Hội nghị Tim mạch Miền Trung & Tây Nguyên 2019

12-13/7/2019

Tips for Management of Patients Who Require Oral Anticoagulation for Atrial Fibrillation and Post-PCI Antiplatelet Therapy

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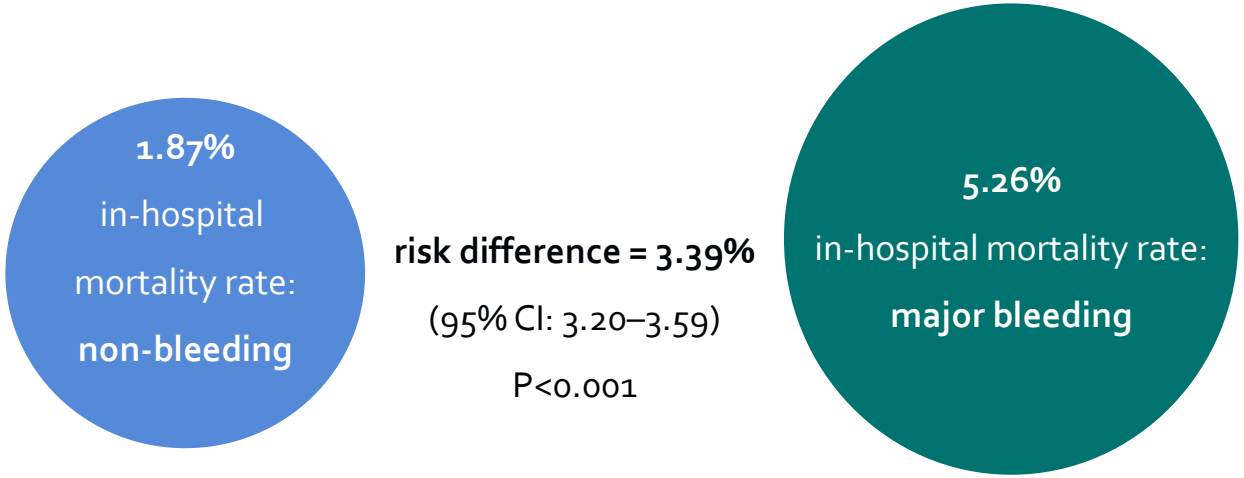
Tam Duc Heart Hospital

Major bleeding was associated with a significant increase in in-hospital mortality, regardless of bleeding site

- 3.3 million PCI procedures (2004–2011 Registry)
- Bleeding: most common non-cardiac complication
- Antithrombotic therapy that minimizes the risk of bleeding complications therefore might be expected to result in better short- and long-term clinical outcomes after PCI



Chhatriwalla et al. JAMA 2013

Triple therapy: OAC plus DAPT

- **Up to 10% of patients undergoing PCI with stenting have an indication for oral anticoagulation (OAC)**
  - atrial fibrillation (AF)
  - venous thromboembolism (VTE)
  - mechanical valves
- **Post-PCI dual antiplatelet therapy (DAPT) plus OAC= Triple therapy (TT)**
  - is associated with a significant increase in the risk of bleeding
  - doubles the risk of serious bleeding and transfusions post-PCI
  - is associated with increased mortality

Pre-PCI Considerations

1. **Assess the need for PCI. Does the patient really need a stent?**

   2017 AUC for PCI (ACC/AHA/SCAI)

   2018 ESC guidelines for myocardial revascularization

2. **Assess the risk of stroke**

   Long-term OAC is recommended for CHA_2DS_2-VASc

   ≥ 2 in men and ≥ 3 in women

3. **Assess the risk of bleeding**

   HAS-BLED score of ≥3 is associated with a high bleeding risk

CHA_2DS_2-VASc

CHA_2DS_2-VASc criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥75 years	**2**
Diabetes mellitus	1
Stroke/transient ischaemic attack/TE	**2**
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65–74 years	1
Sex **c**ategory (i.e. female gender)	1

Lip G et al. Stroke 2010;41:2731–8;

HAS-BLED

HAS-BLED risk criteria	Score
Hypertension (SBP >160 mmHg)	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding (history or predisposition)	1
Labile INRs	1
Elderly (e.g. age >65 years)	1
Drugs or alcohol (1 point each)	1 or 2

Pisters R et al. Chest 2010;138:1093–100

Considerations During PCI

1. **Use radial access preferentially over femoral access for PCI**
   - patients who require post-PCI anticoagulation
2. **Use newer generation DES vs. BMS**
   - Four weeks of DAPT in HBR patients (LEADERS FREE)
   - safety confirmed
   - superior efficacy
3. **Adequate clopidogrel and aspirin loading pre-PCI in all patients**
4. **Continue of aspirin until hospital discharge**

   (even in patients in whom DT is planned on discharge)

The NEW ENGLAND JOURNAL of MEDICINE

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.,

Age ≥75 yr
Oral anticoagulation planned to continue after PCI
Hemoglobin <11 g/liter or transfusion within 4 wk before randomization
Platelet count <100,000/mm^3
Hospital admission for bleeding in previous 12 mo
Stroke in previous 12 mo
Previous intracerebral hemorrhage
Severe chronic liver disease
Creatinine clearance <40 ml/min
Cancer in previous 3 yr¶
Planned major surgery in next 12 mo
Glucocorticoids or NSAID planned for >30 days after PCI
Expected nonadherence to >30 days of dual antiplatelet therapy

N Engl J Med 2015;373:2038- 47

1-month DAPT in HBR?

Đặc điểm bệnh nhân có nguy cơ XH cao

- ≥ 75 tuổi
- Cần tiếp tục dùng kháng đông uống sau PCI
- Hb <11 g/l hoặc có truyền máu trong vòng 4 tuần trước phân nhóm ngẫu nhiên
- Tiểu cầu <100.000/mm^3
- Nhập viện vì xuất huyết trong vòng 12 tháng trước
- Tiền căn đột quỵ trong vòng 12 tháng
- Tiền căn xuất huyết não
- Suy gan nặng
- Độ lọc cầu thận <40ml/phút
- Bệnh lý ung thư trong vòng 3 năm trước
- Có kế hoạch đại phẫu trong 12 tháng tới
- Cần dùng corticoid hoặc NSAID kéo dài hơn 30 ngày sau PCI
- Khả năng tuân trị DAPT> 30 ngày kém

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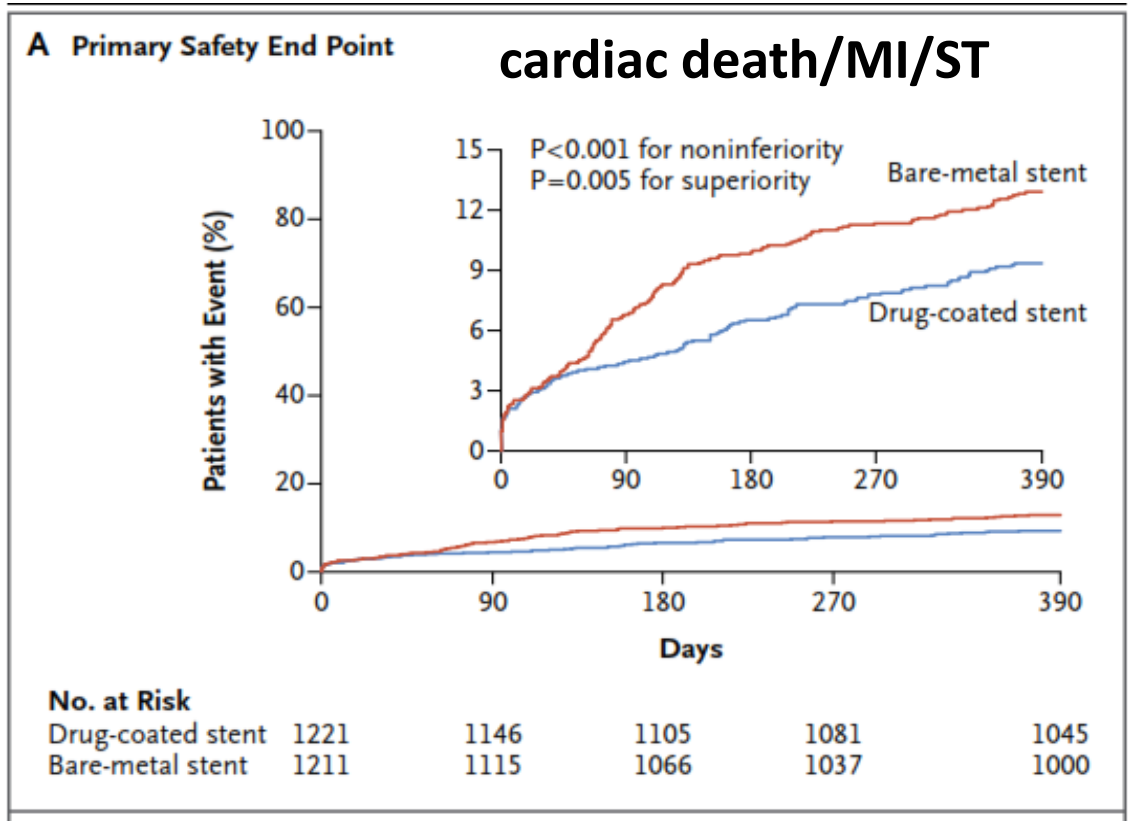
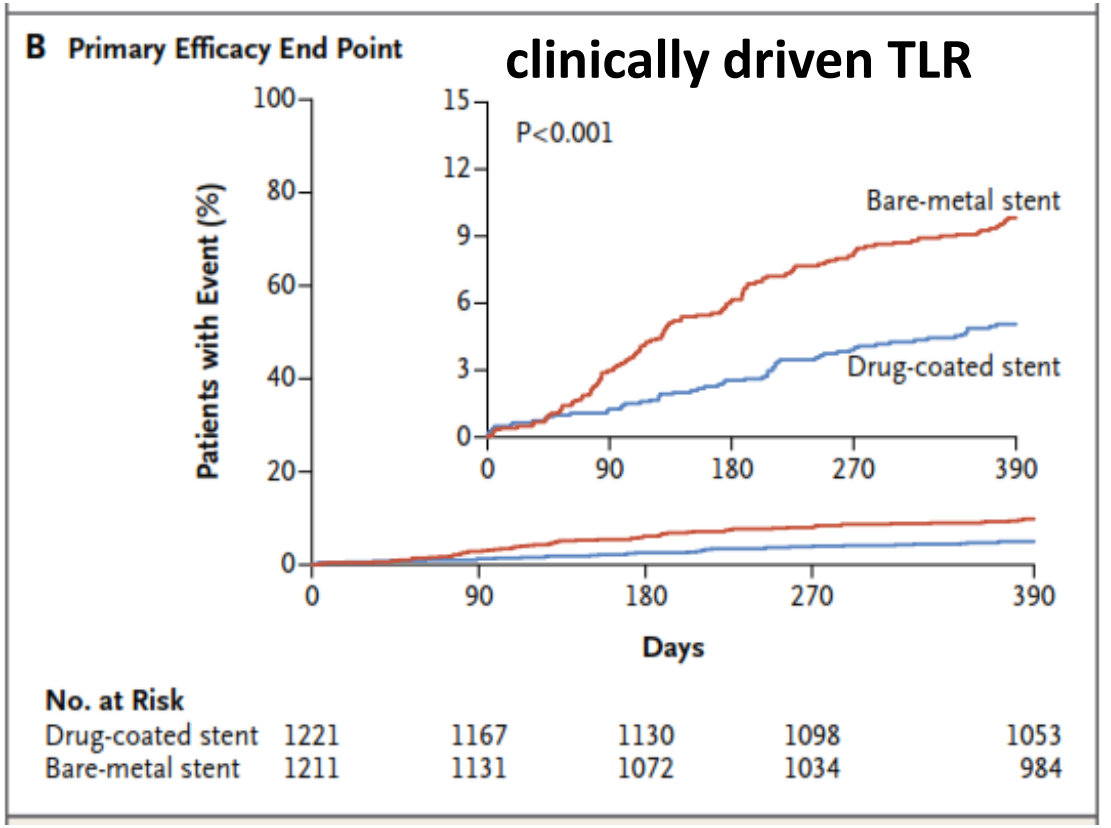
1-month DAPT in HBR patients

Safety & Efficacy



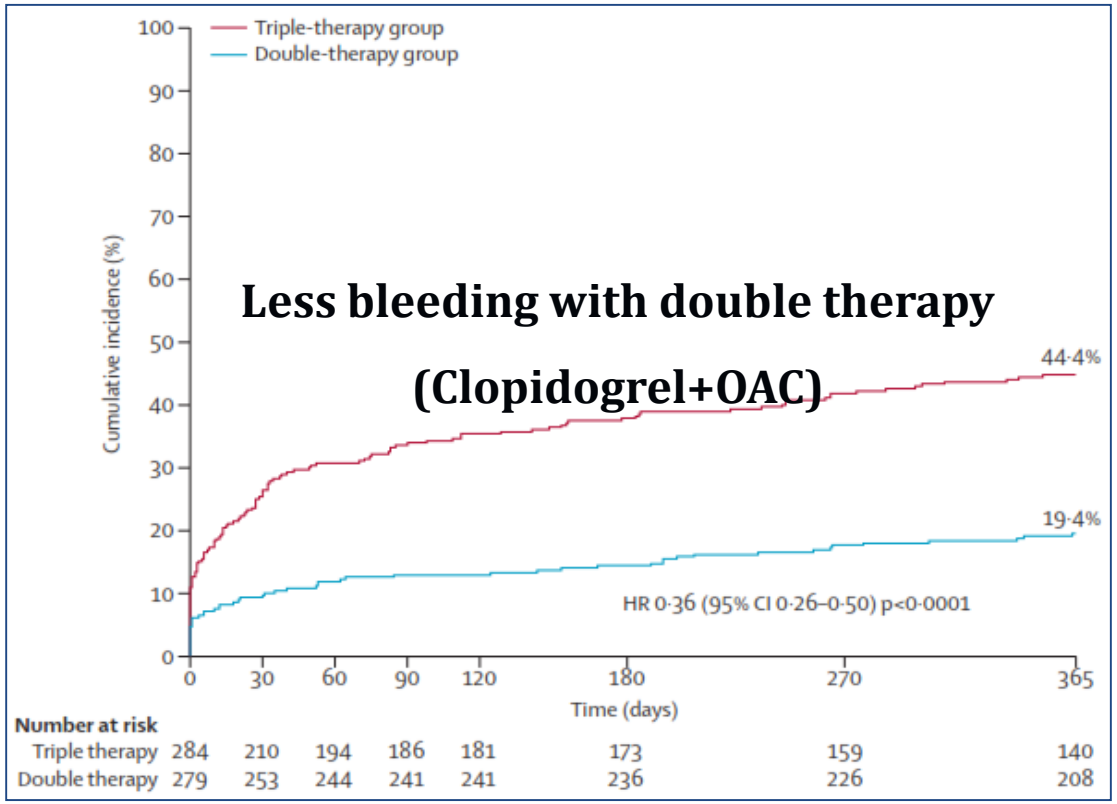


Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

- Open-label, multi-centre, randomised, controlled trial
- 15 centers in Belgium and the Netherlands
- Clopidogrel+OAC vs. Clopidogrel+Aspirin+OAC
- ***PE- any bleeding within 1 year of PCI***

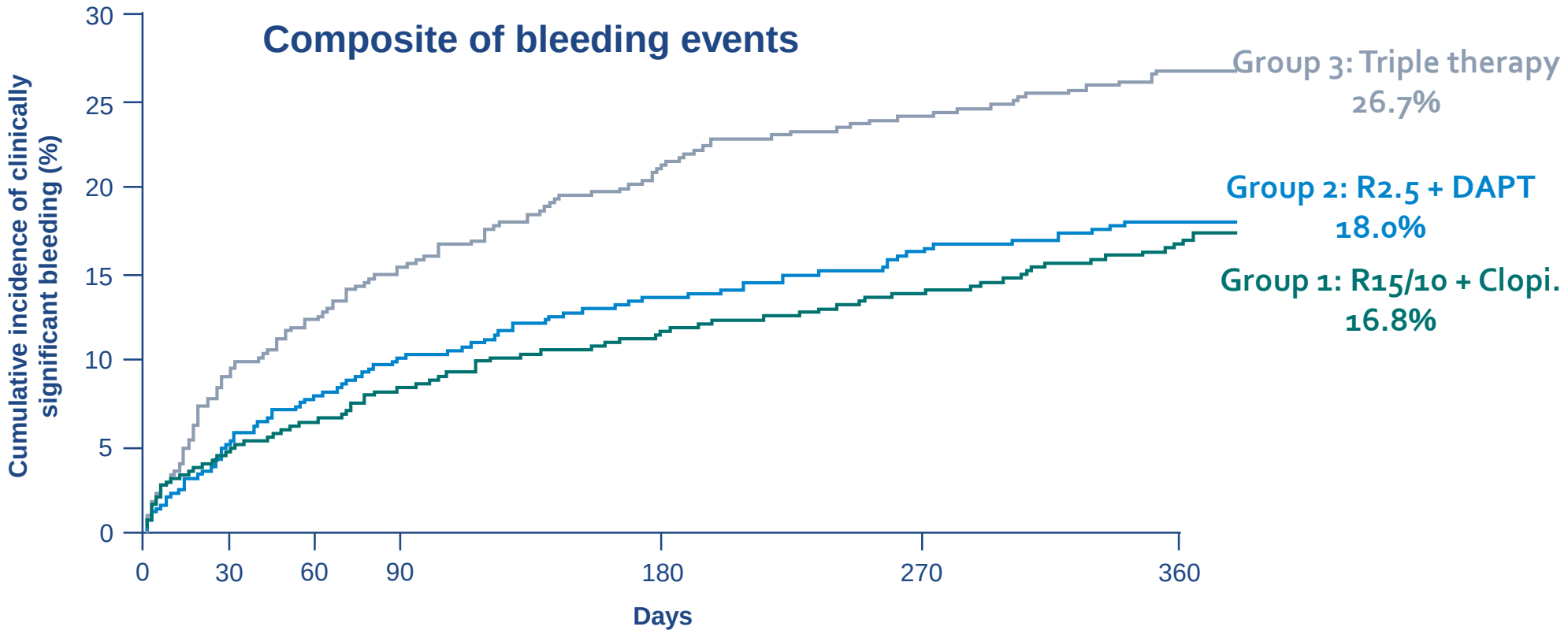
Omission of aspirin from TT resulted in a highly significant 25% absolute RR (NNT =4)



Lancet 2013; 381: 1107–15

PIONEER AF-PCI: lower rate of bleeding risk (PE)

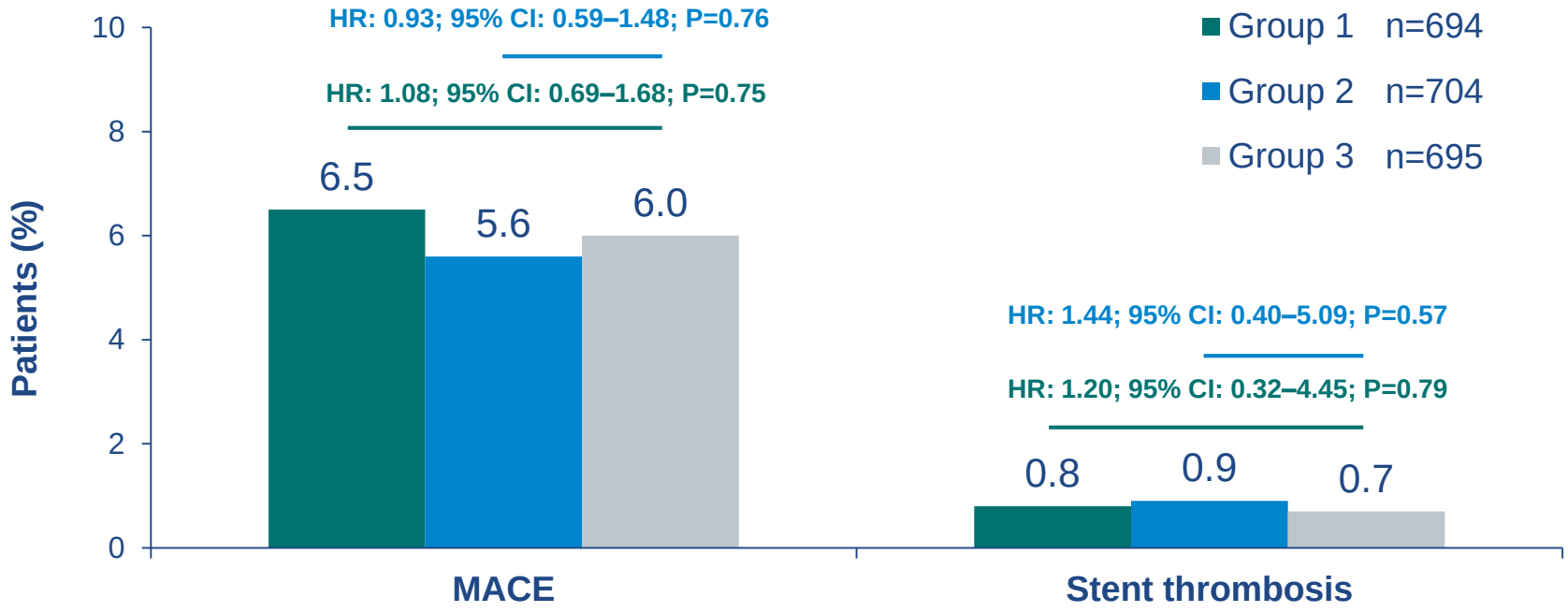
in both rivaroxaban groups vs TT group



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

PIONEER AF-PCI: similar rates of thromboembolic events

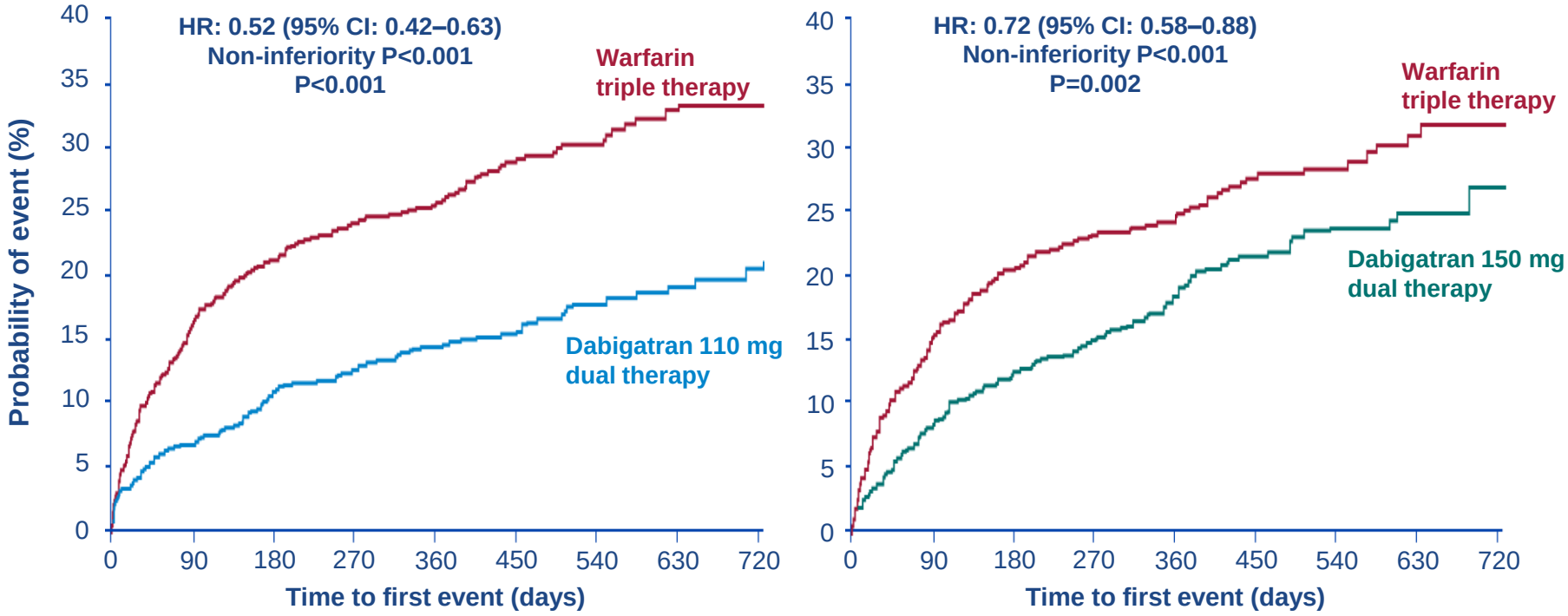
MACE= composite of CV death, MI, and stroke



The study was not powered to show superiority or non-inferiority between treatments in efficacy endpoints

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

RE-DUAL PCI: Significantly lower rates of bleeding risks with dabigatran DT vs. TT



ISTH major bleeding event

- Symptomatic bleeding in a critical area or organ, and/or
- Bleeding associated with reduced haemoglobin ≥2 g/dL (1.24 mmol/L) or transfusion of ≥2 units of blood or packed cells and/or
- Fatal bleed

CRNM bleeding event

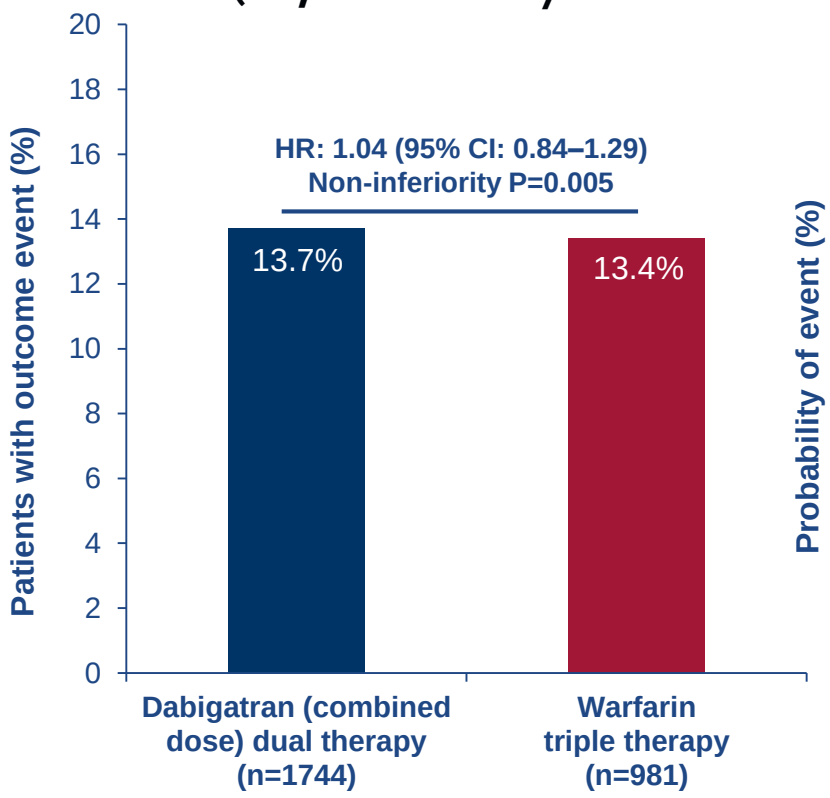
Not meeting criteria for a major bleed but prompts ≥1 of:

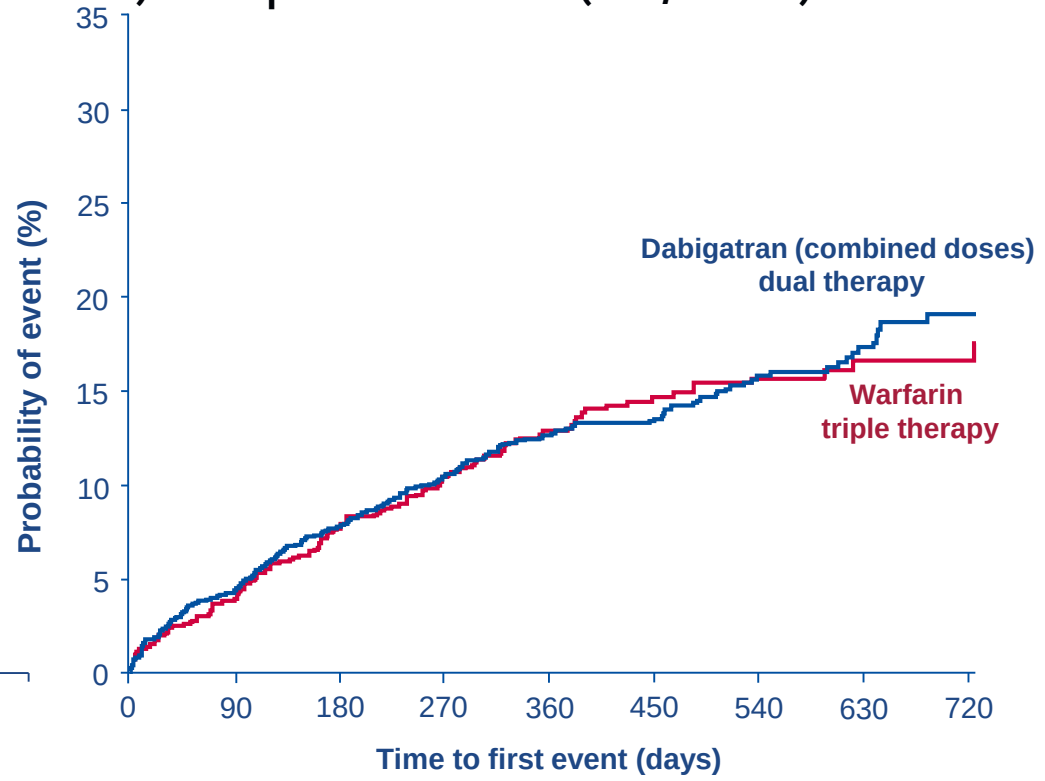
- Hospital admission
- Physician-guided medical or surgical treatment
- Physician-guided change, interruption (≥1 dose) or discontinuation of study drug

Cannon et al. N Engl J Med 2017

REDUAL- PCI: Dabigatran DT was non-inferior to Warfarin TT in efficacy endpoint

Composite endpoint of death or thromboembolic event (MI, stroke or systemic embolism) or unplanned revas. (PCI/CABG)



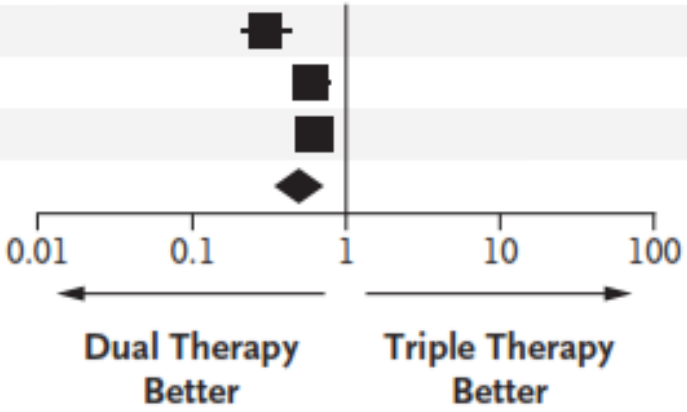


Cannon et al. N Engl J Med 2017; Cannon et al ESC 2017

Meta- analysis: DT vs. TT

A Safety: Major and Minor Bleeding Events

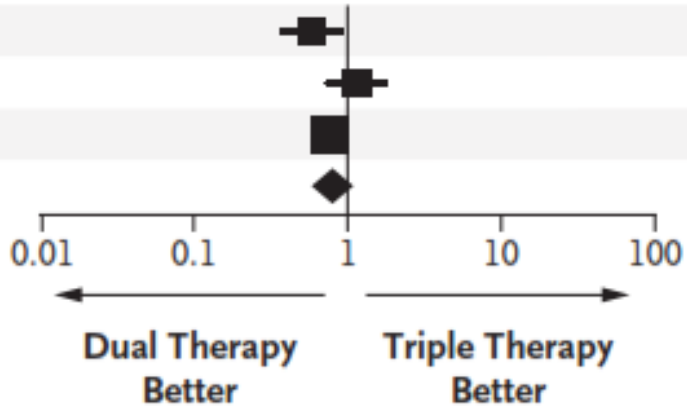
Trial	Dual Therapy	Triple Therapy	Odds Ratio (95% CI)	z Score	Relative Weight	P Value
	no. of events/total no.					
WOEST	54/279	126/284	0.30 (0.21–0.44)	–6.22	29.1	<0.001
PIONEER AF-PCI	109/696	167/697	0.59 (0.45–0.77)	–3.86	34.1	<0.001
RE-DUAL PCI	305/1744	196/764	0.61 (0.50–0.75)	–4.68	36.8	<0.001
Overall			0.49 (0.34–0.72)	–3.70		<0.001
I^2=82.06						



LESS BLEEDING

B Efficacy: Major Adverse Cardiovascular Events

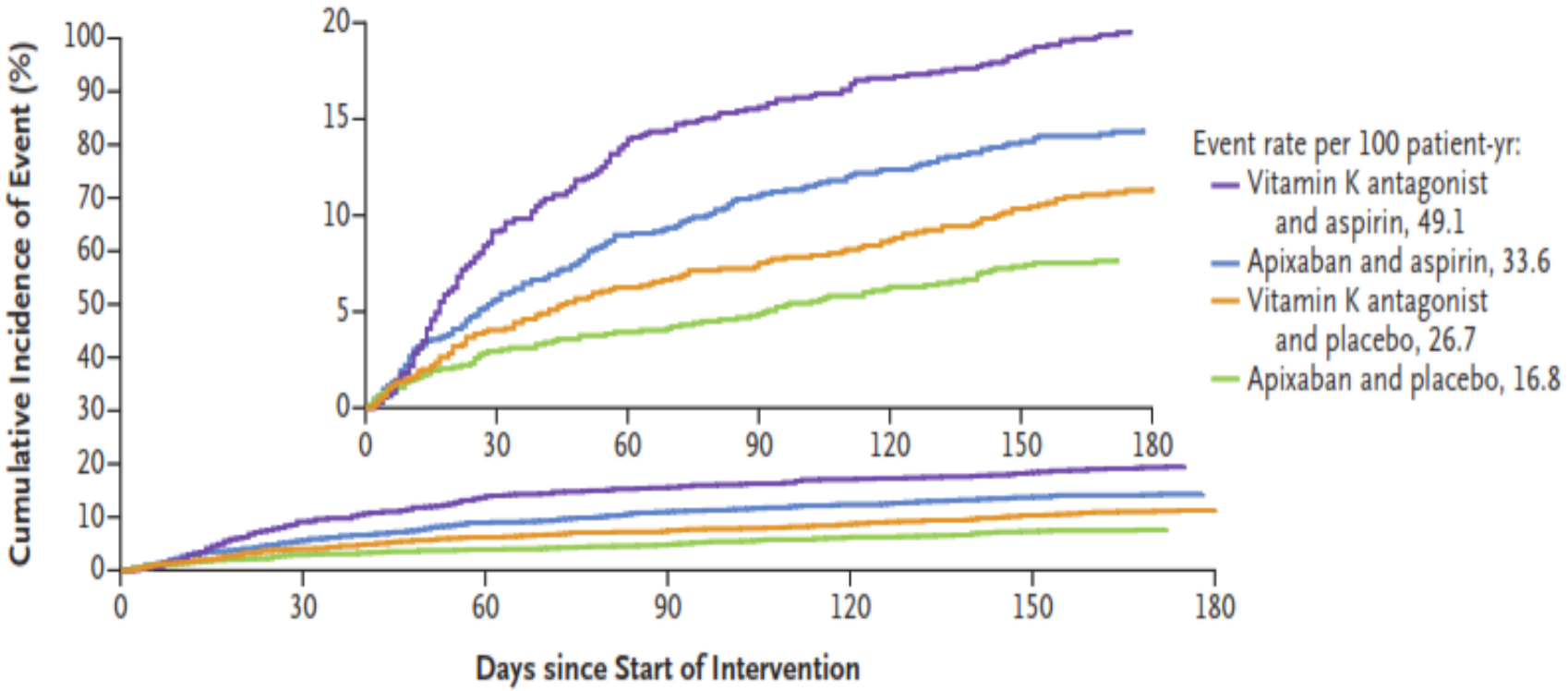
Trial	Dual Therapy	Triple Therapy	Odds Ratio (95% CI)	z Score	Relative Weight	P Value
	no. of events/total no.					
WOEST	31/279	50/284	0.58 (0.36–0.95)	–2.18	25.5	0.03
PIONEER AF-PCI	41/694	36/695	1.15 (0.72–1.82)	0.59	27.0	0.55
RE-DUAL PCI	239/1744	131/764	0.77 (0.61–0.97)	–2.23	47.47	0.03
Overall			0.80 (0.58–1.09)	–1.40		0.16
I^2=51.17						



SIMILAR MACE

Piccini JP, N Engl J Med 2017

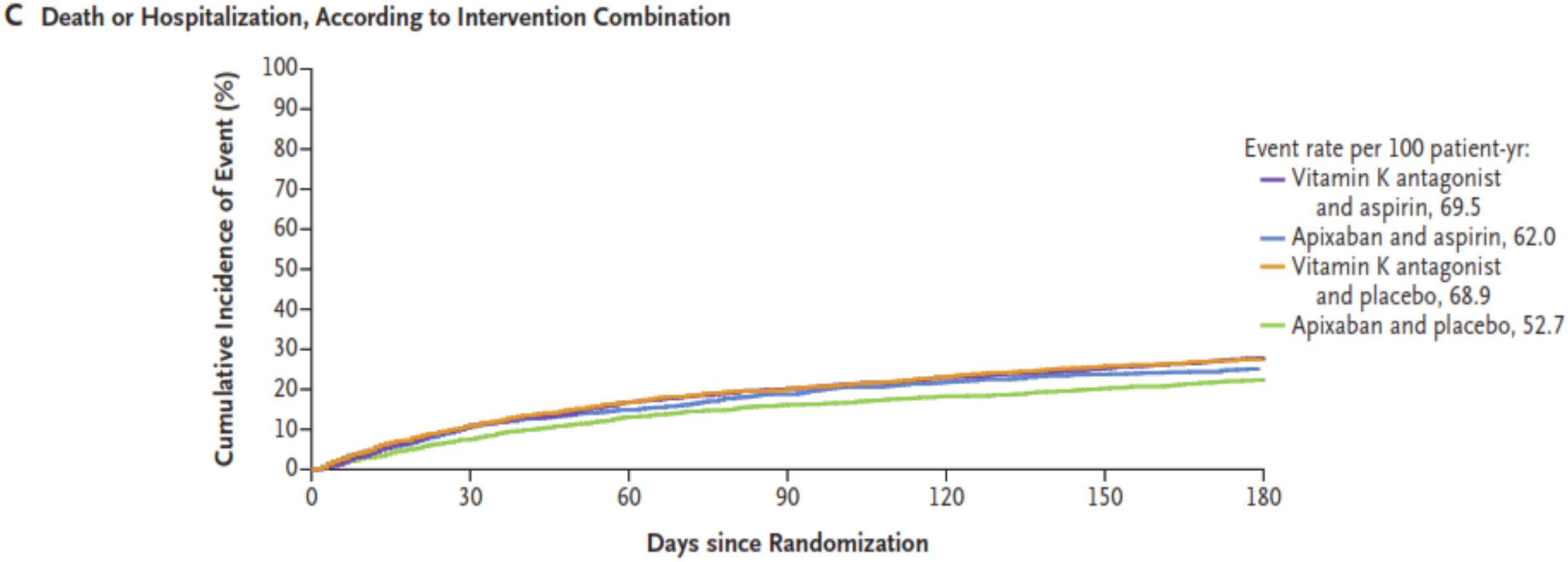
AUGUSTUS: Less bleeding with Apixaban and without Aspirin (DT) in AF and recent ACS or PCI patients treated with P2Y12 inhibitor



- TT: significant increase the risk of bleeding at 6 months (HR 1.89, NNH=14)
- Omission of aspirin lowered bleeding risk by 47%

N Engl J Med. 2019 Apr 18;380(16):1509-24

AUGUSTUS: Less hospitalizations without significant differences in ischemic risk with Apixaban and without Aspirin (DT)

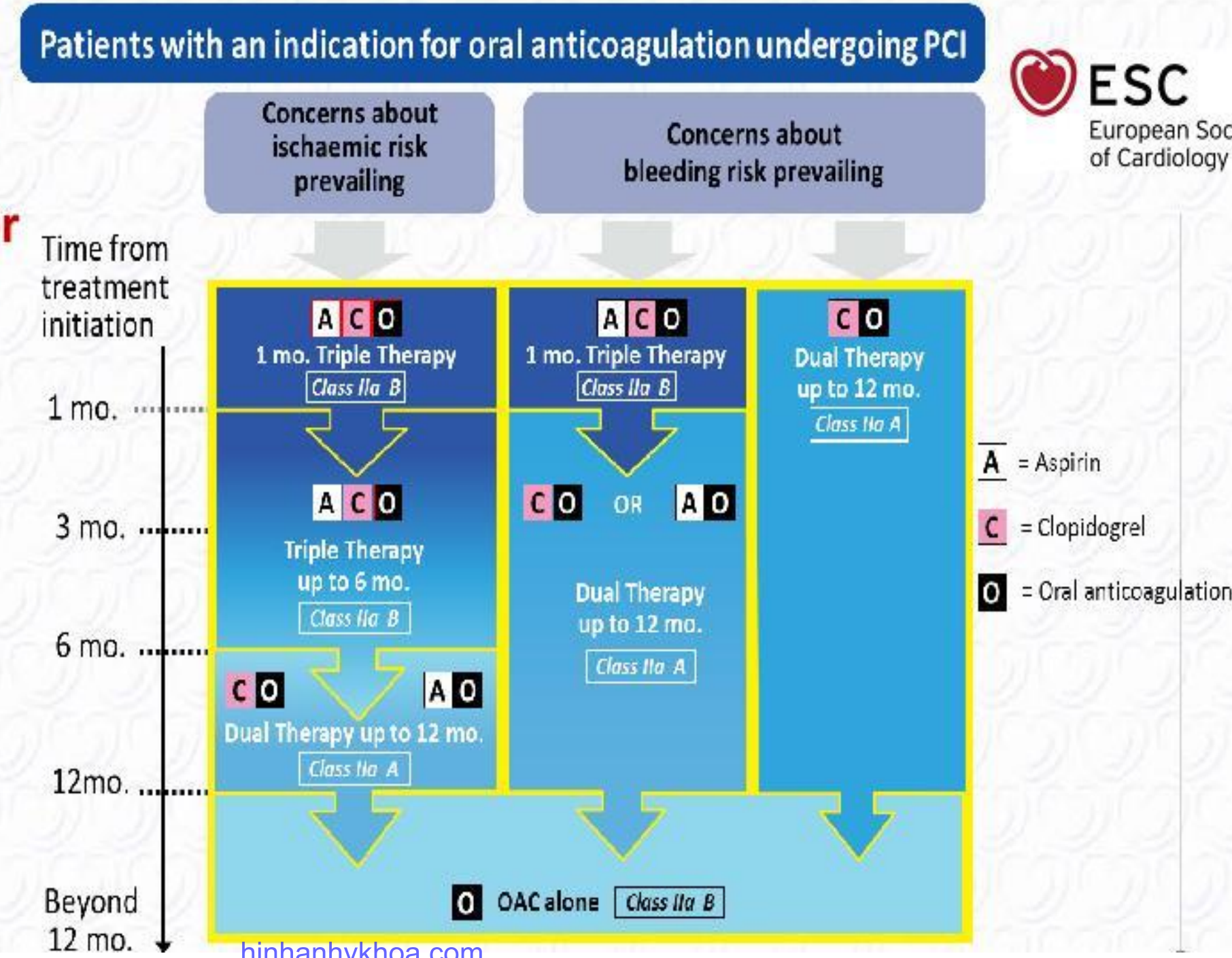


N Engl J Med. 2019 Apr 18;380(16):1509-24

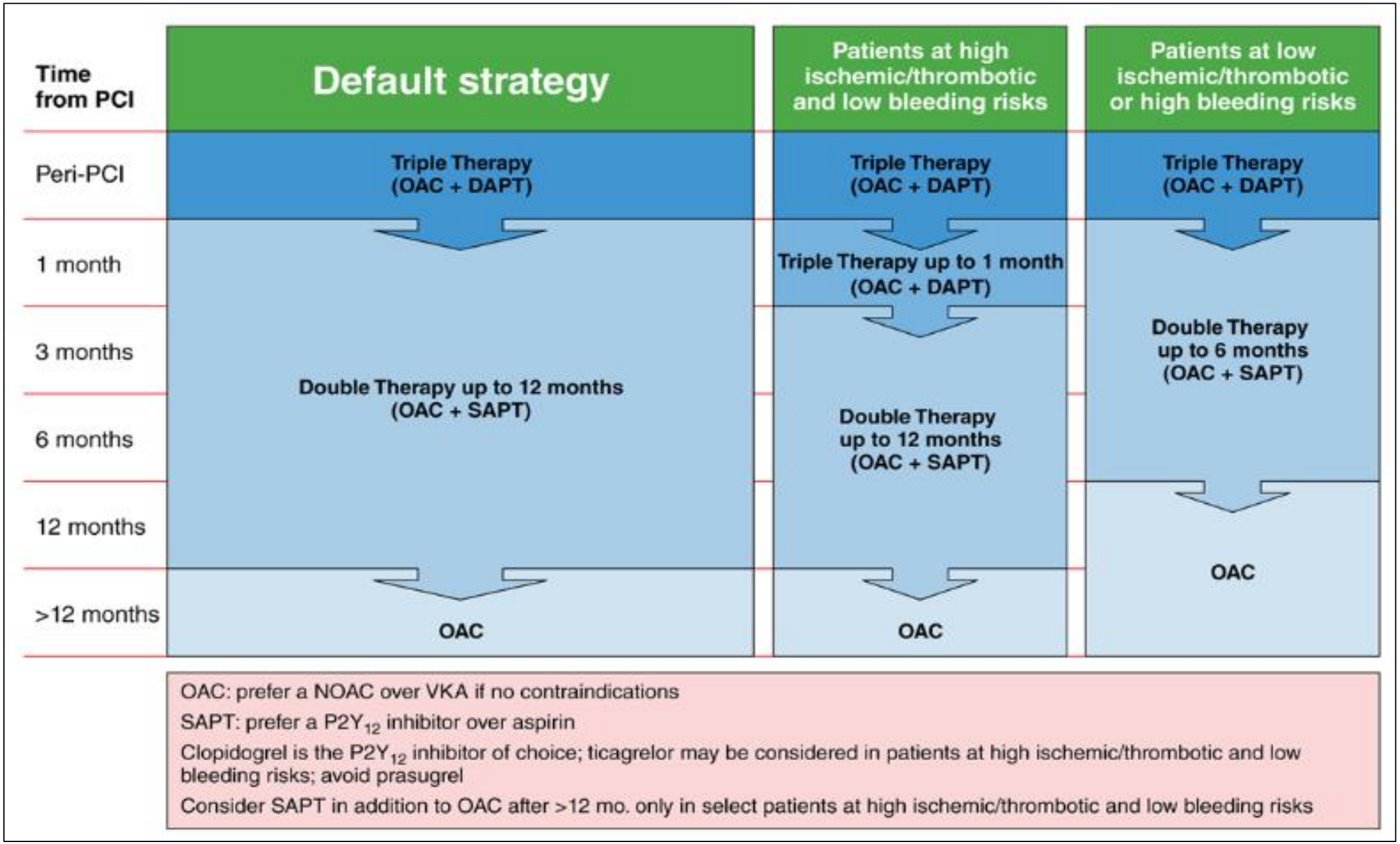
ESC GUIDELINES 2017: strategies to avoid bleeding

- 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 when NOACs are not contra-indicated.
- 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.
- Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
- Use low-dose (≤100 mg daily) aspirin.
- Routine use of PPIs.

Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)



2018 North American Expert Consensus Antithrombotic Therapy for AF patients Treated with OAC Undergoing PCI



Circulation. 2018;138:527–536

Patient type	Treatment Regimens	Comments
Average ischemic & bleeding risk (default strategy)	**DT (C + O) up to 12 months**	North American Expert Consensus update recommendation (2018)
High ischemic risk (ACS) & low bleeding risk	**TT x 1 month followed by DT (C + O) x 11 months** **TT x 6 months followed by DT (C + O or A + O) x six months**	North American Expert Consensus update recommendation (2018) ESC recommendation IIa, LOE B (2017)

Patient type	Treatment Regimens	Comments
High bleeding risk & low ischemic risk (non-ACS)	**DT (C + O) x six months**	North American Expert Consensus update recommendation (2018)
	TT x 1 month followed by DT (C + O or A + O) x 11 months or less	ESC recommendation IIa, LOE B (2017)
	DT (C + O) x 12 months	ESC recommendation IIa, LOE A (2017)
High ischemic & high bleeding risk	**No specific recommendations** **Use clinical judgment and shared decision-making** **Consider referral for left atrial appendage occlusion**	

Antiplatelet agent considerations

1. **Most patients enrolled in recent studies were taking clopidogrel**

   Ticagrelor was used as part of DT in 12 percent of patients in RE-DUAL PCI.

   Prasugrel and ticagrelor should not be used as a component of TT (Class III-harm ESC guidelines)

2. **Aspirin dose should typically ≤ 81 mg**

3. **Consider discontinuation of the antiplatelet agent from dual therapy**

   after one year in patients with low ischemic risk

   after six months in patients with a high bleeding risk

Anticoagulant considerations

1. **Using a DOAC instead of warfarin if there is no contraindication**

   Continue warfarin if the patient was tolerating it or if Creat. Clearance < 30 ml/min

   INR target: 2-2.5

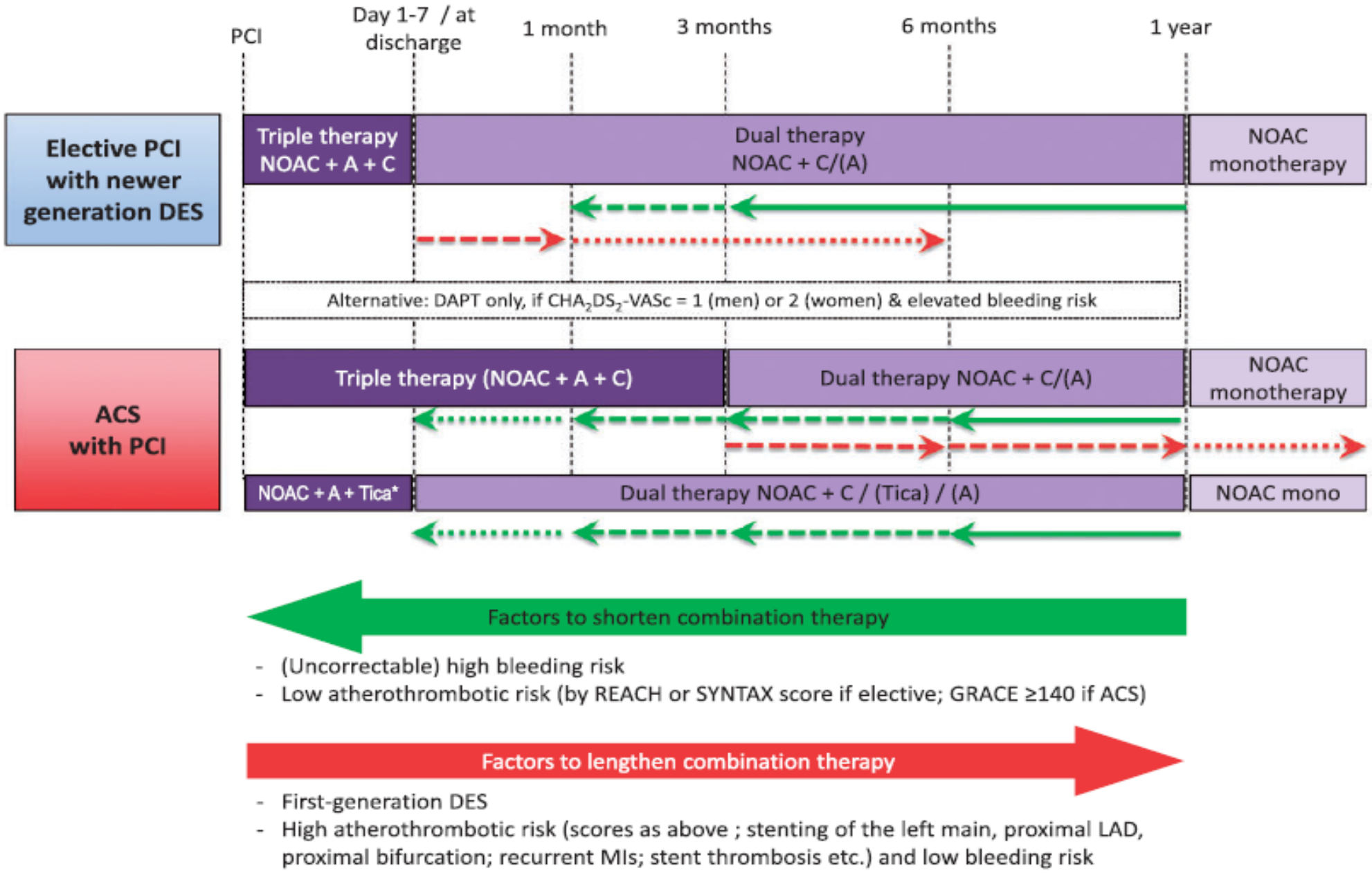
2. **There is no role of withholding OAC in patients with AF post-PCI**

   No role of DAPT for AF patients

3. **DOACs are not approved for "valvular AF"**

   AF in the presence of a mechanical heart valve or moderate-to-severe mitral stenosis.

2018 EHRA Guidelines



European Heart Journal (2018) 00, 1–64

ESC CONSENSUS 2018

Table I Scientific rationale of recommendations[a]

Definitions where related to a treatment or procedure	Consensus statement instruction	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial or is supported by strong observational evidence and authors' consensus (as indicated by an asterisk).	'Should do this'	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on a small number of patients or which is not widely applicable.	'May do this'	
Scientific evidence or general agreement not to use or recommend a treatment or procedure.	'Do not do this'	

[a]This categorization for our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations.

ESC CONSENSUS 2018

When dabigatran is used as part of DAT, the standard doses of 150 mg bid should be used to reduce the risk of ischaemic events.

- As per prescribing label, dabigatran 110 mg bid can be considered in elderly patients, concomitant when PgP inhibitors (e.g. verapamil) are used, and in patients with high bleeding risk
- Both dabigatran 150 mg or 110 mg bid have been shown to be non-inferior (and in the case of 150 mg bid, superior) to warfarin for stroke prevention in AF.

When rivaroxaban is used as part of DAT, reduced dose 15 mg od should be considered.

- The efficacy with respect to stroke prevention of this reduced dose in this population has not been sufficiently evaluated.

When apixaban or edoxaban are used as part of TAT or DAT, the standard dose (5 mg bid and 60 mg od, respectively, unless label-guided dose reduction is indicated) should be selected pending results of ongoing trials.

Key messages

1. **AF plus ACS/PCI: challenge clinical scenario**
   - risk of embolic event (CHA2DS2-VASc)
   - bleeding (HAS-BLED)
2. **Dual therapy (NOACs + Clopidogrel) seems to be**
   - safe (reduce risk of bleeding)
   - efficacy (non-inferiority for thromboembolic events)
3. **Tips for lower bleeding**
   - use of PPIs for gastric protection, avoiding NSAIDs and alcohol
   - avoidance of supra-therapeutic INR
   - blood pressure control
   - adjustment of NOAC dose based on creatinine clearance
   - closer monitoring of patients on TT and those with a HAS-BLED score >3

Thank you!