8th Emirates Cardiac Society Congress in collaboration
with ACC Middle East Conference 2017

Dubai: 19-21 October 2017

Acute Coronary Syndromes

Duration of DAPT after PCI, DAPT for patients needing oral anticoagulation

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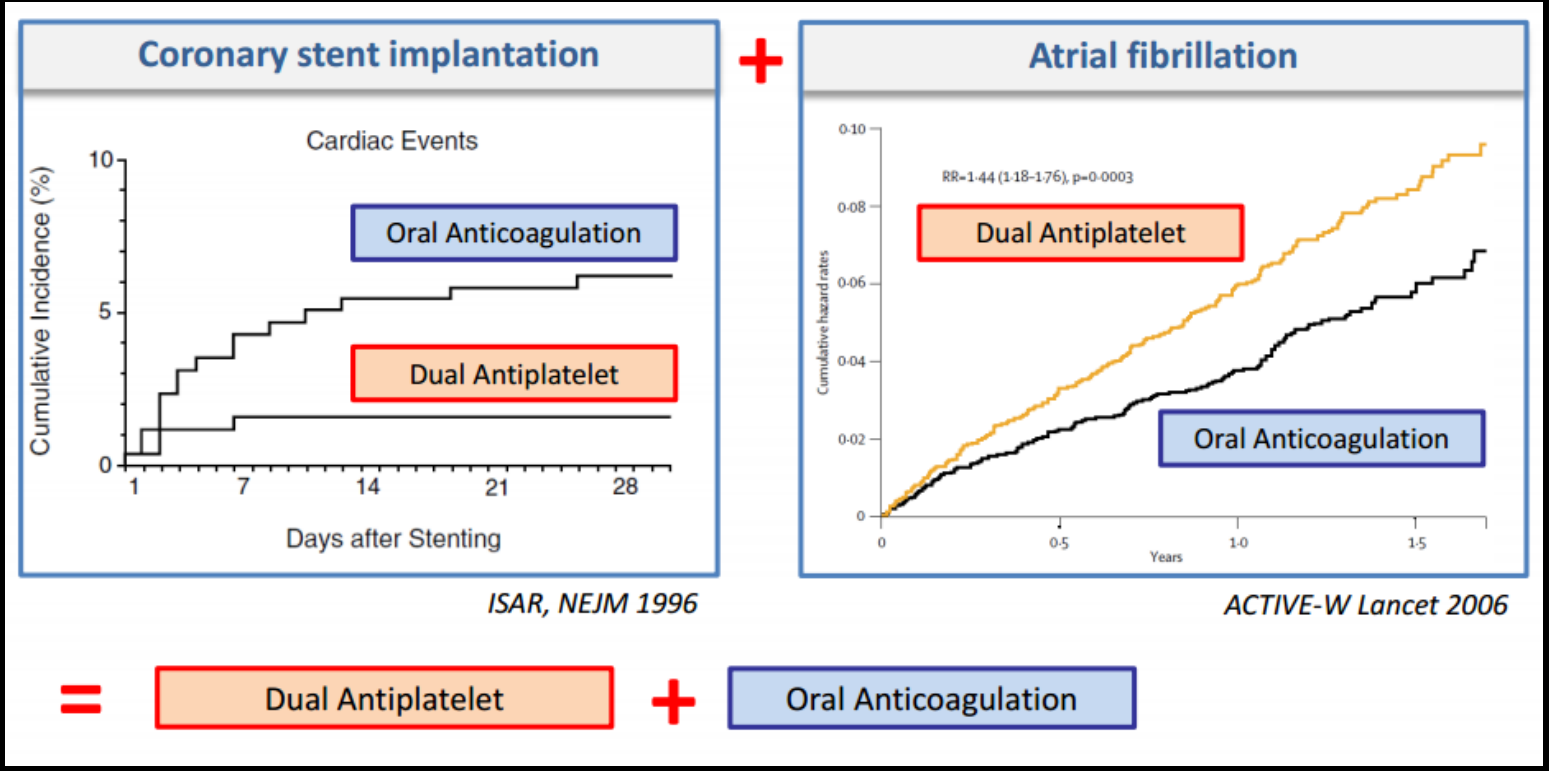
S. Raffaele Scientific Institute, Milan, Italy

Nothing to disclose

Background

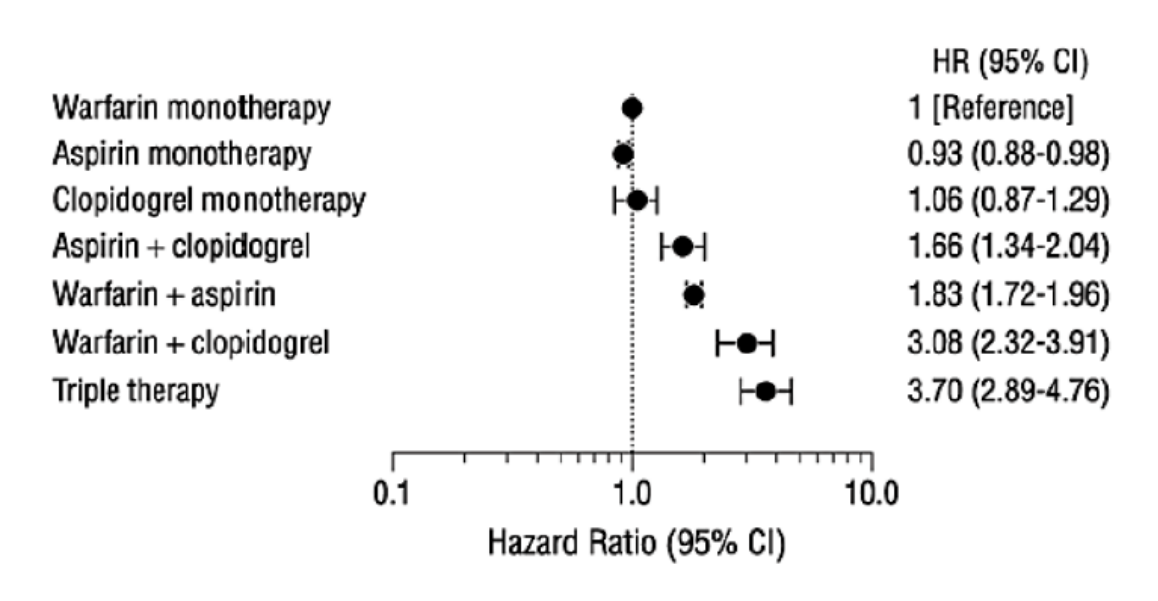
- DAPT is better than oral anticoagulation for stent related events
- Oral anticoagulant therapy is useful for stroke prevention in Afib (and is mandatory for mechanical valves)



Background

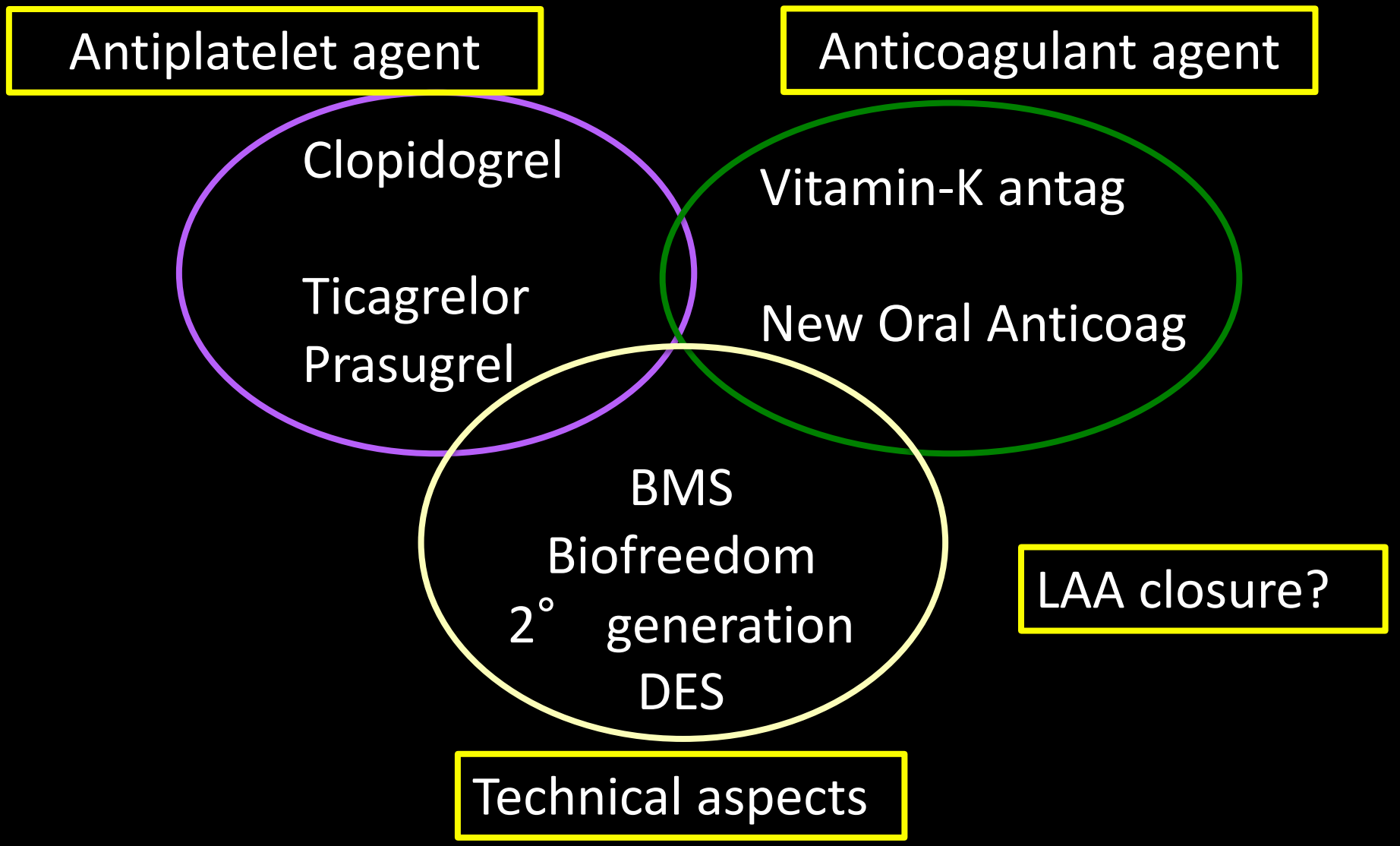
High Bleeding risk of triple therapy:

- 1 year major bleeding 14% (vs 6.9% in DAPT)
- Fatal bleeding 0.9% (vs 0.3% in DAPT)



Arch Intern Med2010;170:1433 – 1441.

Possible choices

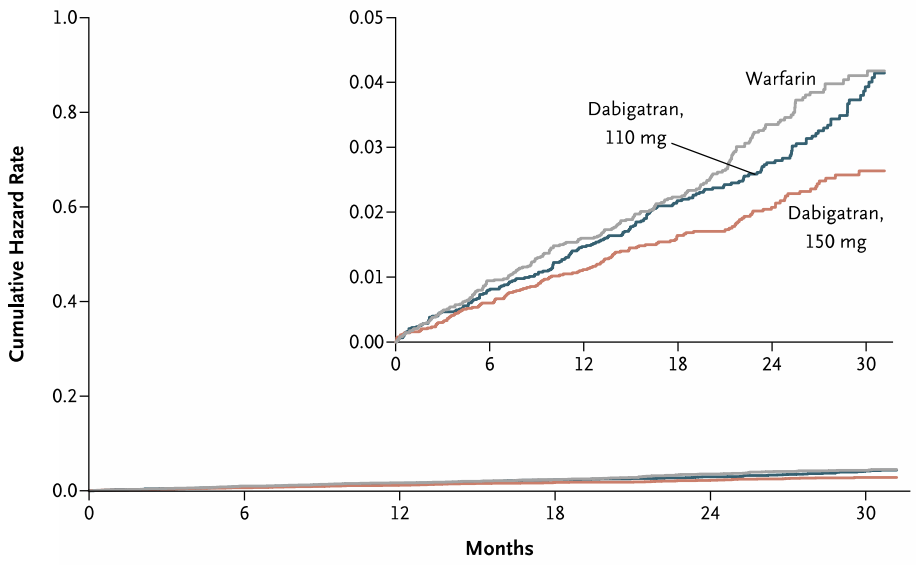


Overview

1. Role of NOACs over VKA
2. WOEST, PIONEER AF and REDUAL PCI
3. LEADERS FREE
4. LAA occlusion
5. GUIDELINES

Role of NOACs over VKA

- RE-LY trial: Dabigatran vs Warfarin



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

The NEW ENGLAND JOURNAL of MEDICINE

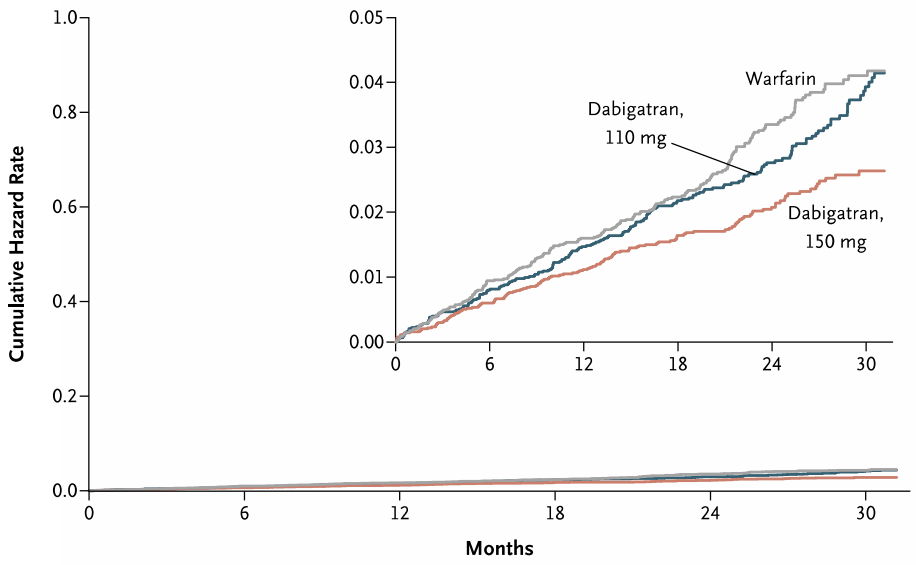
ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

Role of NOACs over VKA

- RE-LY trial: Dabigatran vs Warfarin



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About 5% of patients undergoing PCI have atrial fibrillation

Choosing the best treatment strategy is analogous to navigating the Strait of Messina between Scylla and Charybdis.

Guidelines recommend 'triple therapy' with an oral anticoagulant (OAC) plus dual antiplatelet therapy (DAPT: P2Y12 and aspirin] for 1–6 months depending on the patient's risk of bleeding

Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points	HAS-BLED score (total points)	Bleeds per 100 patient-years ¶
H	Hypertension (ie, uncontrolled blood pressure)	1	0	1.13
A	Abnormal renal and liver function (1 point each)	1 or 2	1	1.02
S	Stroke	1	2	1.88
B	Bleeding tendency or predisposition	1	3	3.74
L	Labile INRs (for patients taking warfarin)	1	4	8.70
E	Elderly (age greater than 65 years)	1	5 to 9	Insufficient data
D	Drugs (concomittant aspirin or NSAIDs) or excess alcohol use (1 point each)	1 or 2		
		Maximum 9 points		

ISAR TRIPLE

TEST HYPOTHESES:

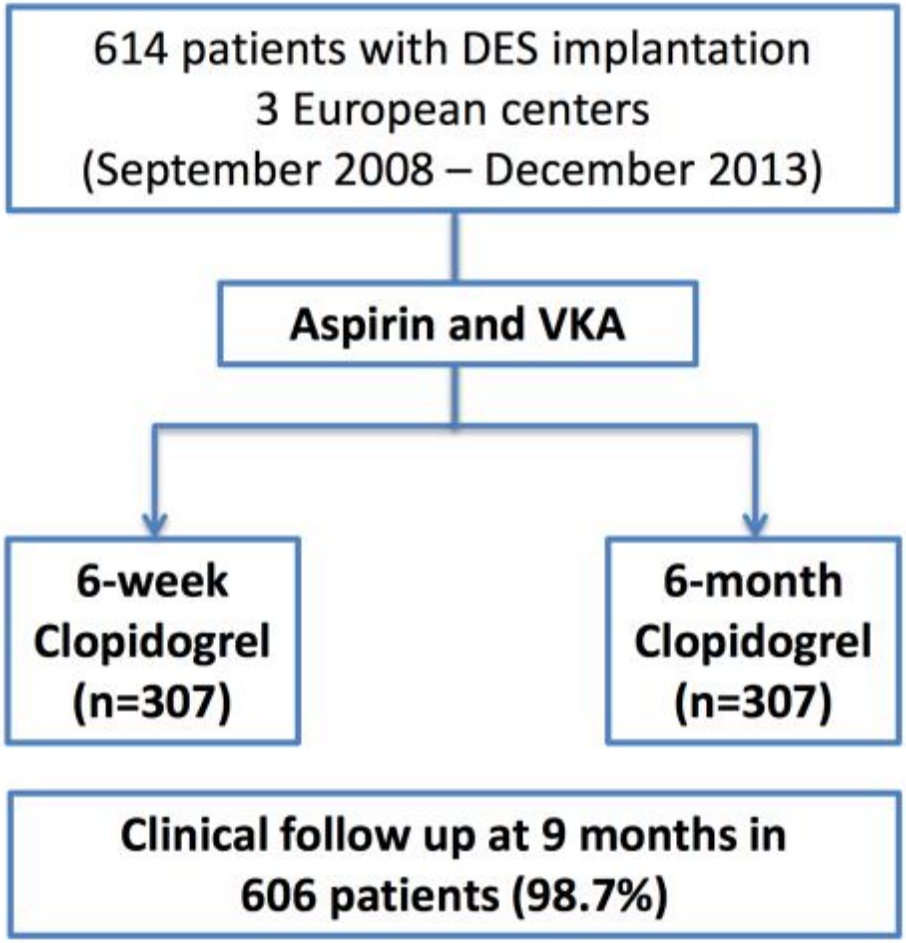
6-week superior to 6-month therapy; Primary Endpoint 10%, Risk reduction 60% with 6-week therapy; Power = 80%, alpha = 0.05; 283 patients per group

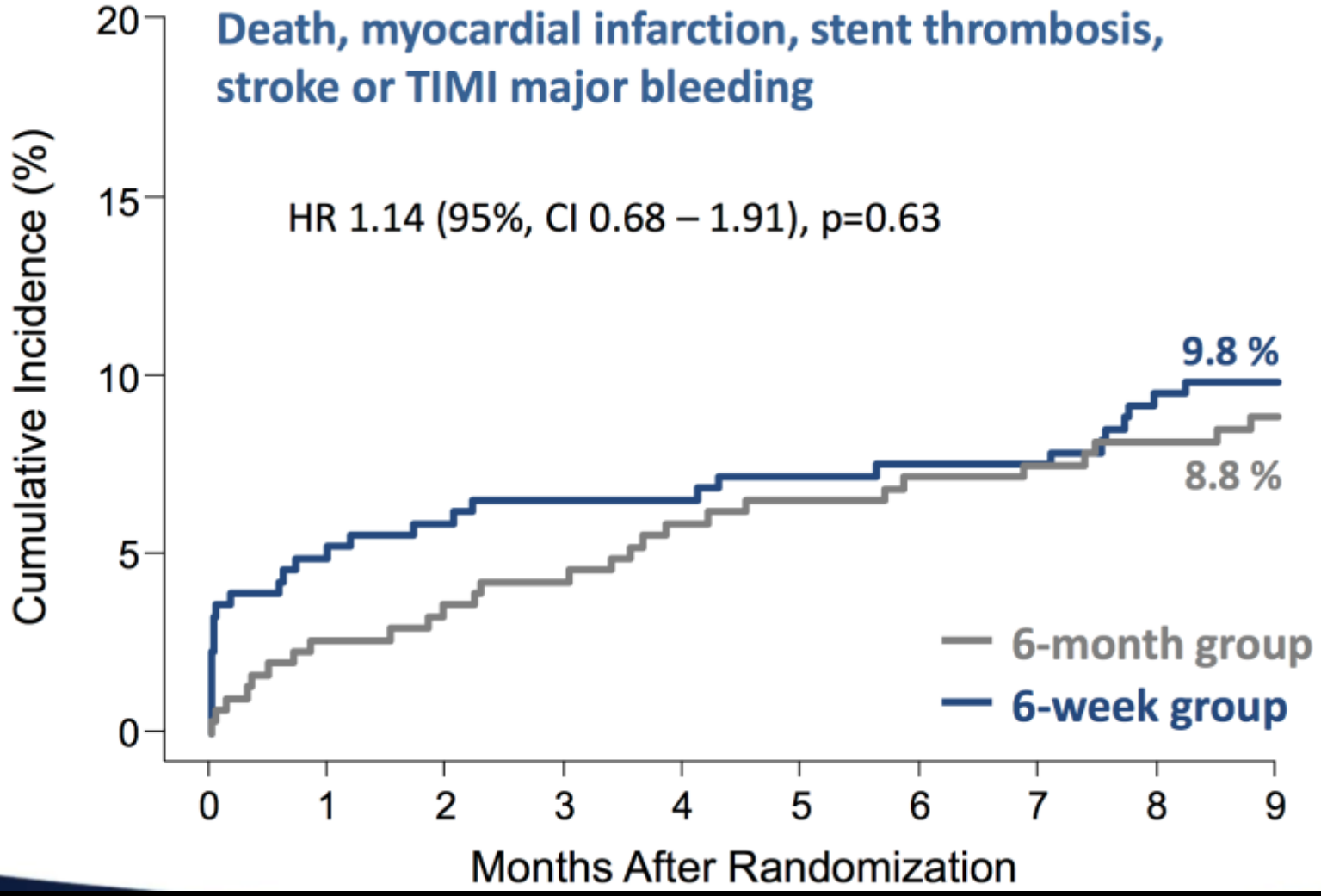
PRIMARY ENDPOINT:

- Death, myocardial infarction, definite stent thrombosis, stroke or TIMI major bleeding at 9 months

SECONDARY ENDPOINTS:

- Ischemic complications: Cardiac death, myocardial infarction, definite stent thrombosis or ischemic stroke
- Bleeding complications (TIMI major)





Inconclusive results

WOEST TRIAL

- Randomized trial (n=573):
  - OAC + **clopidogrel** (study treatment)
  - OAC + **clopidogrel plus aspirin** (control treatment).
- Treatment:
  - For **1-month** after BMS (31% of patients)
  - For **1-year** after DES (65%).

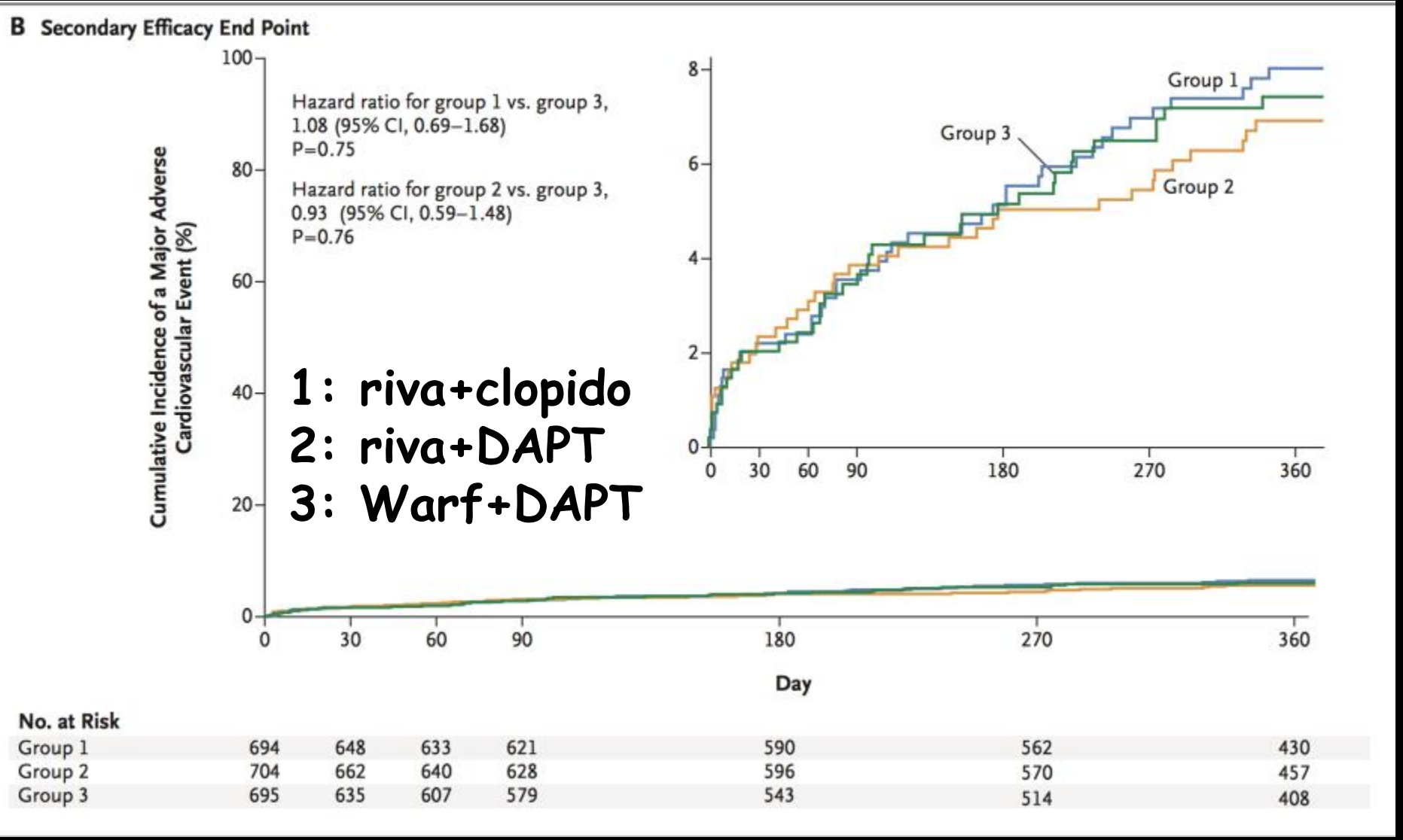
- TIMI **bleeding** is significantly lower in the dual therapy arm, though the rate of major bleeding is not different.
- Ischaemic composite of **MI, stroke, TVR, or stent thrombosis** is less with dual therapy arm.
- All-cause mortality is 61% lower in the triple therapy arm versus the dual therapy arm

The WOEST trial was small (only 279 patients received OAC plus clopidogrel and, of these, only approximately 180 received a DES) and not designed or powered to detect stent thrombosis risk. It is possible that the omission of aspirin may lead to an increased risk of stent thrombosis

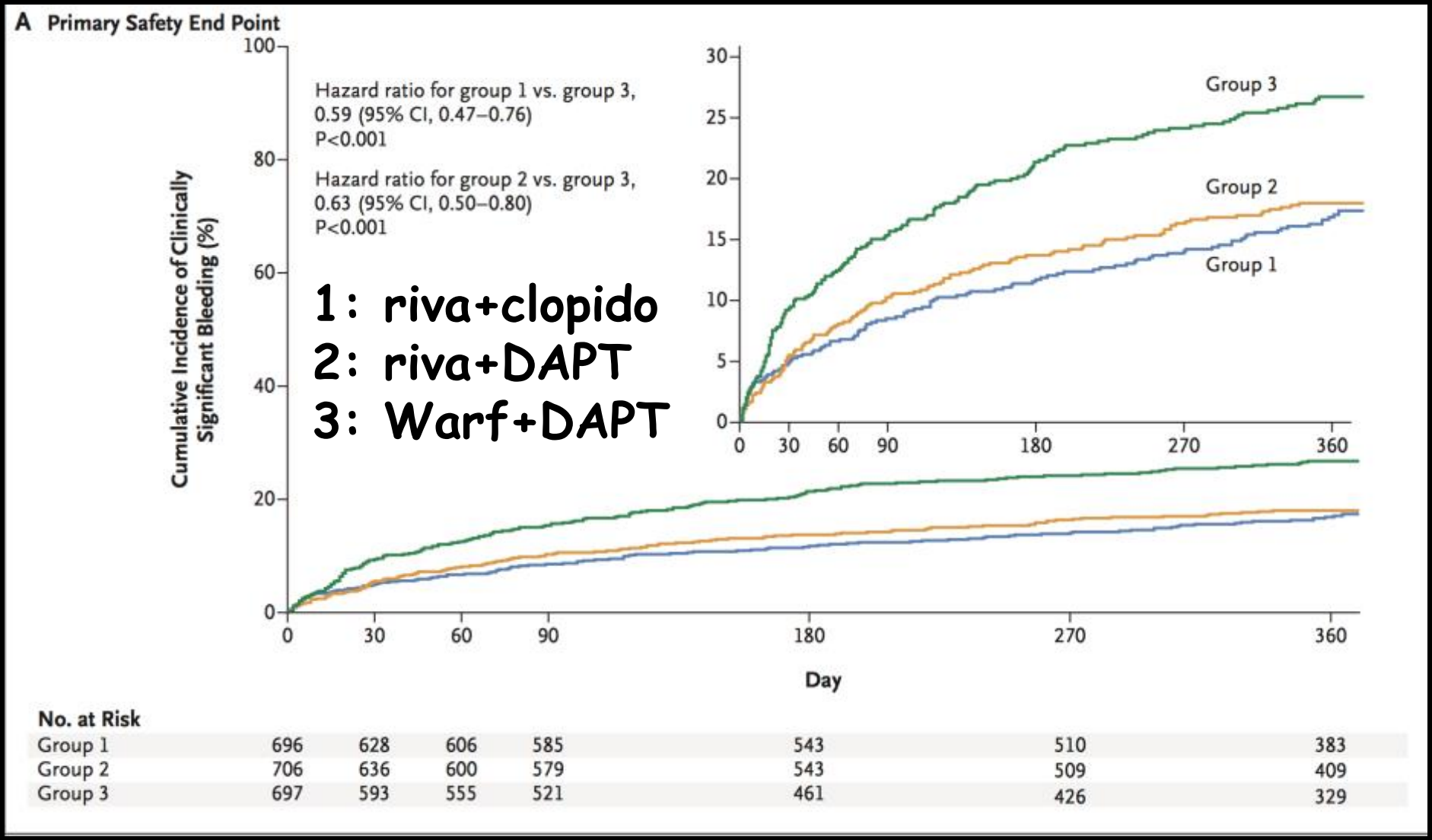
Larger randomized trials are needed. Another concern is that those patients who are resistant to the antiplatelet effect of clopidogrel might have little protection against stent thrombosis

Lancet 2013

PIONEER AF-PCI, *NEJM 2016*



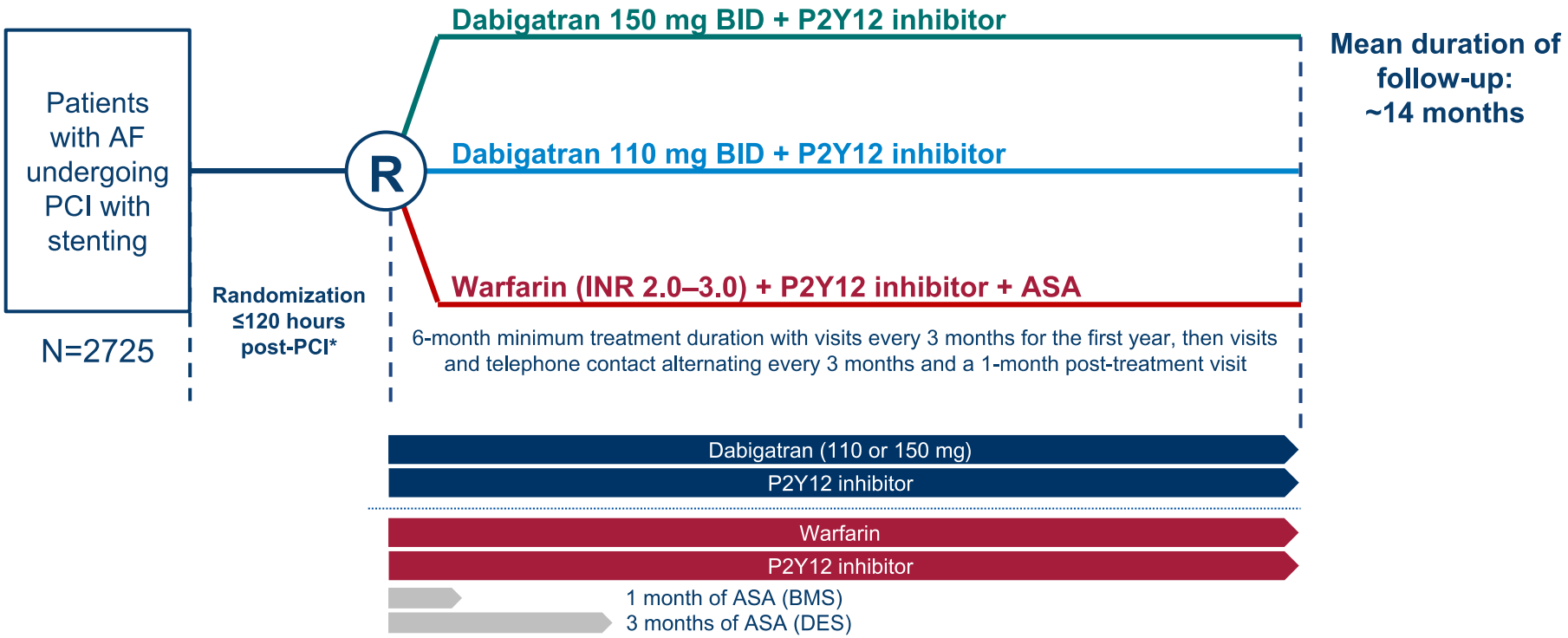
PIONEER AF-PCI, *NEJM 2016*



REDUAL PCI

Study Design: Multicenter, randomized, open-label trial following a PROBE design

RE-DUAL PCI
Study in NVAF patients undergoing PCI



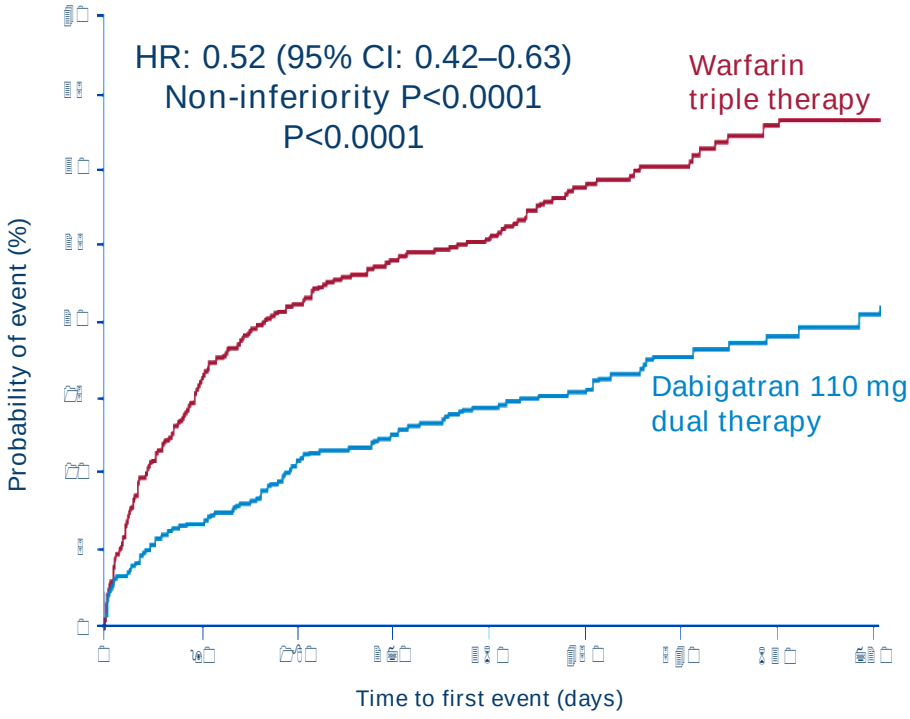
***Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable).** PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016

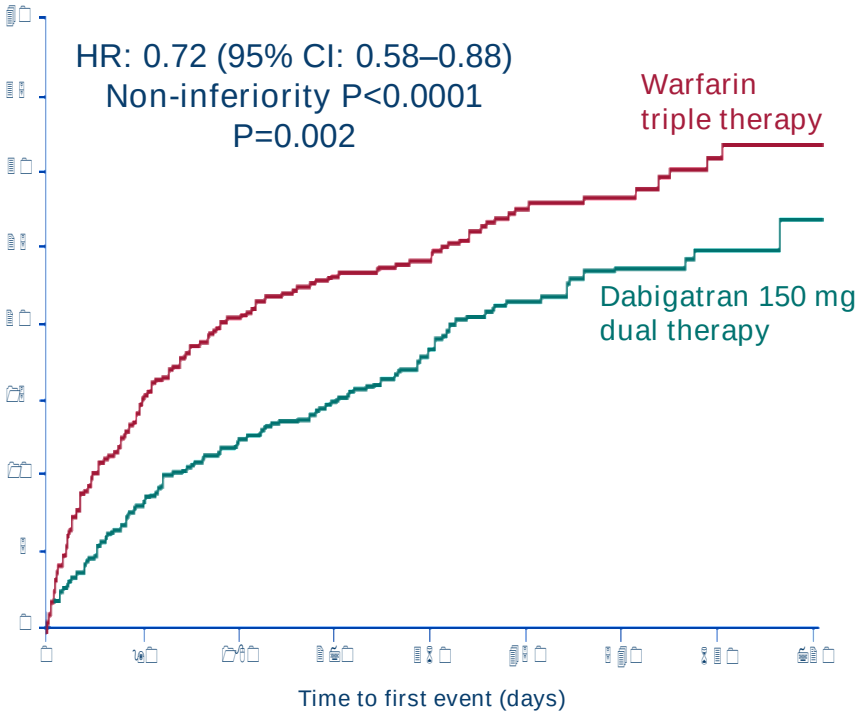
NEJM 2017

REDUAL PCI

Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event

RE-DUAL PCI
Study in NVAF patients undergoing PCI





The RE-DUAL PCI findings provide a compelling reason to move away from traditional triple therapy with warfarin.
Spencer King

This study showed that combining one of two dabigatran doses with a P2Y12 inhibitor lessens bleeding without increasing ischemic events as compared to triple therapy with warfarin, a P2Y12 inhibitor, and aspirin

In the 110 mg dabigatran arm there were numerically more thrombotic events

AUGUSTUS Trial

4000 pts. 2X2 factorial randomized study

- Apixaban+P2Y12
- Apixaban+P2Y12+ASA
- Warfarin+P2Y12
- Warfarin+P2Y12+ASA

LEADERS FREE

- LEADERS FREE trial

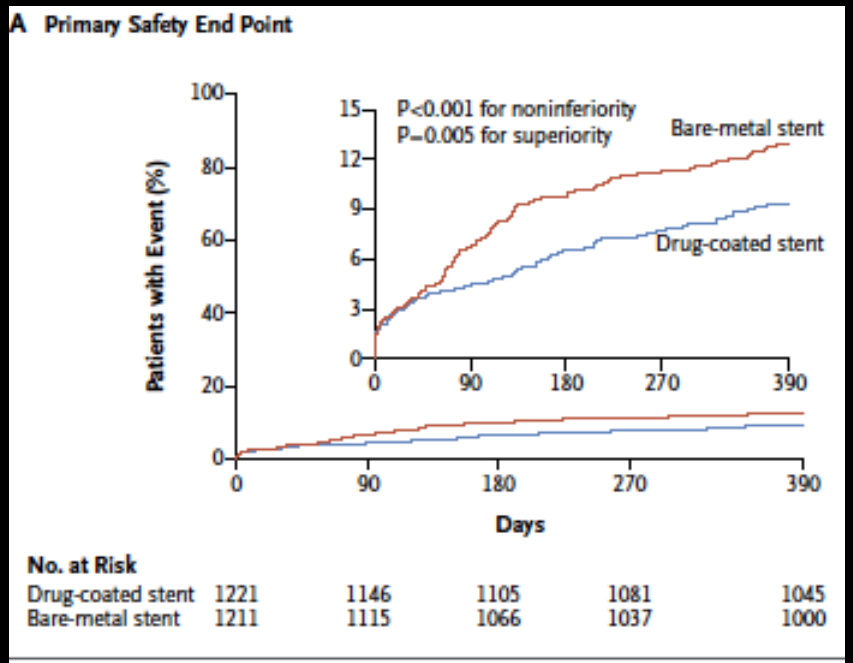
2466 patients randomized 1:1 to bare metal stent vs drug coated stent

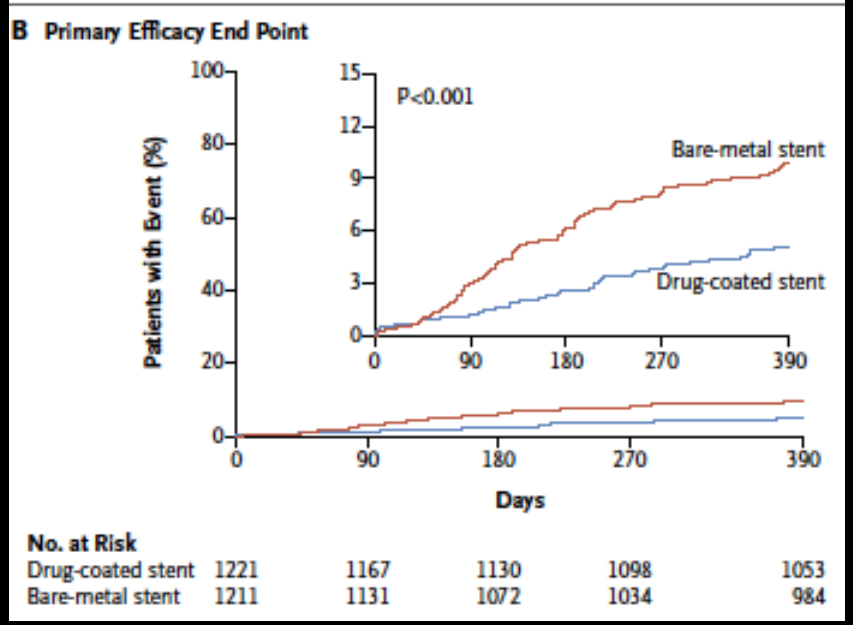
ORIGINAL ARTICLE

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*

LEADERS FREE





Primary safety end point: cardiac death, myocardial infarction or stent thrombosis

Primary efficacy end point: clinically driven target-lesion revascularization

Biofreedom drug coated stent is superior to BMS regarding safety and efficacy and allows reduced DAPT (1 month)

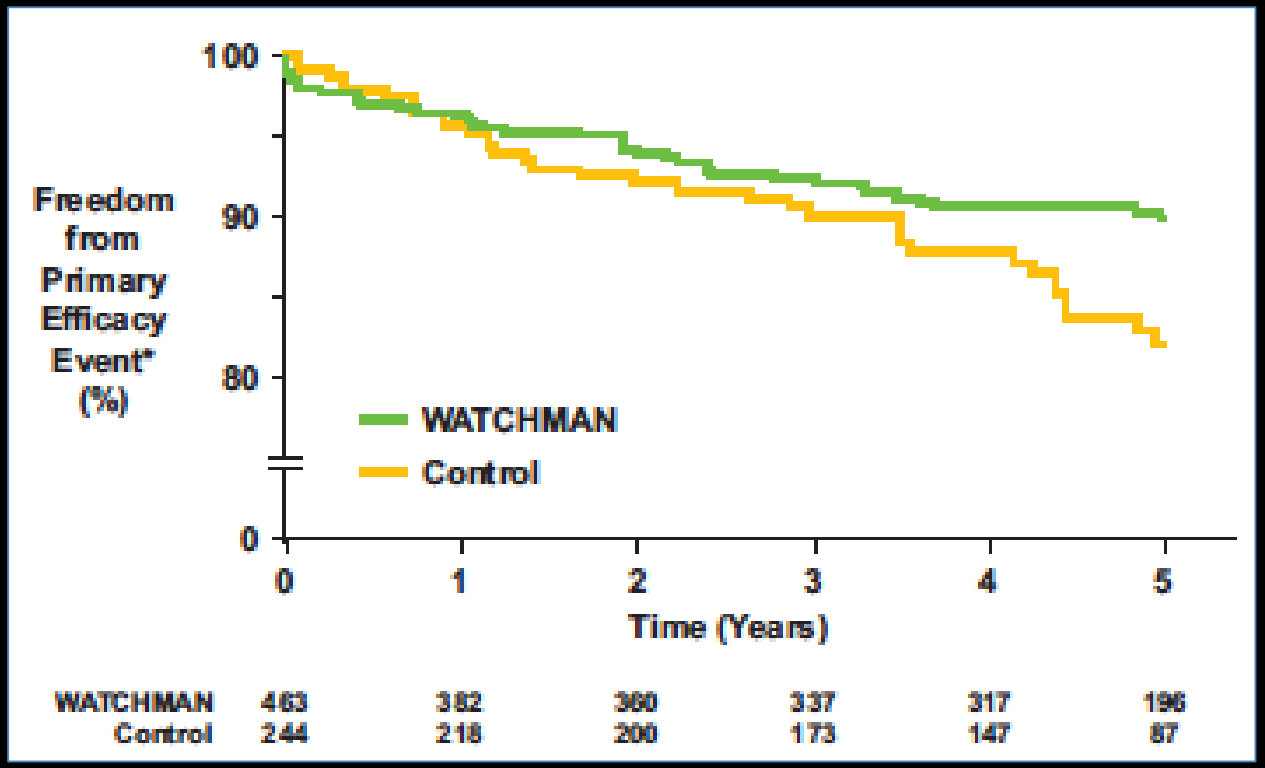
Left atrial appendage closure

- PROTECT-AF and PREVAIL RCTs
- ASAP registry

While RCT data exists only for patients who are eligible for both OAC and LAA occlusion, patients with a high risk of bleeding on OAC or those with contraindications to OAC represent the most accepted clinical indication for LAA occlusion

Left atrial appendage closure

- 4 year follow-up of PROTECT-AF showed superior primary efficacy (all-stroke, systemic embolization, all-death):
  - 2,3%/y in device group; 3,8%/y in VKA

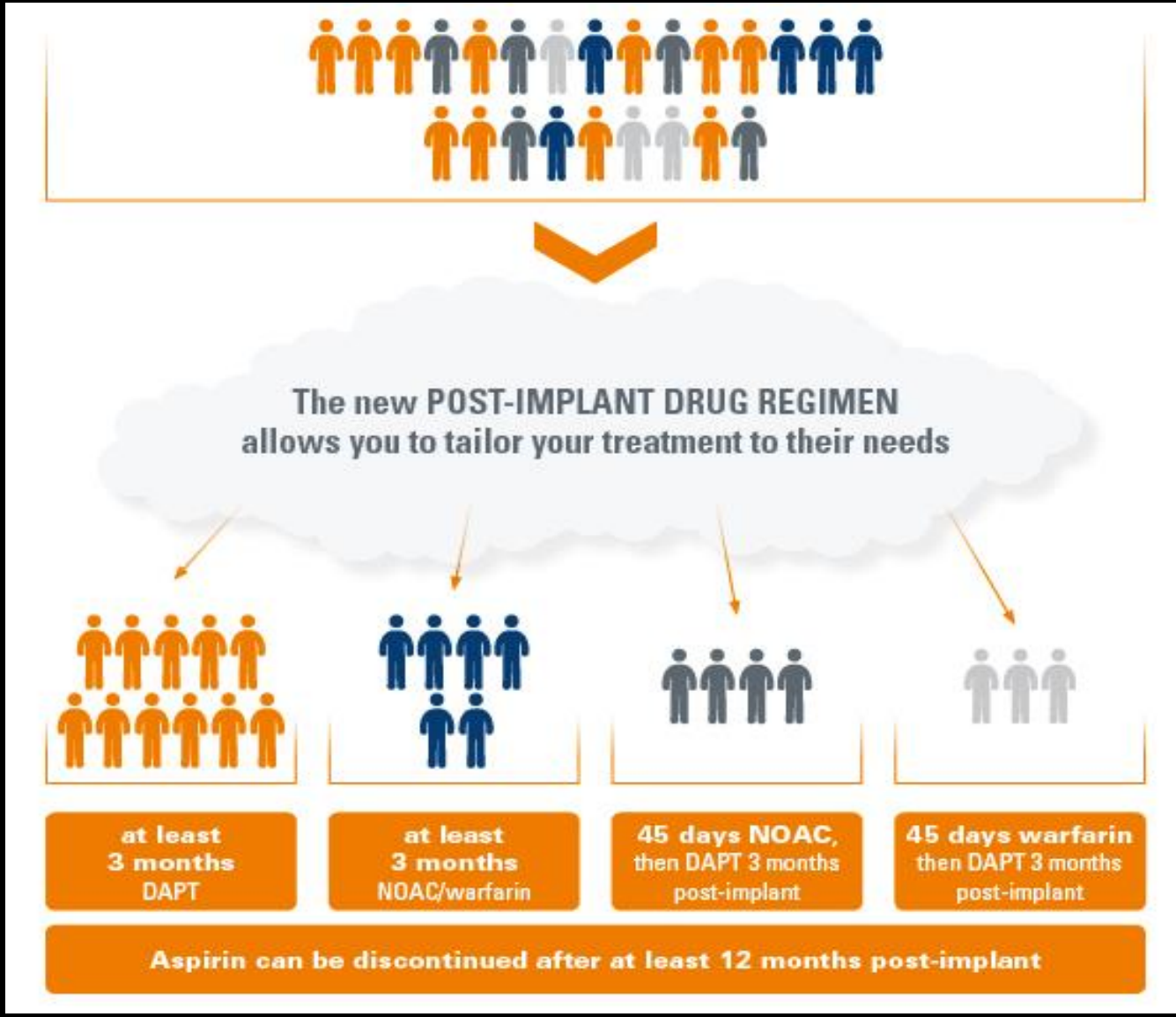


Circulation, 2014

Left atrial appendage closure

- RCTs used Warfarin after LAA occlusion
- Right now for both commercially available devices (Watchman and Amulet) a minimal therapy can be used:

This allows avoidance of triple therapy and reduction of bleeding risk

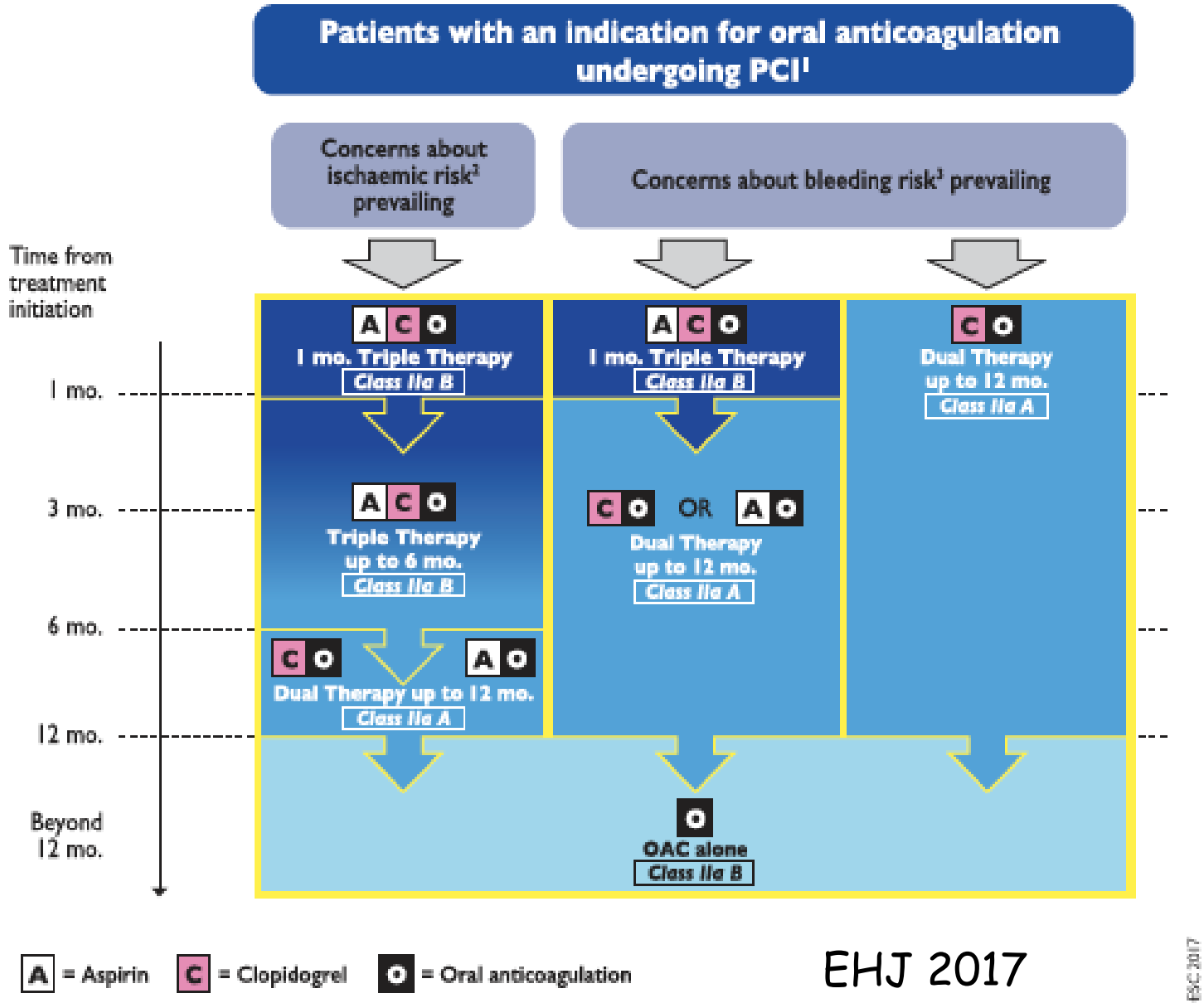


Guidelines

• Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.		
• Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.		
• Consider the use of NOACs instead of VKA.		
• Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. > 65–70%) when VKA is used.		
• Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.[a]		
• Clopidogrel is the $P2Y_{12}$ inhibitor of choice.		
• Use low-dose (≤ 100 mg daily) aspirin.		
• Routine use of PPIs.		
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

EHJ 2017

Guidelines



EHJ 2017

PRACTICAL INDICATIONS
Elective patients

1. Consider LAA occlusion (especially for planned staged procedures and for patients with very high bleeding risk)

2. Drugs:
   - NOACs > Warfarin
   - Low dose > full dose (Rivaroxaban 20 > 15)
   - Only clopidogrel

3. Stents: prefer Biofreedom/DES > BMS

4. Triple:
   - Avoid triple therapy
   - If high ischemic risk (complex procedure, BRS…) choose 1 month of triple therapy followed by NOAC + clopidogrel (or ASA).
   - Consider anticoagulation alone after 6 months

PRACTICAL INDICATIONS
Acute coronary syndromes

1. Drugs:
   - NOACs > Warfarin
   - Low dose > full dose (Rivaroxaban 20 > 15)
   - Clopidogrel > Prasugrel or Ticagrelor

2. Stents: prefer Biofreedom > DES > BMS

3. Triple:
   - At least 1 month of triple therapy (but consider 6-12 months)
   - Afterward, NOAC + clopidogrel (or ASA)
   - Consider anticoagulation alone after 12 months

Conclusions

In patients who underwent DES implantation and treated with oral anticoagulants

ASA can be omitted from DAPT regimen except in patients with high thrombotic risk and low bleeding risk