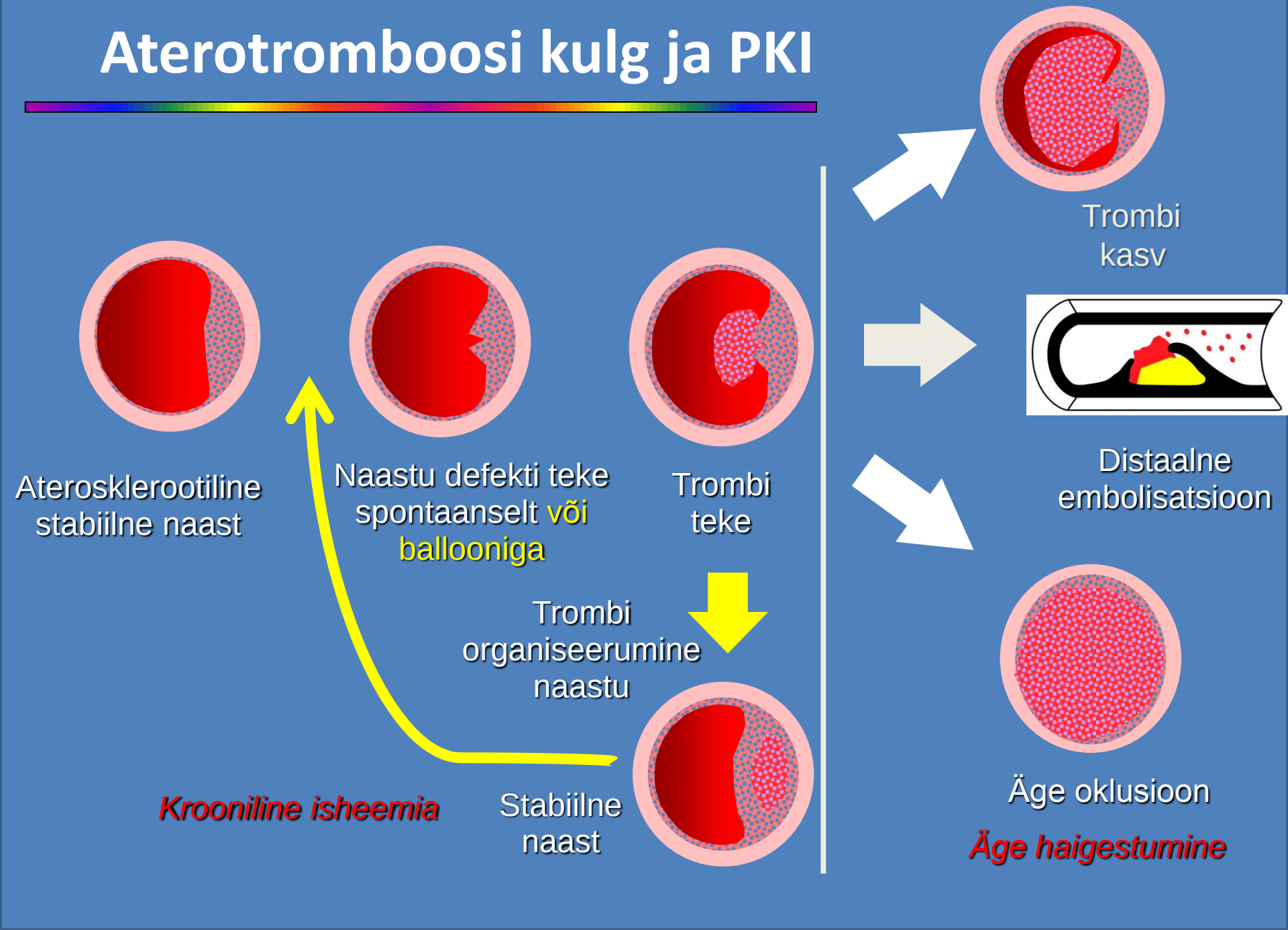
Koronaartõbi (krooniline, äge-nonSTEMI, STEMI) ja tromboos. Antikoagulatsioon invasiivse ravi (PKI,AKŠ) järgselt.

Tarmo Serka

SA PERH

06.05.2015

Aterotromboosi kulg ja PKI



Demonstration of various causes in ACS

Plaque rupture

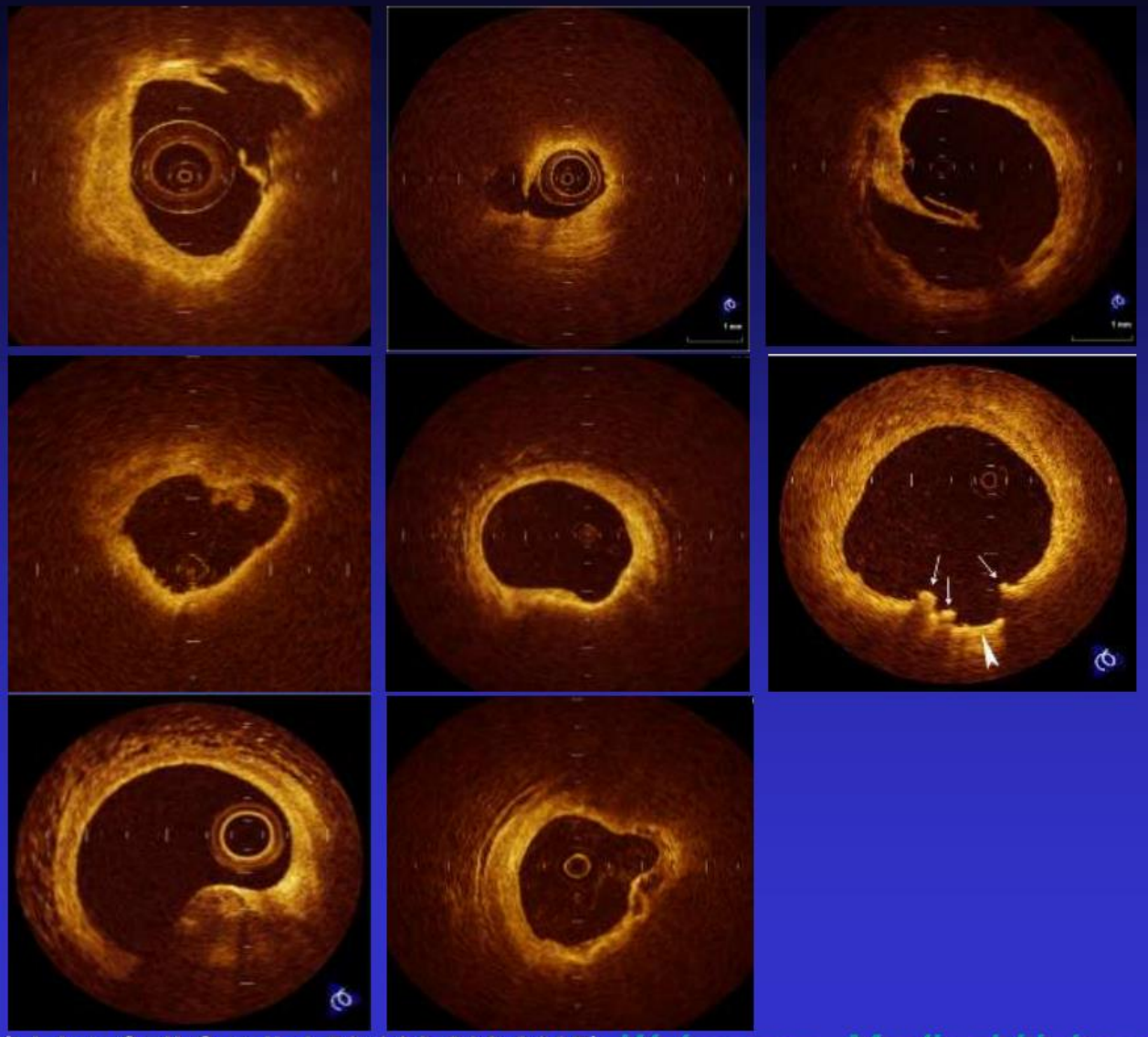
60 – 70 %

Plaque erosion

20 – 30 %

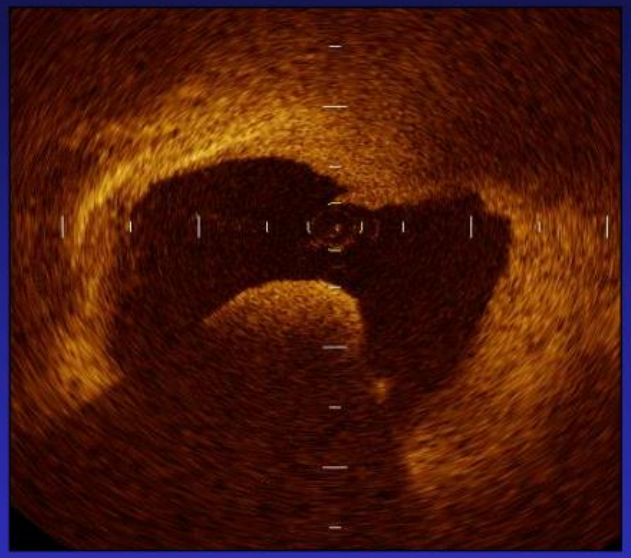
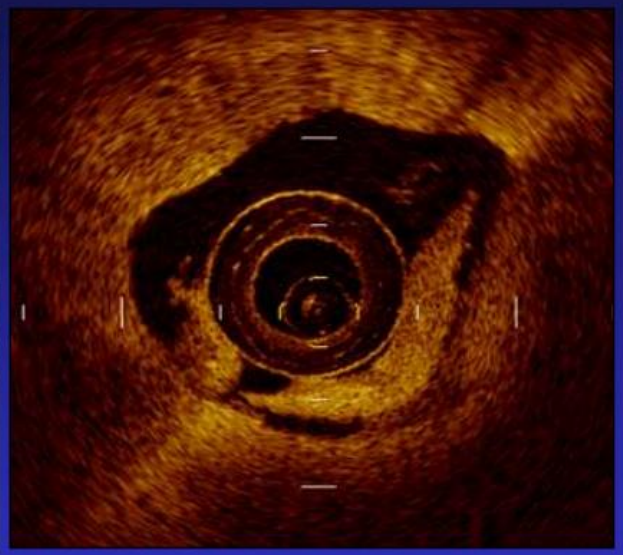
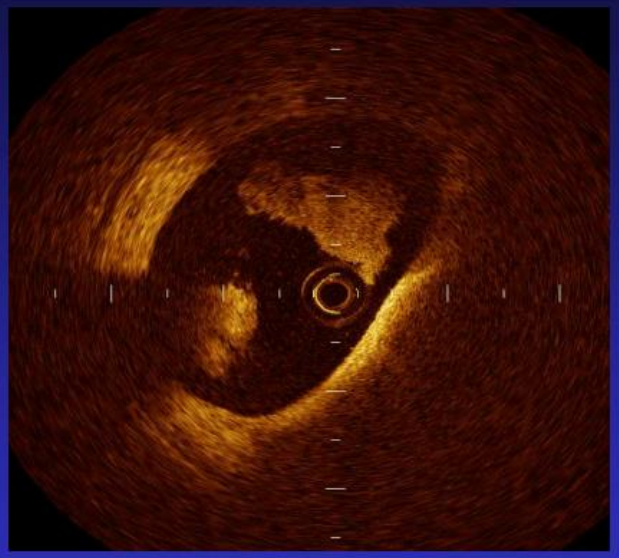
Calcified nodule

5 – 6 %

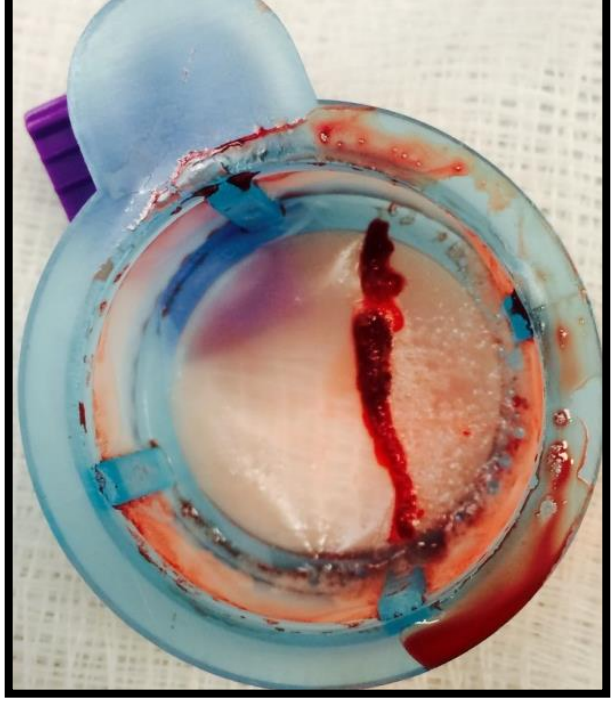


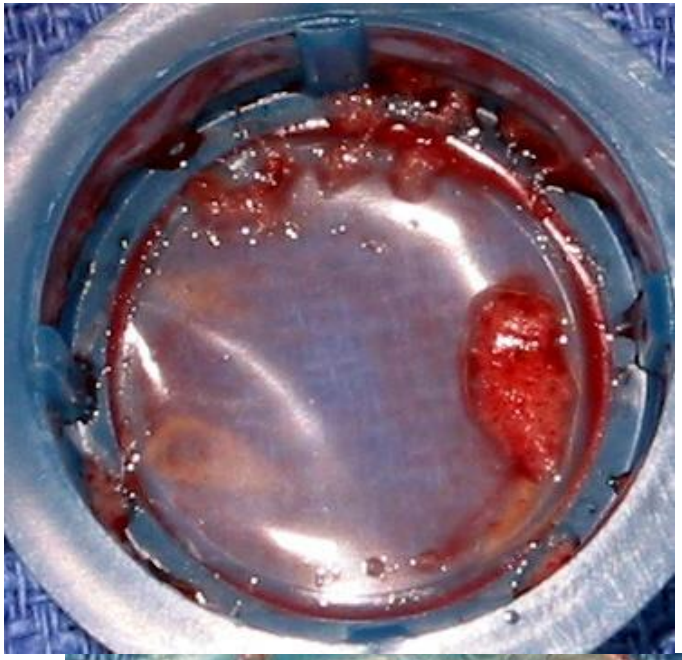
Kubo T, Akasaka T, et al. (J Am Coll Cardiol 50:933-939,2007)

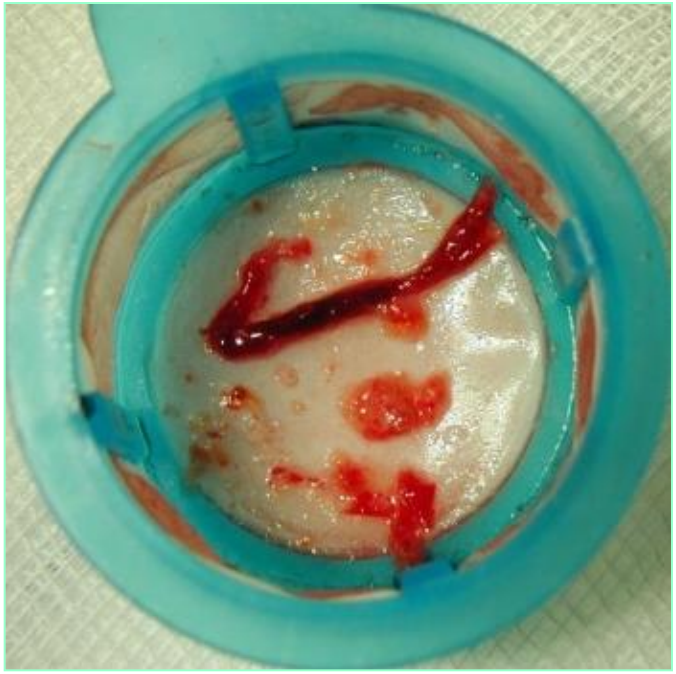
Red & white thrombus

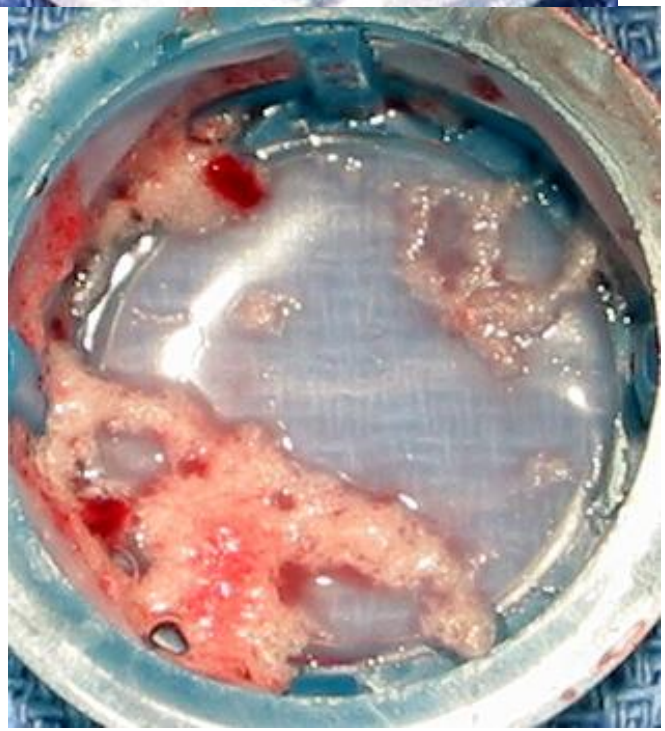
Red thrombus	White thrombus	Mixed thrombus
		
Protrusion mass with shadow	Protrusion mass without shadow	Protrusion mass with & without shadow

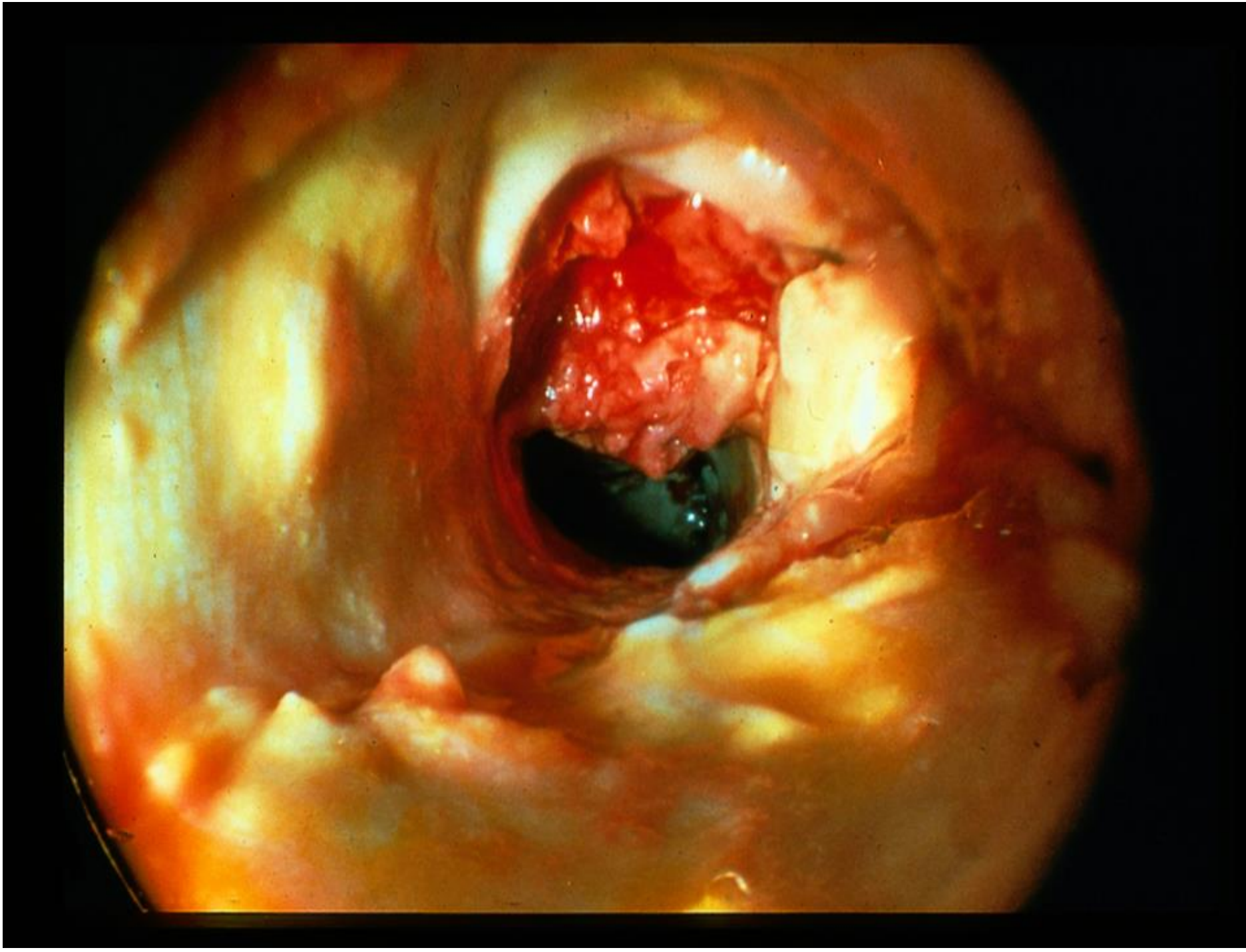
Kume T, Akasaka T, et al (Am J Cardiol 97:1713-1717, 2006)
Kubo T, Akasaka T, et al. (J Am Coll Cardiol 50:933-939,2007)





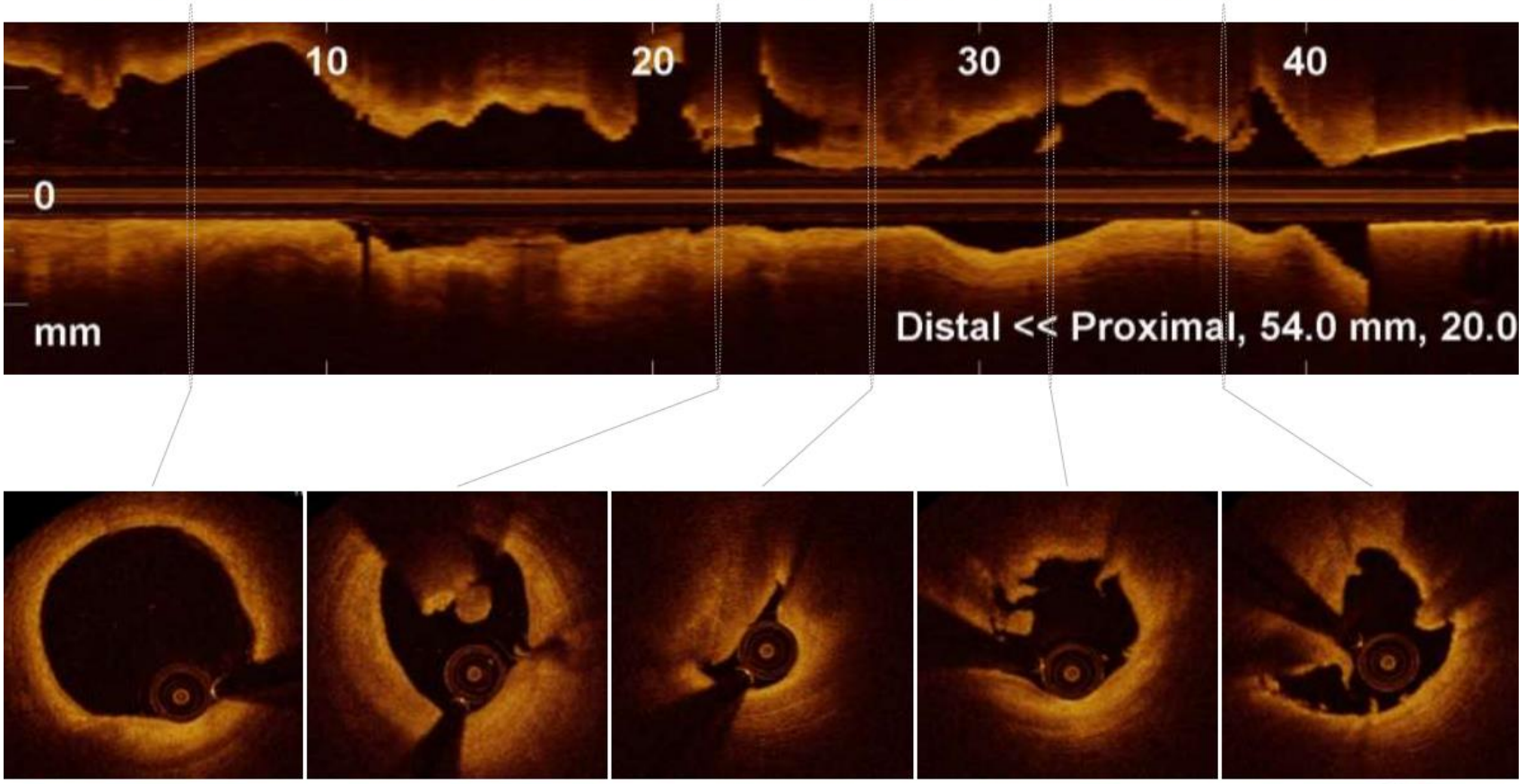






asia PCR Singapore Live 2014

Can easily detect thrombus and guide thrombus removal



Azienda Ospedaliera Papa Giovanni XXIII Bergamo

Regione Lombardia

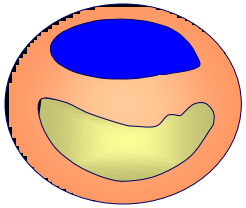
OCTAVIA

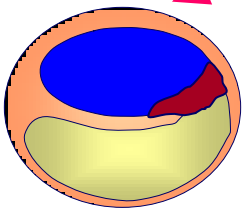
ATEROTROMBOOS ja KLIINIK

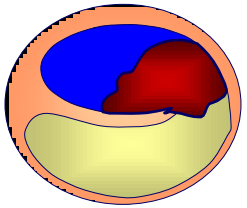
Stabiilne naast

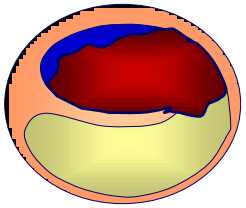
Ebastabiilne naast

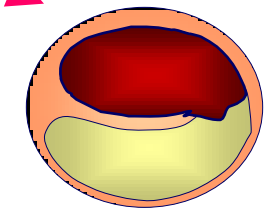
Trombi moodustumine











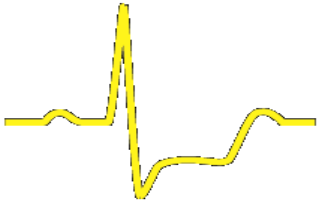
Stabiilne stenokardia

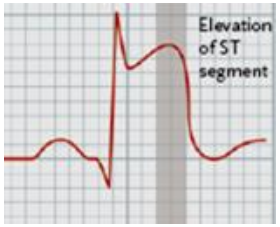
Ebastabiilne stenokardia

Non-ST-elevatsiooniga MI

ST elevatsiooniga-MI

Hospitaliseerimisel EKG leid





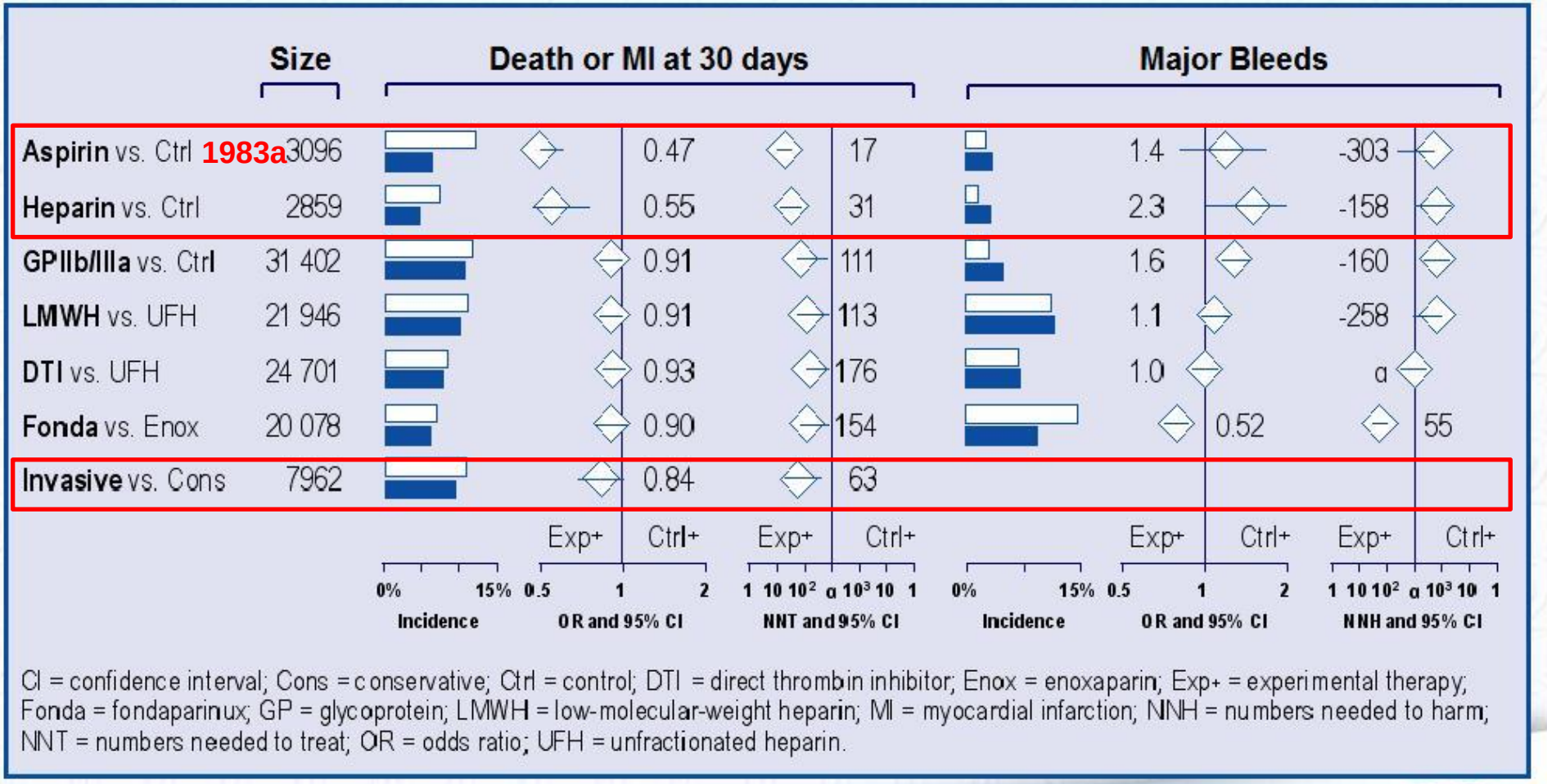
Tot. oklusiooni leiu tõenäosus

5-10%

20→40%

>85-90%

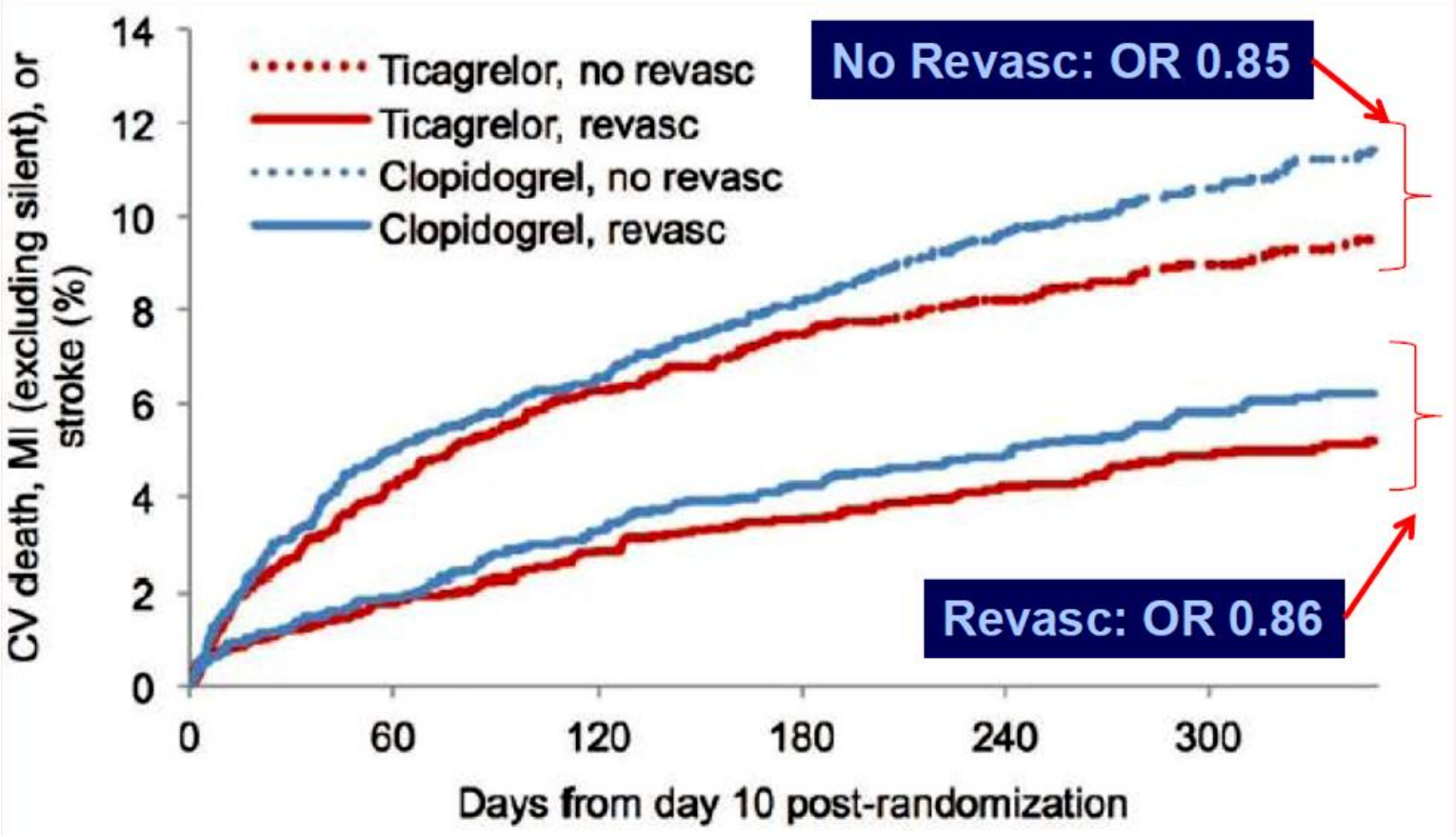
Benefit and risk for different treatment modalities



CI = confidence interval; Cons = conservative; Ctrl = control; DTI = direct thrombin inhibitor; Enox = enoxaparin; Exp+ = experimental therapy; Fonda = fondaparinux; GP = glycoprotein; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NNH = numbers needed to harm; NNT = numbers needed to treat; OR = odds ratio; UFH = unfractionated heparin.

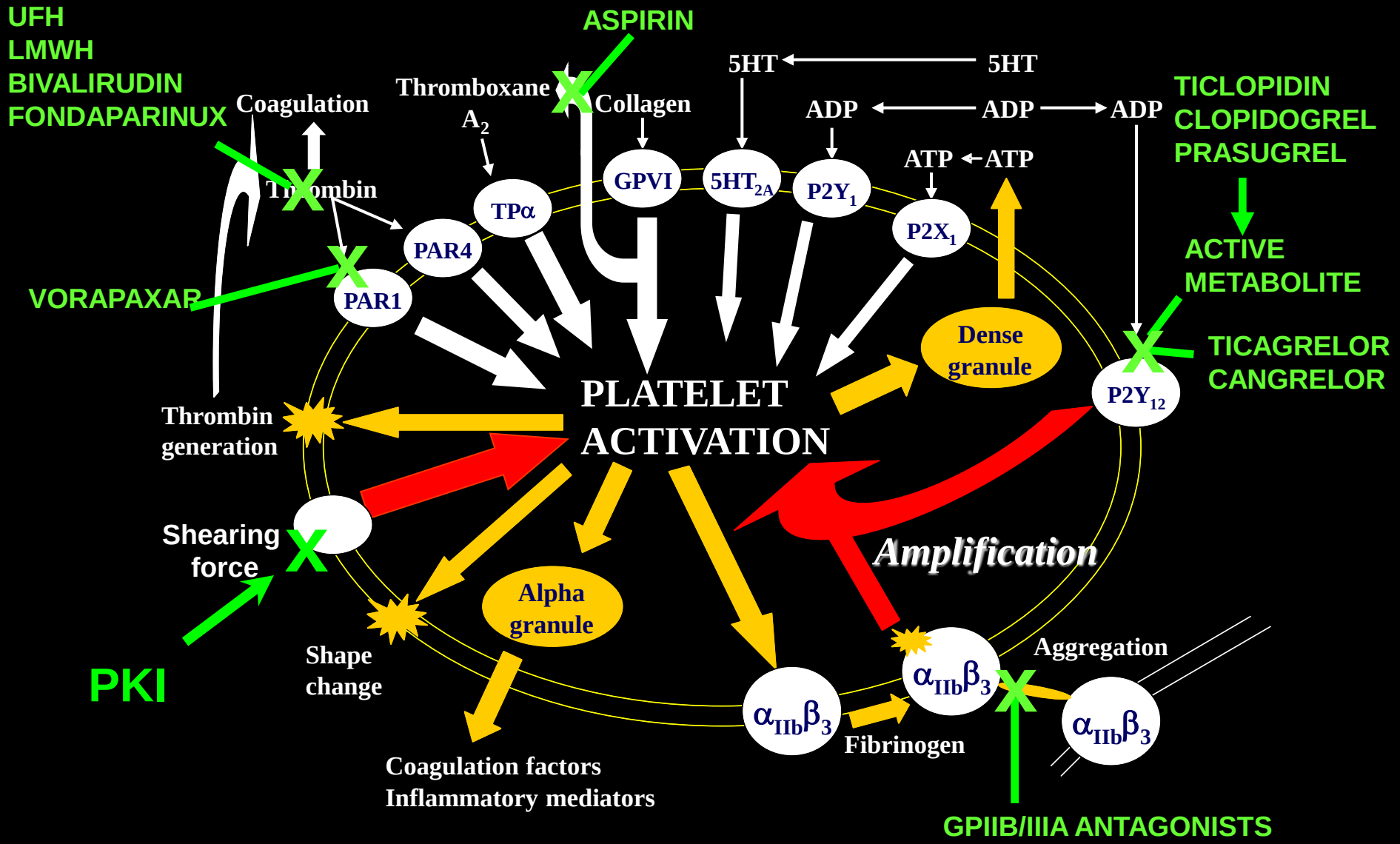
European Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

PLATO UURINGUS KESKMISE JA KÕRGEMA RISKIGA NSTEMI INFARKTIGA HAIGETEL
INVAS VS MED RAVI TULEMUSED DAPT RAVIGA KLOP VS TIKAGRELOOR



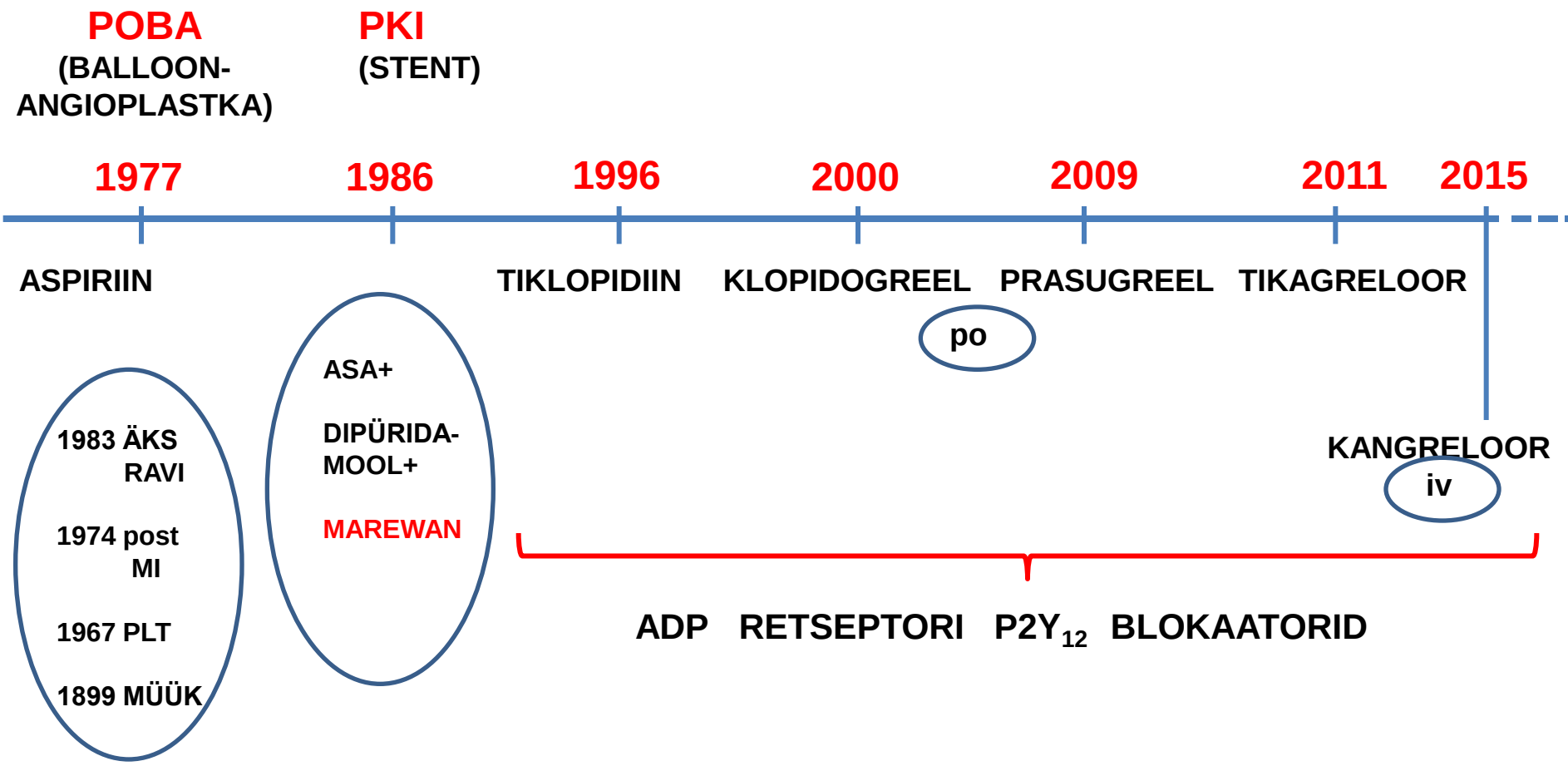
Lindholm European Heart J 2014

ANTITROMBOOTILISTE RAVIMITE TOIMEPUNKTID



Storey RF. *Current Pharmaceutical Design 2006*

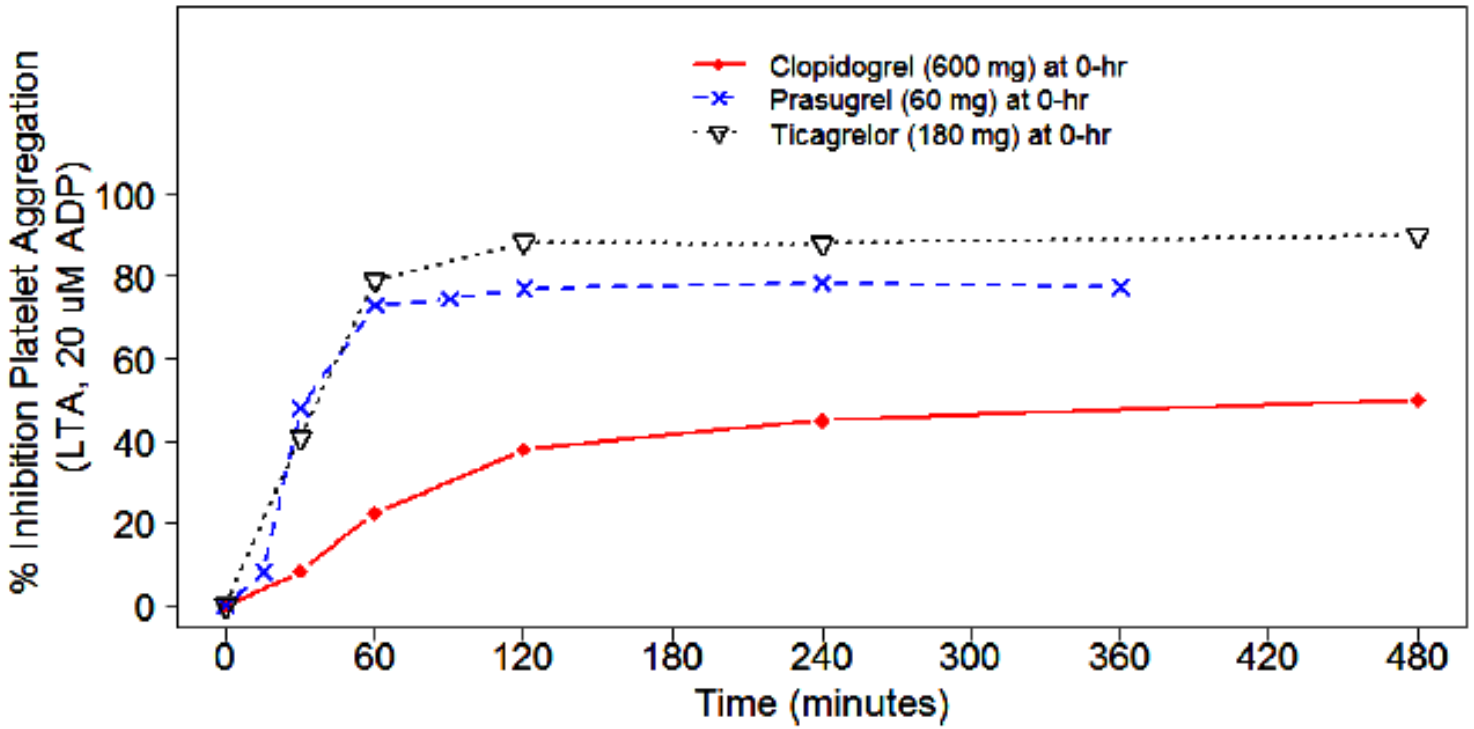
ANTIAGREGANTRAVI ARENG LÄBI ÄKS ja PKI PRISMA



ADP $P2Y_{12}$ retseptori antagonistid

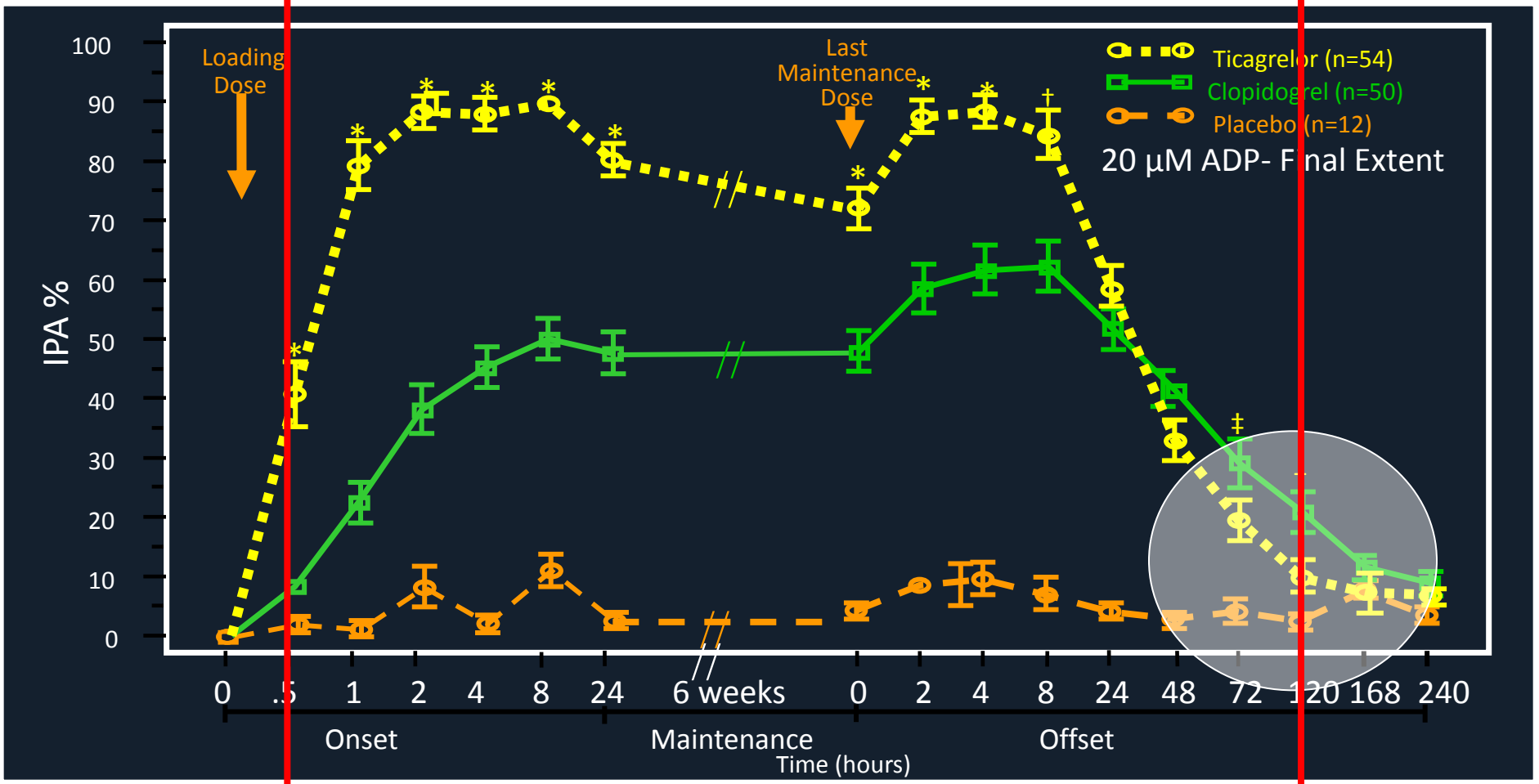
	Klopidogreel (geneerik)	Tikagreloor	Prasugreel	Cangreloor
	Tienopüridiin	Triasolopürimidiin	tienopüridiin	ATP analoog
Toime	Mittepöörduv	Pöörduv	Mittepöörduv	pöörduv
Manustamine	po	po	po	iv
Toime algus löökdoosiga	2-6t	30min- 2t	30min – 4t	Sekundid
Toime kestus*	7-10p	3-5p	7-10p	~60min
eelravim	Jah	Ei	jah	Ei
Resistentsus	+++ (-30%)	---	+	---
IPA (%)ADP 20µmol/ l	40-50%	70-90%	70-80%	> 80%
HOIATUSED		Kõrvalnähud: Düspnoe,av -blokaad,astma	Vastunäidustus: TIA/ stroke püsidoosi ↓5mg: <60kg, >75a	

Figure 6. Percent Inhibition of platelet aggregation for clopidogrel, prasugrel and ticagrelor loading doses



Source: OCP Review-Fig 1

TIKAGRELOORI JA KLOPIDOGREELI ANTIAGREGANTSE TOIME VÕRDLUS



30 minutit

•Gurbel P, et al. Circulation 2009;120:2577-85

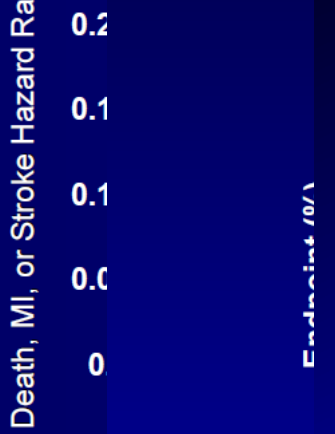
5 päeva

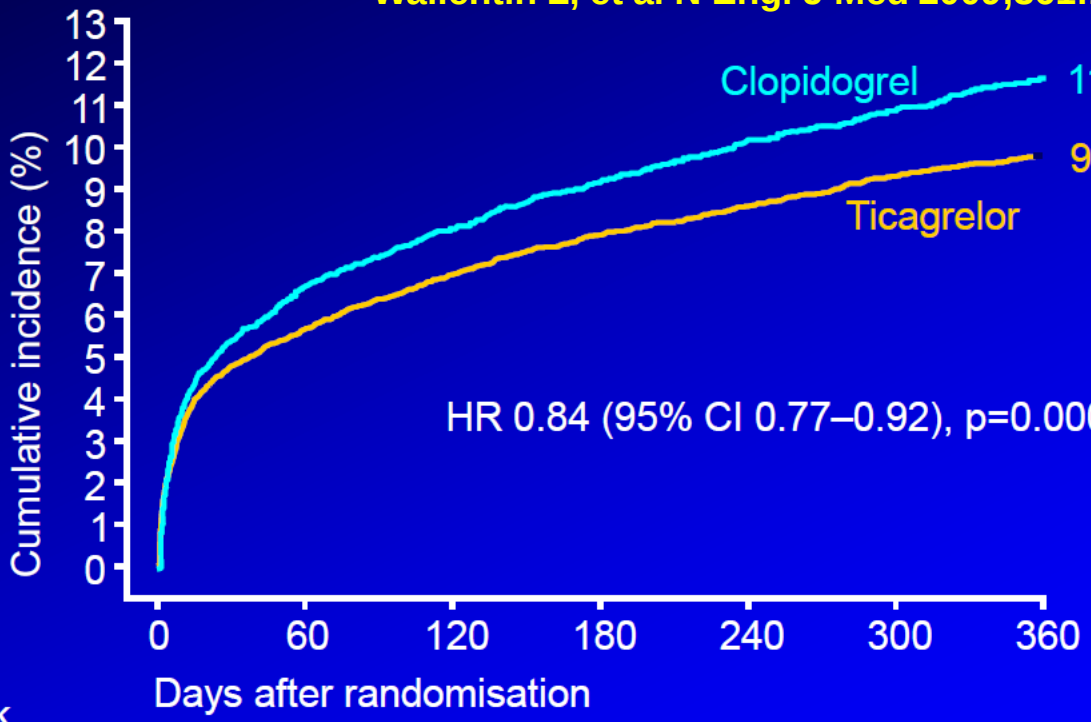
CURE: Long-Term Results by

TRITON-TIMI 38: Prasugrel vs Clopidogrel in ACS Patients Treated With PCI

PLATO: KM estimate of time to first primary efficacy event (CV death, MI or stroke)

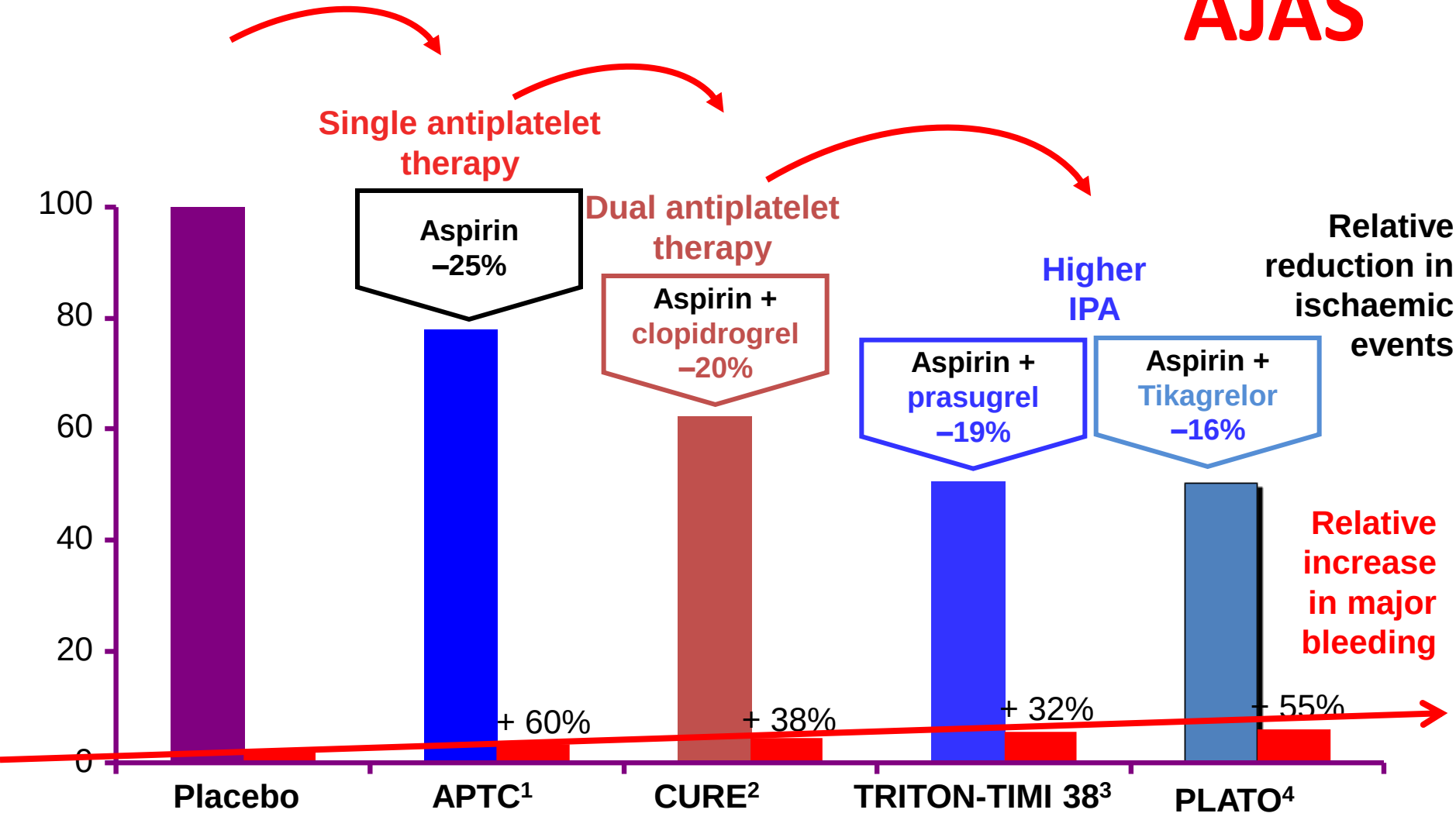
Wallentin L, et al N Engl J Med 2009;361:1045-1057





No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

ANTIAGREGANTRAVI TULEMUSED AJAS



[1]Antiplatelet Trialists' Collaboration. BMJ 1994;308:81–106
[2]Yusuf S, et al. N Engl J Med 2001;345:494–502
[3]Wiviott SD, et al. N Engl J Med 2007;357:2001–15
[4]Wallentin L, et al N Engl J Med 2009;361:1045-1057

GRACE 6k suremuse ja CRUSADE veritsuse skooride sisendid

Kretiniini kliirens

Südamepuudulikkus

HR
hospitaliseerimisel
RR

GRACE 6k suremus

Vanus

Põetud ÄMI

ST ↓
hospitaliseerimisel
Ferm ↑

PKI tegemata

CRUSADE veritsus

Hgb/ hematokrit

Sugu-♀

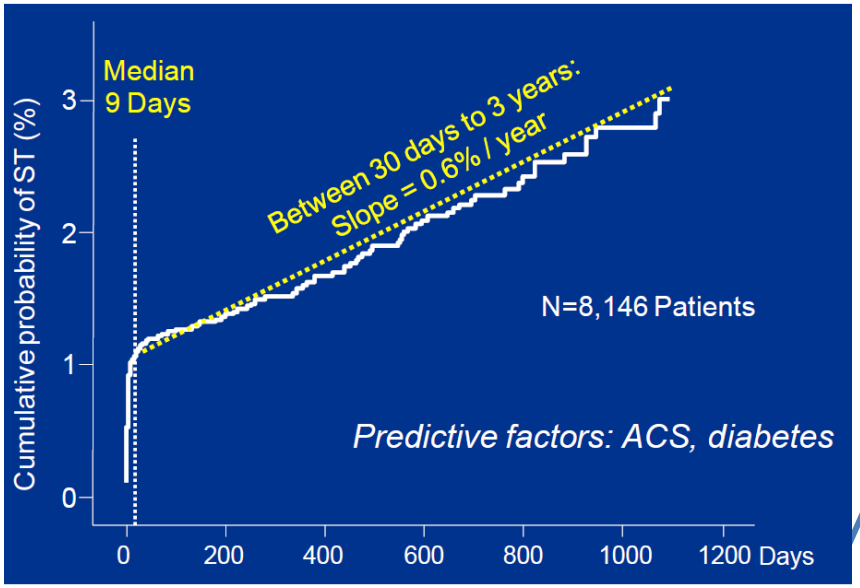
Diabeetik

Põetud insult, klaudikatsioon

Tromboosi risk

Verejooksu risk

DAPT ravi kestus peale ravimit eritavate stentide (DES) kasutamist stendi tromboosi vältimiseks



Daemen J et al. *Lancet* 2007 369: 667–78

2-4 kuud

6 kuud

12 kuud (eluaegne?)

30 kuud?

24 kuud?

ÄKS?

6 kuud (stab stenok)

3 kuud?

1 kuu?

1. Gen DES
2002 Cypher
2003 Taxus

2005 aasta
ESC ravijuhis

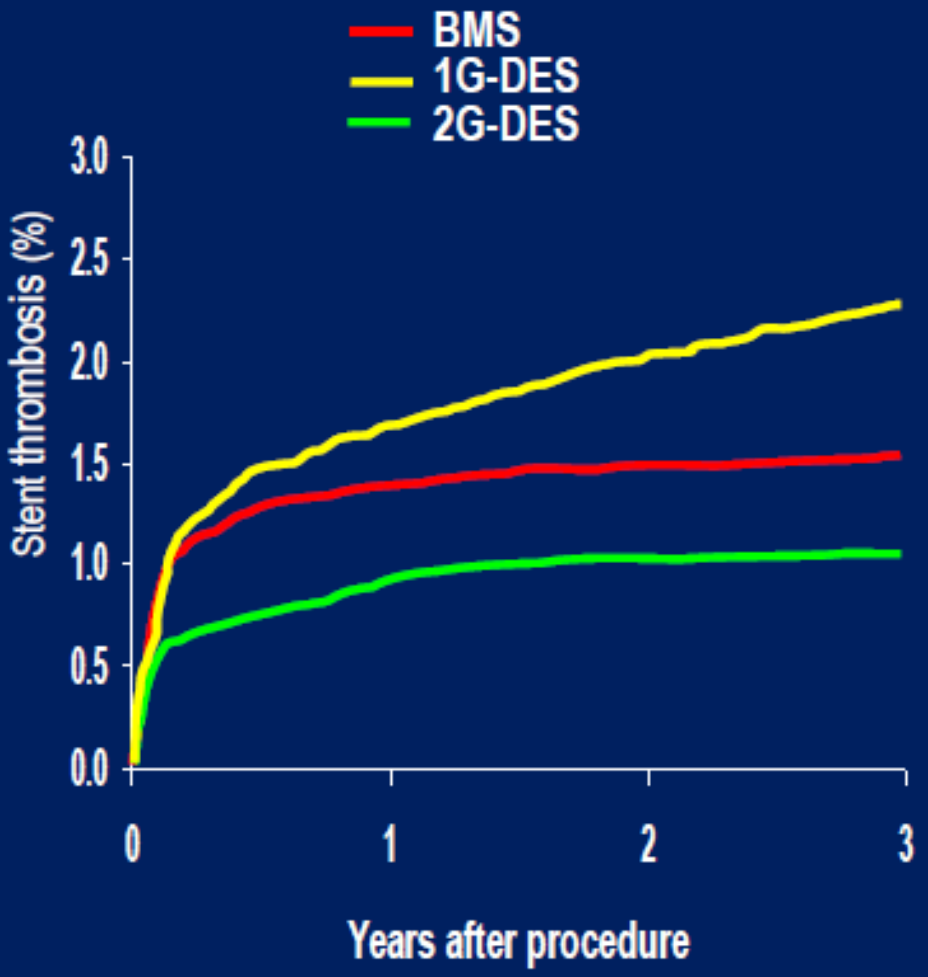
2006 aasta
ESC Barcelona kongress

2006-2010

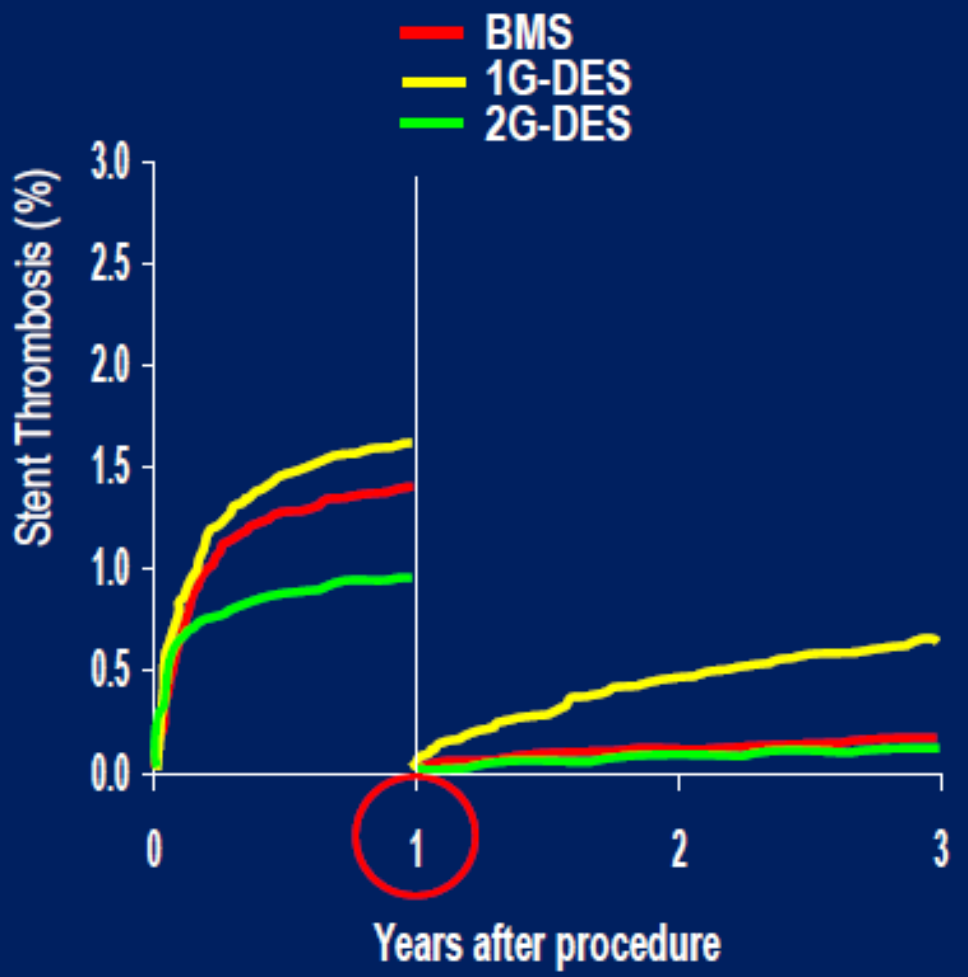
2013 ESC
Stab stenokardia
ravijuhis

Definite Stent Thrombosis Through 3 Years In 18,334 Patients (28,739 Lesions) By Stent Type

3-Year Incidence of Stent Thrombosis



1-Year Landmark Analysis



Tada, Kastrati et al. JACC INTV 2013 (in press)

STABIILSE STENOKARDIA DAPT KESTUS 6 KUUD

Studies of 3-6 month vs. 1-2 year DAPT were all negative

A patient-level pooled meta-analysis of 4 RCTs

Study	N patients	Primary endpoint	Design	Follow-up
EXCELLENT, 2012	6 months (n=722) vs. 12 months (n=721)	Cardiac death/MI/ ischemia-driven TVR	Non-inferiority	1 year
OPTIMIZE, 2013	3 months (n=1,563) vs. 12 months (n=1,556)	Death/MI/CVA/major bleeding	Non-inferiority	1 year
PRODIGY, 2012	6 months (n=751) vs. 12 months (n=750)	Death/MI/CVA	Superiority	2 years
RESET, 2012	3 months (n=1,059) vs. 12 months (n=1,058)	Cardiac death/MI/ST/TVR/ major bleeding	Non-inferiority	1 year

Palmerini T and Stone GW. JACC in press

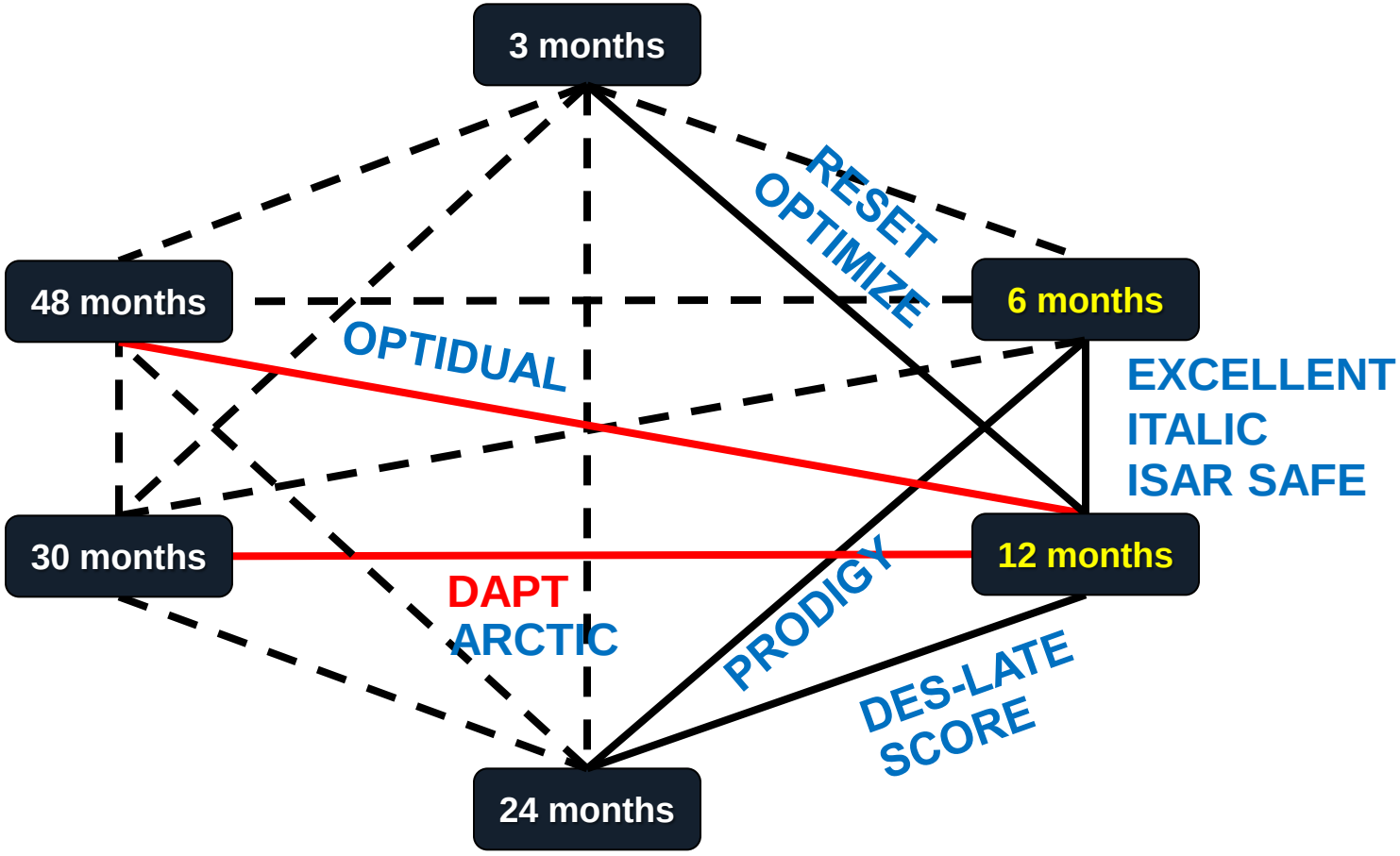
STABIILSE STENOKARDIA DAPT KESTUS 6 KUUD

A patient-level pooled meta-analysis of 4 RCTs
Clinical outcomes of short-term versus long-term DAPT stratified by trial

Events b/t DAPT d/c and 1 year	Hazard ratio (95% CI)	P value
Cardiac death, MI, or def/prob ST	1.21 (0.77-1.89)	0.42
All-cause death	1.14 (0.73-1.79)	0.58
Cardiac death	1.25 (0.71-2.22)	0.43
MI	0.89 (0.47-1.67)	0.70
Definite ST	0.74 (0.28-1.92)	0.54
Definite/probable ST	1.75 (0.42-7.14)	0.45
Stroke	1.56 (0.44-5.56)	0.49
Major or minor bleeding	0.44 (0.21-0.91)	0.03
Major bleeding	0.30 (0.10-0.91)	0.03
Minor bleeding	0.73 (0.28-1.92)	0.53

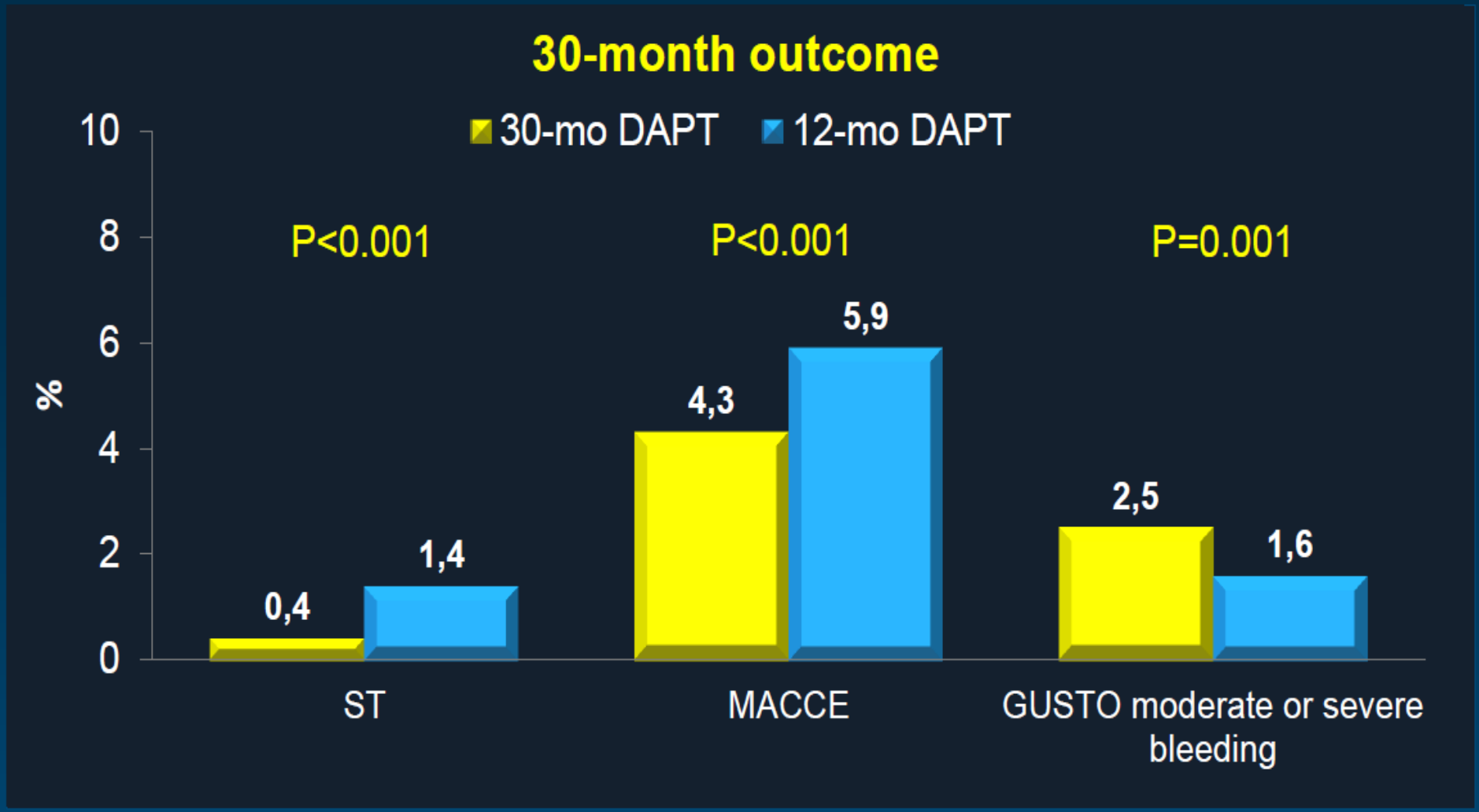
Palmerini T and Stone GW. JACC in press

DAPT ravi kestuse uuringud



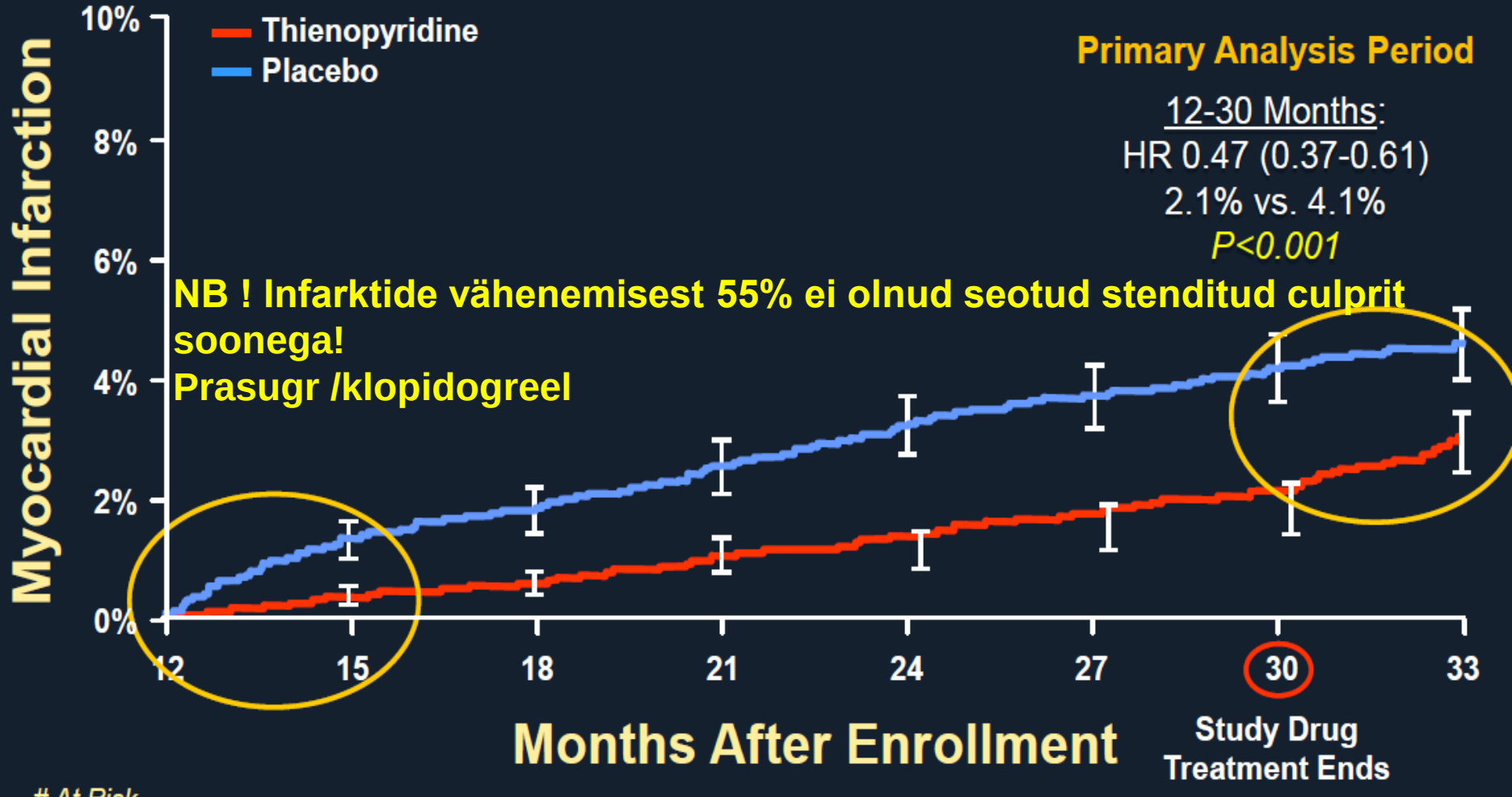
DAPT: 30 months versus 12 months of DAPT after PCI

9961 patients with DES after 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin with no events randomly assigned to continue thienopyridine treatment or to receive placebo



Mauri L., et al. N Engl J Med. 2014; 371:2155-66

Myocardial Infarction



# At Risk							
Thienopyridine 5020	4920	4849	4789	4717	4634	4580	3051
Placebo 4941	4804	4727	4653	4565	4501	4440	3012

Mauri L., et al. N Engl J Med. 2014; 371:2155-66

PKI järgne kaksik-antiagrgantravi (DAPT)

	LÖÖKDOOS	PÜSIDOOS
1.ASA	150-300mg	75-100mg x 1
2.1 Klopidogreel	600mg x 1	a) 75mg x 1
		b) 150mg x 1 7päeva, edasi 75mg x 1
2.2 Tikagreloor	180mg x 1	90mg x 2
		NB! ASA doos >100mg ↓ efektiivsust
2.3 Prasugreel	60mg x 1	10mg x 1 5mg x 1 (<60kg, vanus>75a) (vastunäid TIA/ajuinfarkt)

PKI järgne **DAPT** ravi-
stabiilne stenokardia

DAPT ravi= asa + klopidogreel kestus		
Tavastent (BMS)	vähemalt 1 kuu	I A
Ravimit eritav stent (≥ 2.generatsiooni DES)	(12k →)6 k (USA 12k!)	I B
►kõrge veritsusriski korral (1k Resolute, 3k Xience, Genous 2 nädalat)	<6k	IIb A
►kõrge isheemia riski ja madala veritsusriki korral (difuusne haigus, pikk stenditud ala, peatüve stent, CTO jne)	>6k (>12k?)	IIb C
BVS "ABSORB" stent (täielikult resorbeeruv ravimit eritav stent)	6-12k	C
Üksikantiagregantravi peale DAPT lõpetamist (tavaliselt ASA)	tähtajatult	I A
Tikagreloor/prasugreel kasutamine soovitav vaid kõrge riski Pki puhul (peatüvi,stendi tromboosi oht, diabeetik, resistentsus)		IIb C

PKI järgne DAPT ravi nonSTEMI

DAPT = asa + uued P2Y12, kui ei ole vastunäidustusena kõrget veritsusriski	**12 kuud**	**I A**
►**Tikagreloor** keskmise ja kõrge isheemilise riskiga pt-dele vaatamata eelnevalt alustatud ravile klopidogreeliga, kui pole vastunäidustusi (**NB!** ASA püsidoos 75- 100mg)	**12 kuud**	**I B**
►**Prasugreel** eelnevalt teada oleva koronaarleiuga pt-dele, kui pole vastunäidustusi	**12 kuud**	**I B**
►**Klopidogreel**i kasutamine vaid siis, kui tikagreloor ja prasugreel pole kättesaadavad või on vastunäidustatud (veritsusrisk?)	**12 kuud**	**I B**
Üksikantiagregantravi peale DAPT lõpetamist (tavaliselt ASA)	**tähtajatult**	**I A**

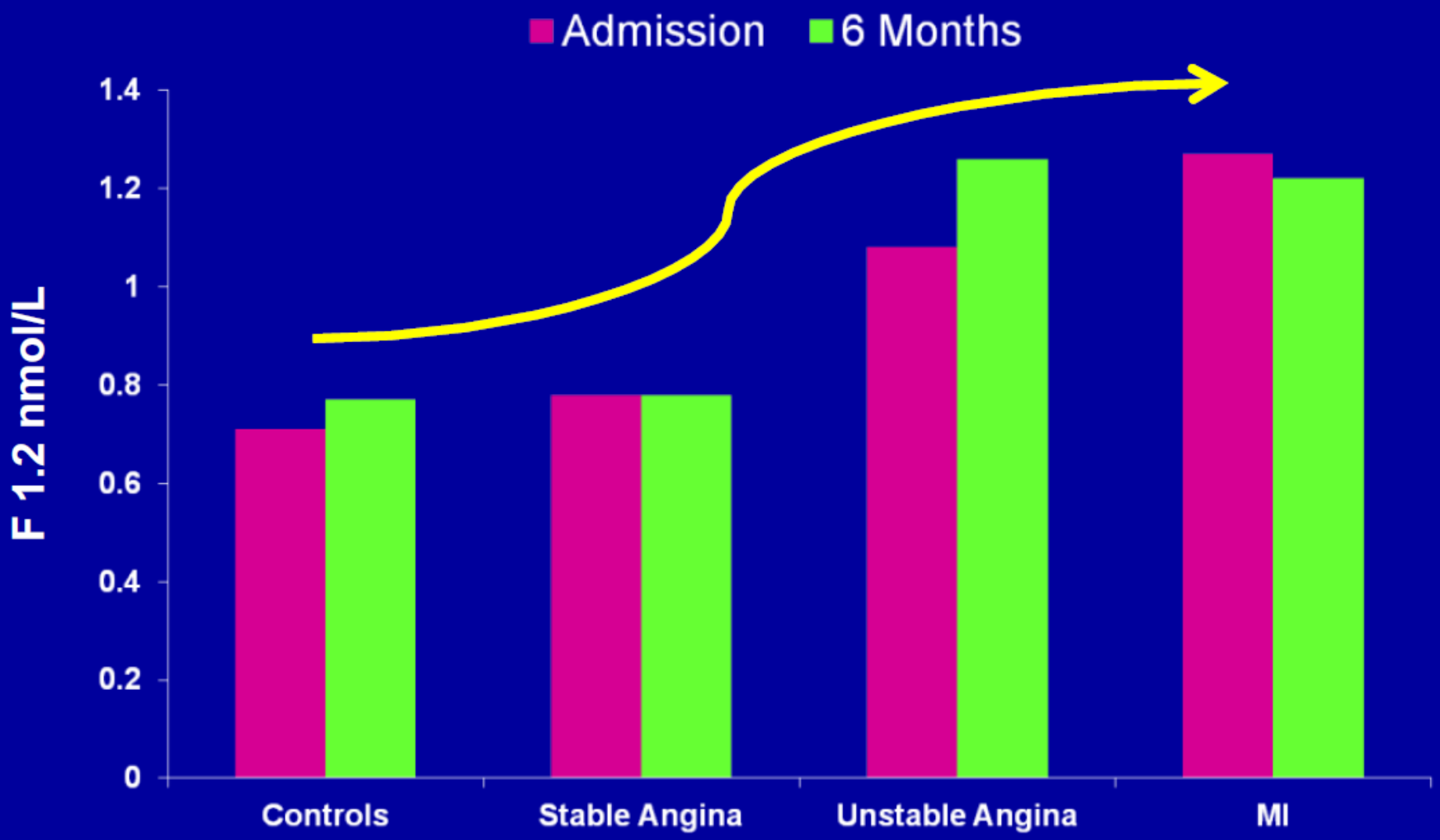
PKI järgne DAPT ravi STEMI haigetel

DAPT = asa + uued P2Y12, kui ei ole vastunäidustusena kõrget veritsusriski	**12 kuud**	**I A**
►**Tikagreloor**, kui pole vastunäidustusi (**NB!** ASA püsidoos 75- 100mg)	**12 kuud**	**I B**
►**Prasugreel**, kui pole vastunäidustusi	**12 kuud**	**I B**
►**Klopidogreel**i kasutamine vaid siis, kui tikagreloor ja prasugreel pole kättesaadavad või on vastunäidustatud (veritsusrisk?)	**12 kuud**	**I B**
Üksikantiagregantravi peale DAPT lõpetamist (tavaliselt ASA)	**tähtajatult**	**I A**

ÜLDISI SOOVITUSI NÕUANDEID DAPT RAVI KASUTAMISEL

DAPT ravi vajaduse ja olemuse selgitamine pt-le	**I C**
Rutiinset trombotsüütide agegatsiooni määramist ei soovitata (ASA/klop)	**III A**
Prootonpumba inhibiitori (v.a. Omeprasool) kasutamine soovitav DAPT ravil olevatel haigetel, kellel anamneesis GI veritsus või peptiline haavand ning mitmete riskifaktorite olemasolu (Helicobacter pylori infektsioon, vanus>65a, kaasuv ravi steroidide, (N?)OAC-ga)??	**I A**
Ei soovitata ASA koos NSAID-ga (selektiivne Cox-2, ja mitteselektiivne NSAID)	**III C**
Stendi tromboosiga haigel klopidogreeli asendamine tikagreloori/prasugreeliga	**C**

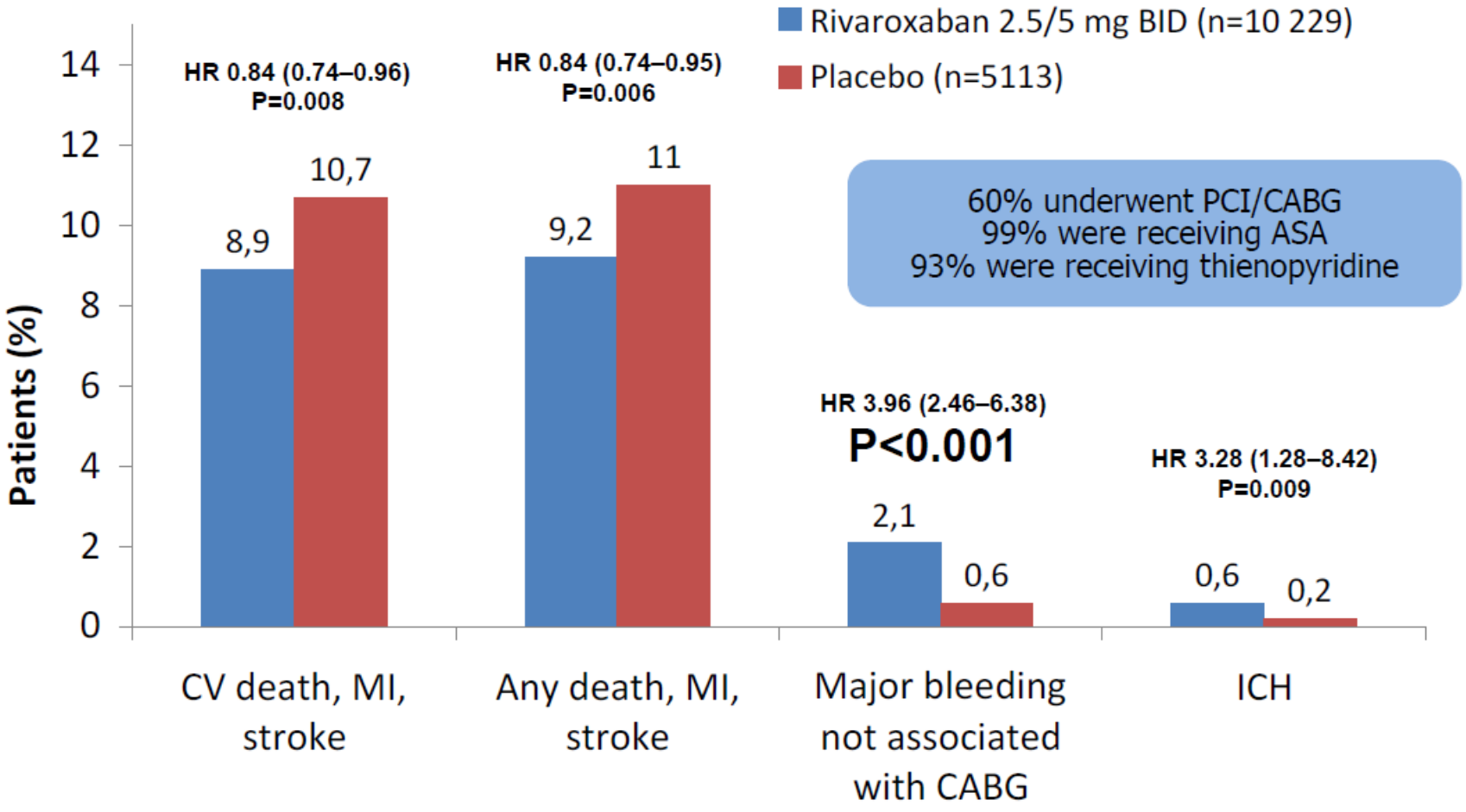
Persistent Elevation of Thrombin Generation in Post-ACS Patients



Slide by C. Michael Gibson, M.S., M.D.

Merlini et al. Circ 1994;90:61-68

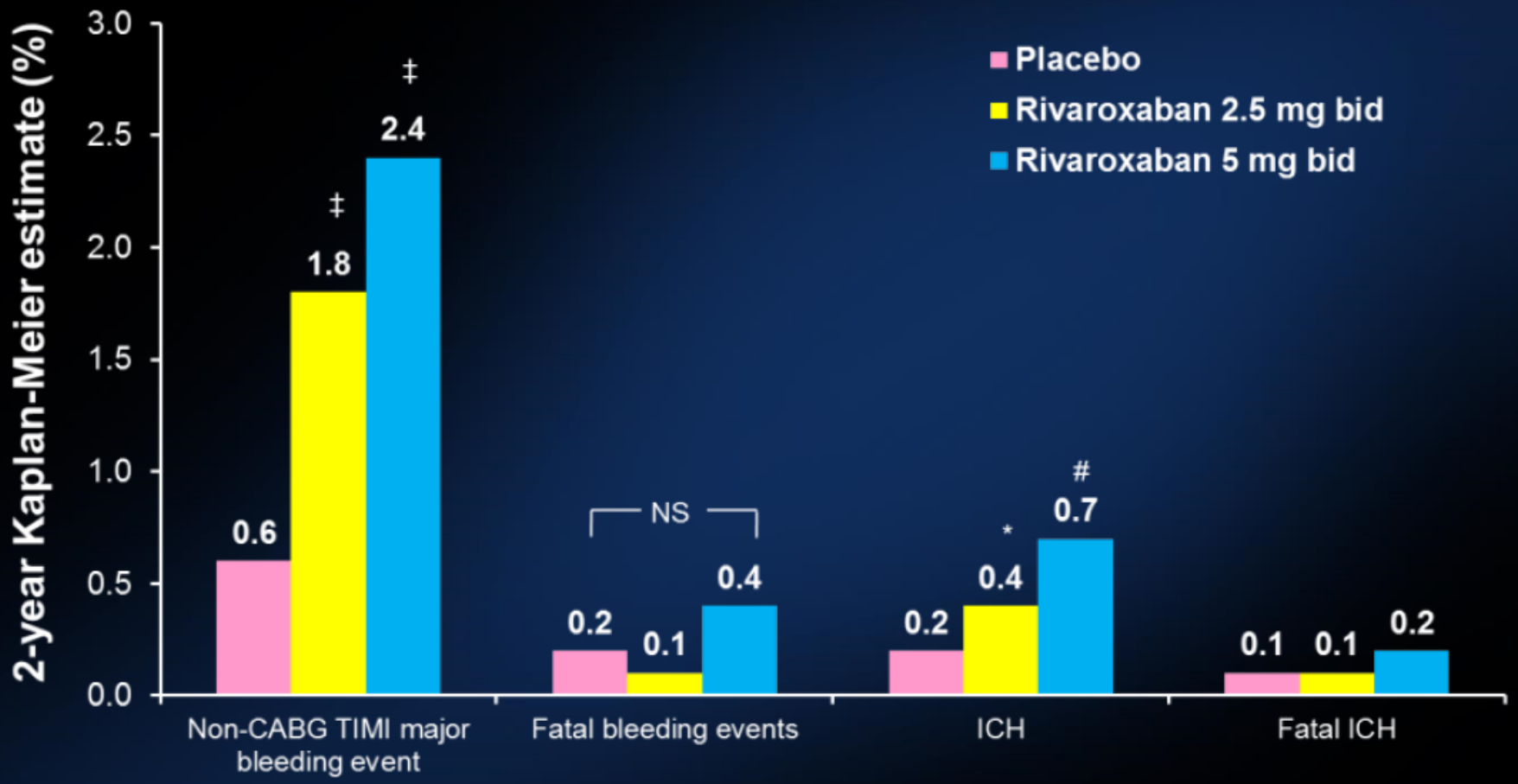
Rivaroxaban plus DAPT in ACS without AF: ATLAS-ACS-2



15 526 patients with recent ACS randomized to rivaroxaban (2.5 mg or 5 mg BID) or placebo for up to 31 months in the ATLAS ACS 2–TIMI 51 trial

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

ATLAS ACS 2-TIMI 51: Rivaroxaban Did Not Increase Fatal Bleeding or Fatal ICH



*p=0.04 vs. placebo; #p=0.005 vs. placebo; ‡p<0.001 vs. placebo.
bid, twice daily; for 2.5 mg, ICH, intracranial haemorrhage; NS, not significant

Slide by C. Michael Gibson, M.S., M.D.

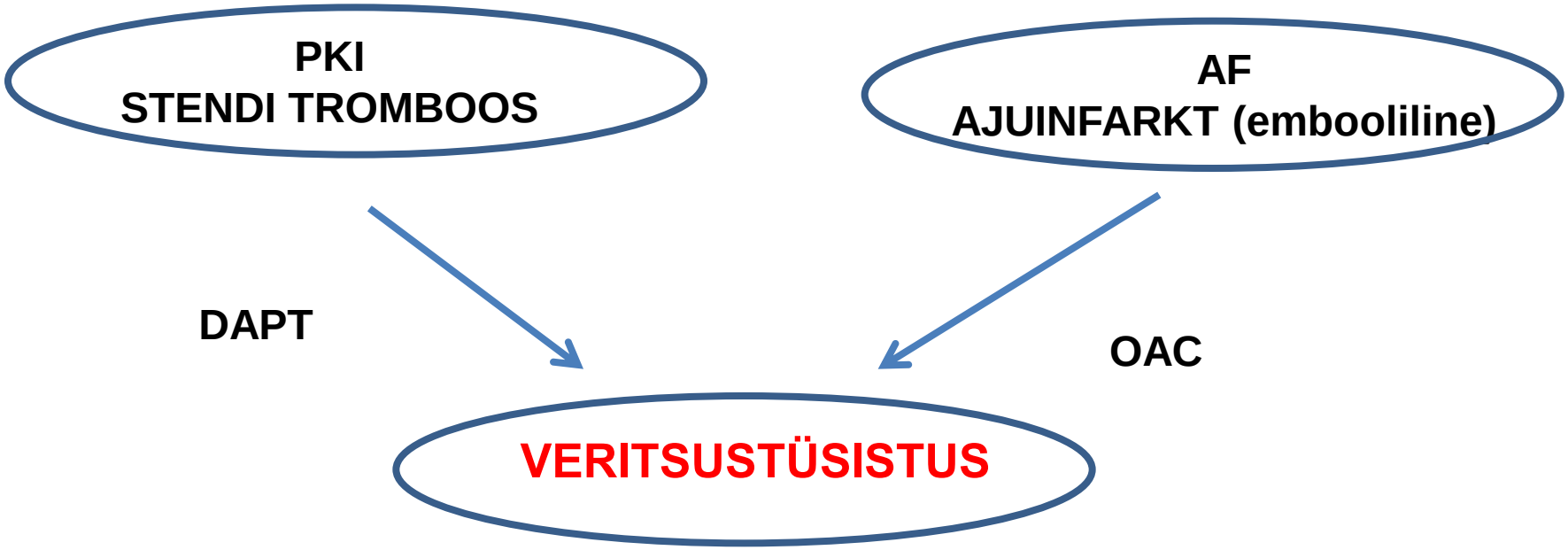
1. Mega JL et al. N Engl J Med 2012;366:9–19;
2. Gibson CM et al. AHA 2011 (www.clinicaltrialresults.org)

STEMI Euroopa 2012 ravijuhis	
Valitud madala veritsusriskiga STEMI infarktiga haigetel, kes saavad DAPT ravi ASA + klopidogreeliga, võib kasutada Rivaroxabani 2,5mg x2	**IIb B**

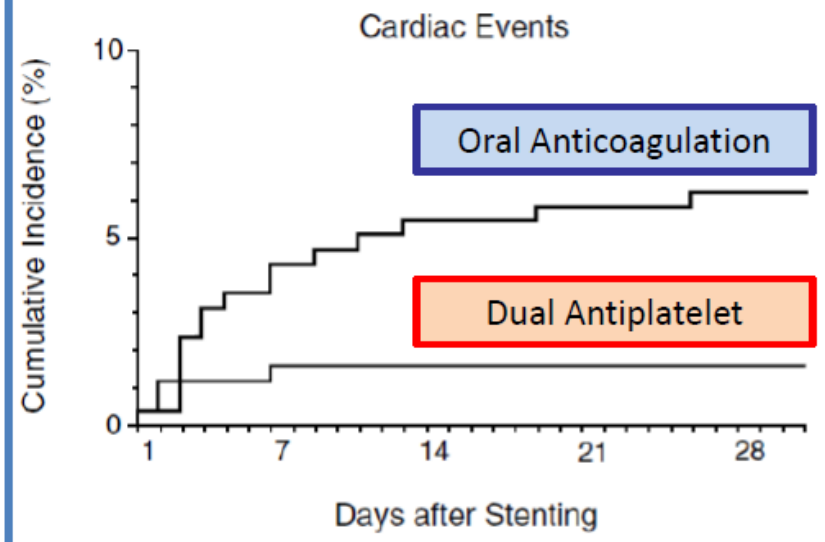
ANTIAGREGANTRAVI DAPT ja AKŠ

ASA ei katkestata enne ega AKŠ ajaks	I B
ADP $P2Y_{12}$ retseptori blokaatoriga ravi katkestatakse enne AKŠ **1. 5p enne klopidogreel, tikagreloor** **2. 7p enne prasugreel**	I B
ASA alustata kohe 6-48t peale AKŠ	I A
DAPT alustamine/jätkamine ÄKS haigetel peale AKŠ 12k ja edasi ASA ∞	
DAPT endarterektoomia kasutamisel 6k ja edasi ASA ∞	

DAPT ravi ja OAC näidustusega haiged



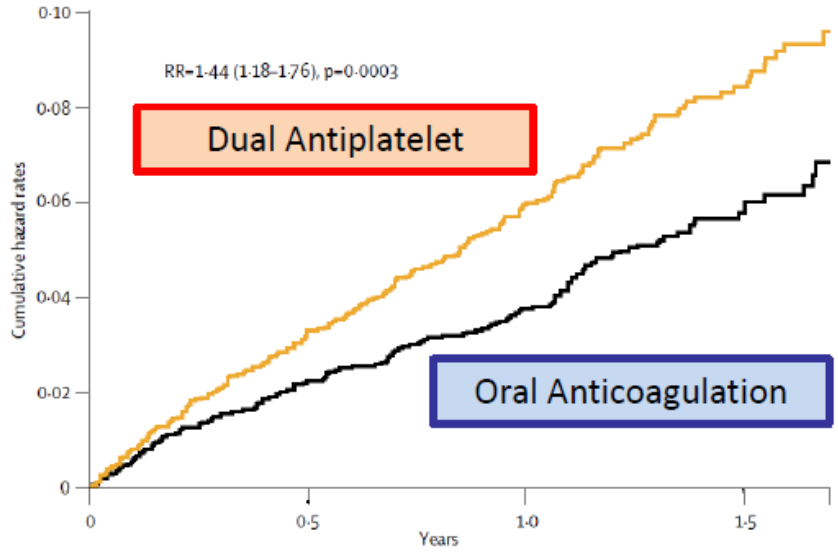
Coronary stent implantation



ISAR, NEJM 1996

+

Atrial fibrillation



ACTIVE-W Lancet 2006

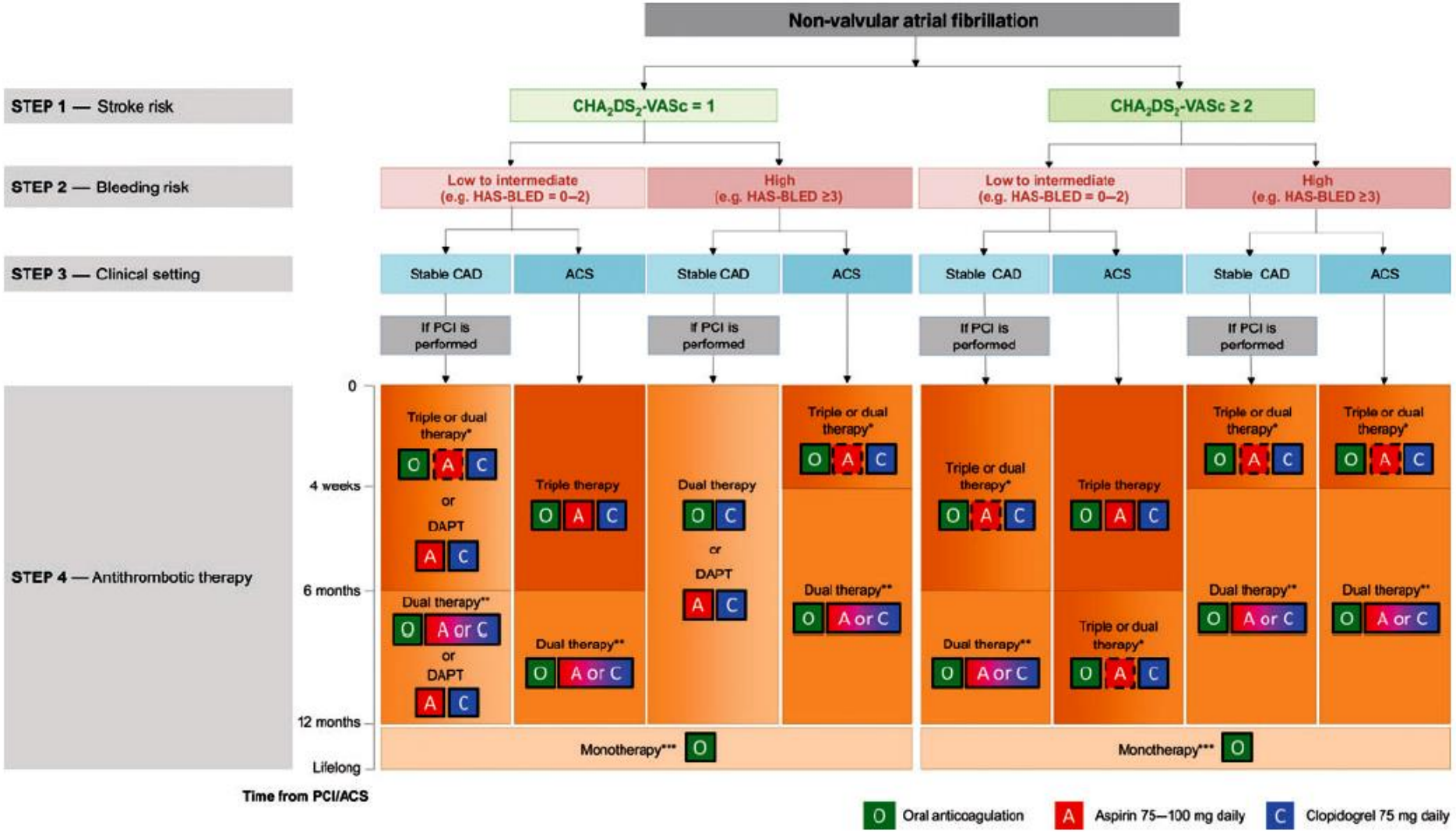
= Dual Antiplatelet + Oral Anticoagulation

Schömig et al. NEJM 1996;334:1084-9.
Connolly et al. Lancet 2006;367:1903-12.

ANTIAGREGANTRAVI DAPT + OAC „triple therapy“ PKI haigetel

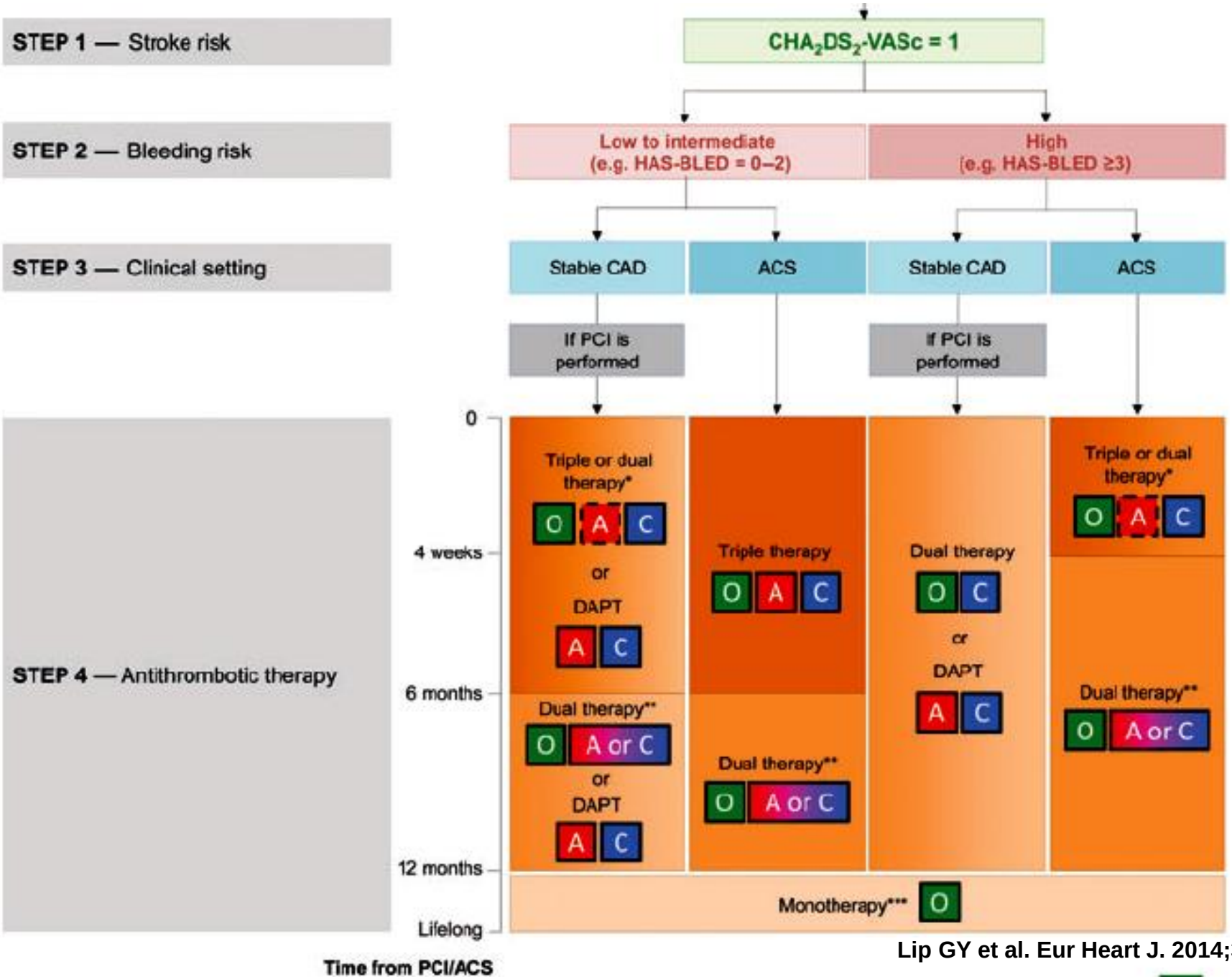
Põhipostulaat-nii vähe kui võimalik ja nii palju kui vaja Skoorid: CHA_2DS_2Vasc , HASBLED, GRACE	
INR 2.0-2,5 <u>tähtajatult</u> (NOAC kasutamiseks uuringud käigus, valida võimalik madalaim doos)	
DAPT + OAC ASA 75-100mg ja klopidogreel 75mgx1 <u>1-12kuud</u> NB! Mitte tikagreloor, prasugreel	
SAPT + OAC klopidogreel (või ASA) +OAC (WOEST trial)	
Stendid <u>≥2. Gen DES või BMS</u> NB! HASBLED ≤ 2 korral eelistatud 2.gen DES , mitte kasutada 1.gen DES (“TAXUS”, “CYPHER”)	
Prootonpumba inhibiitorid soovitavalt kõigil haigetel	

Antitrombootilise ravi valik AF haigetel ÄKS ja/või PKI puhul

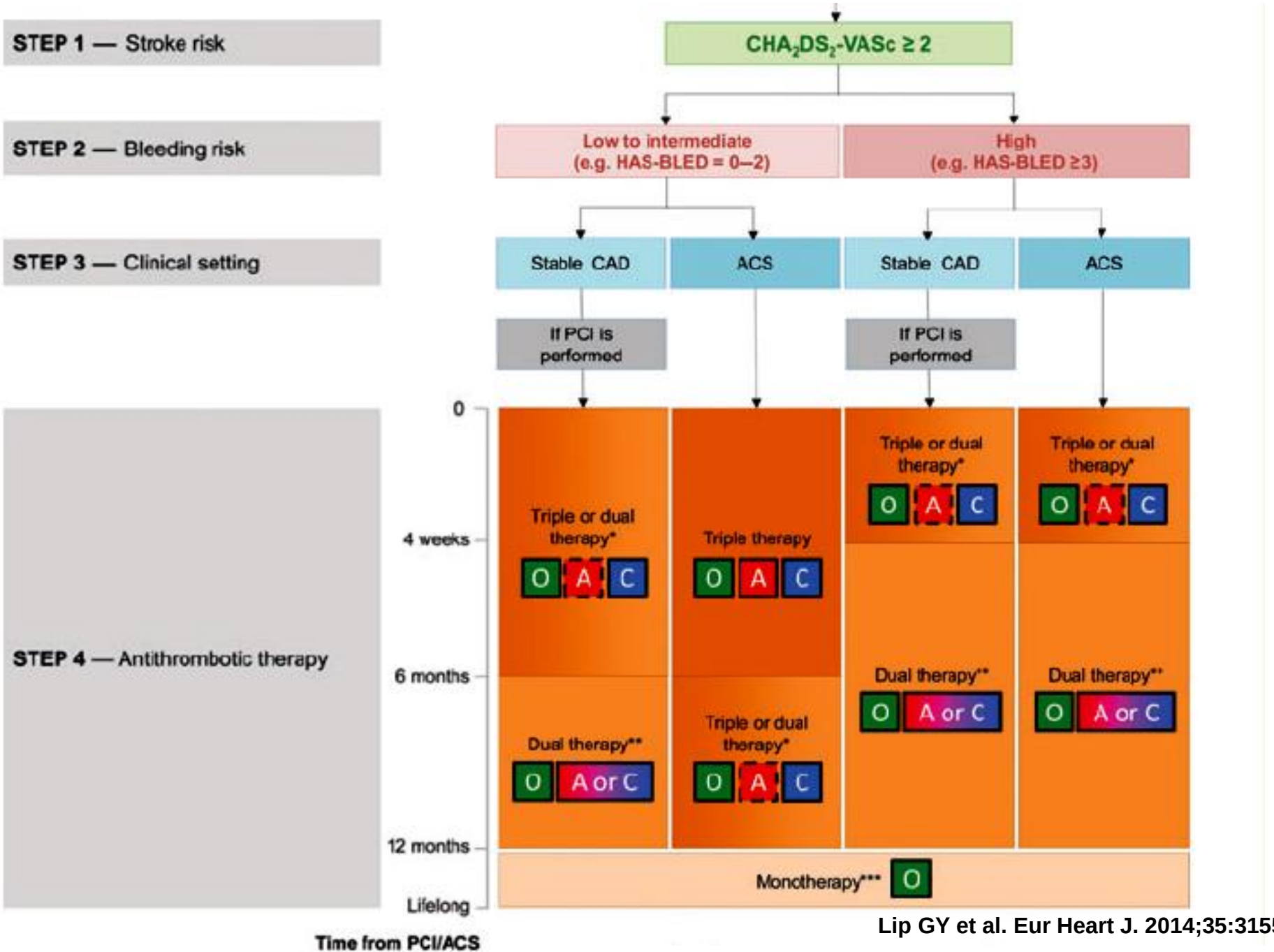


EHRA, EAPCI ja ACCA ühine konsensusdokument AF pt-de antitrombootiliset ravist ÄKS/PKI korral

Lip GY et al. Eur Heart J. 2014;35:3155-79



Lip GY et al. Eur Heart J. 2014;35:3155-79



Lip GY et al. Eur Heart J. 2014;35:3155-79

KOLMIKRAVI peale PKI-d

(ESC, EHRA, EAPCI, ACCA, HRS, APHRS konsensusdokument, august 2014)

SÜNDROOM	HEMORRAAGIA RISK	INSULDI RISK	SOOVITUS
STABIILNE STENOKARDIA	Madal/keskmine HAS-BLED 0-2	Mõõdukas CHADS-VASC 1 ja kõrge CHADS-VASC >2	1. Vähemalt 4 nädalat kolmikravi (OAC+ASA 75-100mgx1+ clopidogrel 75mgx1) 2. Edasi kuni 12 kuud kaksikravi (OAC+copidigrel 75mgx1) 3. Eluaegselt OAC
SATBIILNE STENOKARDIA	Kõrge HAS-BLED >3	Mõõdukas CHADS-VASC 1	1. 12 kuud OAC+clopidogrel 75mgx1 2. Eluaegselt OAC
		Kõrge CHADS-VASC>2	1. Vähemalt 4 nädalat kolmikravi 2. Kuni 12 kuud kaksikaravi 3. Eluaegselt OAC

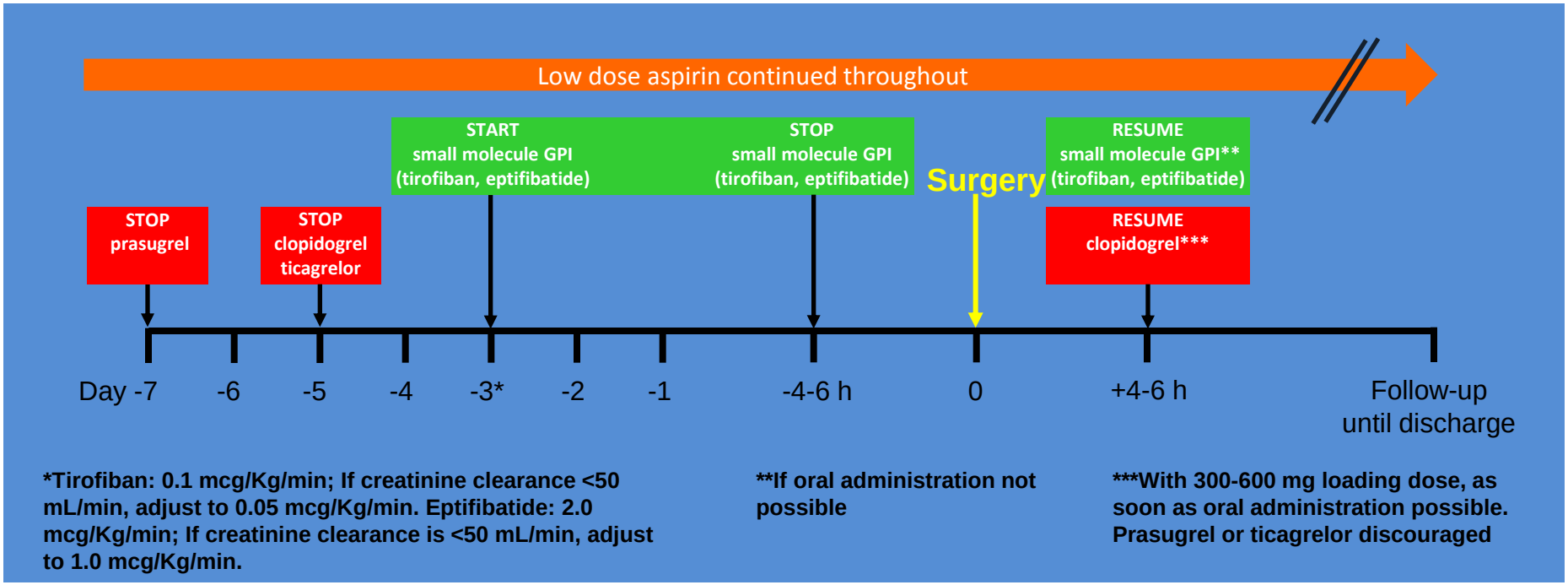
KOLMIKRAVI peale PKI-d

(ESC, EHRA, EAPCI, ACCA, HRS, APHRS, konsensusdokument august 2014)

SÜNDROOM	HEMORRAAGIA RISK	INSULDI RISK	SOOVITUS
ÄKS	Madal või mõõdukas HAS-BLED 0-2	Mõõdukas või kõrge CHADS-VASC 1 või >2	1. 6 kuud kolmikravi 2. 6-12 kuud kaksikravi 3. Eluaegselt OAC
ÄKS	Kõrge HAS-BLED>3	Mõõdukas või kõrge CHADS-VASC 1 või >2	1. 4 nädalat kolmikravi 2. Edasi kuni 12 kuud kaksikravi 3. Eluaegselt OAC

Proposed Bridging Protocols For Patients On DAPT Therapy With Aspirin Plus A $P2Y_{12}$ Receptor Inhibitor Referred To Cardiac Or Noncardiac Surgery

DAPT Bridging Strategy With Small-molecule GPI



*Tirofiban: 0.1 mcg/Kg/min; If creatinine clearance <50 mL/min, adjust to 0.05 mcg/Kg/min. Eptifibatide: 2.0 mcg/Kg/min; If creatinine clearance is <50 mL/min, adjust to 1.0 mcg/Kg/min.

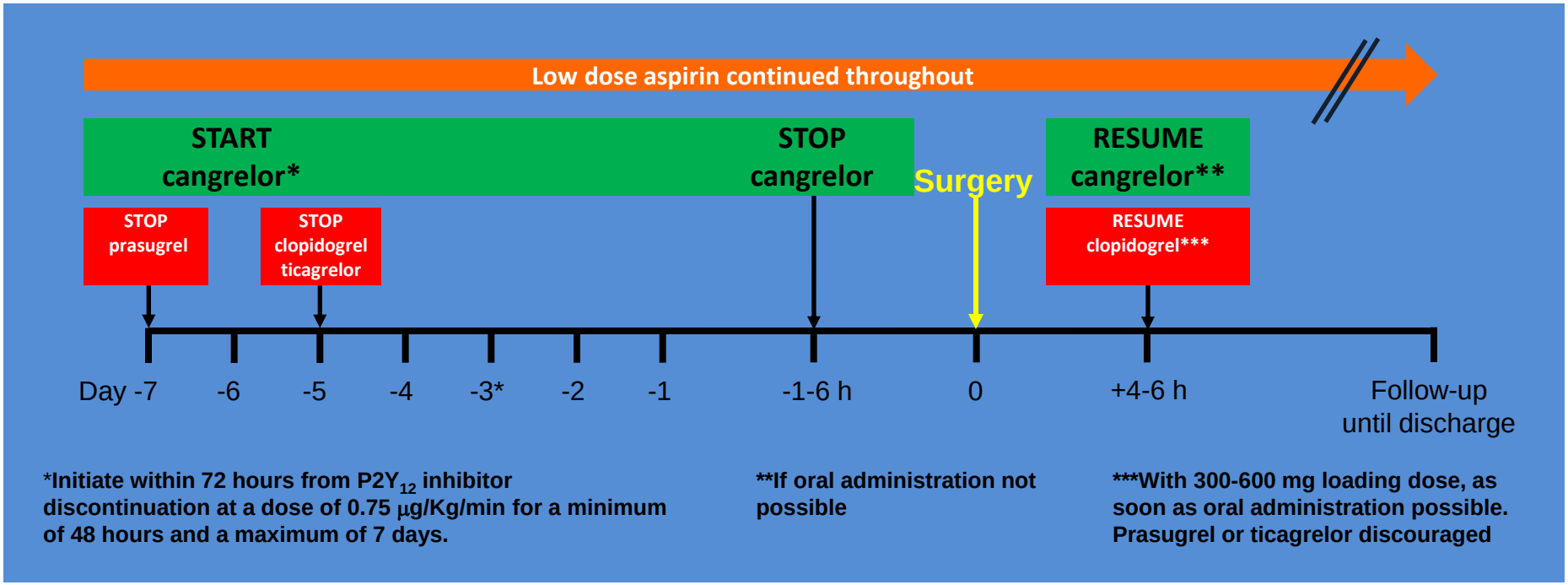
**If oral administration not possible

***With 300-600 mg loading dose, as soon as oral administration possible. Prasugrel or ticagrelor discouraged

•Capodanno D and Angiolillo DJ. Circulation. 2013;128:2785-98

Proposed Bridging Protocols For Patients On DAPT Therapy With Aspirin Plus A $P2Y_{12}$ Receptor Inhibitor Referred To Cardiac Or Noncardiac Surgery

DAPT Bridging Strategy With Cangrelor



2015 FDA ja EMA → „Kengralor“ (*cangrelor*) on lubatud kasutamiseks PKI puhul

•Capodanno D and Angiolillo DJ. Circulation. 2013;128:2785-98

GLOBAL LEADERS

All-Comers PCI Population
ACS and Elective/Stable patients
(n=16,000)

Biolimus-eluting stent (BES)
BioMatrix Flex ™

1:1 Randomization, Open-Label Design

Study Treatment Strategy

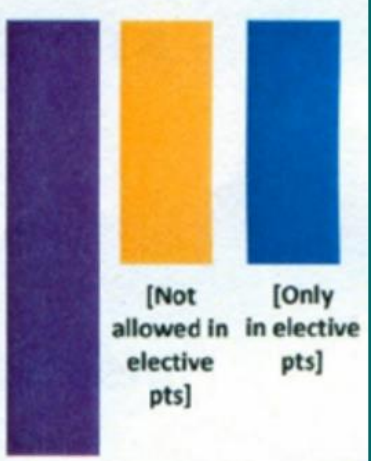
1-month
ASA + Ticagrelor

23-months
monotherapy Ticagrelor

Reference Treatment Strategy

12-months DAPT
ACS pts (ASA + Ticagrelor)
Elective pts (ASA + Clopidogrel)

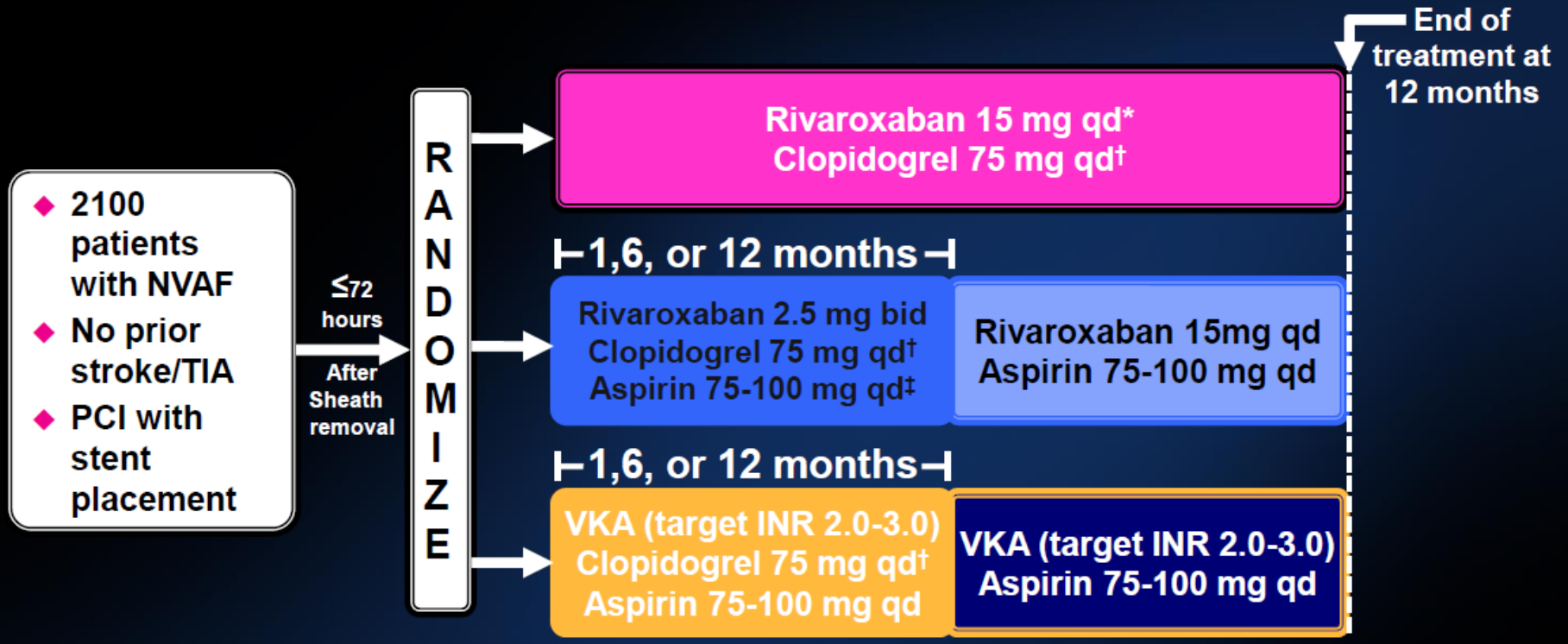
12-months
monotherapy ASA



<u>Primary Endpoint</u>

Study treatment strategy <u>superior</u> to reference treatment strategy on cumulative 2 year composite of all cause mortality and new Q-wave MI

PIONEER AF-PCI



- Primary endpoint: TIMI major, minor, and bleeding requiring medical attention
- Secondary endpoint: CV death, MI, stroke, and stent thrombosis

*XARELTO® dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.

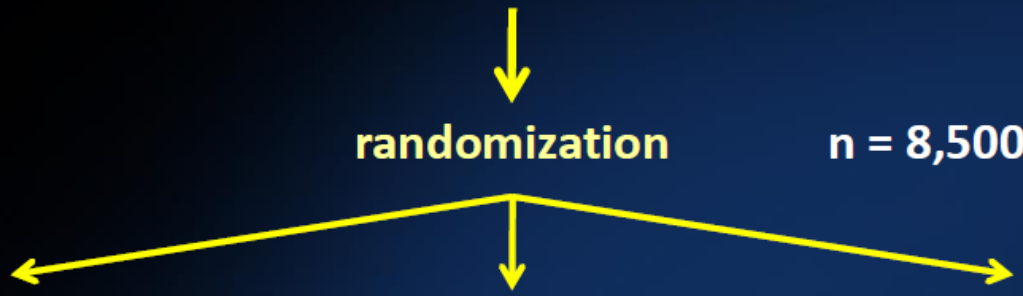
†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.

‡Low-dose aspirin (75-100 mg/d).

Data on File. Janssen Pharmaceuticals, Inc.

Re-DUAL PCI

AF patients undergoing PCI with stent implantation



dabigatran 150mg bid	dabigatran 110 mg bid	warfarin
+	+	+
"P_2Y_{12} blocker"	"P_2Y_{12} blocker"	"dual antiplatelet therapy"

Primary safety endpoint: clinically relevant bleeding

Primary efficacy endpoint: death, MI, stroke

www.boehringerI-ingelheim.com/news/news_releases/press_releases/2013/19_november_2013_dabigatranetexilate1.html

INDIVIDUALISEERIMINE

DAPT ravi kestuse probleemid- pole lihtne otsustada
Kerge otsus-SATpt, major bleeding

Teistes situatsioonides tuleb arvestada mitmeid faktoreid, mis predisponeerivad stendist sõltuvat või mitte sõltuvat isheemilise või veritsusega tüsistuse teket.

Paljudel juhtudel on mõlema tüsistuse jaoks riskifaktorid samad

Individualiseerimine sõltuvali riskidest (isheemiline, veritsus)

SAT risk: PKI tehnikast (bifurkatsioon), anatoomiast
stendi tüüp, hulk, pikkus+, diameeter
complex stenoos ,anatoomia/kahjustus

Kliiniline taust: STEMI >nonSTEMI > Stabiilne
difuusne kahjustus/ generaliseerunud ateroskl (koron/PAD,carotis
CKD, diabeet,
vanus, sugu, *frailty*
veritsuse anamnees, (N)OAC kasutamine
aneemia, trombotsütopeenia