Antithrombotic Strategy of Rivaroxaban for AF Patients Undergoing PCI in Real Practice

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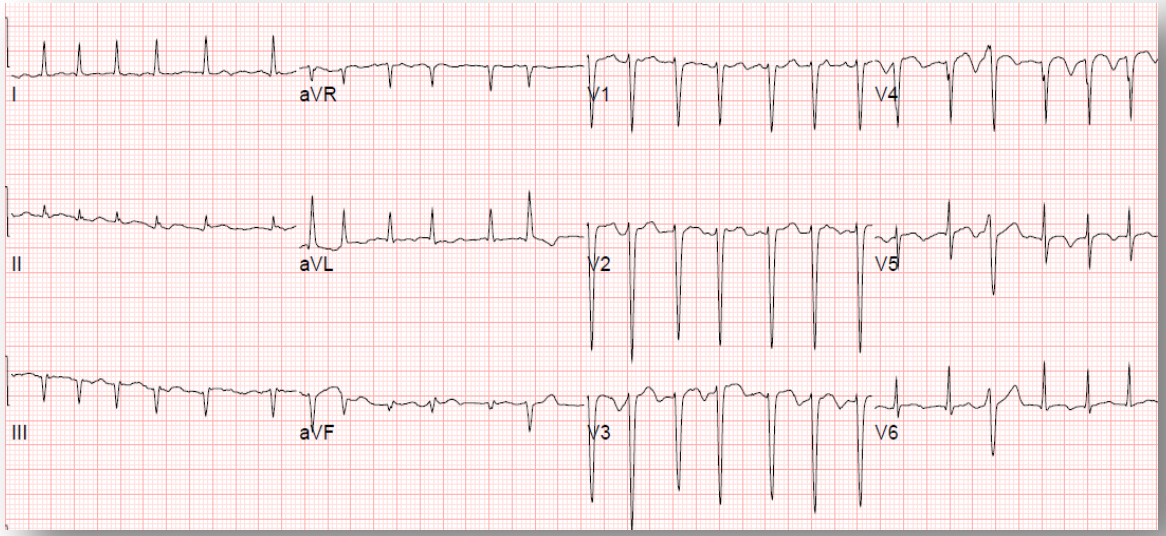
CASE, M/64 C.C; Recently aggravated chest discomfort for 3 days

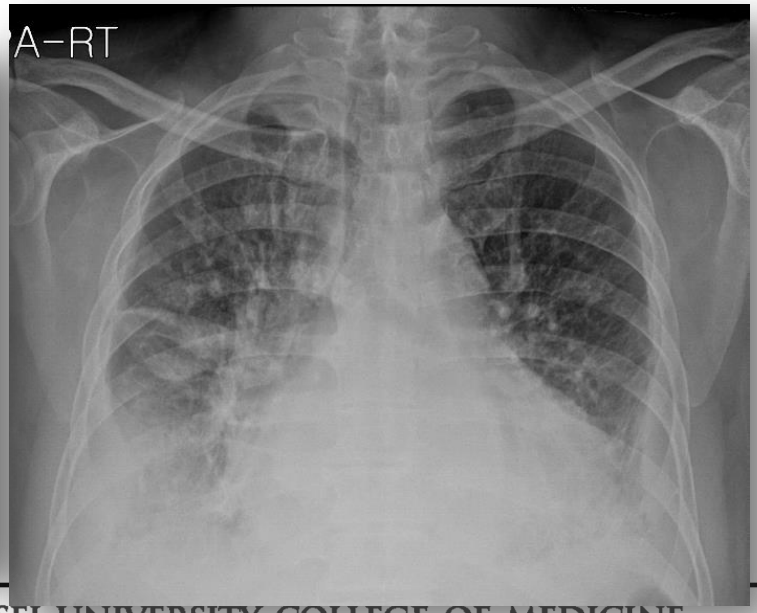
- BP 92/63 mmHg, HR 152 BPM, cTnT (+), 165cm/78kg (BMI 28.6)
- Risk factors; HTN, Dyslipidemia, Ex-smoker, Prior PCI, AF

  → **Dx; NSTEMI (recent MI)**

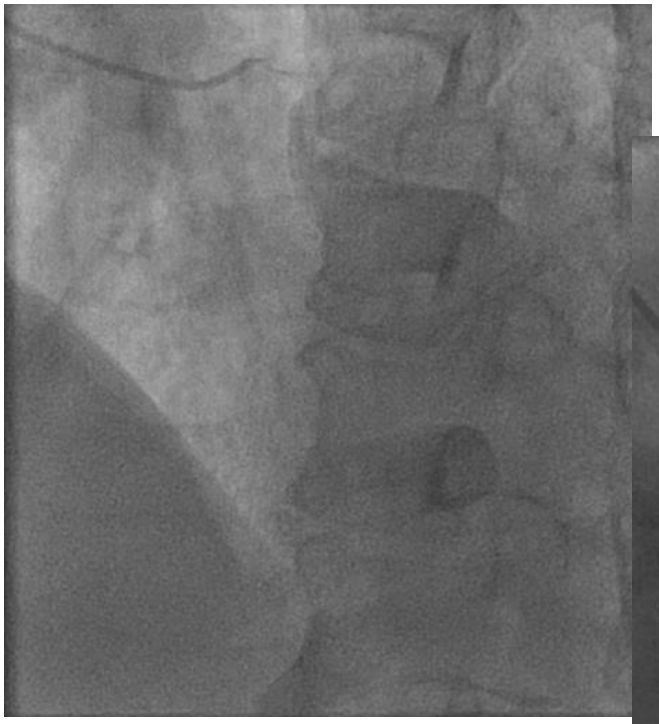
- Echo; Newly developed in RWMA @ ant wall / Increased LA & LV (LVEDD/LVESD: 50/38mm) with reduced LV systolic function (LVEF: 75 → 45%)
- **PHx:** s/p PTCA c stent at **p-dLCx (Xience P 3.0x38)** & **m-RCA (Xience P 3.5x23)** (2012.01) due stable angina

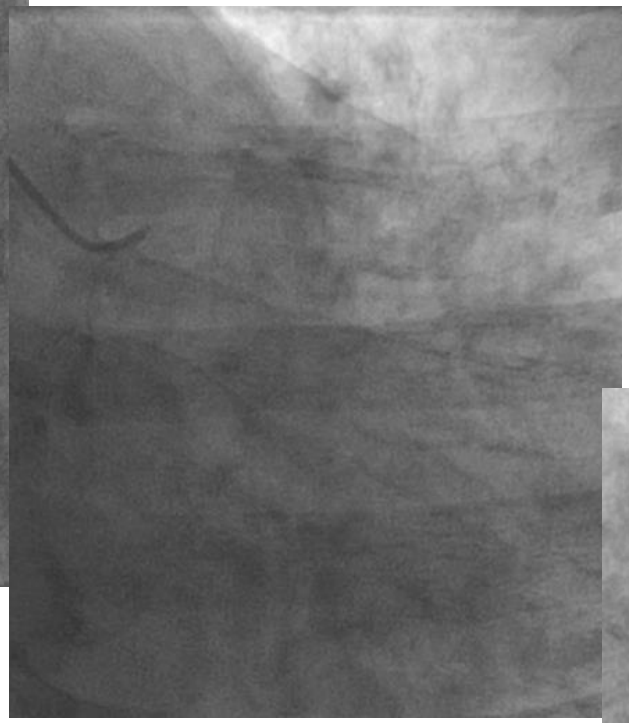
  → f/u CAG: patent previous stent (2013.2)

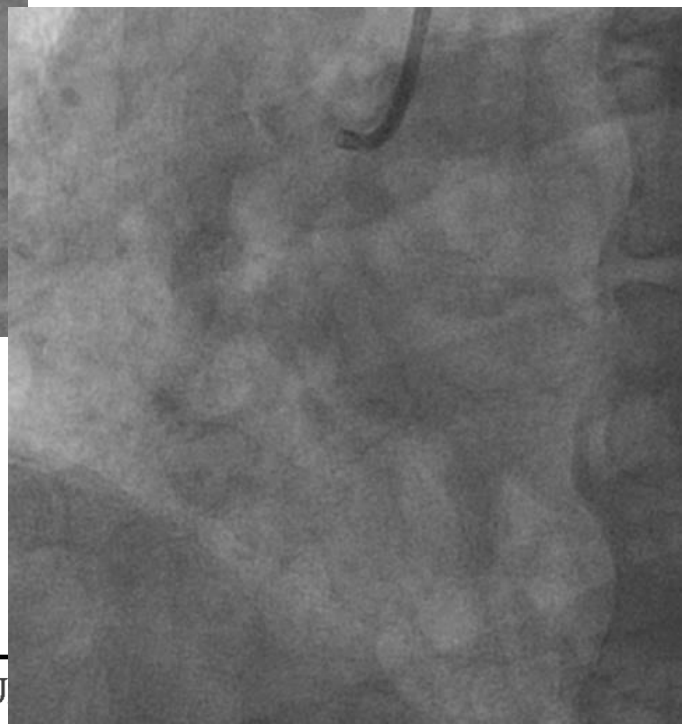




Previous CAG due to exertional chest pain (2012.01)

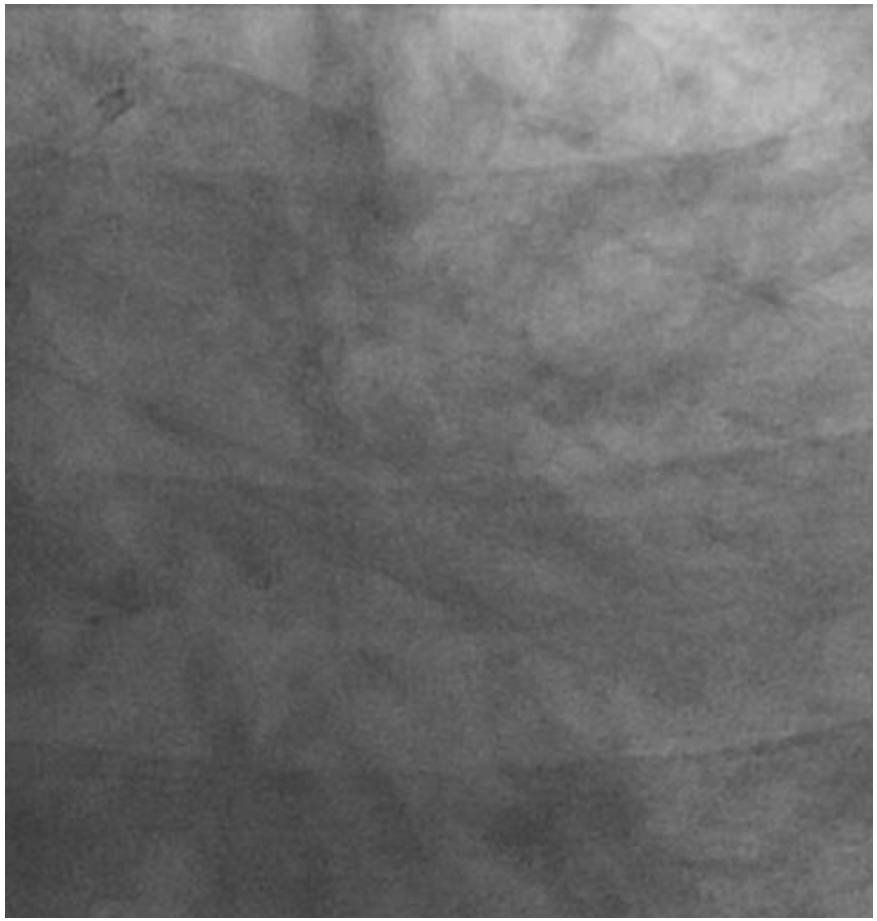


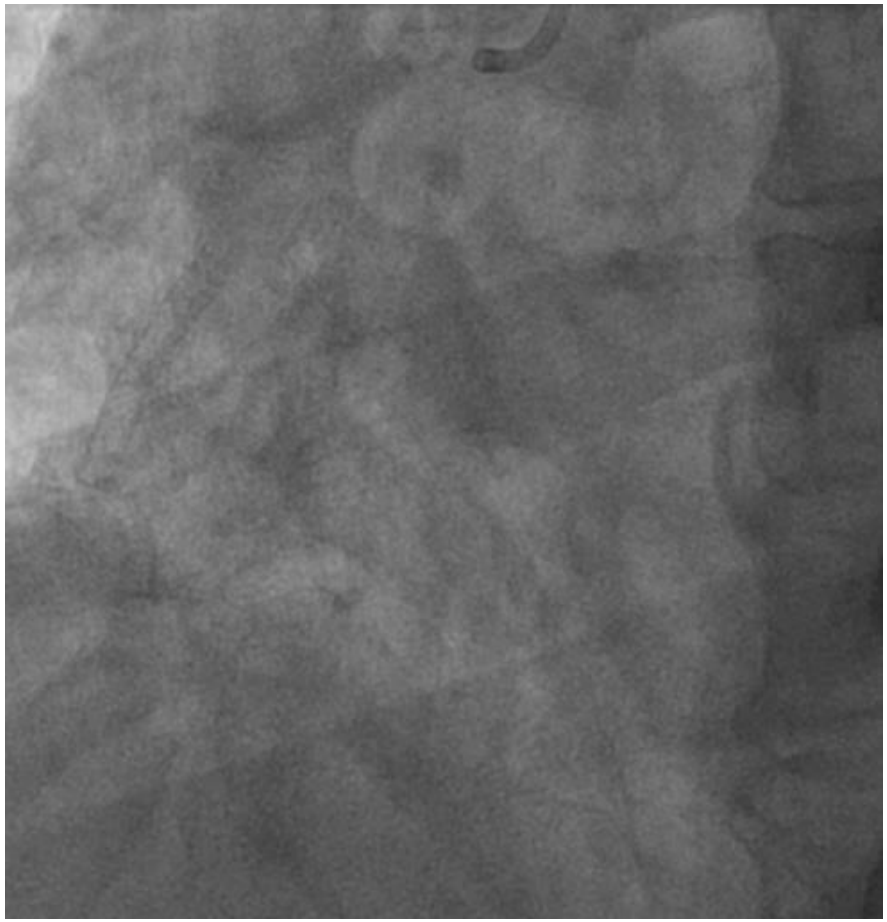




✓ **CAOD (2VD)**

PCI of LCx & RCA @ 2012



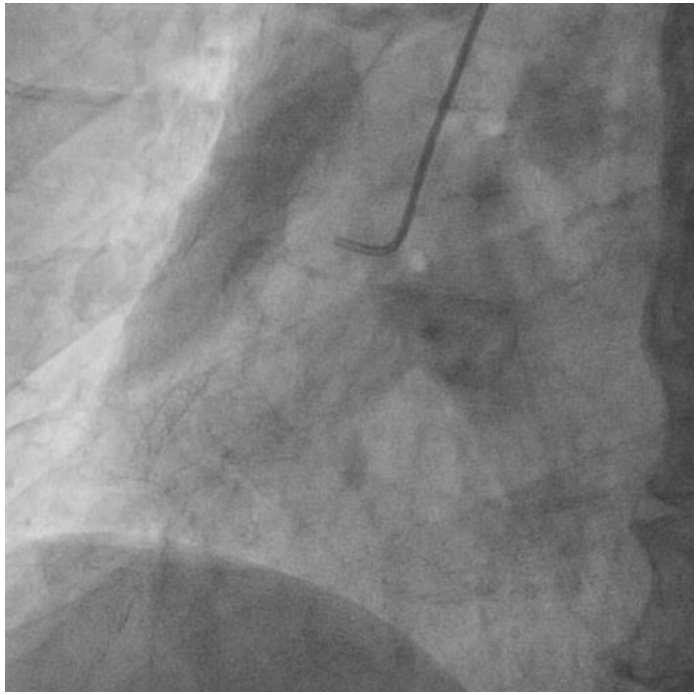


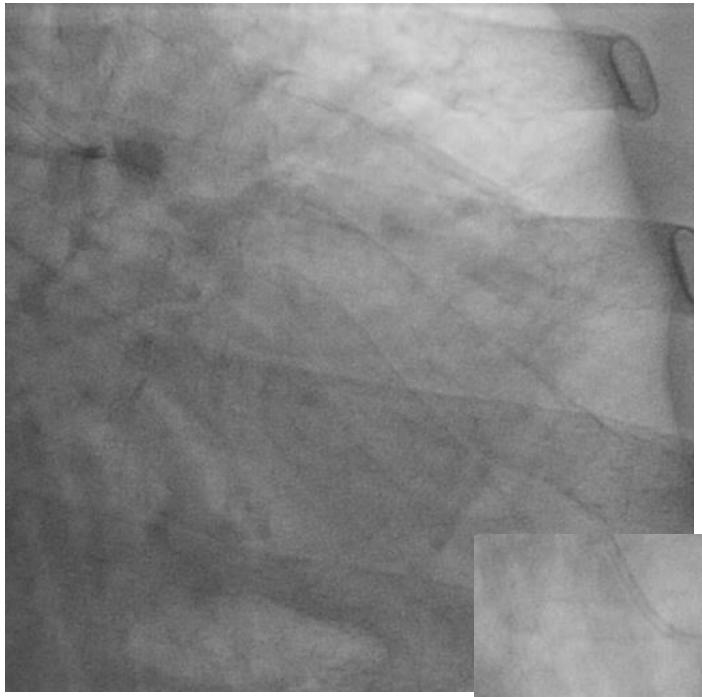
Xience Prime 3.0*38 at LCx

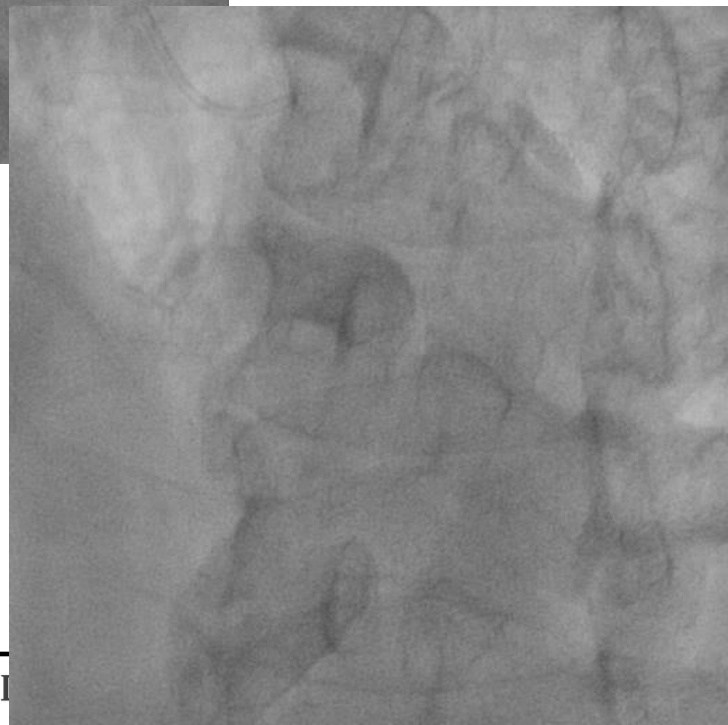
Xience Prime 3.5*23 at m-RCA

→ 12-month follow-up angio, patents DESs & No aggravation of LAD

NSTEMI & Pul edema → CAG (2016.3.31)



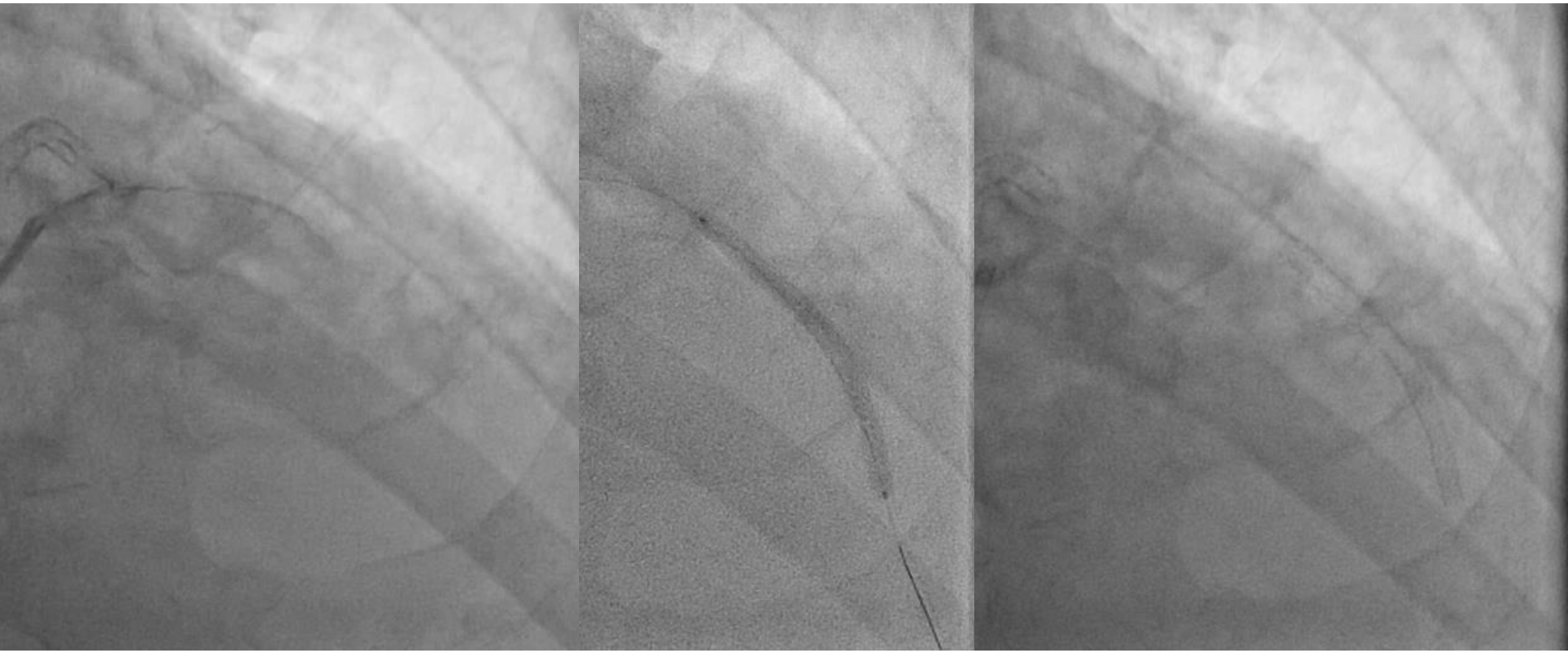




- **Patent previous stents at m-RCA & LCx**

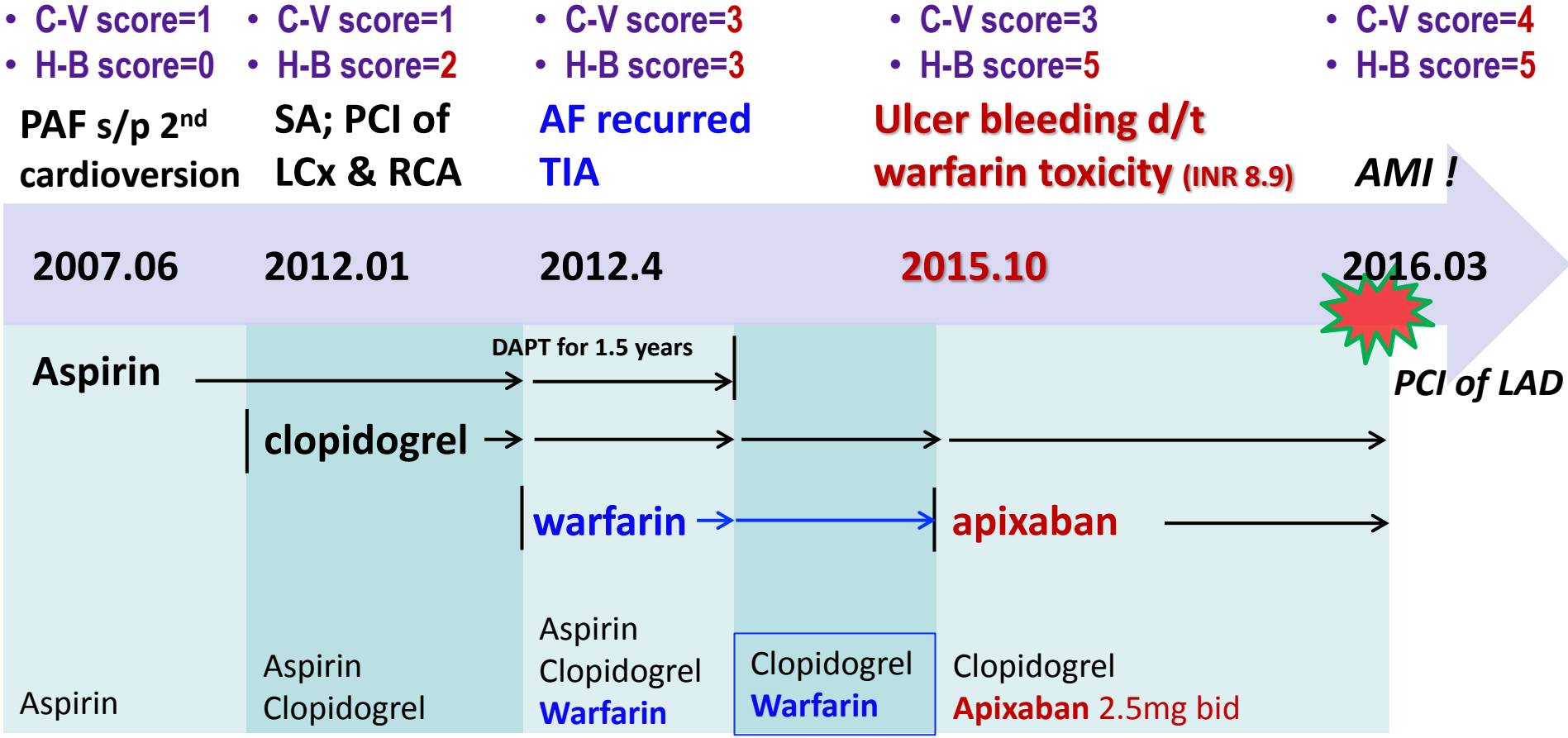
→ Total occlusion of m-LAD !

PCI at LAD (2016.3.31)



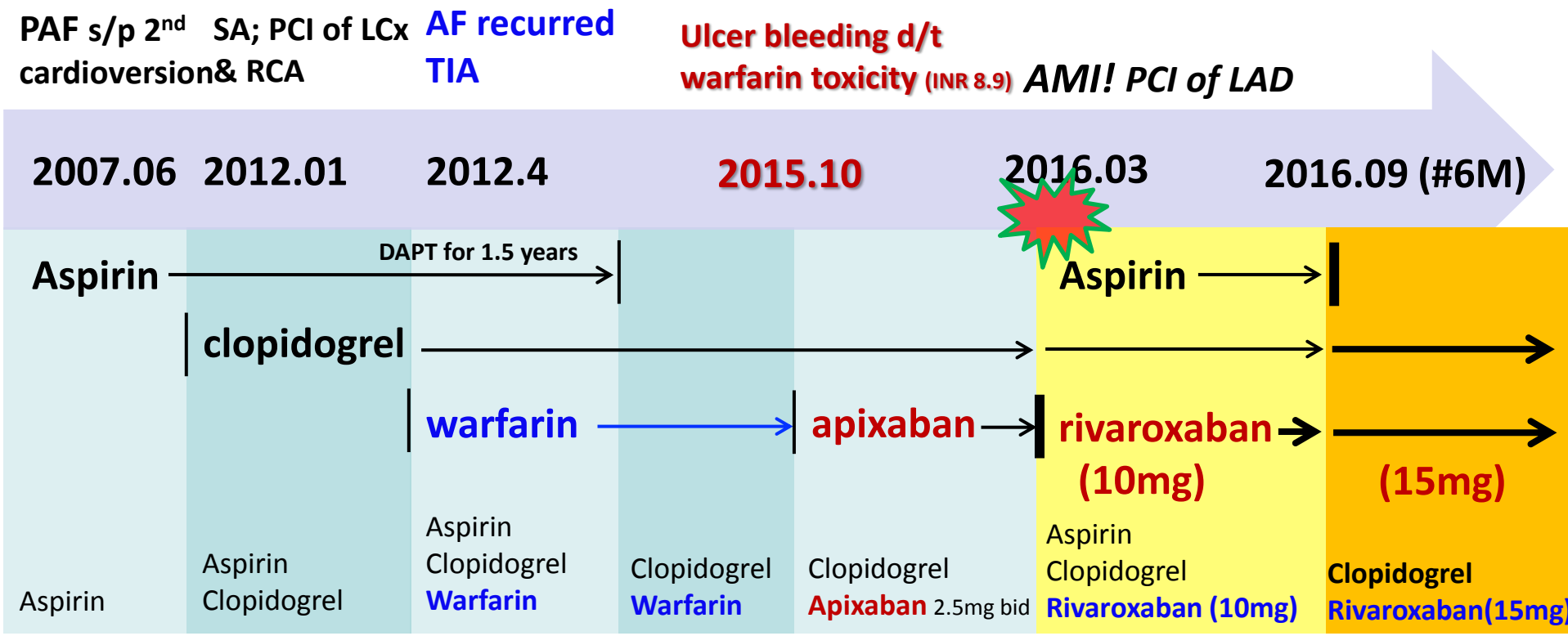
Resolute Onyx 3.0*38 mm at m-dLAD

Summary of medication history (1)

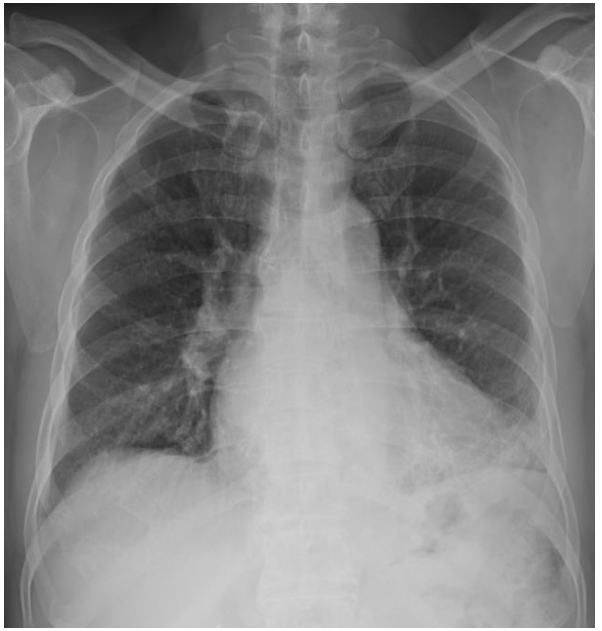


What about Antiplatelet & antithrombotic therapy after AMI?

Summary of medication history (2)



Last OPD visit @ April 18, 2017



- No chest pain, no bleeding sign
- Current med

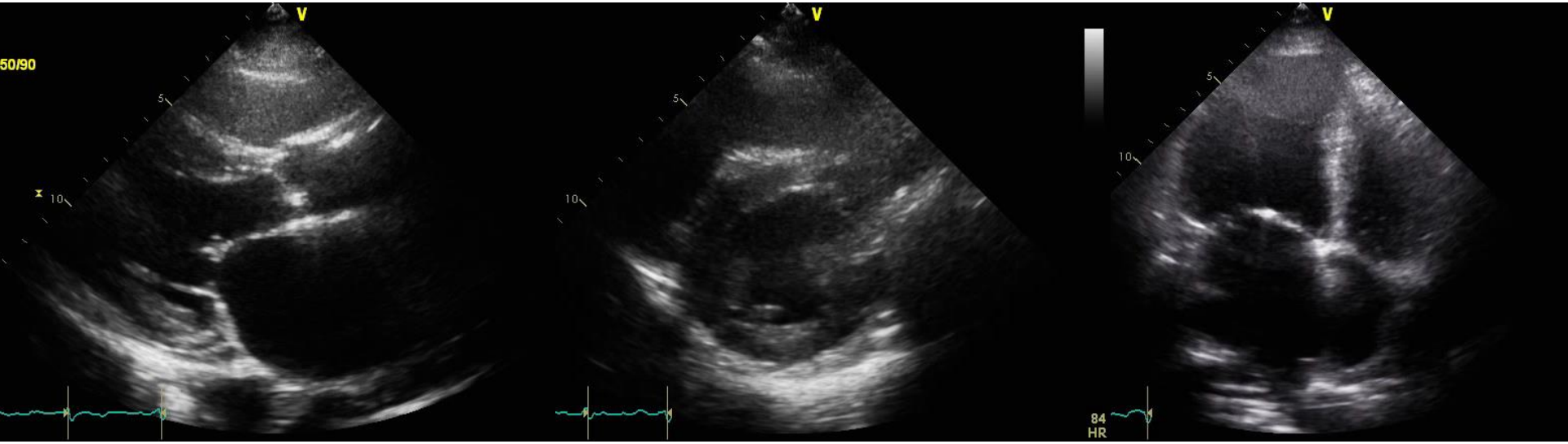
  Rivaroxaban 15mg

  Clopidogrel

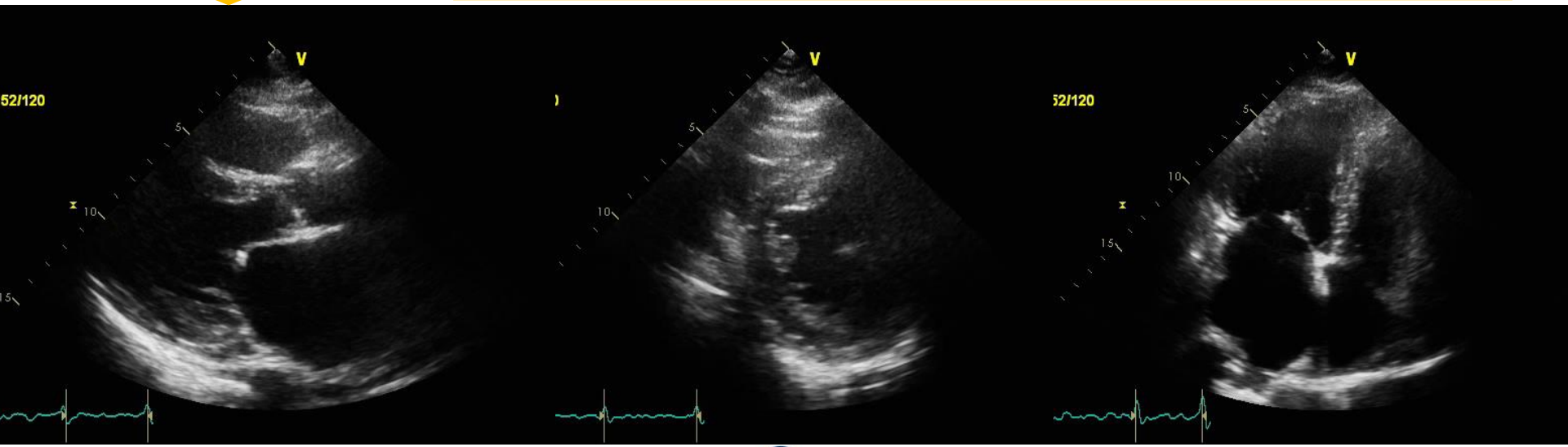
  Dilatrend SR 16mg

  Rosuvastatin 20mg

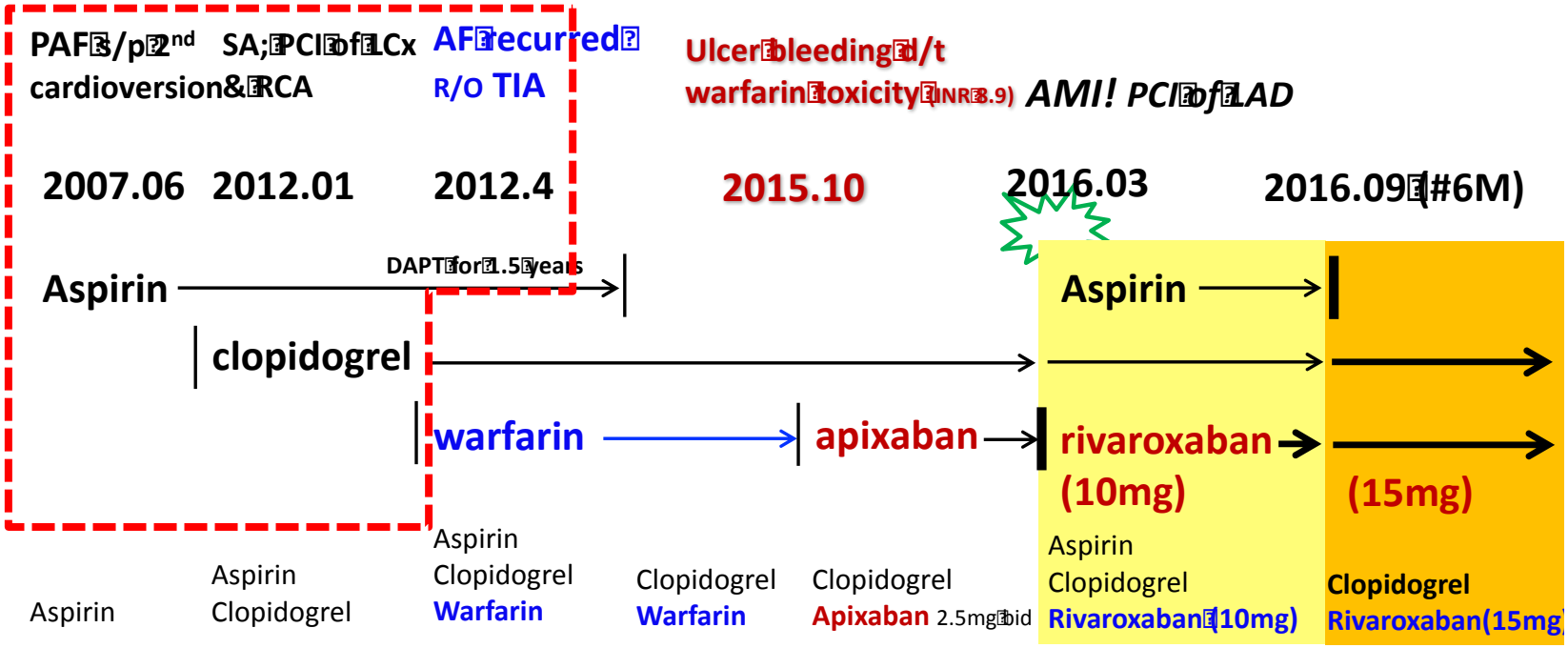
Echo follow-up



Disappeared previous RWMA, LVEF : 45 → 60%



Lessons from the patient's course



Lesson 1.

- ✓ We confirmed that **DAPT was weak in the prevention of thrombotic events in AF/PCI patients.**

For the successful management for CAD with AF

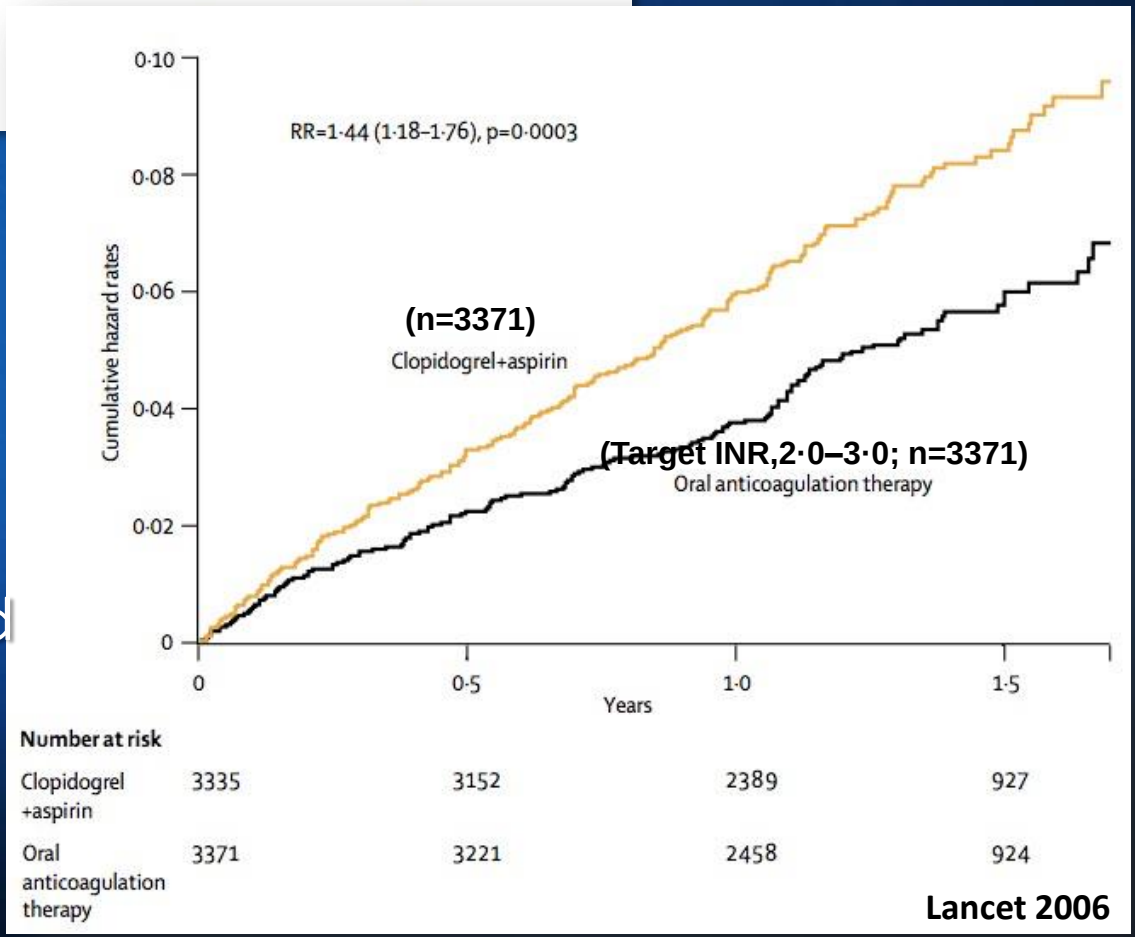
1. Prevention of thromboembolic events ?
2. Prevention of Stent thrombosis or recurrent MI

DAPT vs. OAC ?

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

*The ACTIVE Writing Group on behalf of the ACTIVE Investigators**

 # Primary outcome:
Occurrence of stroke, non-CNS systemic embolus, MI, or vascular death.



Lancet 2006

✔ In preventing ischemic & embolic events associated with AF, **OAC is more effective than DAPT !**

For the successful management for CAD with AF

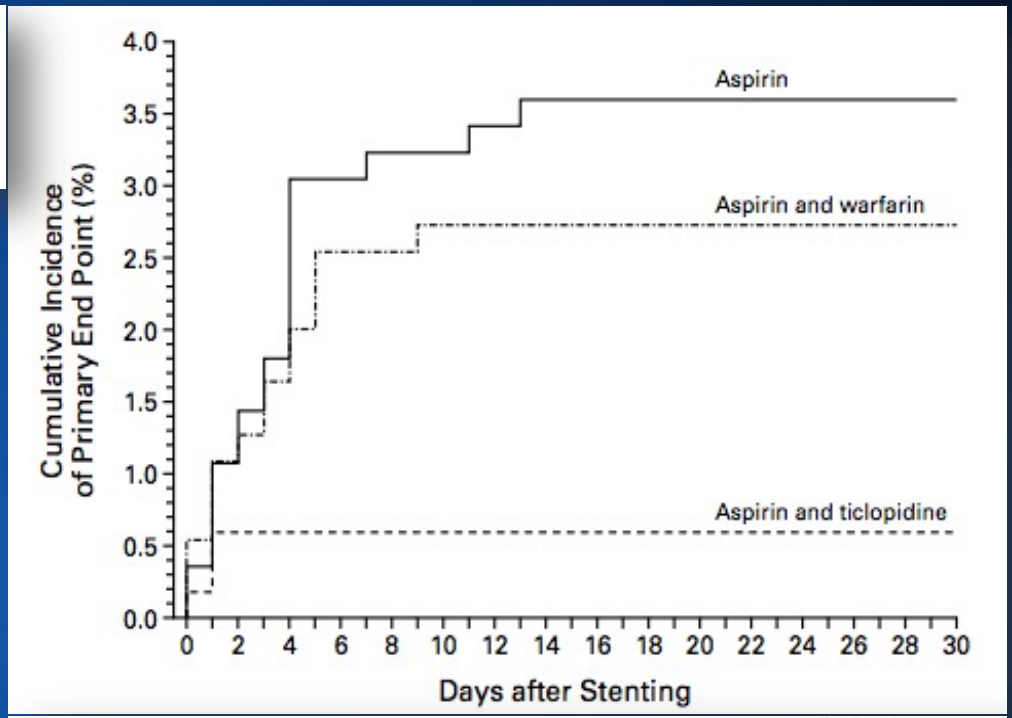
1. ~~Prevention of thromboembolic events~~
2. **Prevention of Stent thrombosis or recurrent MI ?**

DAPT vs. OAC ?

A CLINICAL TRIAL COMPARING THREE ANTITHROMBOTIC-DRUG REGIMENS AFTER CORONARY-ARTERY STENTING

MARTIN B. LEON, M.D., DONALD S. BAIM, M.D., JEFFREY J. POPMA, M.D., PAUL C. GORDON, M.D., DONALD E. CUTLIP, M.D., KALON K.L. HO, M.D., ALEX GIAMBARTOLOMEI, M.D., DANIEL J. DIVER, M.D., DAVID M. LASORDA, D.O., DAVID O. WILLIAMS, M.D., STUART J. POCOCK, PH.D., AND RICHARD E. KUNTZ, M.D., FOR THE STENT ANTICOAGULATION RESTENOSIS STUDY INVESTIGATORS*

Primary end point:
Death, TLR,
Angiographic thrombosis or MI

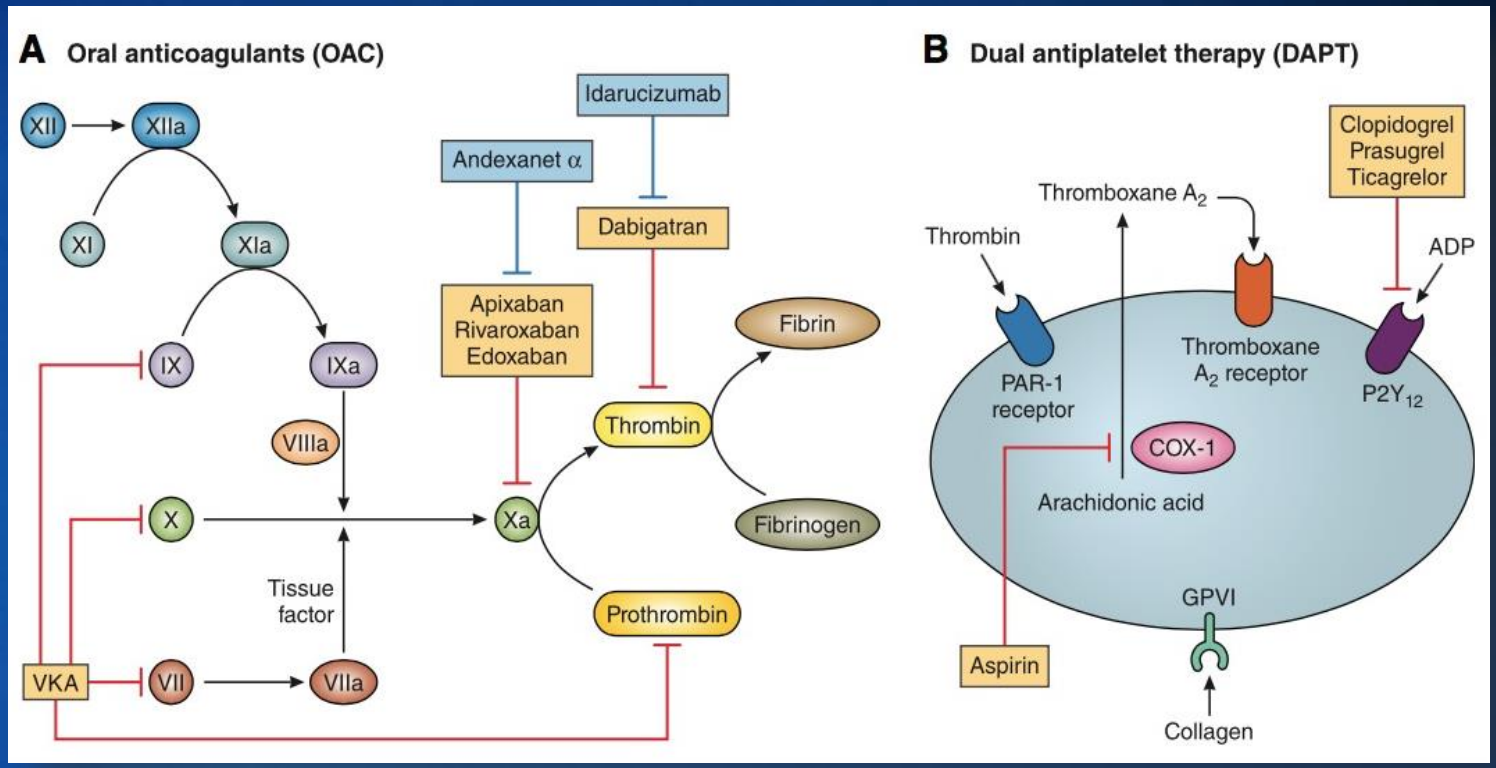


EVENT	RELATIVE RISK (95% CI) AS COMPARED WITH ASPIRIN ALONE	P VALUE	RELATIVE RISK (95% CI) AS COMPARED WITH ASPIRIN AND WARFARIN	P VALUE
Primary end point	0.15 (0.05–0.43)	<0.001	0.20 (0.07–0.61)	0.01
Death	—	—	—	—
Revascularization of target lesion	0.16 (0.06–0.46)	0.001	0.22 (0.07–0.66)	0.02
Angiographically evident thrombosis	0.19 (0.06–0.57)	0.001	0.20 (0.07–0.61)	0.01
Recurrent myocardial infarction	0.20 (0.07–0.62)	0.014	0.27 (0.08–0.90)	0.11

✔ **DAPT was superior to OAC with warfarin in reducing ST risks** among ACS patients requiring stent implantation.

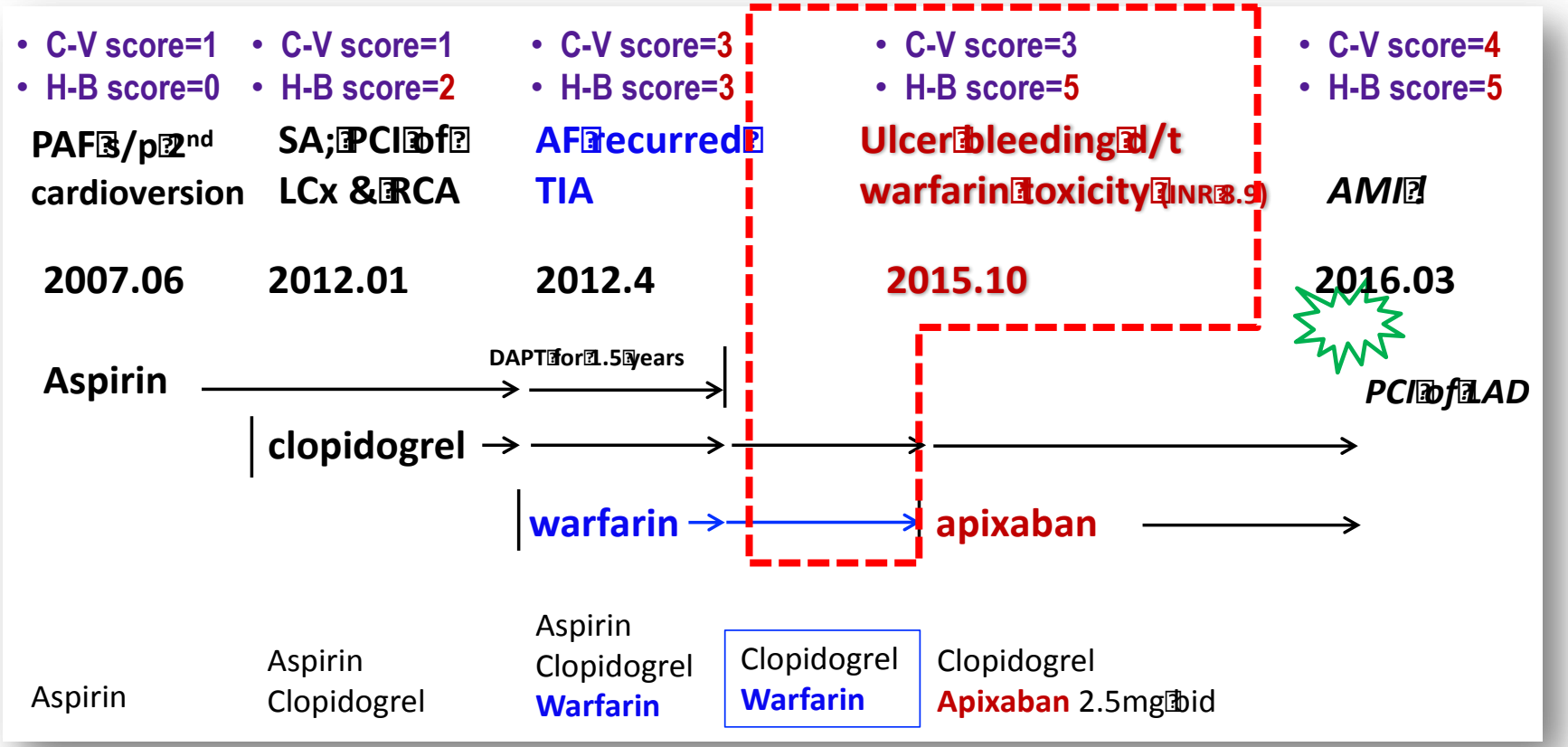
N Engl J Med 1998;339:1665-71

Q; Answer for CAD/ACS/PCI with AF ?



A: Combination of DAPT and OAC … Triple therapy !

Lessons from the patient's course

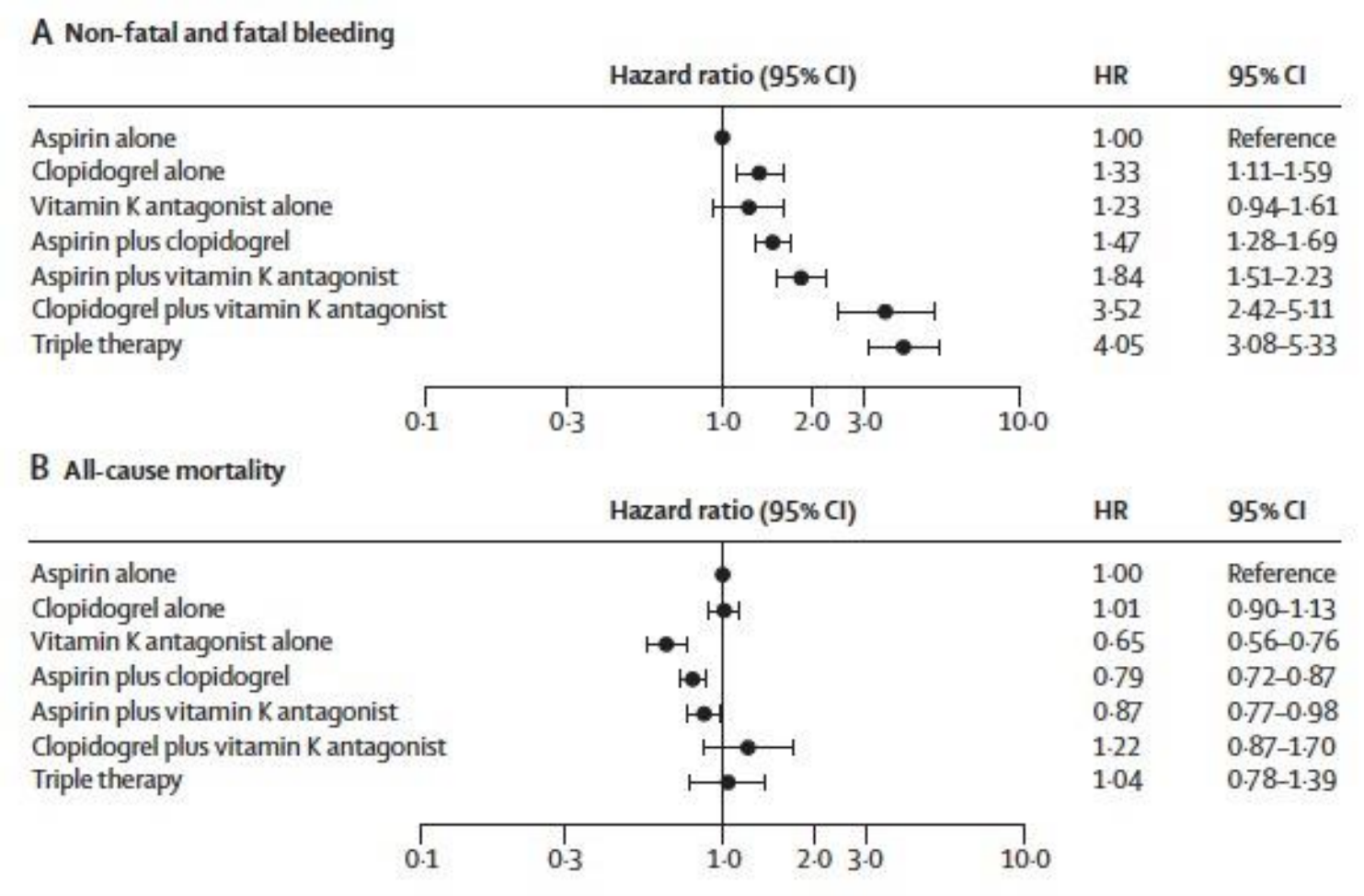


Lesson 2.

- ✓ We confirmed that **Vit-K antagonists might show a higher bleeding tendency in AF/PCI patients requiring antiplatelet therapy.**

Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data (N=40,812 patients)

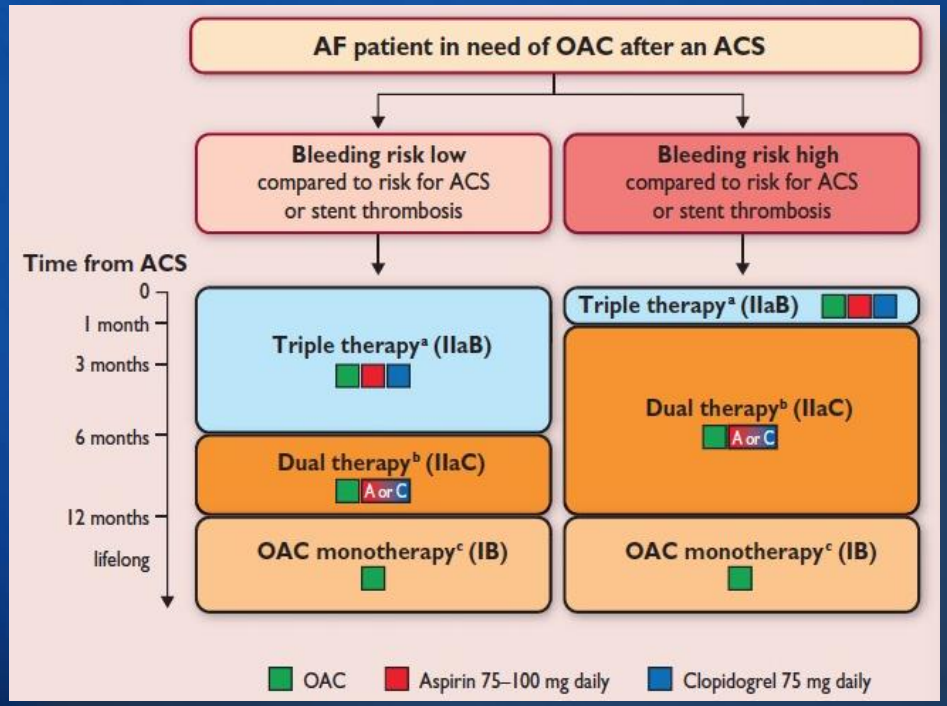
Sørensen R et al *Lancet* 2009; 374: 1967–74

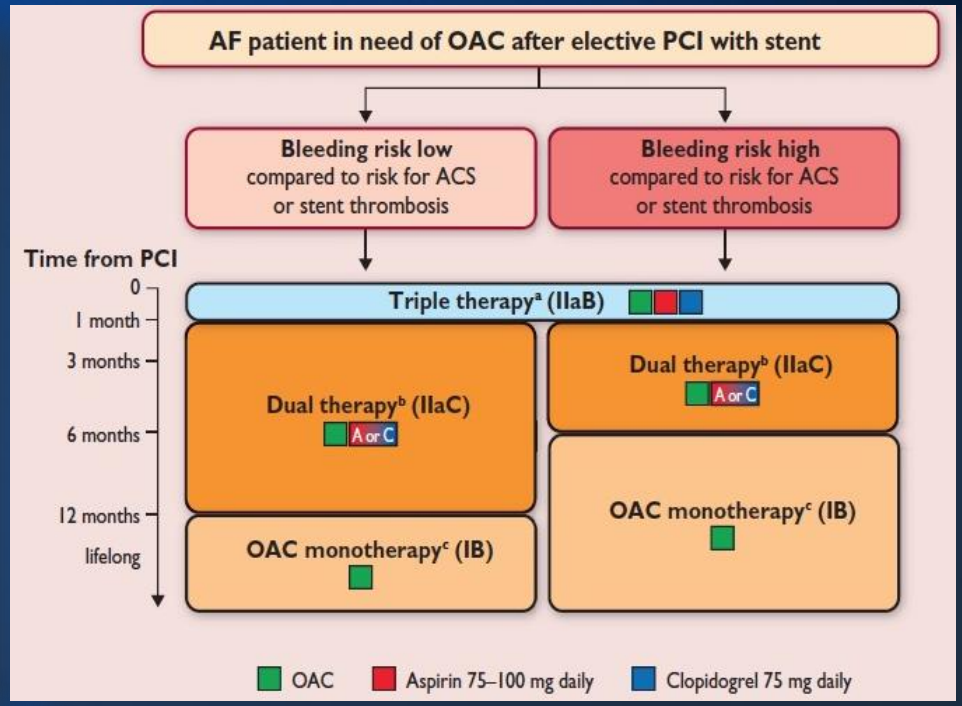


- **In AF with IHD patients*, no survival benefit with combination therapy !**

Individualized treatment in AF with ACS/PCI

- ✓ According to the assessment of the patient's risk of stroke (CHA2DS2-VASc; 1 vs ≥2) and risk of bleeding (HAS-BLED 0-2 vs. . ≥3), …

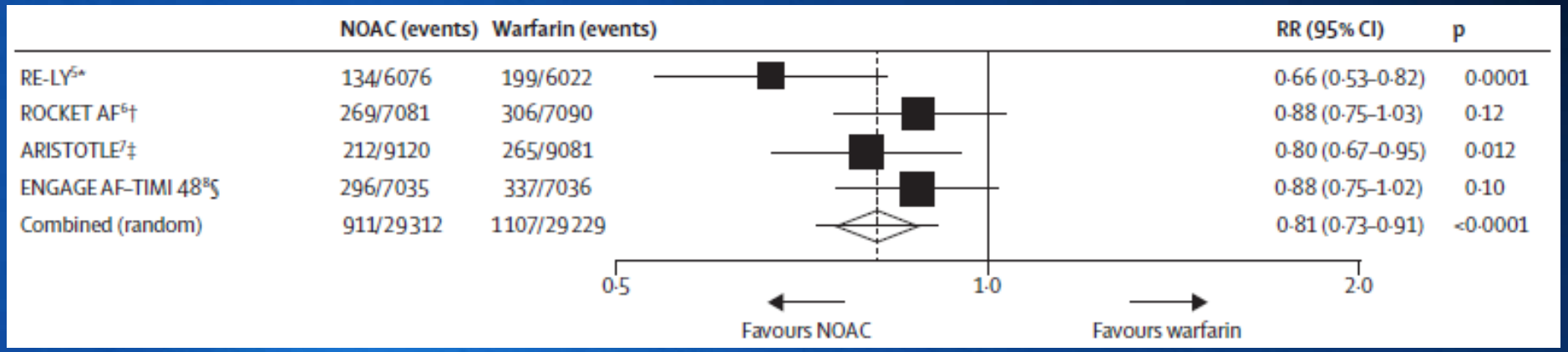




2016 ESC Guidelines, Eur Heart J, 2016.

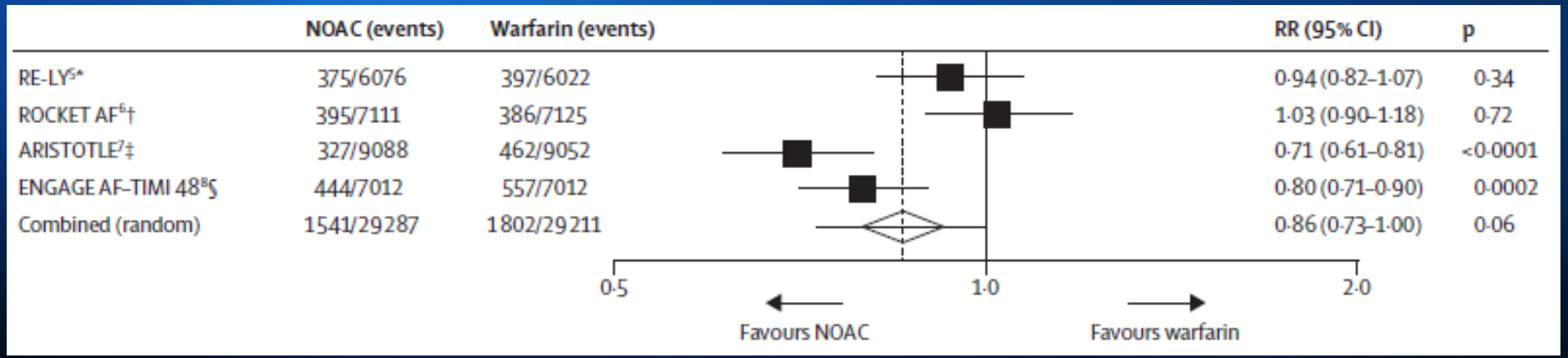
Efficacy and safety outcomes of NOACs compared with warfarin ?

<Stroke and SEE>



	NOAC (events)	Warfarin (events)	RR (95% CI)	p
RE-LY[5]*	134/6076	199/6022	0·66 (0·53–0·82)	0·0001
ROCKET AF[6]†	269/7081	306/7090	0·88 (0·75–1·03)	0·12
ARISTOTLE[7]‡	212/9120	265/9081	0·80 (0·67–0·95)	0·012
ENGAGE AF–TIMI 48[8]§	296/7035	337/7036	0·88 (0·75–1·02)	0·10
Combined (random)	911/29312	1107/29229	0·81 (0·73–0·91)	<0·0001

<Major bleeding>



	NOAC (events)	Warfarin (events)	RR (95% CI)	p
RE-LY[5]*	375/6076	397/6022	0·94 (0·82–1·07)	0·34
ROCKET AF[6]†	395/7111	386/7125	1·03 (0·90–1·18)	0·72
ARISTOTLE[7]‡	327/9088	462/9052	0·71 (0·61–0·81)	<0·0001
ENGAGE AF–TIMI 48[8]§	444/7012	557/7012	0·80 (0·71–0·90)	0·0002
Combined (random)	1541/29287	1802/29211	0·86 (0·73–1·00)	0·06

Lancet 2014; 383: 955–62.

Data on the use of NOACs with DAPT in AF ?

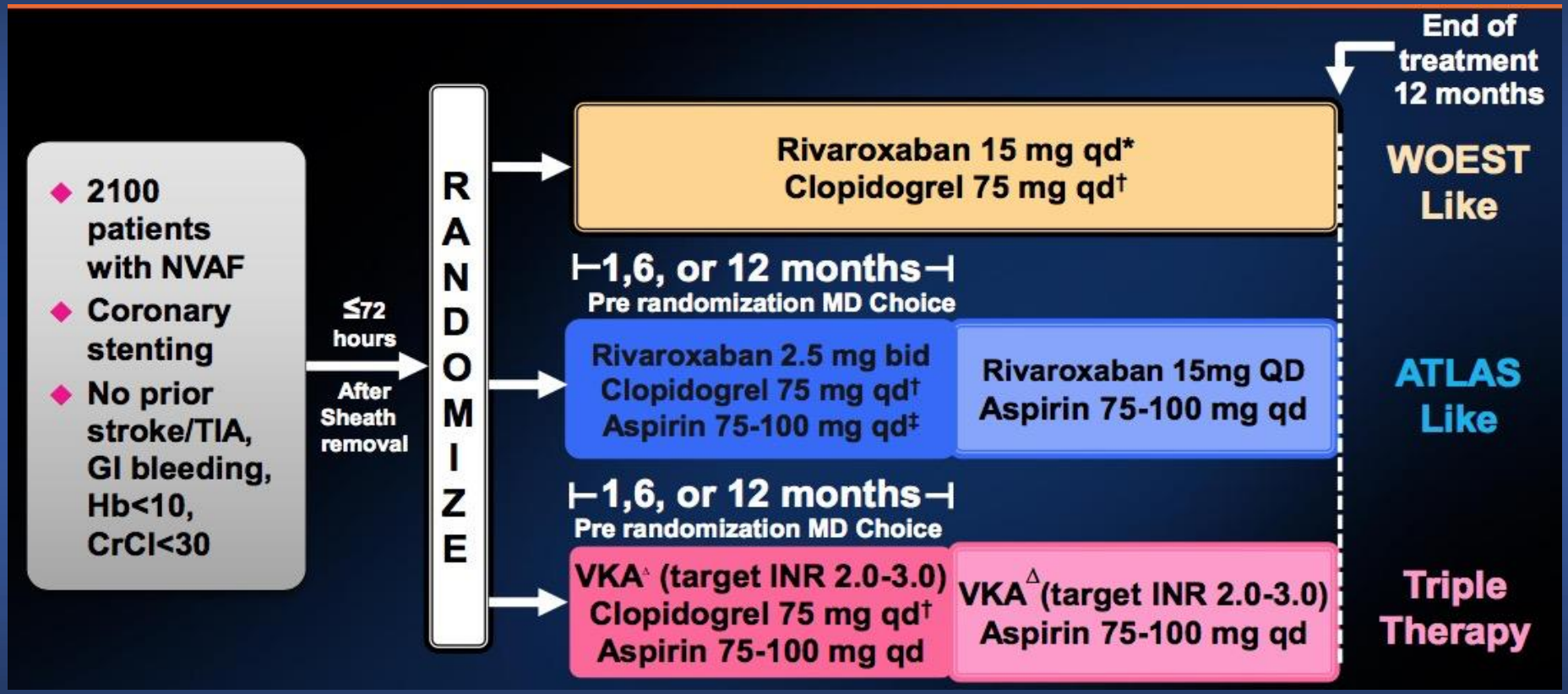
- ***Currently, data on the use of NOACs with DAPT in AF are limited.***

RE-LY®[1]	ROCKET-AF[2]	ARISTOTLE[3]	ENGAGE AF[4]
4.5% received DAPT	**0%** DAPT not permitted	**0%** DAPT not permitted	**0%** DAPT not permitted
32% ASA alone	36% ASA alone	31% ASA alone	29% ASA alone
1.9% clopidogrel alone		1.9% clopidogrel alone	2.3 % clopidogrel alone

ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy. 1. Dans AL et al. Circulation 2013; 2. Patel MR et al. N Engl J Med 2011; 3. Granger CB et al. N Engl J Med 2011; 4. Giugliano RP et al. N Engl J Med. 2013

PIONEER AF-PCI: Rivaroxaban and PCI in Patients with AF

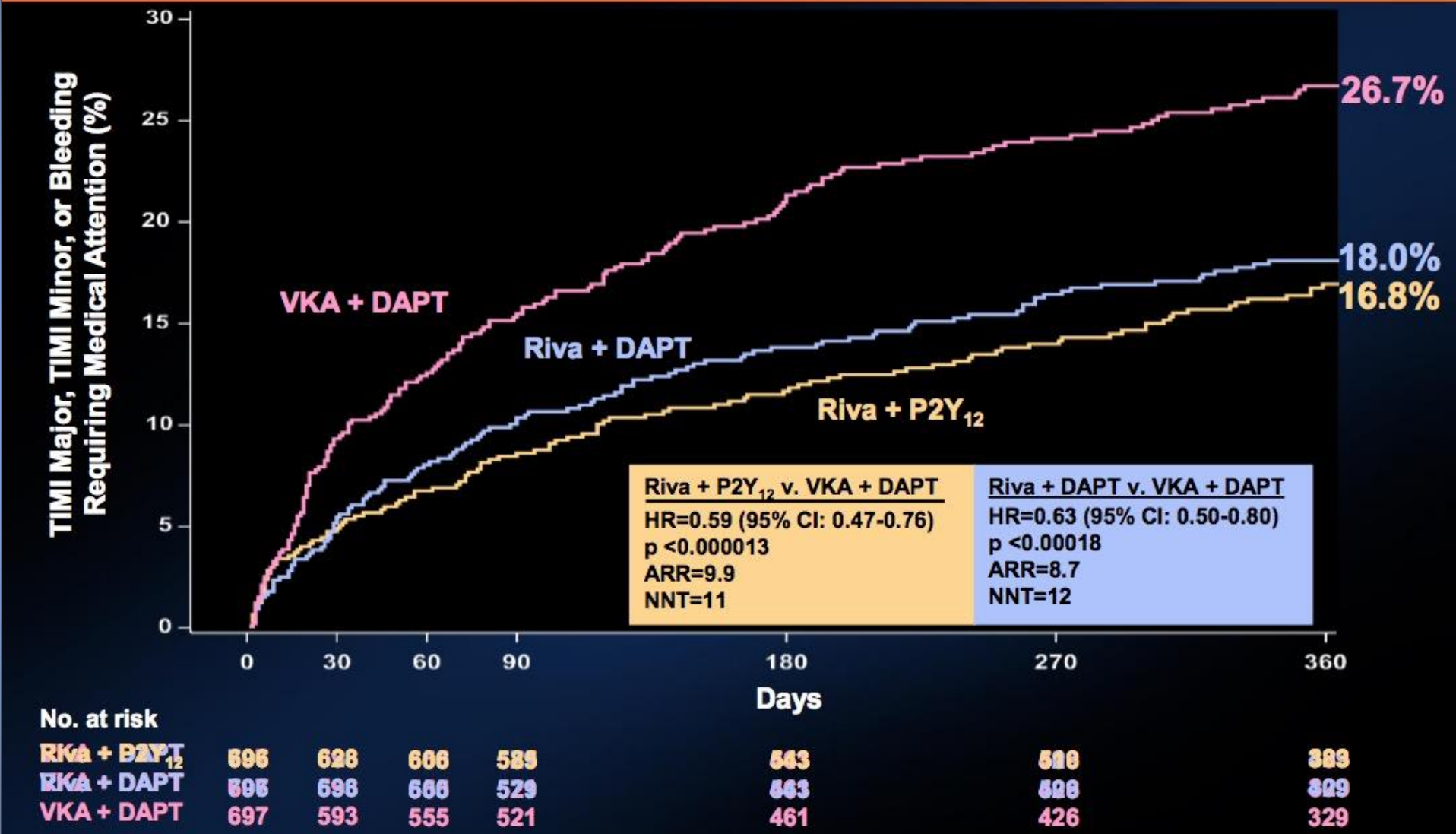
- Aim: to assess the safety of two rivaroxaban regimens vs. VKA after PCI c stenting in non-valvular AF



- Primary safety endpoint: clinically significant bleeding
  - TIMI major or minor bleeding + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke

Gibson et al. 2016 AHA

Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



No. at risk

Riva + P2Y12	696	628	606	589	543	518	389
Riva + DAPT	695	698	666	529	463	426	329
VKA + DAPT	697	593	555	521	461	426	329

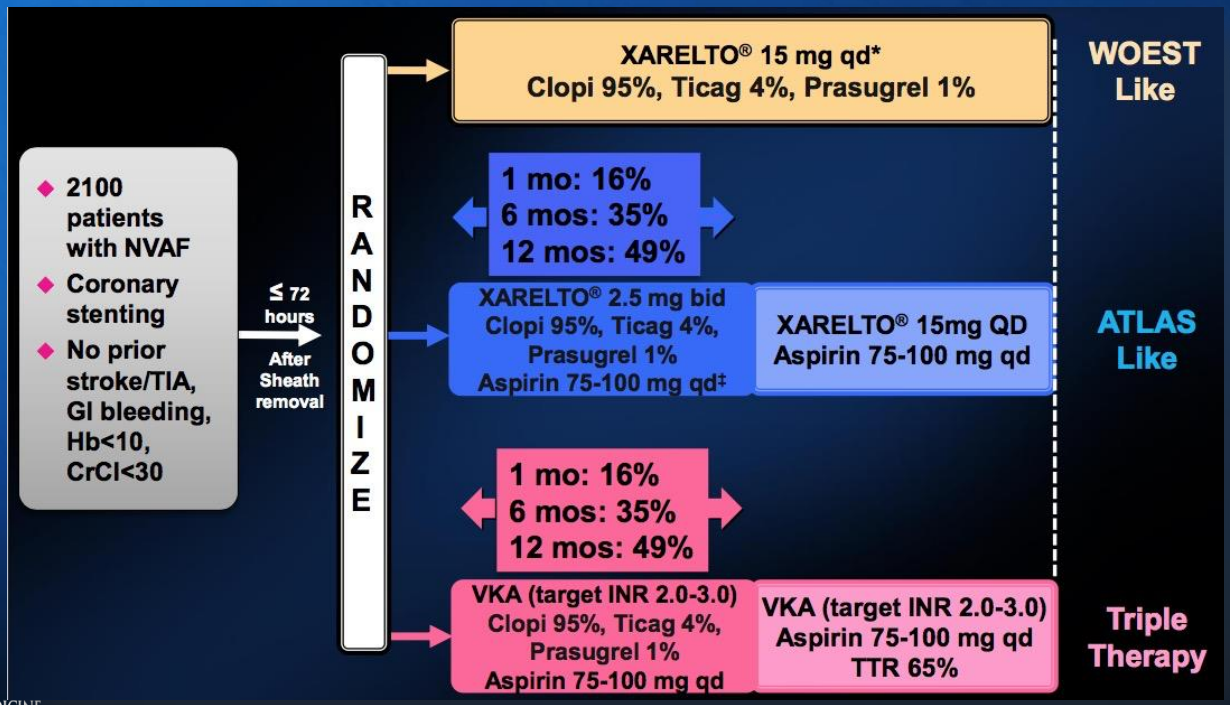
Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.
Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Gibson et al. AHA 2016

Data on the use of NOAC & new-antiplatelet agents (ticagrelor) in ACS ?

- Limited data exists regarding full-dose of NOAC & ticagrelor for AF-PCI patients.

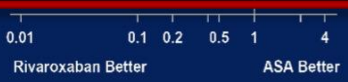
 # PIONEER AF-PCI; use of ticagrelor or prasugrel ≈ 5%



Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind,

TIMI non-CABG clinically significant bleeding subgroups

Characteristic	Number	KM% ASA	KM% Rivaroxaban	Hazard Ratio (95%CI)	Interaction p-value
Prior MI					
No	2378	5.87	6.45	1.15 (0.81, 1.64)	0.5020
Yes	659	6.31	4.68	0.88 (0.43, 1.78)	
Prior PCI					
No	2436	6.15	6.53	1.18 (0.84, 1.67)	0.2291
Yes	601	5.23	4.17	0.68 (0.29, 1.57)	
Prior CABG					
No	2911	5.86	6.09	1.12 (0.81, 1.55)	0.4879
Yes	126	7.92	5.60	0.67 (0.16, 2.80)	
Current smoking					
No	2040	7.22	6.81	1.01 (0.71, 1.44)	0.4303
Yes	997	3.58	4.52	1.39 (0.69, 2.79)	
GRACE risk score					
<100	1724	3.71	5.16	1.37 (0.85, 2.21)	0.2539
100-140	1197	8.78	7.94	0.99 (0.64, 1.54)	
>140	116	10.70	1.85	0.25 (0.03, 2.25)	
P2Y12 at Randomization					
Clopidogrel	1333	4.13	3.71	0.95 (0.53, 1.71)	0.5889
Ticagrelor	1704	7.46	8.09	1.15 (0.79, 1.68)	



TIMI non-CABG clinically significant bleeding: non-CABG major, minor, or requiring medical attention.

Beth Israel Deaconess Medical Center

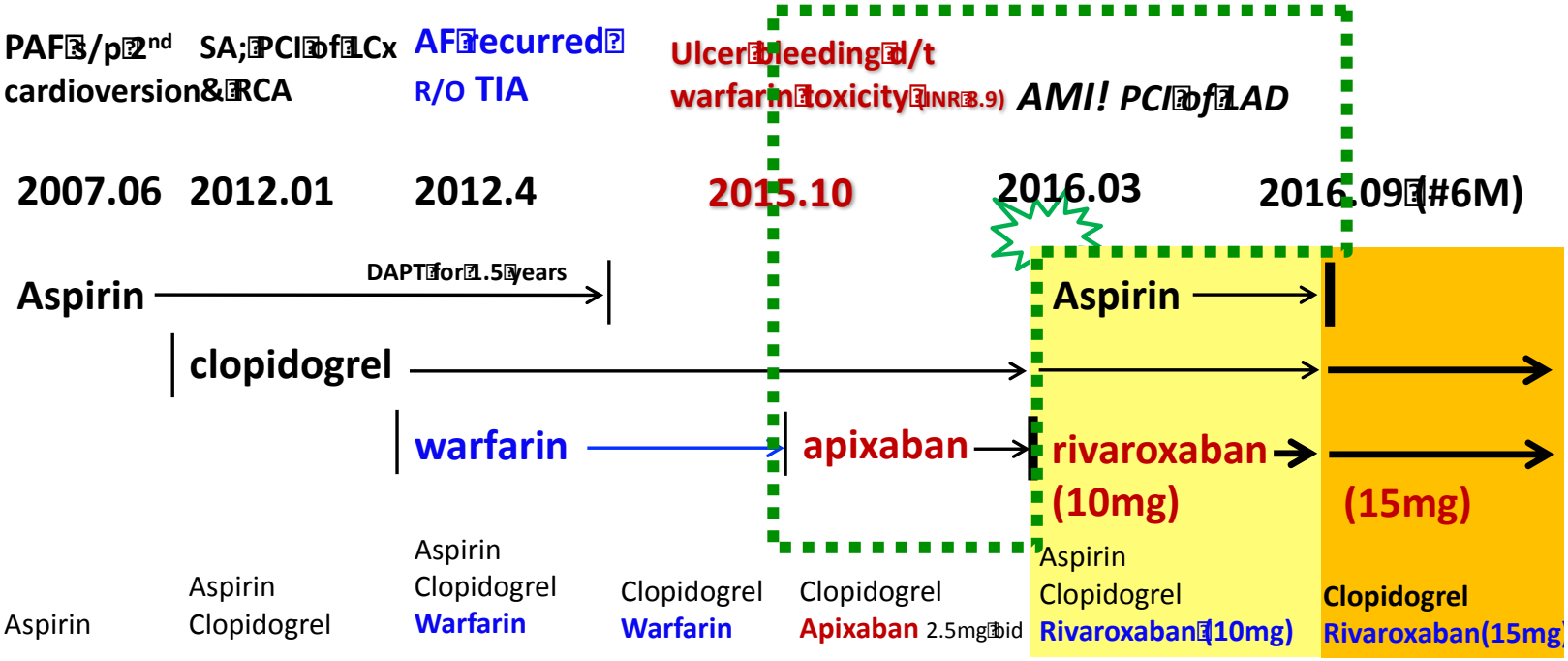
Duke Clinical Research Institute

GEMINI ACS 1

SEVERANCE CARDIOVASCULAR HOSPITAL

Figure 2: **TIMI non-CABG clinically significant bleeding between treatment groups**
TIMI=thrombolysis in myocardial infarction. CABG=coronary artery bypass graft. HR=hazard ratio.

Lessons from the patient's course



Lesson 3.

✓ *NOAC & Prevention of ACS/AMI ?*

- **Effects on the occurrence of MI in AF patients among NOACs ?**

Comparisons among various NOACs

	Stoke/SEE	Ischaemic stroke	Haemorrhagic stroke	Myocardial infarction	All-casue death	Major bleeding	Intra-cranial Haemorrhage	GI bleeding	All bleeding
Dabigatran 150mg	V	V	V			V	V		V
Dabigatran 110mg			V			V	V		V
Rivaroxaban							V		
Apixaban			V			V	V		V
Edoxaban 60mg			V		V	V	V		V

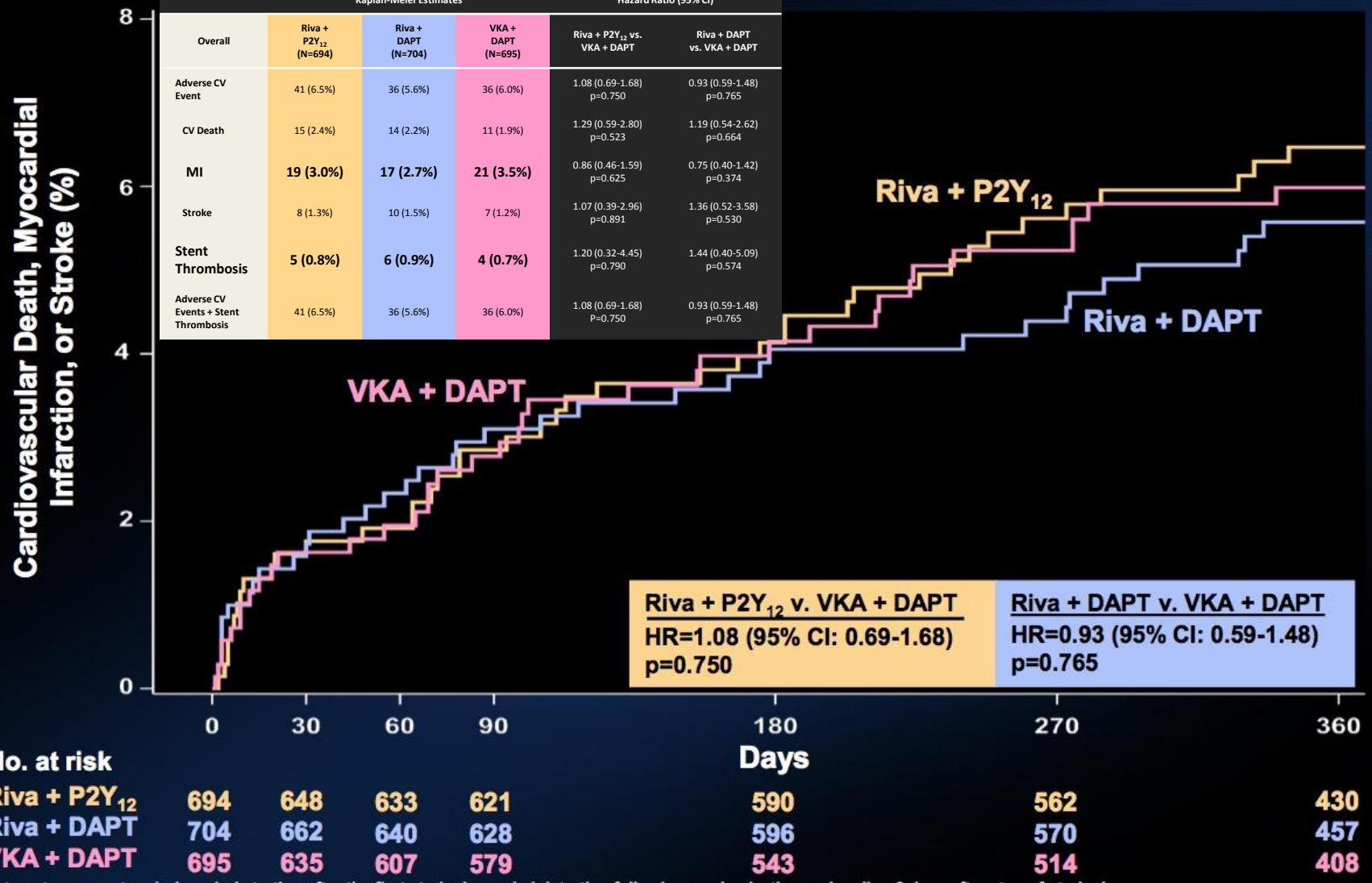
No established data !

[a] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia, Thailand, India.
[b] China, South Korea, Taiwan, Hong Kong.
[c] China, Japan, South Korea, Taiwan, Hong Kong, Philippines, Singapore, Malaysia.
[d] China, Japan, South Korea, Taiwan.

Int J Cardiol. 2015;180:246-54.

Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke

	Kaplan-Meier Estimates			Hazard Ratio (95% CI)	
Overall	Riva + $P2Y_{12}$ (N=694)	Riva + DAPT (N=704)	VKA + DAPT (N=695)	Riva + $P2Y_{12}$ vs. VKA + DAPT	Riva + DAPT vs. VKA + DAPT
Adverse CV Event	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) p=0.750	0.93 (0.59-1.48) p=0.765
CV Death	15 (2.4%)	14 (2.2%)	11 (1.9%)	1.29 (0.59-2.80) p=0.523	1.19 (0.54-2.62) p=0.664
MI	19 (3.0%)	17 (2.7%)	21 (3.5%)	0.86 (0.46-1.59) p=0.625	0.75 (0.40-1.42) p=0.374
Stroke	8 (1.3%)	10 (1.5%)	7 (1.2%)	1.07 (0.39-2.96) p=0.891	1.36 (0.52-3.58) p=0.530
Stent Thrombosis	5 (0.8%)	6 (0.9%)	4 (0.7%)	1.20 (0.32-4.45) p=0.790	1.44 (0.40-5.09) p=0.574
Adverse CV Events + Stent Thrombosis	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) P=0.750	0.93 (0.59-1.48) p=0.765



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6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines

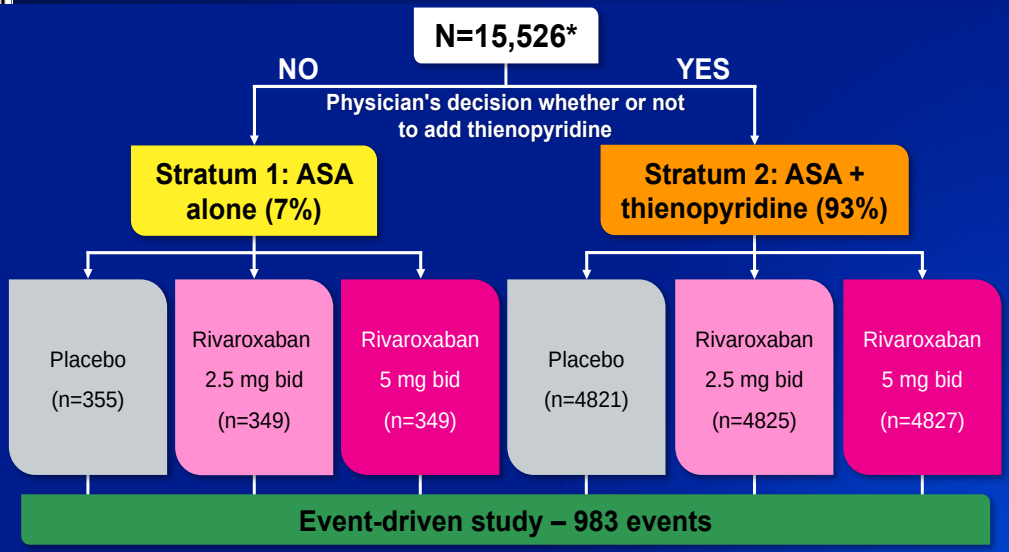
Gibson et al. AHA 2016

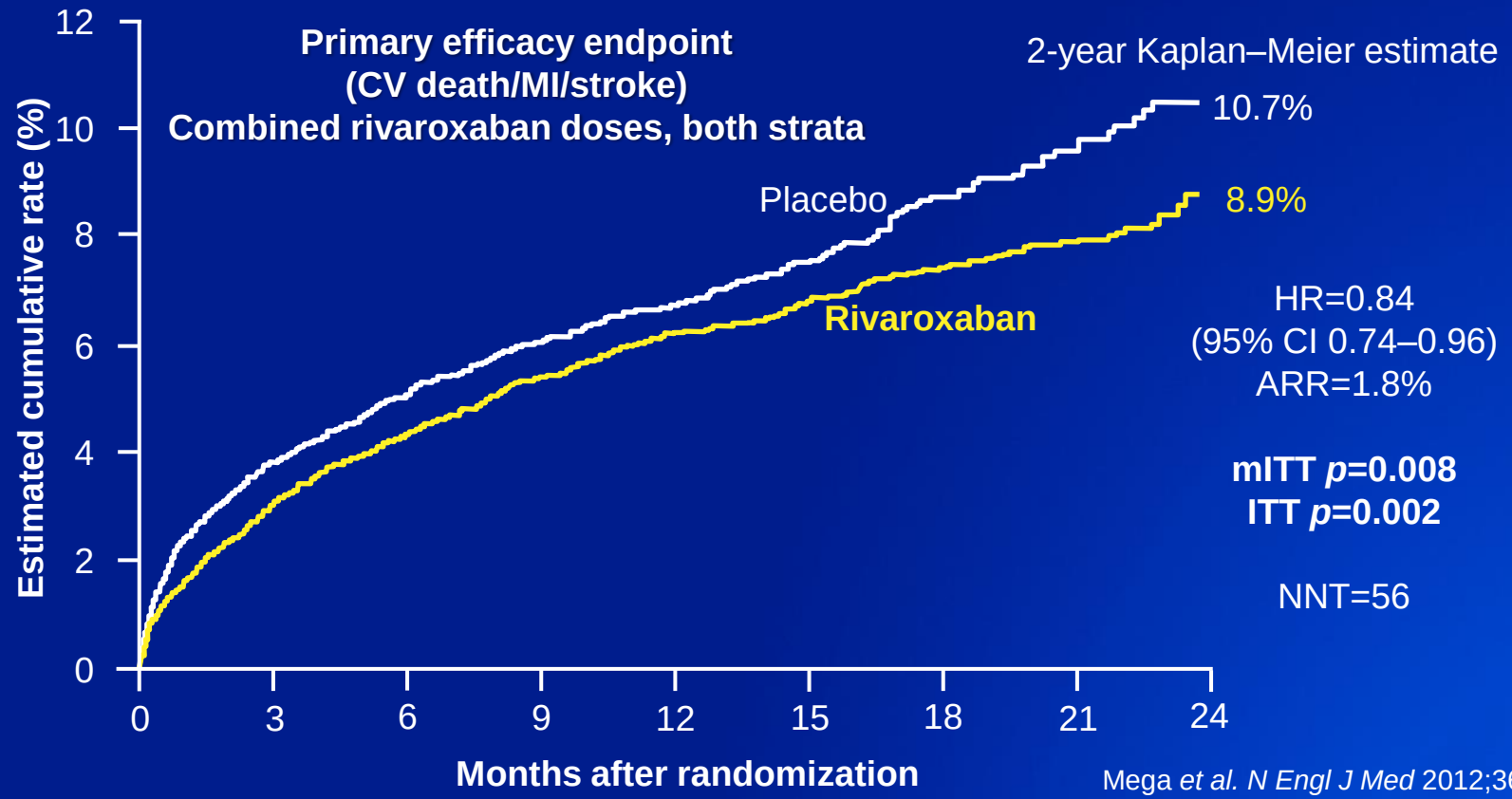
The NEW ENGLAND JOURNAL of MEDICINE

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

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*





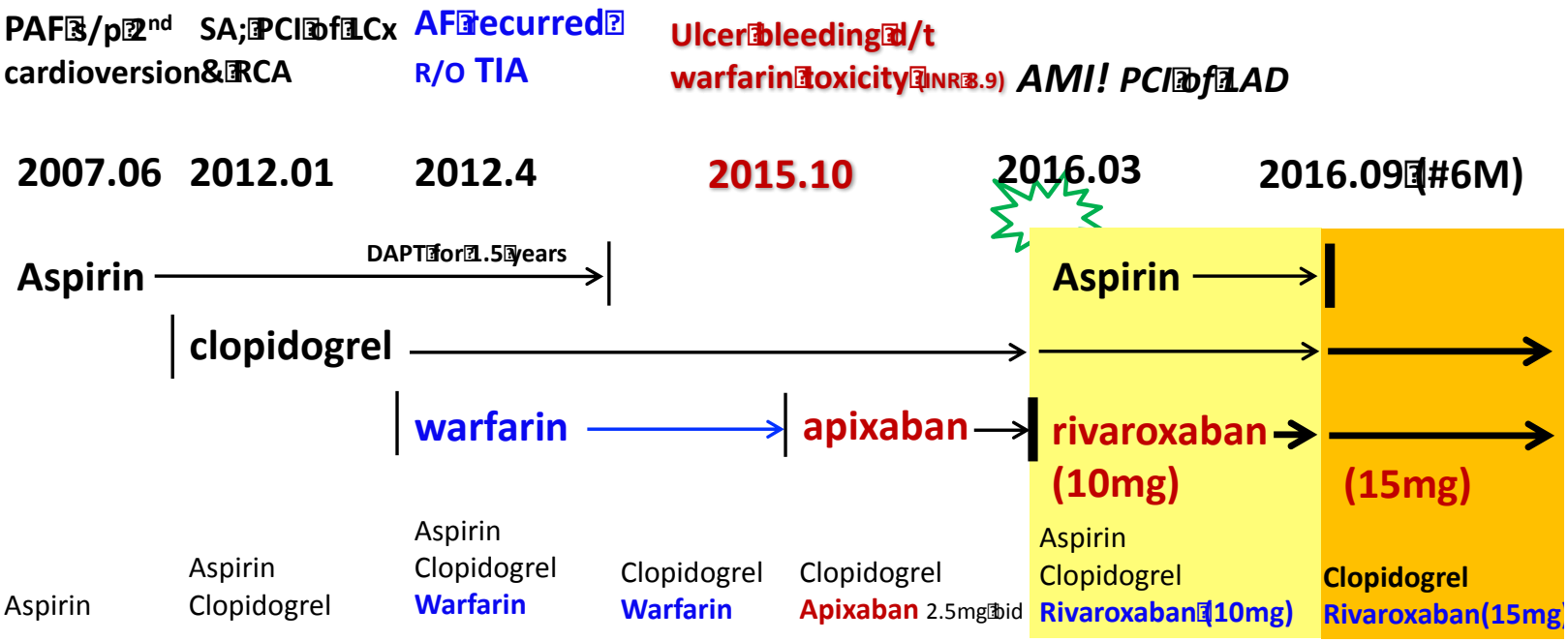
Mega *et al. N Engl J Med* 2012;366:9–19.

Ongoing Trials of NOACs in AF Undergoing PCI

OAC	Study name (Trial ID)	Sample size	Treatment Arms	Phase	Study completion
Rivaroxaban (China only)	RT-AF (NCT02334254)	420*	• Rivaroxaban 2.5mg or 5mg BID plus ticagrelor 90mg BID • Aspirin 100mg OD, clopidogrel 75mg OD, plus warfarin (INR 1.8-2.5)	IV	Jan 2016
Rivaroxaban (Japan only)	AFIRE (NCT02642419)	2200*	• Rivaroxaban 15mg/10mg OD • Rivaroxaban plus single antiplatelet drug: aspirin 81mg or 100mg OD, clopidogrel 75mg/50mg OD or prasugrel 3.75/2.5mg OD	IV	Dec 2017
Apixaban	AUGUSTUS (NCT02415400)	4600*	• Apixaban 5/2.5mg OD | VKA • Aspirin 81mg OD | placebo	IV	Sep 2017
Edoxaban	ENTRUST AF-PCI (NCT02866175)	1500*	• Edoxaban 60/30mg OD • VKA OD plus clopidogrel 75mg OD or with documented clinical need: prasugrel 10/5mg OD or ticagrelor 90mg BID	III	Feb 2019
Dabigatran	REDUAL-PCI (NCT02164864)	2800*	• Dabigatran 110mg or 150 mg BID plus clopidogrel or ticagrelor • Warfarin OD plus aspirin and clopidogrel or ticagrelor	III	May 2017
All anticoagulants (US only)	The AVIATOR 2 Registry (NCT02362659)	2500*	• Antiplatelet plus anticoagulant • DAPT alone • DAPT plus anticoagulant	IV	Sep 2017
All OACs (Japan only)	OAC-ALONE (NCT01962545)	2000*	• OAC alone: warfarin or NOAC • OAC plus single antiplatelet	IV	May 2018

*Estimated enrolment

Final lesson from the patient's course

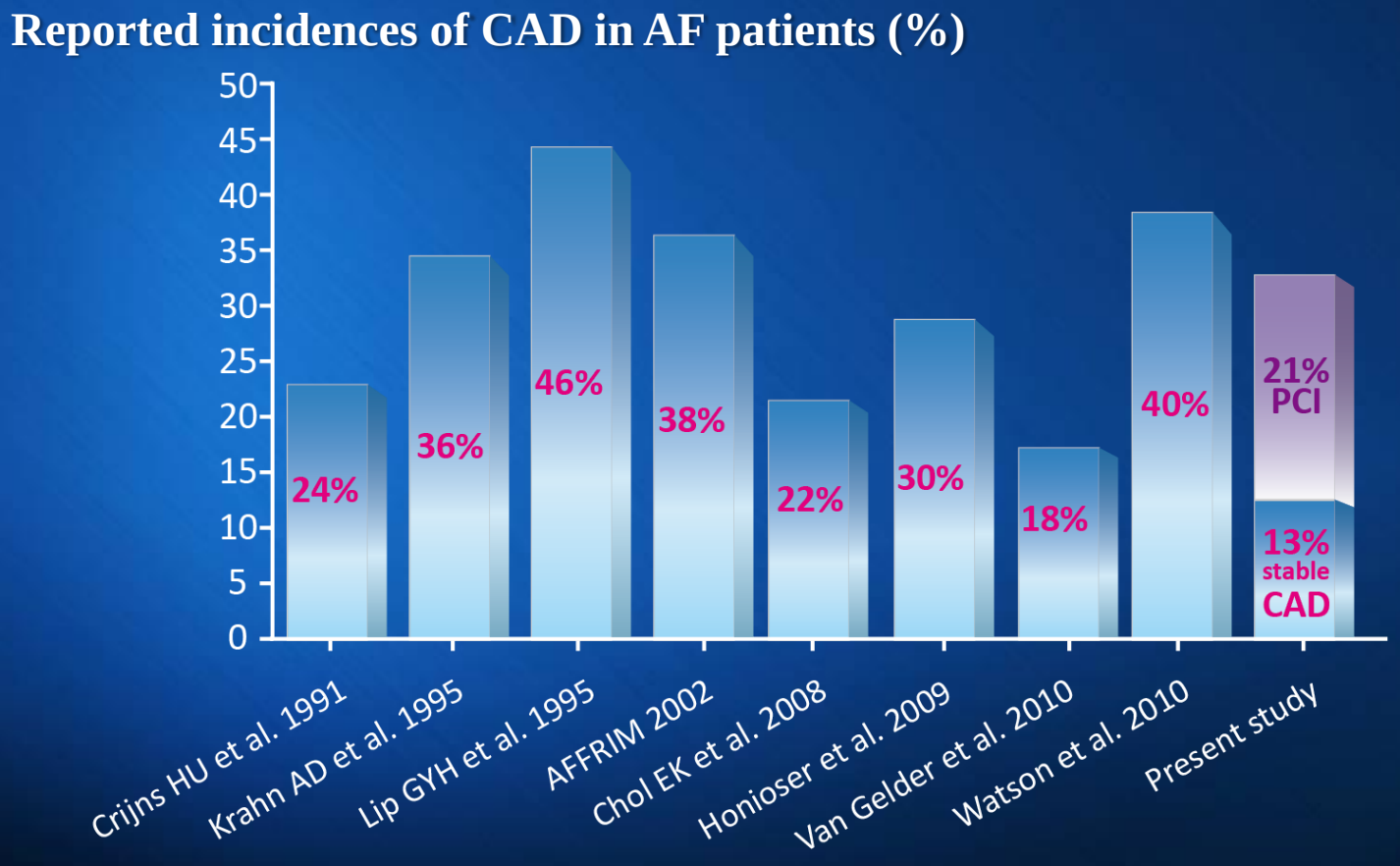


Lesson 4. Never forget !!

- ✓ **The risk of AMI in AF patients is really high !!!**

CAD in AF patients

- Prevalence of **CAD in AF** is high … **18 ~ 47%.**



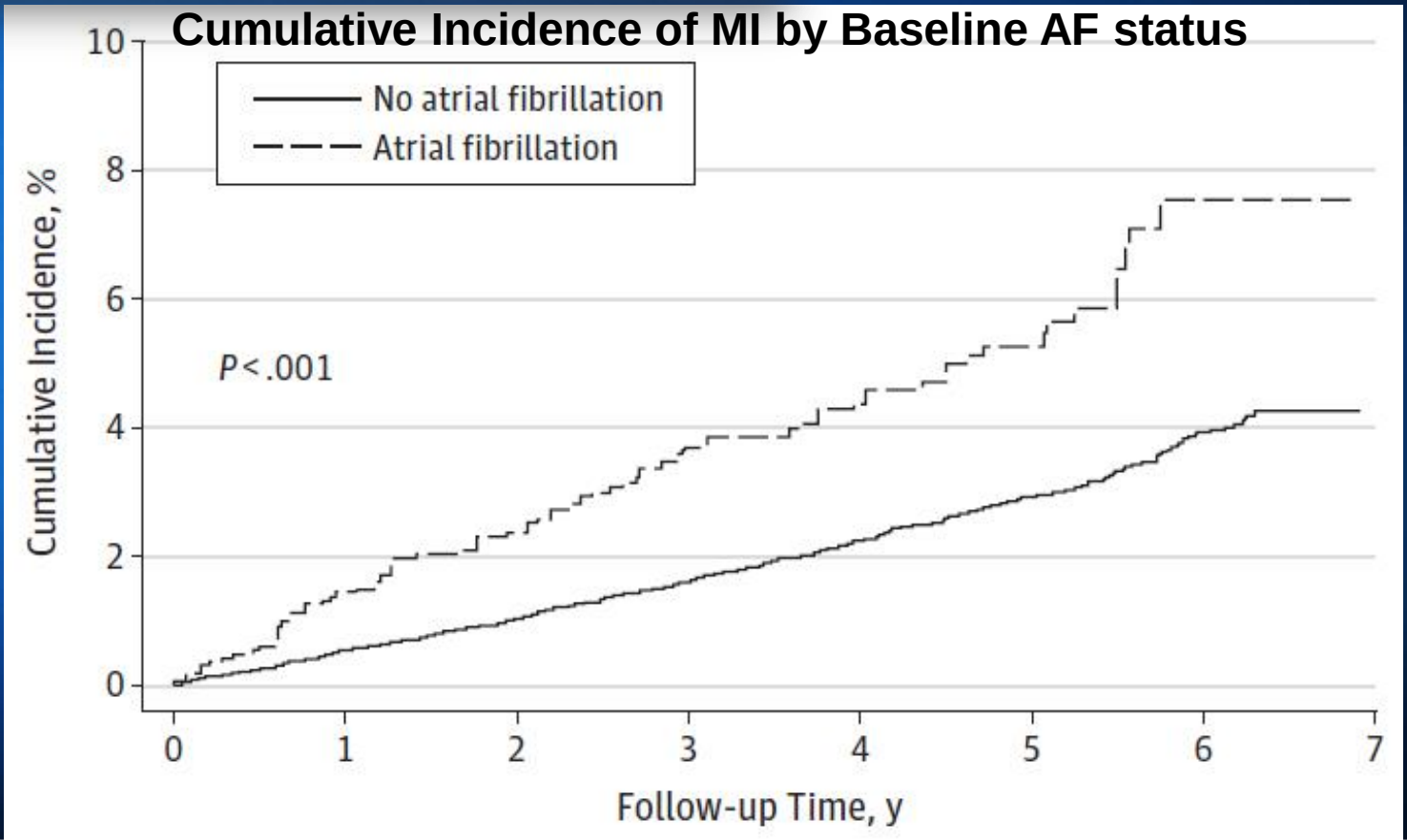
PLoS ONE 6(9): e24964

Published in final edited form as:
JAMA Intern Med. 2014 January ; 174(1): 107–114. doi:10.1001/jamainternmed.2013.11912.

Atrial Fibrillation and the Risk of Myocardial Infarction

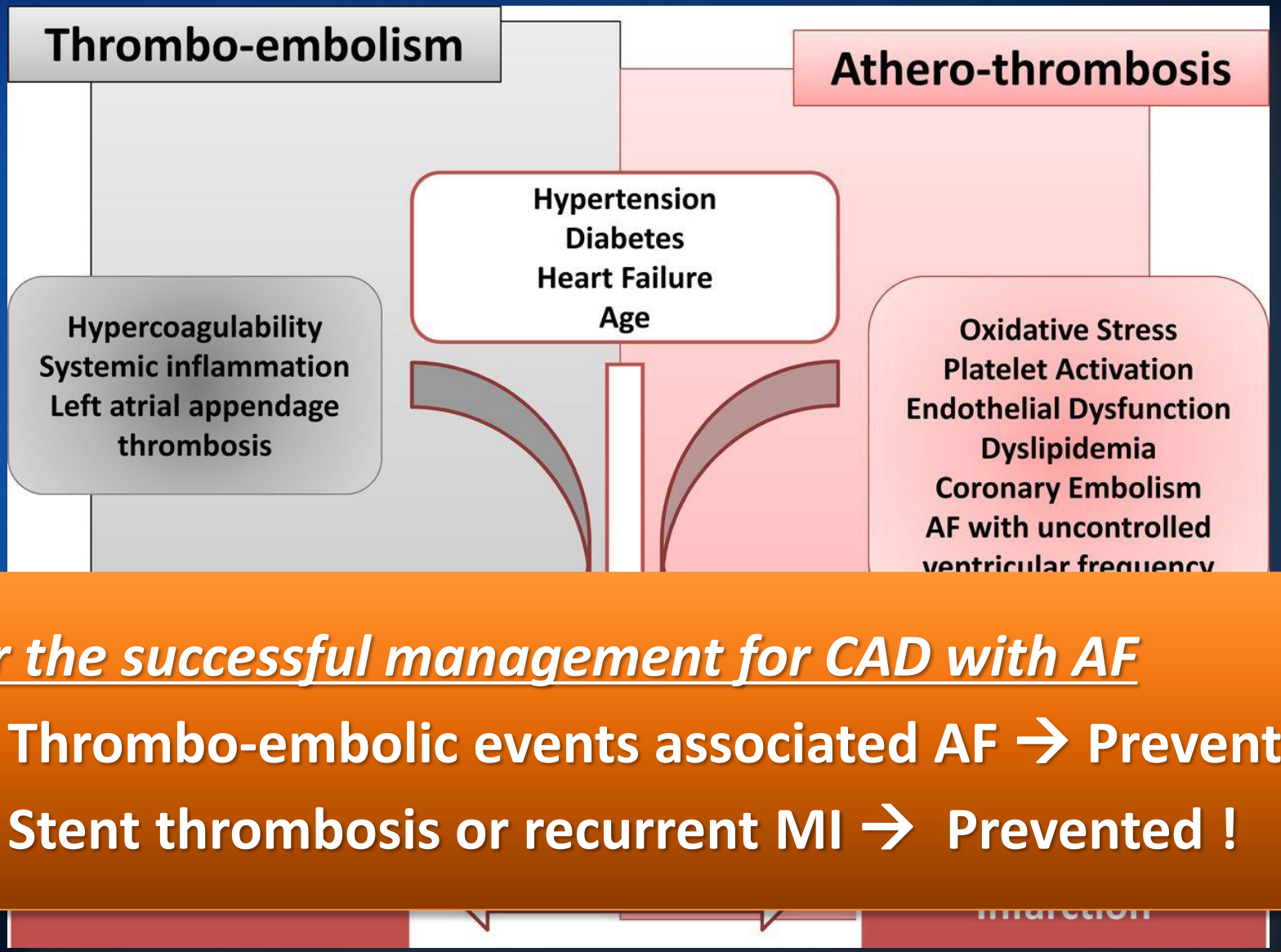
Elsayed Z. Soliman, MD, MSc, MS, Monika M. Safford, MD, Paul Muntner, PhD, Yulia Khodneva, MD, PhD, Farah Z. Dawood, MD, Neil A. Zakai, MD, Evan L. Thacker, PhD, Suzanne Judd, PhD, Virginia J. Howard, PhD, George Howard, DrPH, David M. Herrington, MD, MHS, and **Mary Cushman, MD, MSc**

REGARDS prospective cohort (N=23,928) between 2003 and 2007,



Soliman EZ *et al*. JAMA Intern Med 2014;174:107-14

Mechanisms of Thromboembolism/ Atherothrombosis in AF

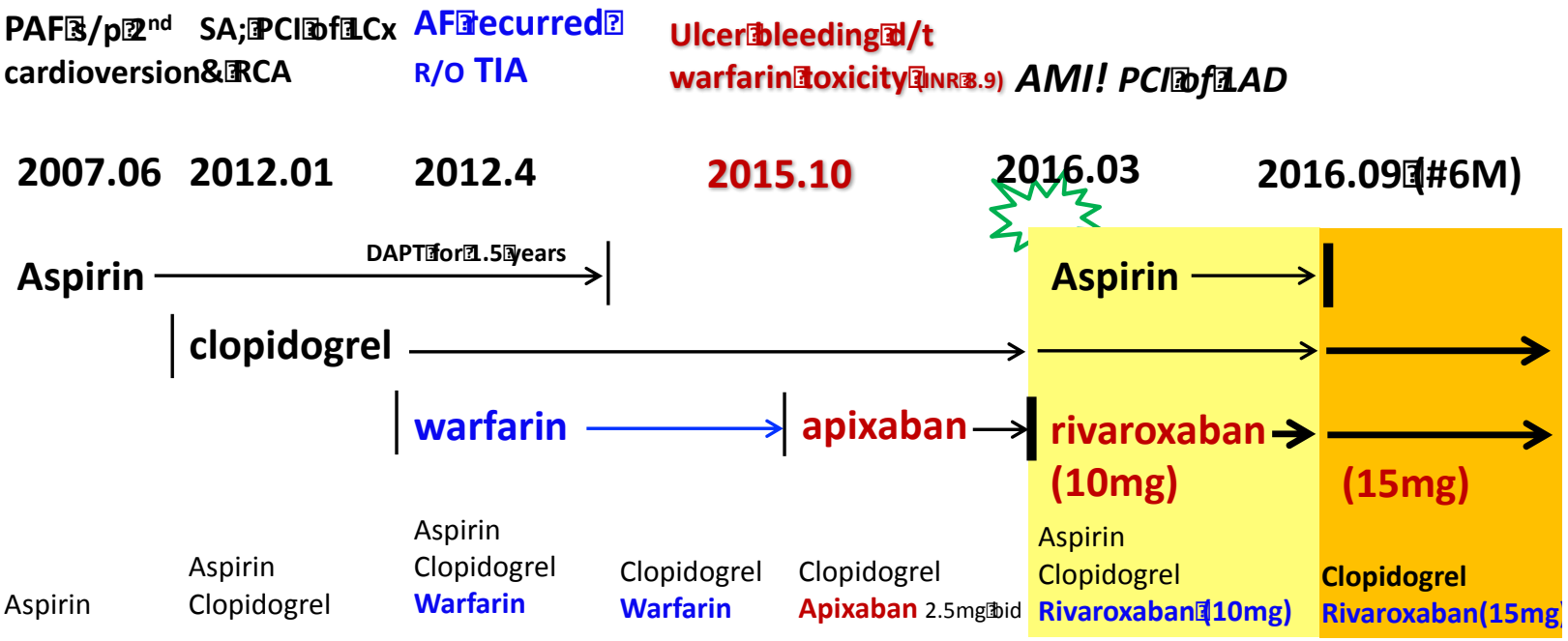


For the successful management for CAD with AF

- ✓ **Thrombo-embolic events associated AF → Prevented !**
- ✓ **Stent thrombosis or recurrent MI → Prevented !**

Violi F *et al*. J Am Heart Assoc 2016;5:e003347

Final lesson from the patient's course

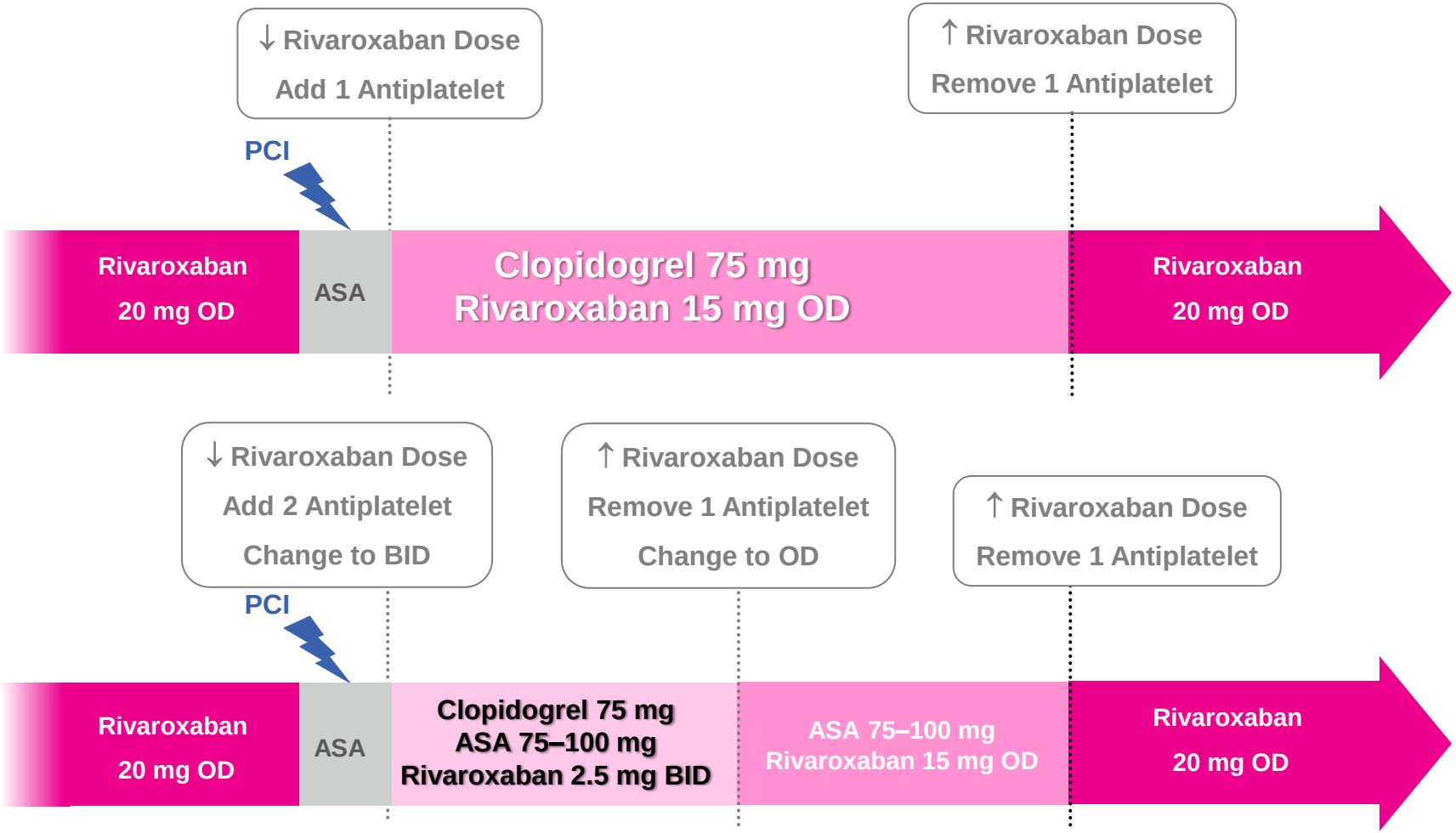


Lesson 5.

Antiplatelet & antithrombotic Tx in AF-PCI after PIONEER trial

Considering Practical Use, Rivaroxaban 15 mg OD Plus Antiplatelet Could Become Approach of Choice*

Illustrative example of practical implications for an AF patient



*The tested dosing regimens with rivaroxaban in PIONEER AF-PCI are currently not approved

Patient with AF and ACS/PCI : *Conclusions*

- **Double jeopardy !**

- **Triple therapy increases bleeding risk and may not further reduce ischemic events;**
  - Current guidelines advise **minimizing the duration of triple therapy**, especially in the new-generation DES era.
  - Individual **tailored therapy** is definitely needed considering patients' thromboembolic, bleeding & cardiovascular risks.
- **NOAC–antiplatelet combinations (as tested in PIONEER AF-PCI using rivaroxaban) reduced bleeding risk without excess ischemic hazard.**

대한심장학회
창립 60주년
SINCE 1957

Thank you for your attention

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Life Up"

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The 61st Annual Scientific Meeting of
The Korean Society of Cardiology

10.12 Thu. - 14 Sat.

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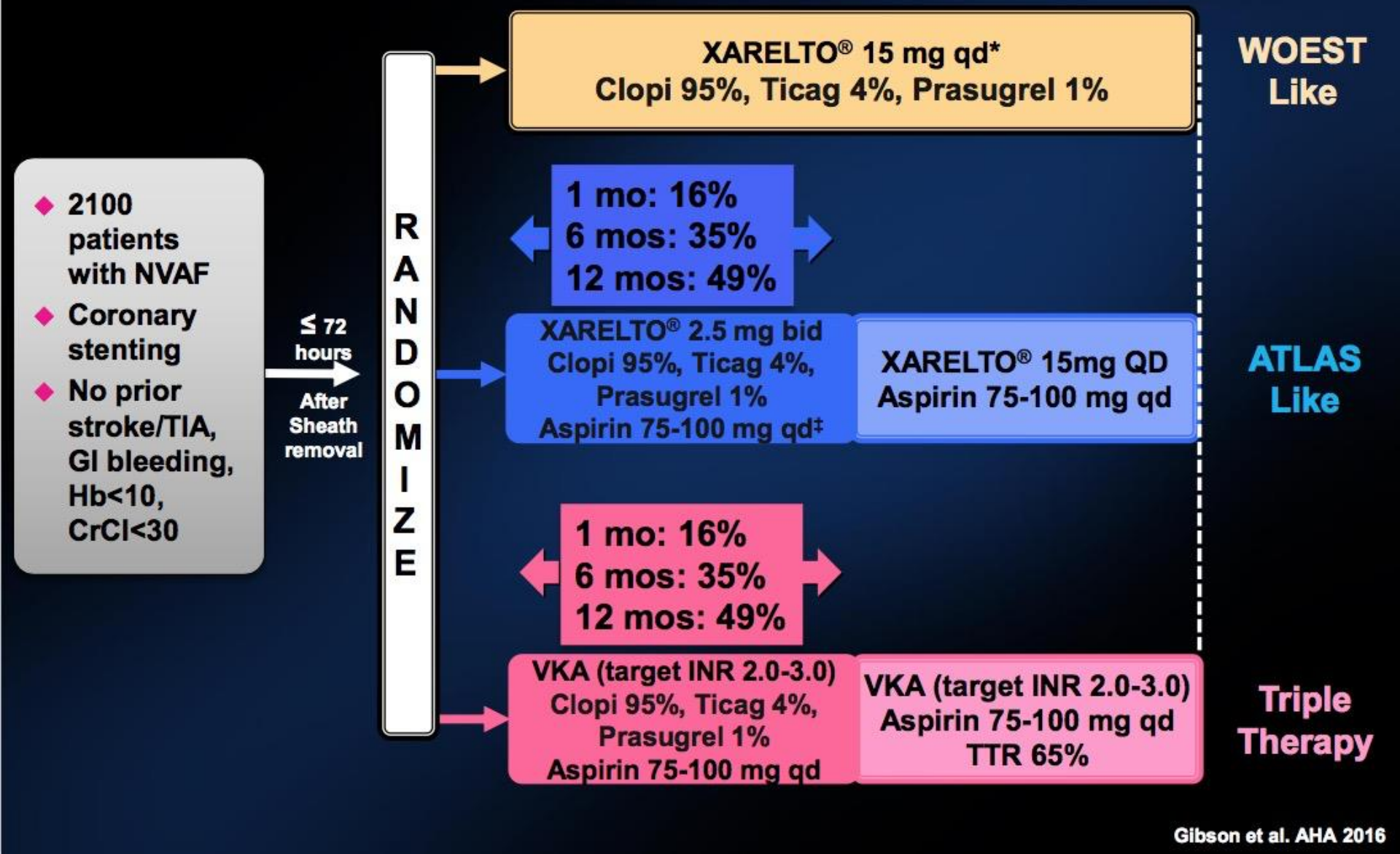
Organized by 대한심장학회 THE KOREAN SOCIETY OF CARDIOLOGY 심장학연구재단 THE KOREAN CARDIAC RESEARCH FOUNDATION

Pre-Randomization Choice of Duration of DAPT & Thienopyridine: PIONEER AF-PCI



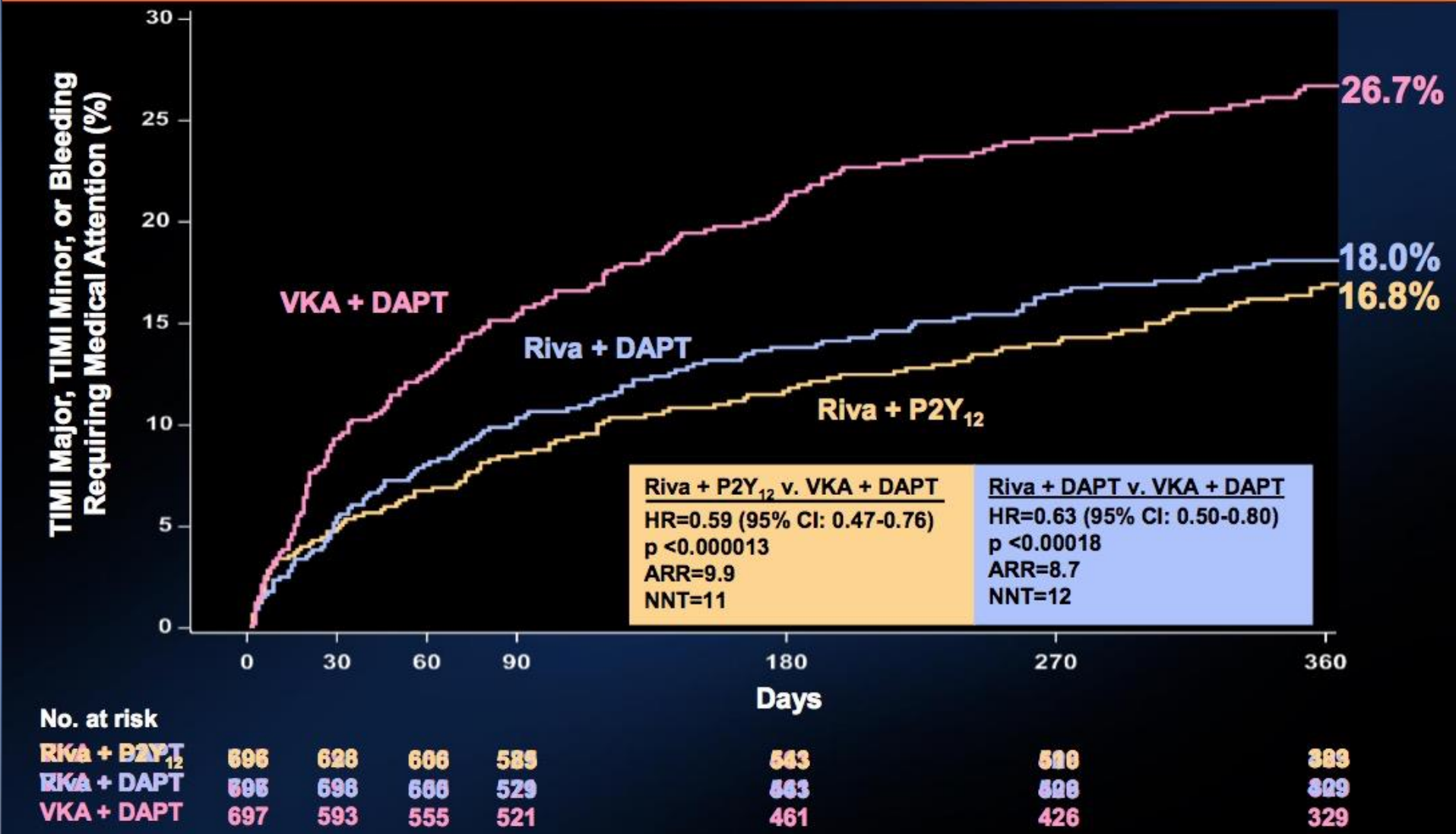
Gibson et al. AHA 2016

Baseline Characteristics

	Riva + $P2Y_{12}$ (N=709)	Riva + DAPT (N=709)	VKA + DAPT (N=706)
Age, mean ± SD	70.4 ± 9.1	70.0 ± 9.1	69.9 ± 8.7
Sex, female, n (%)	181 (25.5%)	174 (24.5%)	188 (26.6%)
Diabetes Mellitus, n (%)	204 (28.8%)	199 (28.1%)	221 (31.1%)
Type of Index Event, n (%)			
NSTEMI	130 (18.5%)	129 (18.4%)	123 (17.8%)
STEMI	86 (12.3%)	97 (13.8%)	74 (10.7%)
Unstable Angina	145 (20.7%)	148 (21.1%)	164 (23.7%)
Stable Angina	340 (48.5%)	329 (46.8%)	330 (47.8%)
Drug-eluting stent, n (%)	464 (65.4%)	471 (66.8%)	468 (66.5%)
Type of Atrial Fibrillation, n (%)			
Persistent	146 (20.6%)	146 (20.6%)	149 (21.1%)
Permanent	262 (37.0%)	238 (33.6%)	243 (34.5%)
Paroxysmal	300 (42.4%)	325 (45.8%)	313 (44.4%)

Gibson et al. AHA 2016

Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



No. at risk

Riva + P2Y12	696	628	606	589	543	518	389
Riva + DAPT	695	698	666	529	463	426	329
VKA + DAPT	697	593	555	521	461	426	329

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.
Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Gibson et al. AHA 2016

Bleeding Endpoints Using TIMI Criteria (Primary Analysis)

	Kaplan-Meier Estimates				Hazard Ratio (95% CI)		
Overall	**Riva + $P2Y_{12}$ (N=696)**	**Riva + DAPT (N=706)**	**Comb. Riva (N=1402)**	**VKA + DAPT (N=697)**	**Riva + $P2Y_{12}$ vs. VKA + DAPT**	**Riva + DAPT vs. VKA + DAPT**	**Combined vs. VKA + DAPT**
Clinically significant bleeding	109 (16.8%)	117 (18.0%)	226 (17.4%)	167 (26.7%)	0.59 (0.47-0.76) **p<0.001**	0.63 (0.50-0.80) **p<0.001**	0.61 (0.50-0.75) **p<0.001**
TIMI Major	14 (2.1%)	12 (1.9%)	26 (2.0%)	20 (3.3%)	0.66 (0.33-1.31) p=0.234	0.57 (0.28-1.16) p=0.114	0.61 (0.34-1.09) p=0.093
TIMI minor	7 (1.1%)	7 (1.1%)	14 (1.1%)	13 (2.2%)	0.51 (0.20-1.28) p=0.144	0.50 (0.20-1.26) p=0.134	0.51 (0.24-1.08) p=0.071
BRMA Requiring medical attention	93 (14.6%)	102 (15.8%)	195 (15.2%)	139 (22.6%)	0.61 (0.47-0.80) **p<0.001**	0.67 (0.52-0.86) **p=0.002**	0.64 (0.51-0.80) **p<0.001**

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA events.
A subject could have more than component event. n = number of subjects with events, N = number of subjects at risk, % = KM estimate at the end of study.
Hazard ratios as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank p-values as compared to VKA group are based on the (stratified, only for Overall 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.
BRMA = Bleeding requiring medical attention, TIMI = Thrombolysis in myocardial infarction, CI = confidence interval, DAPT = dual antiplatelet therapy,
HR = hazard ratio, VKA = vitamin K antagonist

Gibson et al. AHA 2016

Bleeding Events Using GUSTO & BARC Scales (Pre-Specified Secondary Analyses)

	Riva + $P2Y_{12}$ (N = 696)	Riva + DAPT (N = 706)	Combined Riva (N = 1402)	VKA + DAPT (N = 697)	Group 1 vs Group 3 p-value	Group 2 vs Group 3 p-value	Combined vs Group 3 p-value
GUSTO classification							
Severe	**7 (1.0%)**	10 (1.4%)	**17 (1.2%)**	**20 (2.9%)**	**0.012**	0.060	**0.007**
Moderate	13 (1.9%)	10 (1.4%)	23 (1.6%)	9 (1.3%)	0.388	0.839	0.539
Mild	193 (27.7%)	214 (30.3%)	**407 (29.0%)**	**255 (36.6%)**	**<0.001**	**0.013**	**<0.001**
BARC classification							
Type 0	9 (1.3%)	14 (2.0%)	23 (1.6%)	10 (1.4%)	0.820	0.428	0.721
Type 1 (minimal)	125 (18.0%)	153 (21.7%)	**278 (19.8%)**	**167 (24.0%)**	**0.006**	0.307	**0.029**
Type 2 (actionable)	92 (13.2%)	91 (12.9%)	**183 (13.1%)**	**126 (18.1%)**	**0.013**	**0.007**	**0.002**
Type 3a	8 (1.2%)	7 (1.0%)	15 (1.1%)	12 (1.7%)	0.369	0.237	0.212
Type 3b (>5g, pressors)	**13 (1.9%)**	16 (2.3%)	**29 (2.1%)**	**26 (3.7%)**	**0.035**	0.108	**0.025**
Type 3c (ICH)	2 (0.3%)	5 (0.7%)	7 (0.5%)	4 (0.6%)	0.687	>0.999	0.760
Type 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-	-
Type 5a	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	>0.999	0.497	.554
Type 5b (Definite Fatal)	1 (0.1%)	2 (0.3%)	**3 (0.2%)**	**7 (1.0%)**	0.070	0.106	**0.019**

BARC denotes Bleeding Academic Research Consortium, GUSTO Global Utilization Of Streptokinase and Tpa For Occluded Arteries
Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on a utopsy.
Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Gibson et al. AHA 2016

Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke

	Kaplan-Meier Estimates			Hazard Ratio (95% CI)	
Overall	Riva + $P2Y_{12}$ (N=694)	Riva + DAPT (N=704)	VKA + DAPT (N=695)	Riva + $P2Y_{12}$ vs. VKA + DAPT	Riva + DAPT vs. VKA + DAPT
Adverse CV Event	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) p=0.750	0.93 (0.59-1.48) p=0.765
CV Death	15 (2.4%)	14 (2.2%)	11 (1.9%)	1.29 (0.59-2.80) p=0.523	1.19 (0.54-2.62) p=0.664
MI	19 (3.0%)	17 (2.7%)	21 (3.5%)	0.86 (0.46-1.59) p=0.625	0.75 (0.40-1.42) p=0.374
Stroke	8 (1.3%)	10 (1.5%)	7 (1.2%)	1.07 (0.39-2.96) p=0.891	1.36 (0.52-3.58) p=0.530
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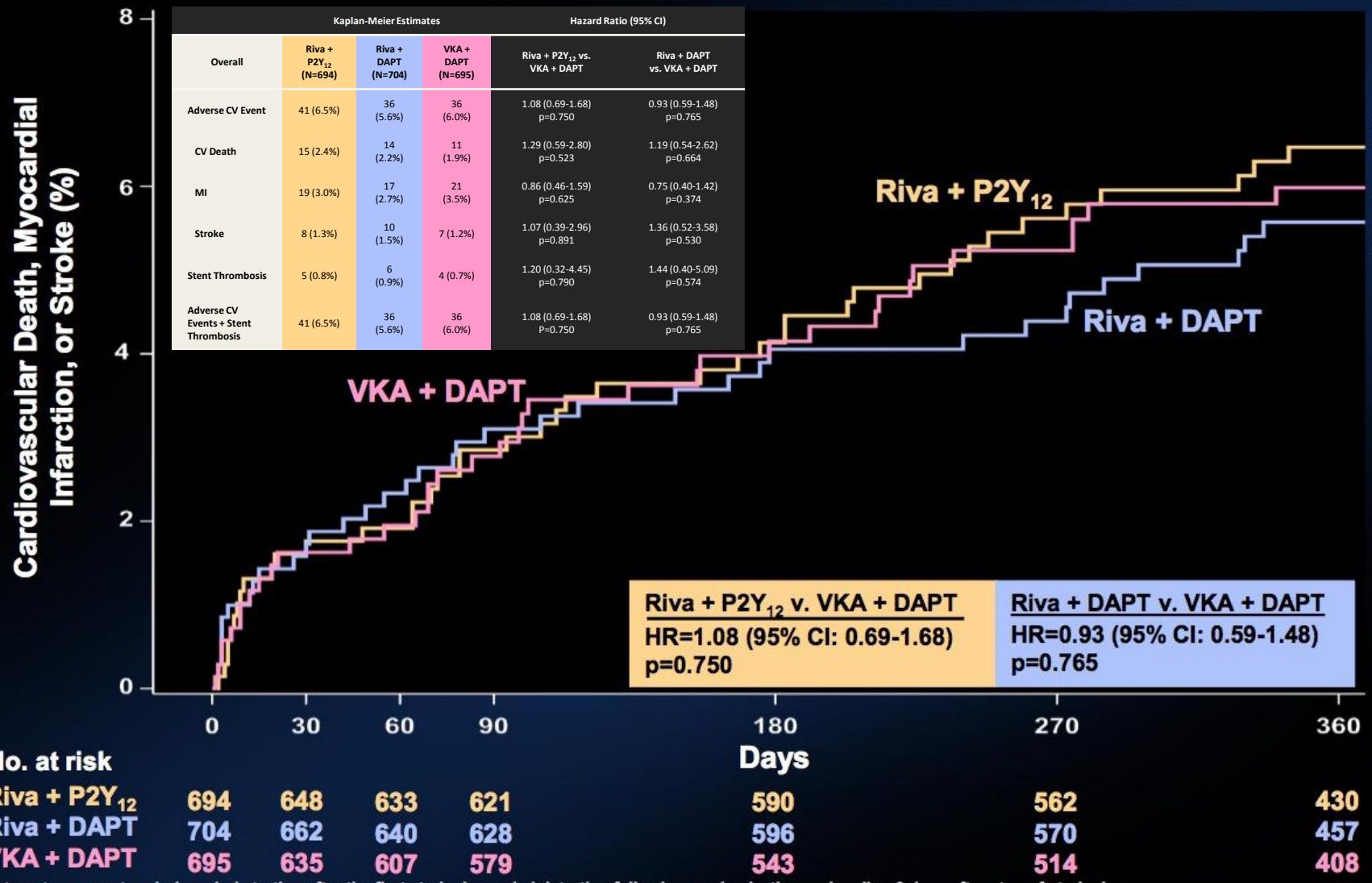
Adverse CV Events + Stent Thrombosis	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) P=0.750	0.93 (0.59-1.48) p=0.765



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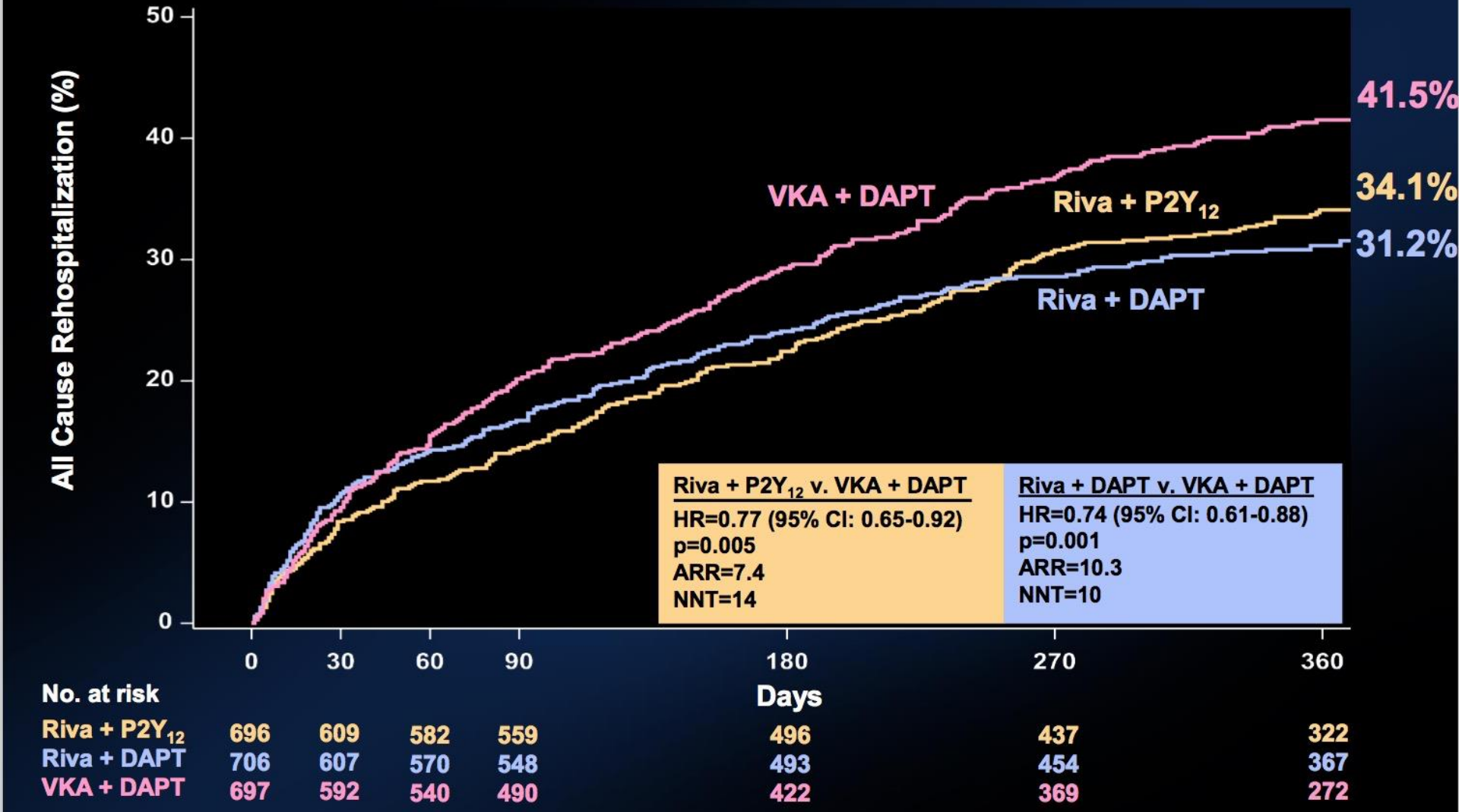
Gibson et al. AHA 2016

All Cause Hospitalization for an Adverse Event

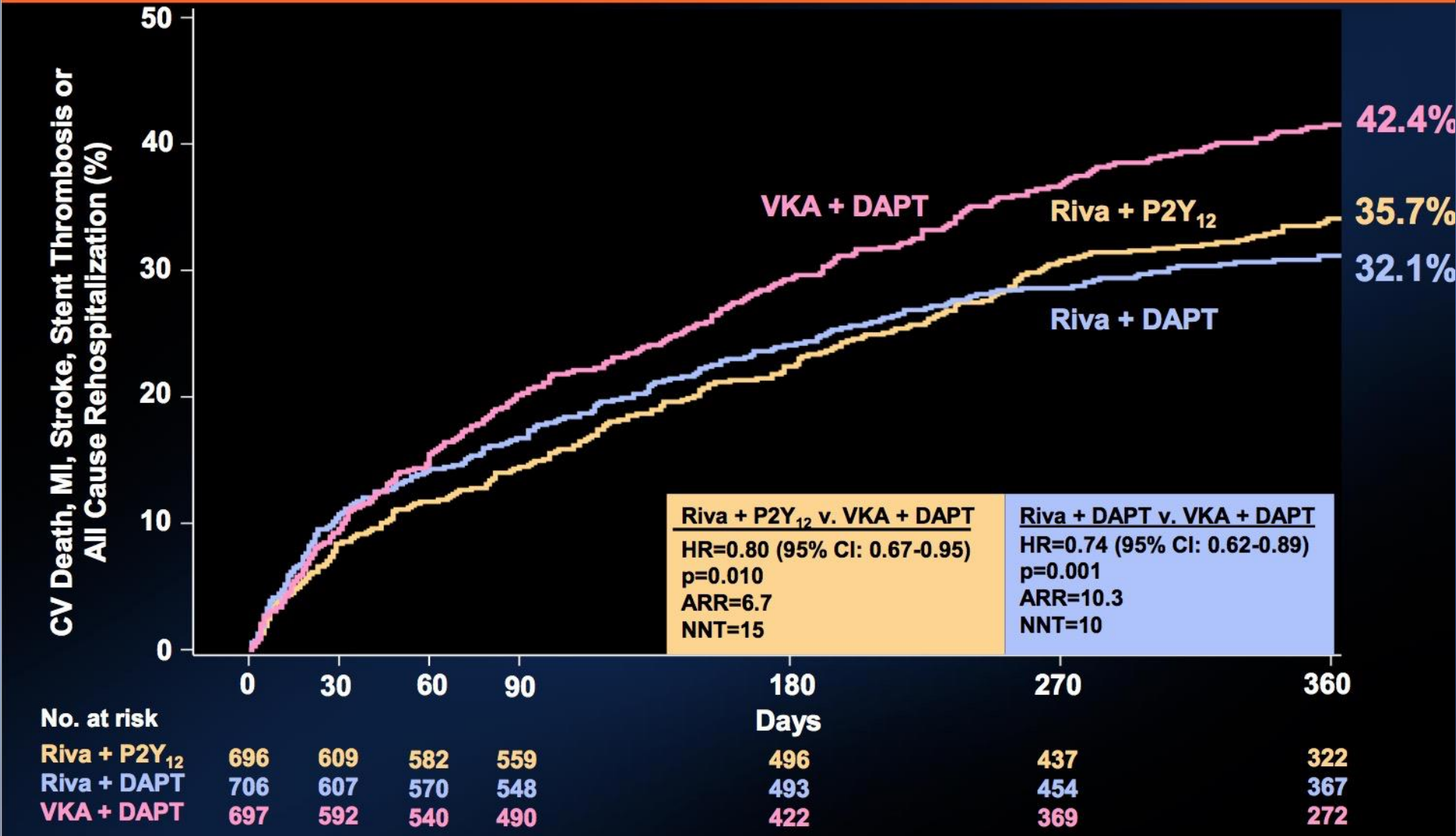


No. at risk							
Riva + P2Y12	696	609	582	559	496	437	322
Riva + DAPT	706	607	570	548	493	454	367
VKA + DAPT	697	592	540	490	422	369	272

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Rehospitalizations do not include the index event and include the first rehospitalization after the index event.
Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the two-sided log rank test.

Gibson et al. AHA 2016

Time to First CV Death, MI, Stroke, Stent Thrombosis or All Cause Recurrent Hospitalization



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Log-Rank P-values as compared to VKA group are based on the two-sided log rank test.

Gibson et al. AHA 2016

Conclusion of PIONEER AF-PCI

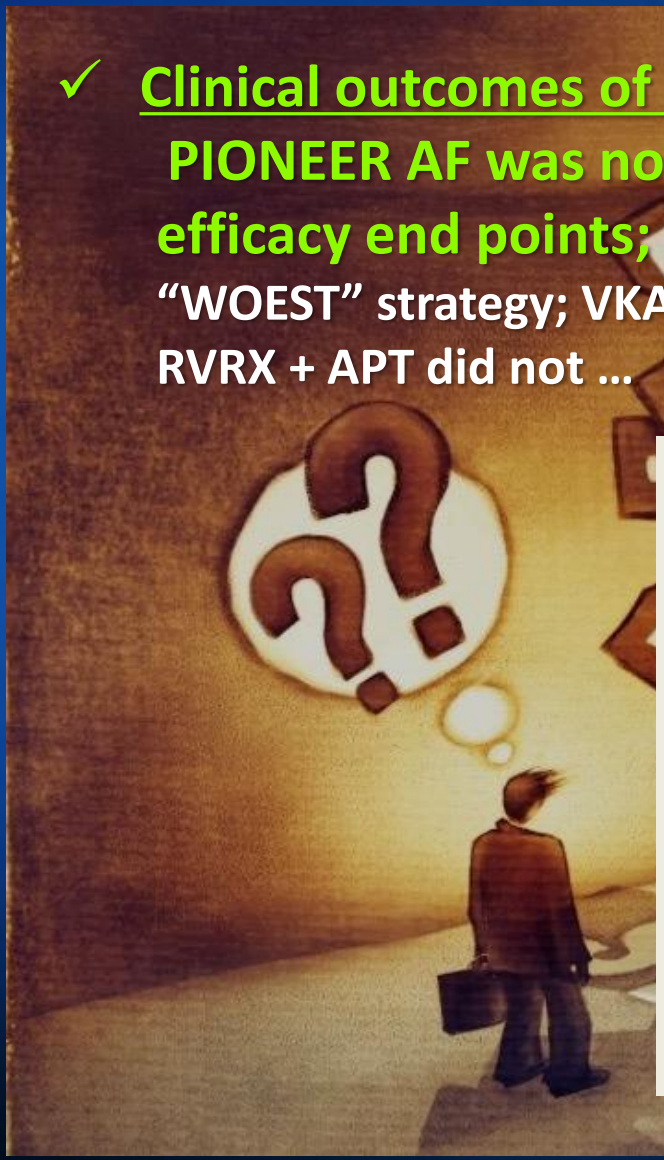
In participants with AF undergoing PCI with stents, the administration of either **low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months** or **very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months** was associated with a lower rate of clinically significant bleeding than was standard therapy with a vitamin K antagonist plus DAPT for 1, 6, or 12 months.

Gibson et al. AHA 2016

Further issues be addressed (1)

- ✓ **Clinical outcomes of PIONEER AF vs. WOEST**

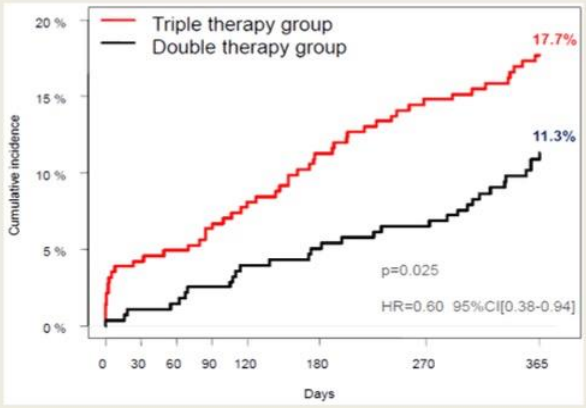
  PIONEER AF was not powered for comparing the secondary efficacy end points; The RVRX strategies were not compared to the "WOEST" strategy; VKA + clopidogrel in WOEST reduced hard events but RVRX + APT did not …



The WOEST strategy (but not RVRX-based strategies) reduces MACE

WOEST

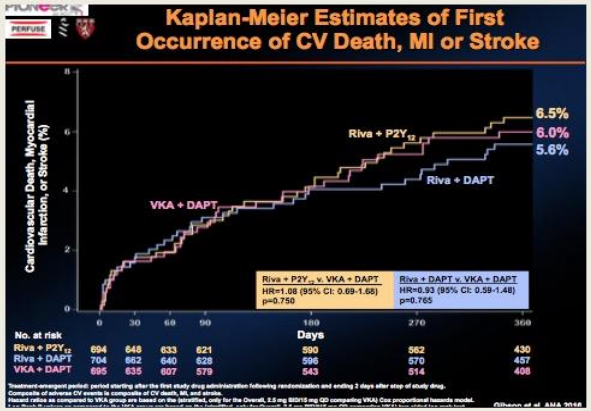
VKA + clopidogrel



Dewilde W et al. ***Lancet*** 2013

PIONEER AF-PCI

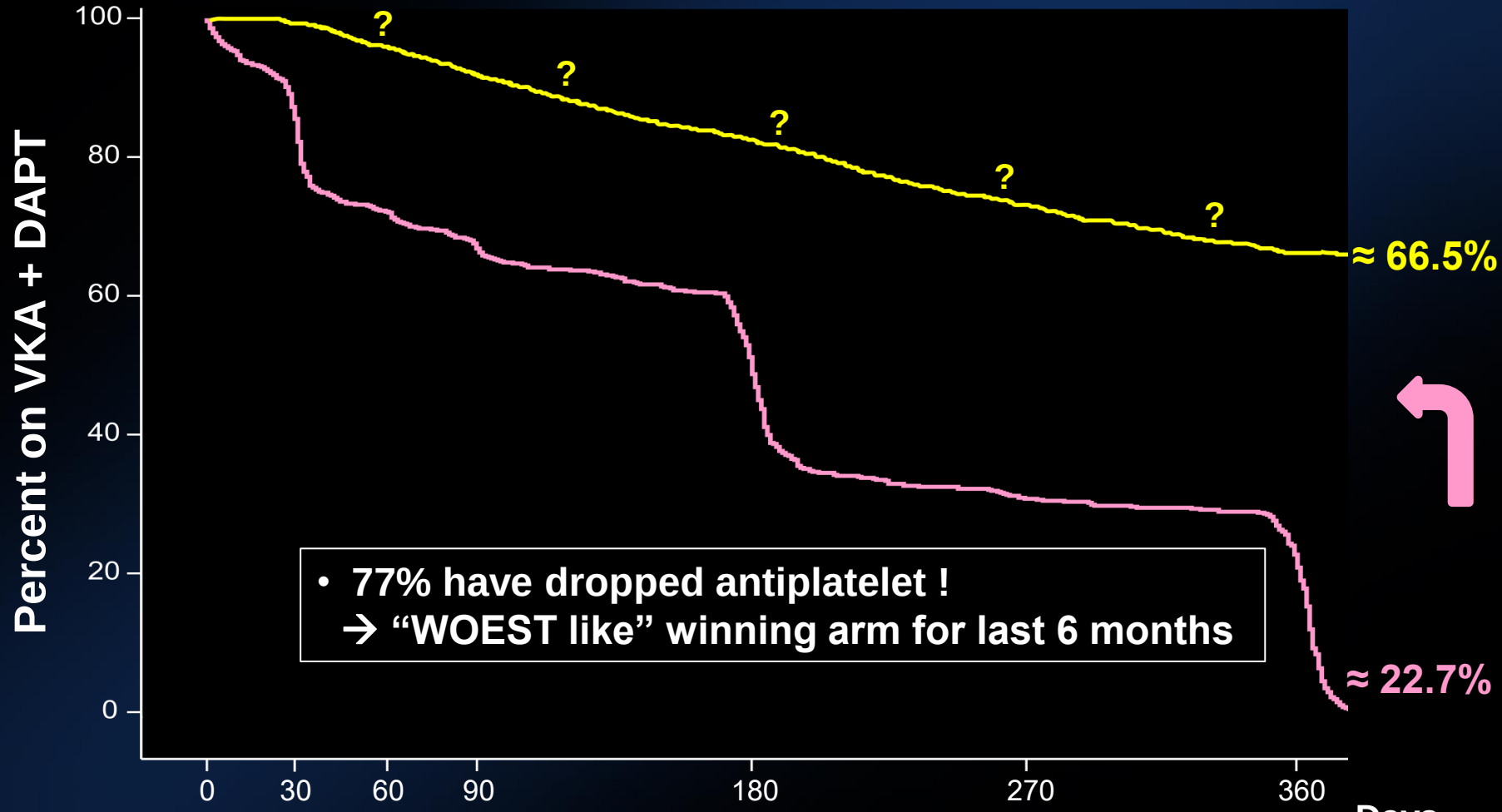
RVRX reduced dose + APT



Gibson CM et al. ***NEJM*** 2016

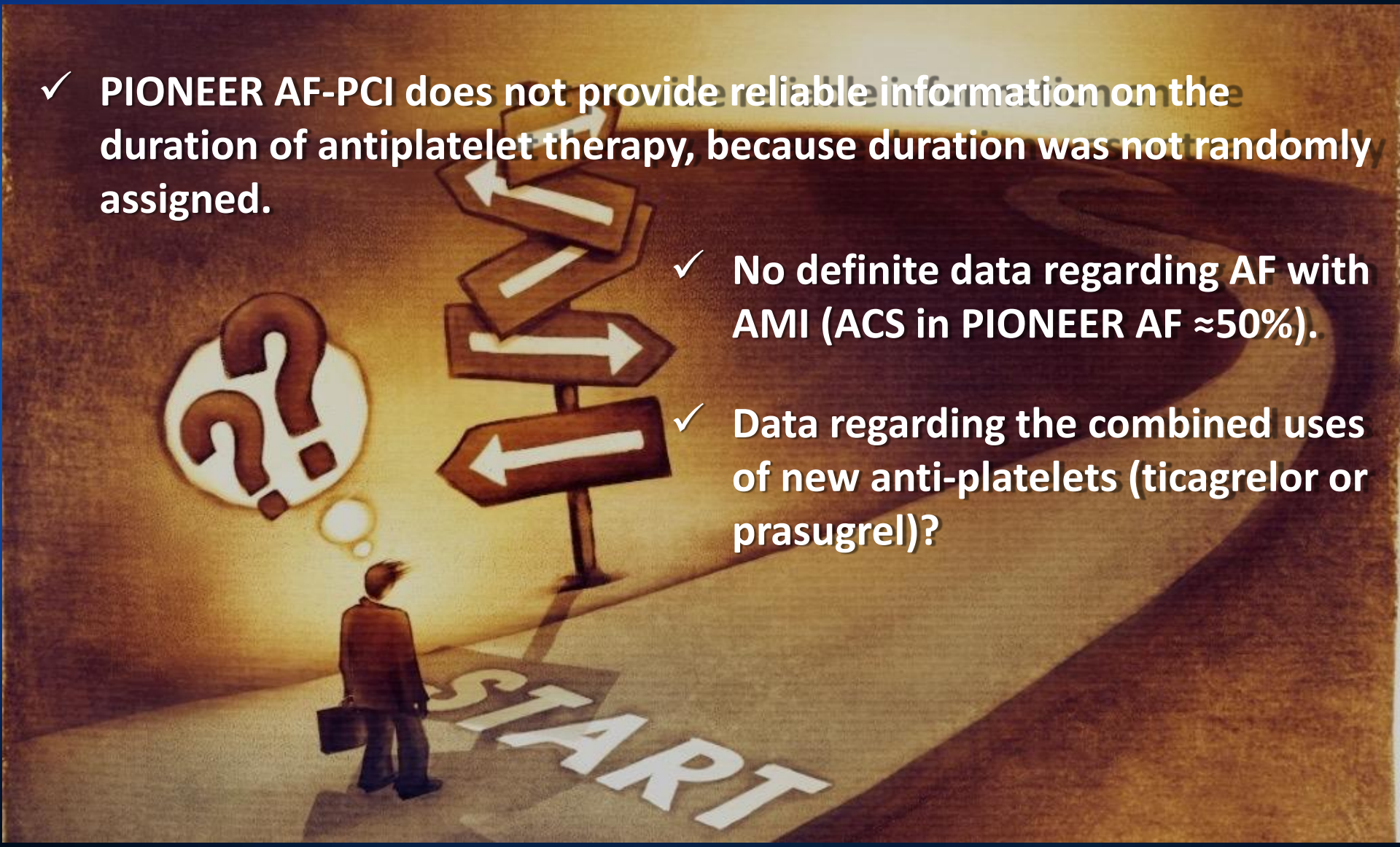
PIONEER AF vs. WOEST?

1. Study population; 100% AF in PIONEER vs. 69% AF in WOEST
2. VKA + DAPT Regimen Discontinuation



Dewilde et al. Lancet 2013 Mar 30;381(9872):1107-15. Gibson et al. AHA 2016

Further issues be addressed (2)



- ✓ **PIONEER AF-PCI does not provide reliable information on the duration of antiplatelet therapy, because duration was not randomly assigned.**
- ✓ **No definite data regarding AF with AMI (ACS in PIONEER AF ≈50%).**
- ✓ **Data regarding the combined uses of new anti-platelets (ticagrelor or prasugrel)?**