Residual ischemic and Benefit of prolonged DAPT; Update lasts clinical trials

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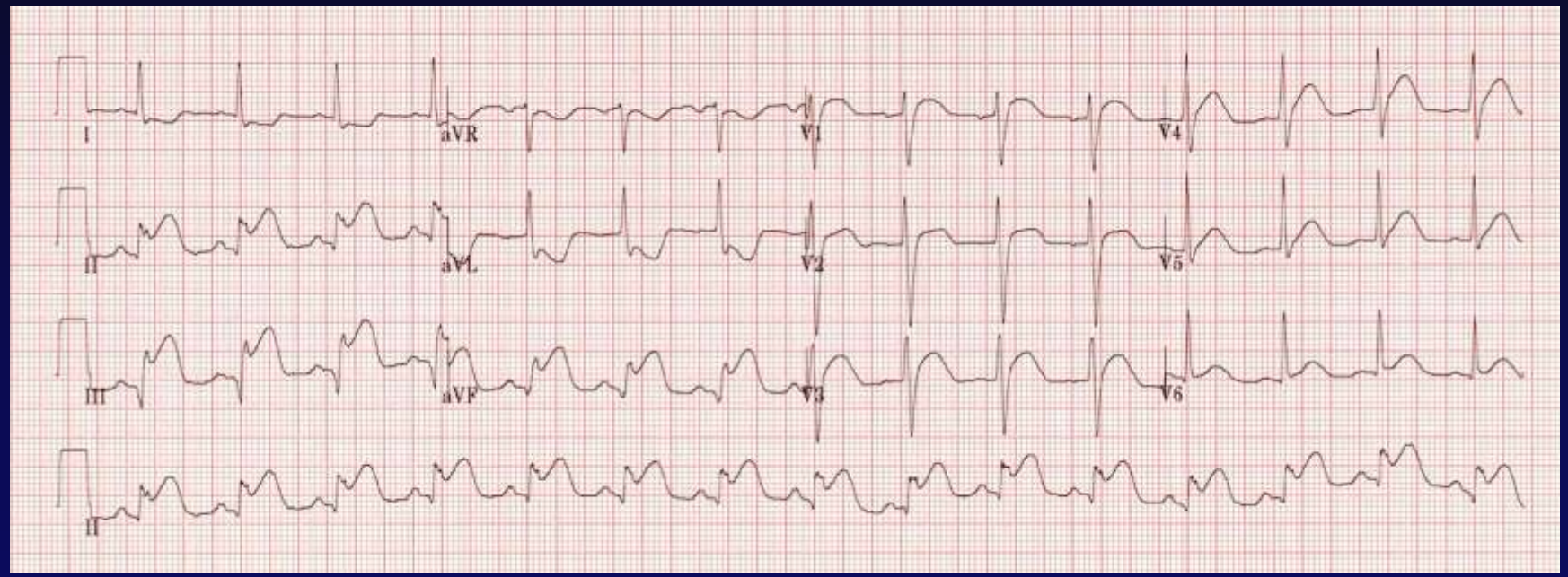
A young Korean male in 21st century

41-year old male,

History of intermittent chest pain

Severe, continuous chest pain since noon

ECG at admission



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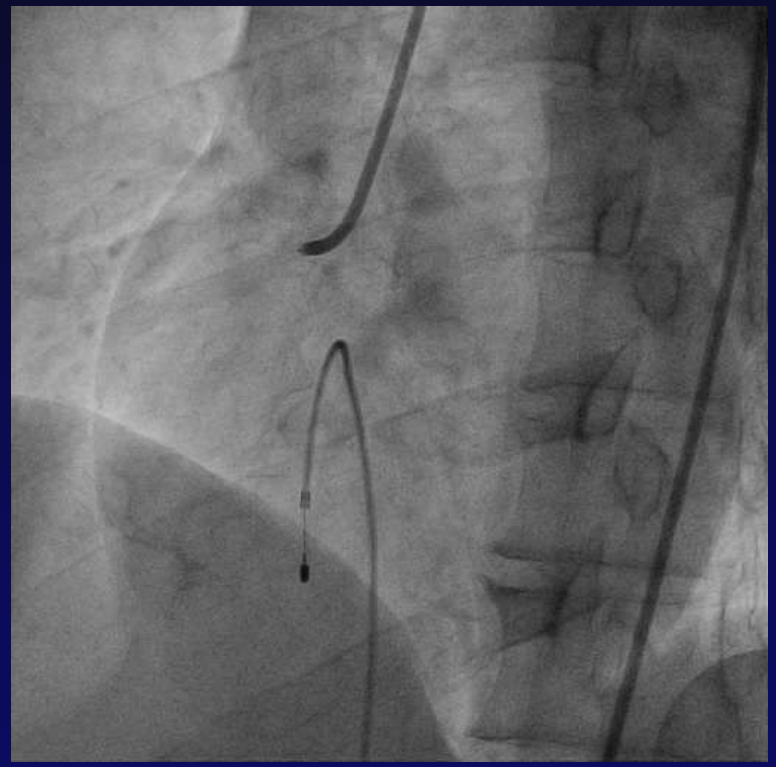
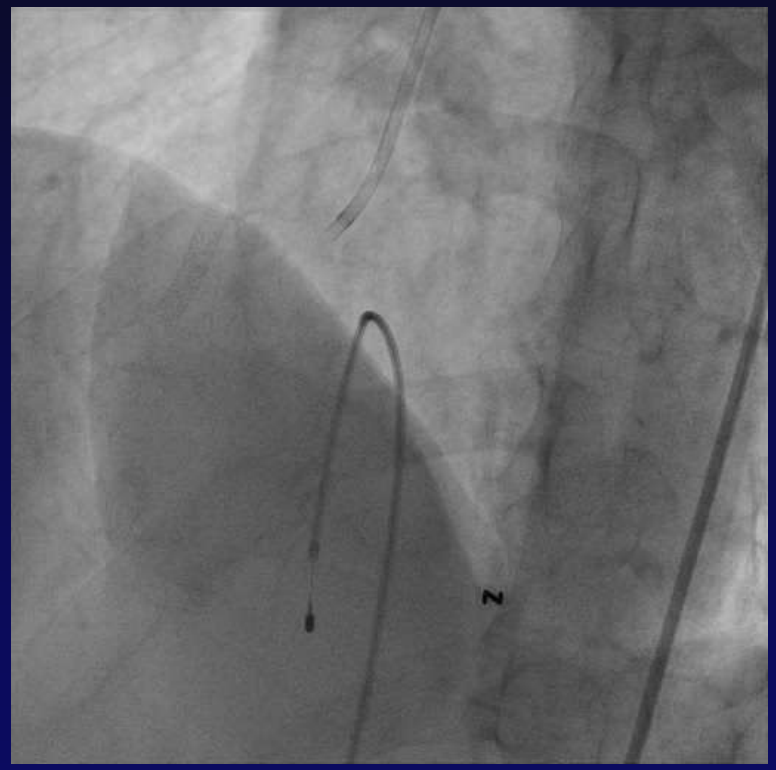


After PCI



Optimal medical therapy

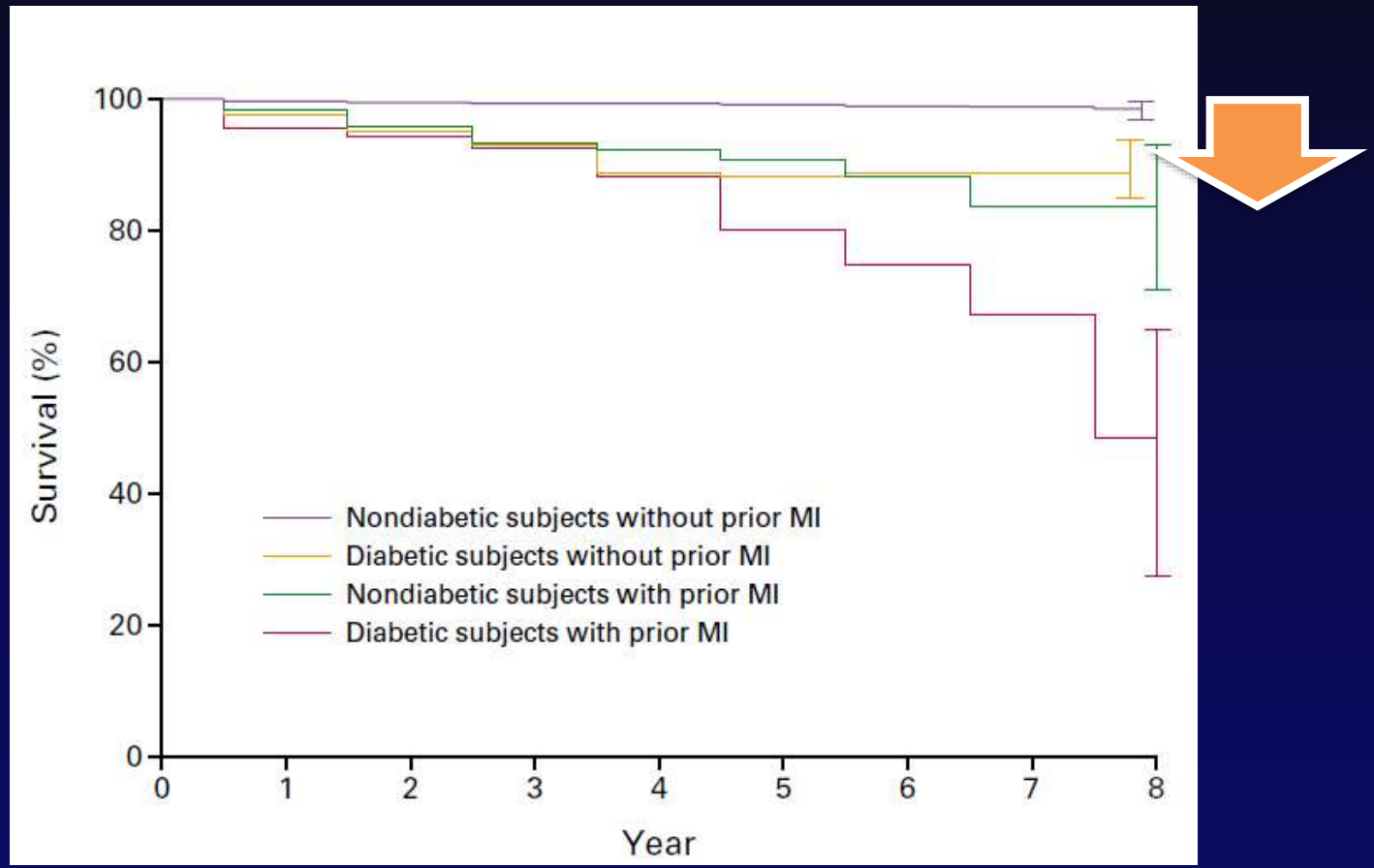
1. Newer generation of stents and improved techniques
2. New antiplatelet agents
3. Beta-blockers, ACEi/ARBs
4. Statins, ezetimibe, PCSK9-I

We may have stabilized the patients,

but are they really stable?

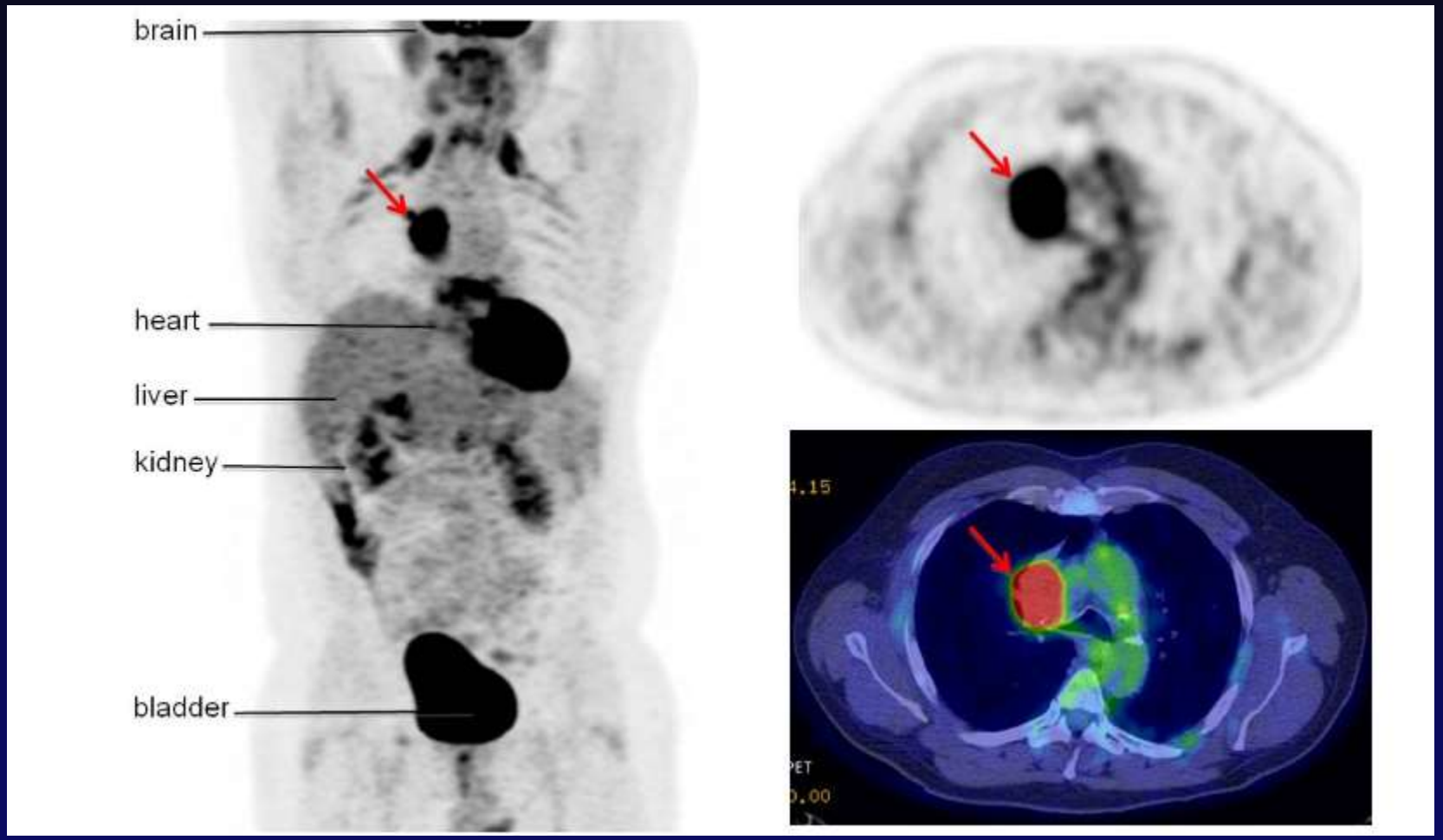
DM as risk factor for worse clinical outcome after AMI

"DM is CAD equivalent"



Haffner et al, NEJM 2001

Have you heard of stable lung cancer?



CONTENTS

Outcome of ST

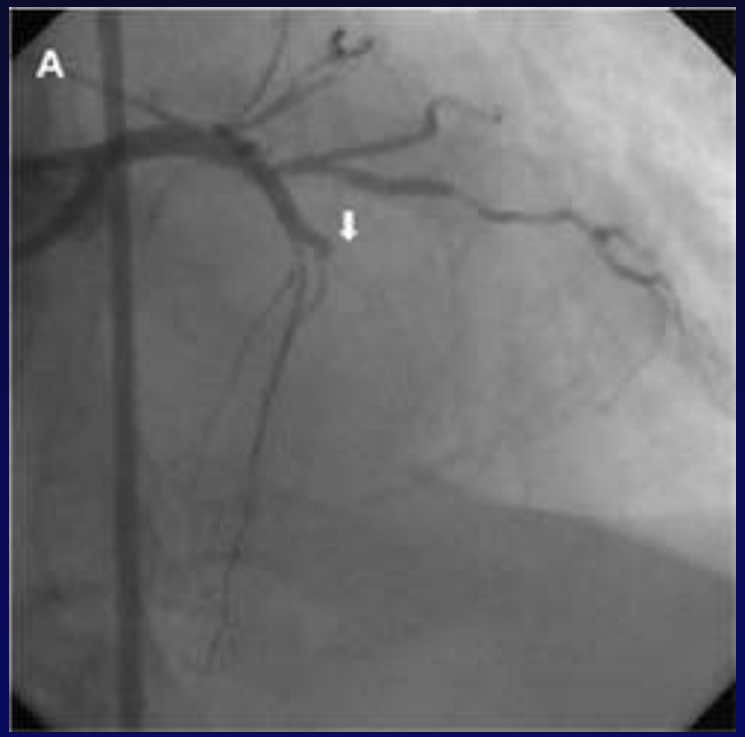


Table 3. Clinical Outcomes in Patients after Definite or Probable Stent Thrombosis.*

Variable	Sirolimus-Stent Trials		Paclitaxel-Stent Trials	
	Sirolimus Stent (N=13)	Bare-Metal Stent (N=15)	Paclitaxel Stent (N=22)	Bare-Metal Stent (N=18)
	no. of events (%)			
Death	4 (30.8)	5 (33.3)	7 (31.8)	5 (27.8)
Myocardial infarction				
Any event	13 (100)	13 (86.7)	17 (77.3)	14 (77.8)
Fatal event	4 (30.8)	4 (26.7)	4 (18.2)	3 (16.7)
Q-wave	8 (61.5)	5 (33.3)	7 (31.8)	5 (27.8)
Non–Q-wave	5 (38.5)	9 (60.0)	10 (45.5)	10 (55.6)

* The definition of definite or probable stent thrombosis is based on criteria set by the Academic Research Consortium (ARC). One patient with a bare-metal stent had both Q-wave and non–Q-wave myocardial infarctions at different times.

Mauri L et al. NEJM 2007, 356:1020-1029

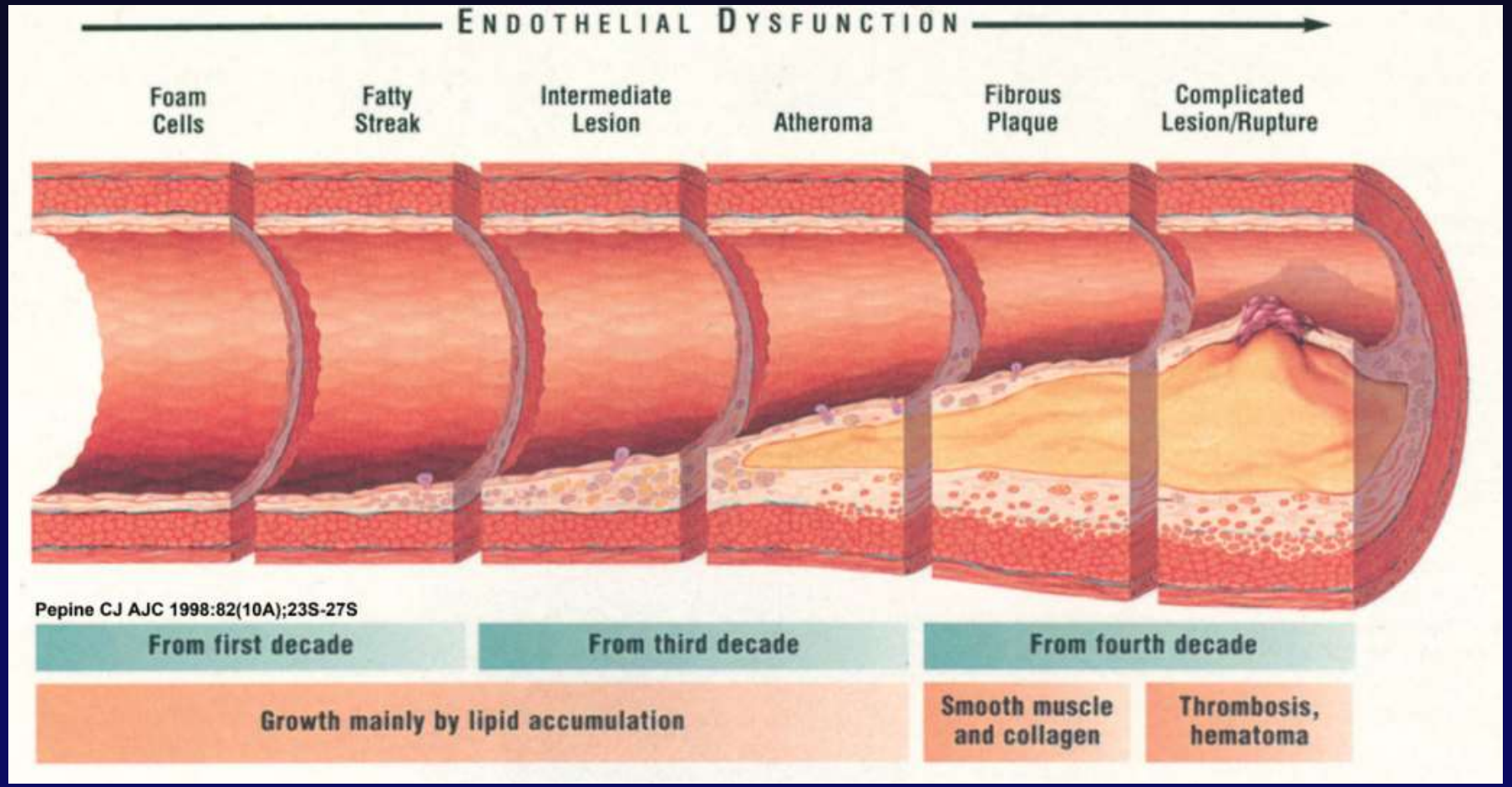
A Great Pathologist

Rudolf Ludwig Karl Virchow,
1821-1902

Virchow Triad

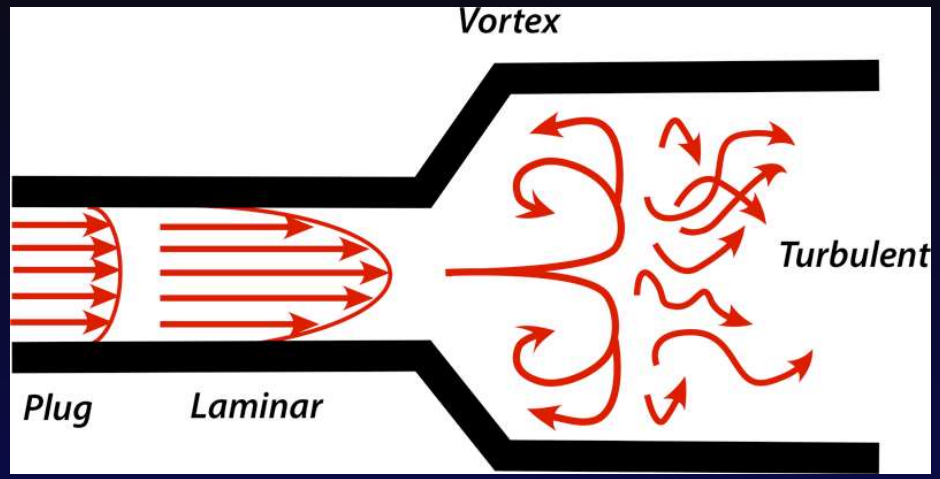
1. Alterations in blood flow
2. Endothelial injury
3. Hypercoagulability

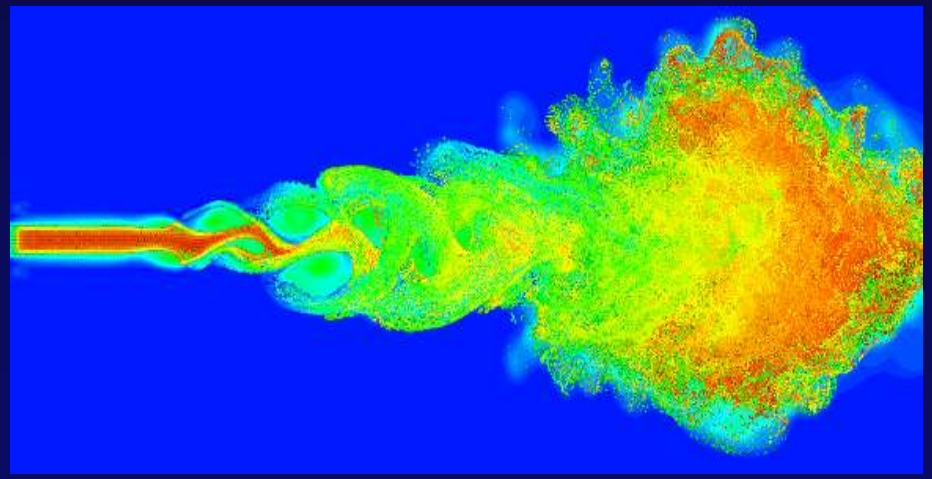
Atherosclerosis timeline

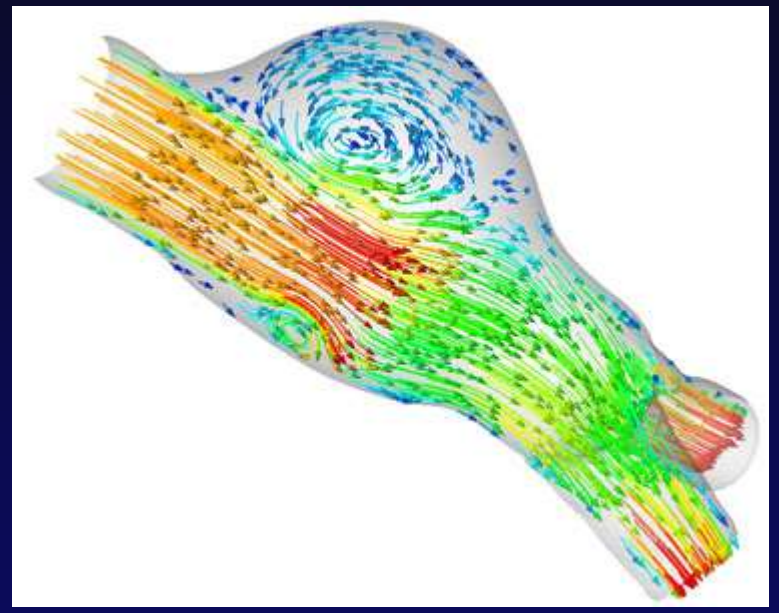


Am J Cardiol 1998;82:23-27

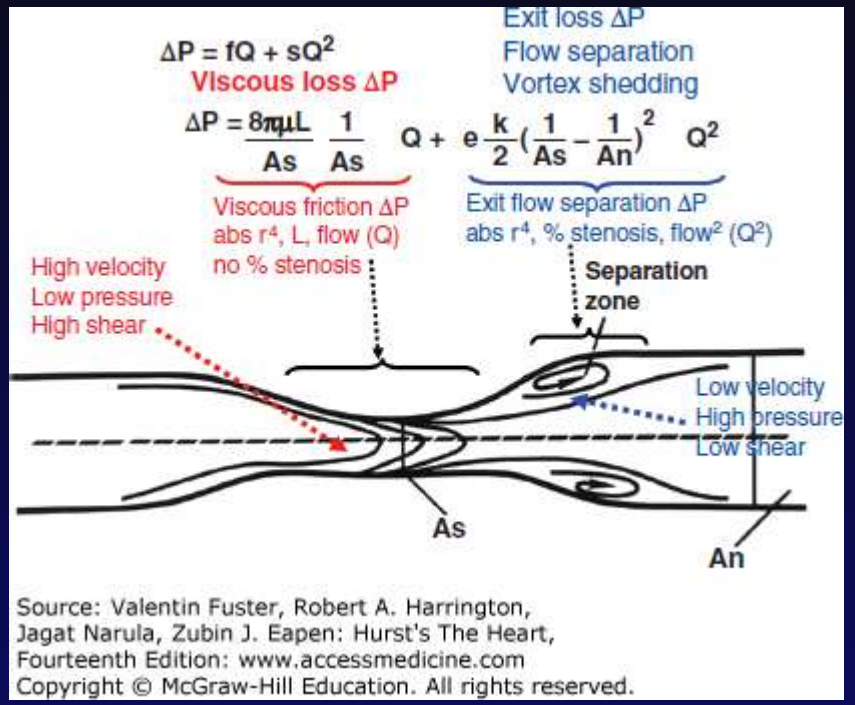
Laminar, turbulent and vortex flow

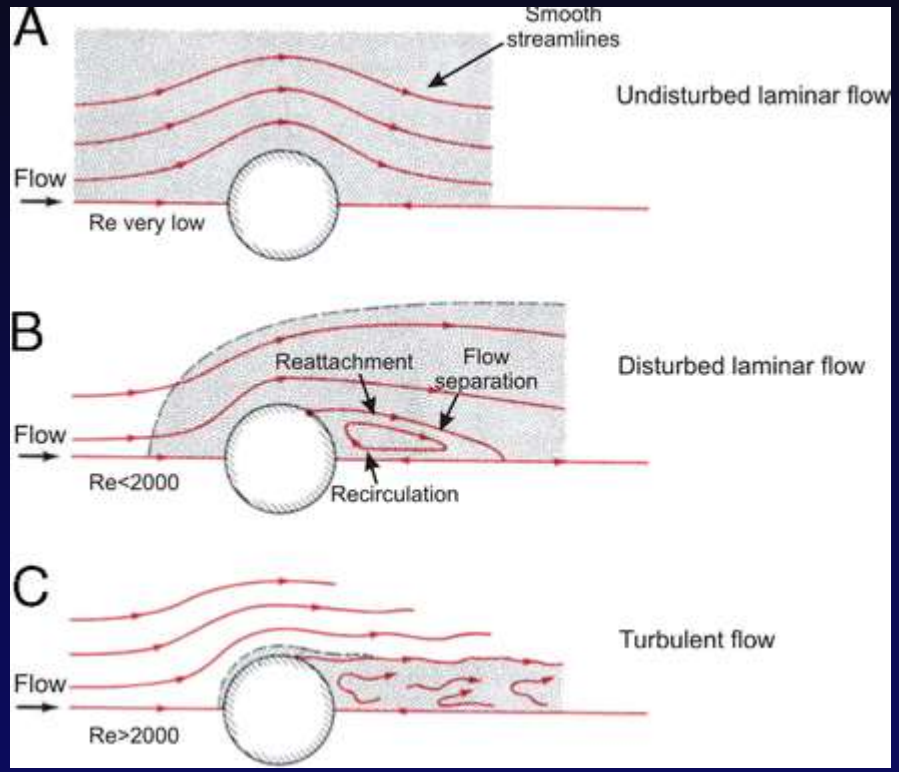






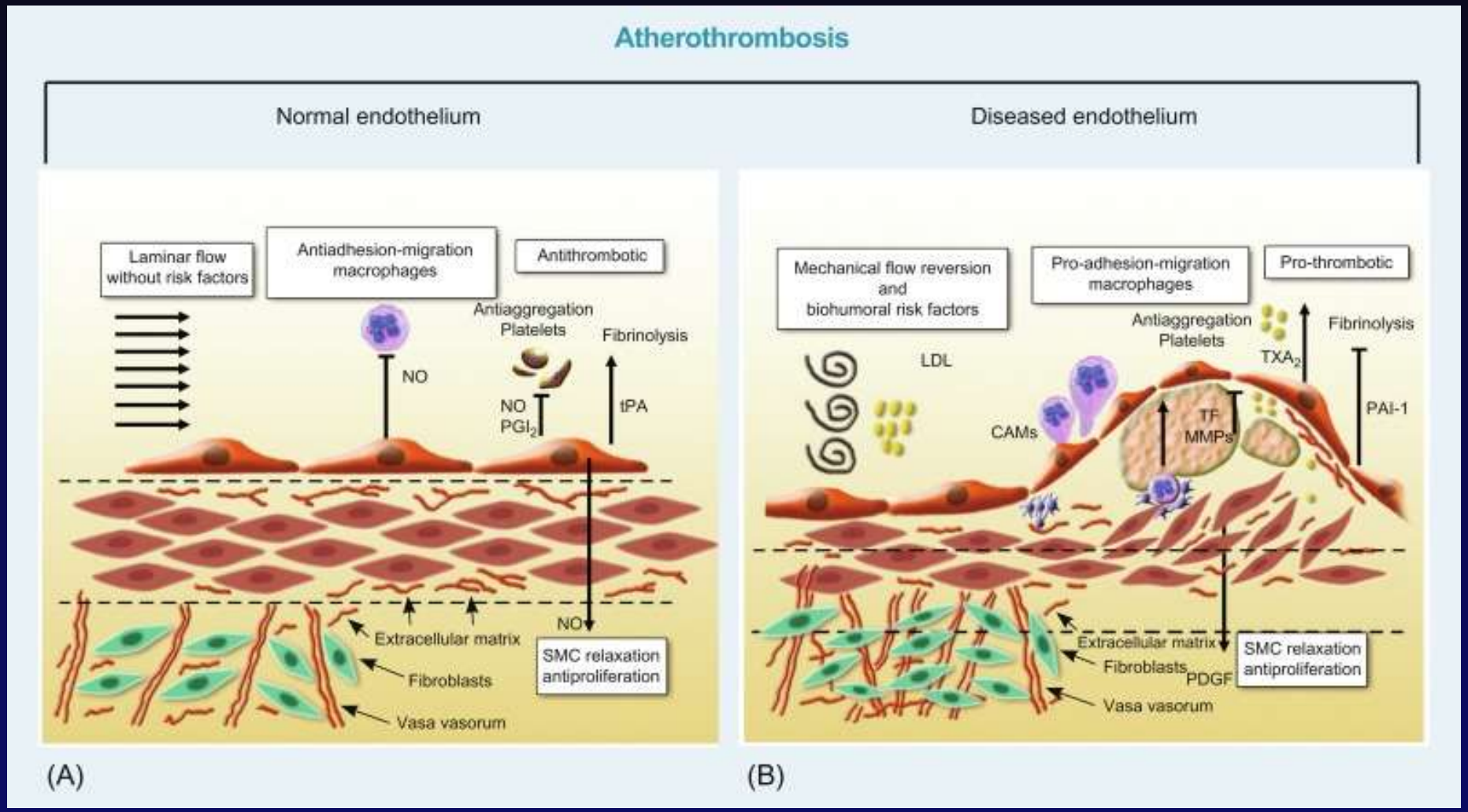
Coronary artery blood flow





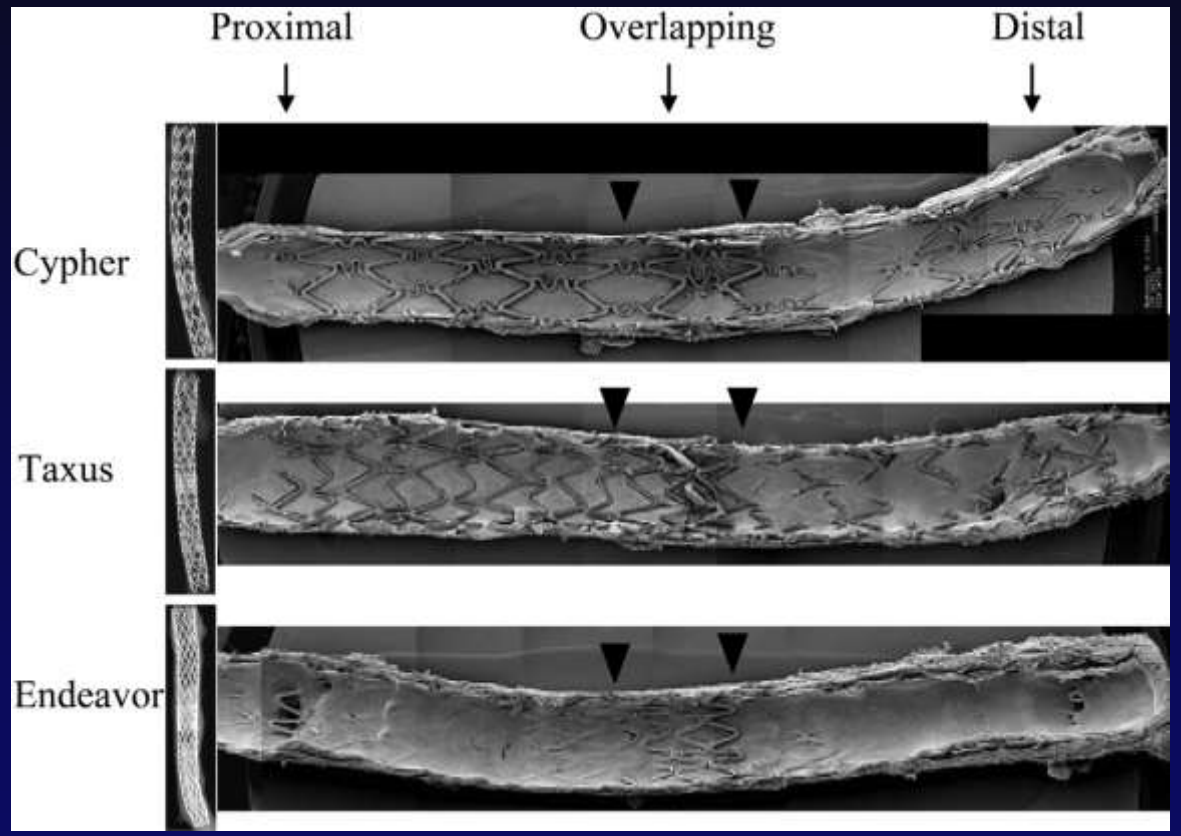
Yiannis S. Chatzizisis JACC 2007

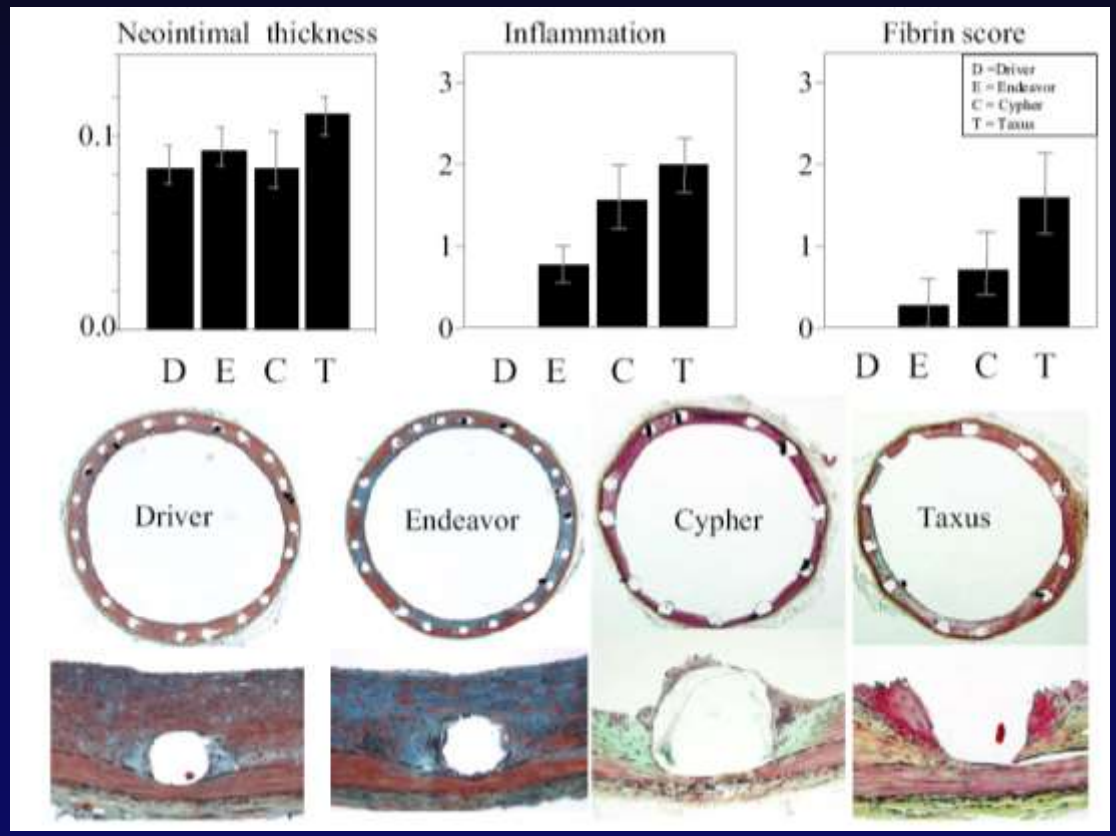
Endothelium in atherosclerosis



Vascular Biology and Clinical Syndromes 2018, Pages 493-512

Poor neointima coverage over DES



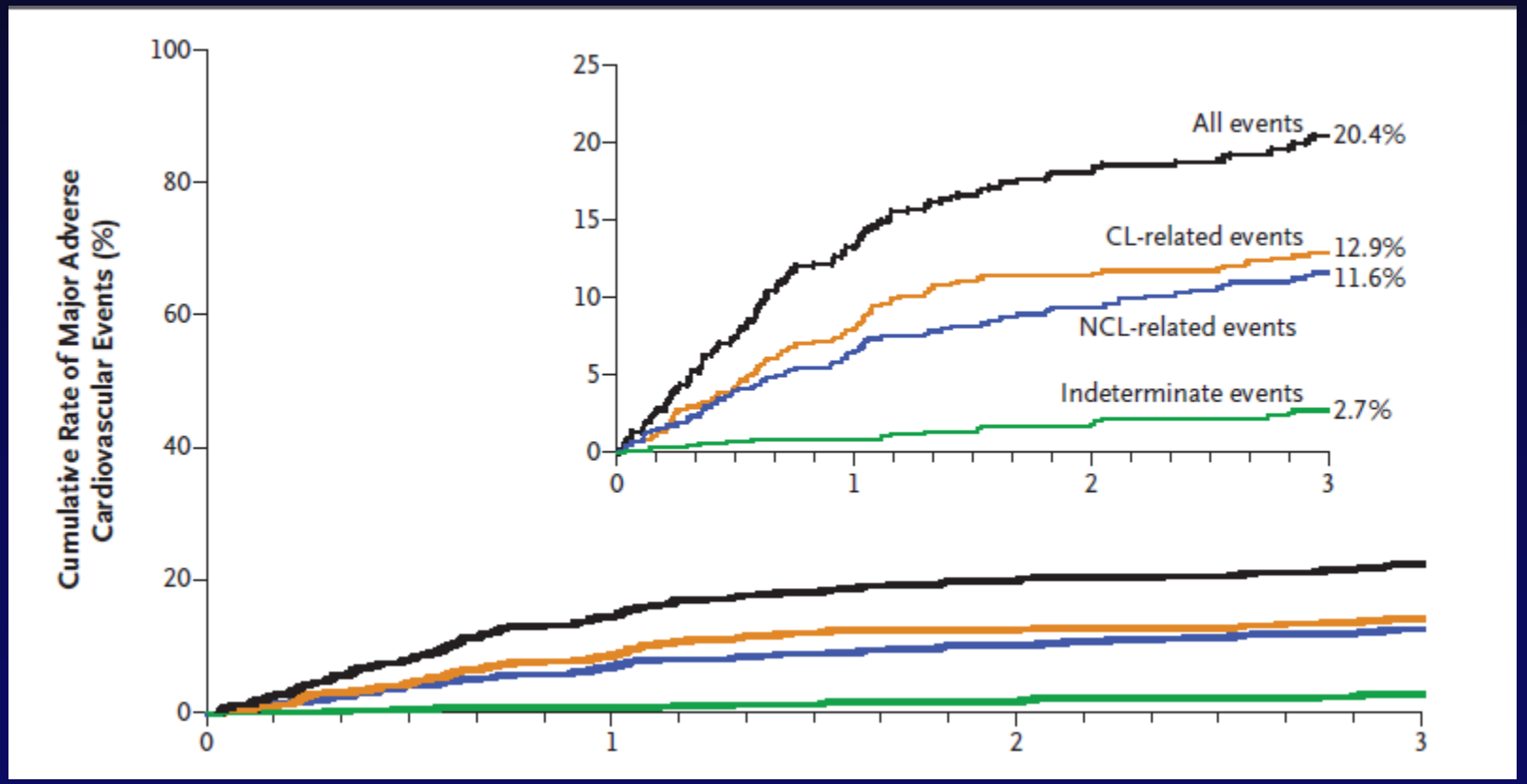


Nakazawa et al. Am J Cardiol 2007;100:36–44

PROSPECT Study | natural history of CAD

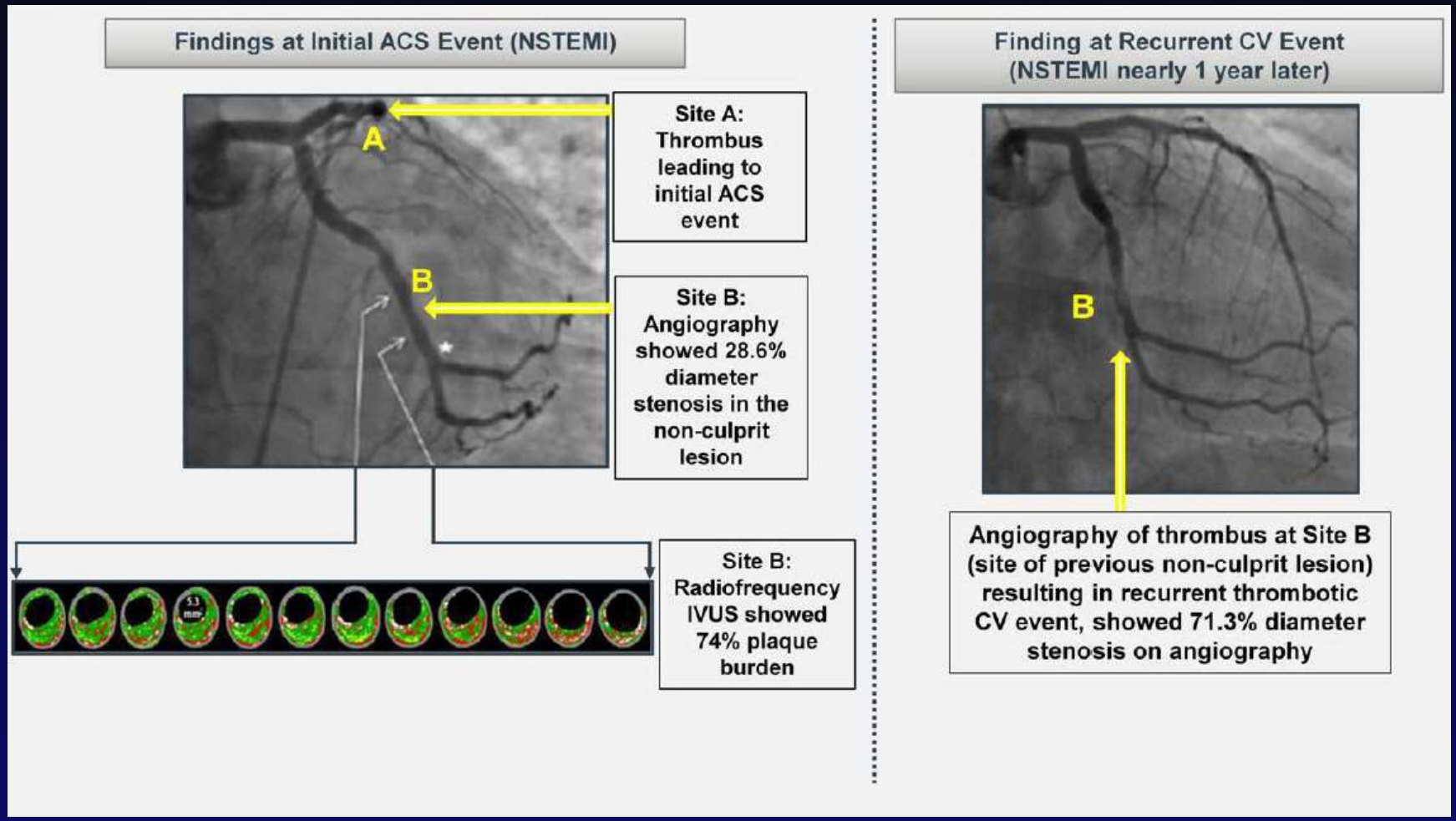
Patient: ACS (n=697) with IVUS imaging after PCI
Outcomes: Origin of MACE (CV death/MI/CV hosp) culprit vs non-culprit vessel, f/u median 3.4 years

Recurrent Events Often Originated From a Previously Untreated Plaque



N Engl J Med. 2011;364:226-235.

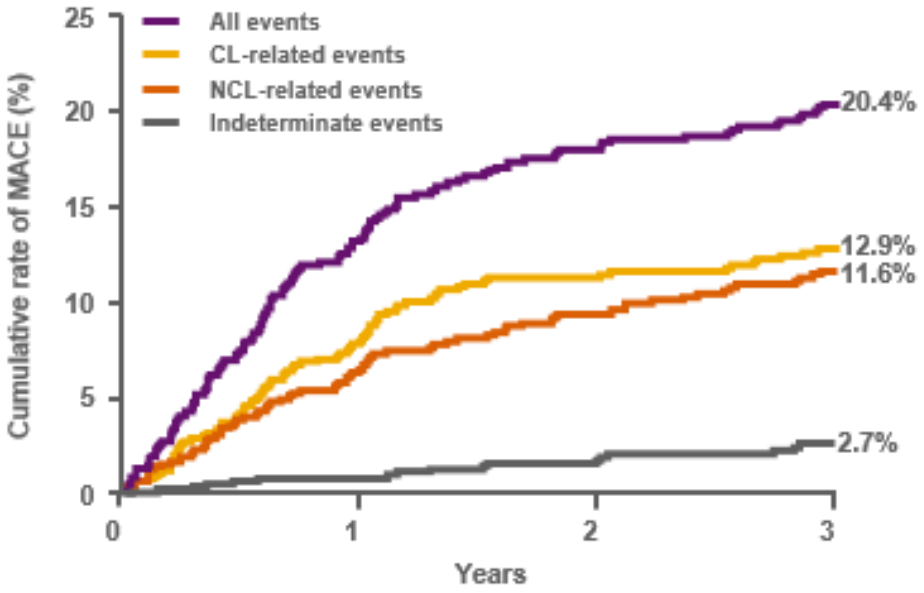
Underlying Atherothrombosis Can Lead to Recurrent CV events



Stone GW, et al. *N Engl J Med* 2011;364:226–235. Supplementary

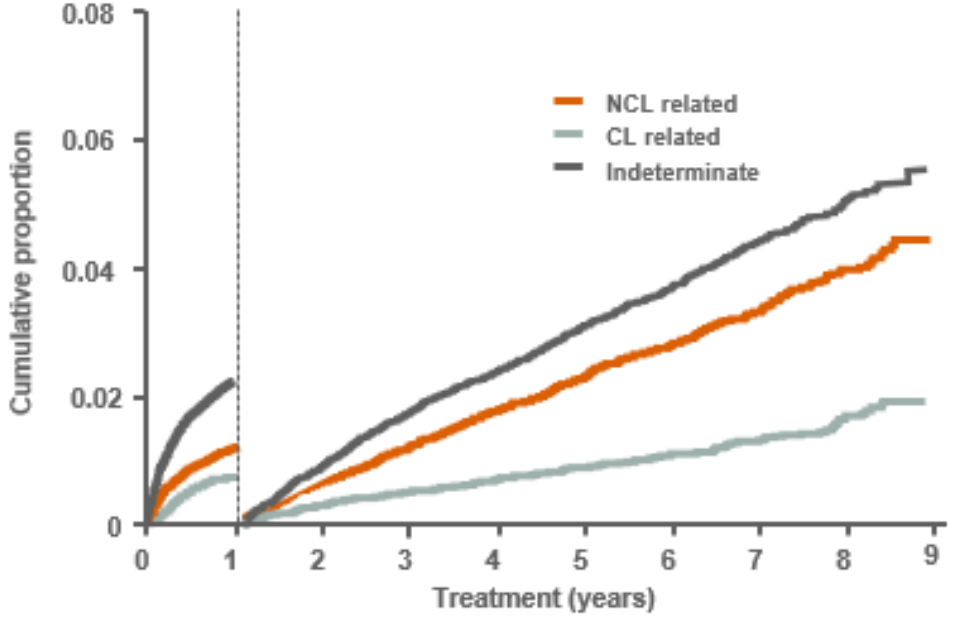
Re-current ischemic risk considers thrombotic risk factor ; Culprit lesion and Non-culprit lesion

The **PROSPECT** study explored the occurrence of MACE, following PCI in 697 ACS patients over a median follow-up of 3.4 years[1]



The rate of recurrent events was similar in “culprit” and “non-culprit” lesions

PRECLUDE: A retrospective study of SWEDEHEART registry data analysed the characteristics of recurrent MIs in 41,789 MI patients with a defined culprit lesion over 8 years follow-up[2]



The rate of recurrent events was twice as high in ‘non-culprit’ lesions than in ‘culprit’ lesions

CL, culprit lesion; NCL, non-culprit lesion

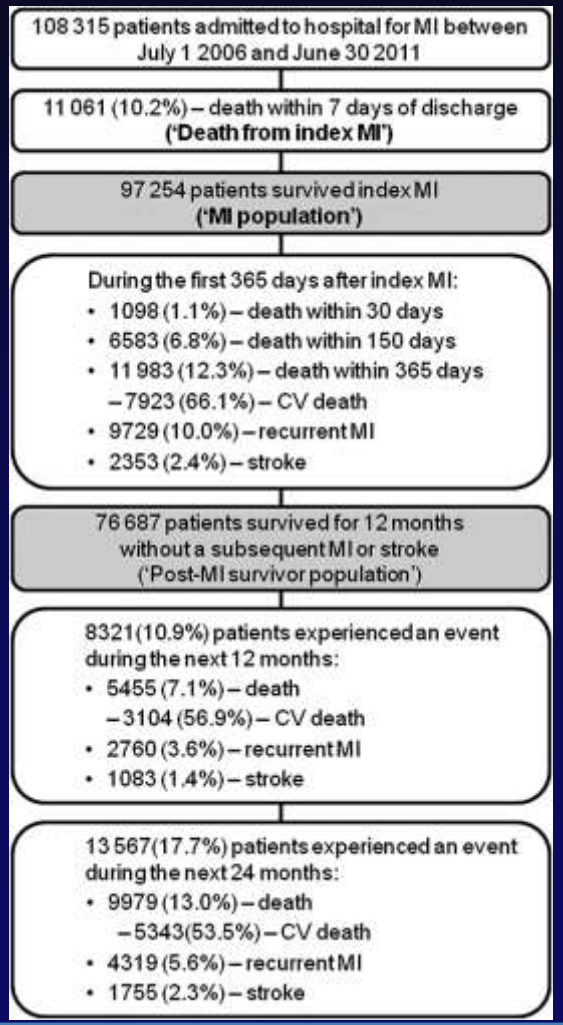
1. Stone GW et al. N Engl J Med 2011;364:226–235; 2. Varenhorst C et al. Presented at AHA 2016, CH.AOS.730 oral sessions

According to PROSPECT study, OAP medication is gradually deceased in 3years

Aspirin use	
- at discharge	675/697 (96.8%)
- at 6 months	625/653 (95.7%)
- at 1-year	606/640 (94.7%)
- at 2-years	572/616 (92.9%)
- at 3 years	527/575 (91.7%)
Thienopyridine use	
- at discharge	676/696 (97.1%)
- at 6 months	555/652 (85.1%)
- at 1-year	455/640 (71.1%)
- at 2-years	254/616 (41.2%)
- at 3 years	202/575 (35.1%)
Statin or lipid lowering therapy use	
- at discharge	594/695 (85.5%)
- at 6 months	552/652 (84.7%)
- at 1-year	537/639 (84.0%)
- at 2-years	514/615 (83.6%)
- at 3 years	485/574 (84.5%)

CV event risk continues beyond 12 months in APOLLO HELICON

Patient: 108 315 patients with a primary MI between 1 July 2006 and 30 June 2011 (index AMI) from Swedish national registry
Outcomes: Origin of MACE (CV death/MI/stroke) at 1 year and thereafter

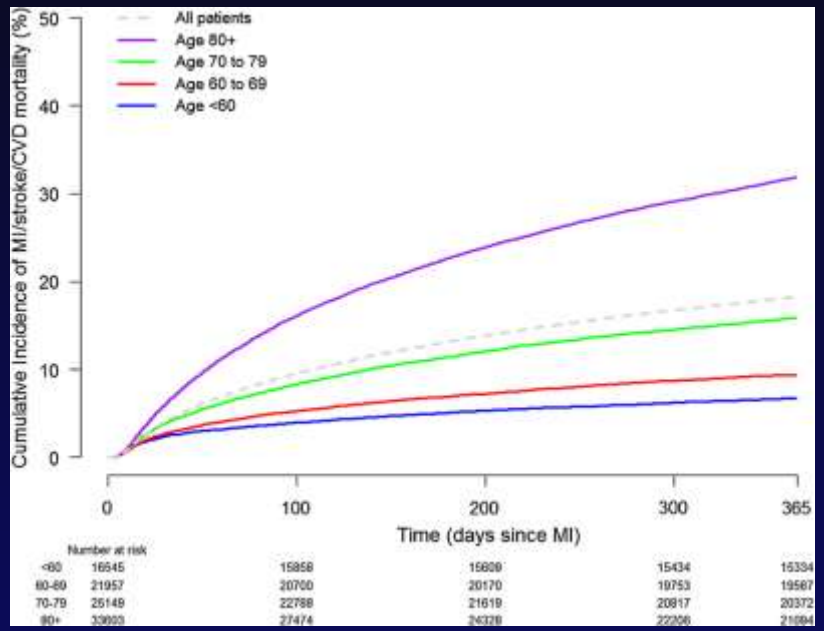


the stable post-MI patients (patients survived for 365 days after index MI without recurrent MI or stroke

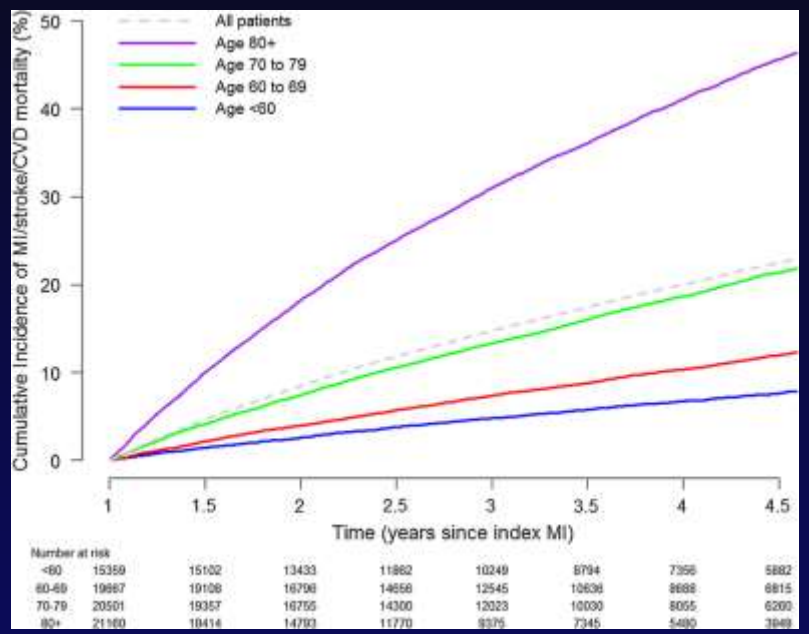
Jernberg T et al. Eur Heart J 2015;36:1163–1170

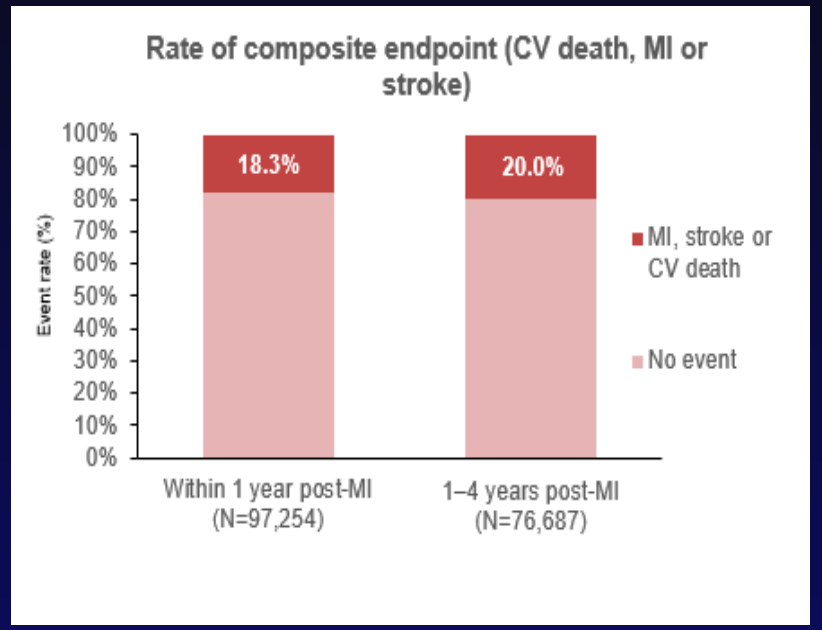
CV event risk continues beyond 12 months in APOLLO HELICON

Within 1 year from index AMI



After 1 year from index AMI

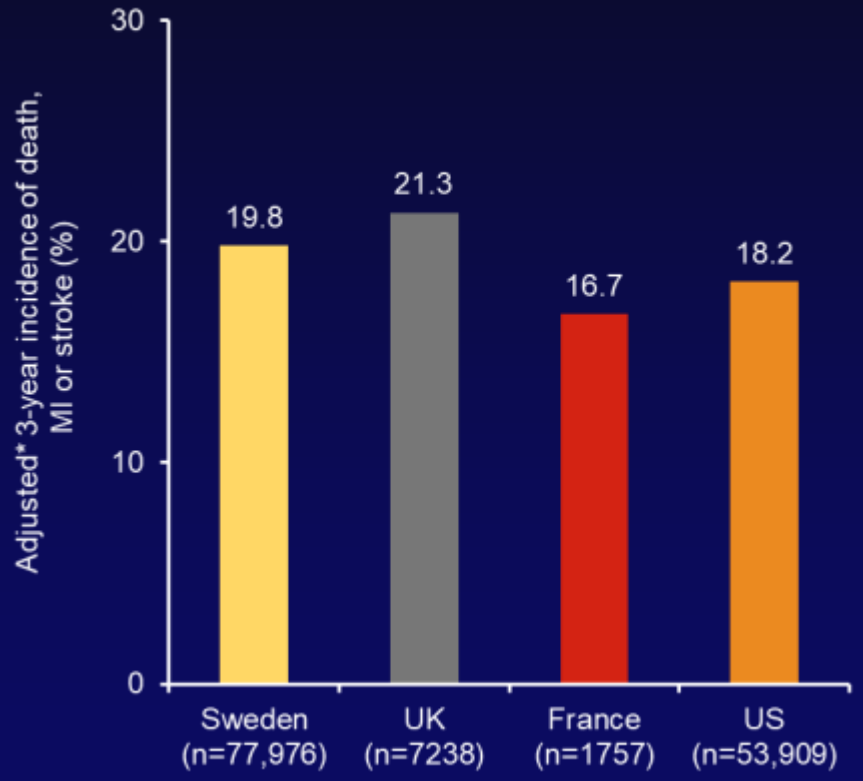


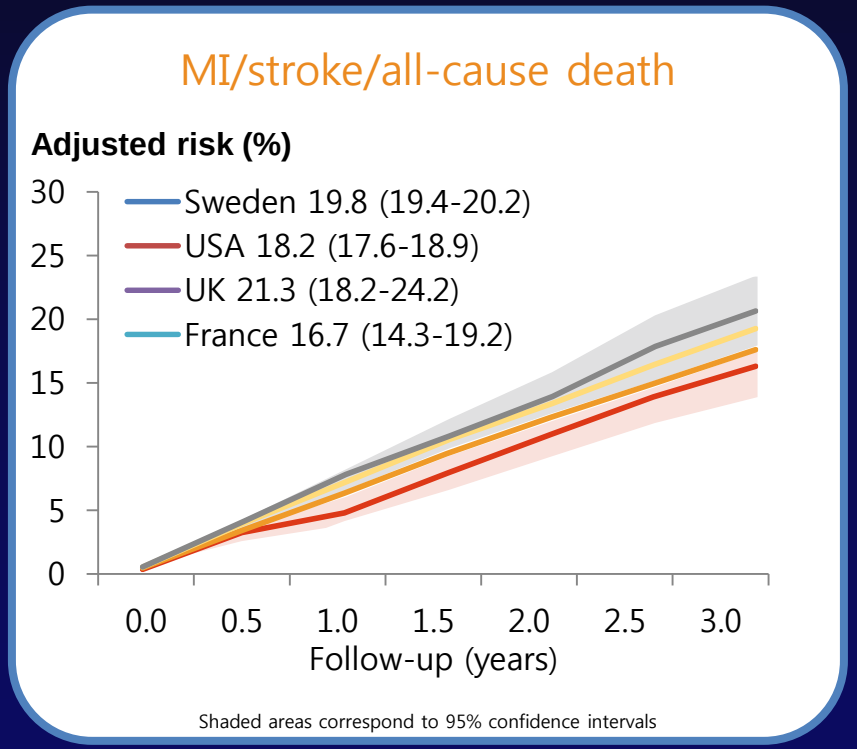


Data from national Swedish registries observed that the **3-year risk of ischaemic events in patients who were event free after 1 year was similar** to the risk of events in the first 12 months following an MI

APOLLO 4-country analysis: adjusted incidence

~1 in 5 patients who are event free for the first year post-MI, will suffer an MI, stroke or death within 3 years

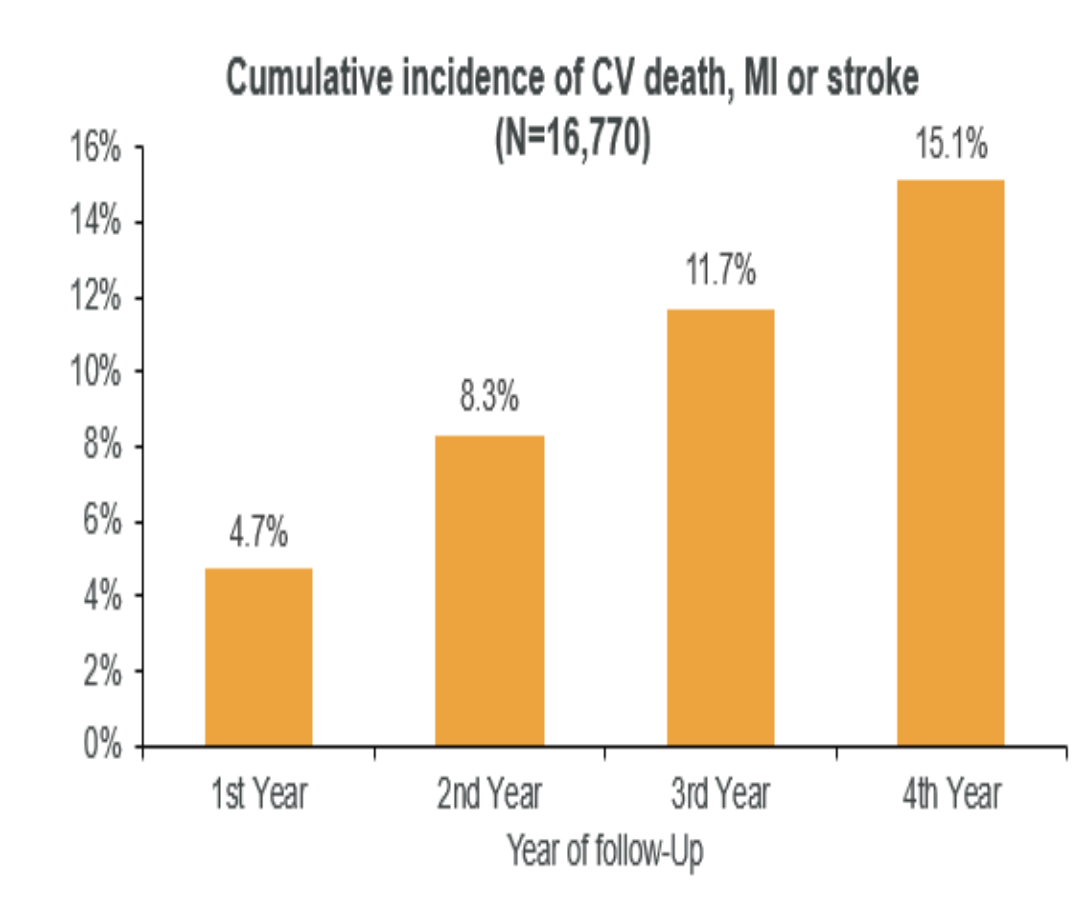




Rapsomaniki E *et al*. ESC Late Breaking Registry presentation 2014.

CV event risk continues to accrue over time in REACH registry

Analyze annual rates of recurrent ischemic events in prior MI patients

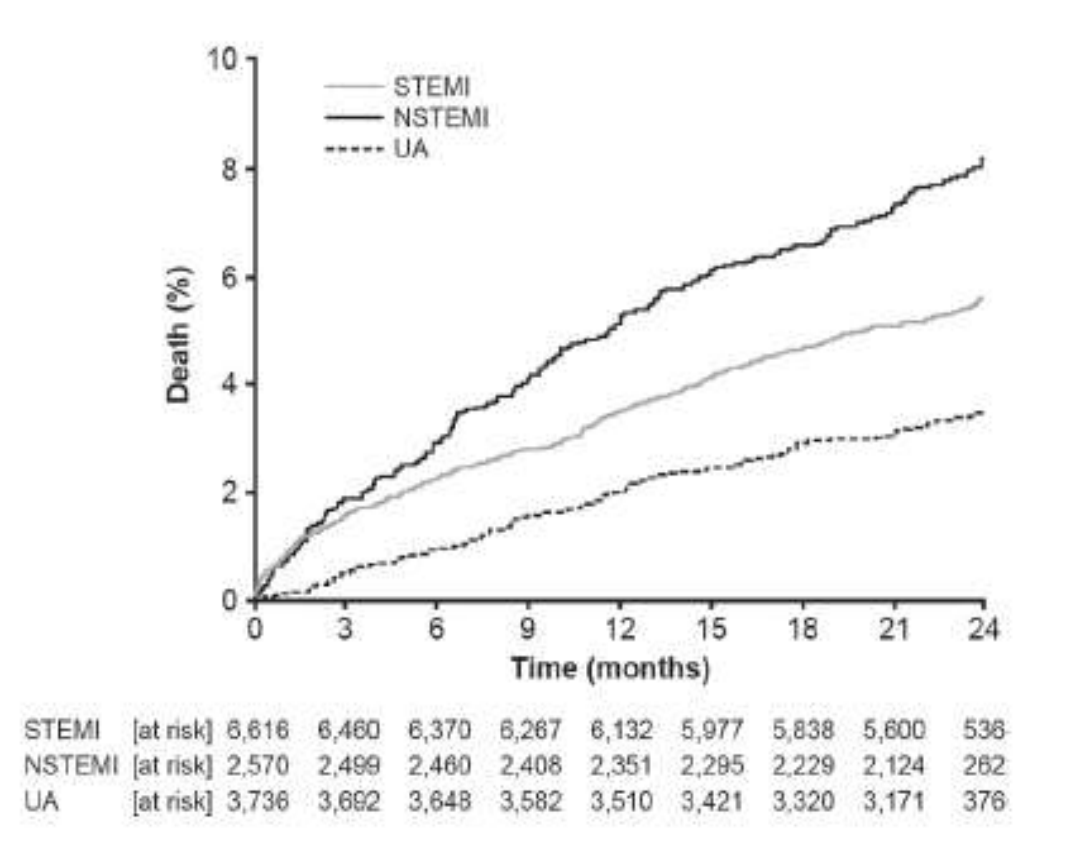


The REACH registry enrolled 16,770 patients with no history of stroke or TIA from 44 countries worldwide, and observed a 15.1% 4-year cumulative incidence of MACE

Abtan J et al. Clin Cardiol 2016;39:670–677

Asian ACS patients consider on ongoing ischemic risk after PCI

EPICOR-Asia was a multinational multicenter, observational, prospective, longitudinal cohort study in a real-life setting, 12,922 hospital survivors of an ACS event from 219 centers in Asia.



- Participating countries and regions included China, Hong Kong, India, Malaysis, Singapore, South Korea, Thailand and Vietnam
- 2-year post-discharge outcomes are reported by diagnosis of STEMI, NSTEMI or UA.

Conclusion: Mortality and vascular event rates are still of concerns in Asian ACS patients

Huo Yong, et al JACC 2015

With Asian patients, CV event also occurs over 10% within 3Year in post MI patients

A total of 11,183 patients were recruited who had survived one year post-myocardial infarction without subsequent events of recurrent myocardial infarction or stroke from the Taiwan National Health Insurance Research Database. Their composite cardiovascular event rates were identified

Table 2. Cumulative cardiovascular outcomes for the stable post-myocardial infarction (MI) population in the three additional years of follow-up.

Cumulative cardiovascular outcome	At 1 year *n* (%)	At 2 years *n* (%)	At 3 years *n* (%)
Composite cardiovascular event[a]	663 (5.9)	1135 (10.1)	1551 (13.8)
Recurrent MI	281 (2.5)	475 (4.2)	654 (5.8)
Any stroke[b]	228 (2.0)	401 (3.5)	563 (5.0)
Ischemic stroke	185 (1.6)	336 (3.0)	479 (4.2)
Hemorrhagic stroke	42 (0.3)	62 (0.5)	81 (0.7)
Unspecified stroke	19 (0.1)	36 (0.3)	51 (0.4)
All-cause death	232 (2.0)	417 (3.7)	582 (5.2)
Coronary revascularization	988 (8.8)	1721 (15.3)	2318 (20.7)
PCI	945 (8.5)	1644 (14.7)	2227 (19.9)
CABG	49 (0.4)	86 (0.7)	101 (0.9)
Heart failure admission	835 (7.47)	1230 (11.0)	1508 (13.4)
Major bleeding	238 (2.13)	392 (3.5)	521 (4.6)

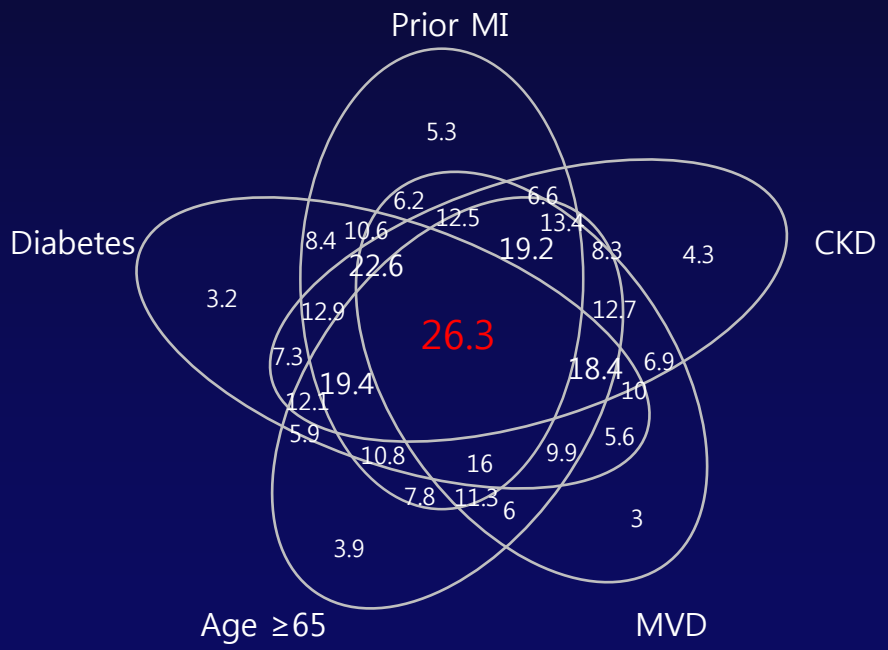
Chen et al. European Heart Journal(2017): Acute Cardiovascular Care 1-9

CONTENTS

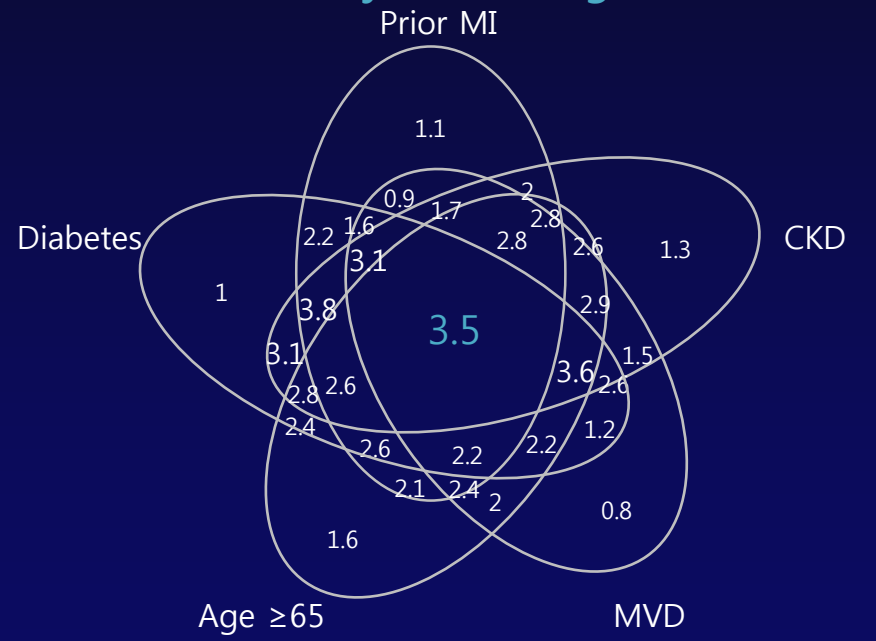
High-risk factors for preventing re-current CV events

High risk conditions lead to increasing re-current CV events

Incidence (events per 100 person-years) of MI, stroke of CV death*



Incidence (events per 100 person-years) of major bleeding*



CKD = chronic kidney disease; CV = cardiovascular; MI = myocardial infarction; MVD = multivessel disease

Lindholm D et al. *Eur Heart J.* 2018;39 (suppl):265. Abs 1398.

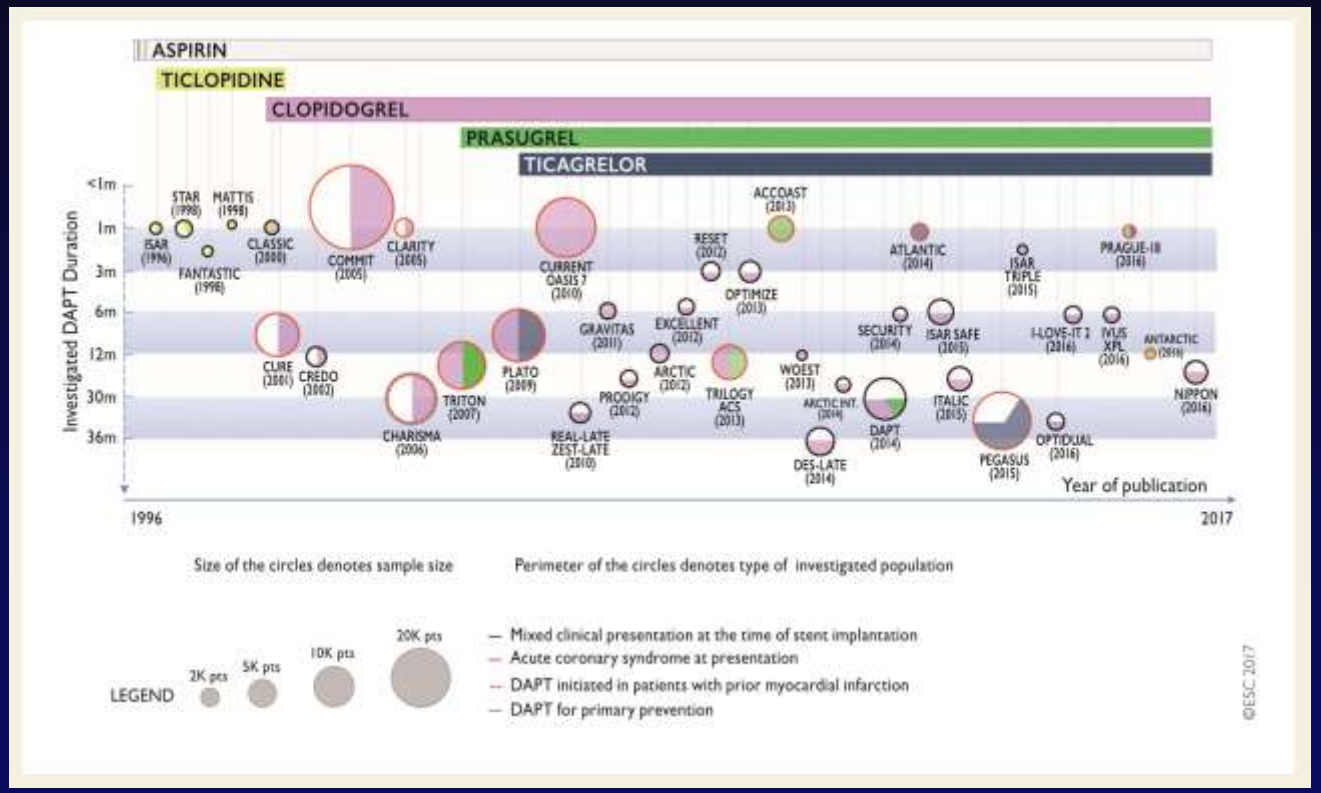
A Great Pathologist

Rudolf Ludwig Karl Virchow,
1821-1902

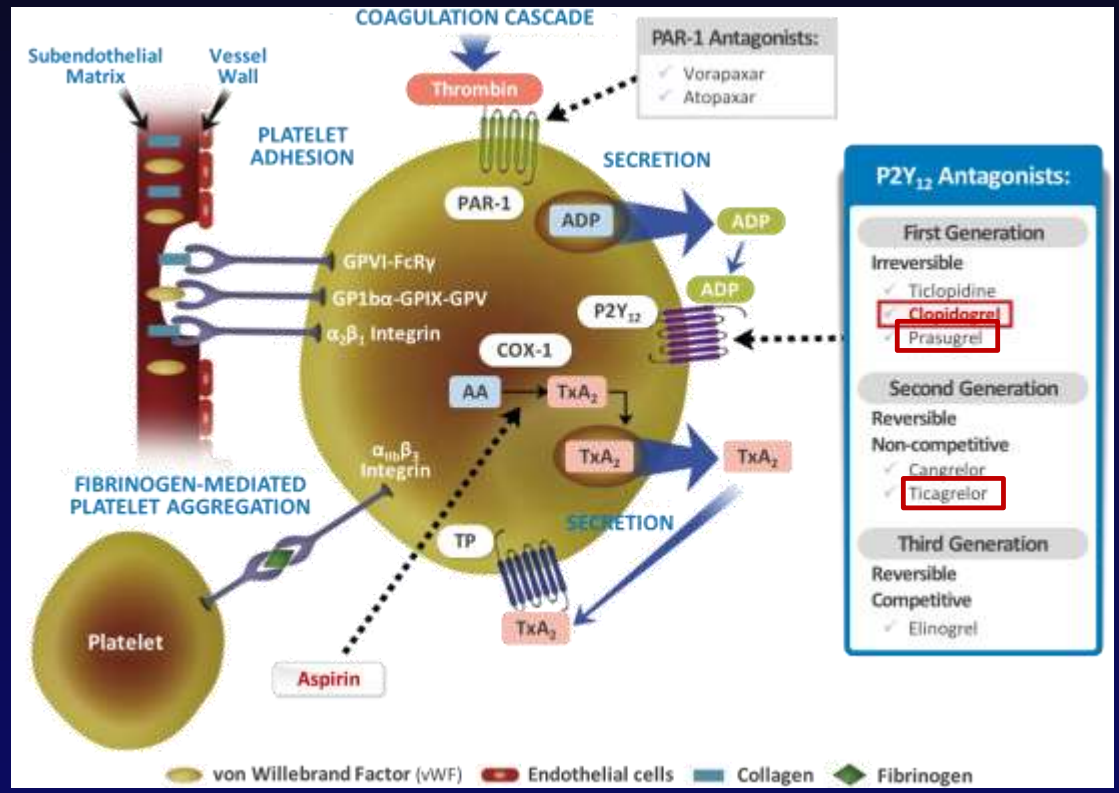
Virchow Triad

1. Alterations in blood flow
2. Endothelial injury
3. Hypercoagulability

Aspirin, clopidogrel, prasugrel, ticagrelor



European Heart Journal 2017;0, 1–48

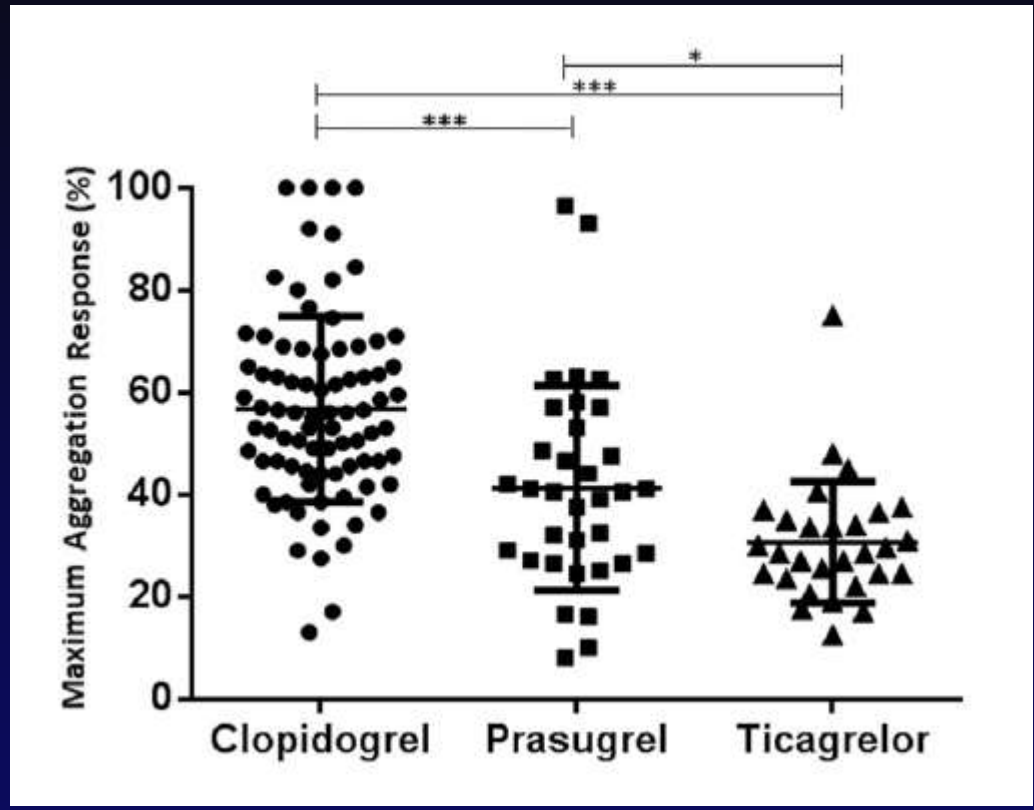


White HD. Am Heart J 2011;161: 450-461.

Evolution of P2Y12 inhibition during maintenance therapy in ACS patients

	Clopidogrel	Prasugrel	Ticagrelor
Activation	Prodrug	Prodrug	Active drug
Reversibility	Irreversible	Irreversible	Reversible
Metabolism	Hepatic (2 steps)	Hepatic (1 step)	Hepatic (CYP3A4)
Half-life	7-8 hours	7 (2-15)	7 hours
Excretion	Renal 50%, biliary 46%	Urine 68%, faces (27%)	Biliary
Onset of effect	2-4hour	30 min	30 min
Duration of effect	3-10 days	5-10 days	3-4 days
Withdrawal before surgery	5 days	7 days	5 days
Administration	75mg	10mg	90mg bid

Roffi et al. European Heart Journal (2016) 37, 267–315



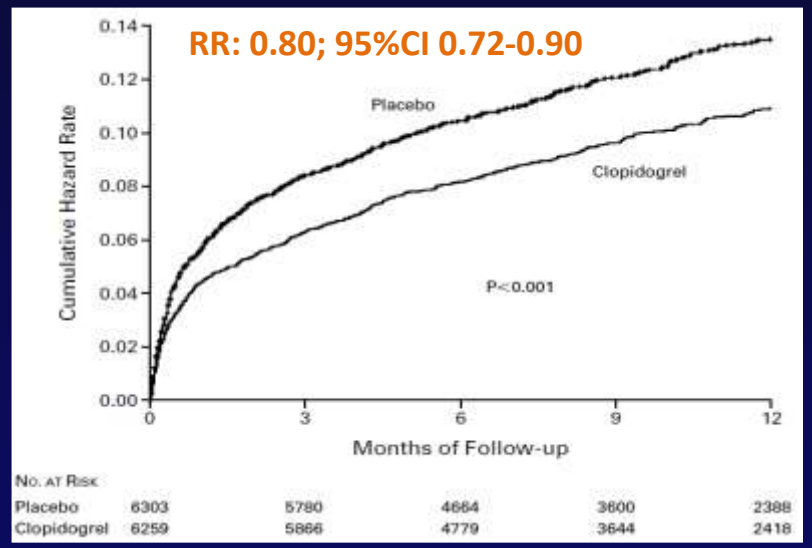
Maximum aggregation responses to ADP 20 mM using LTA for patients treated with clopidogrel [n=82], prasugrel [n=34] and ticagrelor [n=29]
*p=0.05, ** p=0.01, *** p=0.001

Joshi RR et al. Platelets. 2014;25(6):416-22

Clinical outcomes

Clopidogrel | CURE

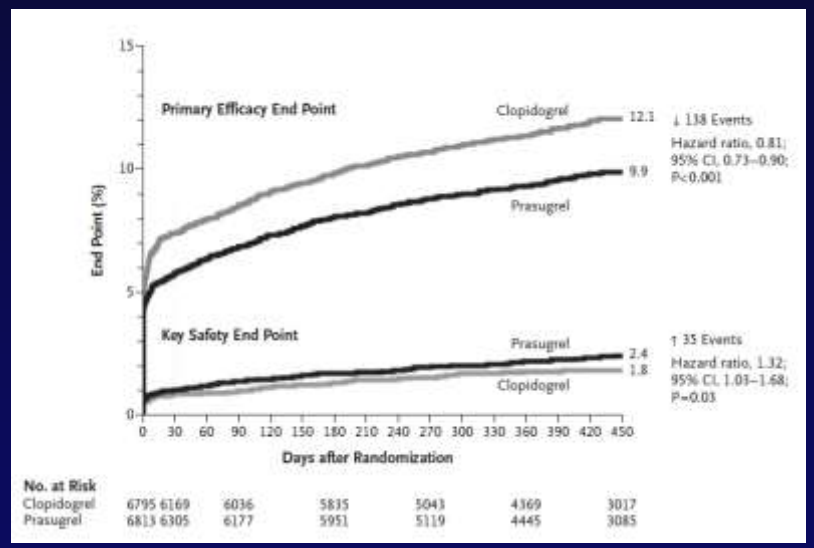
P: 12562 NSTE-ACS
I: Aspirin + Clopidogrel 300mg → 75mg (n=6259)
C: Aspirin + Placebo (n=6303)
O: CV Death, MI, Stroke



CURE Investigators. N Engl J Med. 2001

Prasugrel | TRITON-TIMI 38

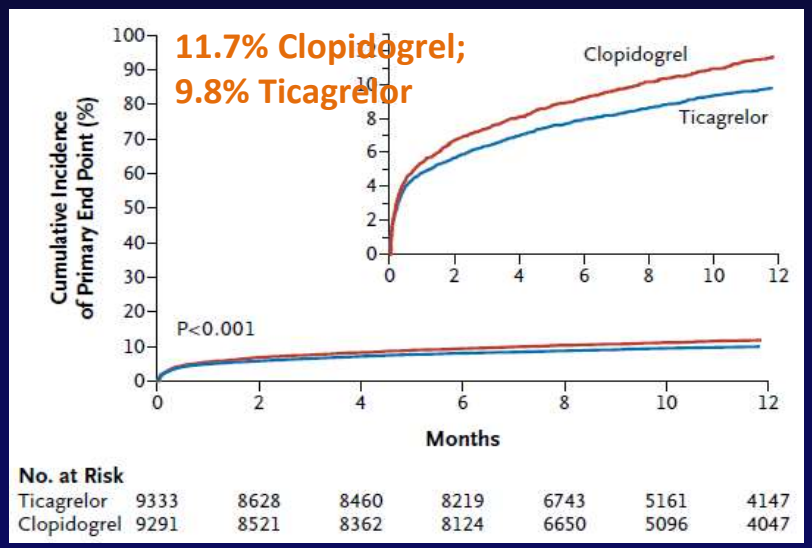
P: 13,608 ACS (STEMI 24%) patients planned for PCI
I: Aspirin + Clopidogrel 300mg/100mg (n=6795)
C: Aspirin + Prasugrel LD 60mg / MD 10mg (n=6813)
O: CV Death, MI, Stroke



N Engl J Med. 2007;357:2001-2015

Ticagrelor | PLATO

P: 18,624 ACS patients
I: Aspirin + Clopidogrel 300mg/100mg (n=9291)
C: Aspirin + Ticagrolor LD 180mg / MD 90mg bid (n=9333)
O: CV Death, MI, Stroke

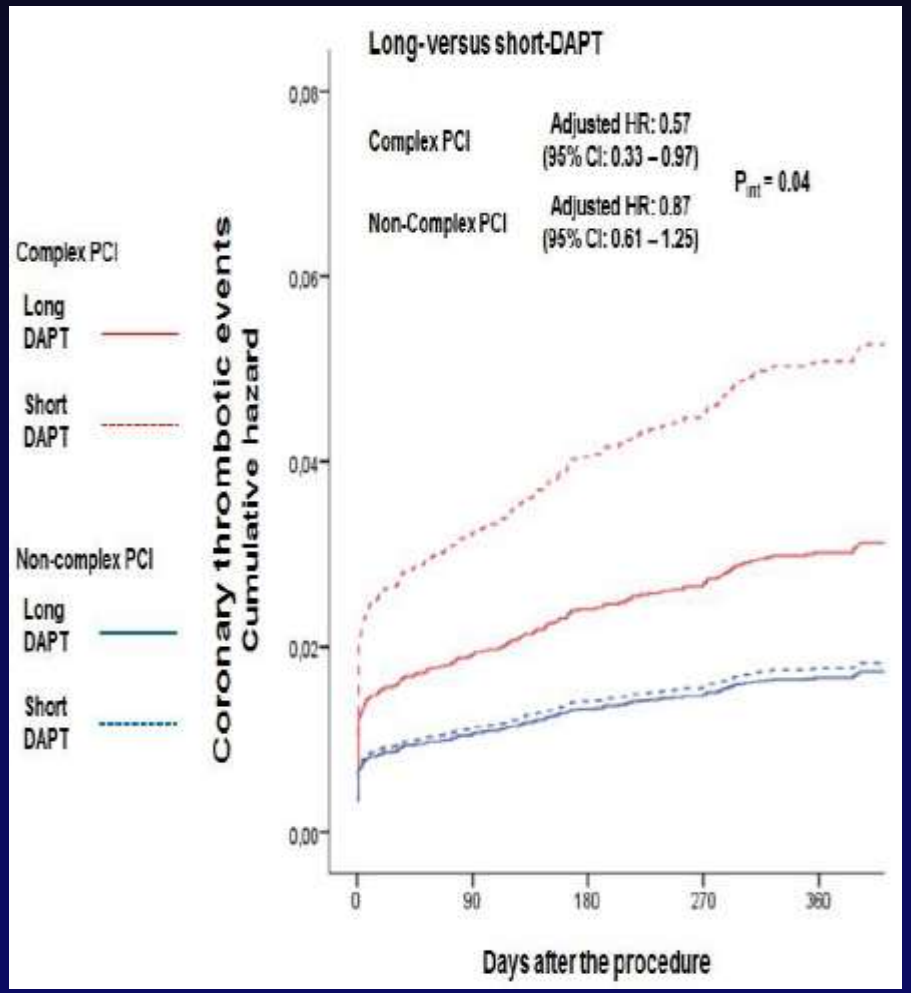


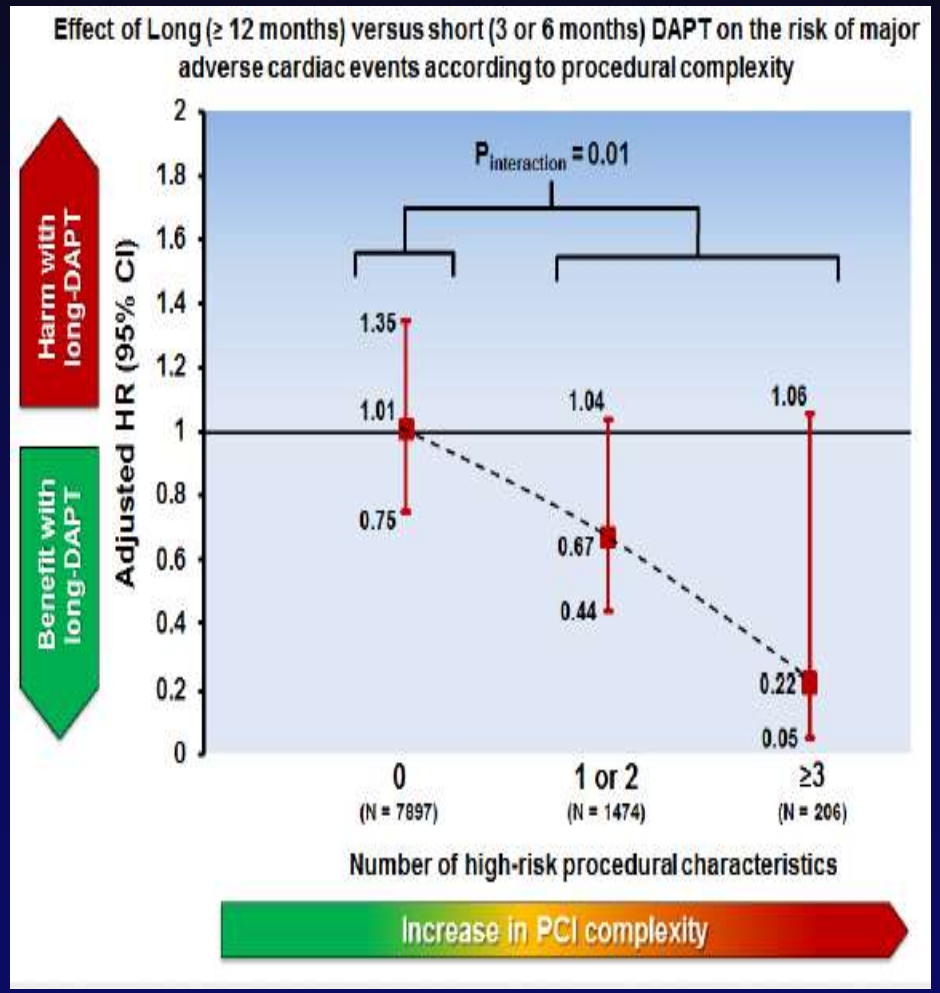
N Engl J Med. 2009;361:1045–1057

CONTENTS

DAPT prolongation significantly benefits patients with complex PCI

Of 9,577 patients included in the pooled dataset for whom procedural variables were available, 1,680 (17.5%) underwent complex PCI.





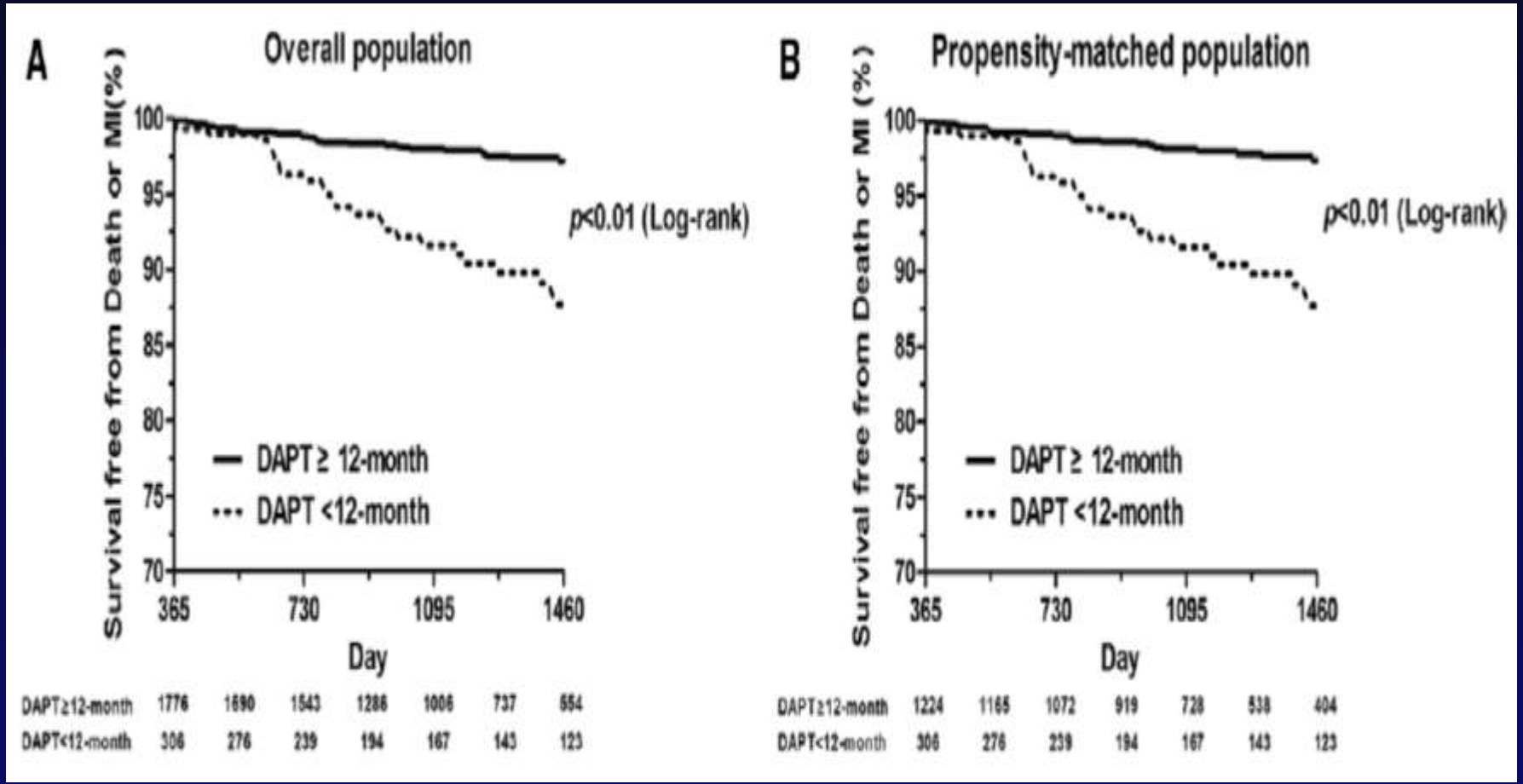
Complex PCI (≥1)

- 3 vessels treated
- ≥3 stents implanted
- ≥3 lesions treated
- bifurcation with 2 stents implanted
- total stent length >60 mm,
- CTO

Giustino et al. J Am Coll Cardiol. 2016;68:B86-B87.

Prolonged DAPT treatment improves long-term clinical outcomes for patients with bifurcation lesions

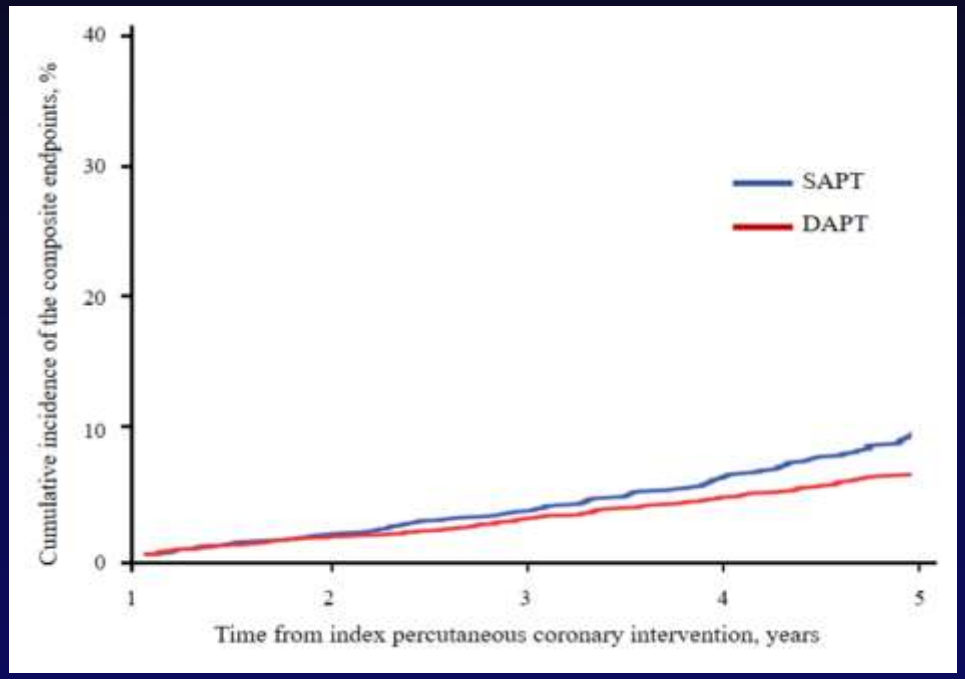
- 2082 patients who were treated with drug-eluting stent for bifurcation lesions and were event free (no death, myocardial infarction [MI], cerebrovascular accident, stent thrombosis, or any revascularization) at 12 months after the index procedure.
- Primary outcome was all-cause death or MI.



Woo Jin Jang et al. Circ Cardiovasc Interv. 2018;11:e005849. DOI: 10.1161/CIRCINTERVENTIONS.117.005849

Prolonged DAPT treatment proves less occurrence of CV events than SAPT in Korean post MI patients

- All-comer AMI patients who underwent PCI were consecutively enrolled in the COREA-AMI registry from January 2004 to August 2014.
- 11,507 patients were alive and stable at 1 year with available data and included in this study;



- **High-risk stable post-MI patients**
  - Diabetes Mellitus requiring medication
  - Prior spontaneous myocardial infraction
  - Multivessel coronary artery disease
  - Chronic renal insufficiency
  - ≥ 65 years of age

	Stable post-MI			
	DAPT	SAPT	Hazard ratio (95% CI)	P value
Ischemic events				
Primary composite outcome	5.6	7.3	1.31 (1.00-1.73)	0.05
Cardiovascular death	2.6	3.1	1.19 (0.91-1.54)	0.18
Myocardial infarction	1.4	1.9	1.32 (0.83-2.10)	0.24
Stroke	1.2	1.7	1.37 (0.84-2.24)	0.21
Stent thrombosis	0.6	1	1.51 (0.61-2.75)	0.20
All-cause death	5.2	5.7	1.11 (0.85-1.44)	0.45
Bleeding events				
BARC type 3 or 5	2.4	2.6	1.08 (0.73-1.60)	0.70
Fatal bleeding	0.2	0.2	0.87 (0.20-3.79)	0.85

	High-risk stable post-MI			
	DAPT	SAPT	Hazard ratio (95% CI)	P value
Ischemic events				
Primary composite outcome	6.1	7.9	1.35 (1.02-1.86)	0.04
Cardiovascular death	2.9	3.6	1.27 (0.83-1.93)	0.31
Myocardial infarction	1.2	1.9	1.58 (0.96-2.49)	0.09
Stroke	1.4	2.1	1.49 (0.90-2.47)	0.13
Stent thrombosis	0.7	1.2	1.65 (0.94-2.84)	0.10
All-cause death	6.2	7.3	1.18 (0.91-1.54)	0.21
Bleeding events				
BARC type 3 or 5	2.8	2.8	1.02 (0.66-1.56)	0.94
Fatal bleeding	0.2	0.3	0.88 (0.20-3.81)	0.86

Kiyuk Chang et al American Heart Association Scientific Sessions 2017; Anaheim, CA, November 11-15, 2017

CHARISMA

Patient:	high risk (CVD or multiple risk factors) (n=15603)
Intervention:	Aspirin + clopidogrel 75mg (n=7802)
Comparison:	Aspirin + placebo (n=7801)
Outcomes:	CV deaths, MI, stroke; median follow-up 28 months

ORIGINAL ARTICLE

Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events

Deepak L. Bhatt, M.D., Keith A.A. Fox, M.B., Ch.B., Werner Hacke, M.D., Peter B. Berger, M.D., Henry R. Black, M.D., William E. Boden, M.D., Patrice Cacoub, M.D., Eric A. Cohen, M.D., Mark A. Creager, M.D., J. Donald Easton, M.D., Marcus D. Flather, M.D., Shawn M. Haffner, M.D., Christian W. Hamm, M.D., Graeme J. Hankey, M.D., S. Claiborne Johnston, M.D., Koon-Hou Mak, M.D., Jean-Louis Mas, M.D., Gilles Montalescot, M.D., Ph.D., Thomas A. Pearson, M.D., P. Gabriel Steg, M.D., Steven R. Steinhubl, M.D., Michael A. Weber, M.D., Danielle M. Brennan, M.S., Liz Fabry-Ribaudo, M.S.N., R.N., Joan Booth, R.N., and Eric J. Topol, M.D., for the CHARISMA Investigators*

ABSTRACT

BACKGROUND

Dual antiplatelet therapy with clopidogrel plus low-dose aspirin has not been studied in a broad population of patients at high risk for atherothrombotic events.

METHODS

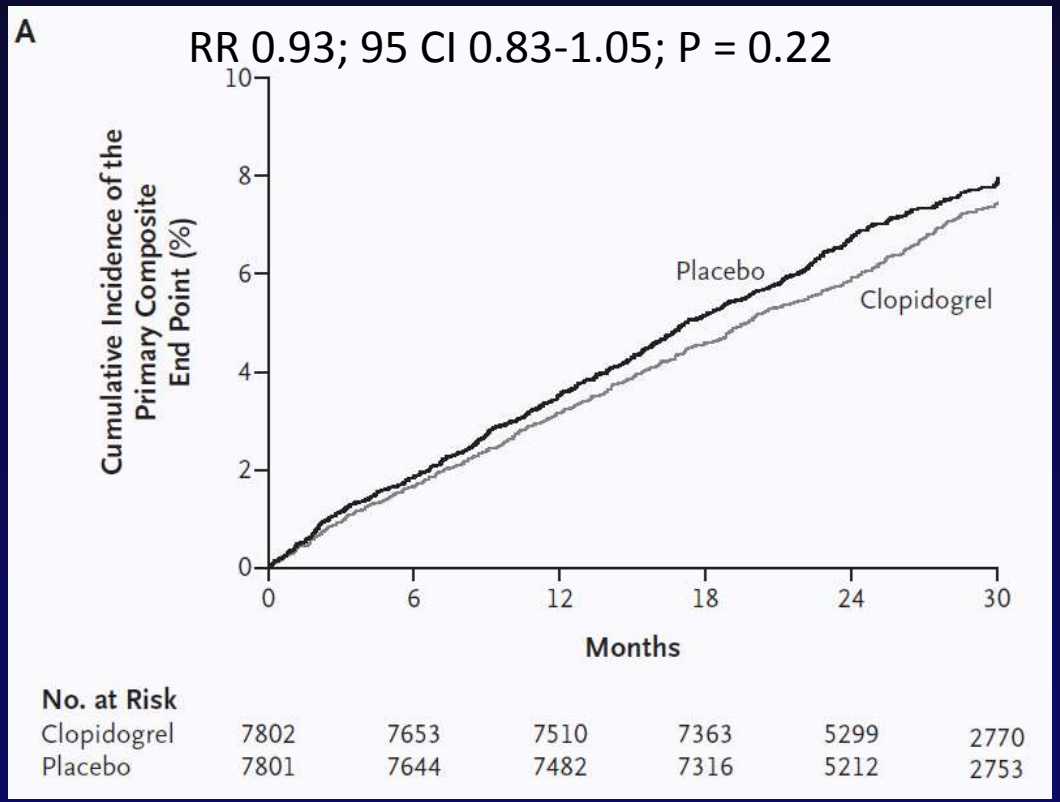
We randomly assigned 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin and followed them for a median of 28 months. The primary efficacy end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

RESULTS

The rate of the primary efficacy end point was 6.8 percent with clopidogrel plus aspirin and 7.3 percent with placebo plus aspirin (relative risk, 0.93; 95 percent confidence interval, 0.83 to 1.05; P=0.22). The respective rate of the principal secondary efficacy end point, which included hospitalizations for ischemic events, was 16.7 percent and 17.9 percent (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.995; P=0.04), and the rate of severe bleeding was 1.7 percent and 1.3 percent (relative risk, 1.25; 95 percent confidence interval, 0.97 to 1.61 percent; P=0.09). The rate of the primary end point among patients with multiple risk factors was 6.6 percent with clopidogrel and 5.5 percent with placebo (relative risk, 1.2; 95 percent confidence interval, 0.91 to 1.59; P=0.20) and the rate of death from cardiovascular causes also was higher with clopidogrel (3.9 percent vs. 2.2 percent, P=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9 percent with clopidogrel and 7.9 percent with placebo (relative risk, 0.88; 95 percent confidence interval, 0.77 to 0.998; P=0.046).

CONCLUSIONS

In this trial, there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors. Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes. (ClinicalTrials.gov number, NCT00050817.)



CHARISMA-Subgroup analysis

Patient:	Prior MI, Stroke, PAD (n=9478)
Intervention:	Aspirin + clopidogrel 75mg (n=7802)
Comparison:	Aspirin + placebo (n=7801)
Outcomes:	CV deaths, MI, stroke; median follow-up 27.6 months

EXPEDITED REVIEW

Patients With Prior Myocardial Infarction, Stroke, or Symptomatic Peripheral Arterial Disease in the CHARISMA Trial

Deepak L. Bhatt, MD, FACC,* Marcus D. Flather, MD,† Werner Hacke, MD,‡ Peter B. Berger, MD, FACC,§ Henry R. Black, MD,‖ William E. Boden, MD, FACC,¶ Patrice Cacoub, MD,# Eric A. Cohen, MD,** Mark A. Creager, MD, FACC,†† J. Donald Easton, MD,‡‡ Christian W. Hamm, MD, FACC,§§ Graeme J. Hankey, MD,‖‖ S. Claiborne Johnston, MD, PhD,¶¶ Koon-Hou Mak, MD, FACC,## Jean-Louis Mas, MD,*** Gilles Montalescot, MD, PhD,††† Thomas A. Pearson, MD, FACC,‡‡‡ P. Gabriel Steg, MD, FACC,§§§ Steven R. Steinhubl, MD, FACC,‖‖‖ Michael A. Weber, MD, FACC,¶¶¶ Liz Fabry-Ribaudo, MSN, RN,* Tingfei Hu, MS,* Eric J. Topol, MD, FACC,### Keith A. A. Fox, MBChB,**** for the CHARISMA Investigators

Cleveland, Ohio; London, and Edinburgh, United Kingdom; Heidelberg and Bad Nauheim, Germany; Danville, Pennsylvania; New York, Buffalo, and Rochester, New York; Paris, France; Toronto, Canada; Boston, Massachusetts; Providence, Rhode Island; Perth, Australia; San Francisco, California; Singapore; and Lexington, Kentucky

Objectives The purpose of this study was to determine the possible benefit of dual antiplatelet therapy in patients with prior myocardial infarction (MI), ischemic stroke, or symptomatic peripheral arterial disease (PAD).

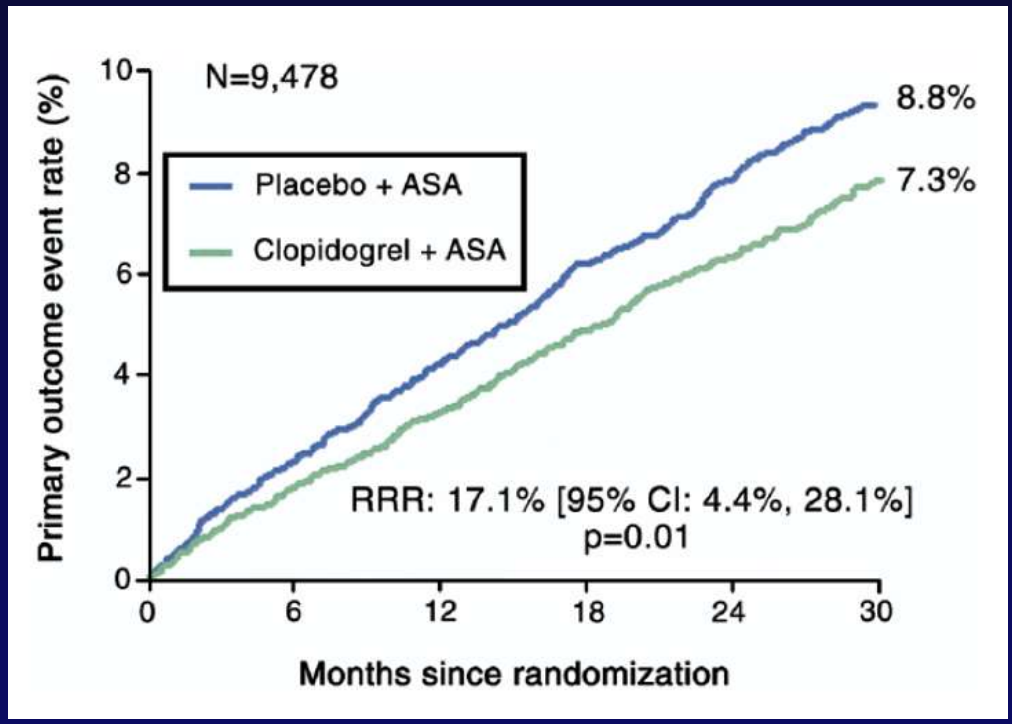
Background Dual antiplatelet therapy with clopidogrel plus aspirin has been validated in the settings of acute coronary syndromes and coronary stenting. The value of this combination was recently evaluated in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, where no statistically significant benefit was found in the overall broad population of stable patients studied.

Methods We identified the subgroup in the CHARISMA trial who were enrolled with documented prior MI, ischemic stroke, or symptomatic PAD.

Results A total of 9,478 patients met the inclusion criteria for this analysis. The median duration of follow-up was 27.6 months. The rate of cardiovascular death, MI, or stroke was significantly lower in the clopidogrel plus aspirin arm than in the placebo plus aspirin arm: 7.3% versus 8.8% (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.72 to 0.96, p = 0.01). Additionally, hospitalizations for ischemia were significantly decreased, 11.4% versus 13.2% (HR 0.86, 95% CI 0.76 to 0.96, p = 0.008). There was no significant difference in the rate of severe bleeding: 1.7% versus 1.5% (HR 1.13, 95% CI 0.81 to 1.53, p = 0.50); moderate bleeding was significantly increased: 2.0% versus 1.3% (HR 1.60, 95% CI 1.16 to 2.20, p = 0.004).

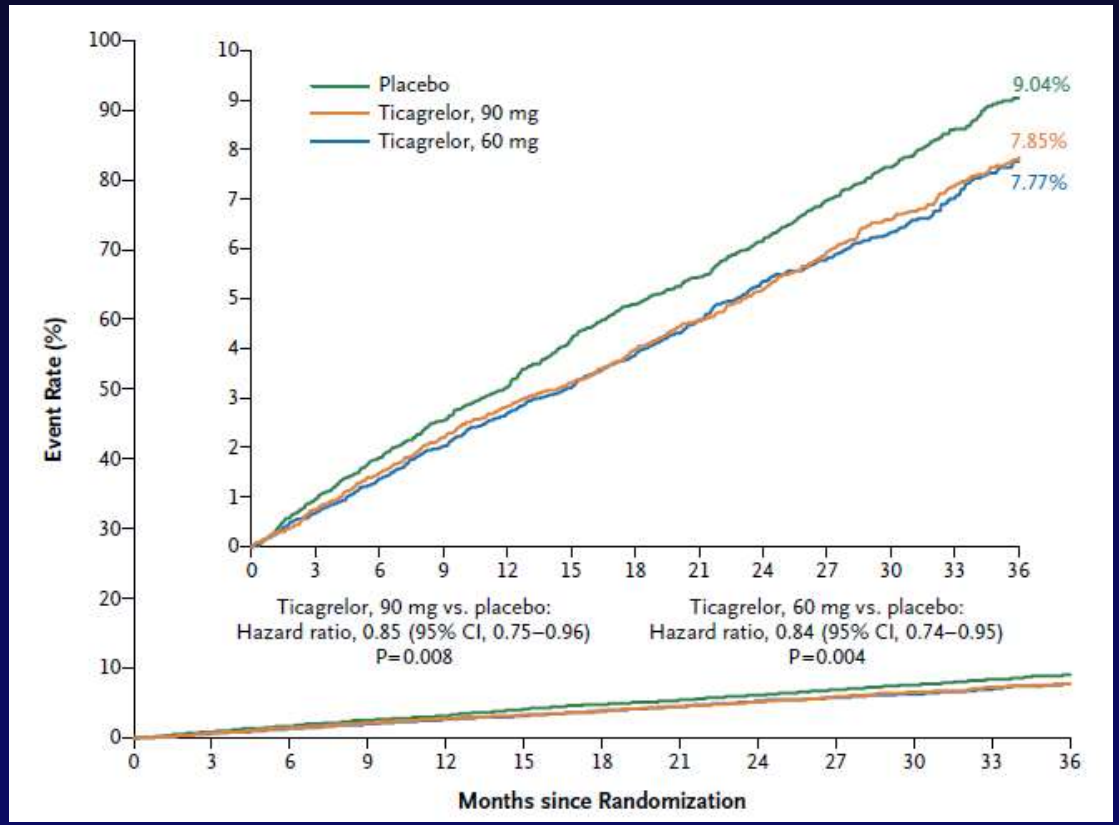
Conclusions In this analysis of the CHARISMA trial, the large number of patients with documented prior MI, ischemic stroke, or symptomatic PAD appeared to derive significant benefit from dual antiplatelet therapy with clopidogrel plus aspirin. Such patients may benefit from intensification of antithrombotic therapy beyond aspirin alone, a concept that future trials will need to validate. (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA]; http://clinicaltrials.gov/ct/show/NCT00050817?order=1; NCT00050817) (J Am Coll Cardiol 2007;49:1982–8) © 2007 by the American College of Cardiology Foundation

HR 0.83, 95% CI 0.72-0.96, p = 0.01



PEGASUS-TIMI

Patient:	AMI + 1 add RF (>50y, DM, 2nd AMI, CKD) (n=21,162)
Intervention:	Ticagrelor 90mg bid (n=7050) 60mg bid (n=7045) on aspirin
Comparison:	Placebo (n=7067)
Outcomes:	Composite of D/MI/Stroke; TIMI major bleeding (33 mo)



Only the 60mg dose is approved for use in patients with a history of MI beyond 12 months.

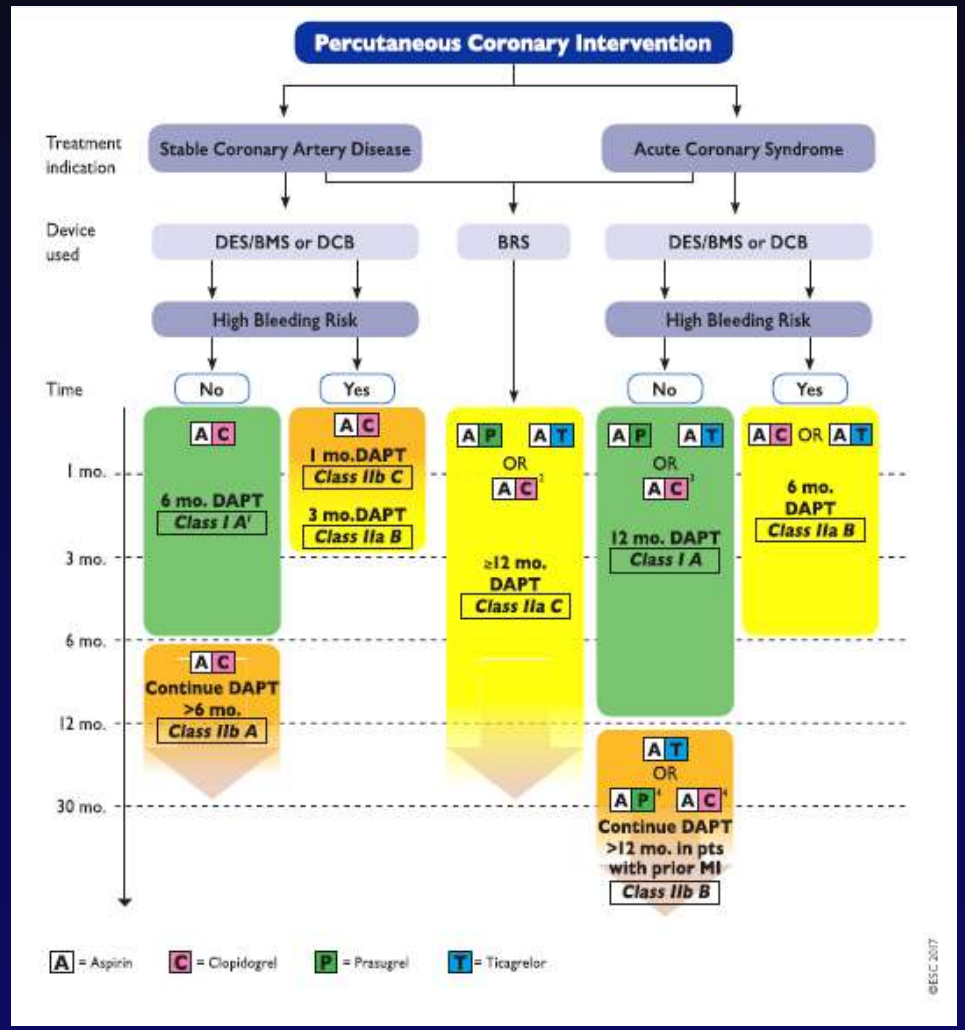
Bonaca et al. N Engl J Med 2015

Prolonged DAPT therapy

Recommendations	Class	Level
In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.	IIb	A
In patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg *b.i.d.* for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.	IIb	B

European Heart Journal (2017) 0, 1–48.

ESC guideline recommends 12Month DAPT treatment in ACS



Marco Valgimigli et al., European Heart Journal (2017) 0, 1–48. doi:10.1093/eurheartj/ehx419

CONTENTS

Summary

- In terms of ACS and Post MI, residual ischemic risk is frequent not only western and but also Asian patients.
- To prevent re-current CV events, need to manage high-risk disease factors differently.
- Prolonged DAPT should be considered as the standard of care in ACS & high-risk post MI patients

Thank You For Your Attention!

Seoul National University Bundang Hospital