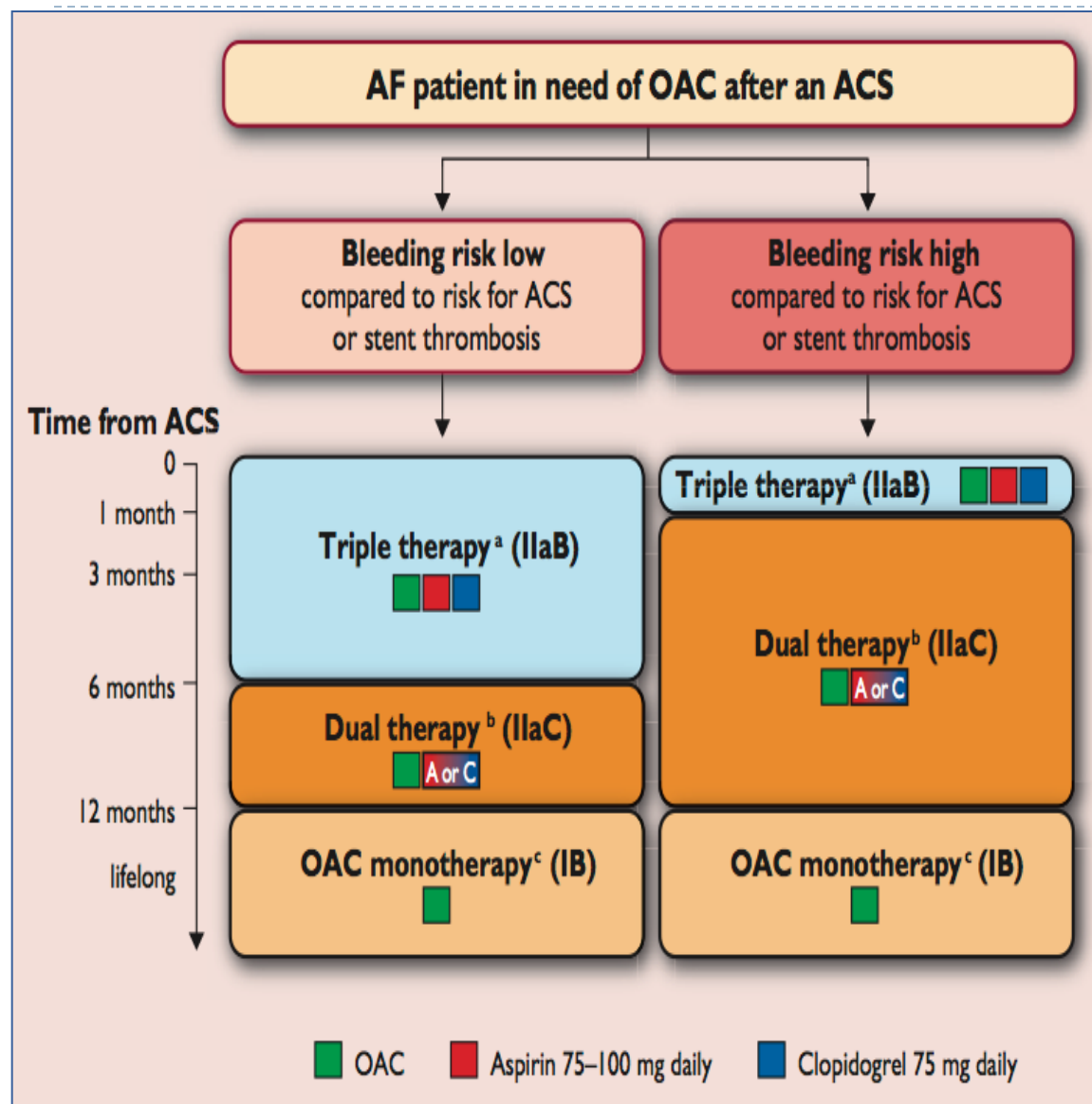
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▶ **The dogma** (also applying to scenario 2: the patient with a recent ACS (<1 year) who develops AF)



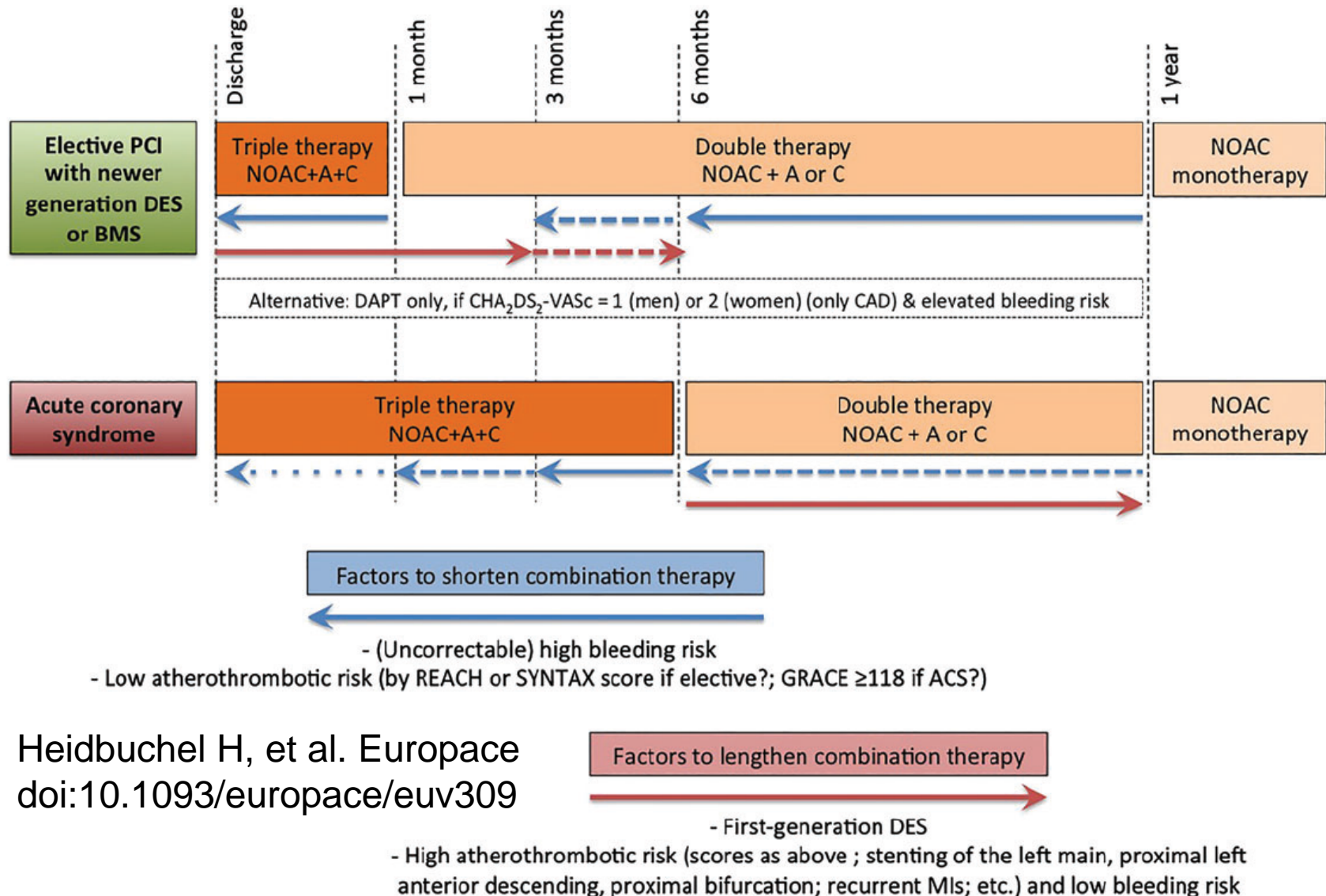
# Antiplatelets + anticoagulation

## 2016 AF Guidelines



Kirchhof, P et al,  
Eur Heart J 2016

# Long-term treatment of patients on (N)OAC therapy after revascularization or ACS



Heidbuchel H, et al. Europace  
doi:10.1093/europace/euv309

## And which dose of NOACs?

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- ▶ My answer: the lowest dose **shown to be effective for stroke prevention in AF**, which means:
  - ▶ Dabigatran 110 mg BID
  - ▶ **Rivaroxaban 20 mg OD**
  - ▶ **Apixaban 5 mg BID**
  - ▶ **Edoxaban 30 mg BID**
- ▶ (at slight variance from recommendations by Lip GY, et al. Eur Heart J 2014;35:3155–79, advising for reduced doses of rivaroxaban 15 mg OD and apixaban 2.5 mg BID)

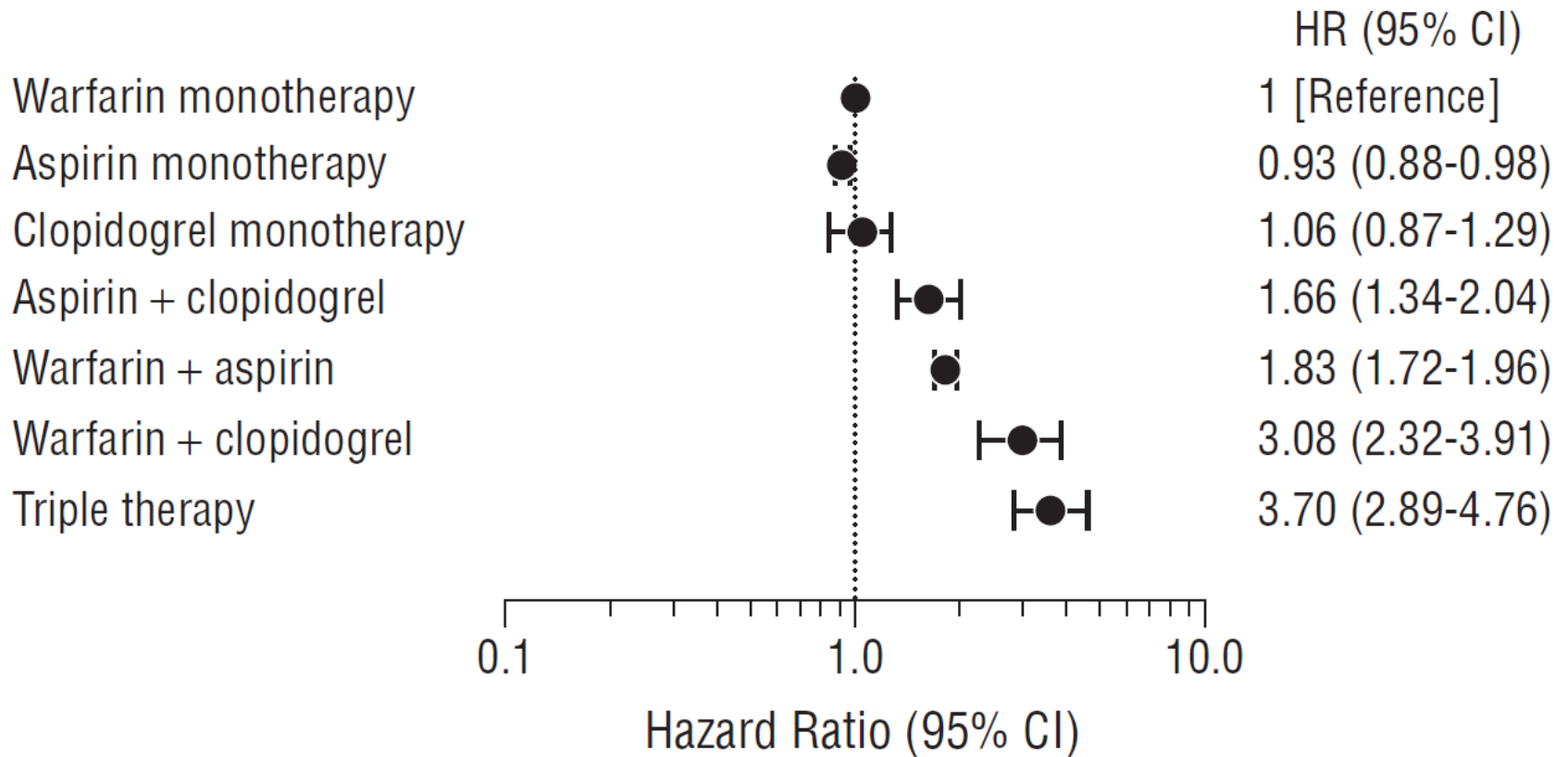
# And then?

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- ▶ The dogma
- ▶ The heresy  
(probably the future)



# Combination therapy increases risk of fatal and non-fatal bleeding





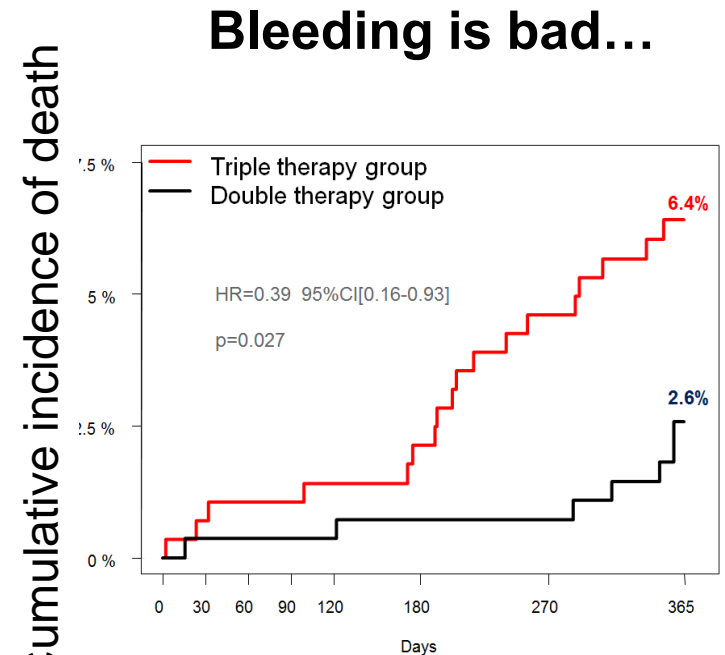
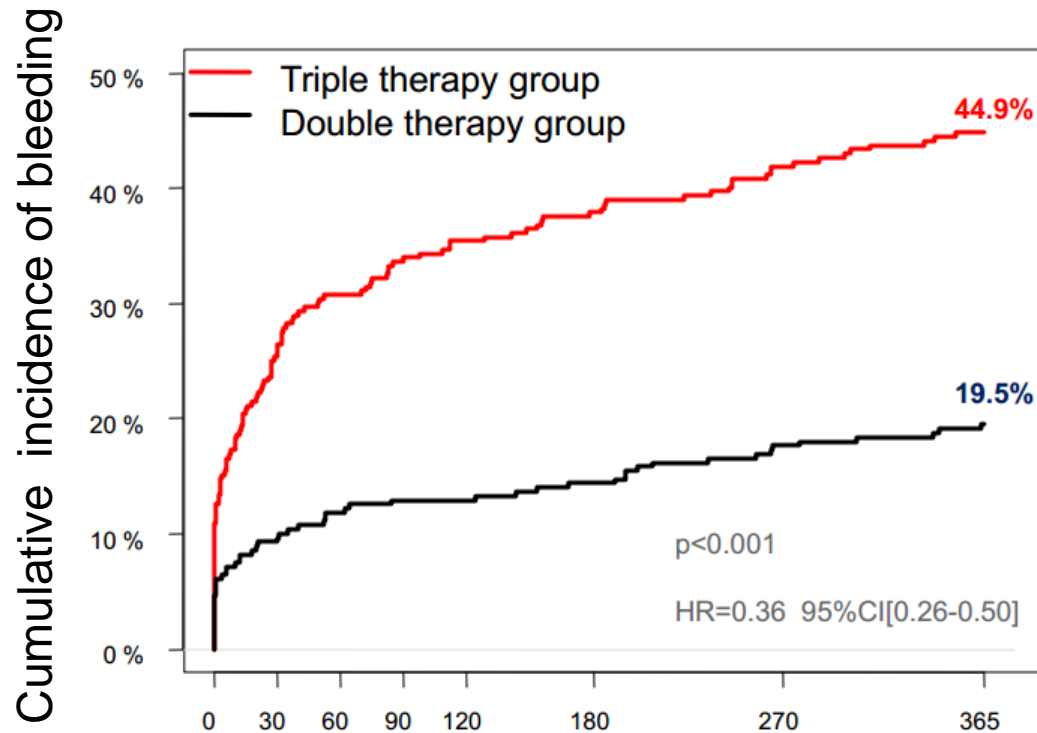
## Bleeding is not an innocuous consequence of excessive antithrombotic therapy

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- ▶ In several previous trials – e.g., OASIS-V, HORIZON-AMI, less initial bleeding translated into increased mortality
- ▶ Therefore there was hope that reducing antithrombotic therapy in such conditions could not only reduce bleeding (expected), but possibly also reduce mortality



# Combined antiplatelets and (N)OACs after acute coronary syndrome: **three is a crowd!**

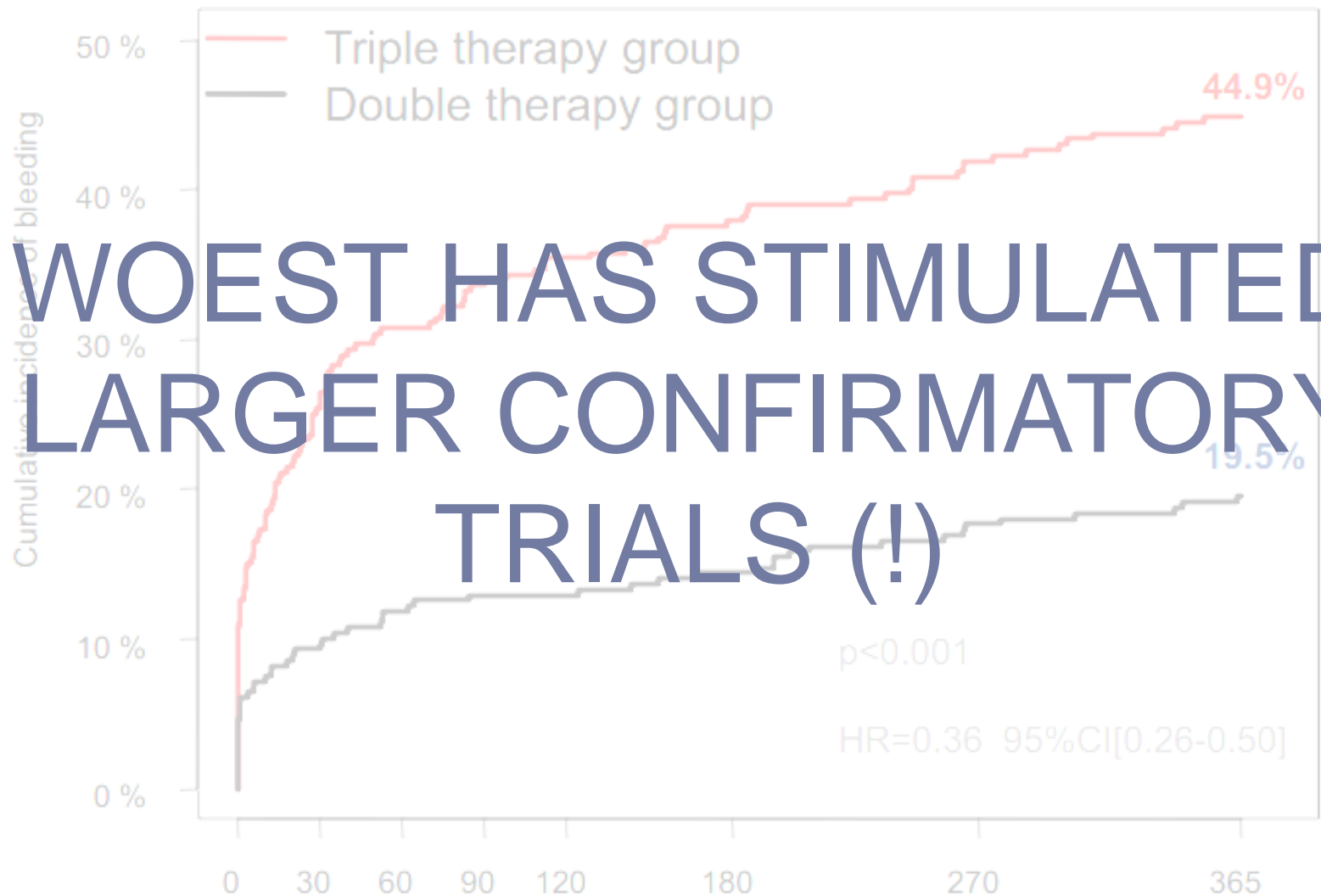


# Why did WOEST decide to drop aspirin instead of dropping clopidogrel?

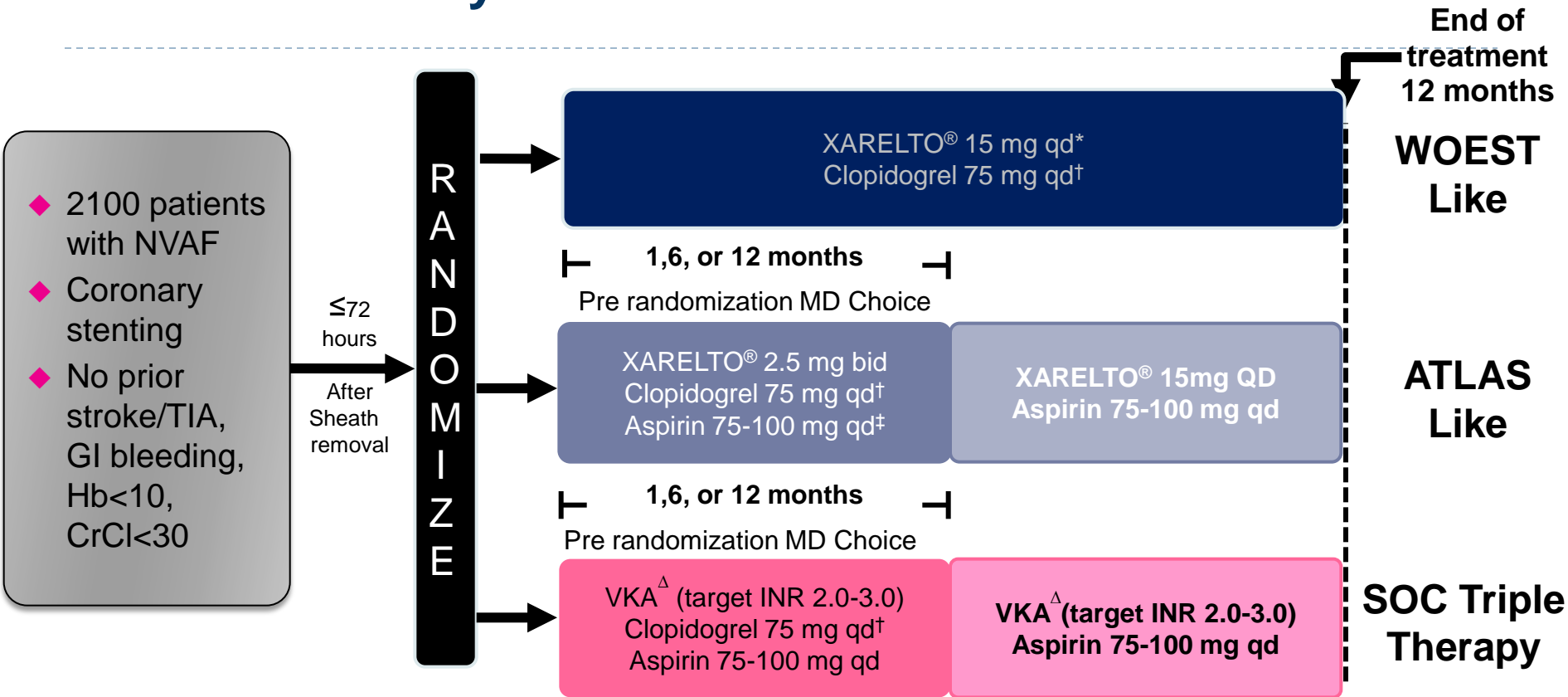
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- ▶ ... «sensation» among the interventionalists that clopidogrel is more effective than aspirin in preventing stent thrombosis...
- ▶ The truth is: NO DATA!





# Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI



- ▶ Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- ▶ Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.

†Alternative P2Y<sub>12</sub> inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.

‡Low-dose aspirin (75-100 mg/d). Δ Open label VKA

# Pre-Randomization Choice of Thienopyridine & Duration of DAPT: PIONEER AF-PCI

- ◆ 2100 patients with NVAF
- ◆ Coronary stenting
- ◆ No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

≤ 72 hours  
After Sheath removal

R  
A  
N  
D  
O  
M  
I  
Z  
E

XARELTO® 15 mg qd\*  
Clopi 95%, Ticag 4%, Prasugrel 1%

**WOEST  
Like**

1 mo: 16%  
6 mos: 35%  
12 mos: 49%

XARELTO® 2.5 mg bid  
Clopi 95%, Ticag 4%,  
Prasugrel 1%  
Aspirin 75-100 mg qd‡

XARELTO® 15mg QD  
Aspirin 75-100 mg qd

**ATLAS  
Like**

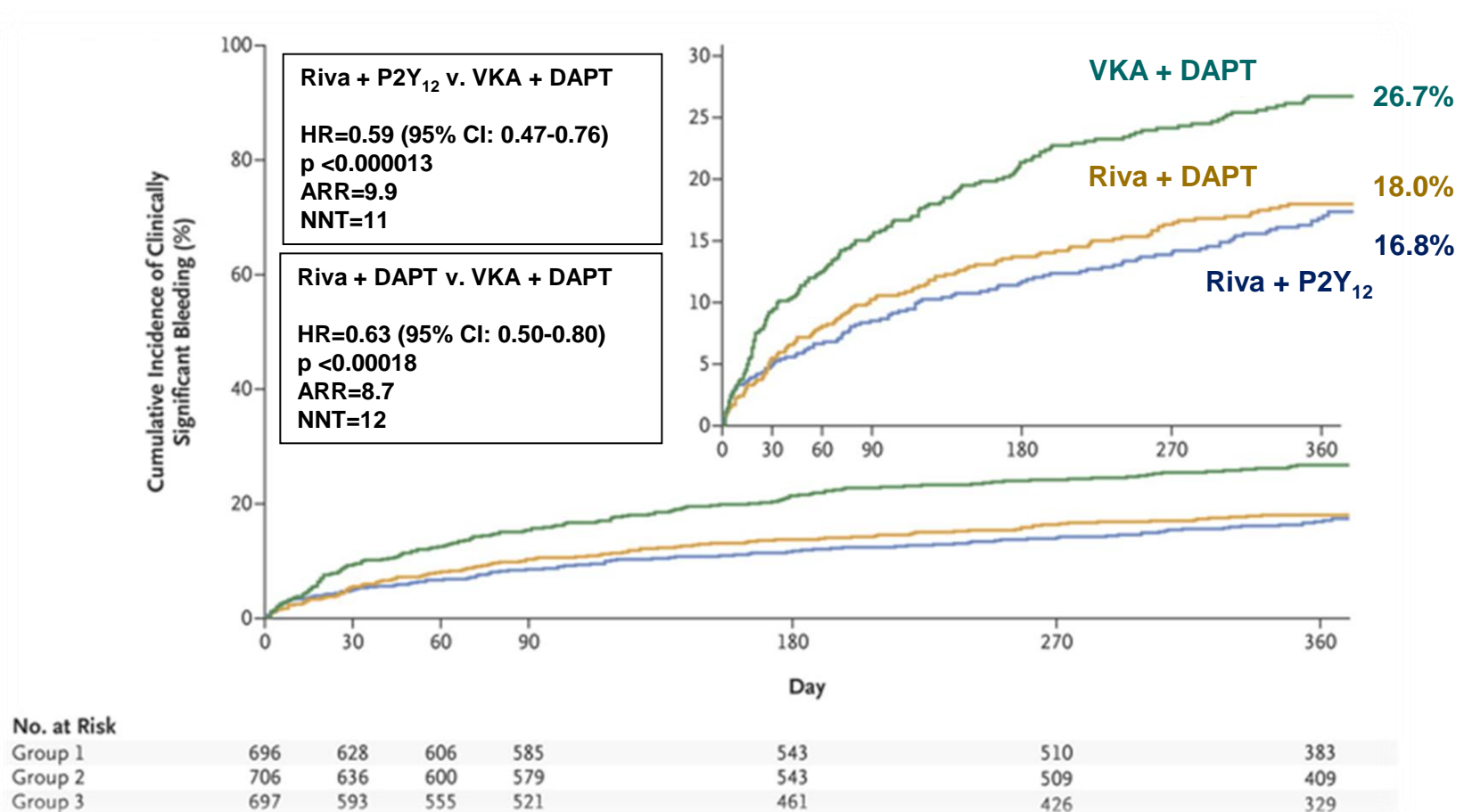
1 mo: 16%  
6 mos: 35%  
12 mos: 49%

VKA (target INR 2.0-3.0)  
Clopi 95%, Ticag 4%, Prasugrel  
1%  
Aspirin 75-100 mg qd

VKA (target INR 2.0-3.0)  
Aspirin 75-100 mg qd  
TTR 65%

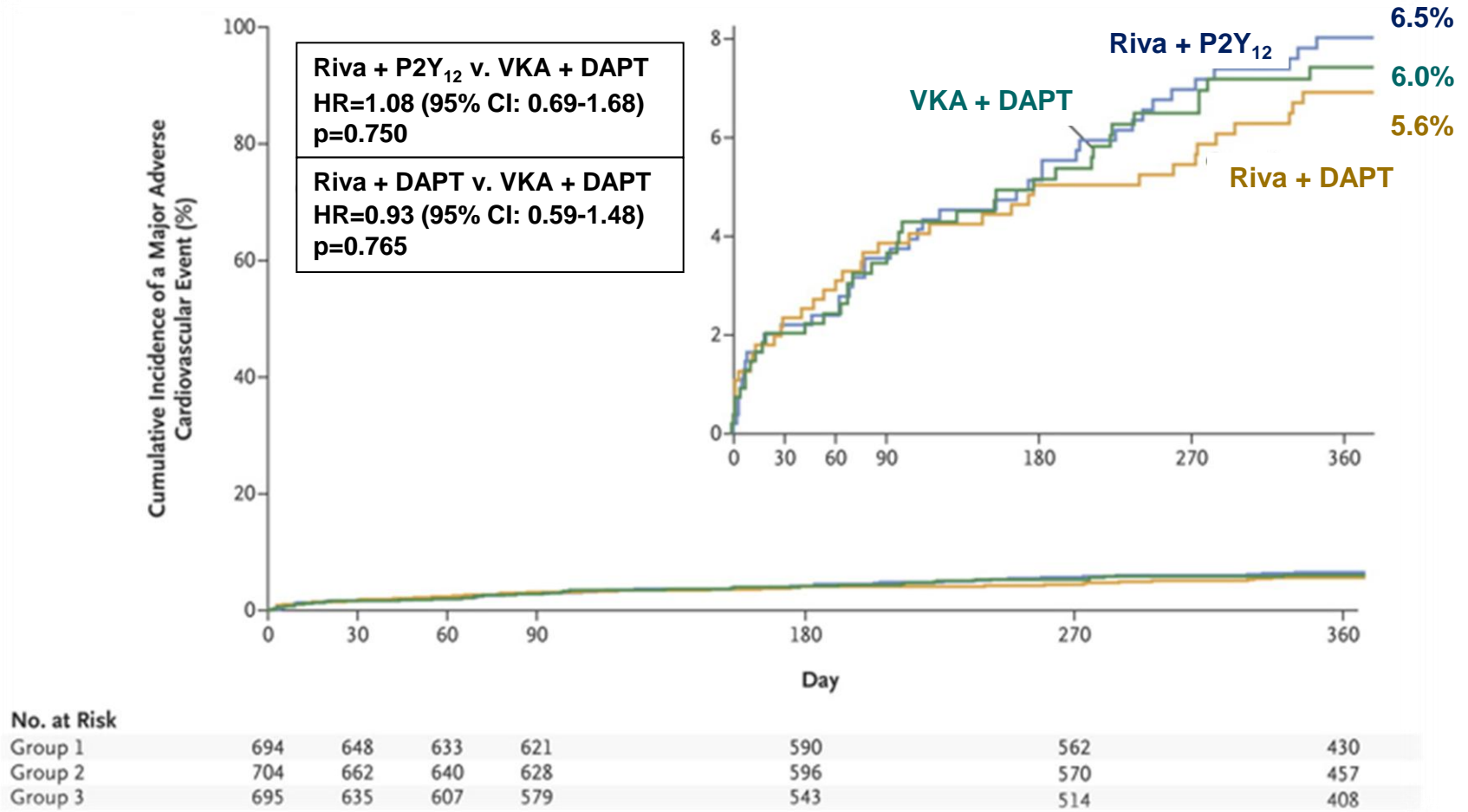
**Triple  
Therapy**

# Rivaroxaban plus DAPT or P2Y<sub>12</sub> reduces clinically relevant bleeding compared with standard therapy



Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug. Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA. Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model. Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

# Similar incidence of MACE with rivaroxaban compared with standard therapy



Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Composite of adverse CV events is composite of CV death, MI, and stroke.

Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.

Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.



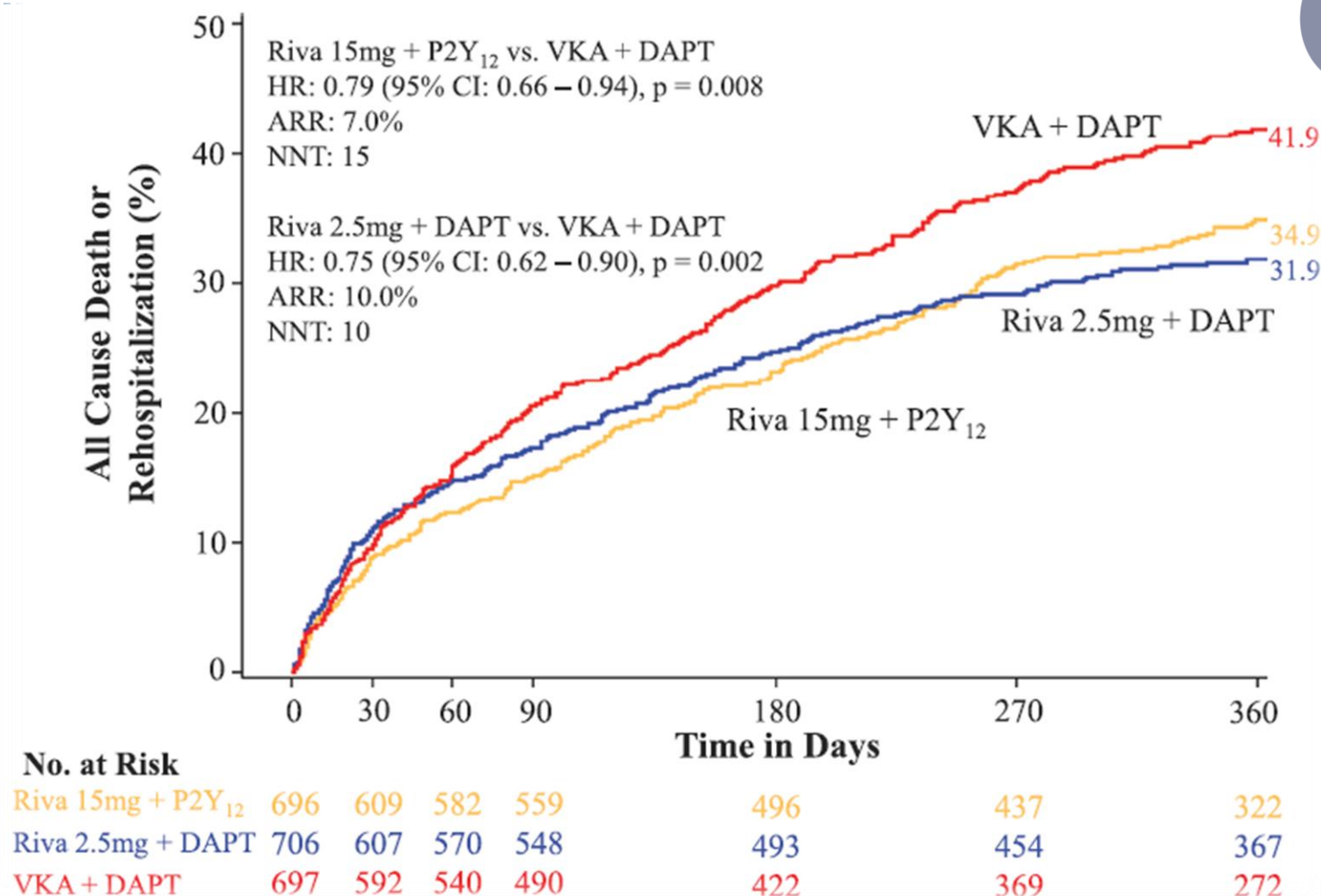
Prevention of Bleeding in Patients with Atrial Fibrillation  
Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D.,  
Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D.,  
Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D.,  
Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

- **DAPT duration was:**
  - 1 month in 16%,
  - 6 months in 35%,
  - **and 12 months in 49%.**
- **Clopidogrel** was the P2Y<sub>12</sub> inhibitor used in **95%** of patients, with ticagrelor (Brilique; AstraZeneca) and prasugrel (Efient; Daiichi Sankyo) used in the rest.
- The **time in therapeutic range** for warfarin-treated patients was 65%.



# Recurrent hospitalisation or death



Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.  
 Rehospitalizations do not include the index event and include the first rehospitalization after the index event.  
 Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.  
 Log-Rank P-values as compared to VKA group are based on the two-sided log rank test.

# Is there a need for more data after PIONEER?

- DAPT duration in the warfarin arm was still 12-months in 49% of patients!
- Lack of a WOEST-like warfarin arm
- No formal testing of the non-inferiority of the rivaroxaban-based regimens compared with warfarin-based triple therapy
- The non-inferiority or clinical equivalence of these strategies is not established



# Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial

## Inclusion

- AF (prior, persistent, or >6 hrs duration)
- Physician decision that oral anticoag is indicated
- ACS and/or PCI with planned P2Y12 inhibitor for 6 months

**Randomize**  
*n = 4,600*  
*Patients*

## Exclusion

- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, mod/sev MS)

**Apixaban**

**Warfarin**

*P2Y12 inhibitor for all patients x 6 months*  
*Aspirin for all on the day of ACS or PCI*  
*Aspirin versus placebo after randomization*

**ASA**

**placebo**

**ASA**

**placebo**

**Primary outcome: major/clinically relevant bleeding (through 6 months)**

**Secondary objective: Death, MI, Stroke, Stent thrombosis**

# Primary study hypothesis: Augustus trial

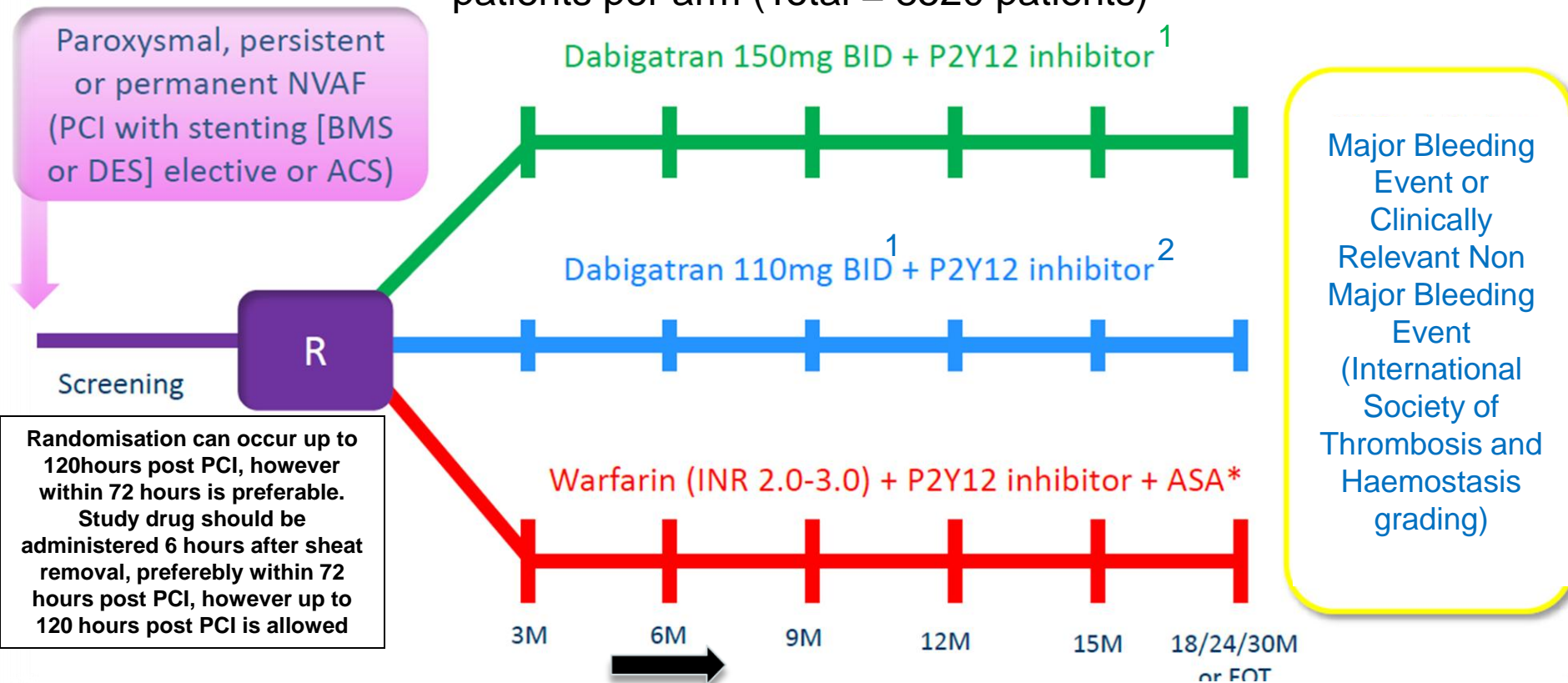
Two Primary Hypotheses (2 x 2 factorial) to be tested in a hierarchical manner:

- ▶ Apixaban is **non-inferior** to warfarin on ISTH (International Society on Thrombosis and Haemostasis) major or clinically relevant non-major bleeding in patients with **AF who develop ACS and/or** undergo **PCI** with planned antiplatelet therapy.
- ▶ Single antiplatelet therapy with a P2Y12 inhibitor is **superior** to dual antiplatelet therapy with a P2Y12 inhibitor and aspirin on ISTH major bleeding or clinically relevant non-major bleeding in patients with AF who develop ACS and/or undergo PCI with concomitant antiplatelet therapy.

# Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting



Worldwide event-driven trial with 2840 patients per arm (Total = 8520 patients)



<sup>1</sup> Clopidogrel or ticagrelor can be discontinued or switched to ASA ( $\leq 100\text{mg QD}$ ) from month 12, at investigator discretion

<sup>2</sup> ASA will be discontinued in patients randomized to receive warfarin at 1 month (BMS) and 3 months (DES)

\* Patients aged  $\geq 80$  years outside of the US will only be randomized to dabigatran etexilate 110mg bid or warfarin

# Primary study hypothesis: RE-DUAL PCI trial

Six Hypotheses to be tested in a hierarchical manner:

- ▶ 1 **Noninferiority** of **110** mg DE-DAT to warfarin–triple antithrombotic therapy in major **bleeding** events/clinically relevant nonmajor bleeding events (**powered**)
- ▶ 2 **Noninferiority** of **150** mg DE-DAT to warfarin–triple antithrombotic therapy in major **bleeding** events/clinically relevant nonmajor bleeding events
- ▶ 3 **Noninferiority** of **150** mg DE-DAT and **110** mg DE-DAT combined to warfarin–triple antithrombotic therapy in **death or thrombotic event (MI, stroke/thrombotic event) and unplanned revascularization** by PCI/CABG
- ▶ 4 **Superiority** of **110** mg DE-DAT to warfarin–triple antithrombotic therapy in major bleeding events/clinically relevant nonmajor **bleeding** events
- ▶ 5 **Noninferiority** of **150** mg DE-DAT and **110** mg DE-DAT combined to warfarin–triple antithrombotic therapy in **death or thrombotic event**
- ▶ 6 **Superiority** of **150** mg DE-DAT to warfarin–triple antithrombotic therapy in major **bleeding** events/clinically relevant nonmajor bleeding events.

If any of the above steps fails to meet statistical significance, the testing procedure will stop and subsequent tests will not be performed.

# ENTRUST-AF-PCI Study Design

**PROBE design: prospective, randomized, open label, blinded evaluation  
edoxaban based regimen vs VKA based regimen in  $N \cong 1500$  AF patients**

12 months:  
end of treatment

## Inclusion Criteria:

- OAC indication for AF for at least 12 months
- Successful PCI with stent placement (goal of at least 25% ACS)

4 hours  
– 5 days  
after  
sheath  
removal

**R  
A  
N  
D  
O  
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I  
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E**

**Edoxaban 60 mg/day\***

**$P2Y_{12}$  antagonist\*\*  
(without ASA)**

**Vitamin K Antagonist\*\*\***

**$P2Y_{12}$  antagonist  
(ASA 1 - 12 months)\*\*\*\***

\*Edoxaban dose reduction to 30 mg OD

- if  $CrCL \leq 50$  ml/min
- $BW \leq 60$  kg
- certain P-gp inhibitors

\*\*Clopidogrel 75mg once-daily or if documented need prasugrel 5 or 10mg once-daily or ticagrelor 90mg twice-daily .  
Predeclared at randomization

\*\*\* VKA, target INR 2-3

\*\*\*\*ASA 100mg OD for 1-12 months guided by clinical presentation (ACS or stable CAD),  $CHA_2DS_2$ -VASC<sub>2</sub> and HAS\_BLED

**Primary outcome:  
ISTH major and clinically relevant non-major bleeding**



# ENTRUST-AF-PCI Study Design

- Multi-national, multicenter, prospective, randomized, open-label study with blinded evaluation of endpoints (PROBE) by an independent Clinical Event Adjudication Committee (CEC).
- Pre-declaration of intended antiplatelet regimen, specifying the type of P2Y12, ASA use and intended treatment duration.
- Investigators are encouraged to follow the current ESC recommendations for antithrombotic management in AF patients undergoing PCI, considering clinical presentation and CHA<sub>2</sub>DS-VASc<sub>2</sub>, HAS-BLED estimates.
- Subjects will be stratified based on their clinical presentation, on the need for edoxaban dose adjustment at randomization and by geographical region.

# In the meantime...

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- ▶ Stick to guideline recommendations with triple therapy (*my personal preference*), but these may change in the near future
- ▶ Lowering riva to 15 OD with aspirin **and** clopidogrel not a crime (based on common sense)
- ▶ Riva 15 OD + clopidogrel or riva 2.5 BID + aspirin + clopidogrel up to 6-12 months possible alternative, and then riva 15 + aspirin up to a year possible (based on PIONEER-AF)

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Thank you!

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