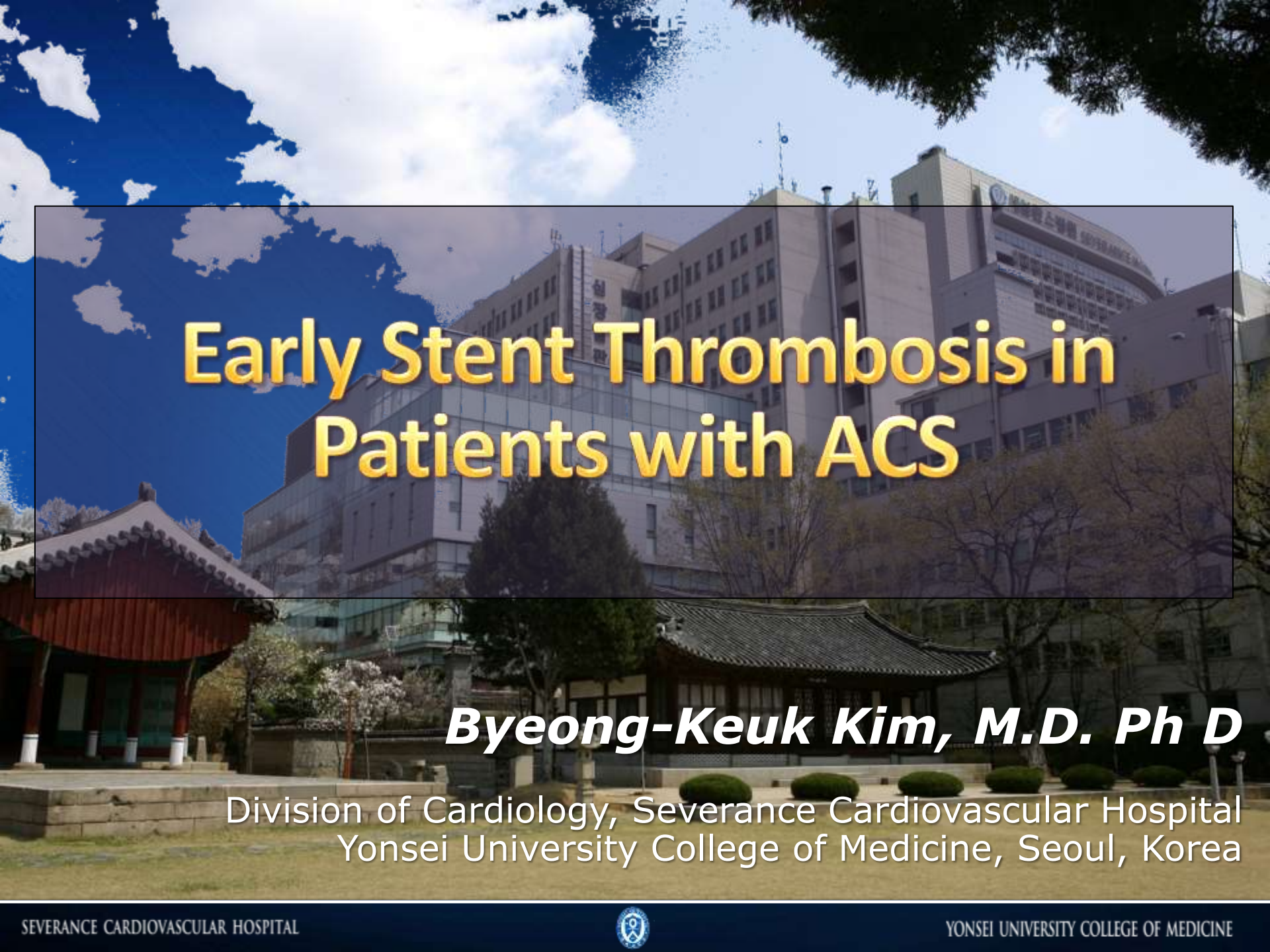
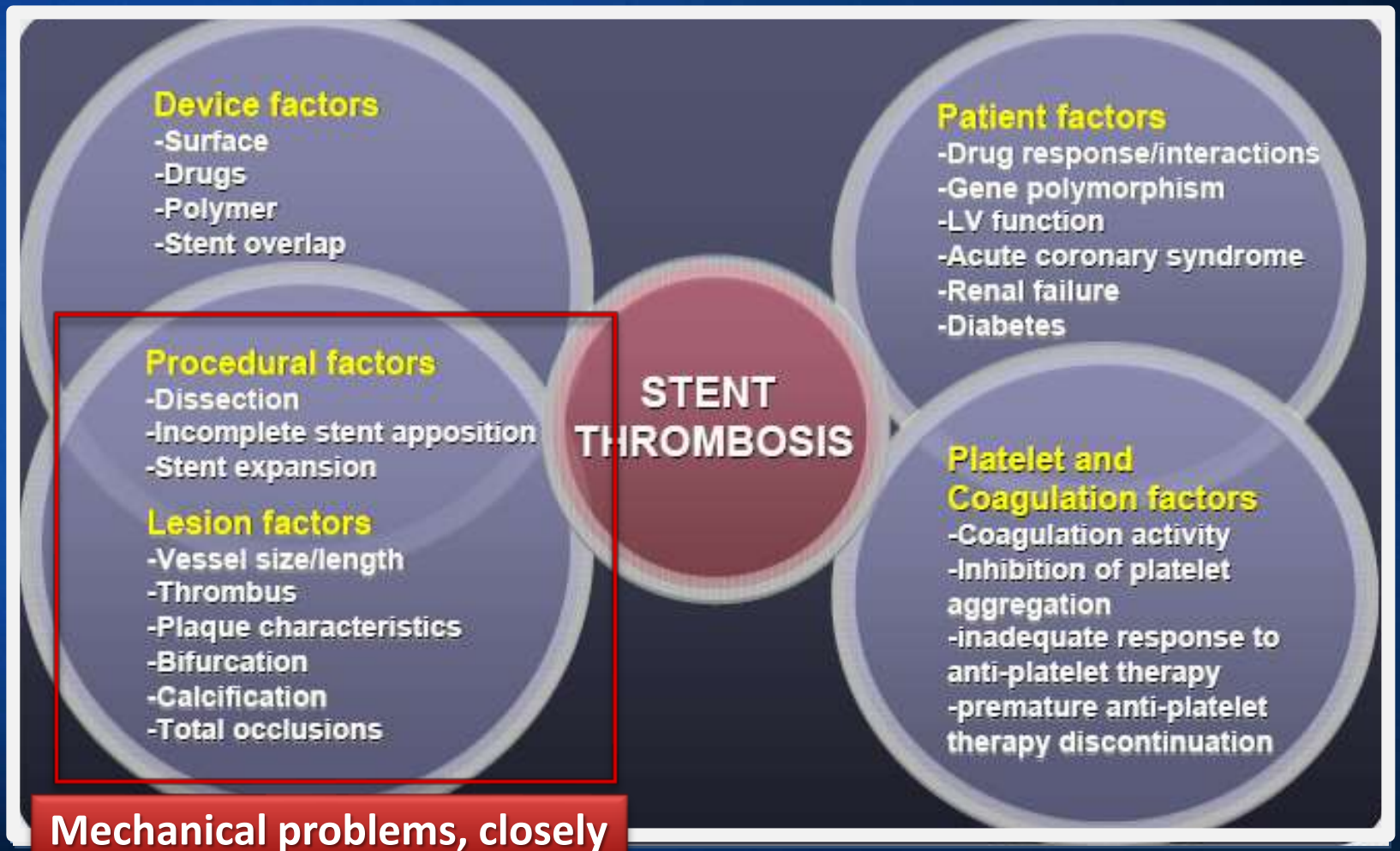


# Early Stent Thrombosis in Patients with ACS

***Byeong-Keuk Kim, M.D. Ph D***

Division of Cardiology, Severance Cardiovascular Hospital
Yonsei University College of Medicine, Seoul, Korea

# Multiple factors involved Stent Thrombosis !




**Mechanical problems, closely related with acute ST**

Windecker S, Meier B. *Circulation 2007;116:1952-65*

*Recent DATA*

# Predictors of stent thrombosis in AMI?

- ✓ From January 2004 to December 2009, a total of 4,748 patients with AMI underwent PCI in COREA registry. → **136 patients diagnosed with ST (3.7%)**; 110 definite ST, and 26 probable ST.

| Variables | Hazard ratio | 95% confidence interval | p Value |
|---|---|---|---|
| All stent thrombosis* | | | |
| No reflow phenomenon | 2.44 | 1.19-5.01 | 0.015 |
| Left ventricle ejection fraction<50% | 2.02 | 1.06-3.85 | 0.033 |
| Very late stent thrombosis§ | | | |
| Previous myocardial infarction | 2.89 | 1.15-7.29 | 0.024 |
| No reflow phenomenon | 2.20 | 1.09-4.44 | 0.027 |

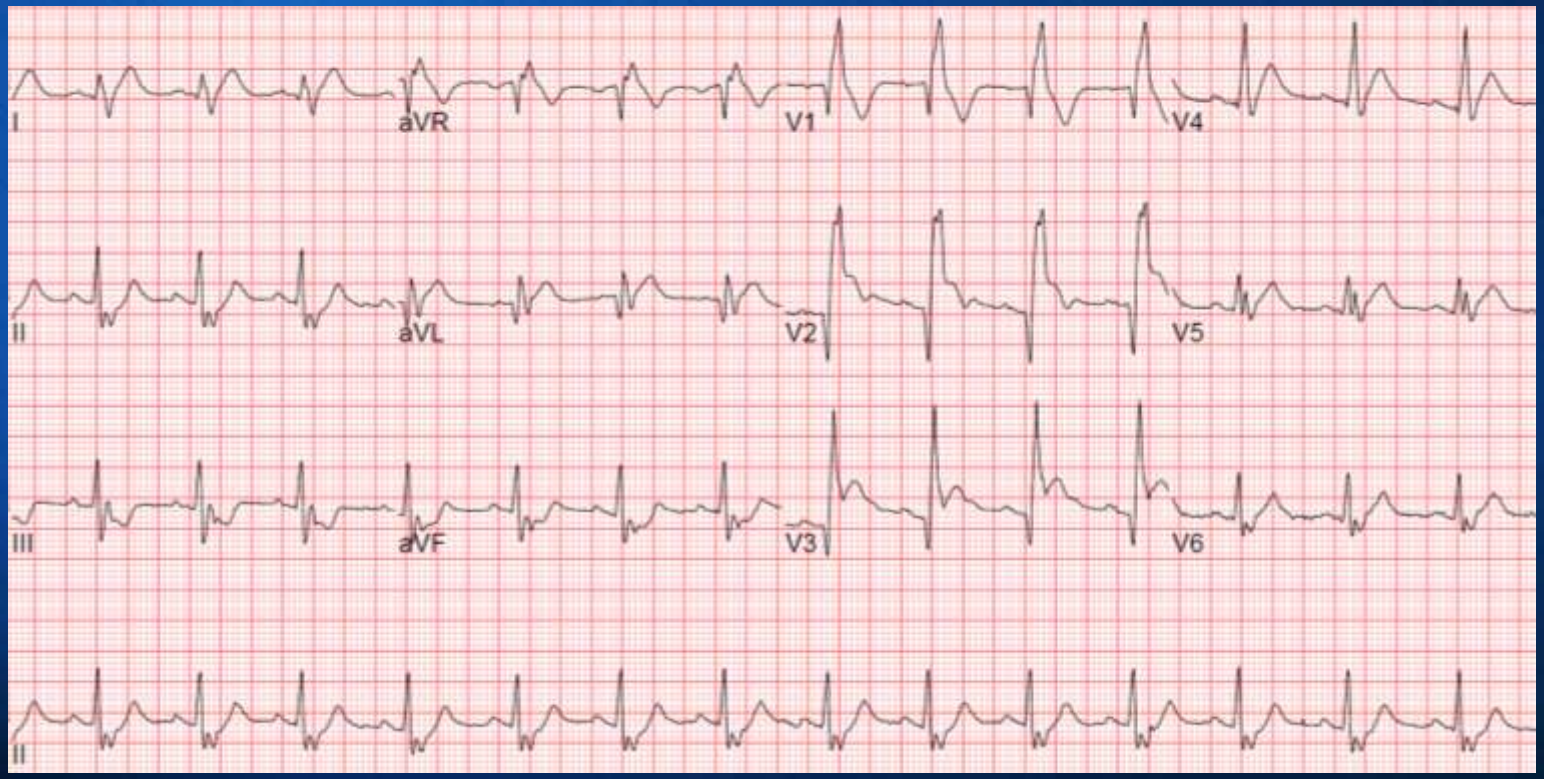
✓ **Only by the solutions to the mechanical problems, would early ST be reduced in patients with ACS ?**



Am J Cardiol. 2016 Mar

# Case 1. M/38

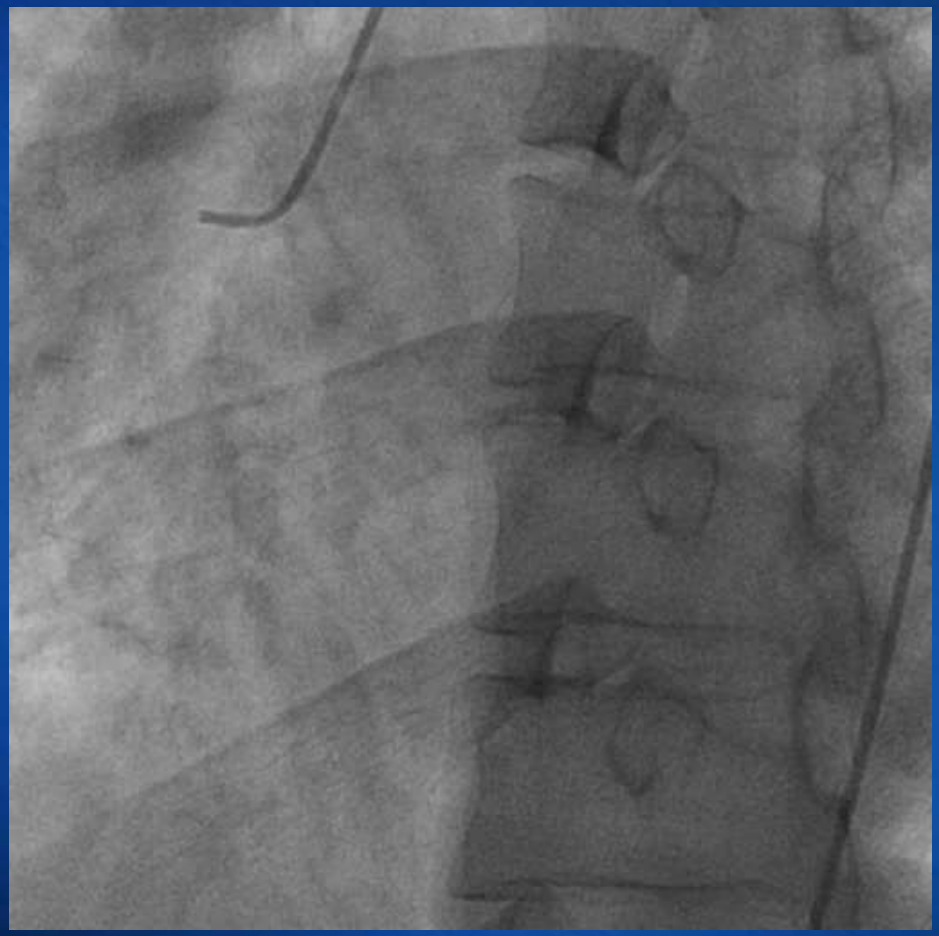
- C.C : Ongoing chest pain & Dyspnea for 30 minutes
  → Visit ER by Ambulance
- Risk factors : current smoker (20 PYRS), HTN/DM (-/-)
- Initial V/S : 132/92mmHg, HR 100bpm

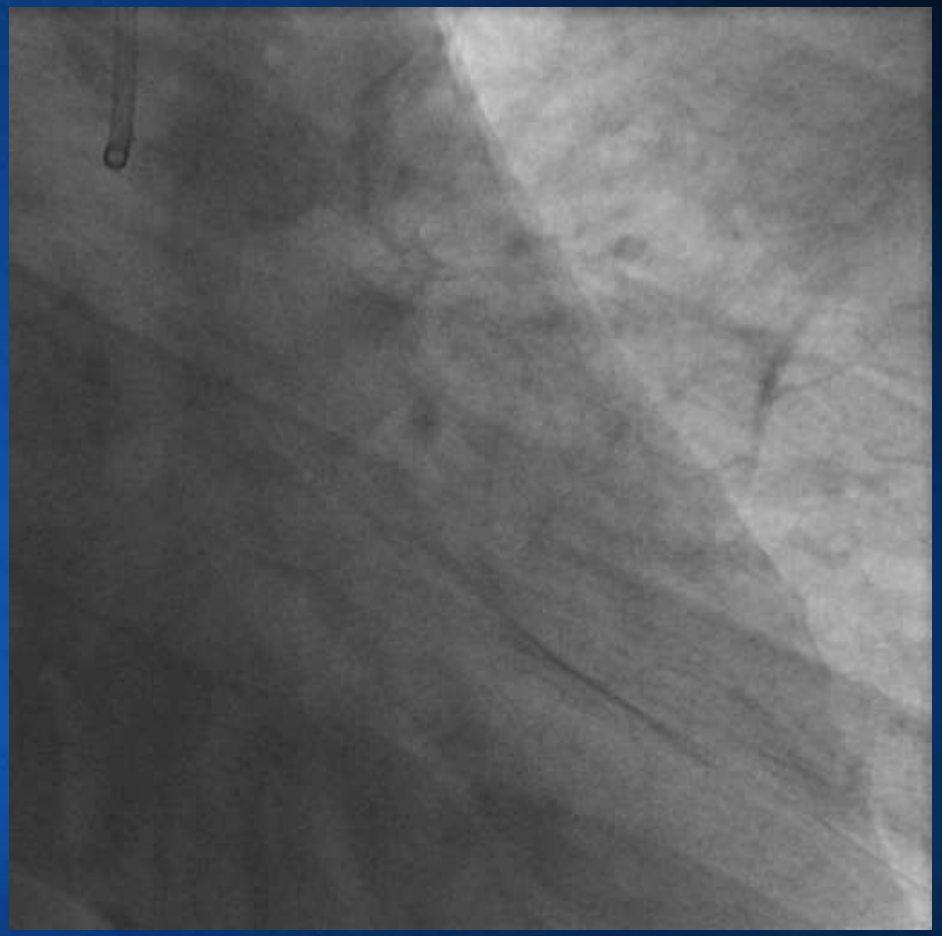



- Dx : ST elevation MI → Direct PCI : Aspirin 200mg, Clopidogrel 600mg

# Coronary Angiogram

3:52 AM



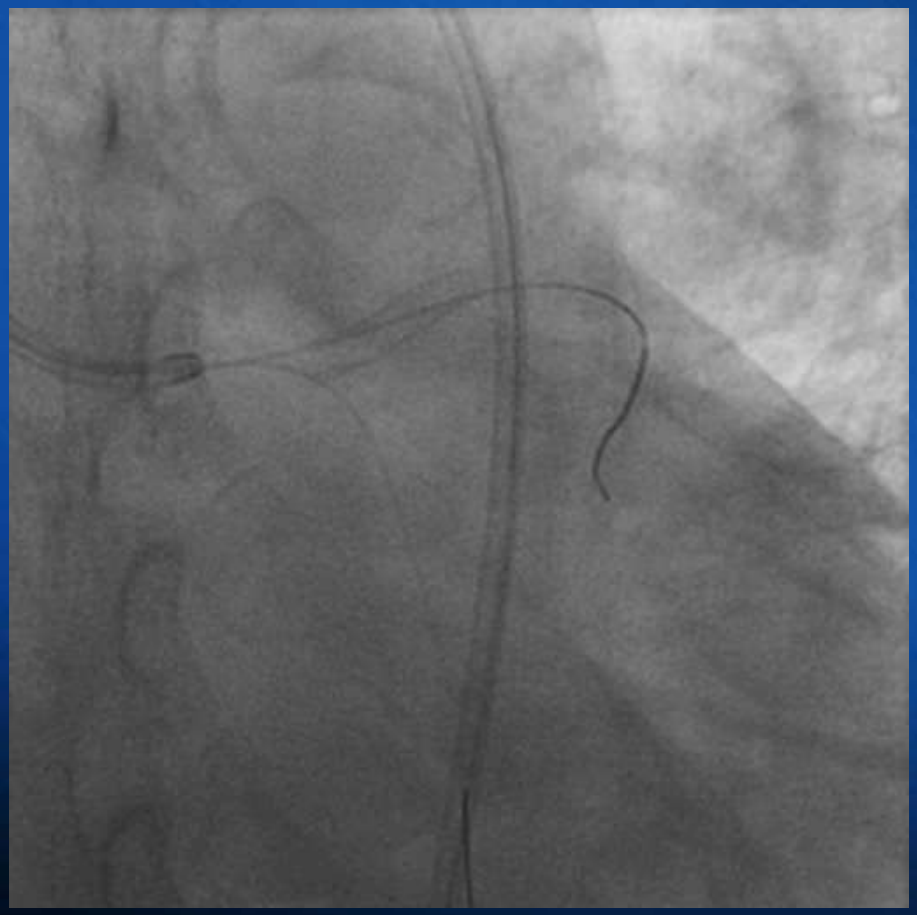


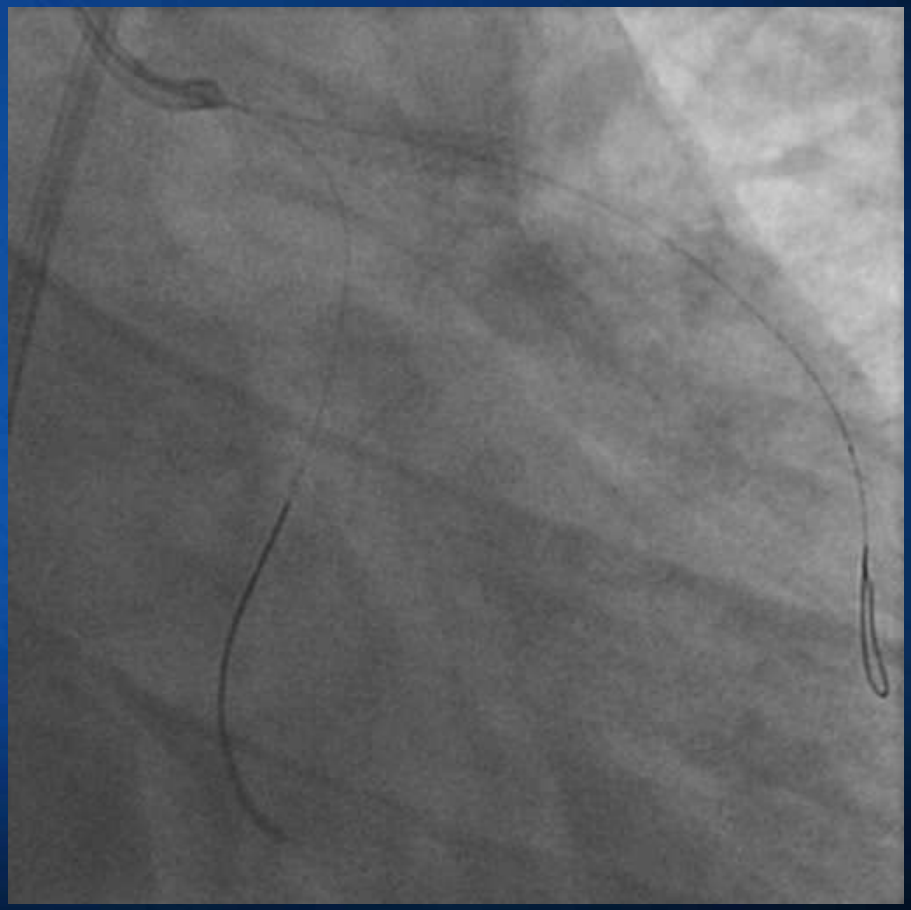
**Approach : Rt. CFA**

**LCA with JL 5-4 revealed total occlusion of pLAD (TIMI  0 flow).**

- Predilation with 2.5 x 15mm balloon (8atm)
- **Stent; 3.5 x 18mm Nobori stent (8atm)**
- **Post-dilation with 3.5mm-sized NC balloon (upto 18 atm)**

# Final CAG

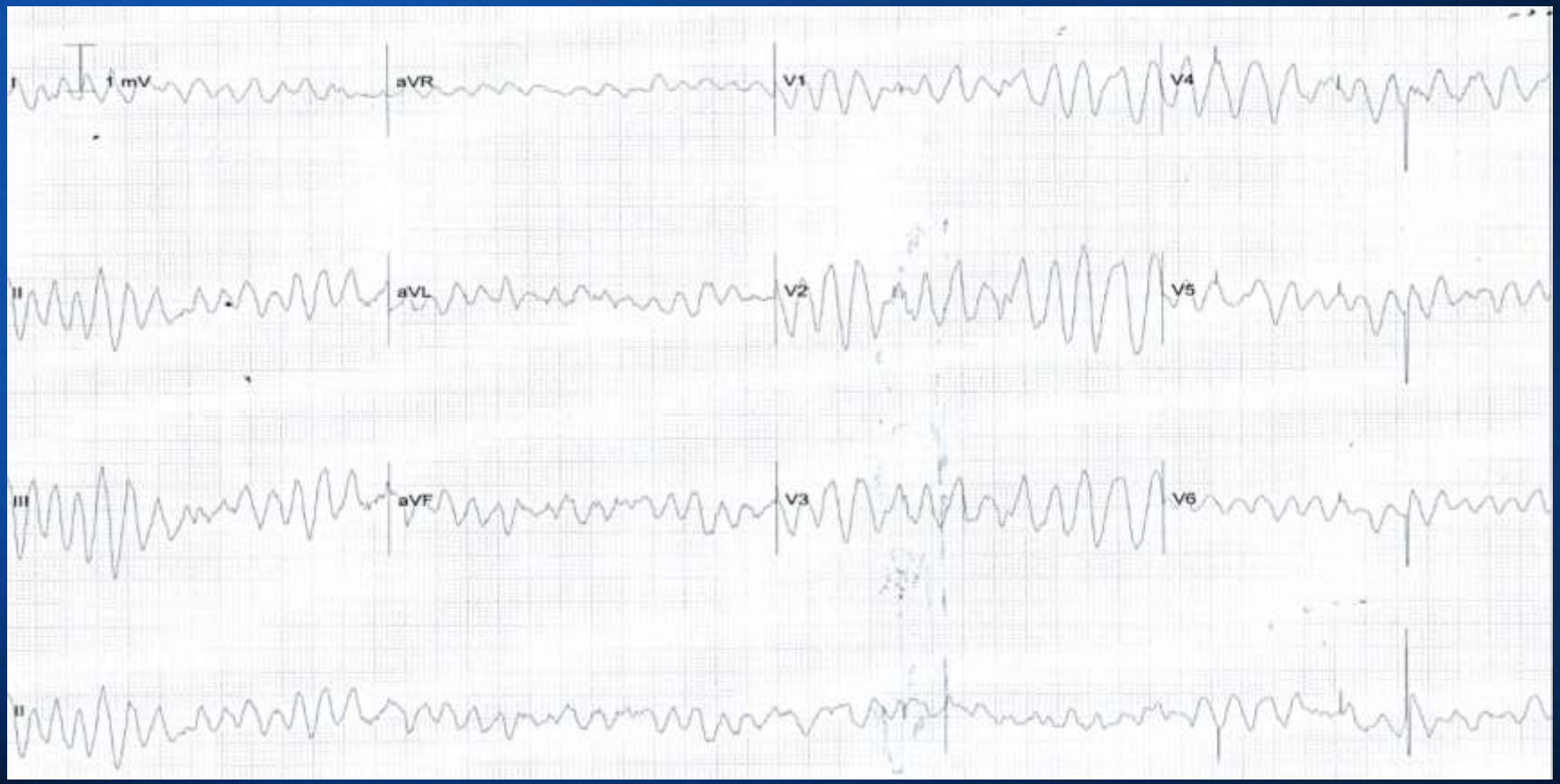




# Chest pain & repeated VT after PCI

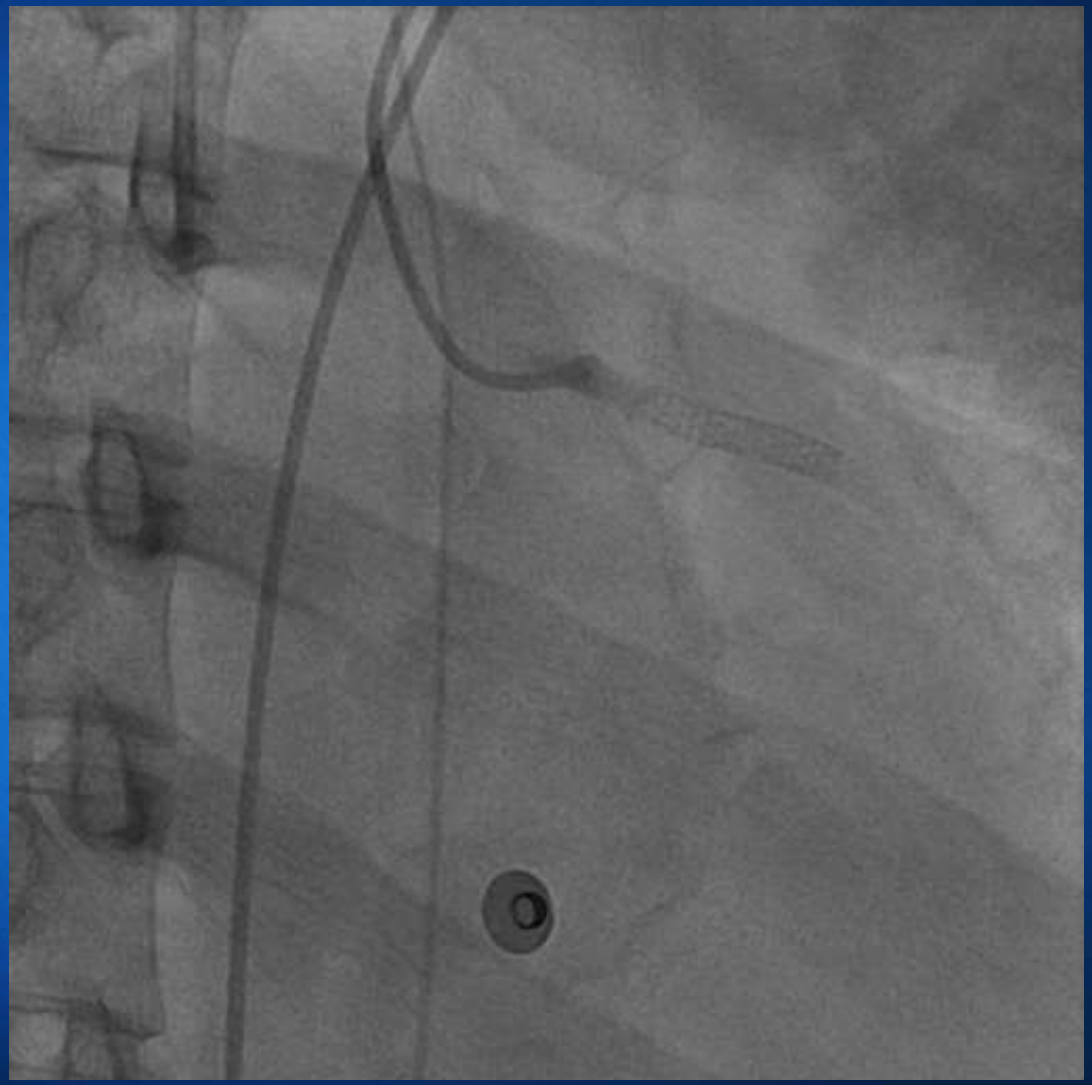
+ 1hr 4:40AM

- During CCU monitoring just after PCI, chest pain and dyspnea suddenly occurred.



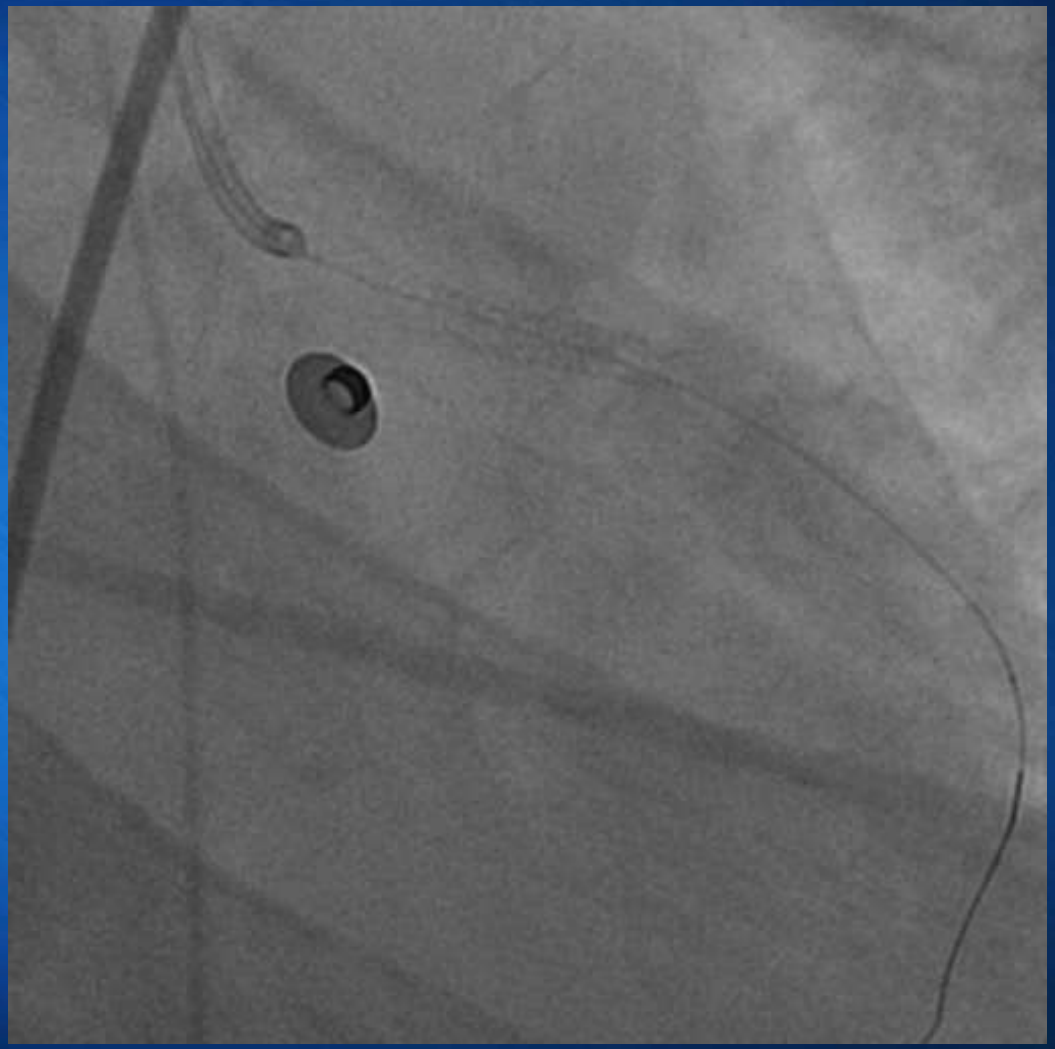

→ **Repeated defibrillation and CPR … Back-to cath room.**

# PCPS first, and then CAG followed up



LCA with JL 5-4 revealed total occlusion of pLAD stent

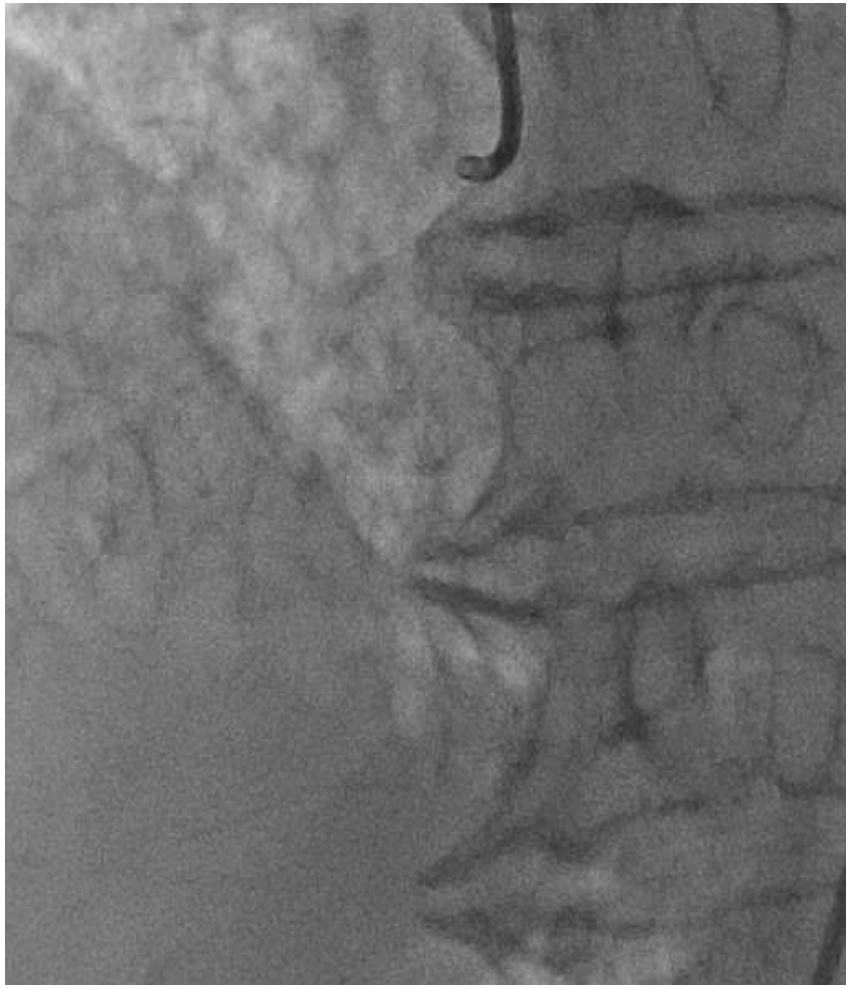
# Final CAG after suction & repeat ballooning

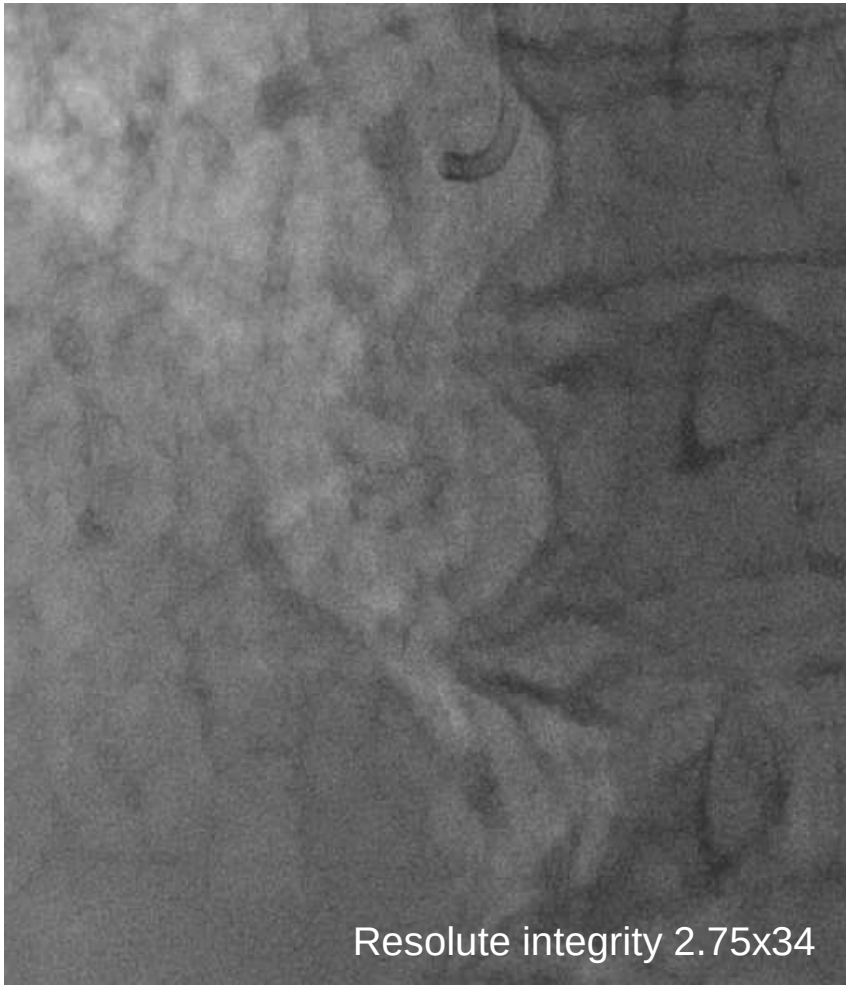


Thrombus aspiration was done 1 time (+ Red thrombi).
Ballooning : 3.5 x 15mm

# Case 2 M/76, Recent aggravated DOE

**DM, HTN, A Fib, Ex-smoker, PAOD → Dx: NSTEMI**

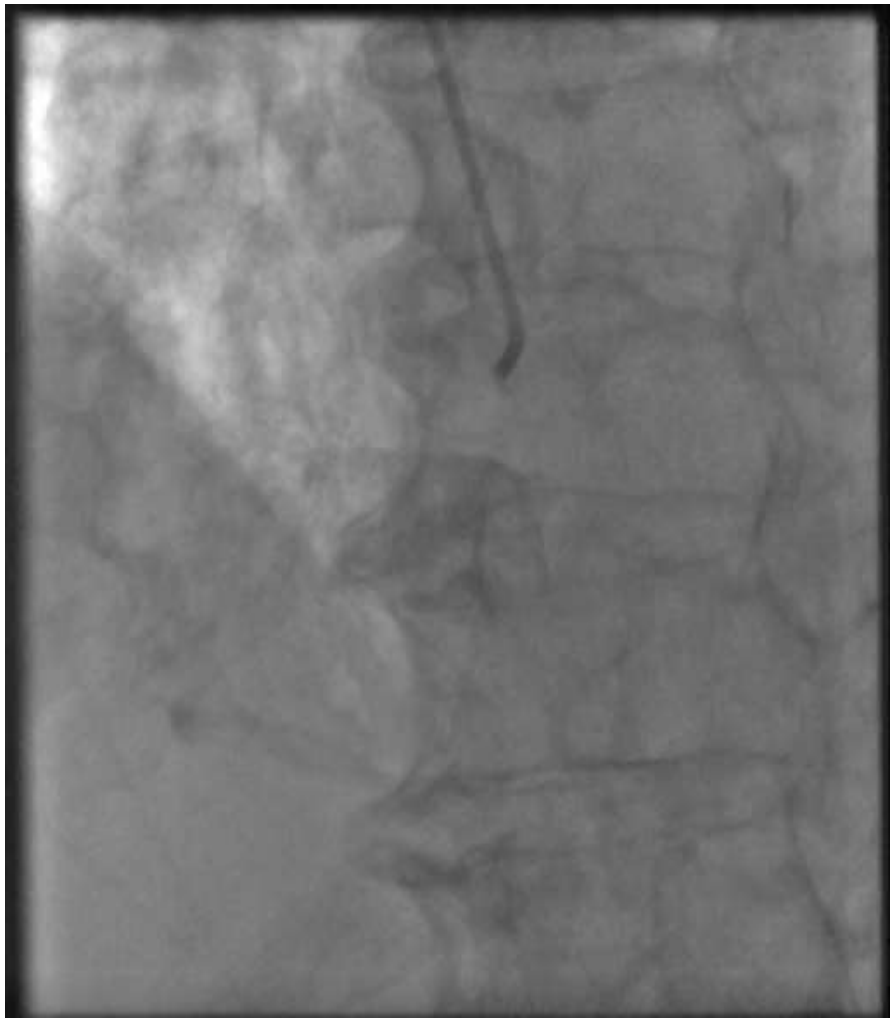


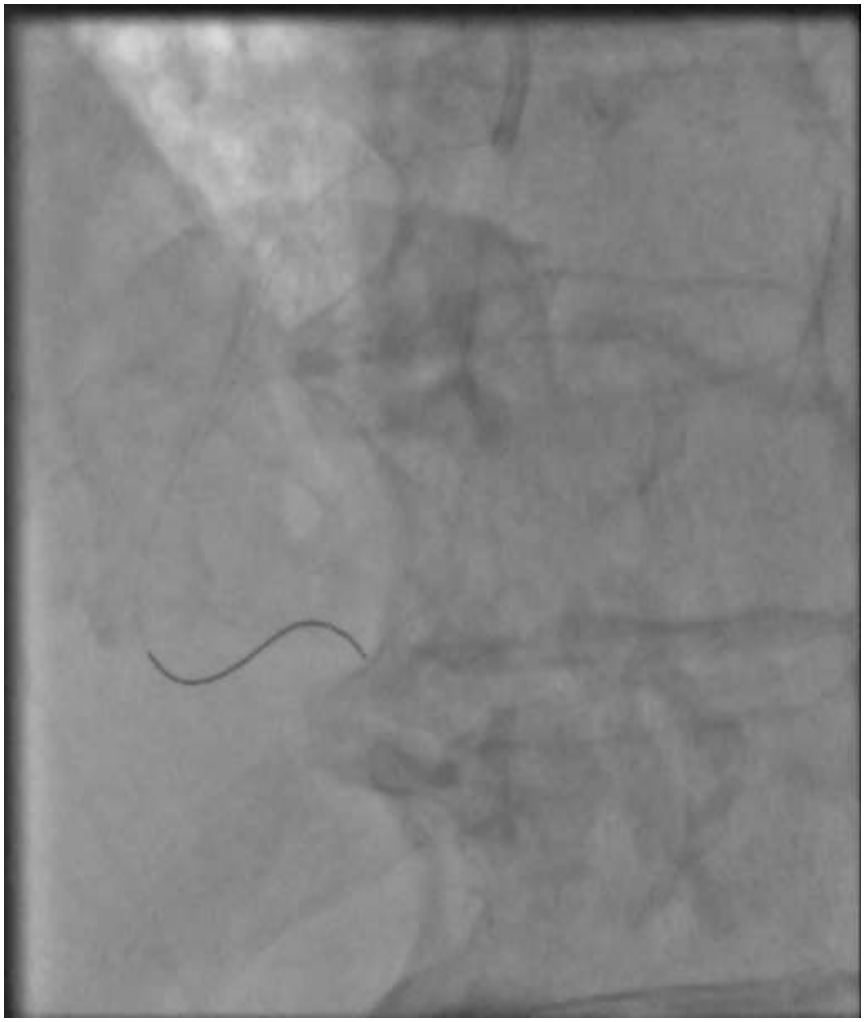



**Discharge medication**: Aspirin, Clopidogrel, Crestor, Exforge, Isoptin, Glupa

**Acute on-going chest pain occurred at home on discharge day**

**→ Visit ER presented as STEMI; *Subacute Stent thrombosis***

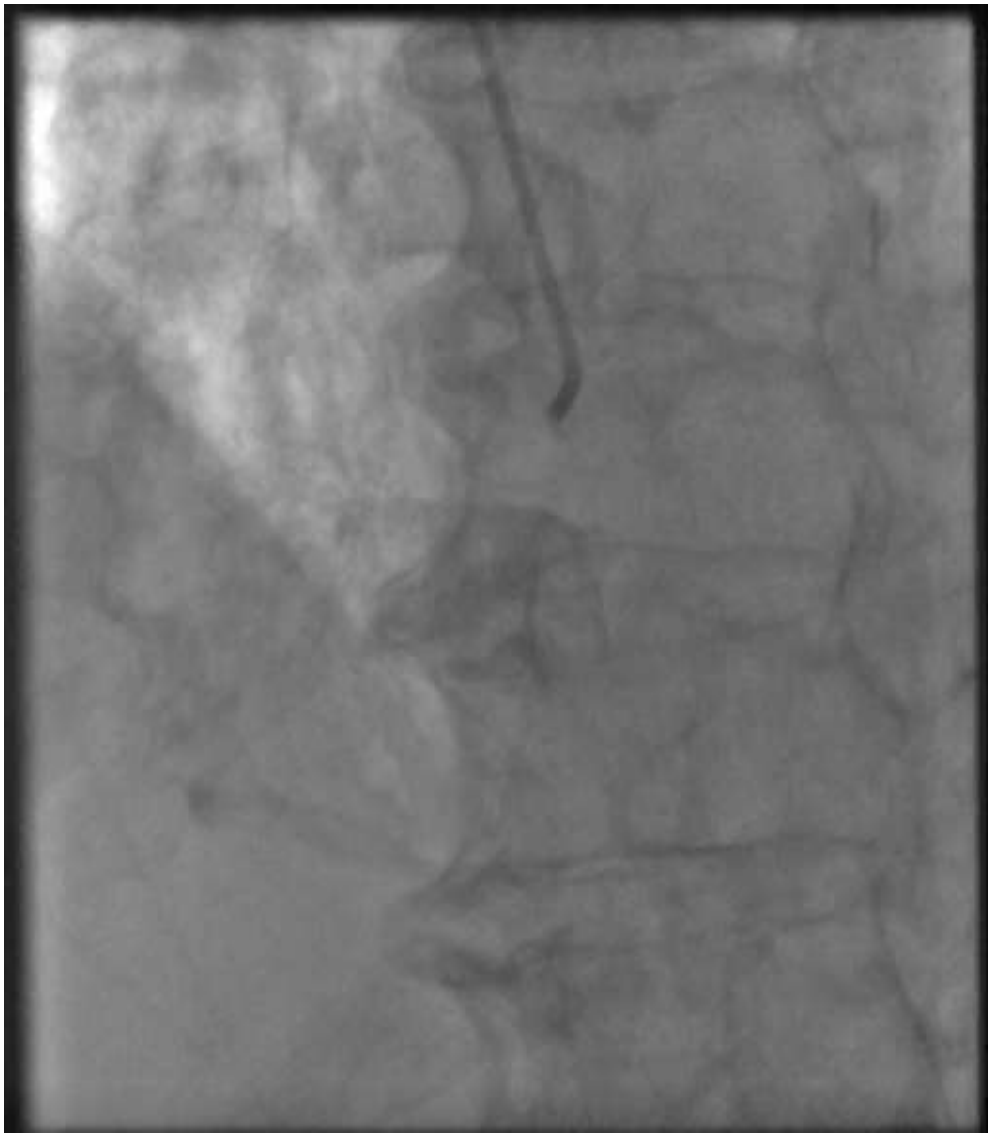




***Discharge with adding of coumadine***

**Recurred chest pain again … Revisit ER …**

**2nd Subacute Stent thrombosis 7 days later …**



# Causes for recurrent early ST and how to prevent ?

# Causes for Early ST in ACS?

- **Mechanical problems?**
  - → Case 1. 3.5mm-sized DES with high-pressure ballooning
  - → Case 2. Repeated ballooning by acute ST

  … Stent thrombosis less likely to have mechanical problems

  - ✓ *These means that **unmet needs still exist** and **other factors could be involved** in the occurrence of early ST in AMI.*
  - ✓ *… **not be reduced only by the changing of PCI strategy.***

# *How to prevent (or reduce) Early ST in patients with ACS?*

- → **Focus on platelets & thrombosis.**
- → **Focus on "New oral medication" in ACS patients after PCI**

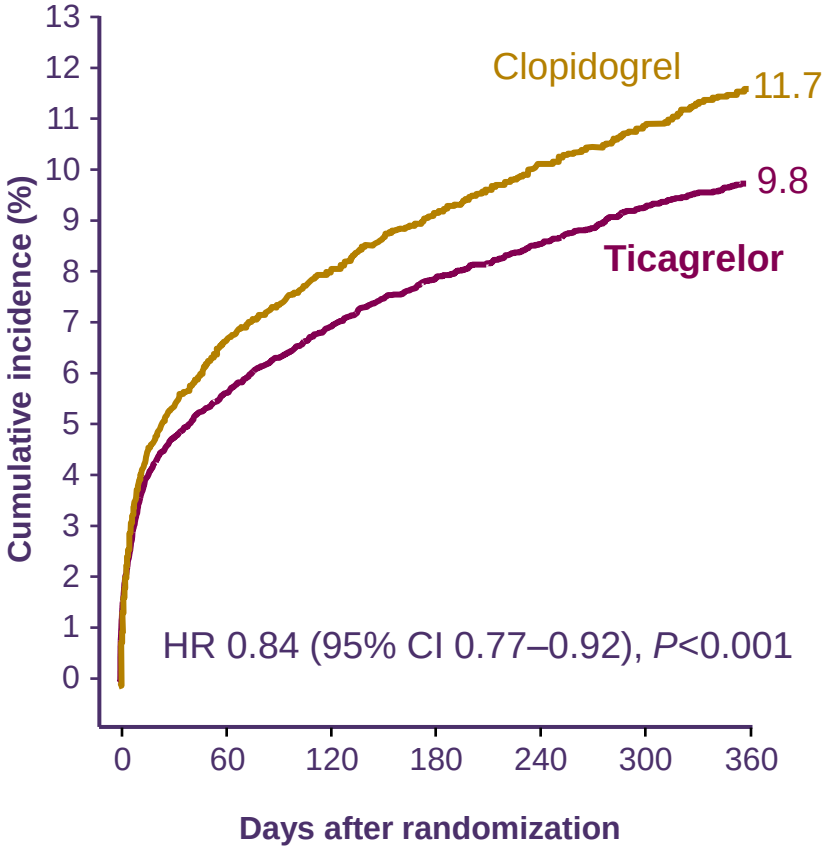
# 1. Ticagrelor

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

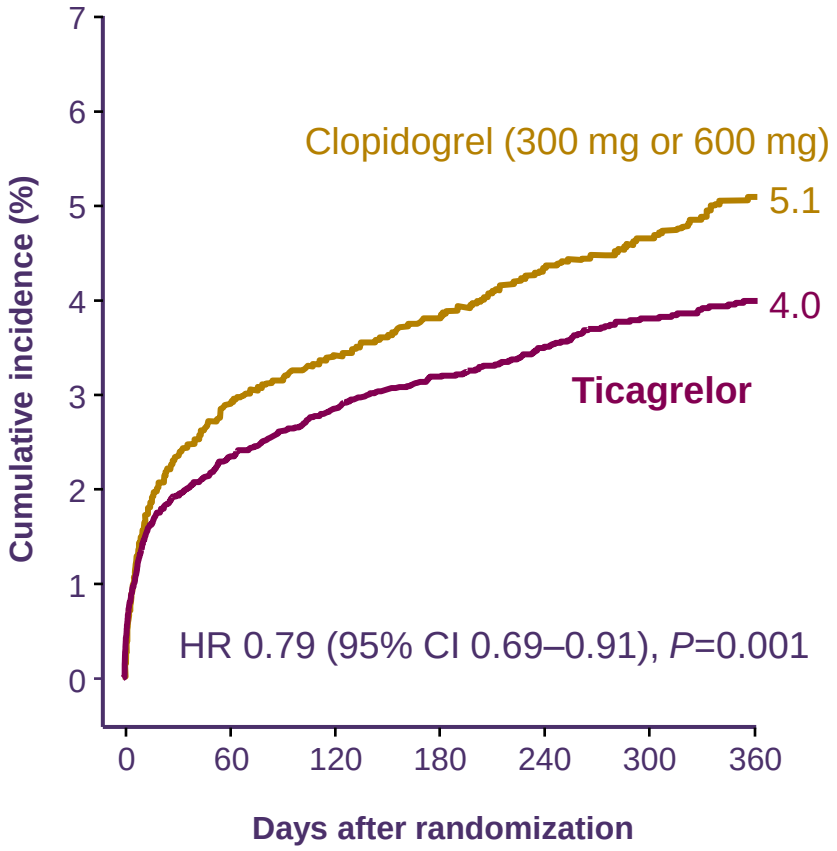
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

# PLATO

**Primary endpoint: time to CV death, MI or stroke**



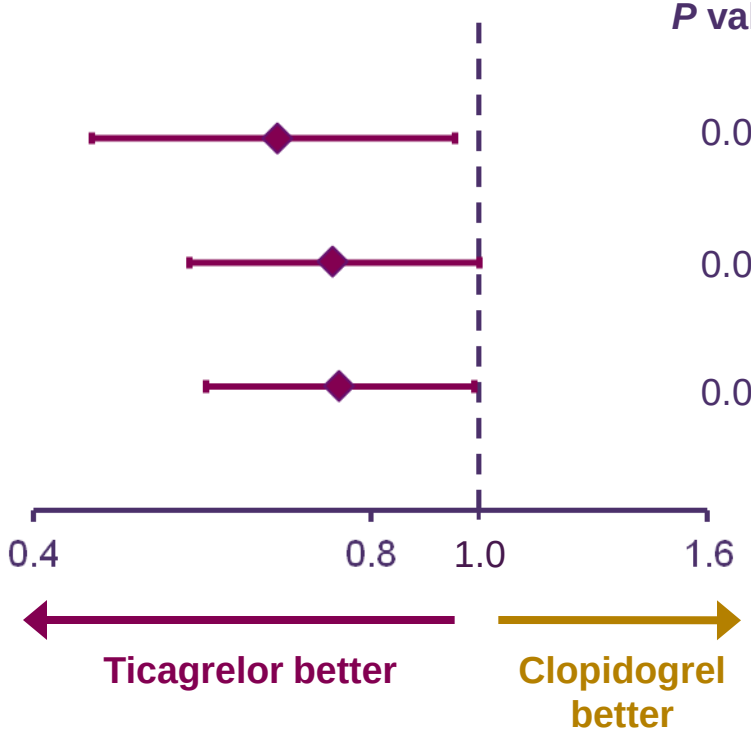

**Cardiovascular death at 12 months**




Wallentin L et al. N Engl J Med 2009;361:1045–1057

# PLATO STEMI substudy: stent thrombosis

| Stent thrombosis* | Ticagrelor (n=3752) | Clopidogrel (n=3792) | HR (95% CI) | *Nominal P* value |
|---|---|---|---|---|
| Definite† | 45 (1.6%) | **70 (2.4%)** | | 0.03 |
| Probable or definite† | 73 (2.6%) | **101 (3.4%)** | | 0.05 |
| Possible, probable or definite† | 90 (3.3%) | **122 (4.3%)** | | 0.04 |

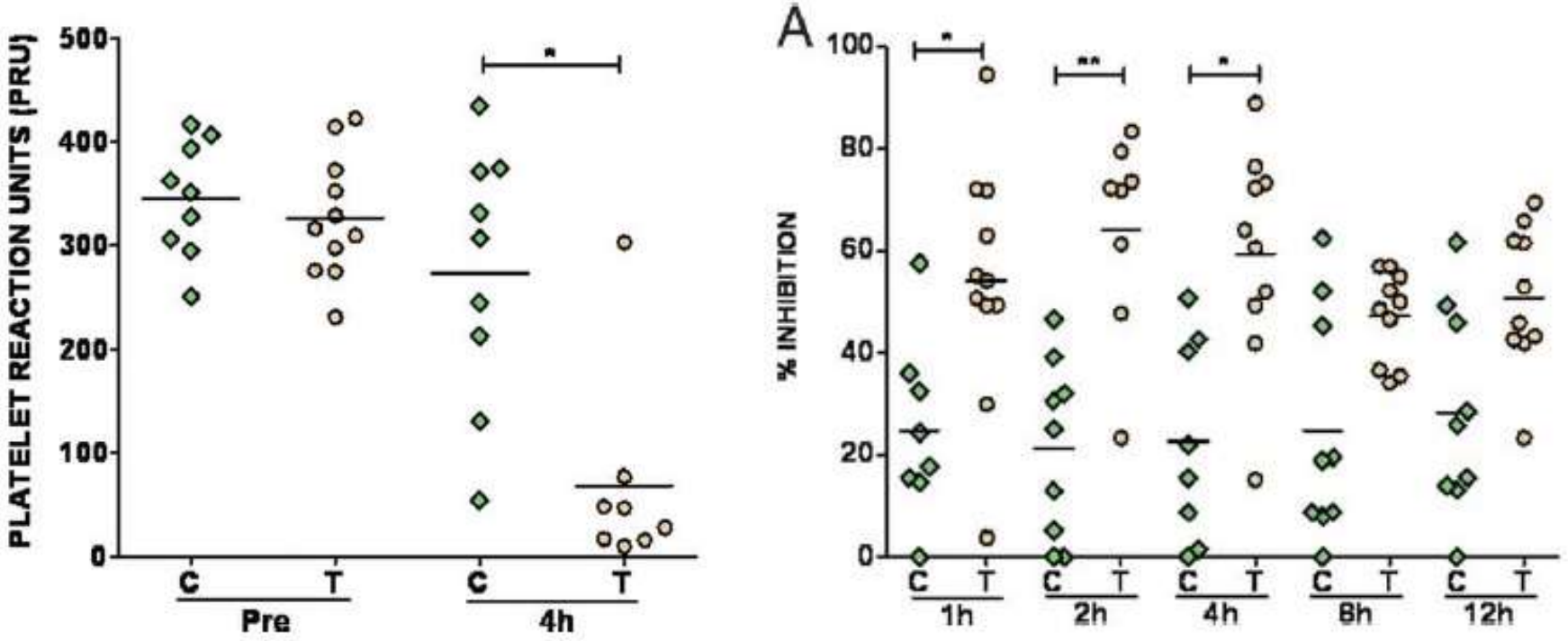



*As per Academic Research Consortium definitions
†Denominator is number of patients receiving at least one stent

# Inhibitory Effects of Ticagrelor Compared With Clopidogrel on Platelet Function in Patients With Acute Coronary Syndromes

RF. Storey, et al., ***J Am Coll Cardiol,*** 2010

Responses to Loading Doses of Clopidogrel and Ticagrelor




**Ticagrelor achieves greater antiplatelet effect than clopidogrel in patients with ACS, both in the first hours of treatment and during maintenance therapy**

# 2. NOAC, Rivaroxaban

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2012 VOL. 366 NO. 1

**ATLAS ACS 2 TIMI 51**

## Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Jessica L. Mega, M.D., M.P.H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., Deepak L. Bhatt, M.D., M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., Nancy Cook-Bruns, M.D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., Alexei N. Plotnikov, M.D., David Schneider, M.D., Xiang Sun, Ph.D., Freek W.A. Verheugt, M.D., and C. Michael Gibson, M.D., for the ATLAS ACS 2–TIMI 51 Investigators*

ABSTRACT

BACKGROUND

Acute coronary syndromes arise from coronary atherosclerosis with superimposed thrombosis. Since factor Xa plays a central role in thrombosis, the inhibition of factor Xa with low-dose rivaroxaban might improve cardiovascular outcomes in patients with a recent acute coronary syndrome.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 15,526 patients with a recent acute coronary syndrome to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke.

RESULTS

Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (hazard ratio in the rivaroxaban group, 0.84; 95% confidence interval [CI], 0.74 to 0.96; P=0.008), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs. 10.7%, P=0.02) and the twice-daily 5-mg dose (8.8% vs. 10.7%, P=0.03). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, P=0.002) and from any cause (2.9% vs. 4.5%, P=0.002), a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting (2.1% vs. 0.6%, P<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, P=0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%, P=0.66) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs. 0.4%, P=0.04).

CONCLUSIONS

In patients with a recent acute coronary syndrome, rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. (Funded by Johnson & Johnson and Bayer Healthcare; ATLAS ACS 2–TIMI 51 ClinicalTrials.gov number, NCT00809965.)

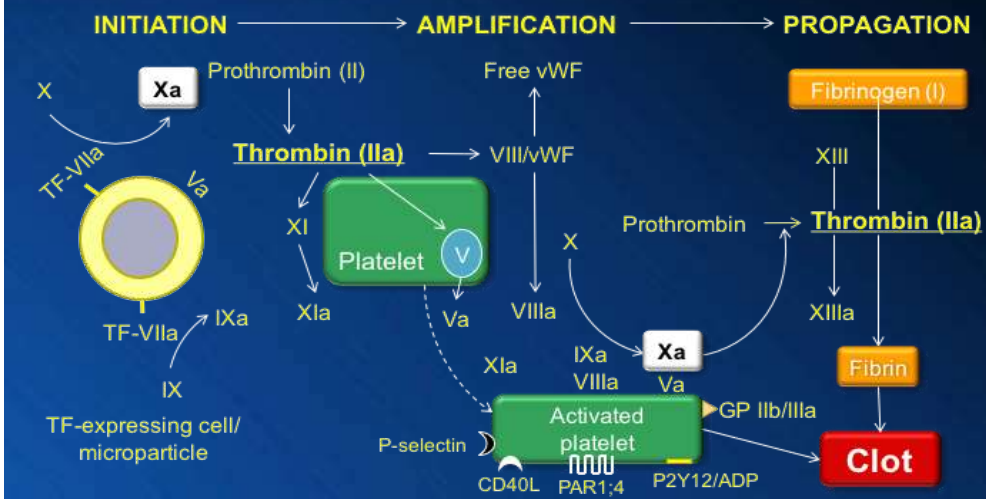
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Mega at the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at jmega@partners.org.

*Investigators in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1112277) was published on November 13, 2011, at NEJM.org.

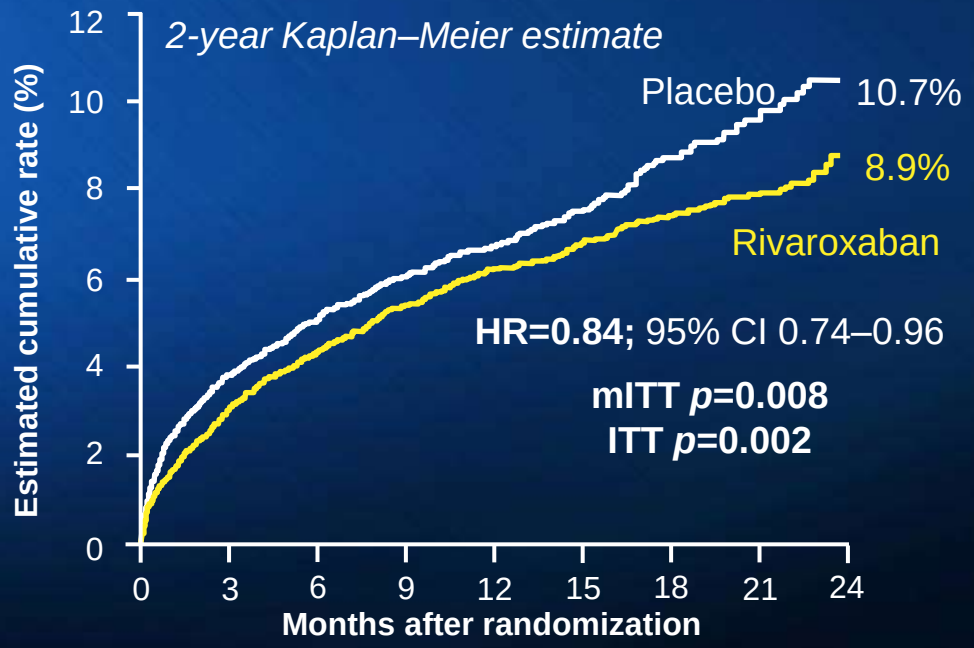
N Engl J Med 2012;366:9-19.





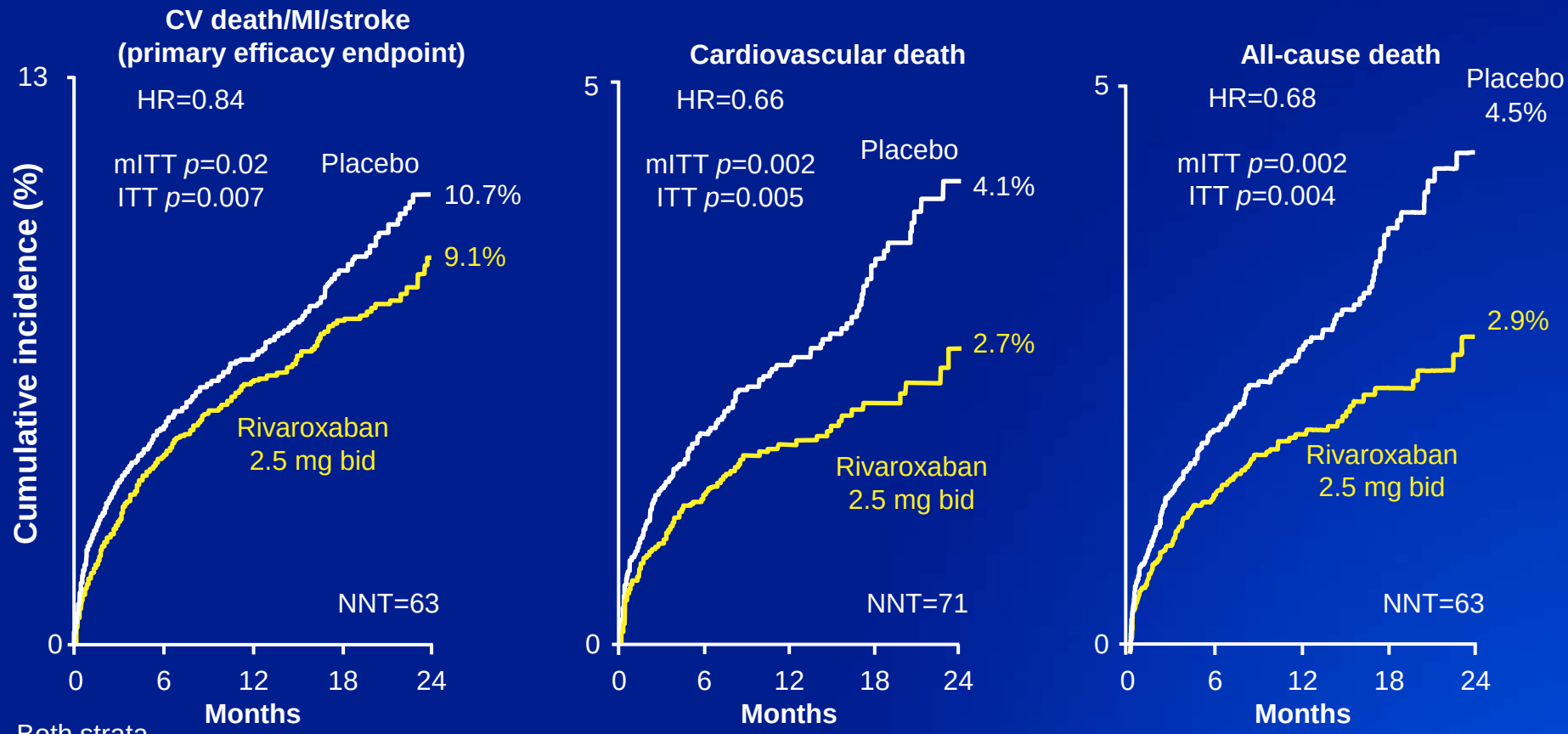

ADP, adenosine diphosphate; GP, glycoprotein; PAR, protease-activated receptor; TF, tissue factor; vWF, von Willebrand factor.
De Caterina *et al. Thromb Haemost* 2013;109:569–79.

## Primary endpoint ; CV death/ MI/ stroke



# ATLAS ACS 2 TIMI 51: **rivaroxaban 2.5 mg bid significantly reduced CV events and death**

## The primary efficacy endpoint reduction was driven by reduced mortality




Both strata.

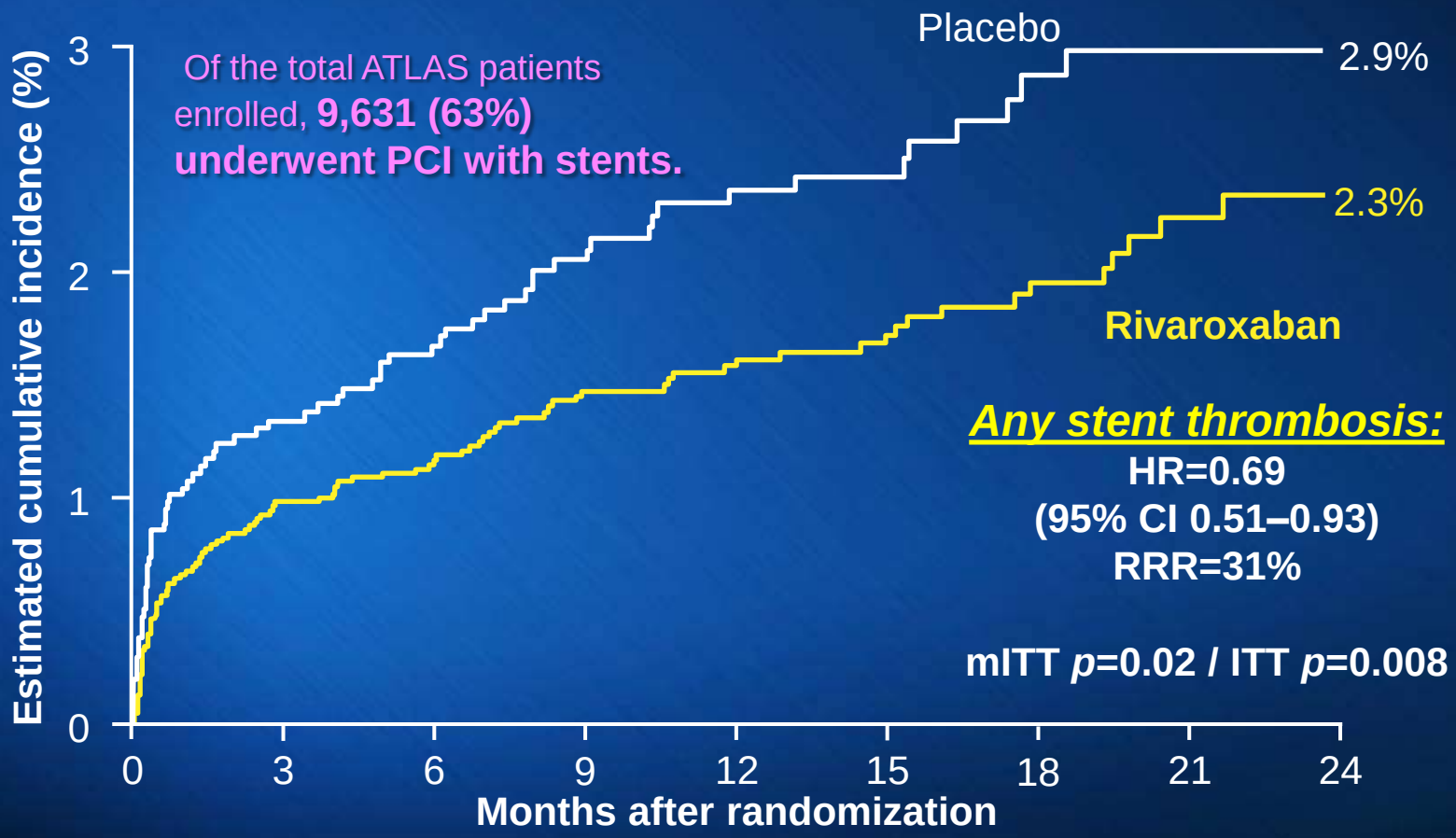
bid, twice daily; CV, cardiovascular; HR, hazard ratio; ITT, intention to treat; MI, myocardial infarction; mITT, modified intention to treat; NNT, number needed to treat.

1. Mega *et al. N Engl J Med* 2012;366:9–19; 2. Gibson *et al.* AHA 2011 (www.clinicaltrialresults.org).

# ATLAS ACS 2 TIMI 51: rivaroxaban significantly reduced stent thrombosis

**Combined rivaroxaban doses, both strata**

**2-year Kaplan–Meier estimate**




***Any stent thrombosis:***

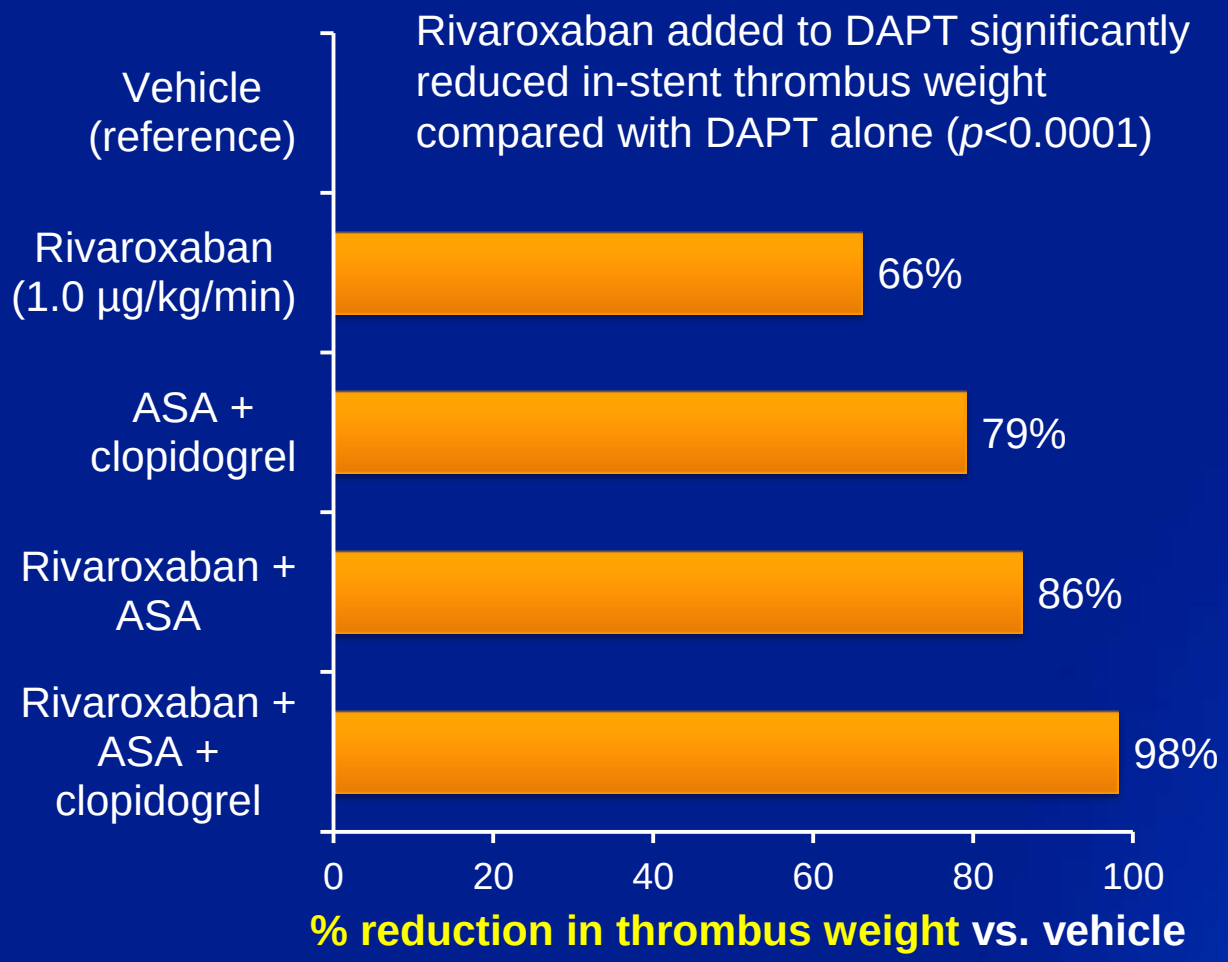
**HR=0.69**
**(95% CI 0.51–0.93)**
**RRR=31%**

**mITT *p*=0.02 / ITT *p*=0.008**

*Stent thrombosis events: definite, probable or possible (Academic Research Consortium [ARC] definitions).
CI, confidence interval; HR, hazard ratio; ITT, intention to treat; mITT, modified intention to treat; RRR, relative risk reduction.

1. Gibson *et al. J Am Coll Cardiol* 2013;62:286–90.

# Porcine experimental ST model shows that oral anticoagulant rivaroxaban with DAPT reduces ST





**Photomicrograph showing stent and corresponding porcine aortic strip**

ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy (ASA + clopidogrel).

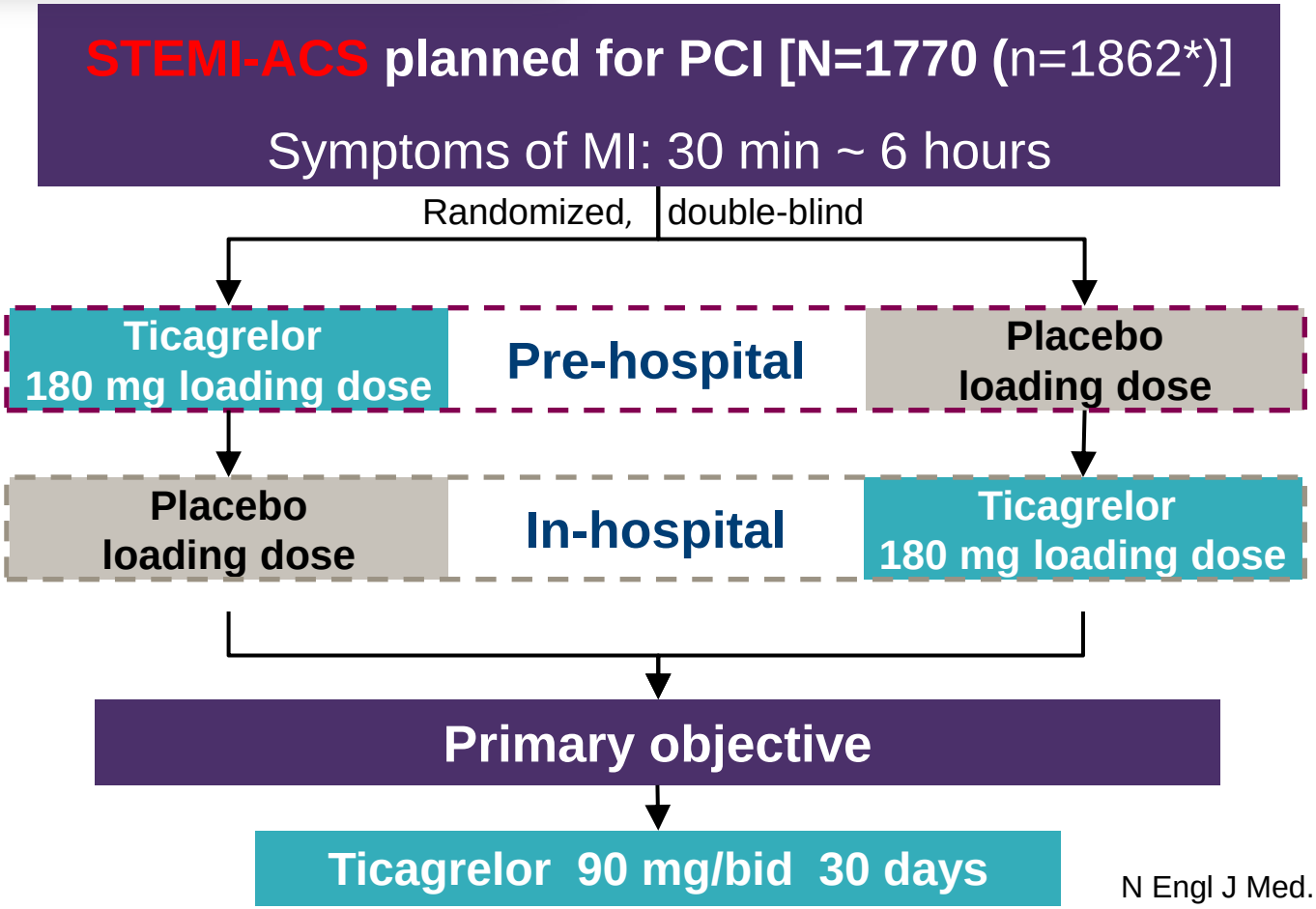
1. Becker *et al. J Thromb Haemost* 2012;10:2470–80.

# 3. A more faster drug-loading can reduce ST in AMI ?

**ATLANTIC**

Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery

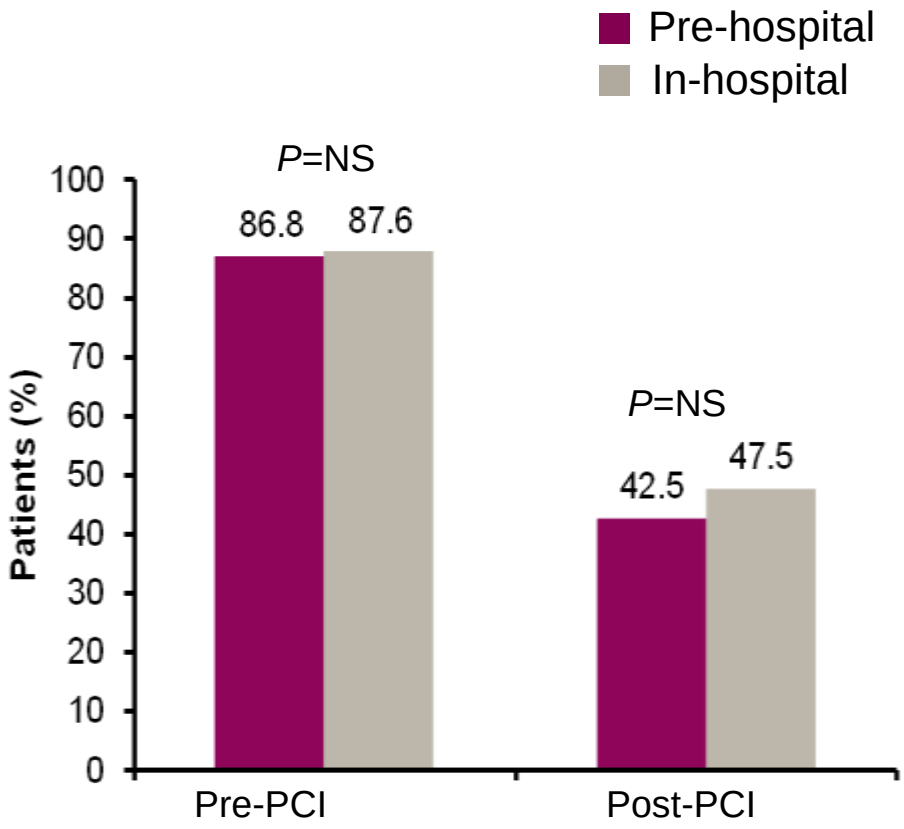
Pre-hospital P2Y12 receptor antagonist can reduce MACE in STEMI ?



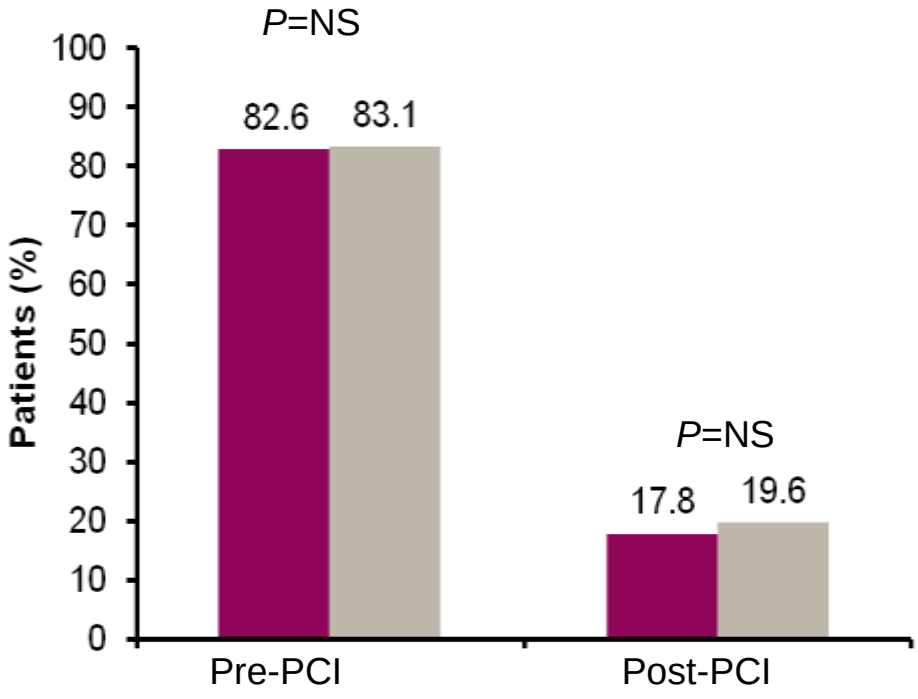

N Engl J Med. 2014;371:1016-27.

# Primary endpoints

## 1. Absence of ST-segment elevation ≥70%

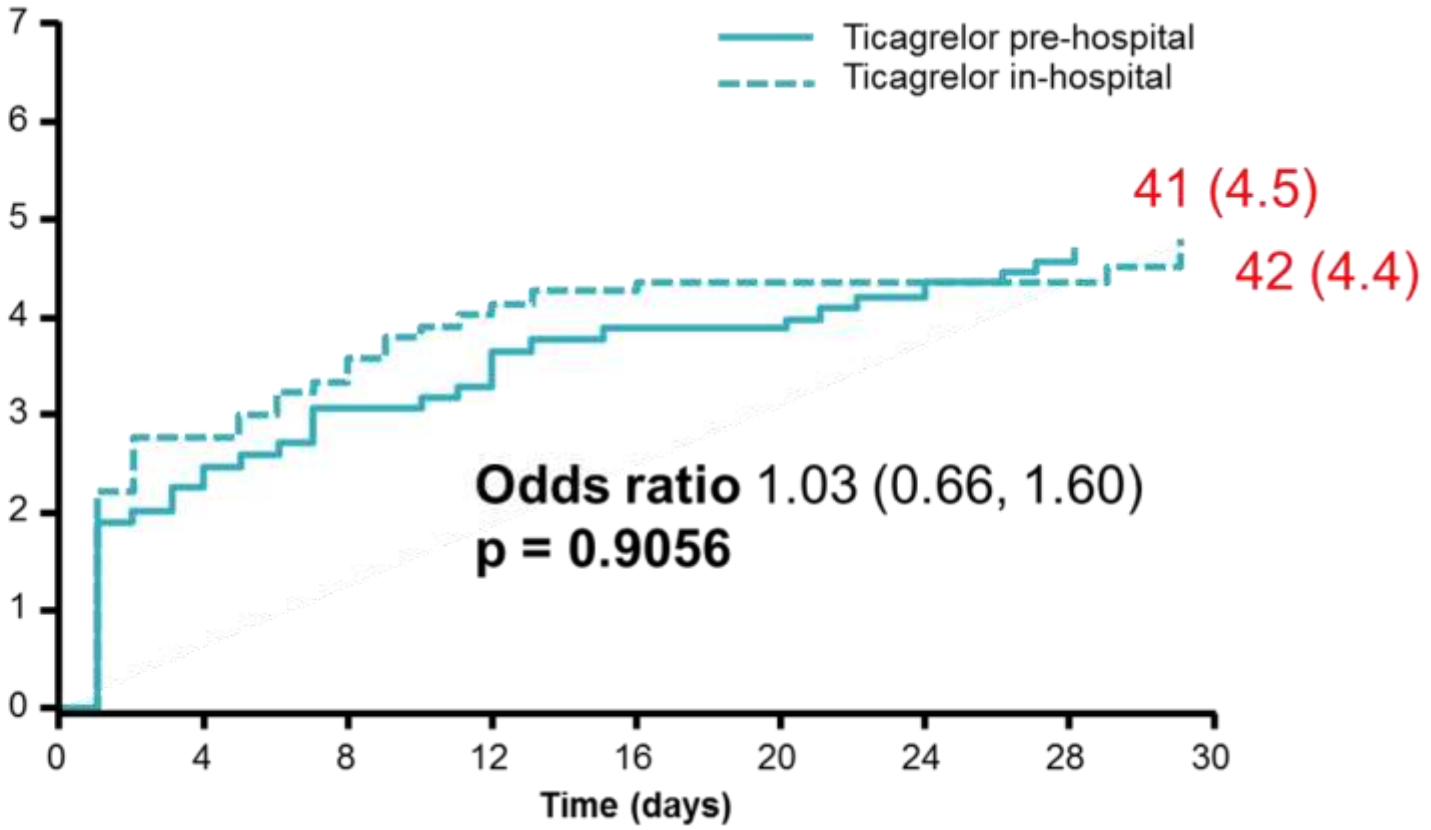



## 2. Absence of TIMI flow 3 in infarct-related artery



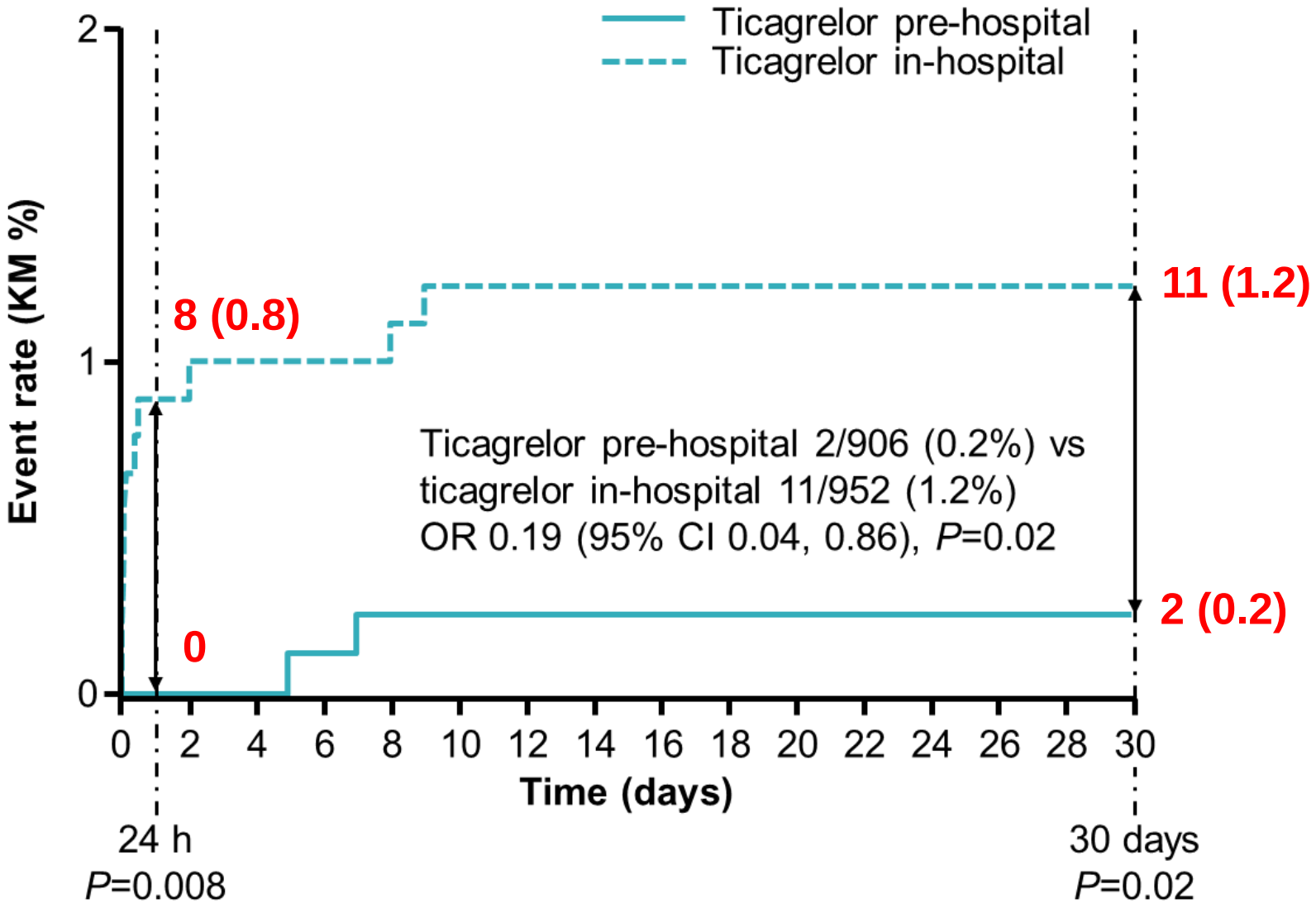
# Composites Endpoints at 30 days

Death/MI/stroke/ urgent revascularization/ definite acute stent thrombosis



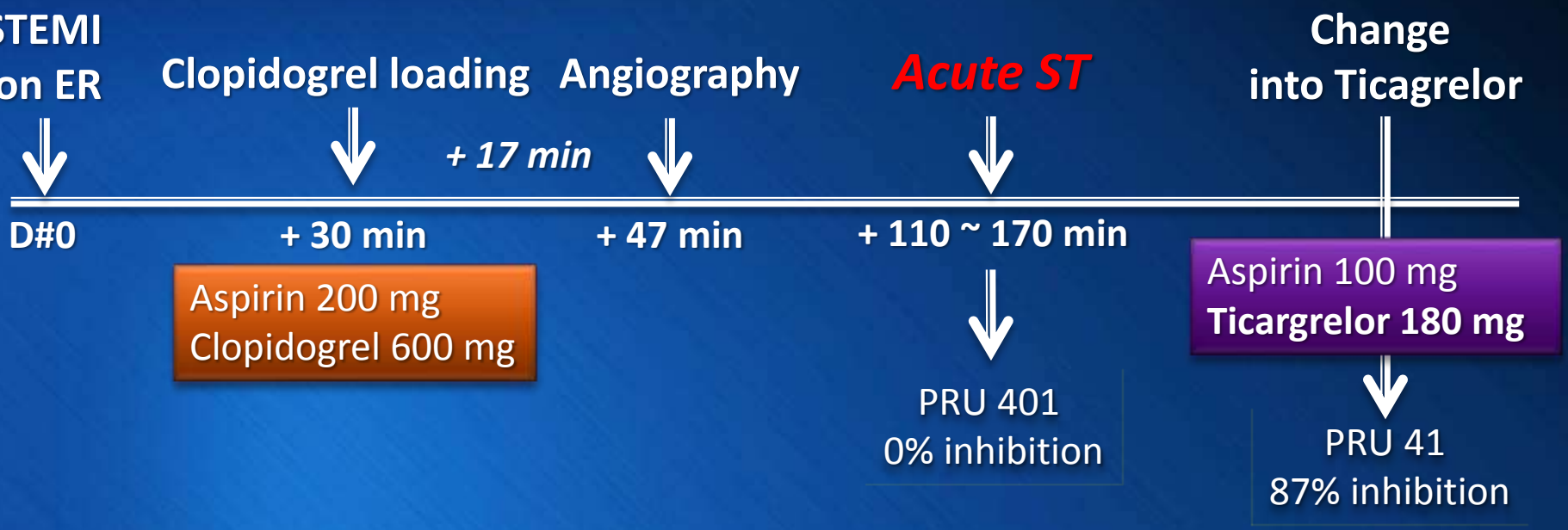
# Definite Stent Thrombosis (ST) for 30 days

– Definite ST occurred less frequently in the pre-hospital arm (0% vs 0.8% in the first 24 hours; 0.2% vs 1.2% at 30 days)



# Review of 2 cases

*Case 1.*



# Review of two cases

## Case 1.

STEMI on ER → Clopidogrel loading → (+ 17 min) Angiography → Acute ST → Change into Ticagrelor

D#0 → + 35 min → + 47 min → + 110 ~ 170 min

- + 35 min: Aspirin 200 mg, Clopidogrel 600 mg
- + 110 ~ 170 min: PRU 401, 0% inhibition
- Change into Ticagrelor: Aspirin 100 mg, **Ticargrelor 180 mg** → PRU 41, 87% inhibition

Initial pre-hospital ticagrelor loading?

## Case 2.

NSTEMI, AF → Discharge → 1st ST → 2nd ST

D#0 → … months

- Aspirin 100 mg, Clopidogrel 75 mg
- Clopidogrel 75 mg, Warfarin 2.5 mg
- Aspirin 100 mg, **Prasugrel 10 mg** → PRU 476, 0% inhibition → **Change** into Ticagrelor
- Aspirin 100 mg, **Ticargrelor 180 mg** → PRU 349, 10% inhibition

or **Use of rivaroxaban**

**Question;**

✓ ***Early ST prevented by these ?***

# Summary

- The **mechanism of early ST** might **differ according to the clinical presentation.**

  → suggesting that the **different strategy for the prevention of ST would be needed.**

- As for **"early ST in patients with ACS",** the roles of **1) new anti-platelet agent (ticagrelor), 2) NOAC (rivaroxaban), and 3) pre-hospital drug loading** should be investigated in the future.


Thank you
for your attention
연세대학교 의료원
YONSEI UNIVERSITY HEALTH SYSTEM