

# P2Y<sub>12</sub> Receptor Antagonists

## Cases Around the Globe

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# Agenda

## Introduction to P2Y<sub>12</sub> Receptor Antagonists

Dominick J. Angiolillo, MD, PhD, FACC, FESC, FSCAI

## STEMI and Nausea/Vomiting

Davide Capodanno, MD, PhD, FESC

## STEMI and Cardiac Arrest

Roxana Mehran, MD, FACC, FAHA, MSCAI, FESC

## How Do You Manage This High-Risk Patient According to Angiography Results?

Gilles Montalescot, MD, PhD

## When an ACS Is an Unclear Diagnosis

Rikard Linder, MD, PhD, FESC

## Meet the Experts: From Guidelines to Practice

Dominick J. Angiolillo, MD, PhD, FACC, FESC, FSCAI and Roxana Mehran, MD, FACC, FAHA, MSCAI, FESC



# P2Y<sub>12</sub> Receptor Antagonists

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
<b>Class of agent</b>	Thienopyridine	Thienopyridine	Cyclo-pentyl-triazolo-pyrimidine	Adenosine triphosphate analogue
<b>Prodrug</b>	Yes	Yes	No	No
<b>Route</b>	Oral	Oral	Oral	IV
<b>Binding</b>	Irreversible	Irreversible	Reversible	Reversible
<b>Onset after loading dose</b>	2-6 h	0.5-4 h	0.5-2 h	Immediate: 2 min
<b>Duration of action after discontinuation</b>	3 to 10 d	5 to 10 d	3 to 4 d	30 to 60 min
<b>Dosing frequency</b>	Once daily	Once daily	Twice daily	30 µg/kg IV bolus 4 µg/kg IV infusion

# STEMI and Nausea/Vomiting

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## FACULTY

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Catania, Italy

# Case Study

## *Patient Presentation*



Male, 68 years old

### **Presentation**

- Epigastric pain
- Shortness of breath
- Diaphoresis with radiation to the jaw
- Fatigue and nausea

### **Physical examination**

- Bradycardia
- Hypotension

# Case Study

## Patient Presentation (cont)



Male, 68 years old

### ECG findings

- ST-segment elevation in leads II, III, and aVF
- ST-segment depression in lead aVL
- ST-segment elevation right-sided lead V4R

- ECG findings suggestive of **inferior STEMI** and **right-sided infarction**
- Catheterization laboratory was activated



# ECG With ST Elevation – Antiplatelet Pretreatment

## *ESC Guidelines for Myocardial Revascularization*

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“A **potent P2Y12 inhibitor** (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended **before** (or at latest at the time of) **PCI** and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding”

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# What Antiplatelet Treatment for This Patient?

## *Case Study*



**Ticagrelor 180 mg?**



**Vomiting**

Before intake of ticagrelor,  
suggesting no chance for  
good absorption

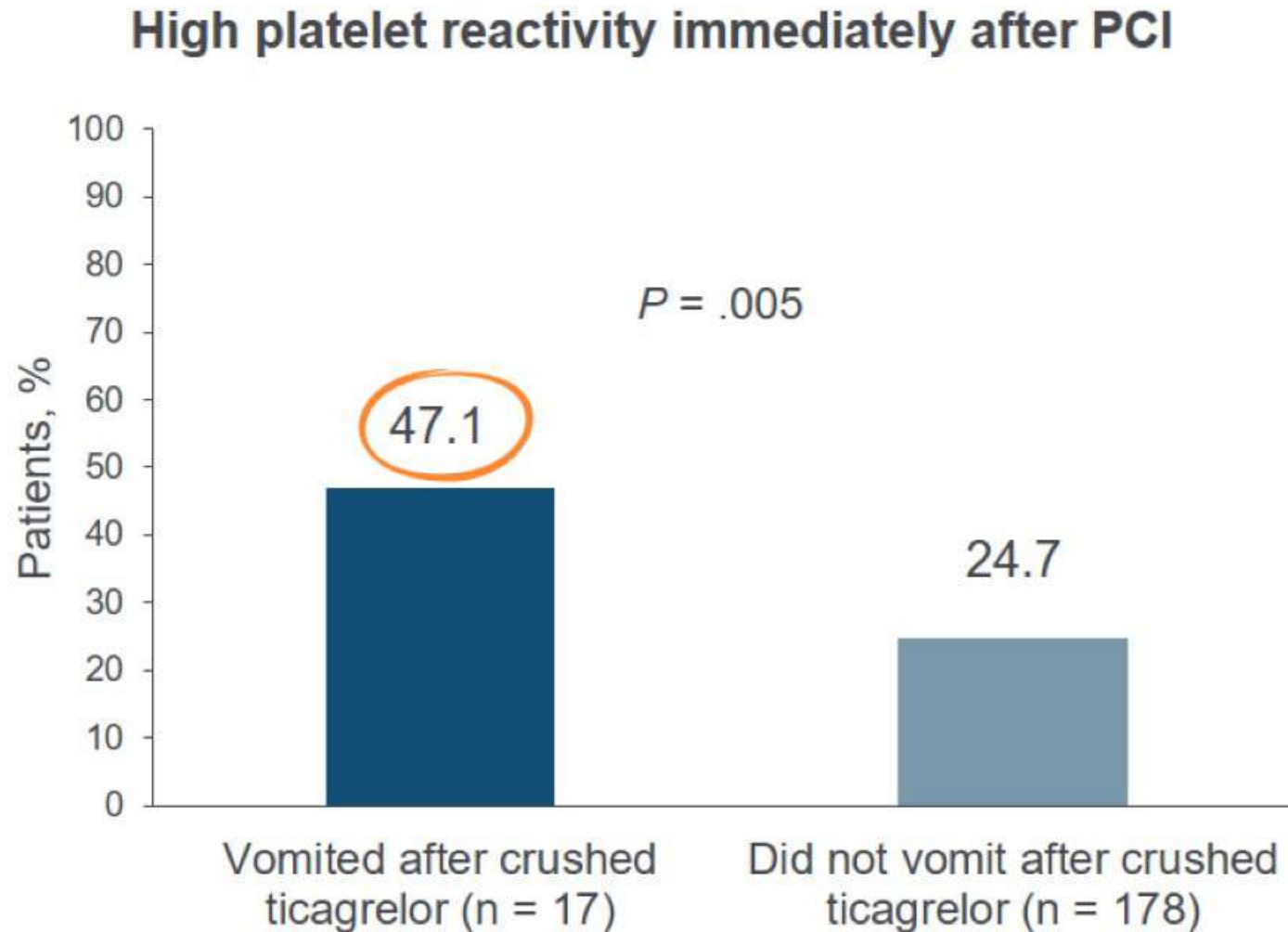


**Crushed  
ticagrelor?**

Considered, but the idea  
was abandoned after a  
telephone call to the  
interventional cardiologist

# Impact of Vomiting on P2Y12 Platelet Inhibition in Patients With STEMI

## *A Prespecified Subanalysis of the ON-TIME 3 Trial*



**Vomiting** was associated with high platelet reactivity immediately after primary PCI

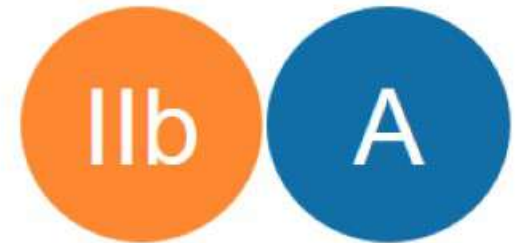
# ECG With ST Elevation – Antiplatelet Pretreatment

## *ESC Guidelines for Myocardial Revascularization (cont)*

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"**Cangrelor** may be considered in P2Y12 inhibitor-naïve patients undergoing PCI"

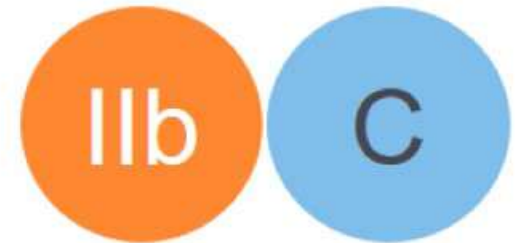
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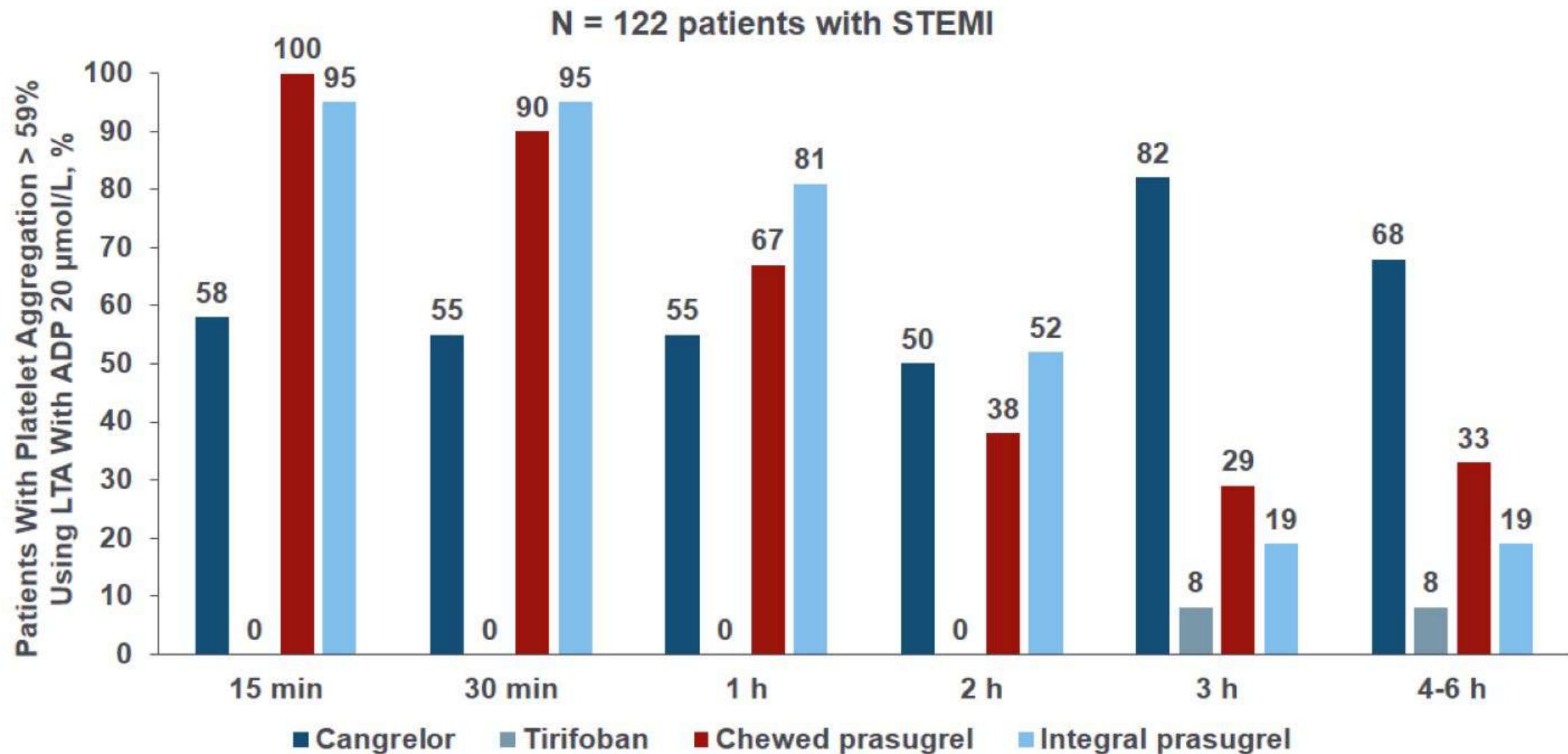
"**GP IIb/IIIa antagonists** may be considered in P2Y12 inhibitor-naïve patients undergoing PCI"

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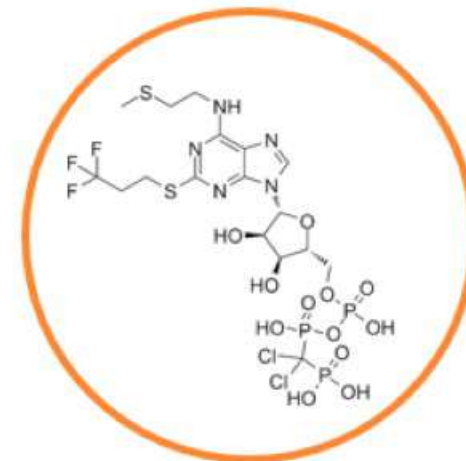
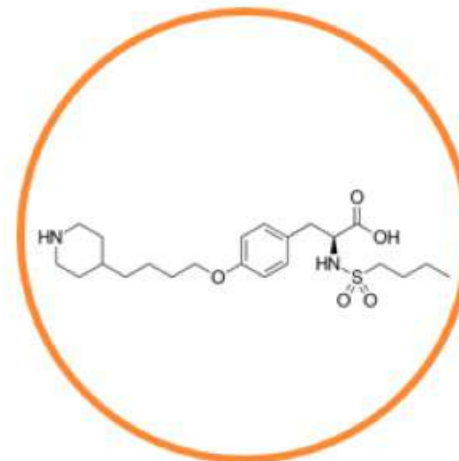
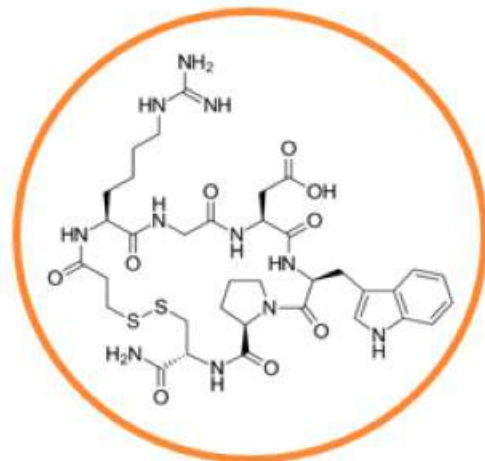




# FABOLUS-FASTER Trial



# Intravenous Antiplatelet Therapies in Patients Undergoing PCI



	Eptifibatide	Tirofiban	Cangrelor
<b>Molecule</b>	Synthetic peptide	Nonpeptide mimetic	ATP analogue
<b>Binding</b>	Competitive	Competitive	Competitive
<b>Half-life</b>	2 to 2.5 h	2 h	3 to 6 min
<b>Renal adjustment</b>	Yes	Yes	No

# Case Study

## *In the Catheterization Laboratory*



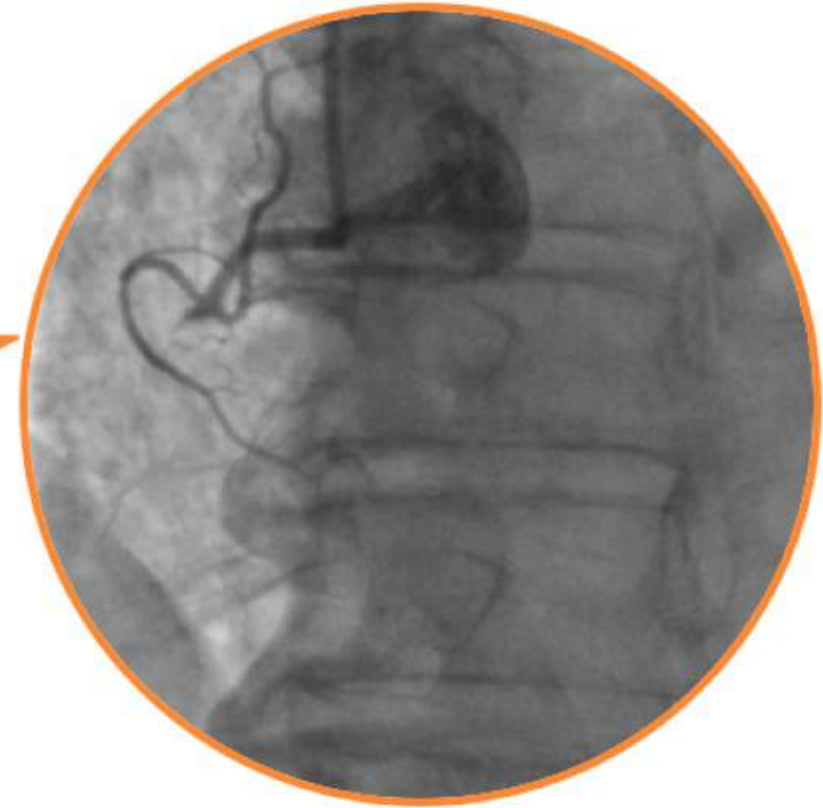
Male, 68 years old

### Coronary angiography

- RCA occlusion

### Antiplatelet therapy

- Cangrelor bolus 30  $\mu\text{g}/\text{kg}$  before PCI, followed by 4  $\mu\text{g}/\text{kg}/\text{min}$  infusion for  $\geq 2$  h





# Case Study

## *In the Catheterization Laboratory (cont)*



Male, 68 years old

### PCI

### Antiplatelet therapy

- Drug-eluting stent implanted and flow in the vessel was restored
- Ticagrelor was given in the coronary ICU, during the 2-h infusion, once the patient was able to swallow the pill with no vomit



# Conclusion

- Vomiting in the early hours of STEMI is associated with lower plasma levels of oral P2Y<sub>12</sub> inhibitors and higher levels of platelet reactivity
  - This notion supports reloading with a loading dose and/or treatment with IV platelet inhibitors, such as cangrelor or GP IIa/IIIb antagonists, in patients with STEMI who vomit



# STEMI and Cardiac Arrest

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## FACULTY

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Professor of Medicine in Cardiology and Population Health Science and Policy

Mount Sinai Endowed Professor in Cardiovascular Clinical Research and Outcomes

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Icahn School of Medicine at Mount Sinai

New York, New York



# Case Study

## Patient Presentation



Male, 68 years old

### Presentation

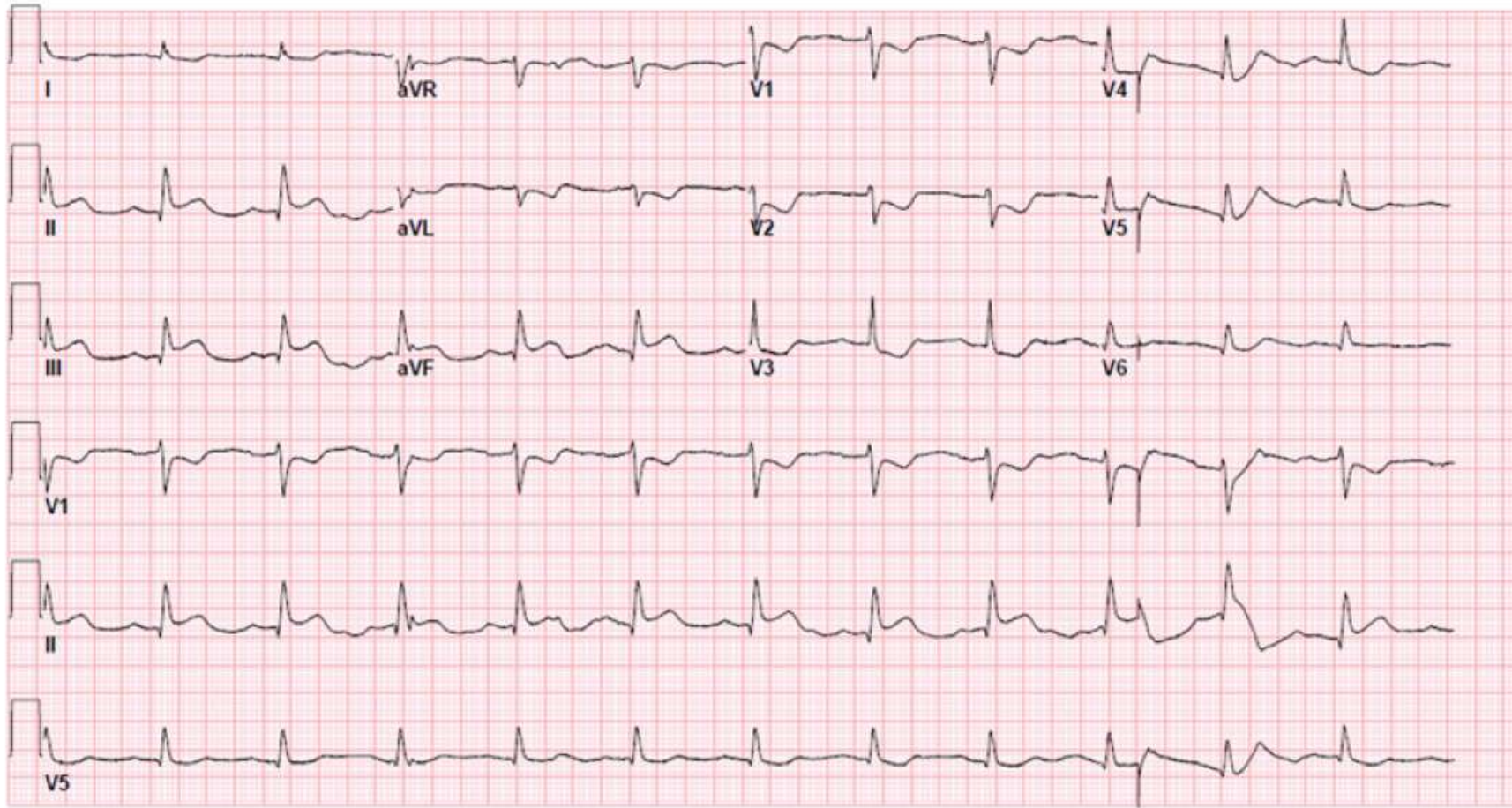
- Collapsed at home in presence of his wife
- No flow-time: 3 minutes
- First detected rhythm: atrial fibrillation
- Return to spontaneous circulation: 4 min CRP, 1 shock and 1 mg epinephrine
  - BP 90/60 mm Hg; heart rate: 60 bpm; pO<sub>2</sub>: 94%
  - Glasgow coma score: 5

### History

- Hypertension, dyslipidemia
- Minor hemorrhagic stroke
- No previous CAD

# Case Study

## *ECG in the Emergency Department*

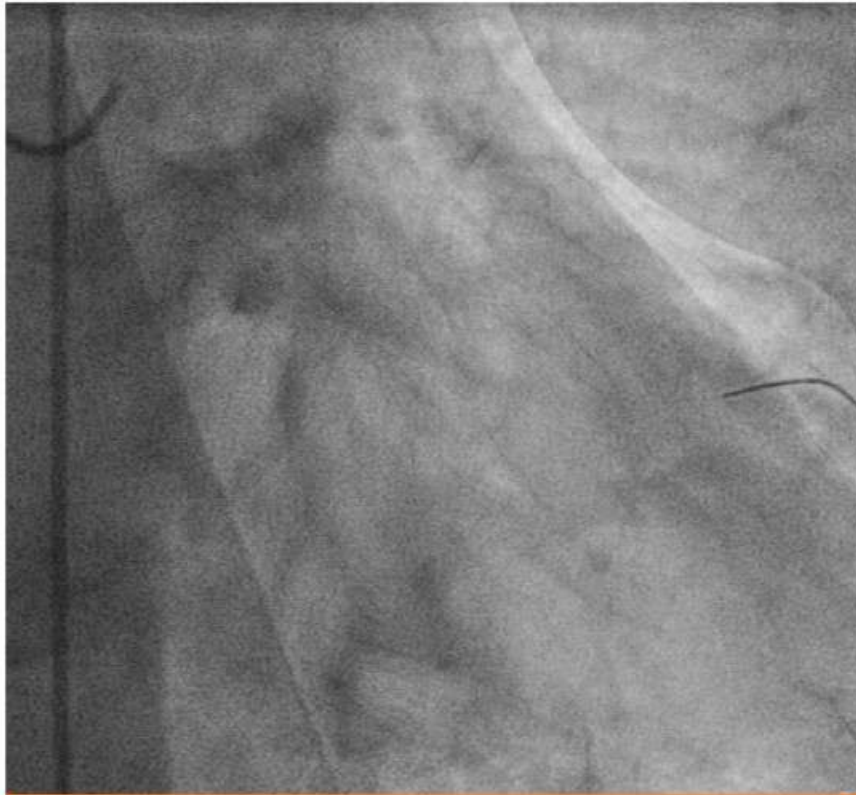


- **ST-segment elevation** in the inferior wall with reciprocal changes down into the septum and lateral walls
- 325 mg aspirin
- 5000 IU heparin
- Patients transferred directly to the **catheterization laboratory**

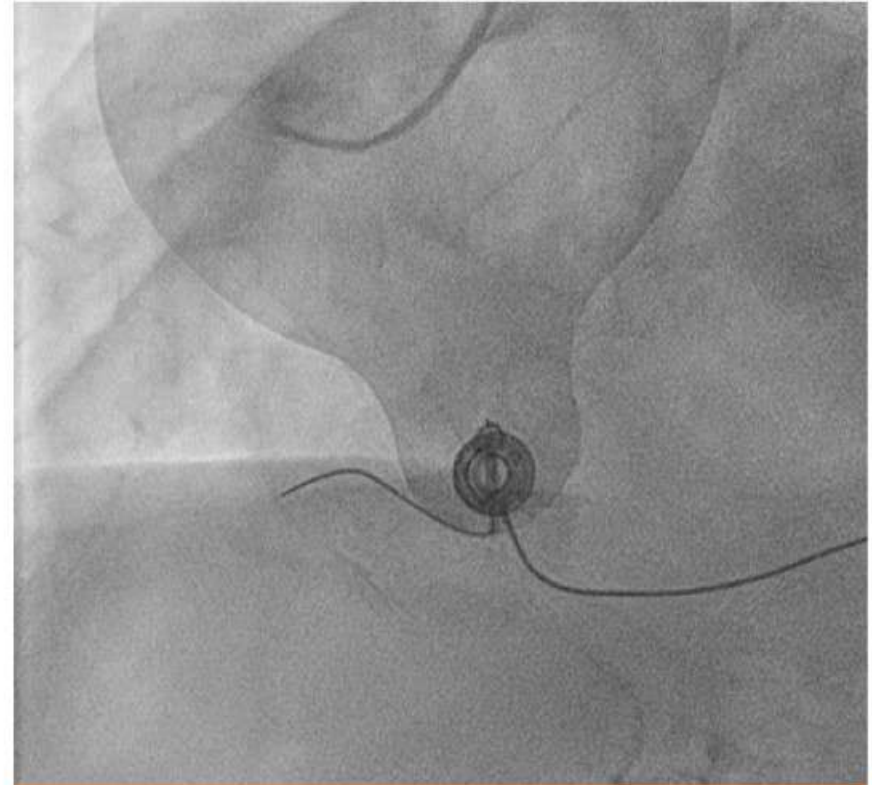


# Case Study

## *Coronary Angiography*



**OM2: chronic total occlusion**  
**D2: 90-90% calcified stenosis**



**RCA mid: 95% thrombotic stenosis**  
**RCA ectatic**

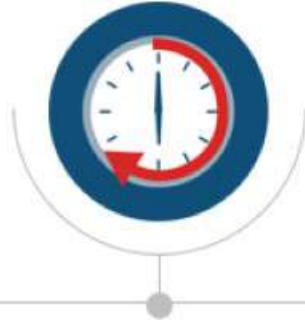


# How to Select the Appropriate P2Y<sub>12</sub> Receptor Antagonist for This Patient?

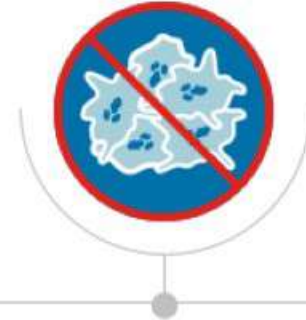


## Type of P2Y<sub>12</sub> inhibitor?

- Clopidogrel
- Ticagrelor
- Prasugrel
- Cangrelor



## Timing of administration?



## Dual antiplatelet therapy duration?

# P2Y12 Receptor Antagonists

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
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<b>Dosing frequency</b>	Once daily	Once daily	Twice daily	30 µg/kg IV bolus 4 µg/kg IV infusion

# Guideline Recommendations on P2Y12 Receptor Antagonists

## 2017 ESC Guidelines for the management of STEMI<sup>[a]</sup>

Recommendations	Class	Level
<b>Antiplatelet therapy</b>		
<b>A potent P2Y12 inhibitor</b> (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 mo, <b>unless</b> there are contraindications such as <b>excessive risk or bleeding</b>	I	A
<b>Cangrelor</b> may be considered in patients who have not received P2Y12 receptor inhibitors	IIb	A

## 2021 ACC/AHA/SCAI Revascularization Guidelines<sup>[b]</sup>

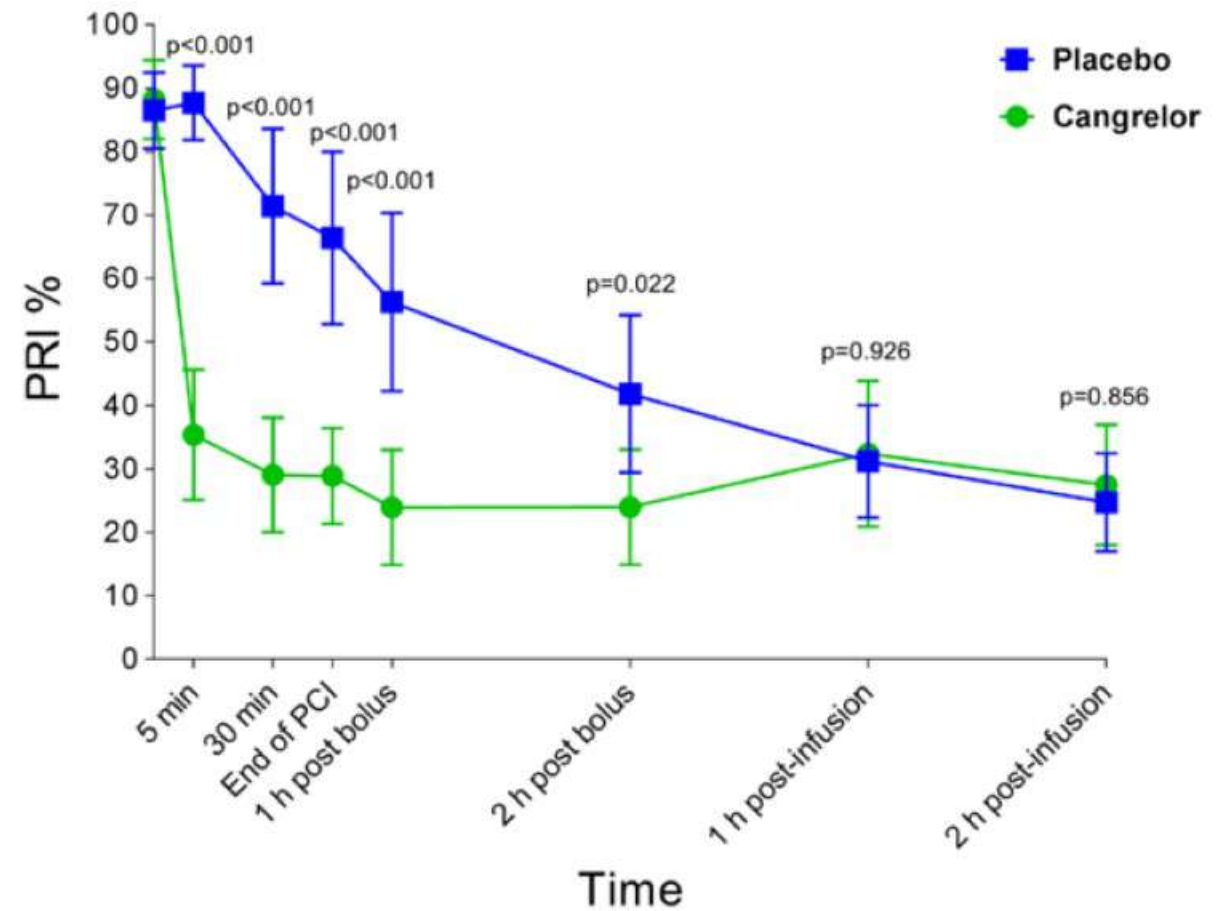
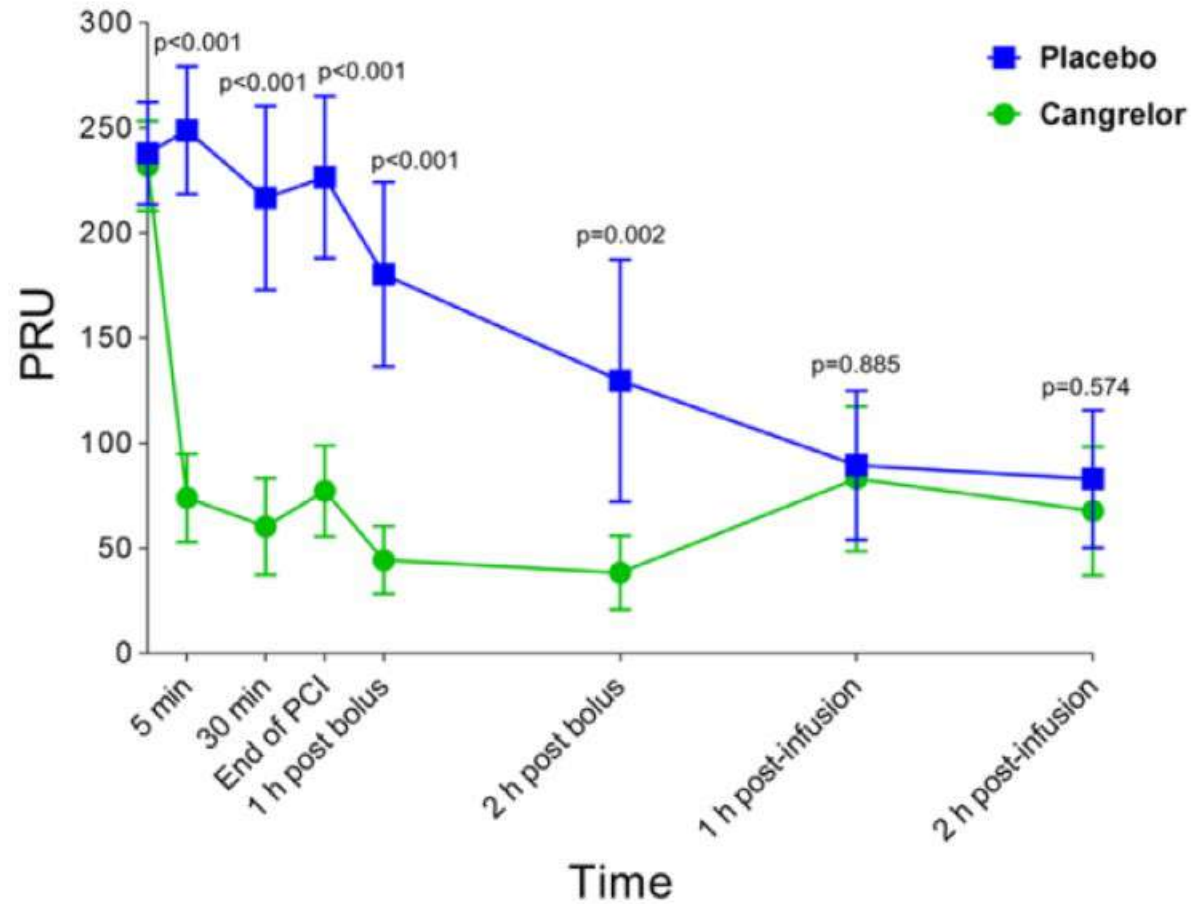
Recommendations	Class	Level
In patients undergoing PCI, a loading dose of P2Y12 inhibitor, followed by daily dosing, is recommended to reduce ischemic events	1	B-R
In patients with ACS undergoing PCI, it is reasonable to use <b>ticagrelor or prasugrel</b> in preference to clopidogrel to reduce ischemic events	2a	B-R
In patients undergoing PCI who have a <b>history of stroke</b> or transient ischemic attack, <b>prasugrel should not be administered</b>	3: Harm	B-R
In patients undergoing PCI who are P2Y12 inhibitor naïve, intravenous <b>cangrelor</b> may be reasonable to reduce periprocedural ischemic events	2b	B-R

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Circulation.2022;145:e18-e114  
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# Crushed Ticagrelor With vs Without Pre-PCI Cangrelor *CANTIC Study*

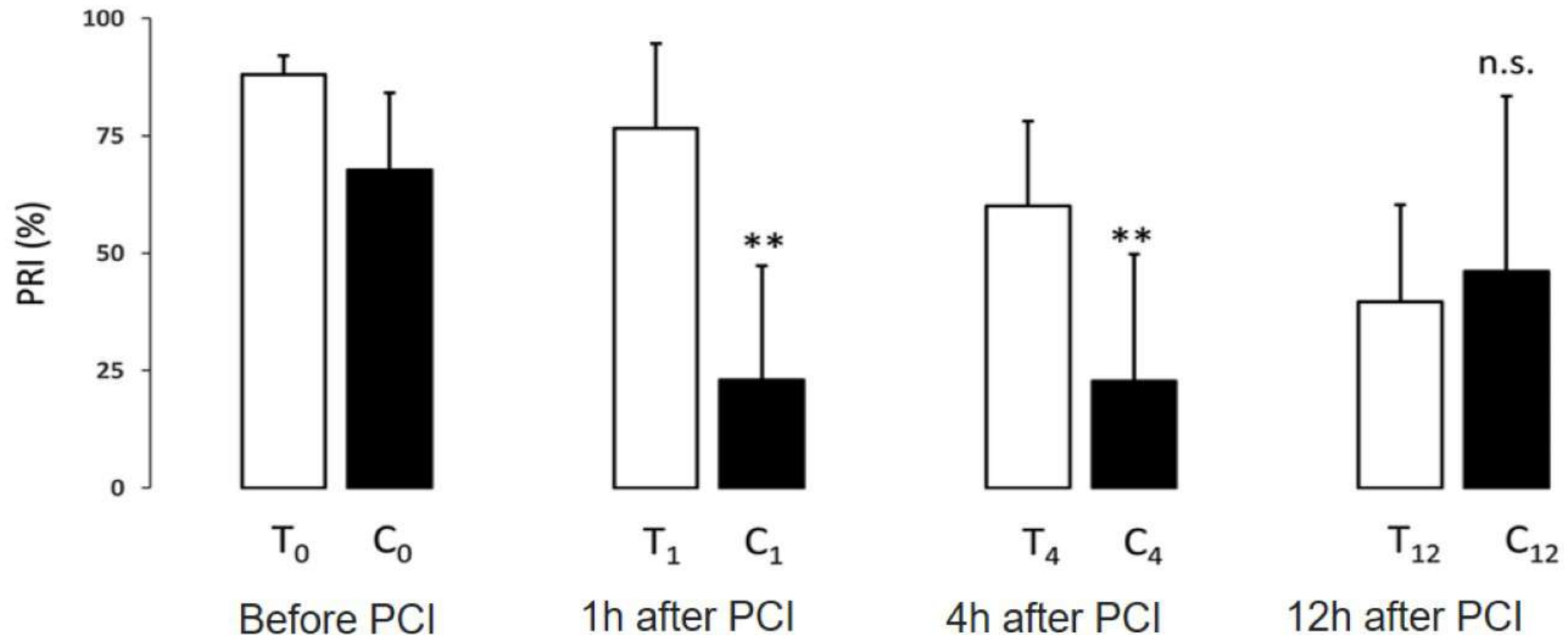
N = 50 patients with STEMI. Cangrelor was administered as a bolus 30 µg/kg before PCI, followed by a continuous infusion of 4 µg/kg/min for 4 h



# Crushed Ticagrelor With vs Without Pre-PCI Cangrelor

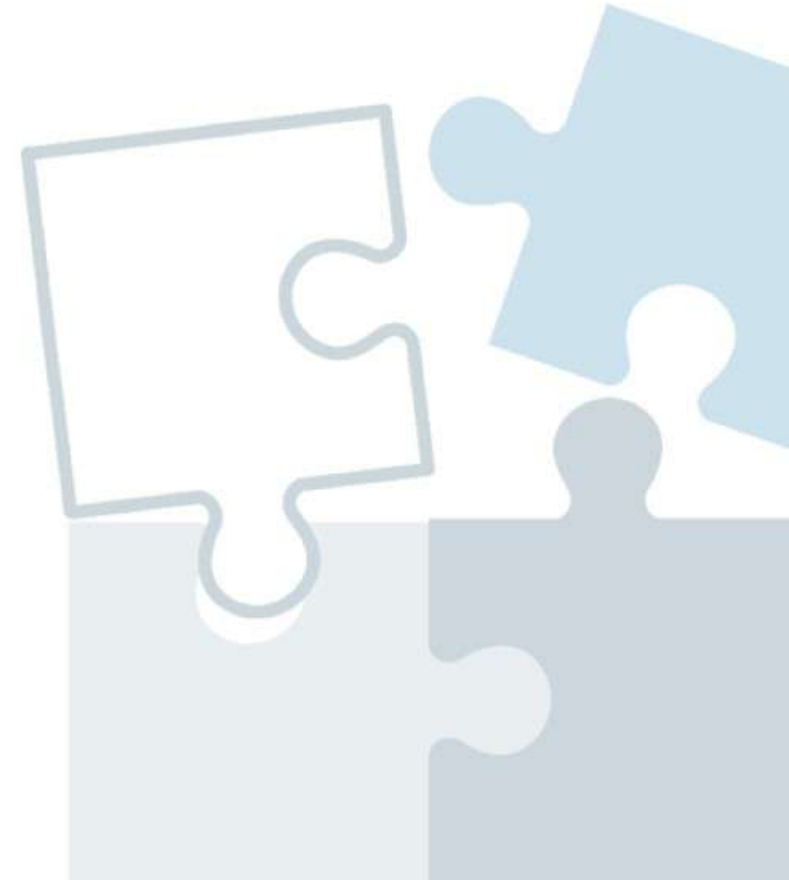
## 22 Patients With OHCA

N = 22 patients with OHCA. Cangrelor was administered as a bolus 30 µg/kg before PCI, followed by a continuous infusion of 4 µg/kg/min for 4 h



# Conclusion

- Early administration of a loading dose of potent P2Y<sub>12</sub> inhibitor is recommended for patients undergoing PCI
  - IV cangrelor may be reasonable to reduce periprocedural ischemic events in patients naive to P2Y<sub>12</sub> inhibitors (eg, oral administration challenging or gastrointestinal absorption impaired)
  - Administration of cangrelor together with a potent P2Y<sub>12</sub> inhibitor (eg, crushed ticagrelor) enables a significantly faster inhibition of platelet activity





# How Do You Manage This High-Risk Patient According to Angiography Results?

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## FACULTY

**Gilles Montalescot, MD, PhD**

Professor of Cardiology

ACTION Study Group, Institute of Cardiology

Pitié-Salpêtrière Hospital

Paris, France

# Case Study

## Patient Presentation



Male, 71-year-old doctor

### Presentation

Effort angina

### History

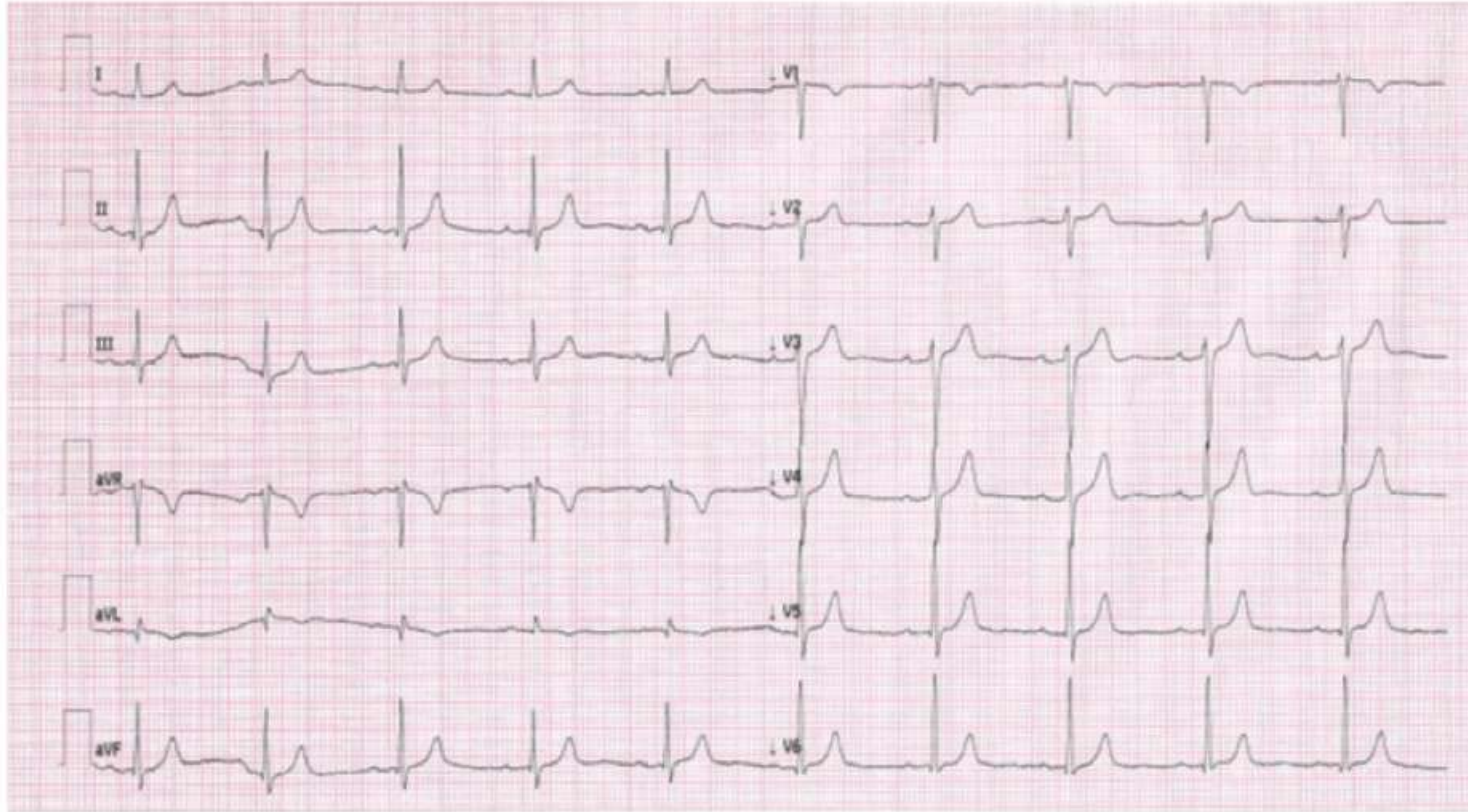
- Hypertension well controlled by ACE inhibitor
- No smoking, no diabetes, no dyslipidemia, no overweight
- Well-fit and exercising regularly

### Coronary angiogram scheduled

- Medications while waiting for angiogram: beta-blockers, nitrates, aspirin
- Patient reports spontaneous chest pain occurred over the weekend before angiogram

# Case Study

## Patient Admission



- Asymptomatic
- Troponin T = 10.6 ng/L (ULN = 14 ng/L)
- Normal EKG



# Case Study

## *Coronary Angiogram*



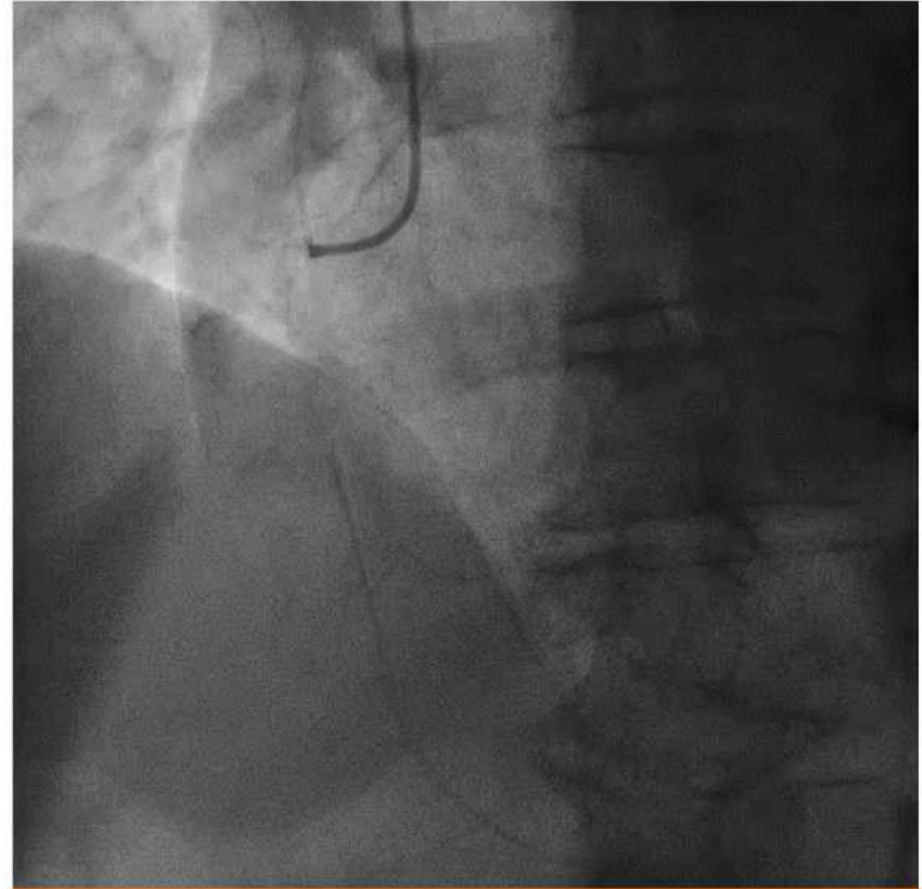
**LAD: tight stenosis**

# Case Study

## *Coronary Angiogram*



**LAD: tight stenosis**



**RCA: stenosis and thrombus?**

# Case Study

## *Clinical Decision*

Management options •

Revascularization

CABG

PCI – which artery(ies)?



# Case Study

## *Clinical Decision*

Management options •

Revascularization

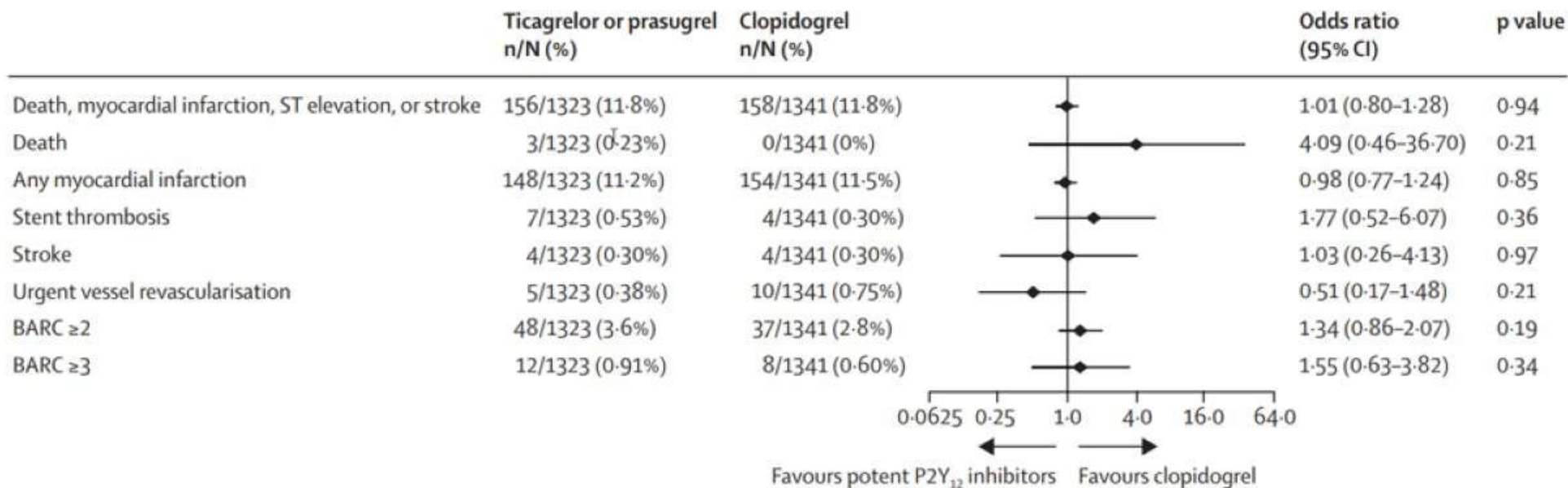
CABG

PCI – culprit artery

# What P2Y12 Receptor Antagonist Should Be Used for This Patient?

ESC guidelines recommend the use of clopidogrel as a P2Y12 receptor antagonist for patients with stable (chronic) coronary syndromes<sup>[a]</sup>

## Pooled Analysis of the Results of the ALPHEUS and SASSICAIA Trials<sup>[b]</sup>

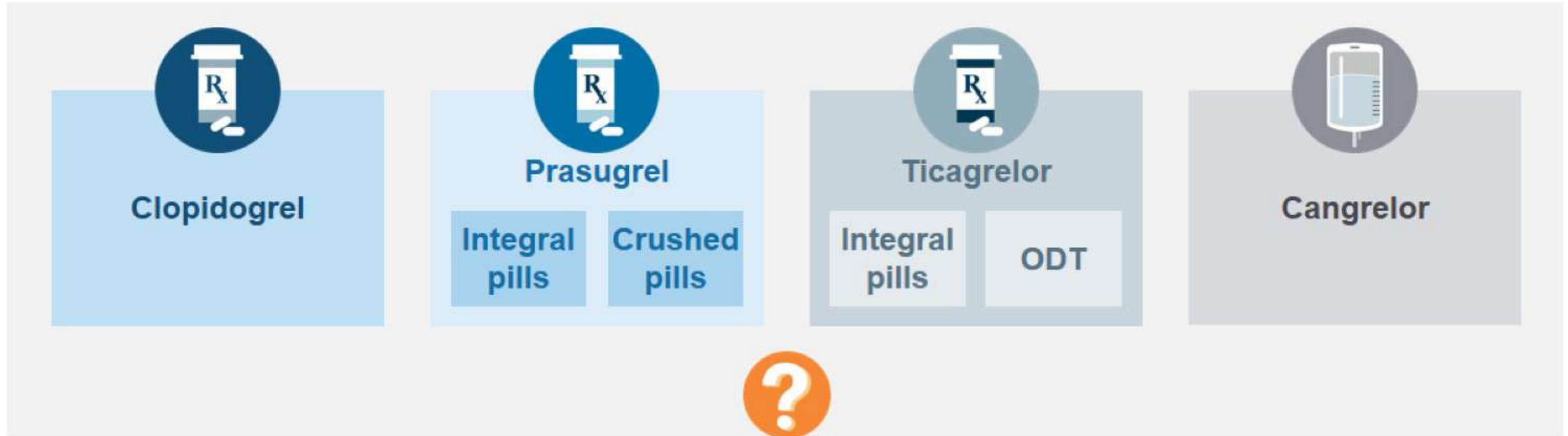


**No benefit was shown in using ticagrelor or prasugrel compared with clopidogrel for stable coronary patients undergoing PCI**

BARC, Bleeding Academic Research Consortium.

a. Knuuti J, et al. Eur Heart J. 2019;41:407-477; b. Silvain J, et al. Lancet. 2020;396:1737-1744.

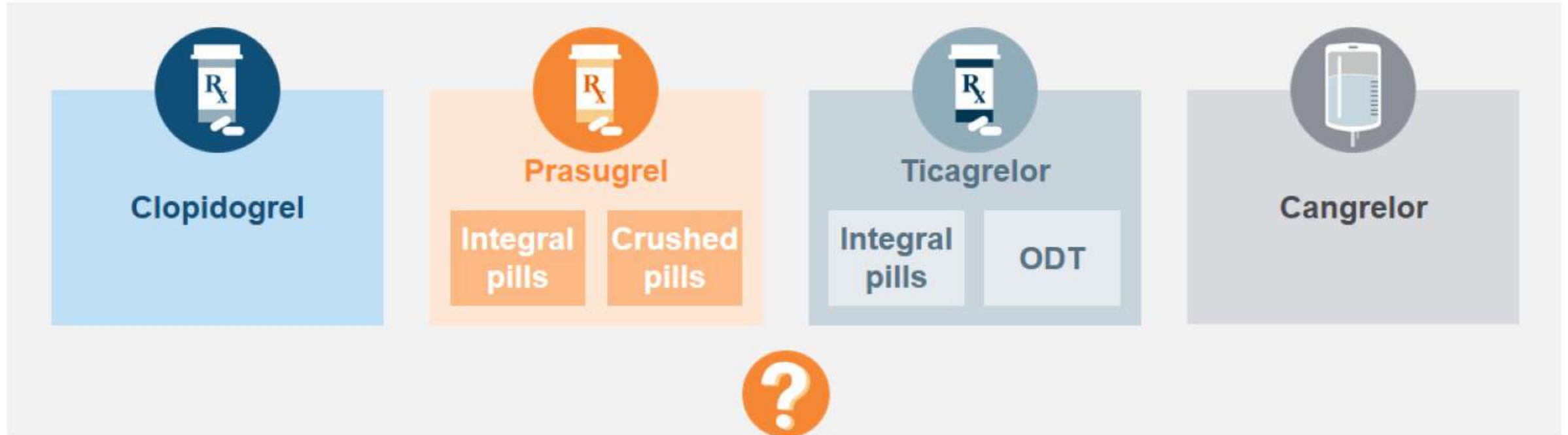
# How to Select the Appropriate P2Y12 Receptor Antagonist for This Patient



- Before PCI – on the table
- After PCI
- Postpone PCI and pretreat



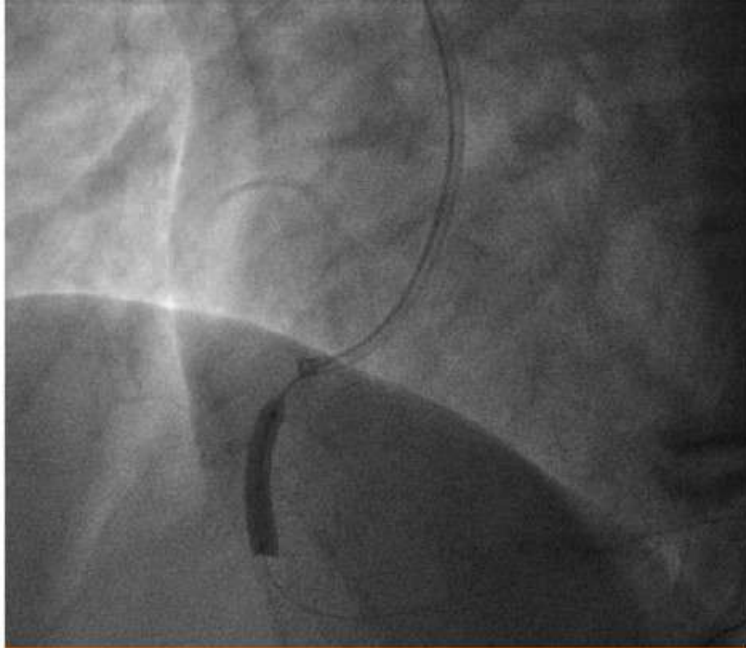
# How to Select the Appropriate P2Y12 Receptor Antagonist for This Patient



- **Before PCI – on the table**
- After PCI
- Postpone PCI and pretreat

# Case Study

## *PCI of the RCA*

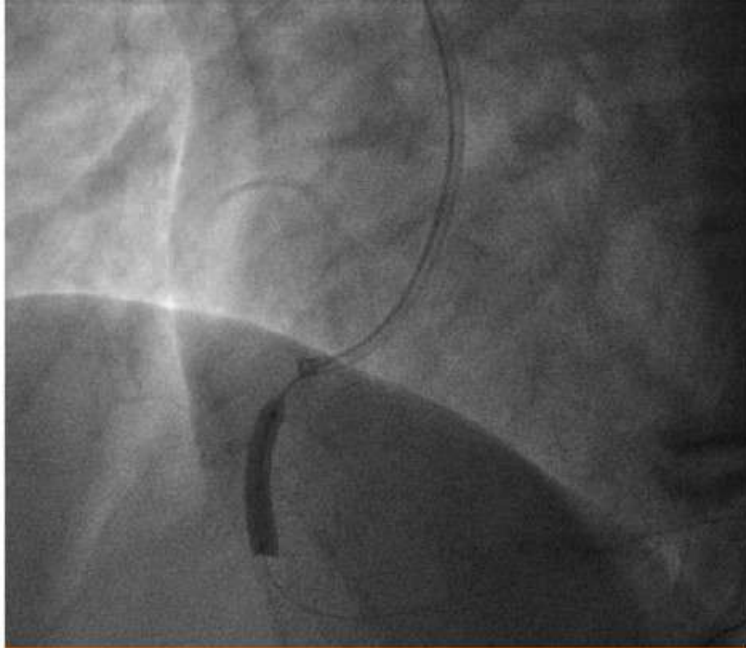


- **Direct stenting with drug-eluting stent**

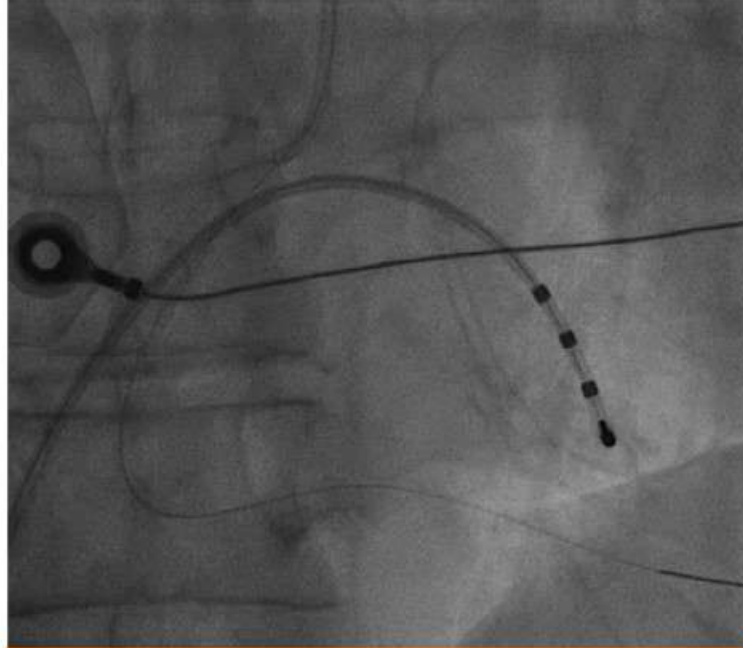


# Case Study

## *PCI of the RCA*



- Direct stenting with drug-eluting stent



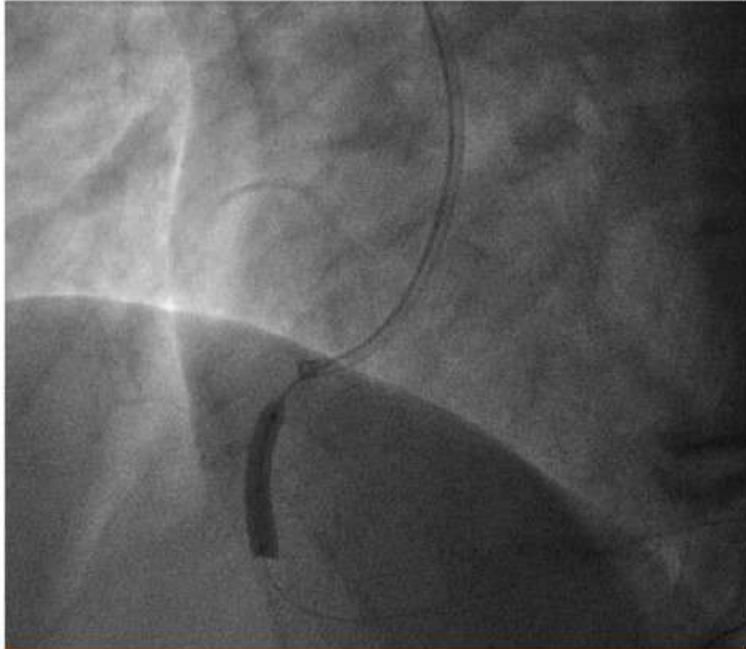
- Distal embolization
- Huge chest pain
- ST-segment elevation
- Complete AV block
- Shock



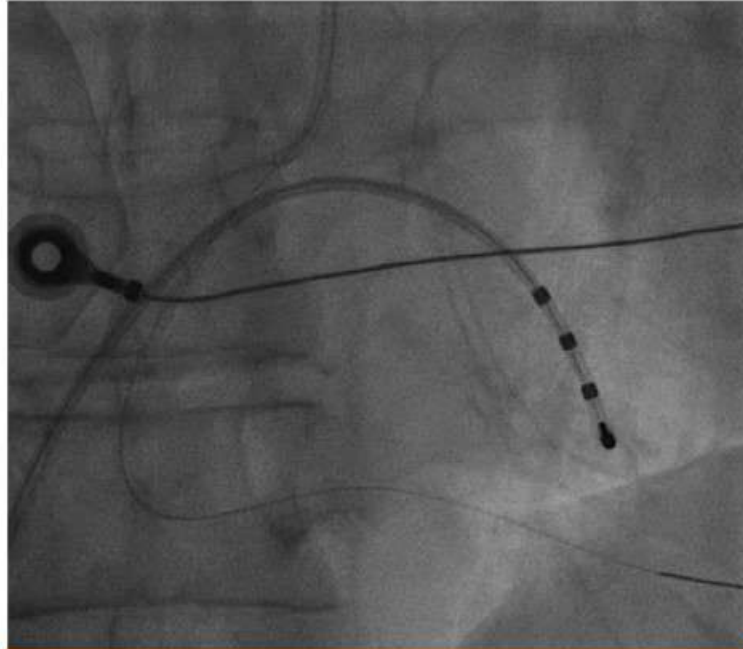


# Case Study

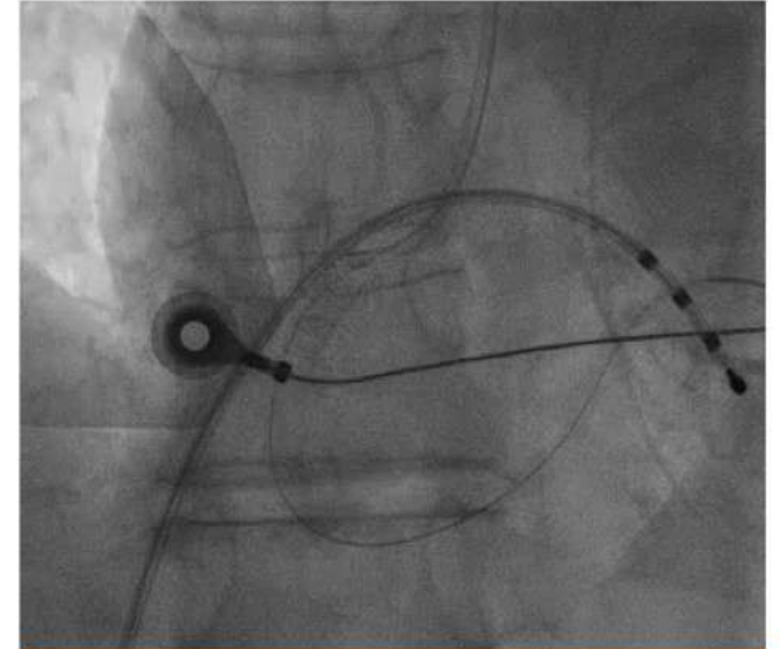
## *PCI of the RCA*



- Direct stenting with drug-eluting stent



- Distal embolization
- Huge chest pain
- ST-segment elevation
- Complete AV block
- Shock

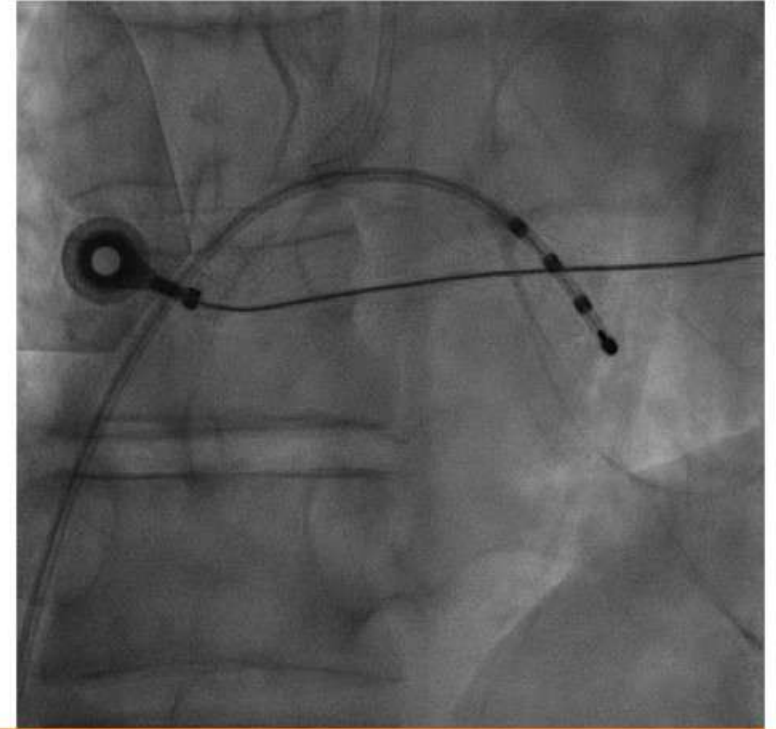
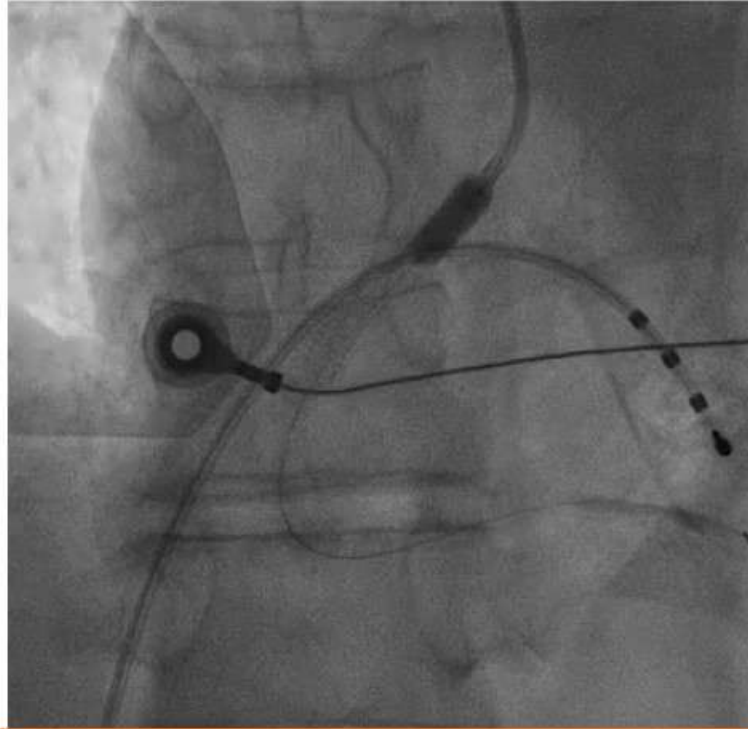
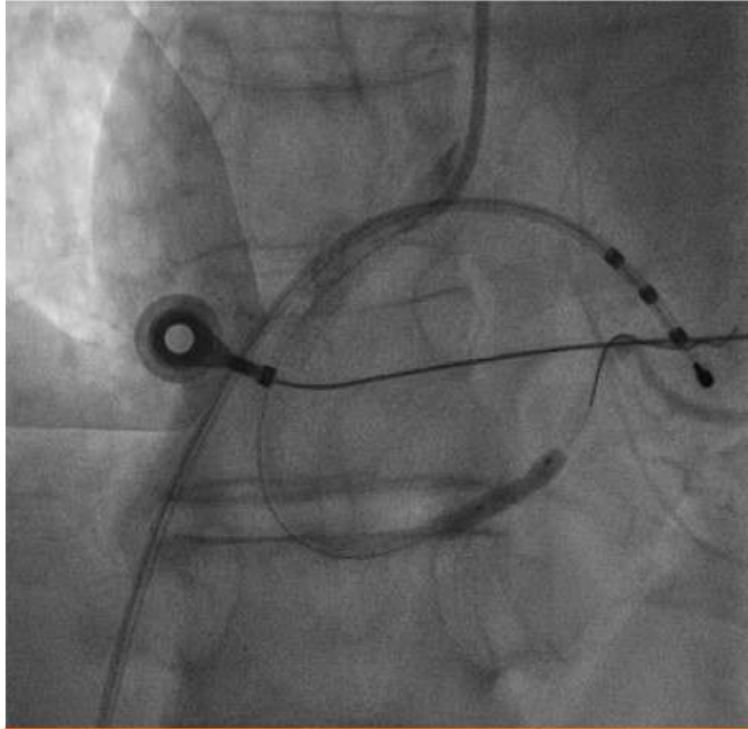


- External heart massage
- Electrostimulation
- Thrombectomy
- Cangrelor, tirofiban, morphine, epinephrine



# Case Study

## *Finalization of the PCI Procedure*

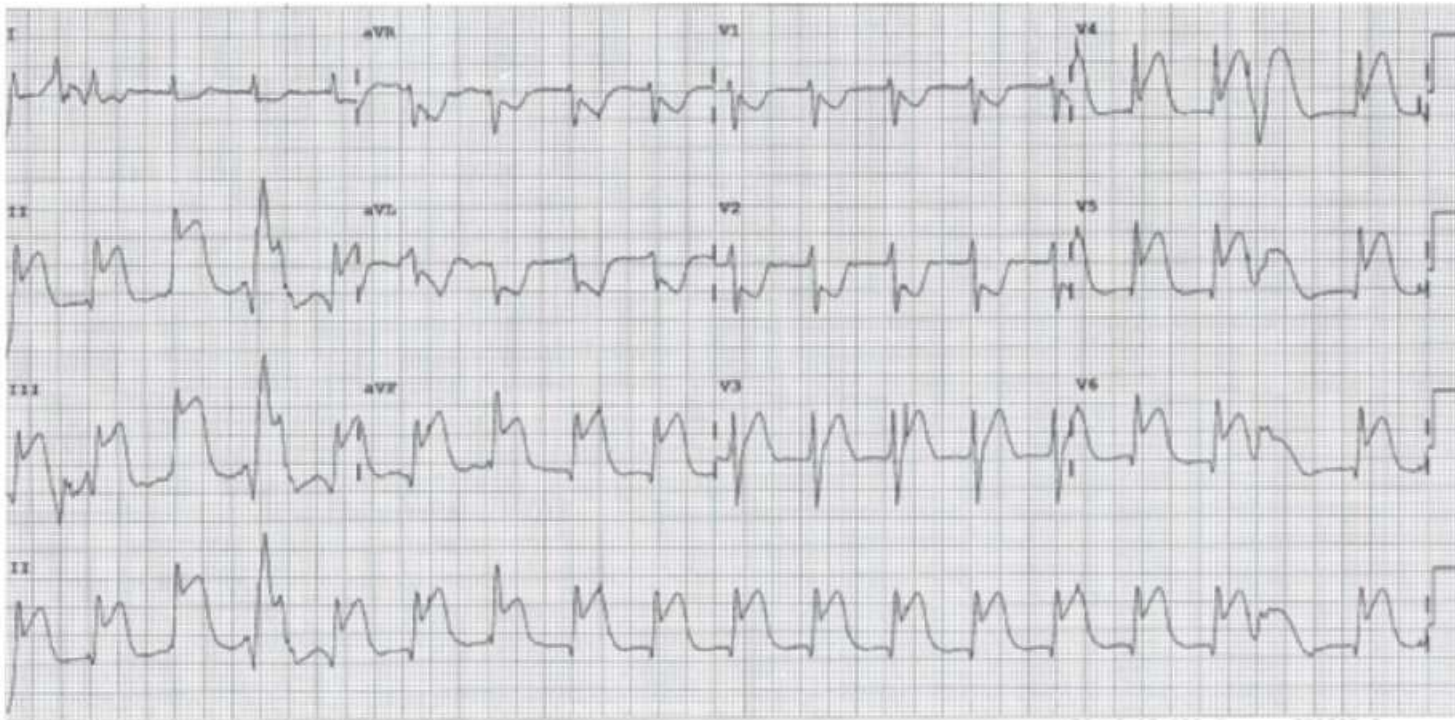


**Angioplasty of the distal part of the RCA**

# Case Study

## *Clinical Evolution*

### ECG in catheterization laboratory



- Troponin peak next day: 800 ng/mL
- Lactate peak: 5.3 mmol/L returning rapidly to normal
- EF at discharge: 50%



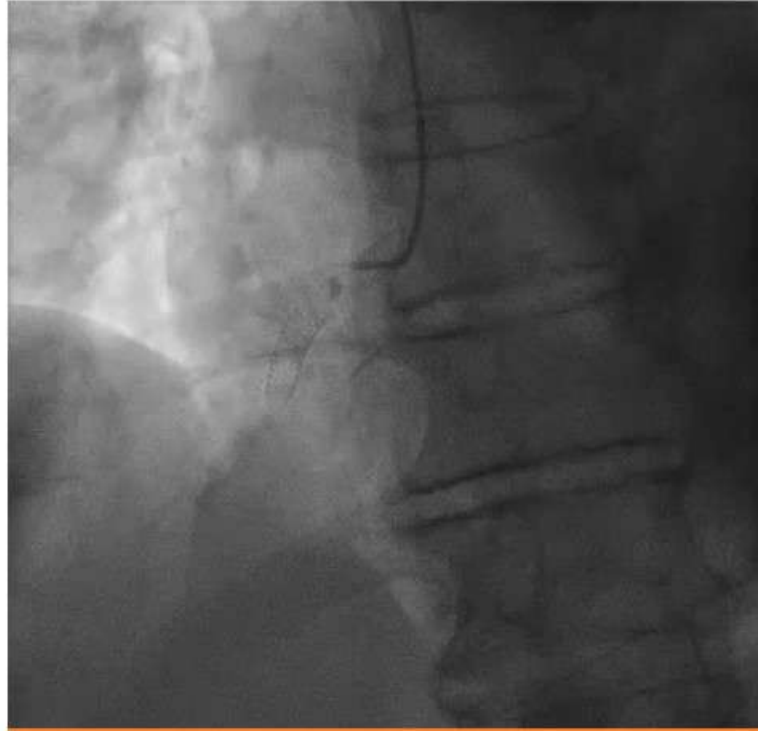
# Take-Home Messages

- **Cangrelor** on the table is always an option for high-risk cases of patients undergoing PCI
  - **GPIs** are also an option
- There is no guarantee against complications

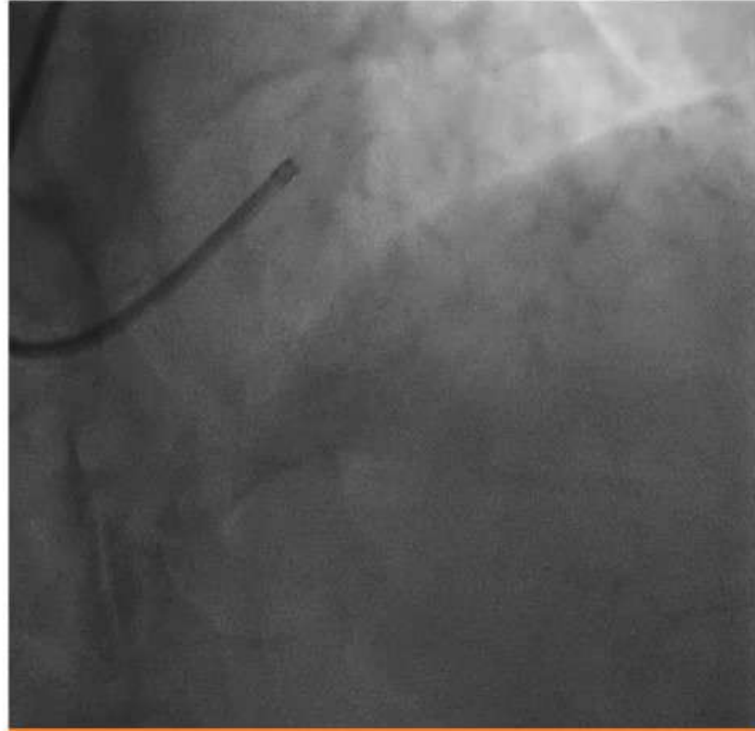


# Case Study

## *One Month Later, Back to the Catheterization Laboratory*



Patent RCA



Tight stenosis in LAD



LAD: PCI with drug-eluting stent

# When an ACS Is an Unclear Diagnosis

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## FACULTY

**Rikard Linder, MD, PhD, FESC**

Senior Consultant

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# Case Study

## Patient Presentation



Male, 48 years old

### Presentation

- Intermittent episodes of chest and back pain radiating to the left arm for 2 d
- TnT = 634 ng/L (> 14 abnormal) at ED

### History

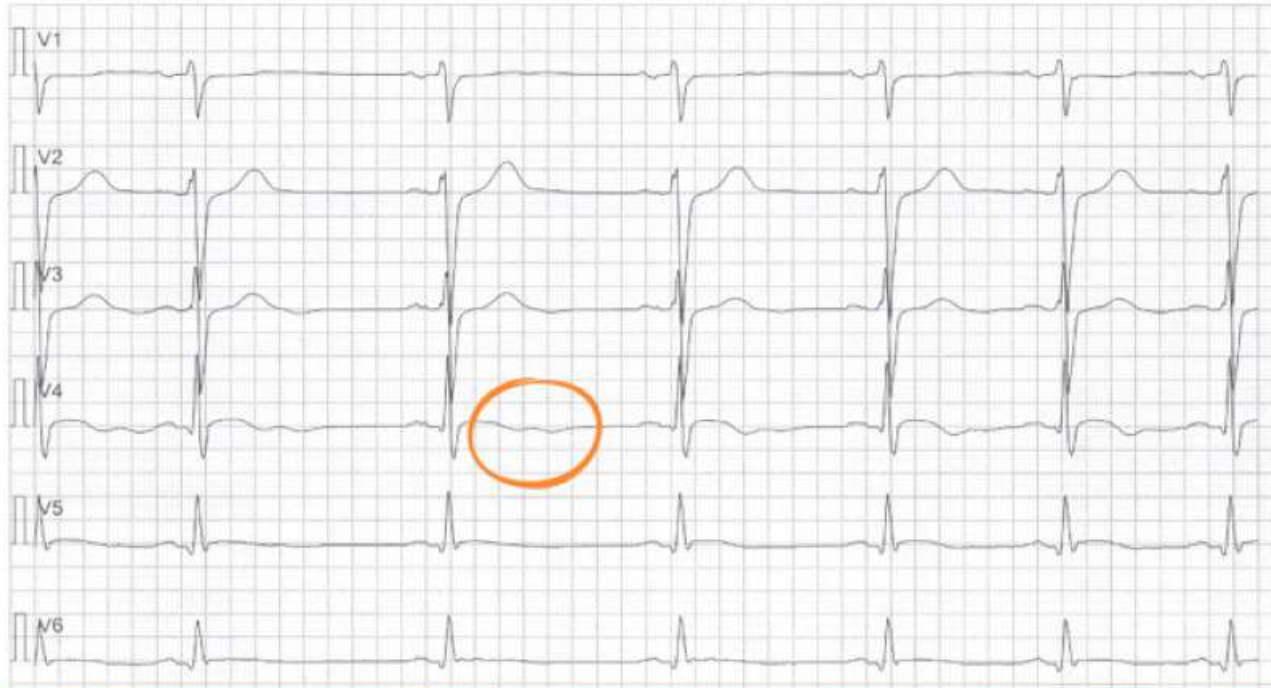
- Previous smoker
- Hypertension and hyperlipidemia

### Same day coronary angiogram

- Minimal atheromatosis without significant lesions

# Case Study

## *Patient Presentation*



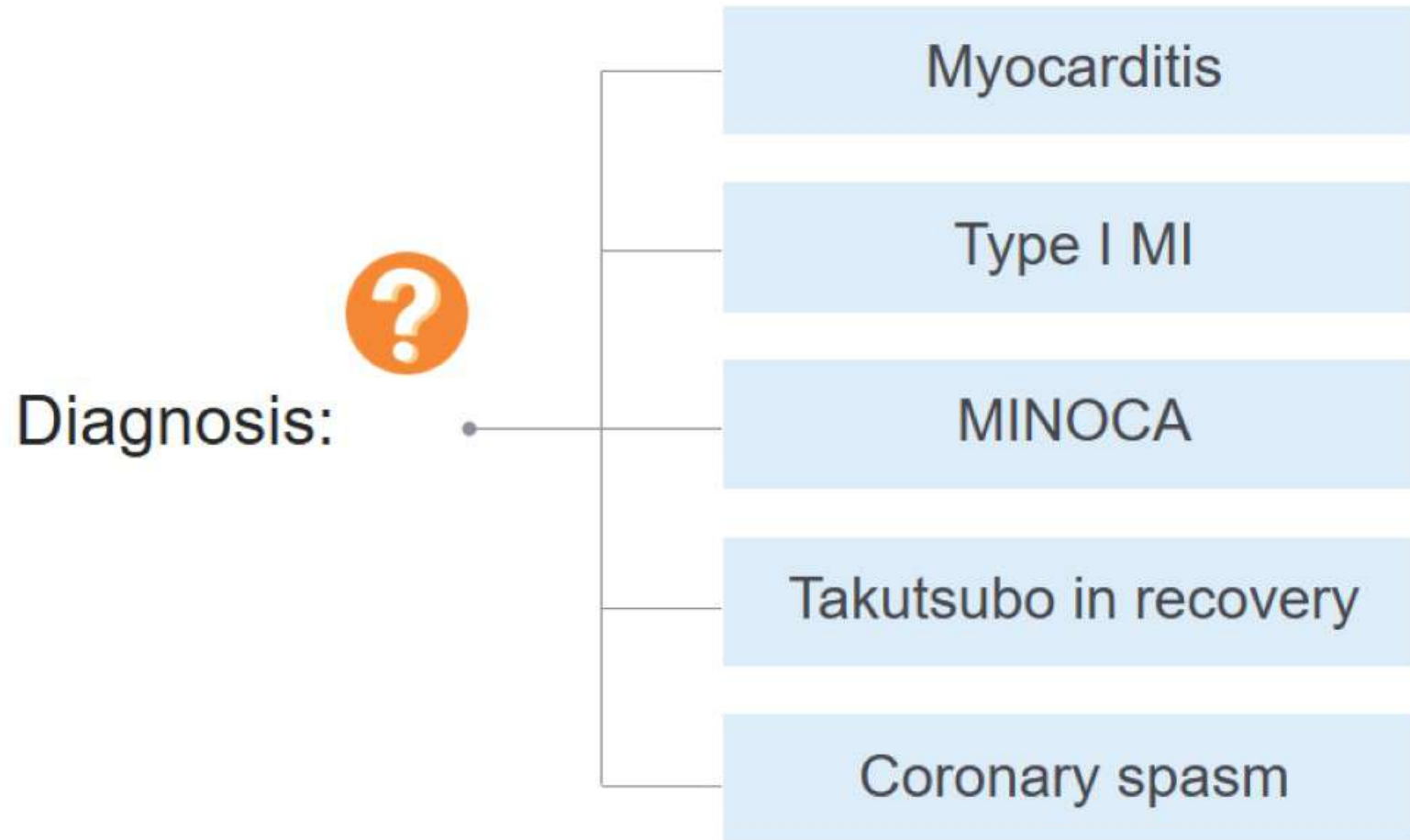
**ECG: signs of ischemia**



**Echocardiogram: mild hypokinesia of the apex**

# Case Study

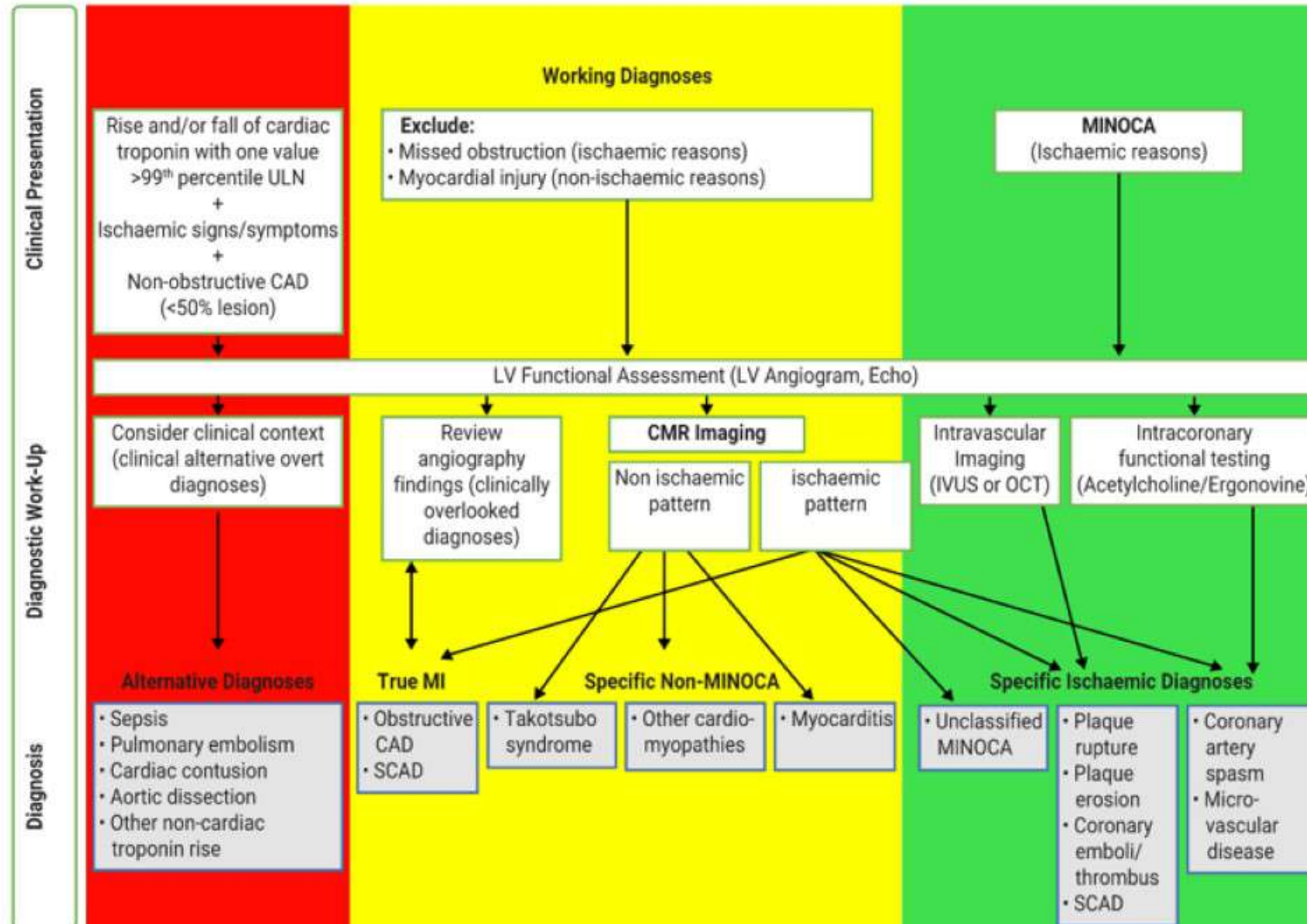
## Diagnosis





# Diagnostic Algorithm for MINOCA Using a Traffic Light Scheme

## ESC Guidelines



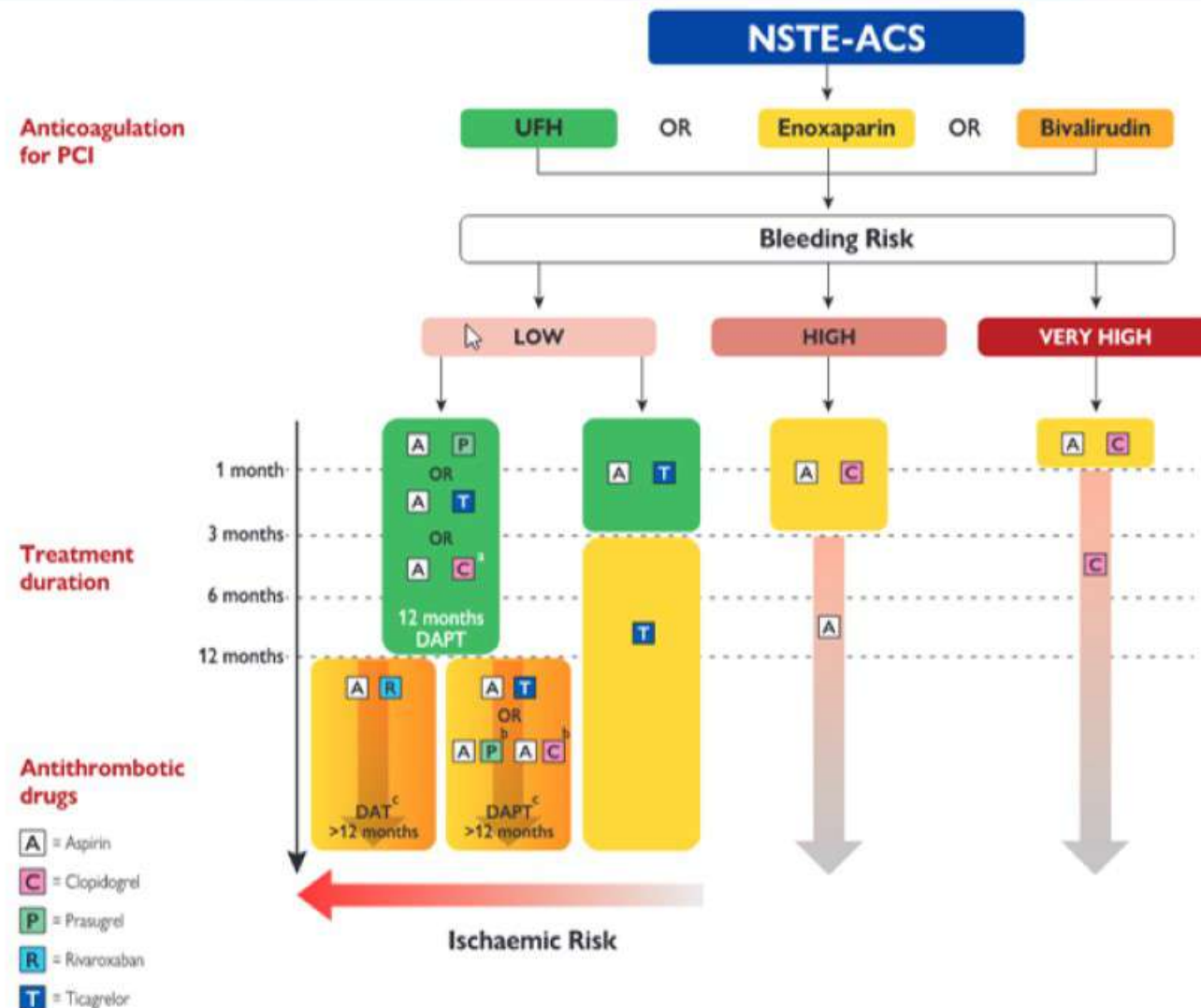
Imaging is crucial

IVUS, intravascular ultrasound; OCT, optical coherence tomography; SCAD, spontaneous coronary artery dissection.

Collet JP, et al., 020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289-1367. By permission of Oxford University Press.

# Antithrombotic Therapy in Patients With NSTEMI-ACS Without AF Undergoing PCI

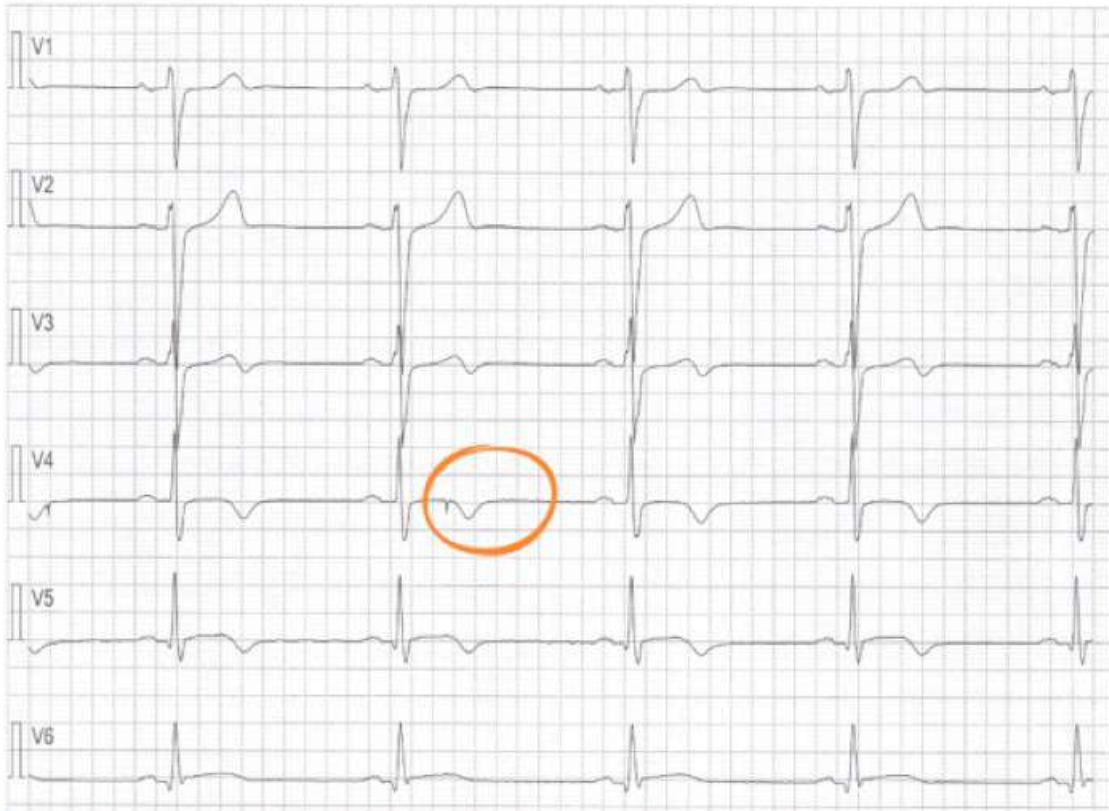
## ESC Guidelines



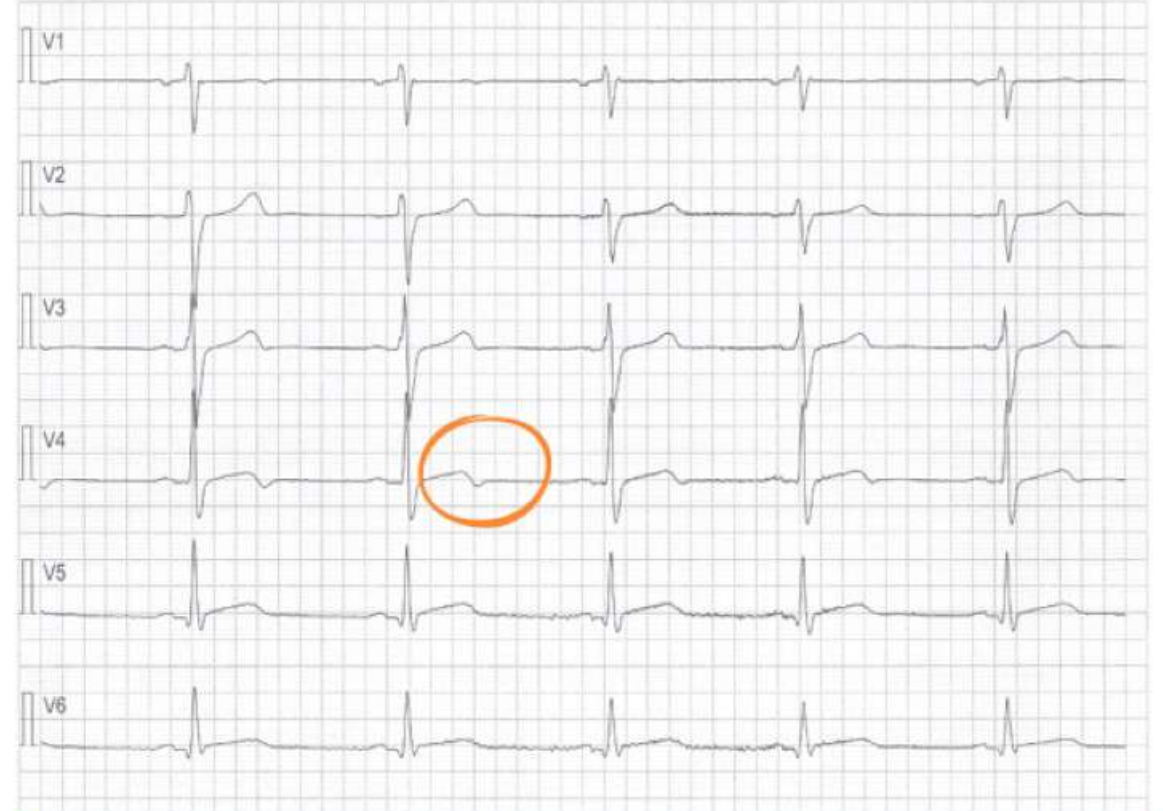
- This patient did not undergo PCI
- Lack of guidelines/data in this specific situation
- Most likely to receive aspirin as antithrombotic treatment

# Case Study

## *Evolution*



**Continuing episodes of chest pain and further rise in troponin**

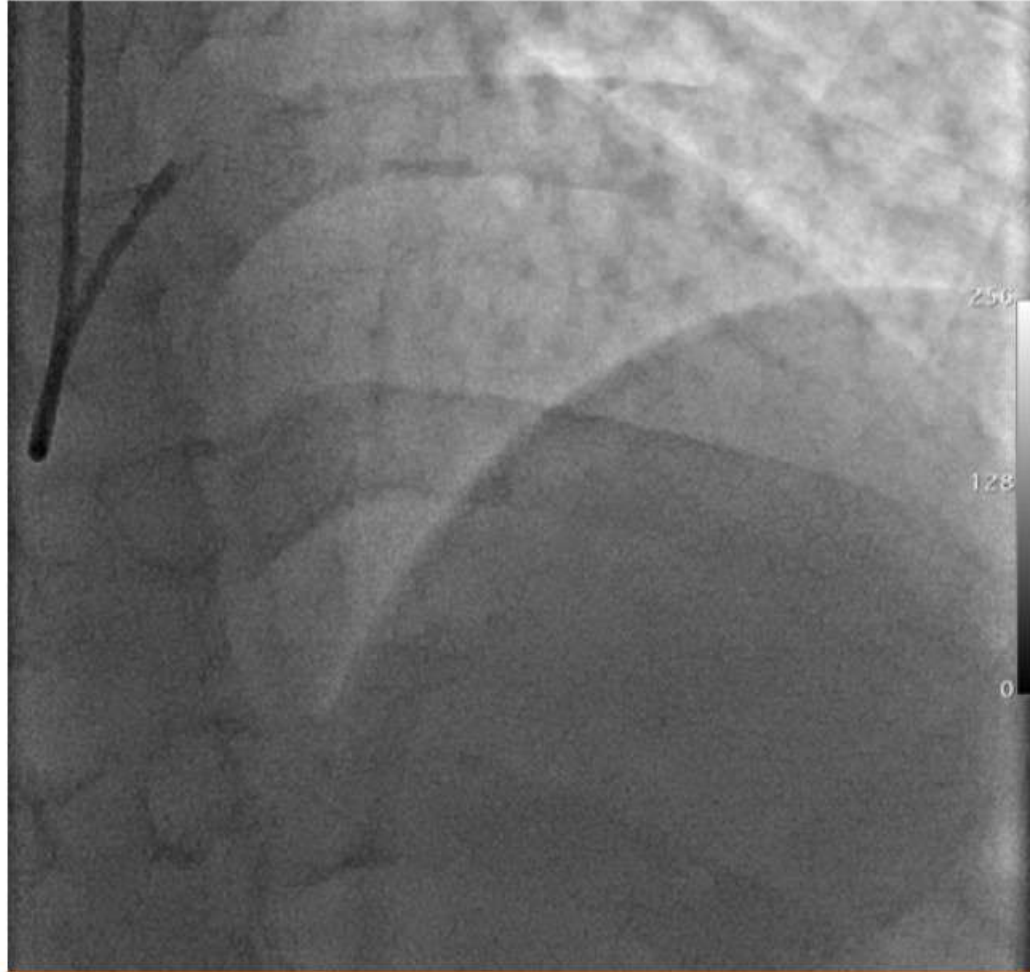


**Episodes of chest pain and dynamic ECG changes**



# Case Study

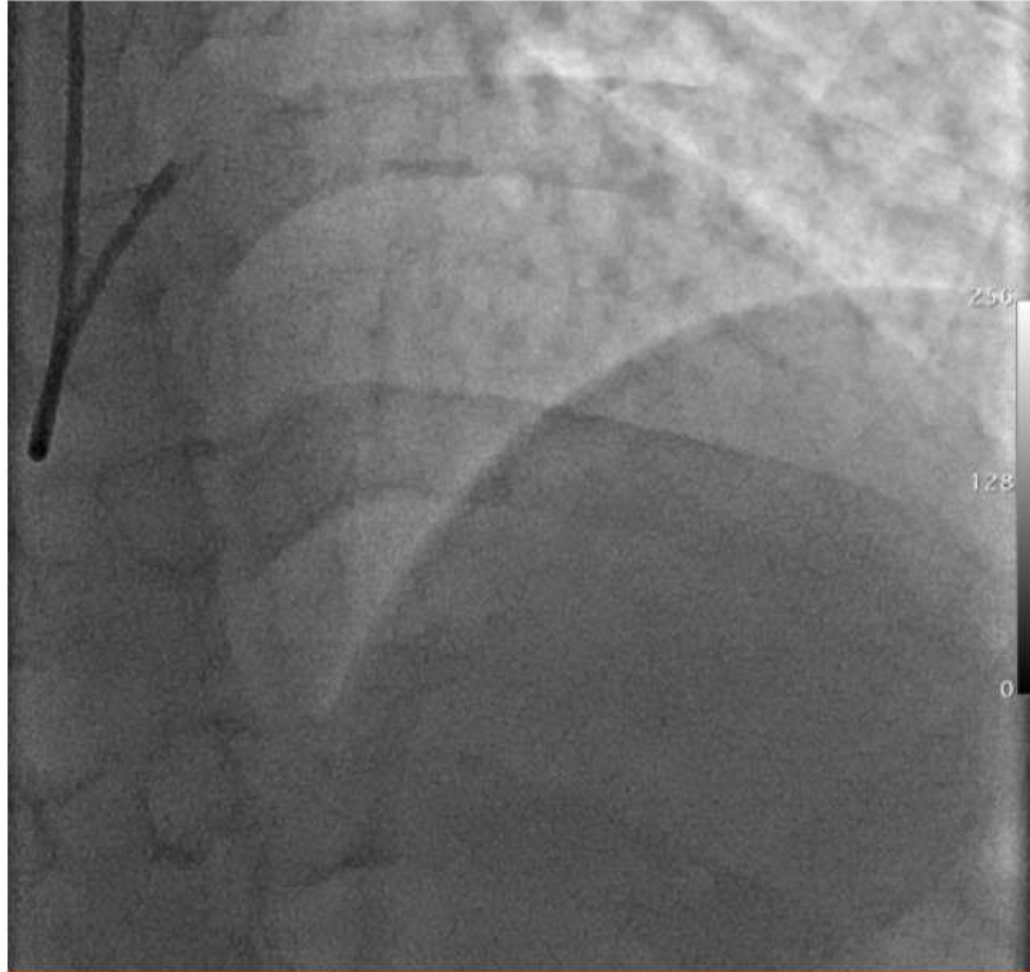
## *Additional Imaging*



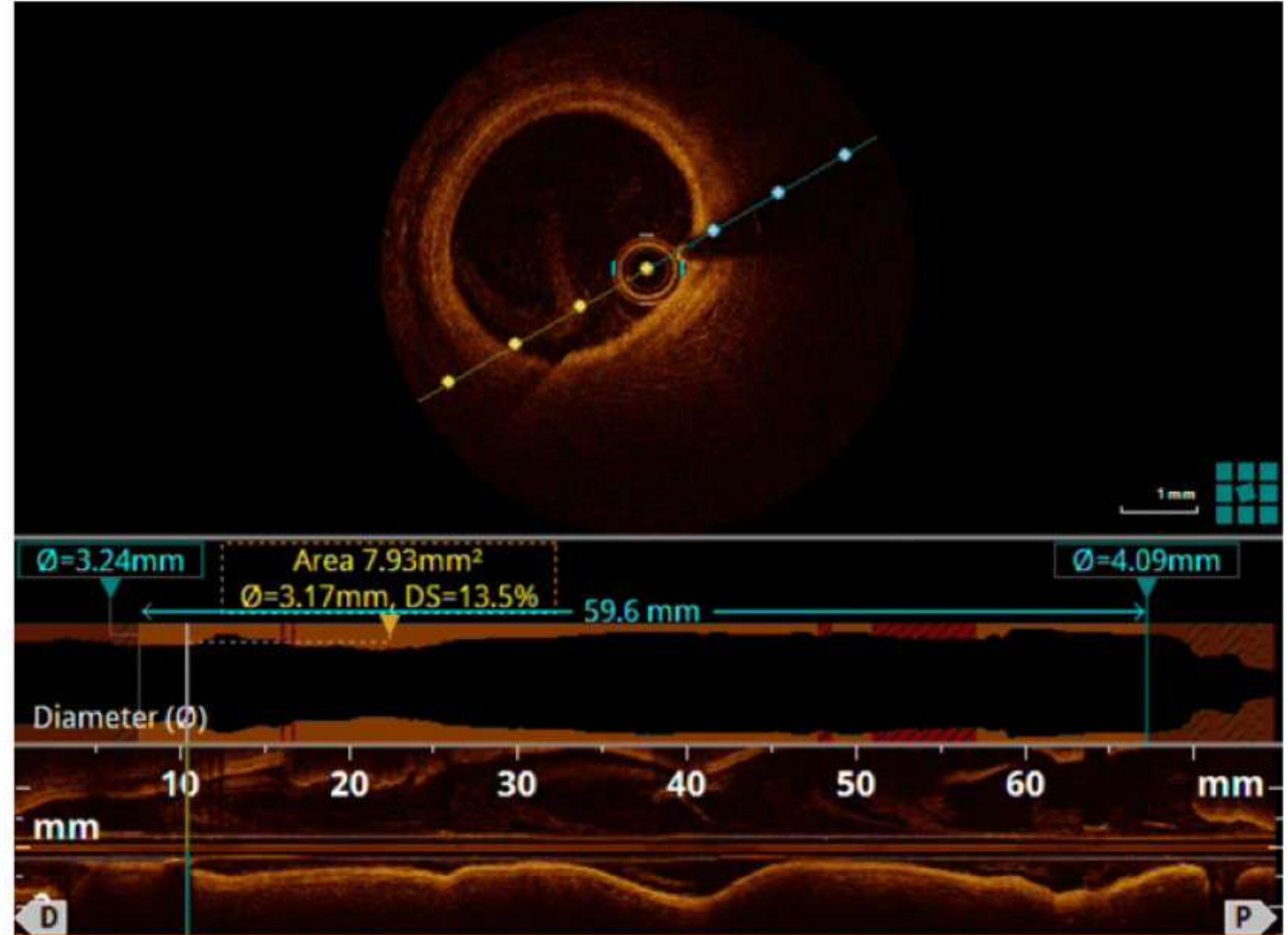
Angiogram Day 4: mild irregularities  
mid LAD

# Case Study

## *Additional Imaging*



Angiogram Day 4: mild irregularities  
mid LAD



OCT: thrombus in the LAD covering > 50% of the lumen

# Case Study

## *PCI Procedure After Confirming Diagnosis*

Diagnosis: type I myocardial infarction



PCI: stent placed



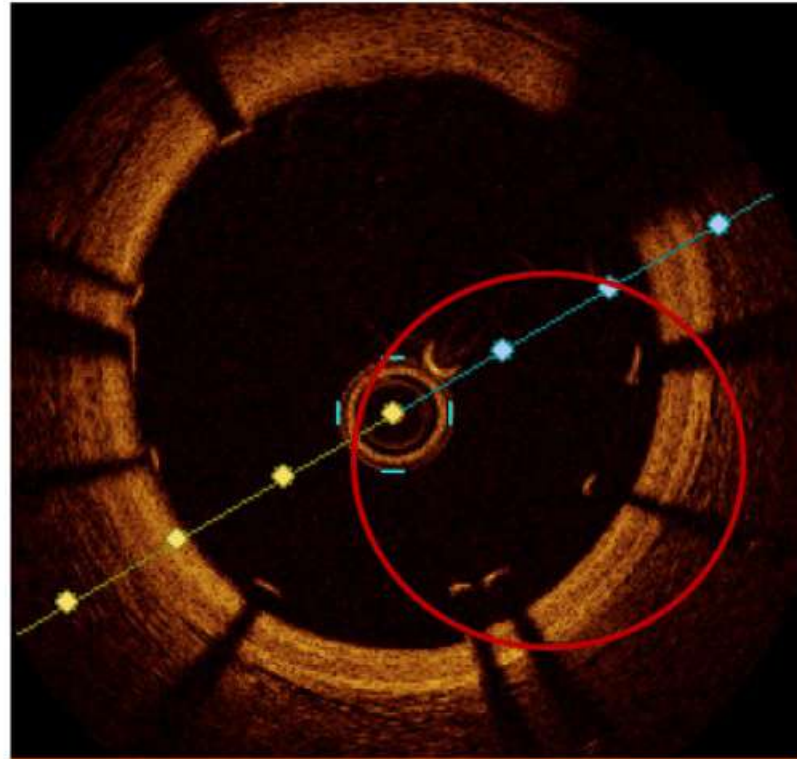
# Case Study

## *PCI Procedure After Confirming Diagnosis*

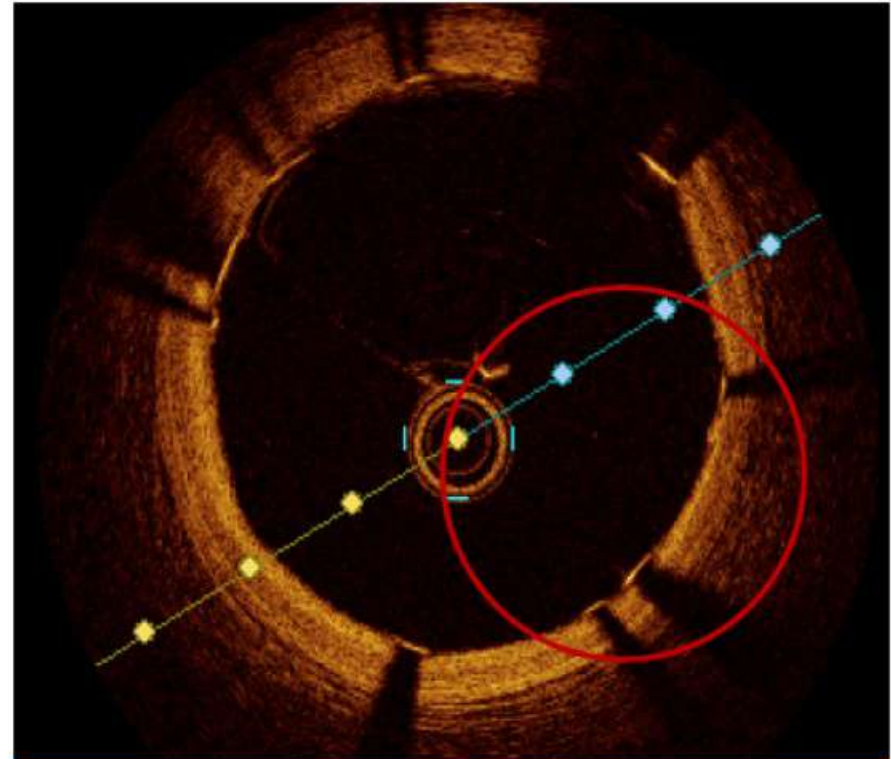
Diagnosis: type I myocardial infarction



PCI: stent placed



IVUS: stent malapposition



IVUS: postdilatation with  
noncompliant balloon

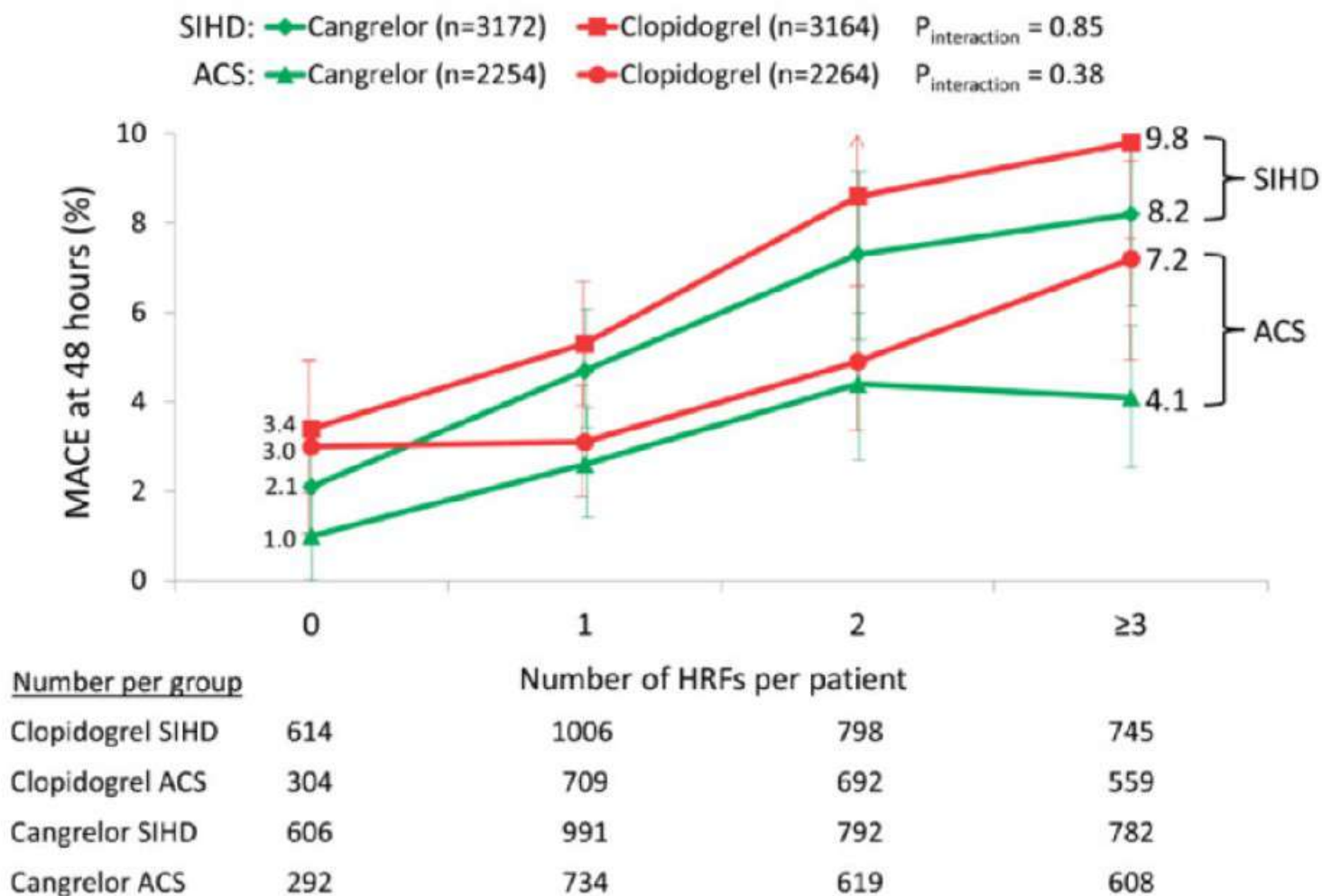
# Case Study

## *Final Angiogram After PCI*



# Cangrelor vs Clopidogrel for Reducing 48-h MACE After PCI

## CHAMPION PHOENIX Trial



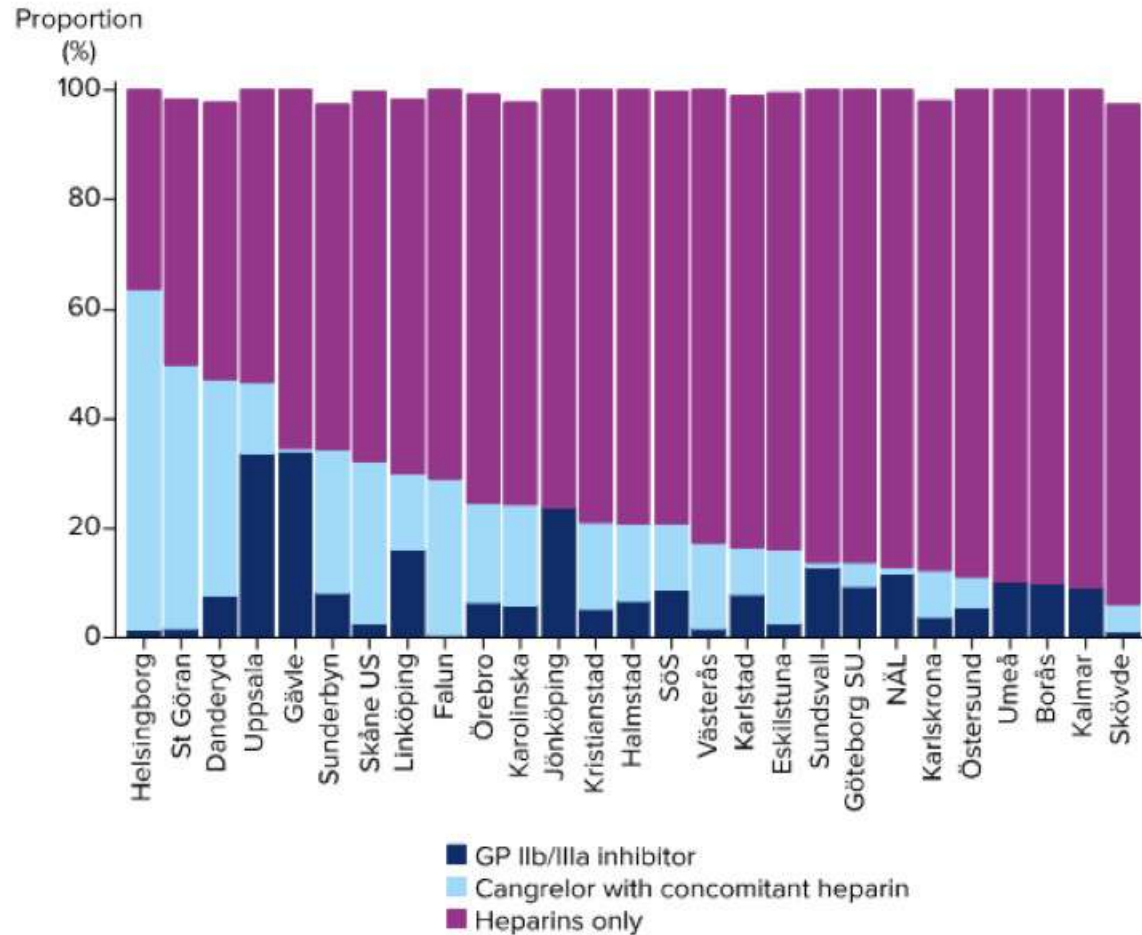
- Periprocedural MACE within 48 hours after PCI were reduced with cangrelor compared with clopidogrel<sup>[a]</sup>
- Cangrelor may be considered in P2Y12 inhibitor-naïve patients undergoing PCI<sup>[b]</sup>



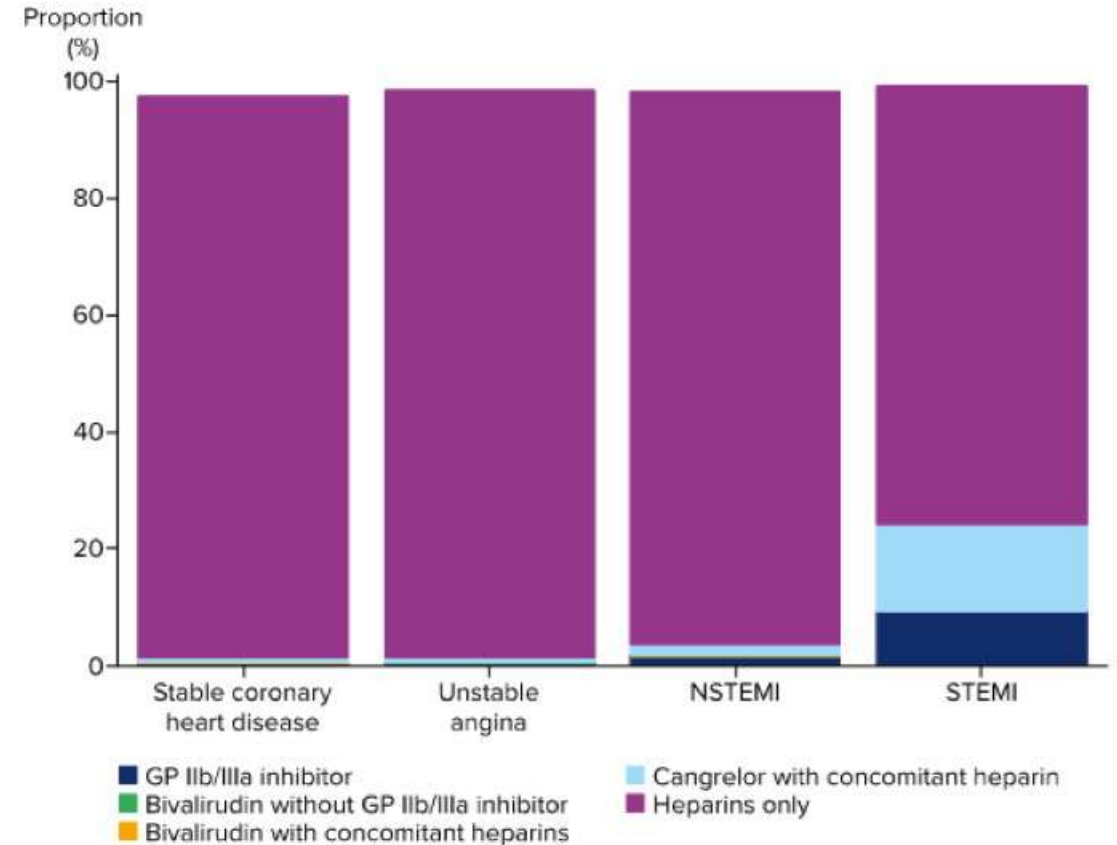
# Antithrombotic Treatment Before or During PCI in Sweden

## SCAAR 2022

Proportion of GP IIb/IIIa inhibitor and cangrelor before or during PCI in patients with STEMI

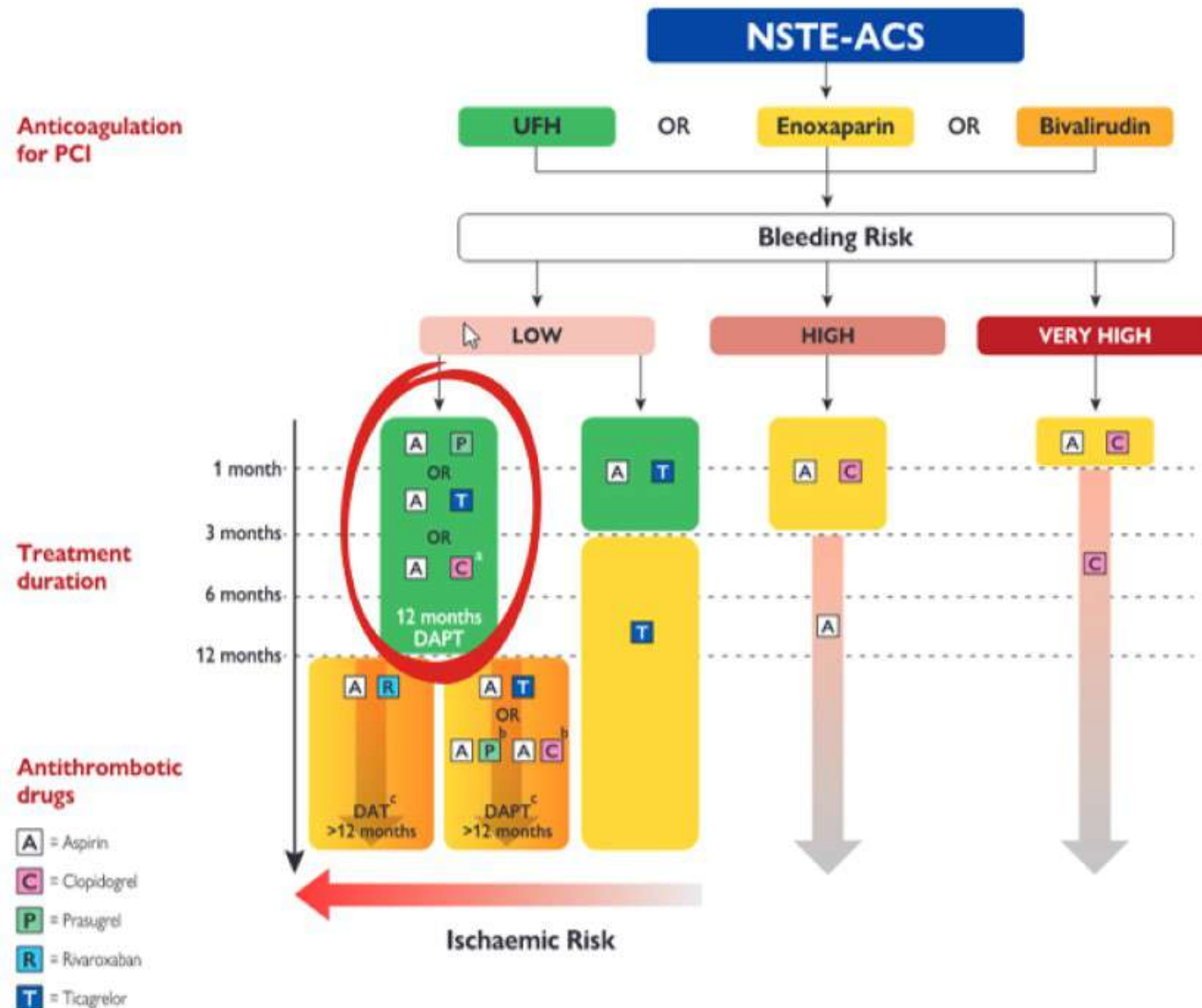


Proportion of GP IIb/IIIa inhibitor, bivalirudin and cangrelor before or during PCI in patients with MI



# What Antithrombotic Treatment to Select After PCI for Our Patient?

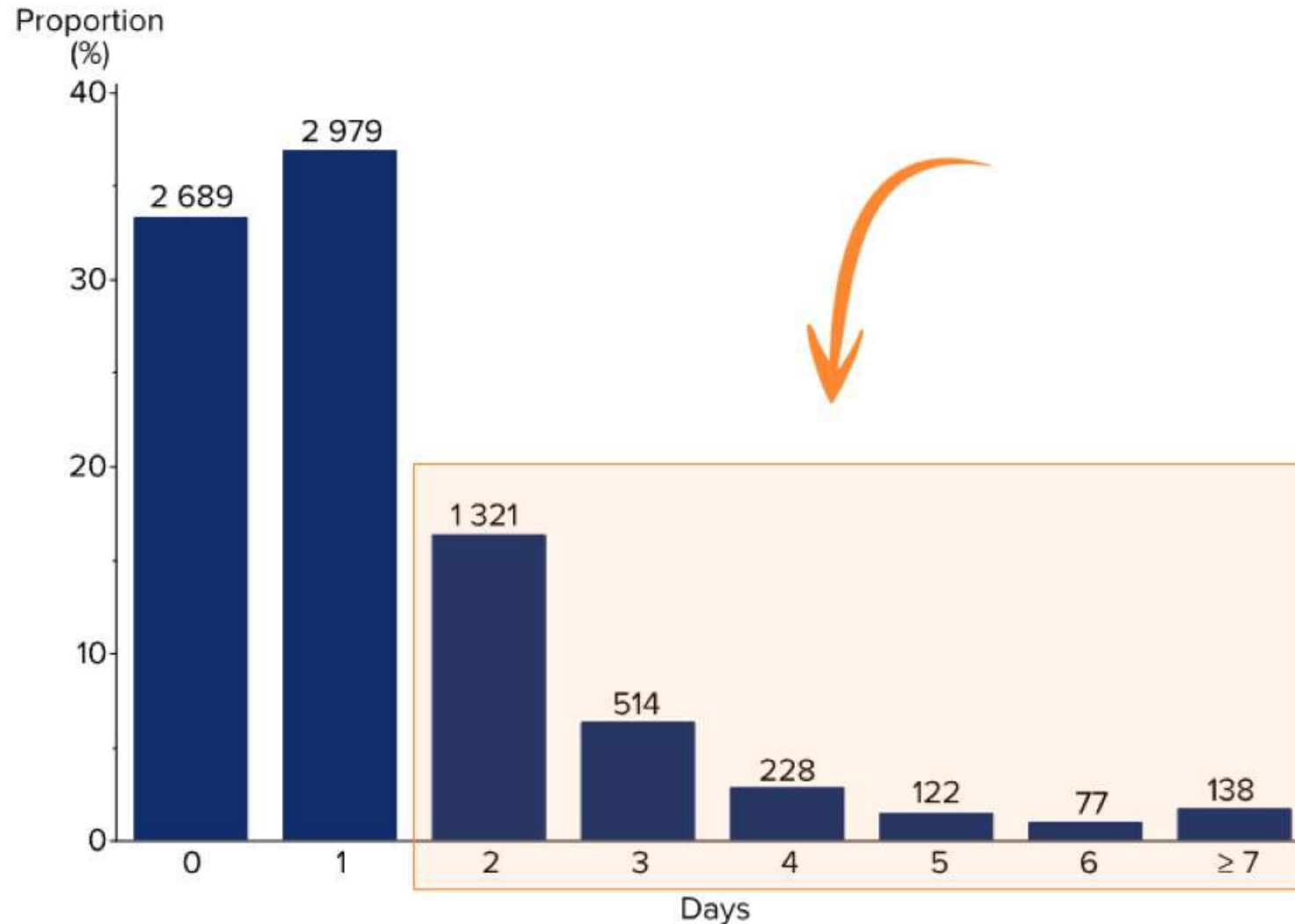
## ESC Guidelines



- Guidelines recommend combining **aspirin** with either **prasugrel** or **ticagrelor** or **clopidogrel**
- Pretreatment** with prasugrel is not indicated while ticagrelor pretreatment is mandated by the guidelines when > 24 h wait before angiography

# Days From Admission to Coronary Angiography for Patients With NSTEMI

## SCAAR 2022

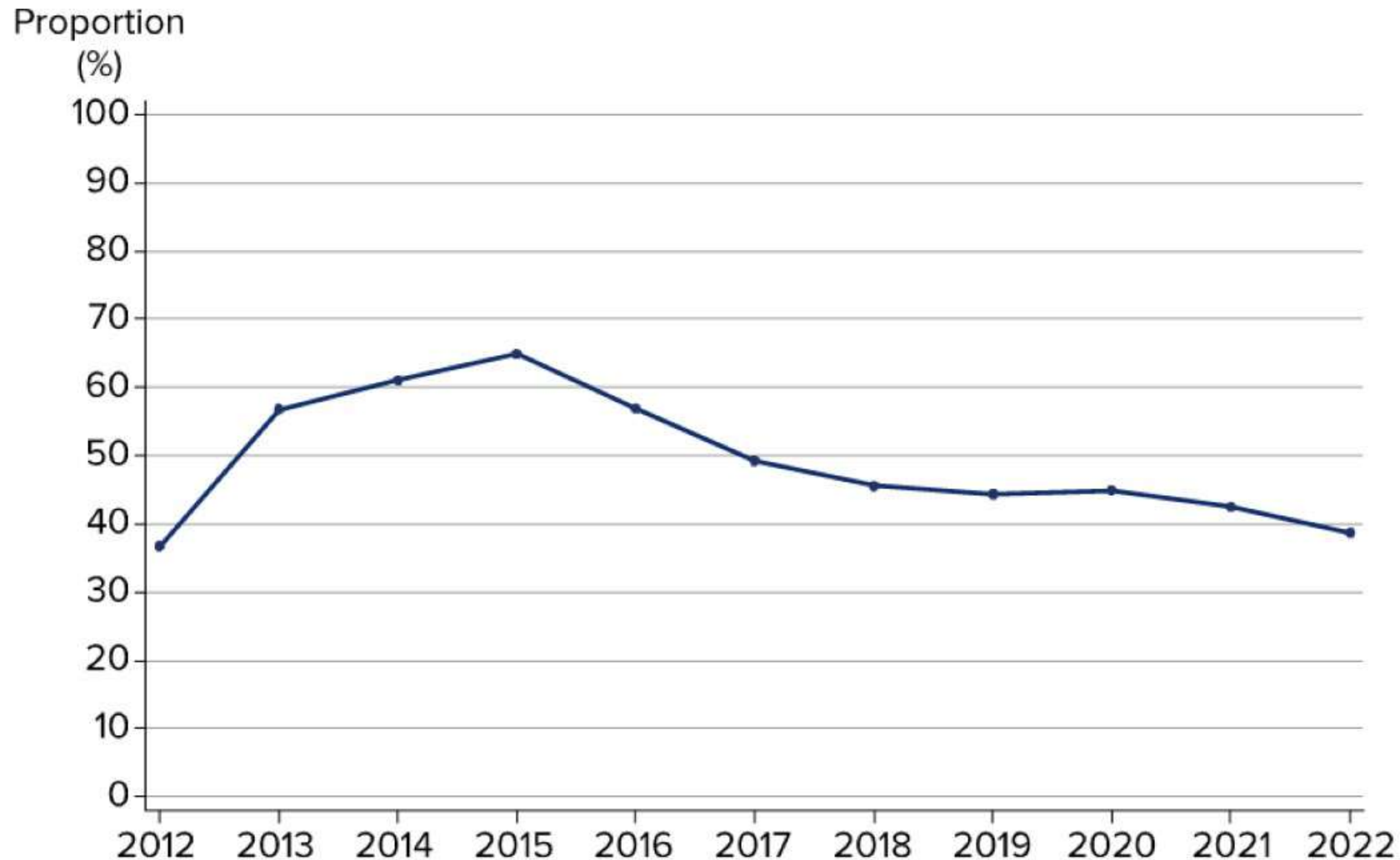


A large proportion of patients had > 24 h waiting for the coronary angiogram time after hospital admission in Sweden in 2022



# Proportion of Patients With STEMI Pretreated With Ticagrelor or Prasugrel

## SCAAR 2022



# Case Study

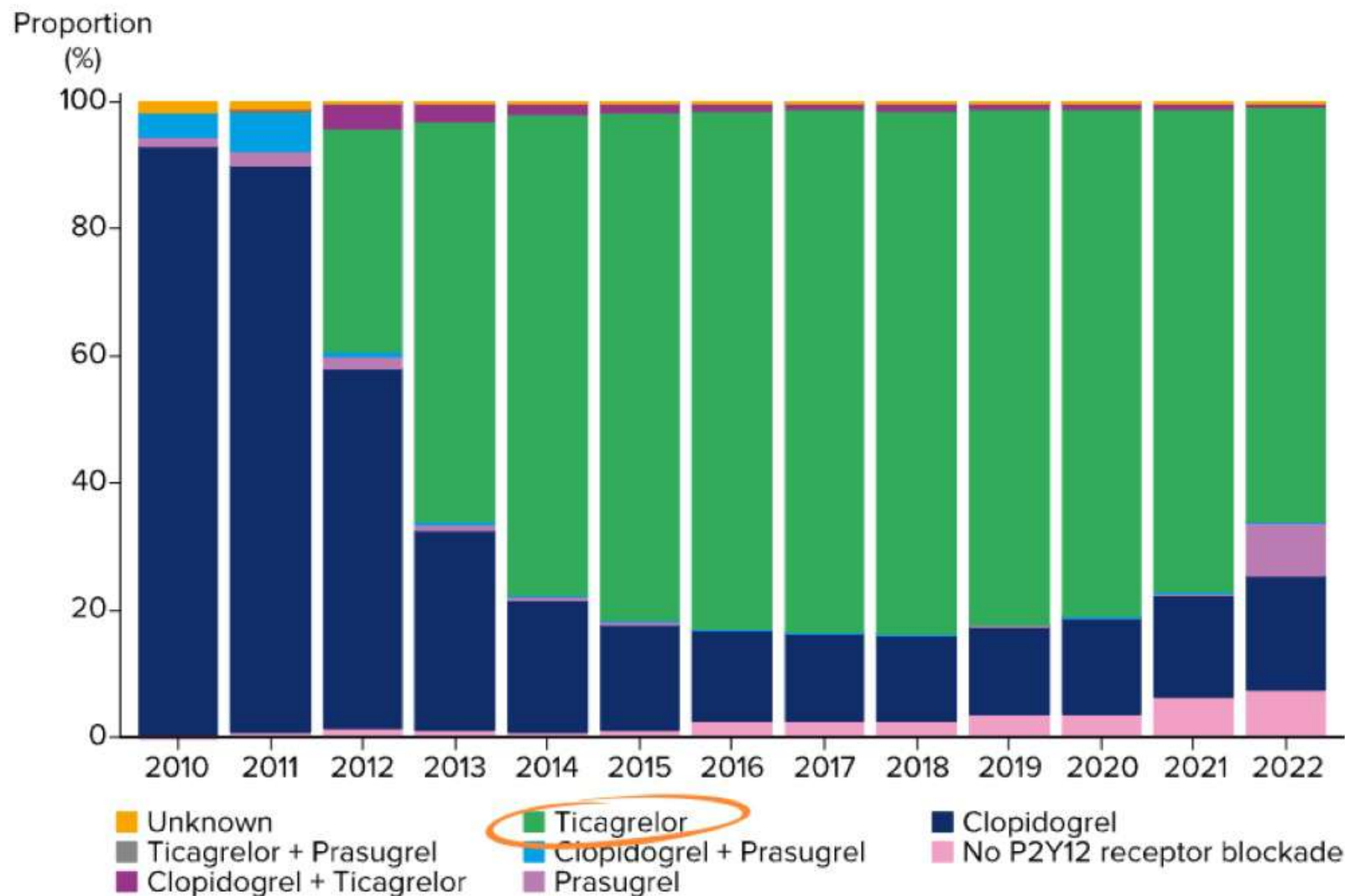
## *Ticagrelor vs Prasugrel*

**If medical treatment only,  
ticagrelor could have been  
selected for treating this patient**

**Ticagrelor and cangrelor work in  
harmony while prasugrel is  
displaced by cangrelor**

# Patients With PCI With NSTEMI Treated With Oral P2Y12 Receptor Antagonists

## SCAAR 2022





# Take-Home Messages

“

**Individualize treatment. It is important, and each patient is unique.**

”

# Meet the Experts

## From Guidelines to Practice

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### MODERATOR

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Icahn School of Medicine at Mount Sinai

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# P2Y<sub>12</sub> Receptor Antagonists

## Current Guidelines

### 2017 ESC Guidelines for the Management of STEMI<sup>[a]</sup>

Recommendations	Class	Level
<b>Antiplatelet therapy</b>		
<b>A potent P2Y<sub>12</sub> inhibitor</b> (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 mo, <b>unless</b> there are contraindications such as <b>excessive risk or bleeding</b>	I	A
<b>Cangrelor</b> may be considered in patients who have not received P2Y <sub>12</sub> receptor inhibitors	IIb	A

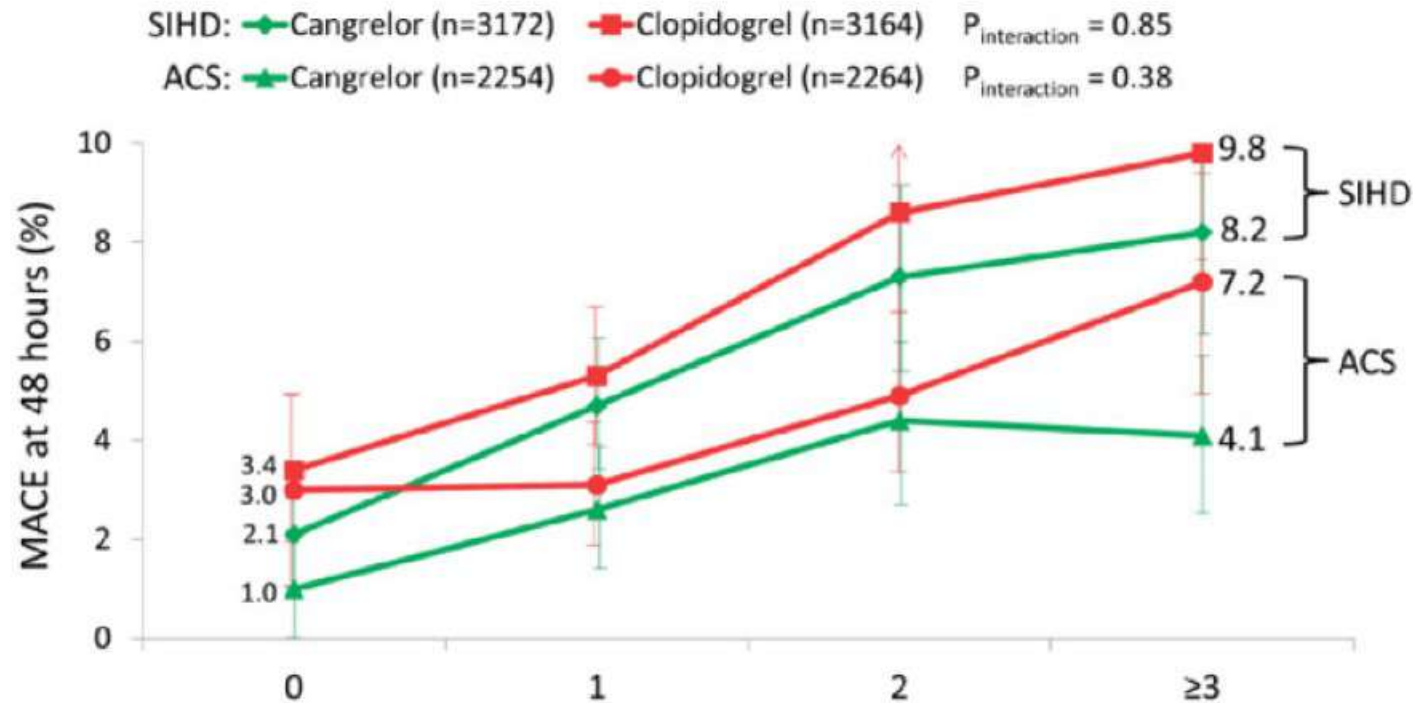
### 2021 ACC/AHA/SCAI Revascularization Guidelines<sup>[b]</sup>

Recommendations	Class	Level
In patients undergoing PCI, a loading dose of P2Y <sub>12</sub> inhibitor, followed by daily dosing, is recommended to reduce ischemic events	1	B-R
In patients with ACS undergoing PCI, it is reasonable to use <b>ticagrelor or prasugrel</b> in preference to clopidogrel to reduce ischemic events	2a	B-R
In patients undergoing PCI who have a <b>history of stroke</b> or transient ischemic attack, <b>prasugrel should not be administered</b>	3: Harm	B-R
In patients undergoing PCI who are P2Y <sub>12</sub> inhibitor naïve, intravenous <b>cangrelor</b> may be reasonable to reduce periprocedural ischemic events	2b	B-R



# Cangrelor vs Clopidogrel for Reducing 48-Hour MACE After PCI

## CHAMPION PHOENIX Trial



	Number of HRFs per patient			
Number per group	0	1	2	≥3
Clopidogrel SIHD	614	1006	798	745
Clopidogrel ACS	304	709	692	559
Cangrelor SIHD	606	991	792	782
Cangrelor ACS	292	734	619	608

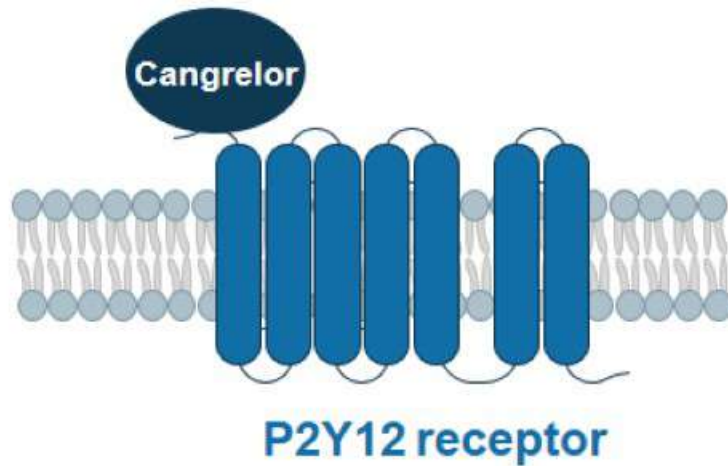
- Periprocedural MACE within 48 h after PCI were reduced with cangrelor compared with clopidogrel<sup>[a]</sup>
- Cangrelor may be considered in P2Y<sub>12</sub> inhibitor-naïve patients undergoing PCI<sup>[b]</sup>

MACE, major adverse cardiovascular event; SIHD, stable ischemic heart disease.

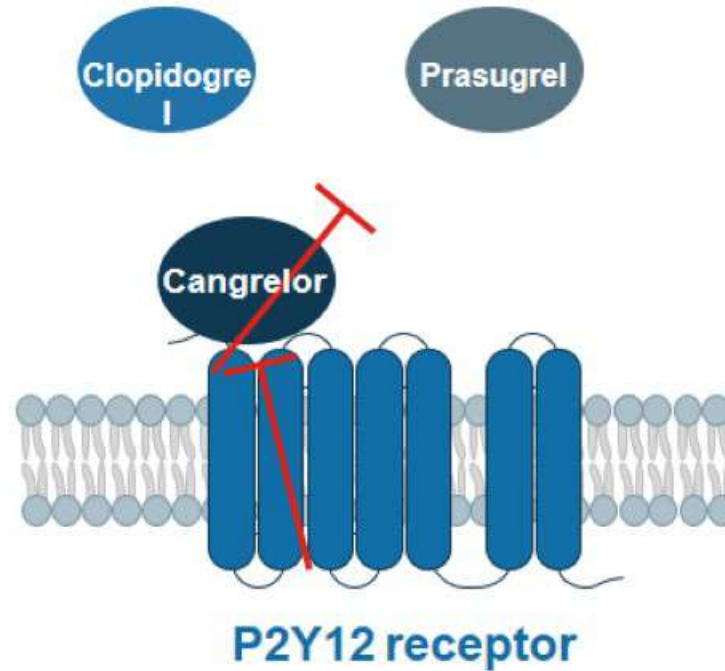
a. Stone GW, et al. Eur Heart J. 2018;39:4112-4121; b. Collet JP, et al. Eur Heart J. 2021;42:1289-1367.

# Cangrelor Affects Binding of Clopidogrel and Prasugrel but Not Ticagrelor

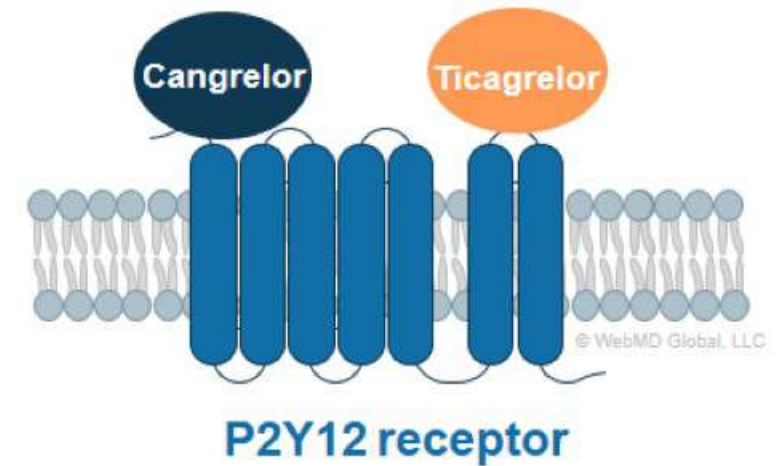
Cangrelor



Clopidogrel and prasugrel **cannot bind** to P2Y12 with cangrelor present

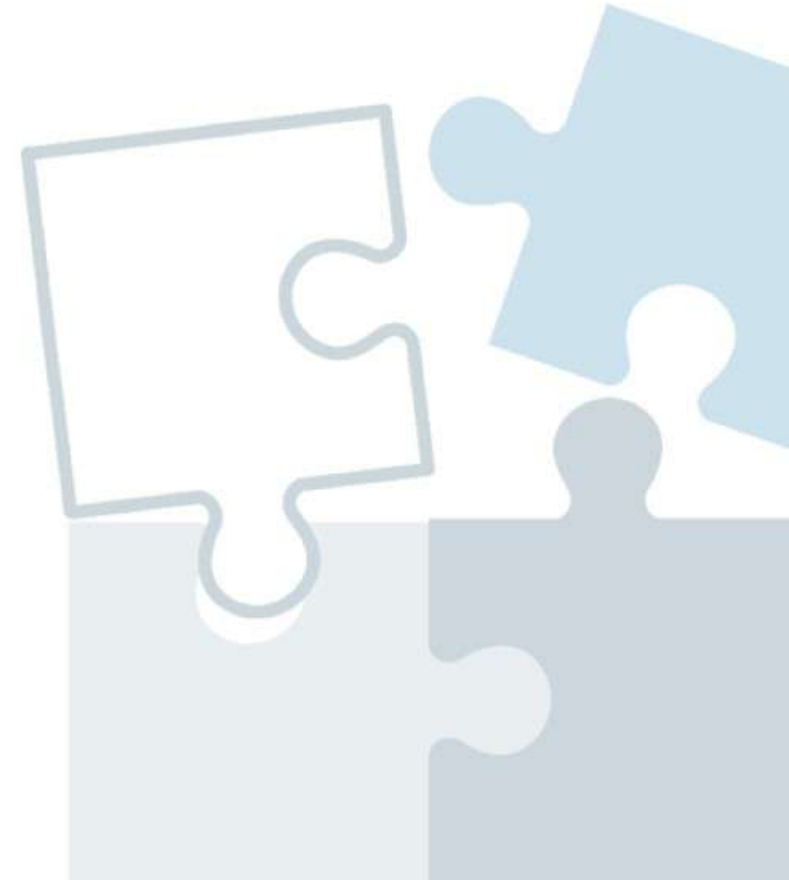


Ticagrelor binding is **not affected** by cangrelor



# Conclusion

- Different P2Y<sub>12</sub> receptor antagonists have different PK/PD, particularly oral vs IV agents
- It is crucial to risk-stratify patients and to accordingly individualize the selection of the best P2Y<sub>12</sub> receptor antagonist for each patient





# Thank you for participating in this activity.

Find useful tools and resources on the right-hand side of this page.