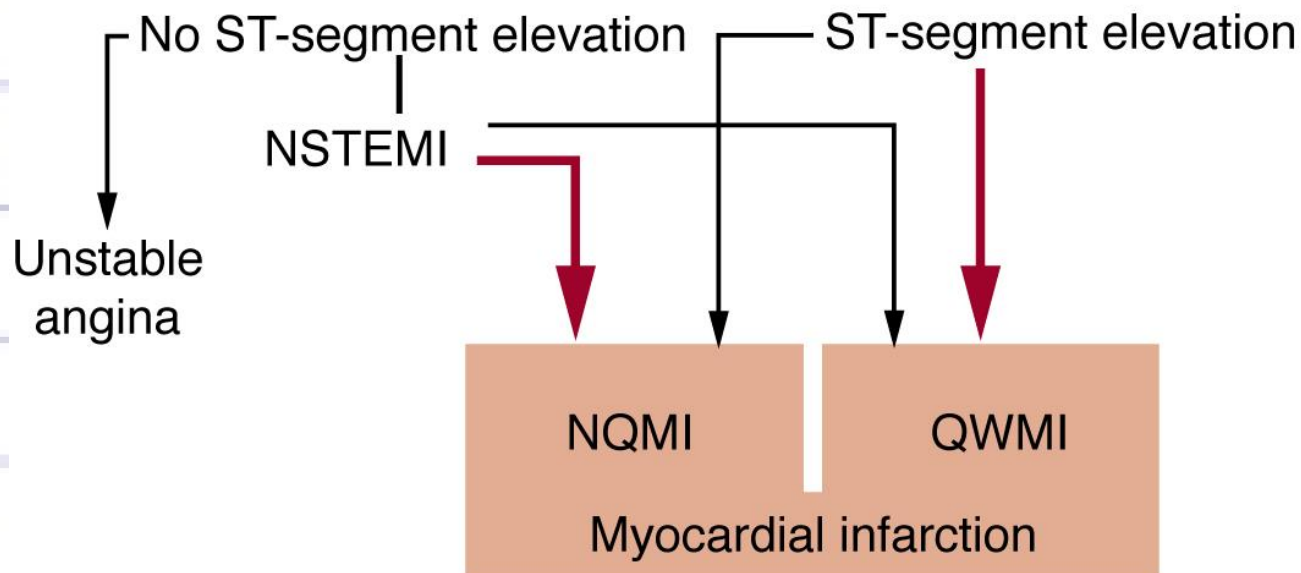
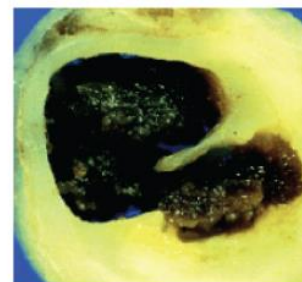
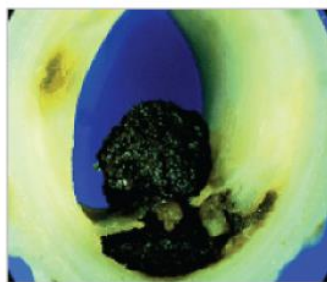


ĐIỀU TRỊ HỘI CHỨNG ĐMVC 2016: TẦM QUAN TRỌNG CỦA THUỐC KHÁNG KẾT TẬP TIỂU CẦU KÉP

PGS. TS. Phạm Nguyễn Vinh
Đại học Y khoa Phạm Ngọc Thạch
Đại học Y khoa Tân Tạo
Bệnh viện Tim Tâm Đức
Viện Tim Tp. HCM

Các định nghĩa và sinh lý bệnh hội chứng động mạch vành cấp (HCĐMVC)

Acute coronary syndrome



Các biện pháp điều trị cấp thời HCĐMVC/KSTC

- Điều trị chống TMCB: chẹn bêta, nitrates, ức chế calci (nhóm non-DHP), nicorandil
- Điều trị chống đông
- Chống kết tập tiểu cầu
- Tái lưu thông ĐMV

Khuyến cáo sử dụng thuốc chống TMCB trên b/n HCĐMVC/KSTC

Recommendations	Class ^a	Level ^b	Ref. ^c
Early initiation of beta-blocker treatment is recommended in patients with ongoing ischaemic symptoms and without contraindications.	I	B	119
It is recommended to continue chronic beta-blocker therapy, unless the patient is in Killip class III or higher.	I	B	126
Sublingual or i.v. nitrates are recommended to relieve angina; ^d i.v. treatment is recommended in patients with recurrent angina, uncontrolled hypertension or signs of heart failure.	I	C	
In patients with suspected/confirmed vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B	127

i.v. = intravenous.

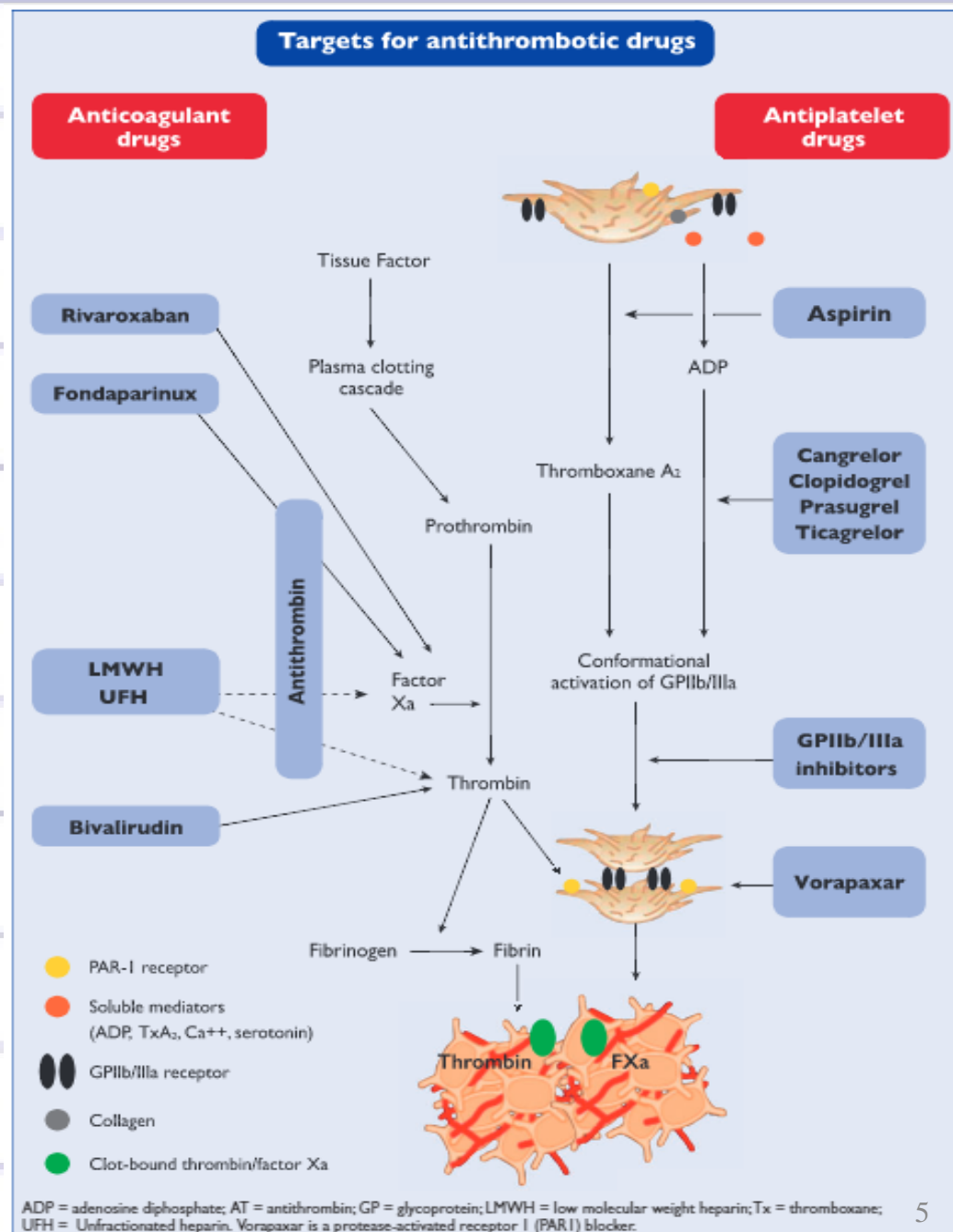
^aClass of recommendation.

^bLevel of evidence.

^cReferences supporting level of evidence.

^dShould not be administered in patients with recent intake of sildenafil or vardenafil (<24 h) or tadalafil (<48 h).

Mục tiêu thuốc chống huyết khối



TL: Roffi M et al. 2015 ESC Guidelines for the management of non STEMI. Eur. H. J 2015, doi: 10.1093/eurheartf/ehv 320

So sánh hiệu quả điều trị các thuốc chống kết tập tiểu cầu mới với clopidogrel (1)

Recommendations	Class ^a	Level ^b	Ref. ^c
Oral antiplatelet therapy			
Aspirin is recommended for all patients without contraindications at an initial oral loading dose ^d of 150–300 mg (in aspirin-naïve patients) and a maintenance dose of 75–100 mg/day long-term regardless of treatment strategy.	I	A	129–132
A P2Y ₁₂ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A	137, 148, 153
<ul style="list-style-type: none"> Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,^e for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started). 	I	B	153
<ul style="list-style-type: none"> Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.^e 	I	B	148, 164
<ul style="list-style-type: none"> Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation. 	I	B	137
P2Y ₁₂ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A	187–189, 192

TL: Roffi M et al. 2015 ESC Guidelines for the management of non STEMI. Eur. H. J 2015, doi: 10.1093/eurheartf/ehv 320

So sánh
hiệu quả
điều trị các
thuốc chống
kết tập tiểu
cầu mới với
clopidogrel
(2)

It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.	III	B	164
Intravenous antiplatelet therapy			
GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.	IIa	C	
Cangrelor may be considered in P2Y ₁₂ inhibitor-naive patients undergoing PCI.	IIb	A	158–161
It is not recommended to administer GPIIb/IIIa inhibitors in patients in whom coronary anatomy is not known.	III	A	198, 199
Long-term P2Y₁₂ inhibition			
P2Y ₁₂ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	IIb	A	184, 186

So sánh hiệu quả điều trị các thuốc chống kết tập tiểu cầu mới với clopidogrel (3)

General recommendations			
A proton pump inhibitor in combination with DAPT is recommended in patients at higher than average risk of gastrointestinal bleeds (i.e. history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAID/ corticosteroid use or two or more of the following: age \geq 65 years, dyspepsia, gastro-oesophageal reflux disease, <i>Helicobacter pylori</i> infection, chronic alcohol use).	I	B	208, 209
In patients on P2Y ₁₂ inhibitors who need to undergo non-emergency major non-cardiac surgery, ^f postponing surgery for at least 5 days after cessation of ticagrelor or clopidogrel and for 7 days for prasugrel, should be considered if clinically feasible and unless the patient is at high risk of ischaemic events.	IIa	C	
In case of a non-cardiac surgical procedure that cannot be postponed or of a bleeding complication, discontinuation of the P2Y ₁₂ inhibitor may be considered after a minimum of 1 and 3 months from PCI with BMS and new-generation DES, respectively.	IIb	C	

TL: Roffi M et al. 2015 ESC Guidelines for the management of non STEMI. Eur. H. J 2015, doi: 10.1093/eurheartf/ehv 320

Điều trị 2
chống kết tập
tiểu
cầu/HCĐMVC
/ điều trị nội

COR	LOE	Recommendations
I	B-R	In patients with ACS who are managed with <u>medical therapy</u> alone (without revascularization or fibrinolytic therapy) and treated with DAPT, P2Y ₁₂ inhibitor therapy (either clopidogrel or ticagrelor) should be continued for at least 12 months.
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended.
IIa	B-R	In patients with NSTEMI-ACS who are managed with <u>medical therapy</u> alone (without revascularization or fibrinolytic therapy) treated with DAPT, it is reasonable to use <u>ticagrelor in preference to clopidogrel</u> for maintenance P2Y ₁₂ inhibitor therapy.
IIb	A ^{SR}	In patients with ACS treated with medical therapy alone (without revascularization or fibrinolytic therapy) who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT <u>for longer than 12 months</u> may be reasonable.

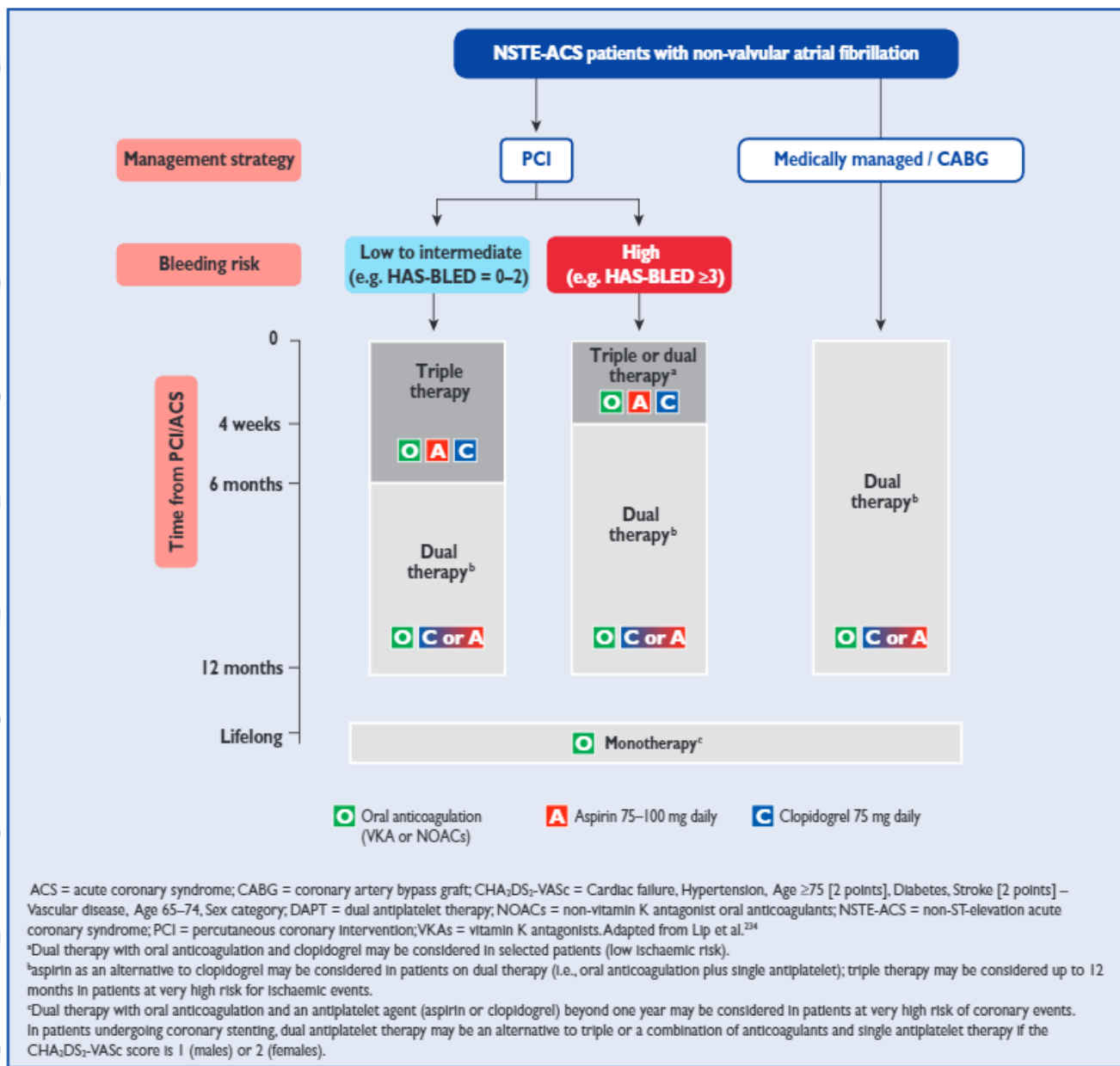
Điều trị 2
chống kết
tập tiểu cầu/
HĐMVC/
đã đặt stent

COR	LOE	Recommendations
I	B-R	In patients with <u>ACS treated with DAPT after BMS or DES implantation</u> , P2Y ₁₂ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months.
I	B-NR	In patients treated with DAPT, a daily aspirin dose of <u>81 mg (range, 75 mg to 100 mg)</u> is recommended.
IIa	B-R	In patients with <u>ACS treated with DAPT after coronary stent implantation</u> , it is reasonable to use <u>ticagrelor in preference to clopidogrel for maintenance P2Y₁₂ inhibitor therapy.</u>
IIa	B-R	In patients with <u>ACS treated with DAPT after coronary stent implantation</u> , who are not at high risk <u>for bleeding complications</u> and who do <u>not have a history of stroke or TIA</u> , it is reasonable to choose prasugrel over clopidogrel for maintenance P2Y ₁₂ inhibitor therapy.

Điều trị 2
chống kết
tập tiểu cầu
lâu dài/
HĐMV đã
đặt stent

COR	LOE	Recommendations
IIb	A ^{SR}	In patients with ACS treated with coronary stent implantation who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use) continuation of DAPT for longer than 12 months may be reasonable.
IIb	C-LD	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y ₁₂ therapy after 6 months may be reasonable.
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA.

Thuốc chống huyết khối trên HCĐMVC kèm rung nhĩ không do van tim



Các chỉ điểm tiên đoán nguy cơ huyết khối hay nguy cơ cao dẫn đến NMCT cần chụp ĐMV khẩn cấp

Very-high-risk criteria

- Haemodynamic instability or cardiogenic shock
- Recurrent or ongoing chest pain refractory to medical treatment
- Life-threatening arrhythmias or cardiac arrest
- Mechanical complications of MI
- Acute heart failure
- Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation

High-risk criteria

- Rise or fall in cardiac troponin compatible with MI
- Dynamic ST- or T-wave changes (symptomatic or silent)
- GRACE score >140

Intermediate-risk criteria

- Diabetes mellitus
- Renal insufficiency (eGFR <60 mL/min/1.73 m²)
- LVEF <40% or congestive heart failure
- Early post-infarction angina
- Prior PCI
- Prior CABG
- GRACE risk score >109 and <140

Low-risk criteria

- Any characteristics not mentioned above

CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; MI = myocardial infarction.

TL: Roffi M et al. 2015 ESC Guidelines for the management of non STEMI. Eur. H. J 2015, doi: 10.1093/eurheartf/ehv 320

2014 ESC/EACTS Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

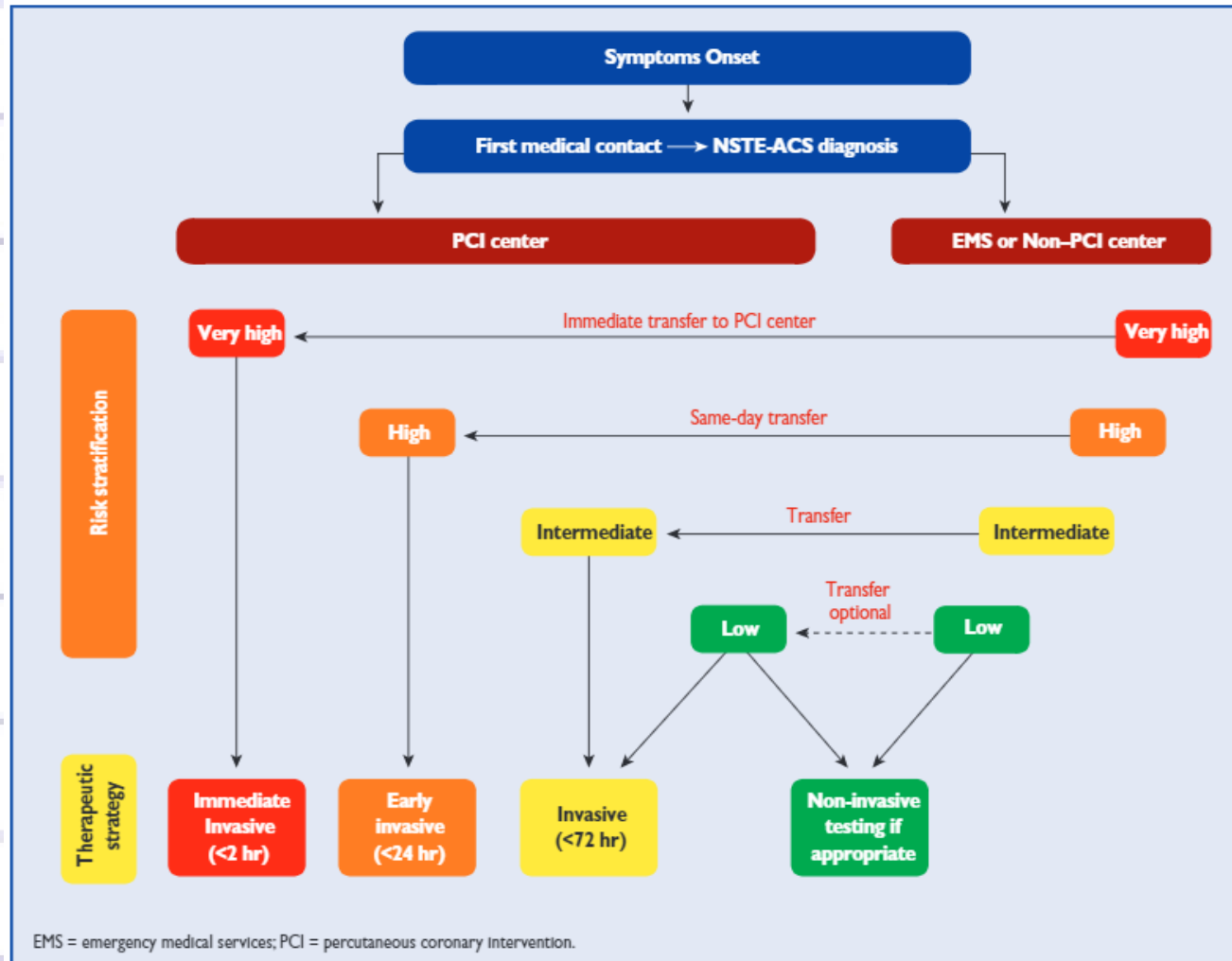
Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI)

Authors/Task Force members: Stephan Windecker* (ESC Chairperson) (Switzerland), Philippe Kolh* (EACTS Chairperson) (Belgium), Fernando Alfonso (Spain), Jean-Philippe Collet (France), Jochen Cremer (Germany), Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece), Christian Hamm (Germany), Stuart J. Head (The Netherlands), Peter Juni (Switzerland), A. Pieter Kappetein (The Netherlands), Adnan Kastrati (Germany), Juhani Knuuti (Finland), Ulf Landmesser (Switzerland), Günther Laufer (Austria), Franz-Josef Neumann (Germany), Dimitrios J. Richter (Greece), Patrick Schauerte (Germany), Miguel Sousa Uva (Portugal), Giulio G. Stefanini (Switzerland), David Paul Taggart (UK), Lucia Torracca (Italy), Marco Valgimigli (Italy), William Wijns (Belgium), and Adam Witkowski (Poland).

Khuyến cáo điều trị chống huyết khối/ HCĐMV- KSTC cần can thiệp ĐMV

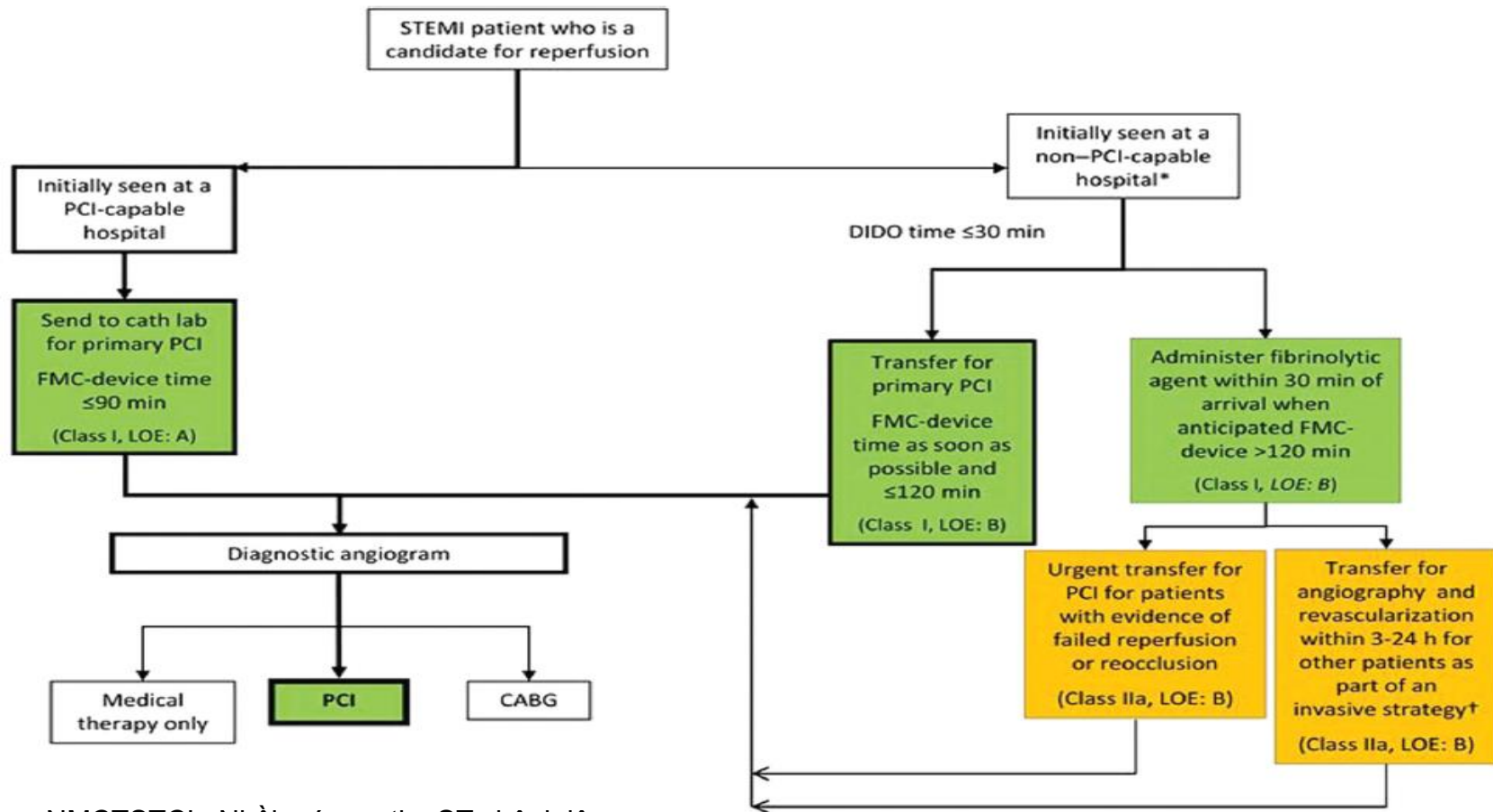
Recommendations	Class ^a	Level ^b	Ref ^c
Antiplatelet therapy			
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	774,776,794
A P2Y ₁₂ inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A	337,341,825
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication.	I	B	337
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication.	I	B	341
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B	812,825
GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications.	IIa	C	
Pre-treatment with prasugrel in patients in whom coronary anatomy not known, is not recommended.	III	B	826
Pre-treatment with GP IIb/IIIa antagonists in patients in not known, is not recommended.	III	A	357,815

Quy trình xác định thời điểm tái thông ĐMVC/HCĐMVC- KSTCL



**KHUYẾN CÁO 2013 CỦA HỘI TIM HOA KỲ/
HỘI TIM ĐẠI HỌC HOA KỲ VỀ XỬ TRÍ NHỒI
MÁU CƠ TIM ST CHÊNH LÊN**

Điều trị tái tưới máu bệnh nhân NMCTSTCL



NMCTSTCL: Nhồi máu cơ tim ST chênh lên

*Patients with cardiogenic shock or severe heart failure initially seen at a non-PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of time delay from MI onset (Class I, LOE: B). †Angiography and revascularization should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy.

Điều trị tái tưới máu và thời điểm

I IIa IIb III



Điều trị tái tưới máu: tất cả bệnh nhân NMCTSTCL trong 12 giờ đầu

I IIa IIb III



Can thiệp ĐMV biện pháp hàng đầu

*The proposed time windows are system goals. For any individual patient, every effort should be made to provide reperfusion therapy as rapidly as possible.

TL: O' Gara PT et al. 2013 ACCF/AHA Guideline for the Management of ST Elevation Myocardial Infarction. JACC 2013; 61: 485-510

Điều trị chống kết tập tiểu cầu/NMCTSTCL can thiệp tiên phát



Aspirin 162 to 325 mg should be given before primary PCI.



After PCI, aspirin should be continued indefinitely.

TL: O' Gara PT et al. 2013 ACCF/AHA Guideline for the Management of ST Elevation Myocardial Infarction. JACC 2013; 61: 485-510

Điều trị chống kết tập tiểu cầu/NMCTSTCL can thiệp tiên phát



Liều nạp ức chế thụ thể P2Y12 cho sớm hay vào thời điểm can thiệp tiên phát NMCTSTCL

- Clopidogrel 600 mg; or
- Prasugrel 60 mg; or
- Ticagrelor 180 mg

TL: O' Gara PT et al. 2013 ACCF/AHA Guideline for the Management of ST Elevation Myocardial Infarction. JACC 2013; 61: 485-510

Điều trị chống kết tập tiểu cầu/NMCTSTCL can thiệp tiên phát



Điều trị ức chế thụ thể P2Y₁₂ kéo dài 1 năm/ bệnh nhân NMCTSTCL có stent (DES hoặc BMS)

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day*

*Liều aspirin phối hợp với ticagrelor khi điều trị duy trì là 81 mg/ng .

TL: O' Gara PT et al. 2013 ACCF/AHA Guideline for the Management of ST Elevation Myocardial Infarction. JACC 2013; 61: 485-510

Điều trị chống kết tập tiểu cầu/NMCTSTCL can thiệp tiên phát



Nên sử dụng liều duy trì aspirin 81 mg, hơn là liều cao sau can thiệp tiên phát.

Có nên sử dụng kháng kết tập tiểu cầu kép trên 12 tháng?



Comparison of Ischemic and Bleeding Events After Drug-Eluting Stents or Bare Metal Stents in Subjects Receiving Dual Antiplatelet Therapy: Results from the Randomized Dual Antiplatelet Therapy (DAPT) Study

Dean J. Kereiakes, Robert Yeh, Joseph M. Massaro, Priscilla-Driscoll-Shempp, Donald E. Cutlip, Sharon-Lise T. Normand, P. Gabriel Steg, Anthony Gershlick, Jean Francois Tanguay, Stephan Windecker, Kirk Garratt, David Kandzari, David Lee, Daniel Simon, Adrian Comeliu Iancu, Jaroslaw Trebacz, Laura Mauri, on behalf of the Dual Antiplatelet Therapy (DAPT) Study Investigators

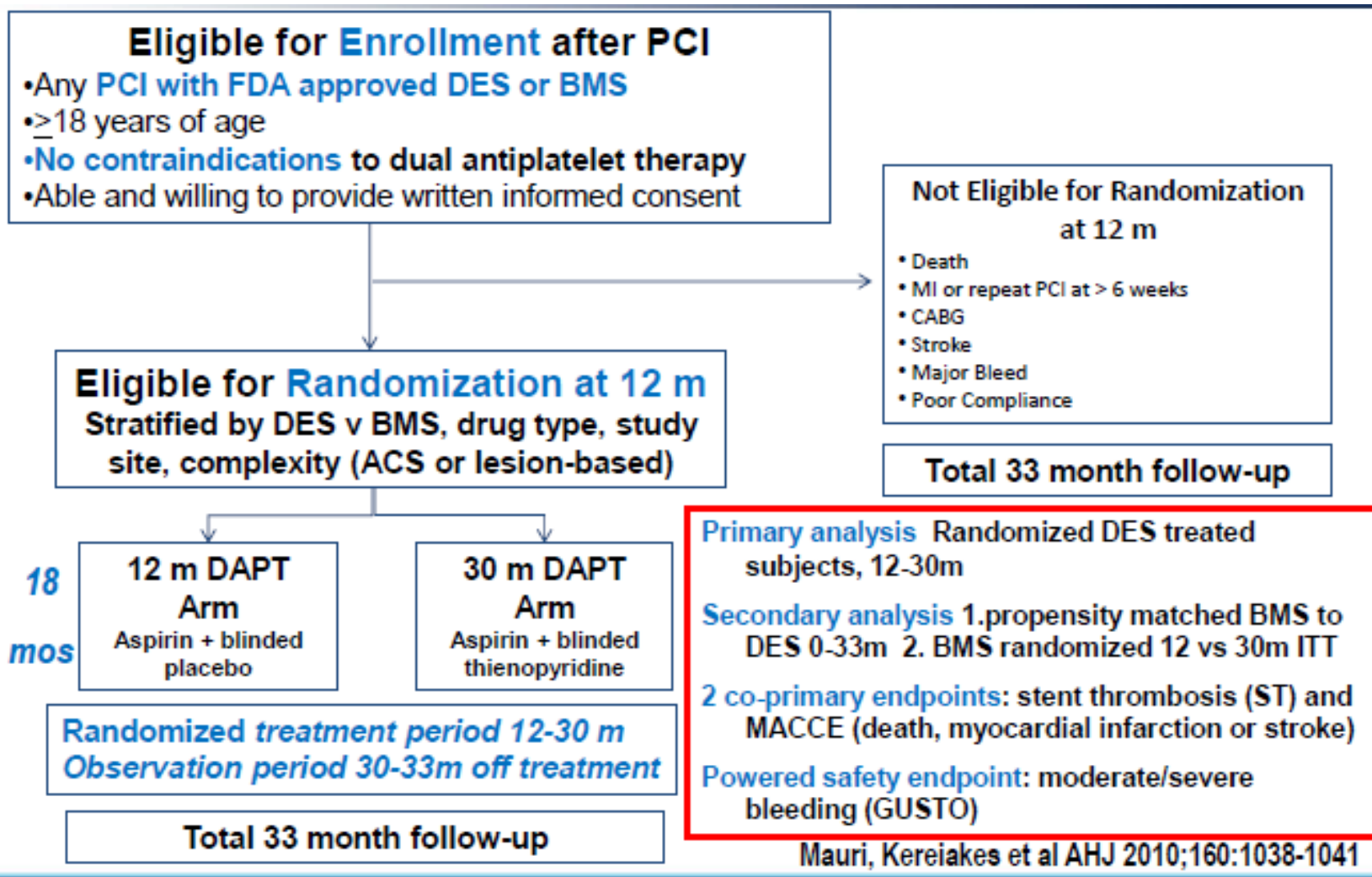


Bối cảnh nghiên cứu

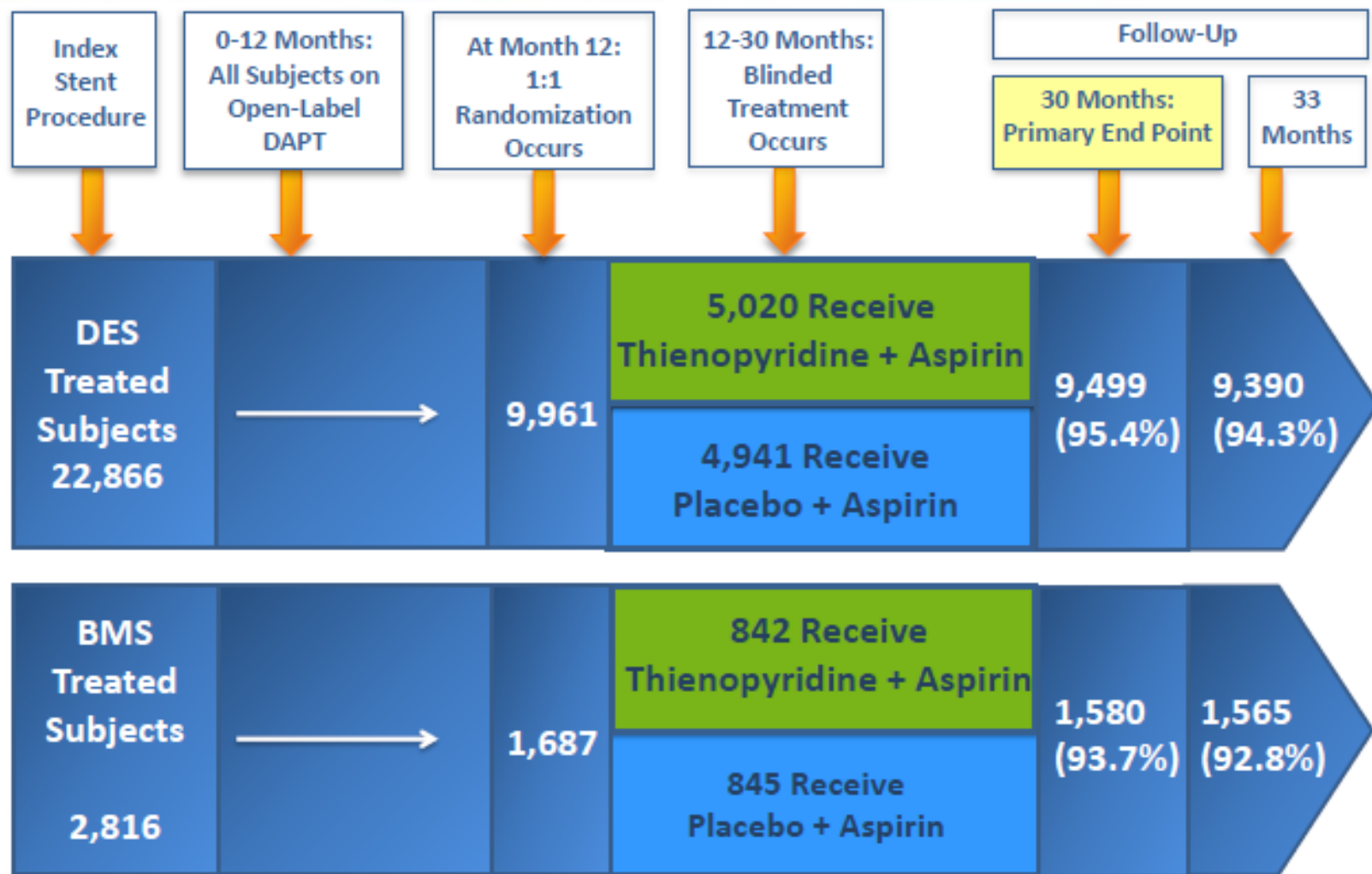
Bare metal stents are a commonly used alternative to drug eluting stents (DES) particularly for patients presenting with acute coronary syndromes or in whom dual antiplatelet therapy (DAPT) has perceived increased bleeding risk. We aimed to determine:

- 1. Whether the risks of stent thrombosis (ST) and major adverse cardiovascular and cerebrovascular events (MACCE) differ from BMS and DES**
- 2. Whether the optimal duration of DAPT therapy differs for BMS and DES**

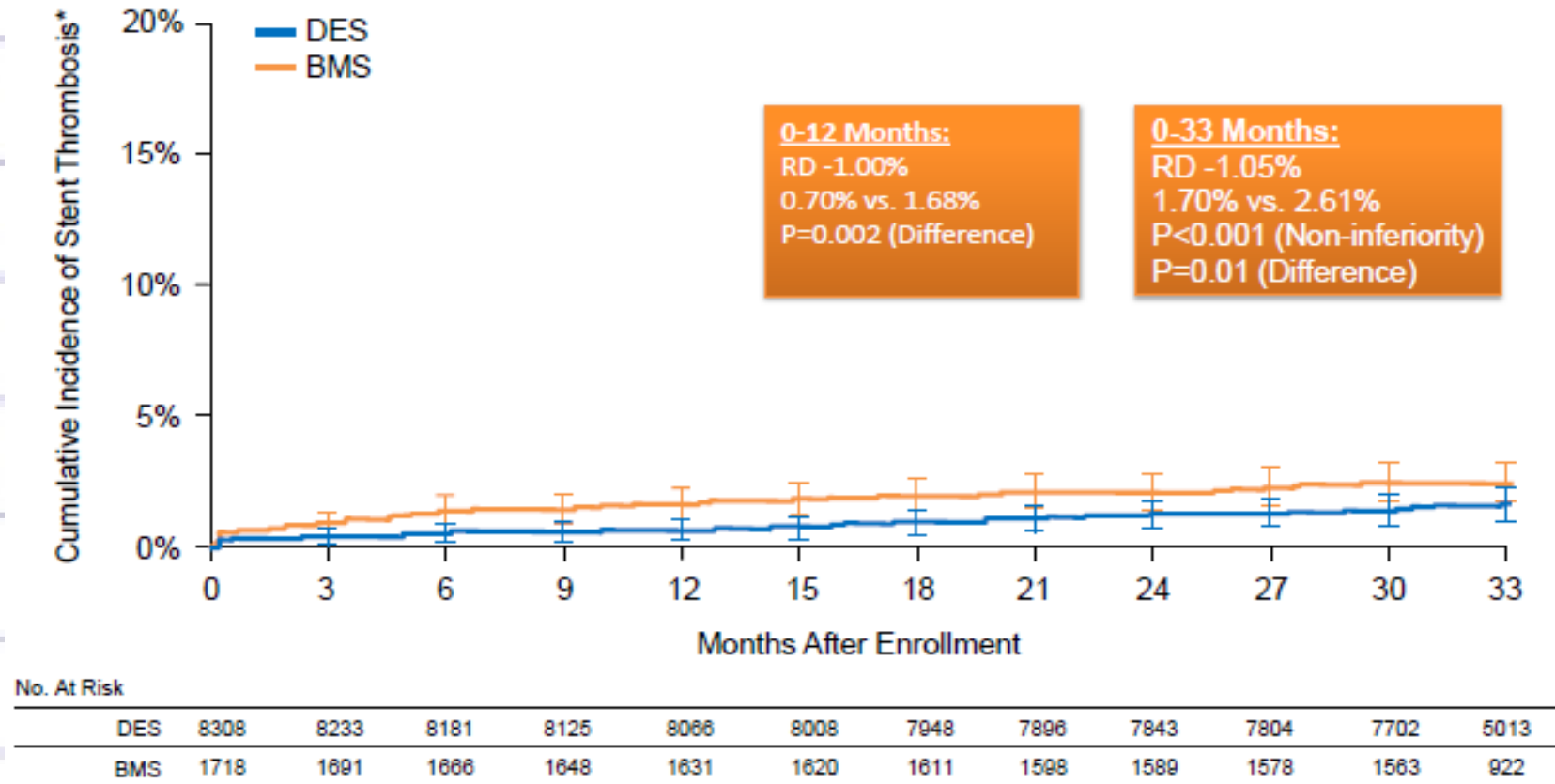
Thiết kế nghiên cứu DAPT



Đối tượng nghiên cứu: 452 địa điểm/ 11 nước

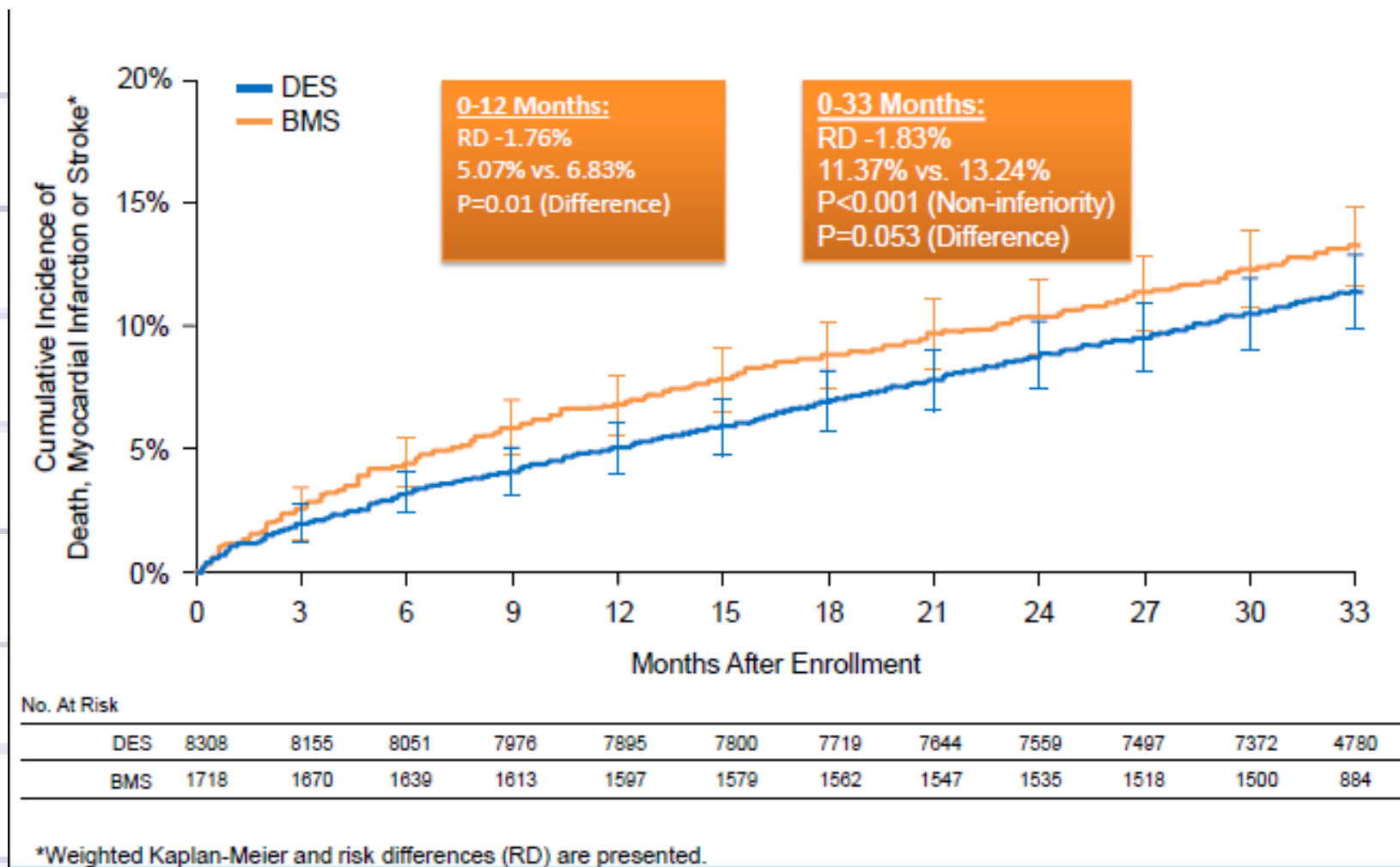


Khả năng bị huyết khối trong stent: so sánh giữa b/n DES và BMS

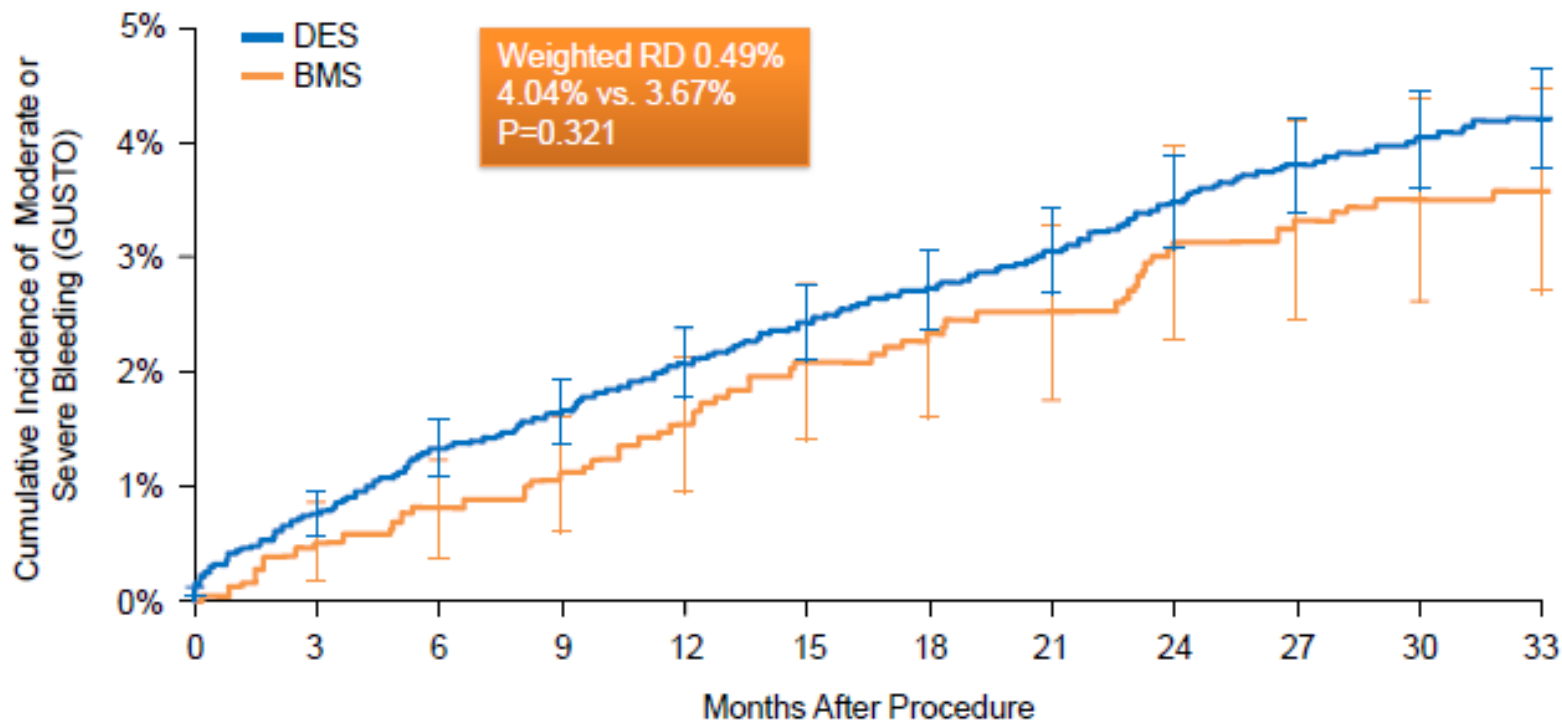


*Weighted Kaplan-Meier and risk differences (RD) are presented.

Khả năng bị biến cố nặng: so sánh giữa b/n DES và BMS



Khả năng xuất huyết nặng hoặc vừa: so sánh giữa b/n DES và BMS



No. At Risk

DES	8308	8197	8110	8037	7954	7883	7819	7756	7688	7636	7527	4910
BMS	1718	1695	1670	1646	1627	1611	1599	1585	1567	1555	1543	914

*Weighted Kaplan-Meier and risk differences (RD) are presented.

Nghiên cứu DAPT (1)

DES vs BMS Propensity Matched Comparison

- **DES not inferior to BMS for ST and MACCE over the 0-33 month follow-up period**
- **DES superior to BMS for ST** over the 0-33 month follow-up period (for MACCE 0-12 month)
- **Greatest portion of risk difference between stent platforms accrues within the first 12 months for both ST and MACCE**

ST: stent thrombois

Nghiên cứu DAPT (2)

BMS 12 vs 30 months Randomized ITT

- Magnitude of reduction in ST risk with longer (30 months) duration thienopyridine therapy appears consistent for both BMS and DES, based on lack of interaction ($P_{int}=0.42$) and hazard ratios < 1.0 (DES HR 0.29, BMS HR 0.49)
- In BMS treated patients, prolonged thienopyridine therapy (30 months or longer) may provide durable ischemic benefit in addition to increased bleeding risk, and requires further study.

Liệu pháp kháng tiểu cầu kép là nền tảng chính trong điều trị kháng KTTC trong HCMVC và PCI

Hiệu quả của clopidogrel đã được chứng minh trên các đối tượng và trong nhiều nghiên cứu:

PCI:

CLASSICS, CREDO, PCI-CLARITY, PCI-CURE, CURRENT-OASIS7

NSTE-ACS:

CURE

STEMI:

CLARITY-TIMI 28, COMMIT-CCS2

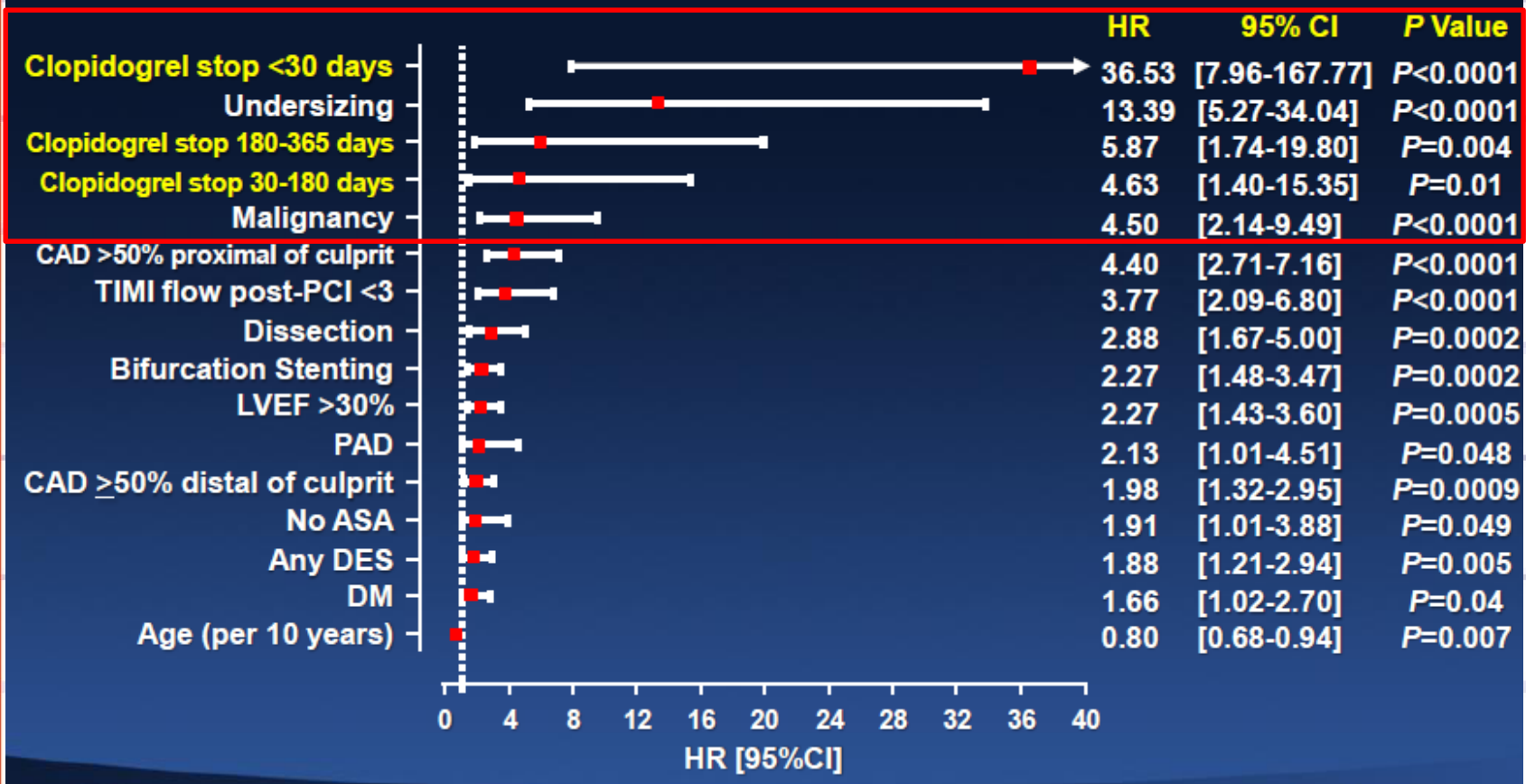
PCI CÓ SỬ DỤNG TIÊU SỢI HUYẾT TRƯỚC ĐÓ:

CLARITY-TIMI 28

CLARITY = Clopidogrel as Adjunctive Reperfusion Therapy; CLASSICS = Clopidogrel Aspirin Stent International Cooperative Study; COMMIT-CCS2 = Clopidogrel and Metoprolol in Myocardial Infarction Trial – Second Chinese Cardiac Study; CREDO = Clopidogrel for the Reduction of Events During Observation; CURE = Clopidogrel in Unstable angina to prevent Recurrent Events; NSTE-ACS = non-ST-segment elevation acute coronary syndromes; STEMI = ST-segment elevation myocardial infarction.

Ngưng kết tập tiểu cầu kép là YTCN cao nhất NC DUTCH REGISTRY (n = 21009 BN)

Definite stent thrombosis occurred in 437 (2.1%) pts





Nghiên cứu sổ bộ PARIS

Patterns of Non-Adherence to Anti-Platelet Regimens In Stented Patients: An Observational Single Arm Study

- Đa trung tâm, đa quốc gia, quan sát
- 5.033 BN được theo dõi trong gần 24 tháng sau đặt stent
- Thu nhận BN đặt stent thường hay phủ thuốc

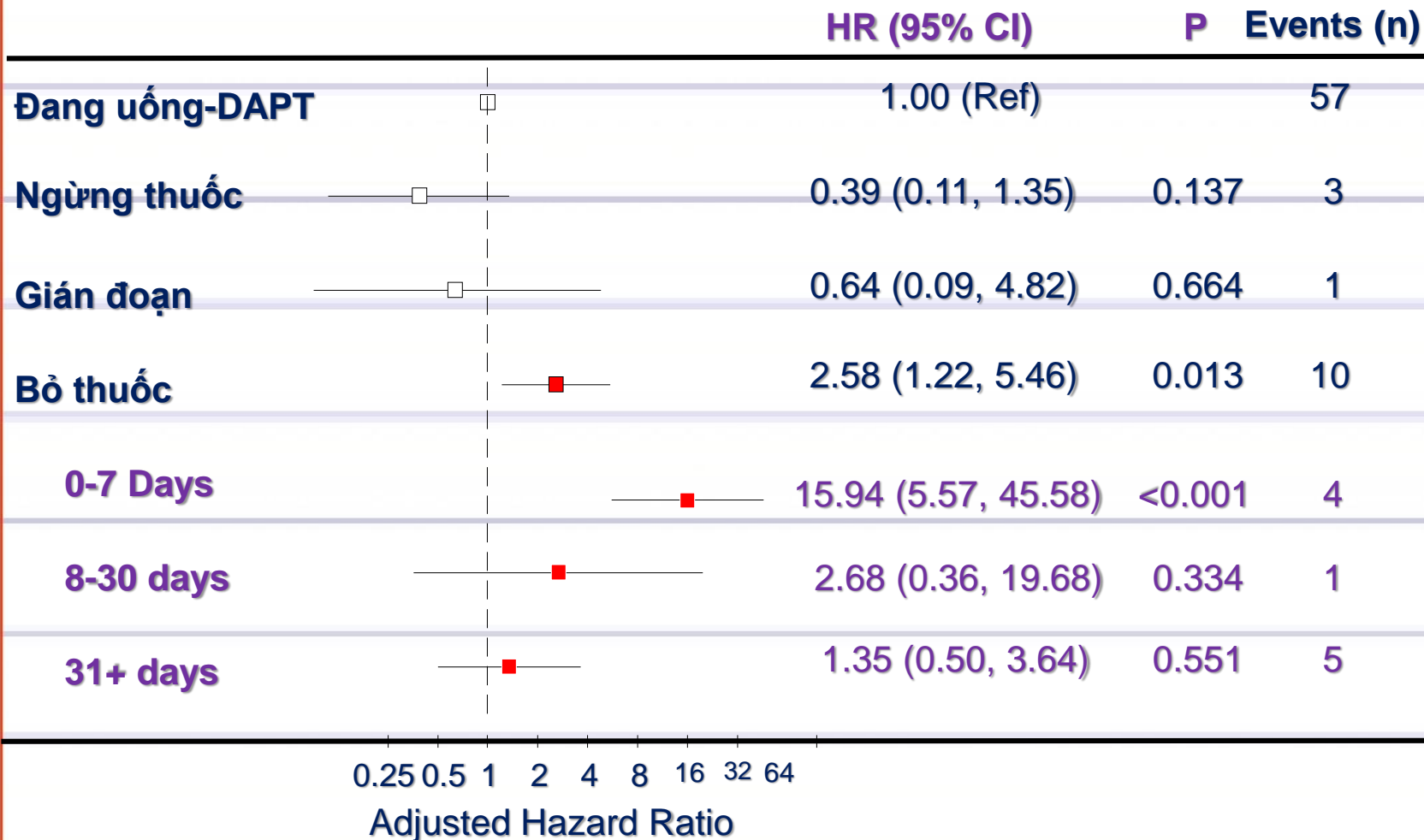


Các định nghĩa không tuân thủ

- ❑ **Ngừng thuốc (Discontinuation):** BN ngừng 2 thuốc theo y lệnh do BS nghĩ rằng không cần thiết phải điều trị nữa.
- ❑ **Gián đoạn (Interruption):** BN gián đoạn dùng 2 thuốc kháng TC là do tự nguyện và dưới sự hướng dẫn và khuyến cáo của Bs do cần phải phẫu thuật. Hai thuốc kháng TC được sử dụng lại sau 14 ngày.
- ❑ **Bỏ thuốc (Disruption):** BN ngừng hoàn toàn 2 thuốc kháng TC do xuất huyết hay không tuân thủ. Bao gồm dùng thuốc với liều thấp hơn kê toa.



Ngưng kết tập tiểu cầu kép và ảnh hưởng trên HK stent (Definite/Probable)



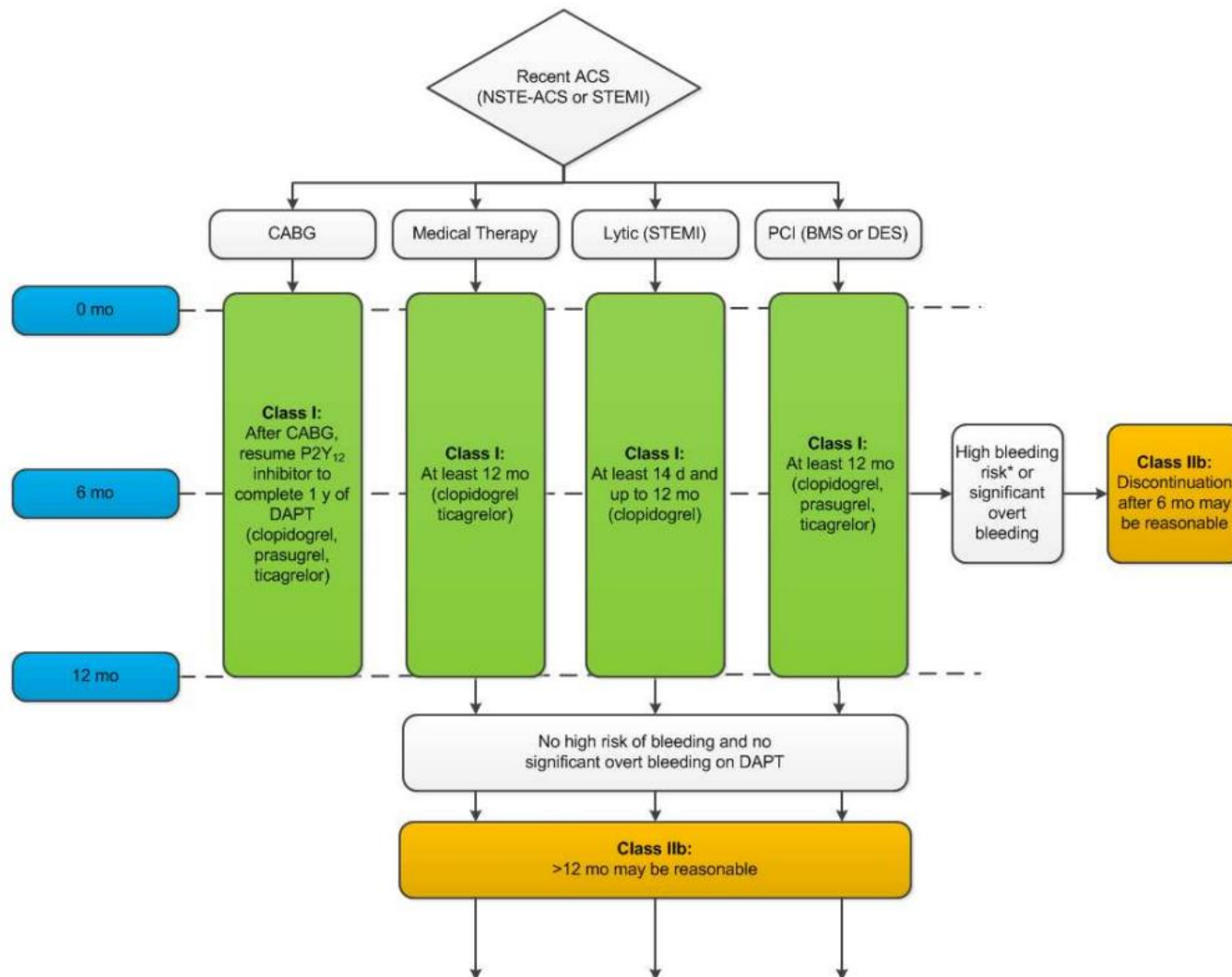
Nguy cơ tương đối huyết khối trong stent đối với không tuân thủ

Các NC	Tuân thủ	Không tuân thủ	RR
PARIS Registry	0.5%	2.9%	5.8
Airoldi et al ¹	0.9%	4.2%	4.7
eSELECT Registry ²	0.5%	4.6%	9.2

1. Airoldi F et al. Circulation. 2007 Aug 14;116(7):745-54.

2. Urban P et al. J Am Coll Cardiol 2011;57:1445-54.

Quy trình điều trị kháng kết tập tiểu cầu kép/HCĐMVC



TL: Levine GN et al. 2016 ACC/AHA Guideline focused update on Duration of Dual Antiplatelet therapy in Patients with coronary artery Disease. Circulation 2016; 133: 000-000

Kết luận

- Chẩn đoán HCĐMVC/KSTCL:
 - Lâm sàng, ECG, troponin
 - Quy trình 0-3 giờ; 0-1 giờ
 - Chỉ số GRACE, TIMI
- Điều trị NMCTC/KSTCL:
 - Thuốc giảm TMCB
 - Thuốc kéo dài đời sống
 - Thời điểm tái lưu thông ĐMV: 2 giờ, 24 giờ, 72 giờ
- Điều trị NMCTC/STCL: can thiệp ngay hoặc tiêu sợi huyết
- Điều trị kháng kết tập tiểu cầu kép: KC 2016 có thể trên 1 năm