Speaker's name: Thomas Cuisset, MD, PhD

X **I have the following potential conflicts of interest to report:**

x Consulting: Astra Zeneca, Daiichi Sankyo, Eli Lilly, Medicines Company

❒ Employment in industry

❒ Stockholder of a healthcare company

❒ Owner of a healthcare company

x Others: Lecture Fee

Abbott Vascular, Astra Zeneca, Biotronik, Boston Scientific, Cordis, Daichi Sankyo, Edwards, Eli Lilly, Hexacath, Iroko Cardio, Medtronic, Servier , Terumo

❒ **I do not have any potential conflict of interest**

Stratégie antiplaquettaire dans le SCA

Thomas Cuisset, CHU Timone, Marseille

Jeudi 25 Février 2016

Trois grandes questions

Lequel ?

New P2Y12 blockers for which patients ?

Quand commencer ?

Pre treatment with P2Y12 blockers before cathlab ?

Quand Arrêter ?

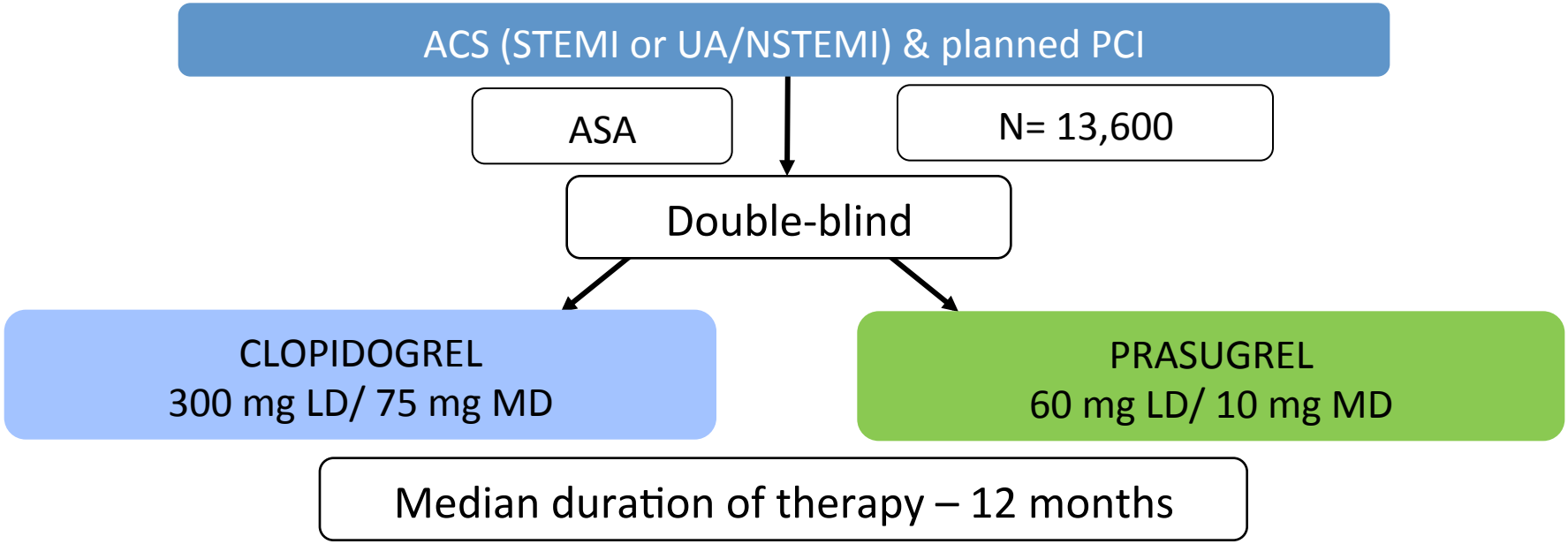
Duration of DAPT after ACS / DES ?

Trois grandes questions

Lequel ?

New P2Y12 blockers for which patients ?

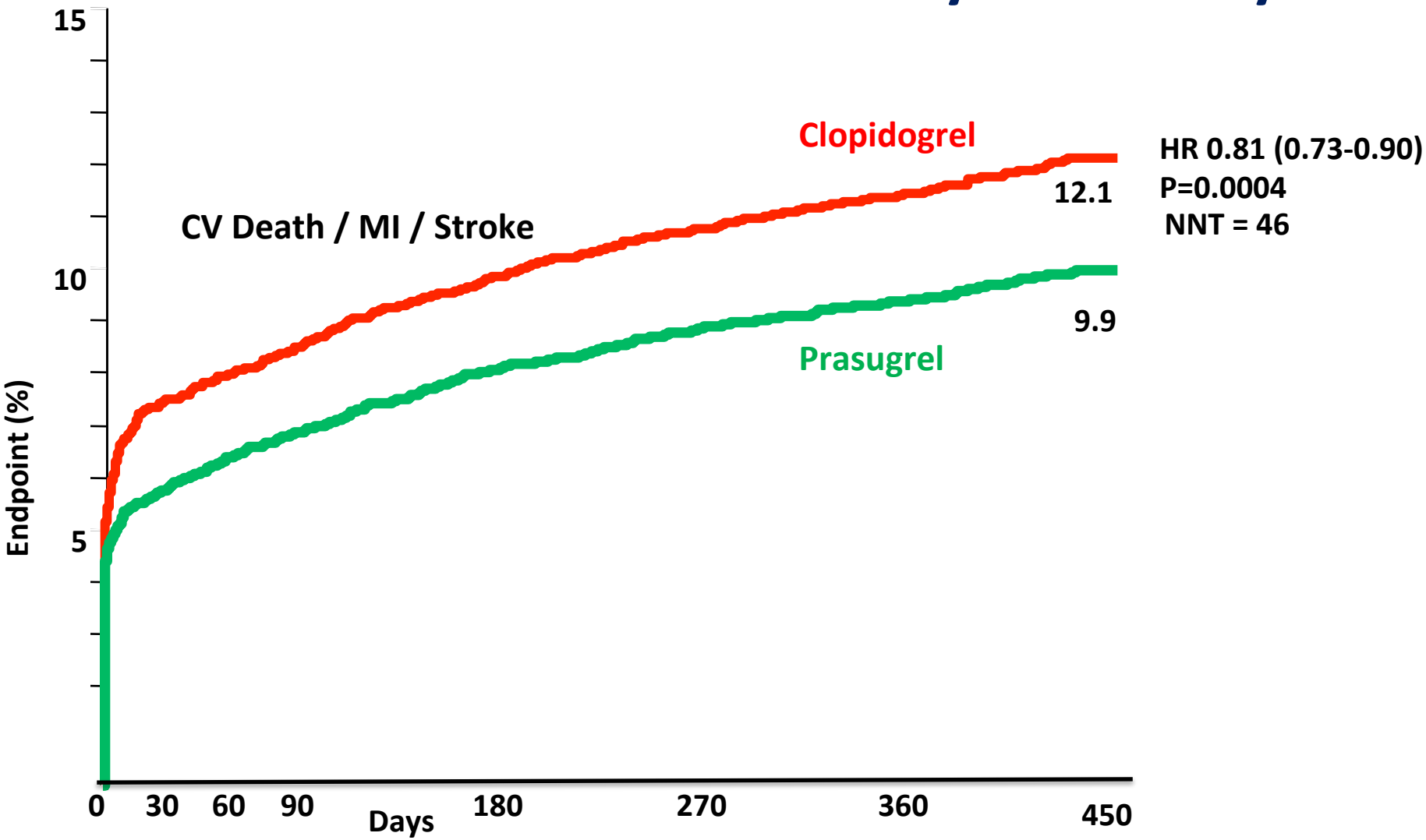
Prasugrel versus clopidogrel in patients with ACS



1º endpoint:	CV death, MI, stroke
2º endpoints:	CV death, MI, stroke, rehosp-rec isch
	CV death, MI, UTVR
	Stent thrombosis (ARC definite/prob.)
Safety endpoints:	TIMI major bleeds, Life-threatening bleeds
Key substudies:	Pharmacokinetic, genomic

Wiviott SD et al. N Engl J Med 2007

TRITON: Balance of Efficacy and Safety



Wiviott SD et al. N Engl J Med 2007

Ticagrelor: PLATO study

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg qd maintenance;
(additional 300 mg allowed pre PCI)

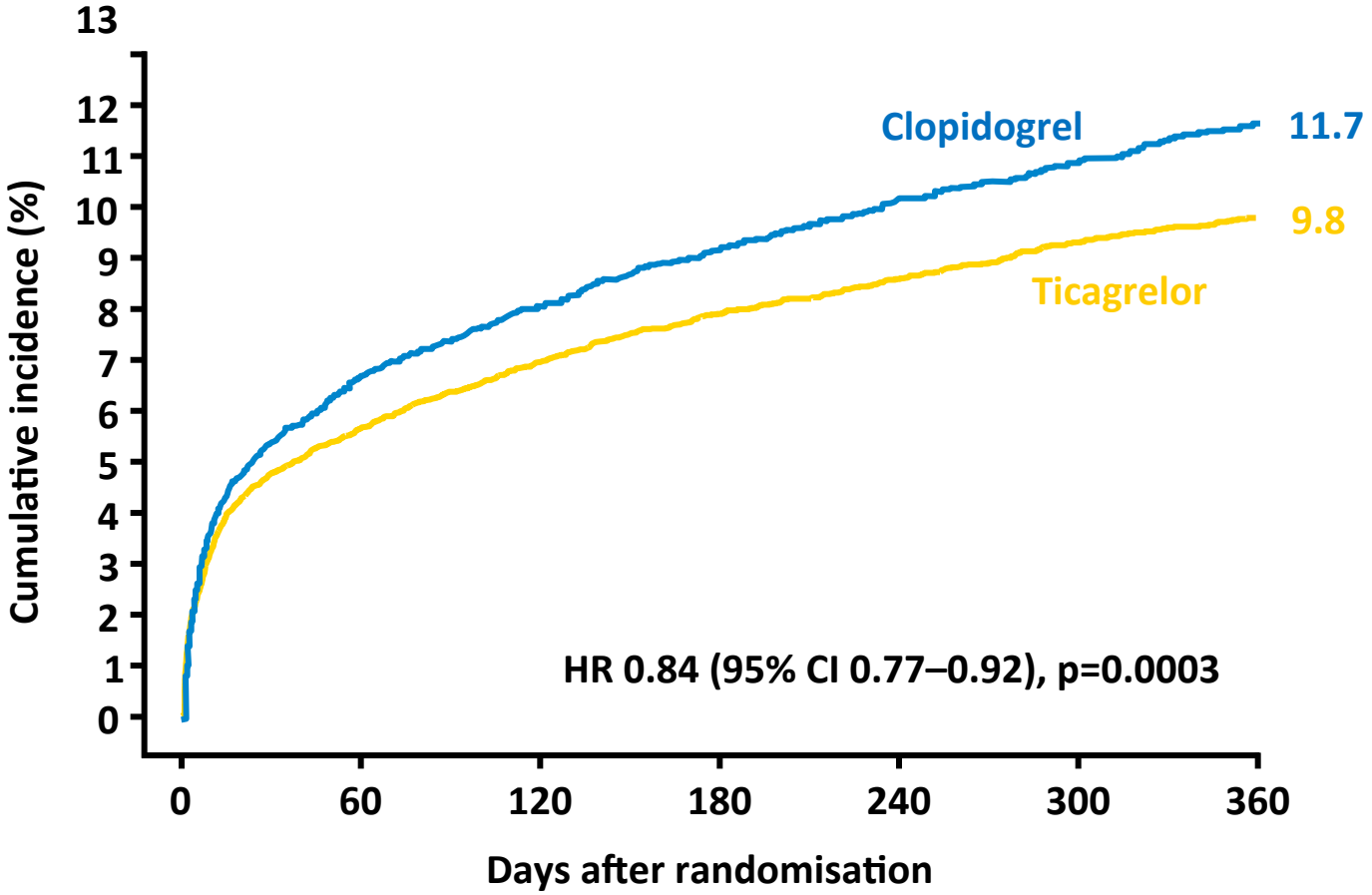
Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

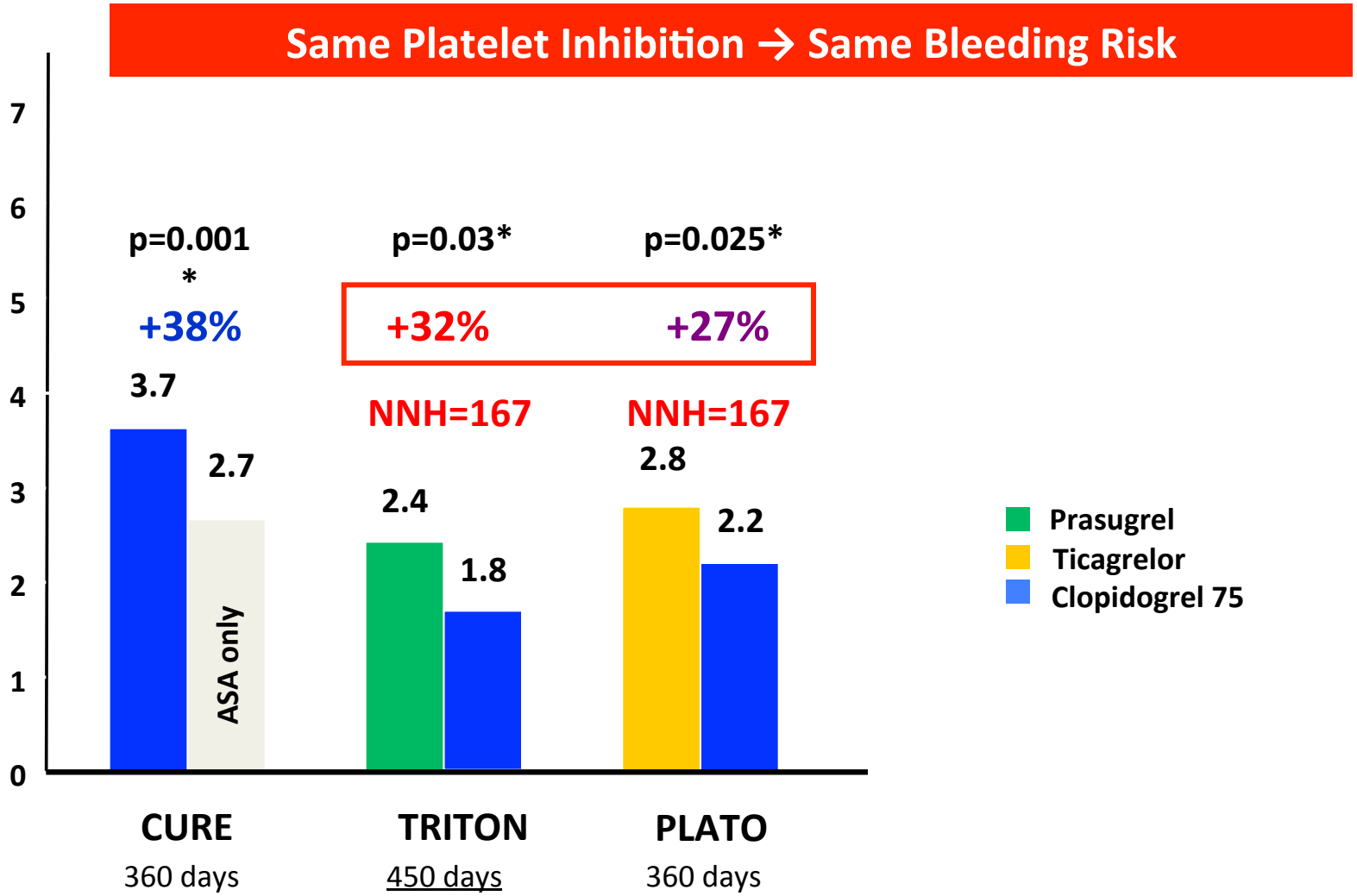
Wallentin et al, N Engl J Med 2010

Primary EP (CV death, MI or stroke)



Wallentin et al, N Engl J Med 2010

Safety = Non-CABG related TIMI major bleedings

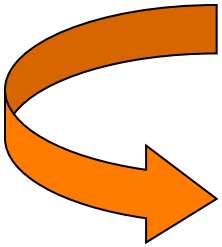


Wiviott et al, NEJM 2007, Wallentin et al, NEJM 2010

Choice of P2Y12 inhibitors

Ischemic Risk

Bleeding Risk



Selection of patients +++

New P2Y12 blockers for each patients ?

Ischemic Risk  **ACS patients** *Bleeding Risk*	**High risk** **STEMI** **Diabetes mellitus, CKD** **High-risk NSTE ACS** **(Tn + and/or ST changes)** **Recurrent event on clopidogrel** **Stent Thrombosis**	**Low risk ACS***** **No ST changes** **No Troponin elevation** **PCI for stable CAD***** ***(Patients not in Triton / Plato)***
High risk: **Prior stroke/TIA*** **Age > 75 y.o, Weight < 60 kg** **Active bleeding** **Chronic OAC**, Prior Bleeding**	Individual Decision	Clopidogrel 600/150
Low risk **No prior stroke/TIA/Bleeding** **Age < 75 y.o** **Weight > 60 kg** **No Chronic OAC**	New P2Y12 Blockers	Clopidogrel 600/150

*** CI Prasugrel**

**** CI Prasugrel and ticagrelor**

***** New P2Y12 blockers in selected cases**

Trois grandes questions

Lequel ?

New P2Y12 blockers for which patients ?

Quand commencer ?

Pre treatment with P2Y12 blockers before cathlab ?

Antiplatelet « upstream » before the cathlab

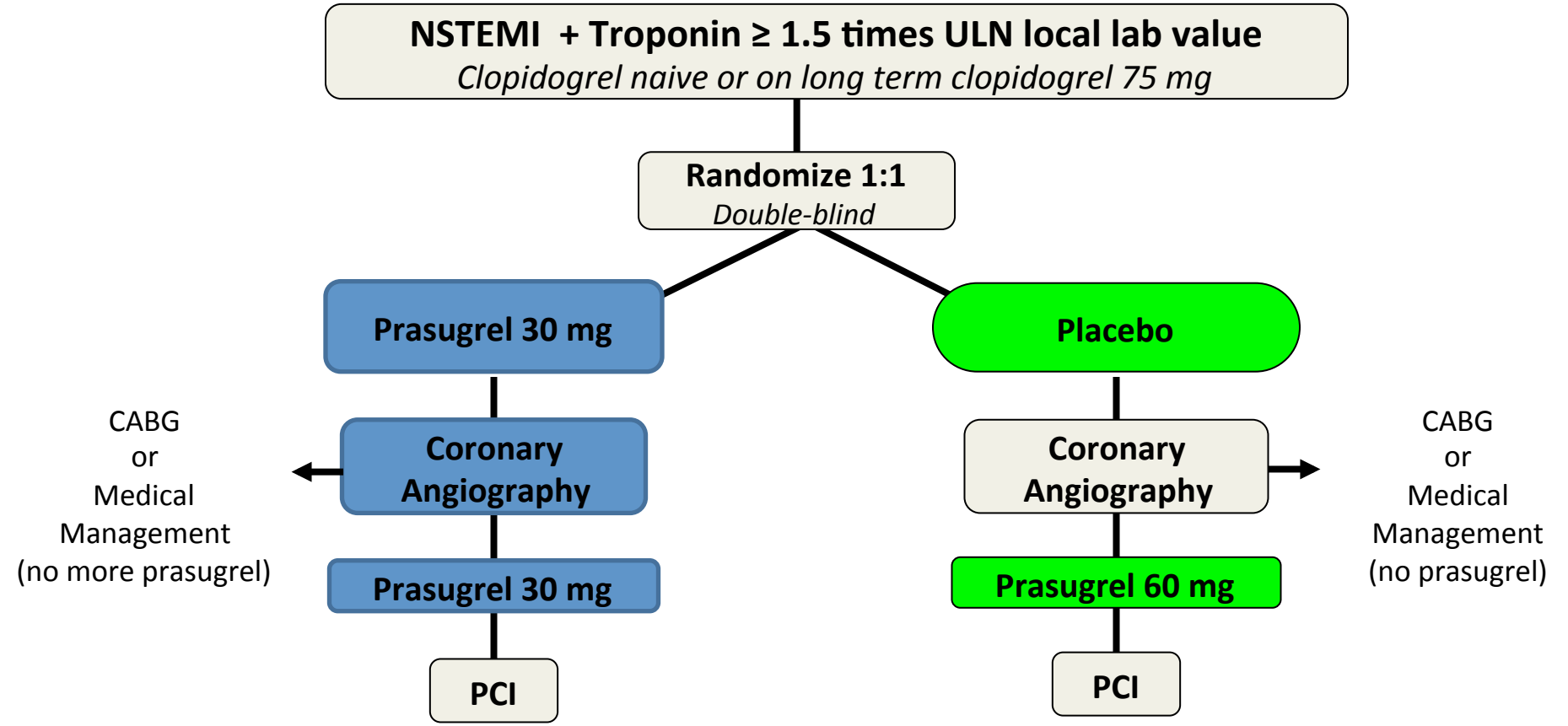
NSTEMI

Before ACCOAST (ESC 2013)…

Pre treatment with DAPT for all NSTEMI

Based on which evidence ?

ACCOAST study

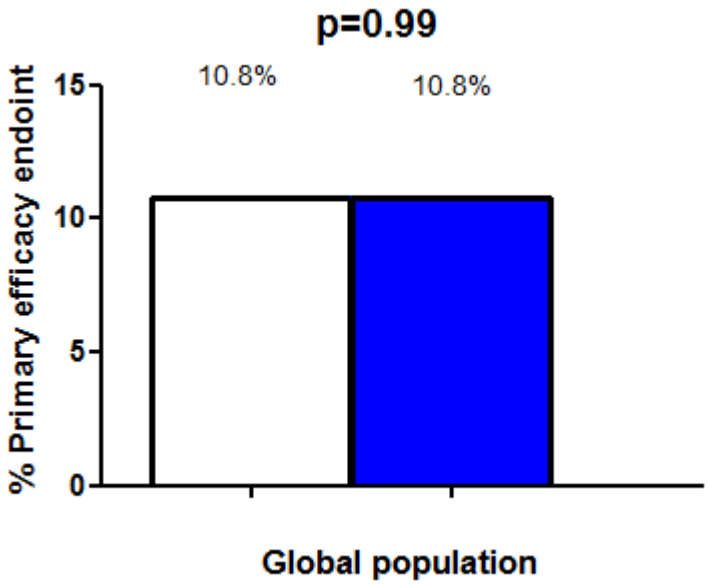


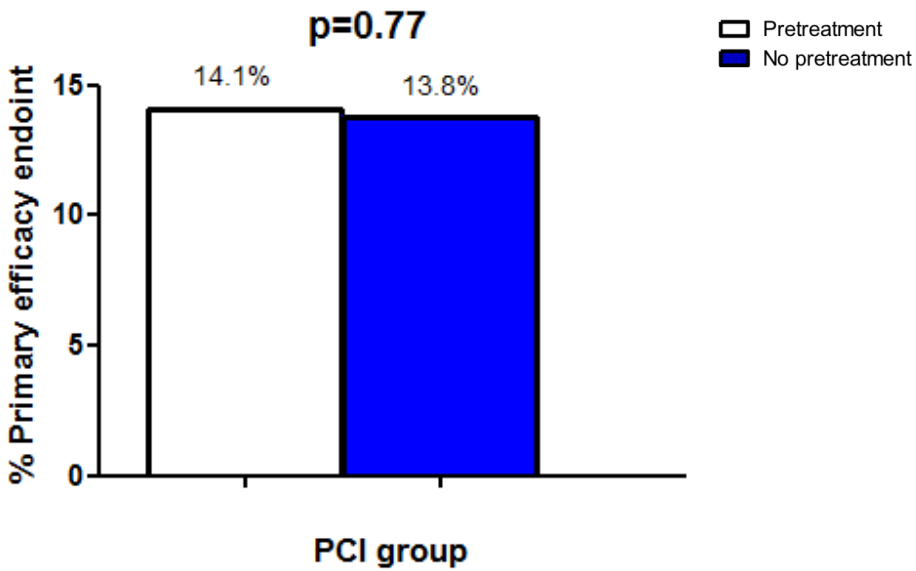
Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

<u>1° Endpoint:</u> CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days

Montalescot et al. NEJM 2013

ACCOAST: results

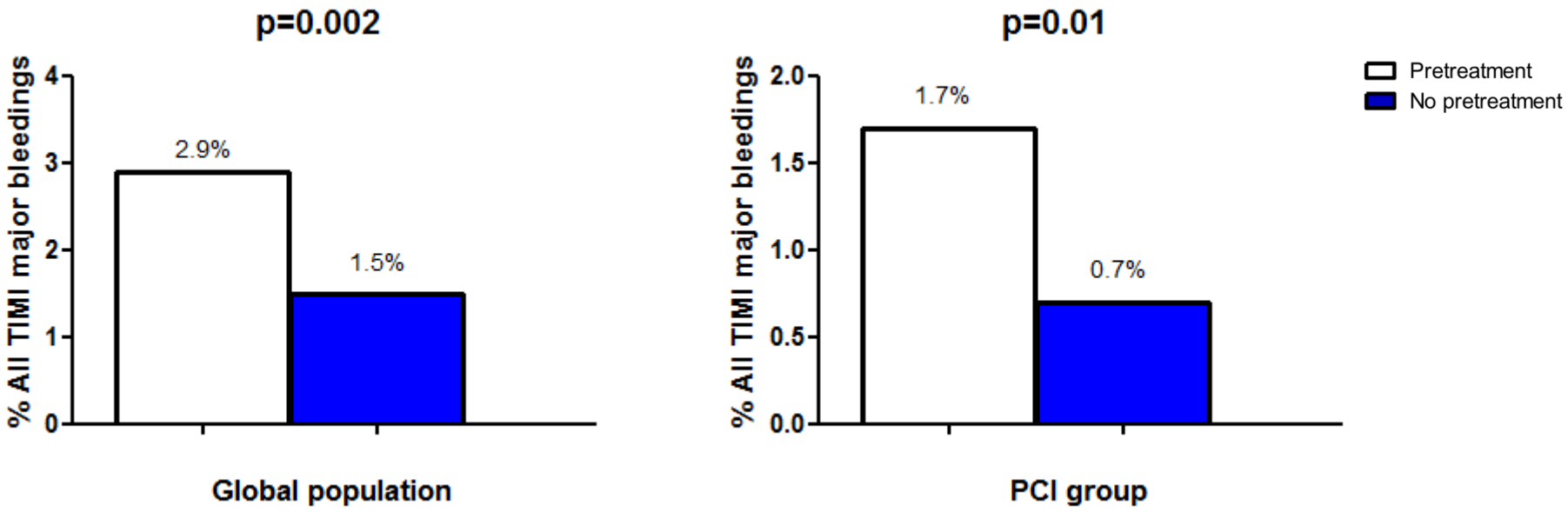




No ischemic benefit

Montalescot G et al. NEJM 2012

ACCOAST: results



Majoration des complications hémorragiques

Montalescot G et al. NEJM 2012

ACCOAST: Conclusion

- No benefit of «pre TTT» with prasugrel in NSTEMI
- No benefit in PCI patients
- Excess of bleeding complications

After ACCOAST…in NSTEMI

- No« pre treatment » with prasugrel: OK

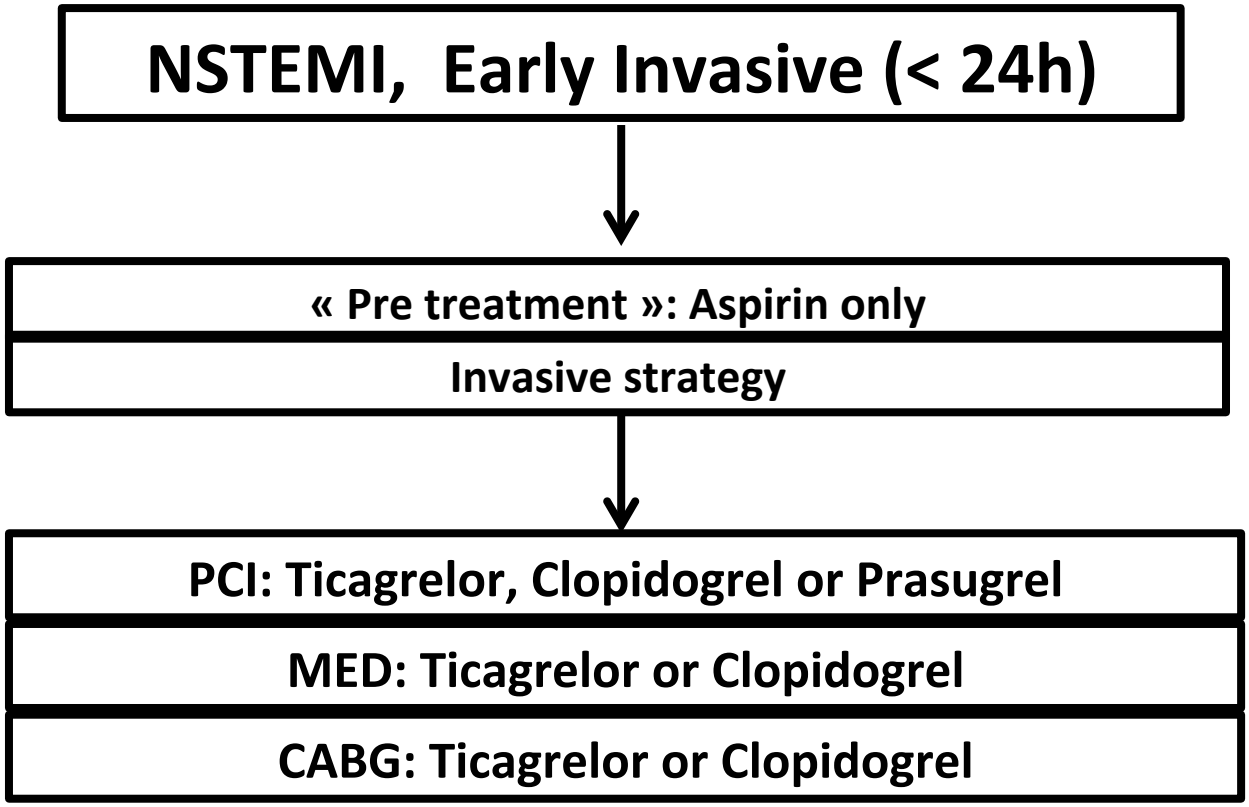
- Idem for Ticagrelor…? YES

*Failure of **STRATEGY** «strong platelet inhibition» upstream*

- and Clopidogrel ?

Why less potent would provide any ischemic benefit ?

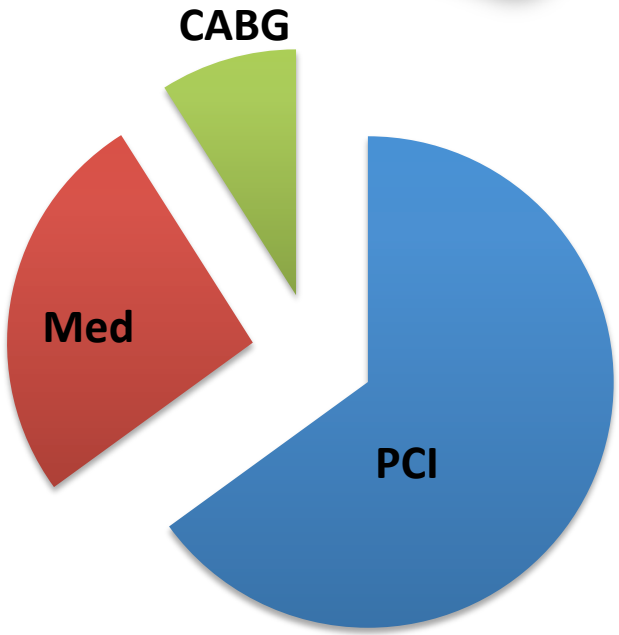
Our practice in NSTEMI



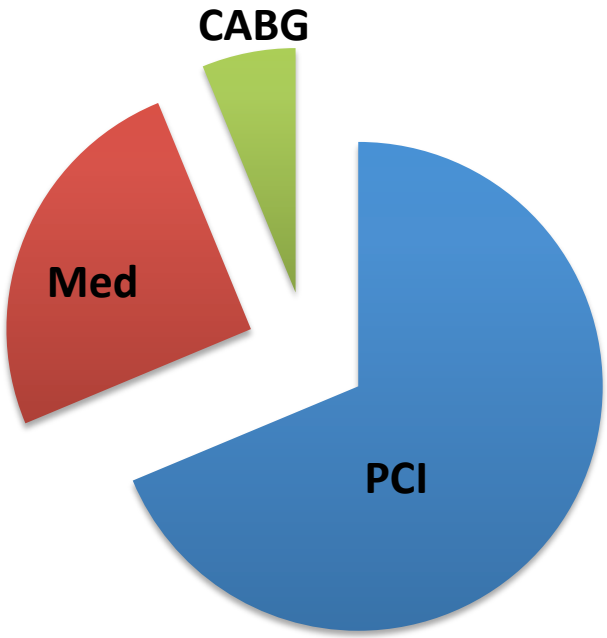
Rationale to avoid pre treatment in NTEMI ?

NSTEMI #1

5 to 10 % CABG



Adapted from the **ABOARD** study.
Montalescot *et a*l JAMA 2009



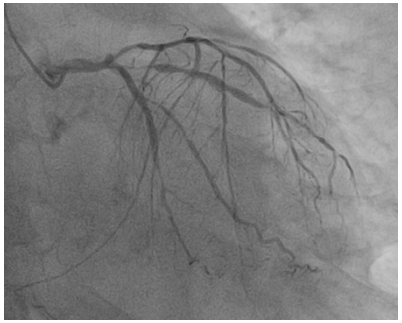
Adapted from the **ACCOAST** study.
Montalescot *et al* NEJM 2013

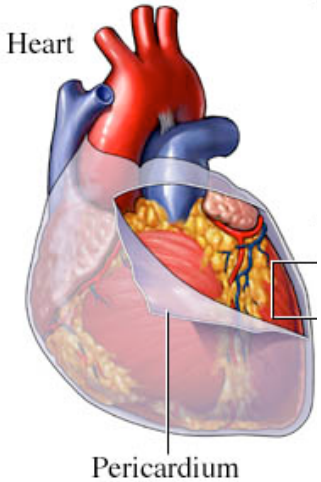
NSTEMI #2

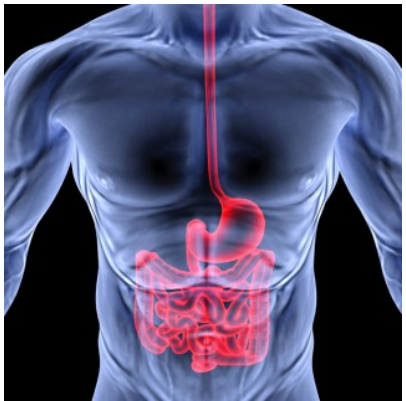
25 % of NSTEMI patients: Medical Treatment

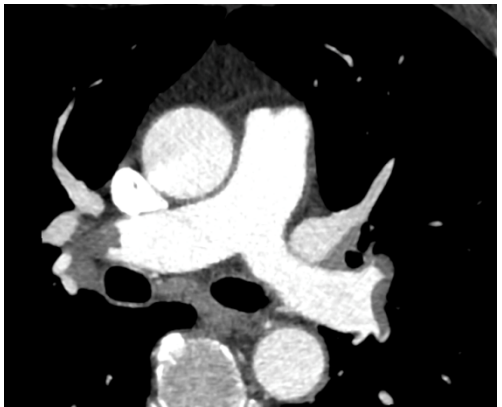
Medical Treatment:

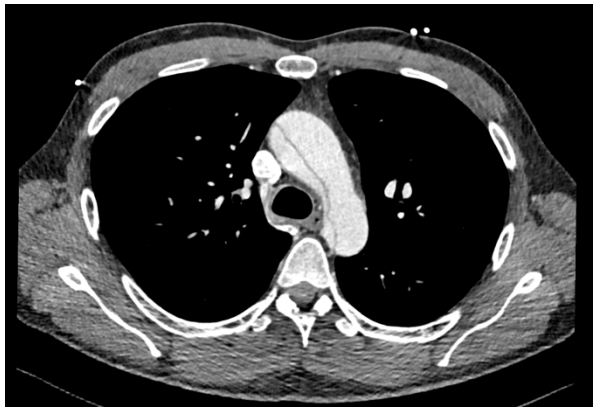
1) **Distal Lesions**
2) **Myocarditis**
3) **PE**
4) **Digestive disease**
5) **Aortic disease**
6) **Normal angiography**







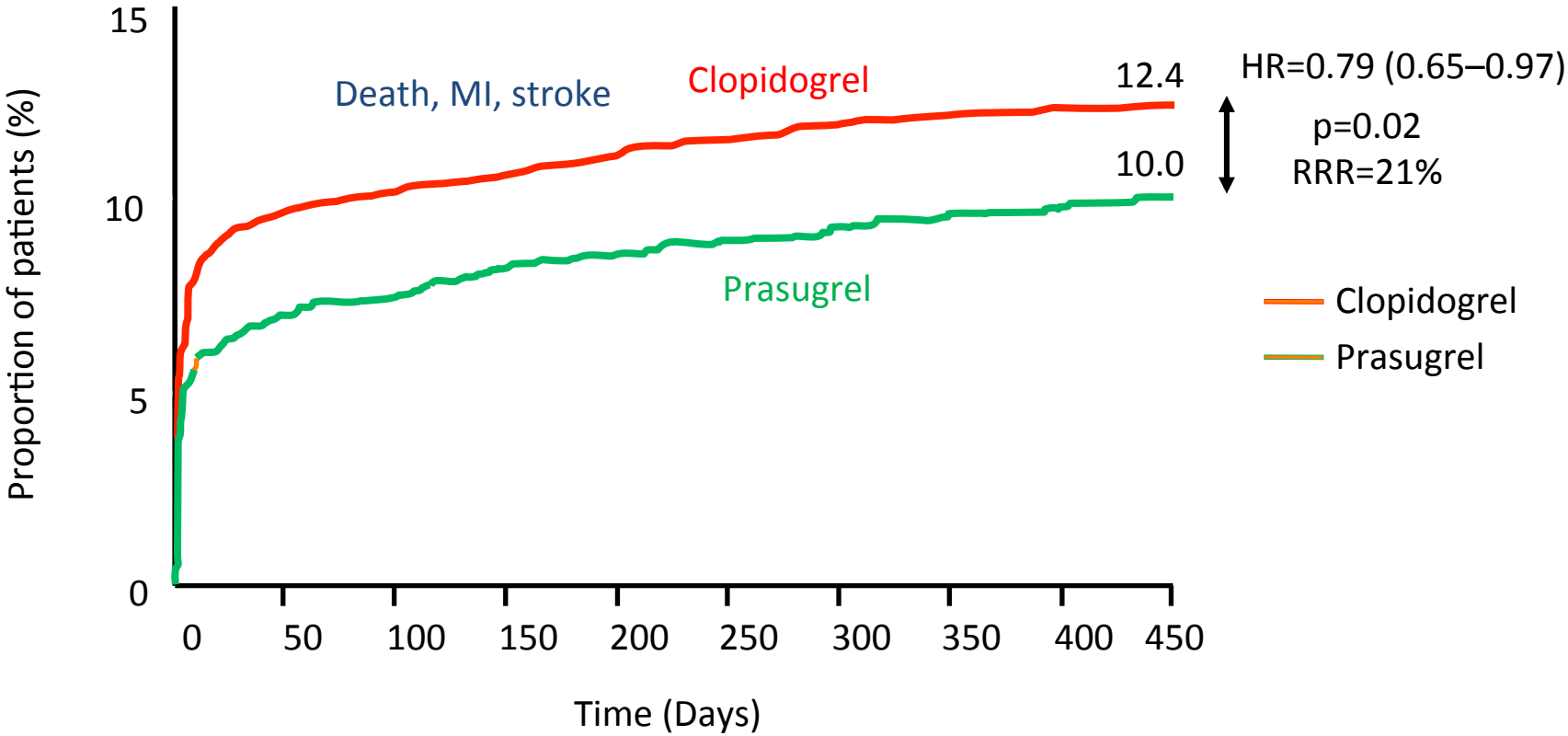




Antiplatelet « upstream » before the cathlab

STEMI

Prasugrel in STEMI: TRITON STEMI

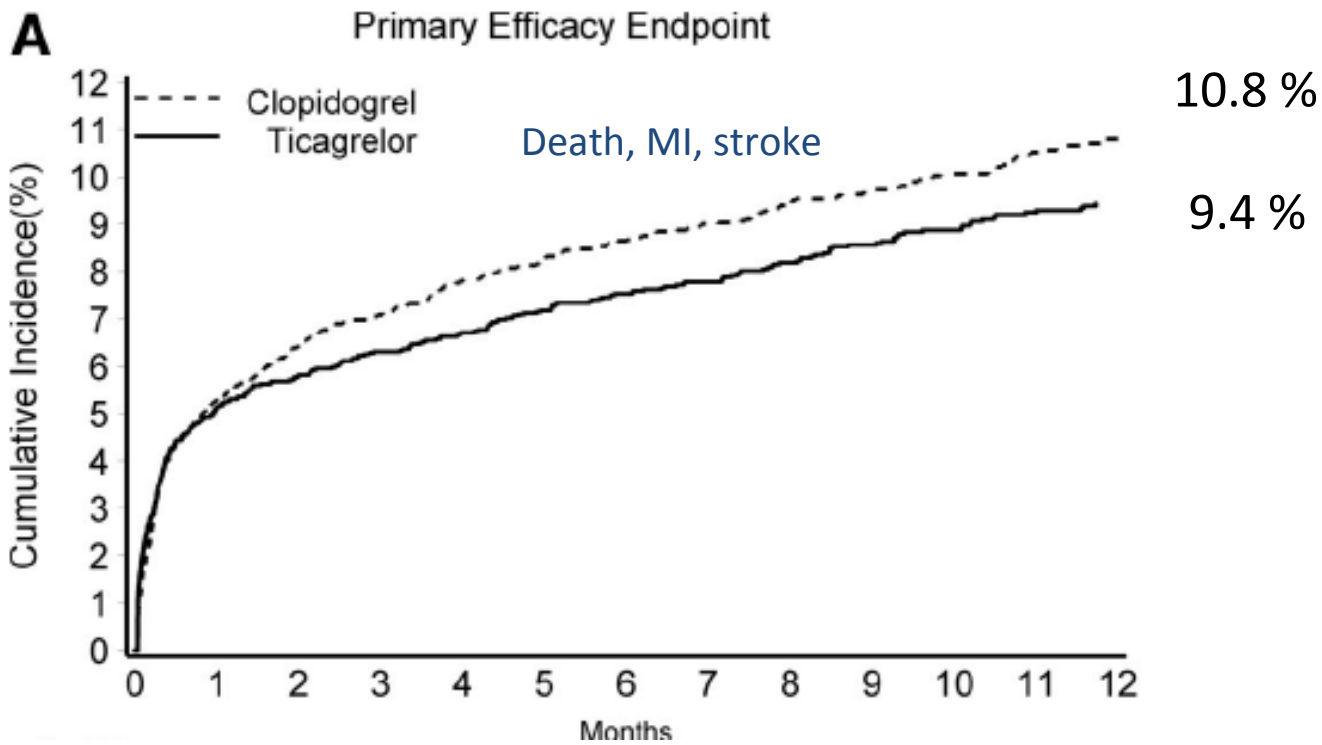


No excess of bleeding in STEMI

N=3534

Montalescot et al. Lancet 2009

Ticagrelor in STEMI: PLATO STEMI



No excess of bleeding in STEMI

N=7544

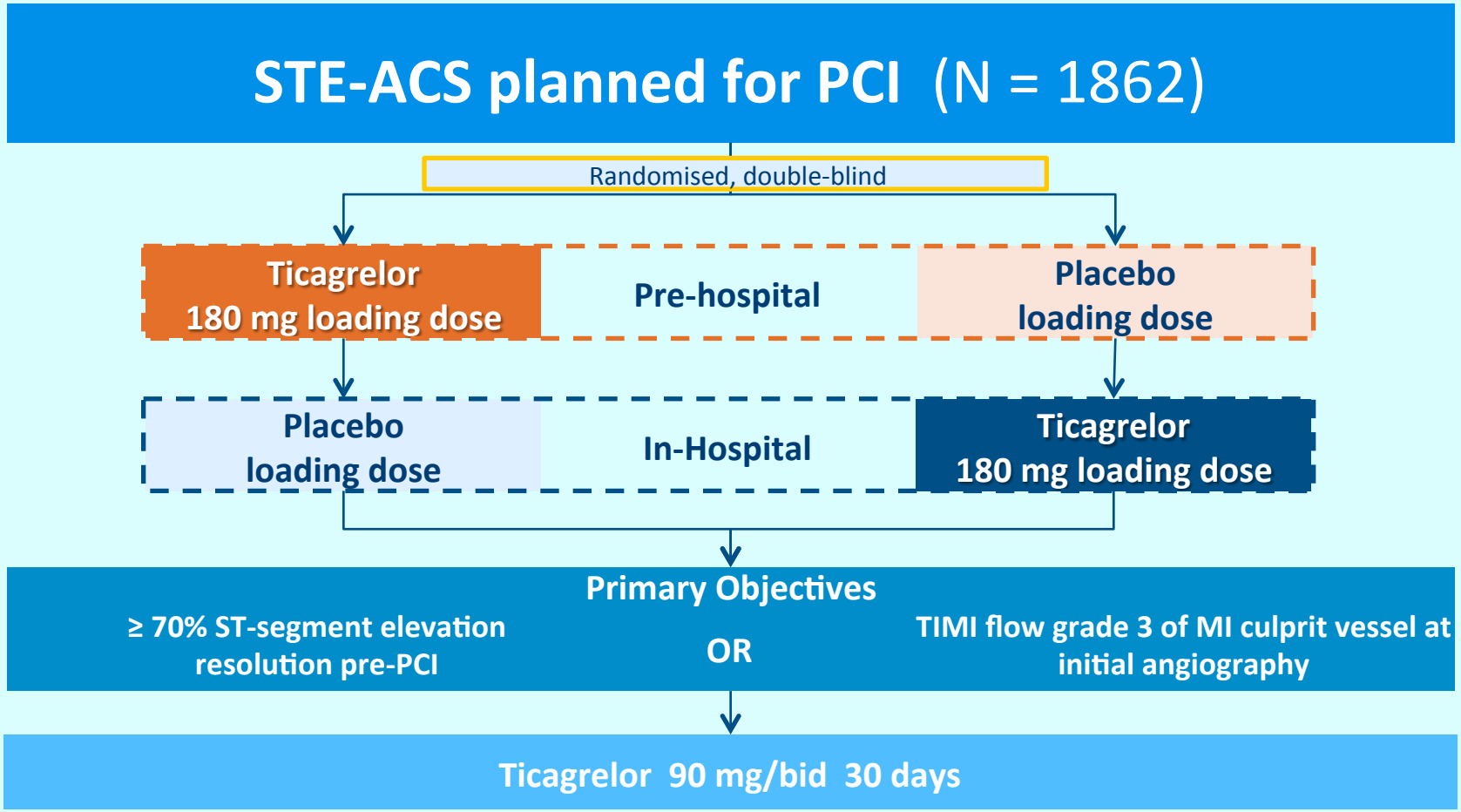
Steg et al, Circulation 2010

Choice of P2Y12 in STEMI

New P2Y12 as gold standard in STEMI
(… but still clopidogrel in 1/3 patients)

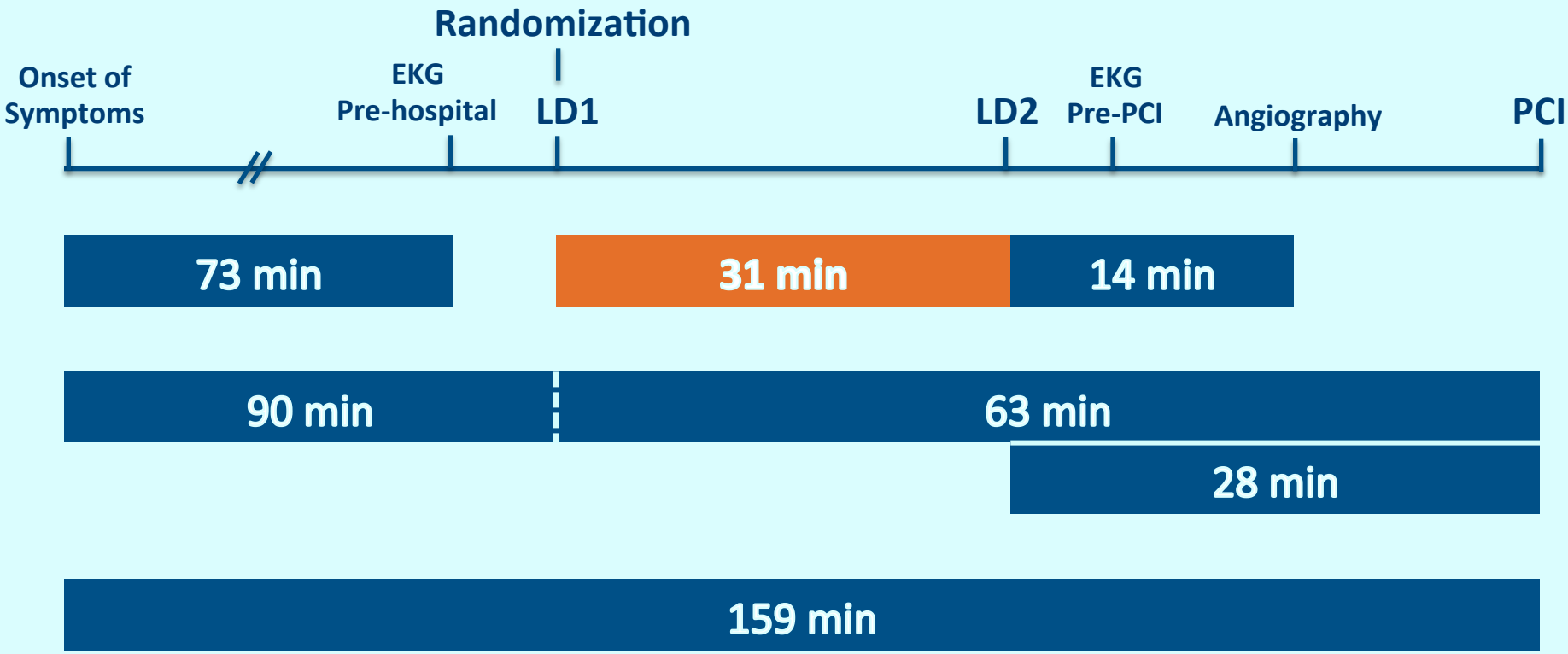
Timing of new P2Y12 in STEMI
Pre-Cathlab vs. Cathlab ? *ATLANTIC study*

Study population and design



Montalescot G et al. NEJM 2014

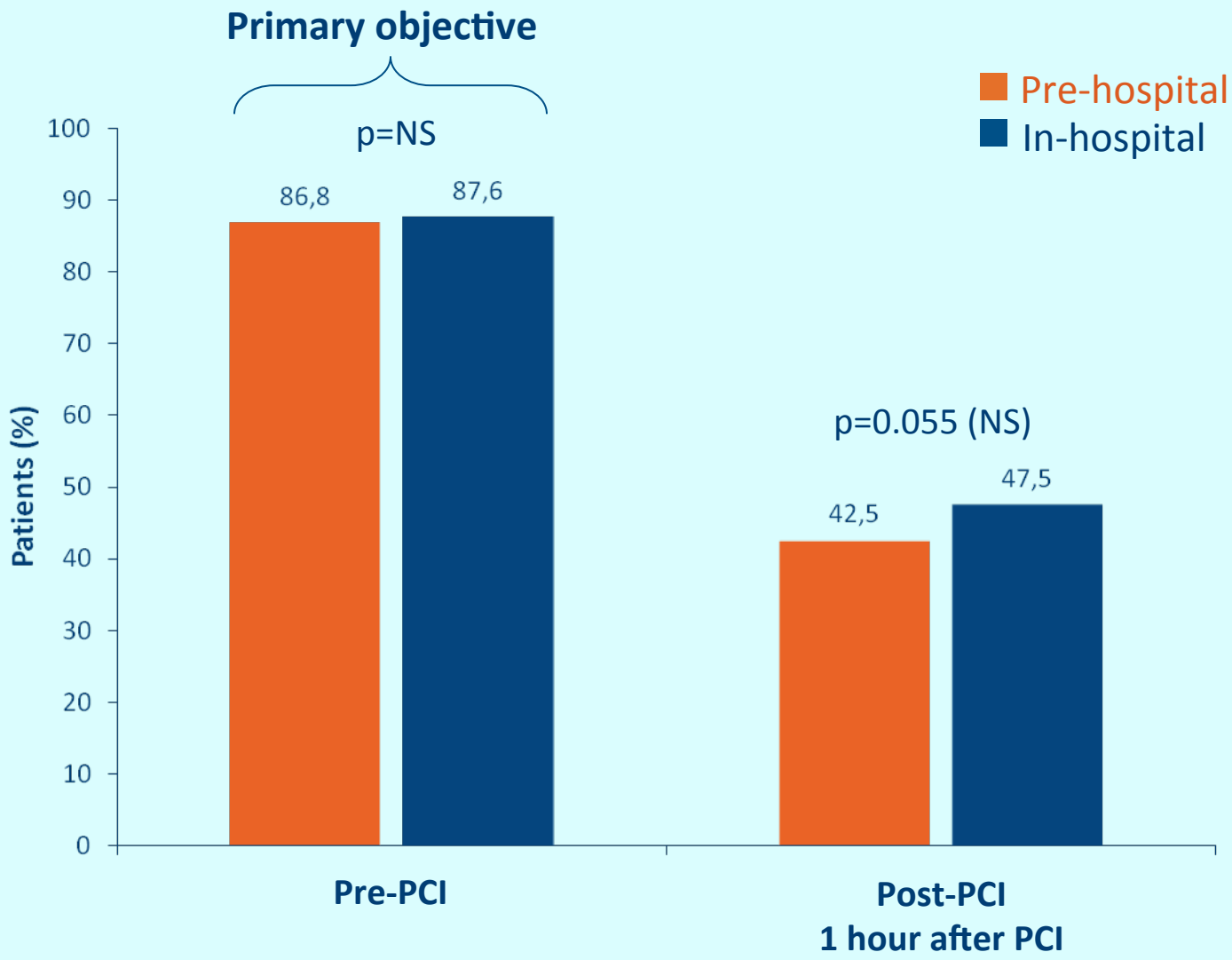
Median times to pre- and in-hospital steps



Montalescot G et al. NEJM 2014

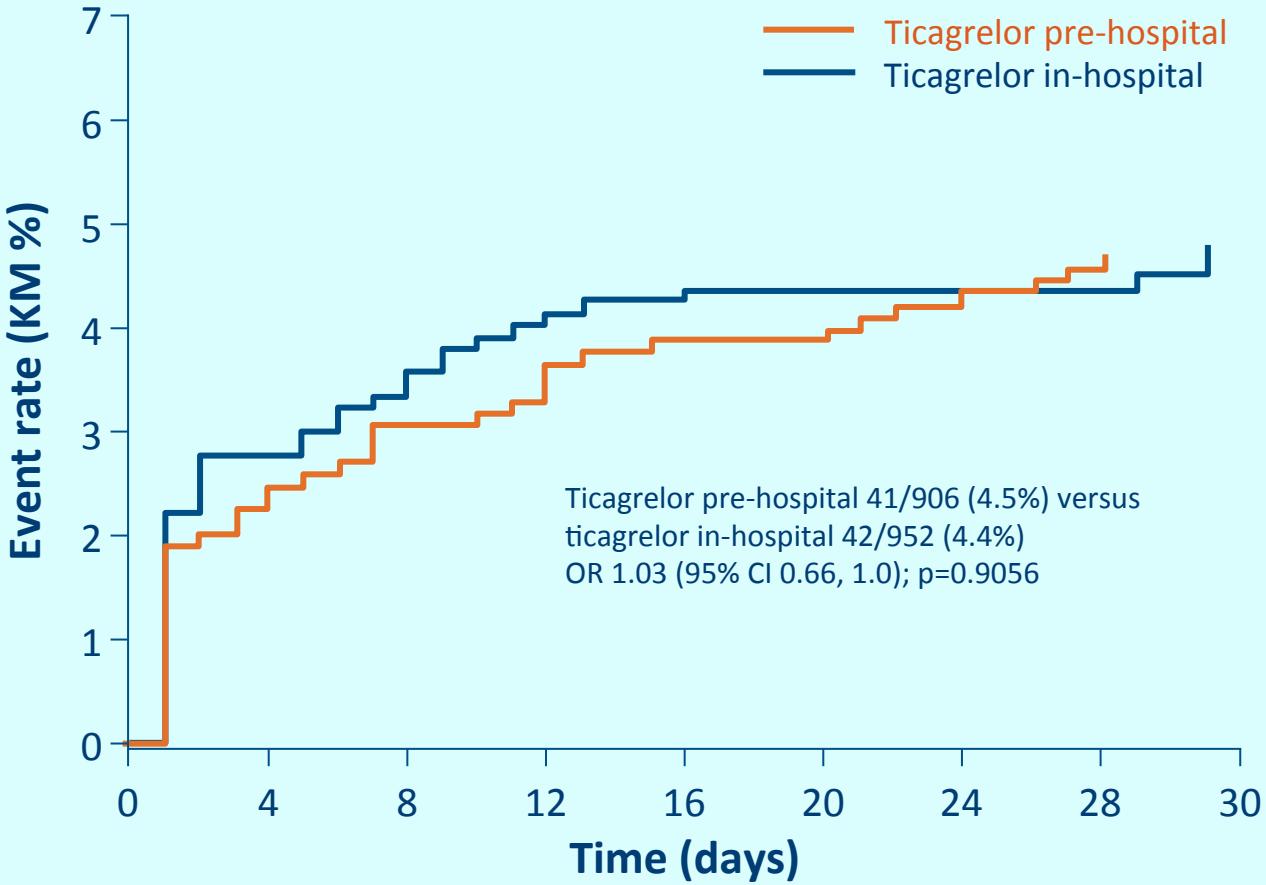
Co-primary efficacy endpoints (mITT)

Absence of ST-segment elevation ≥70%



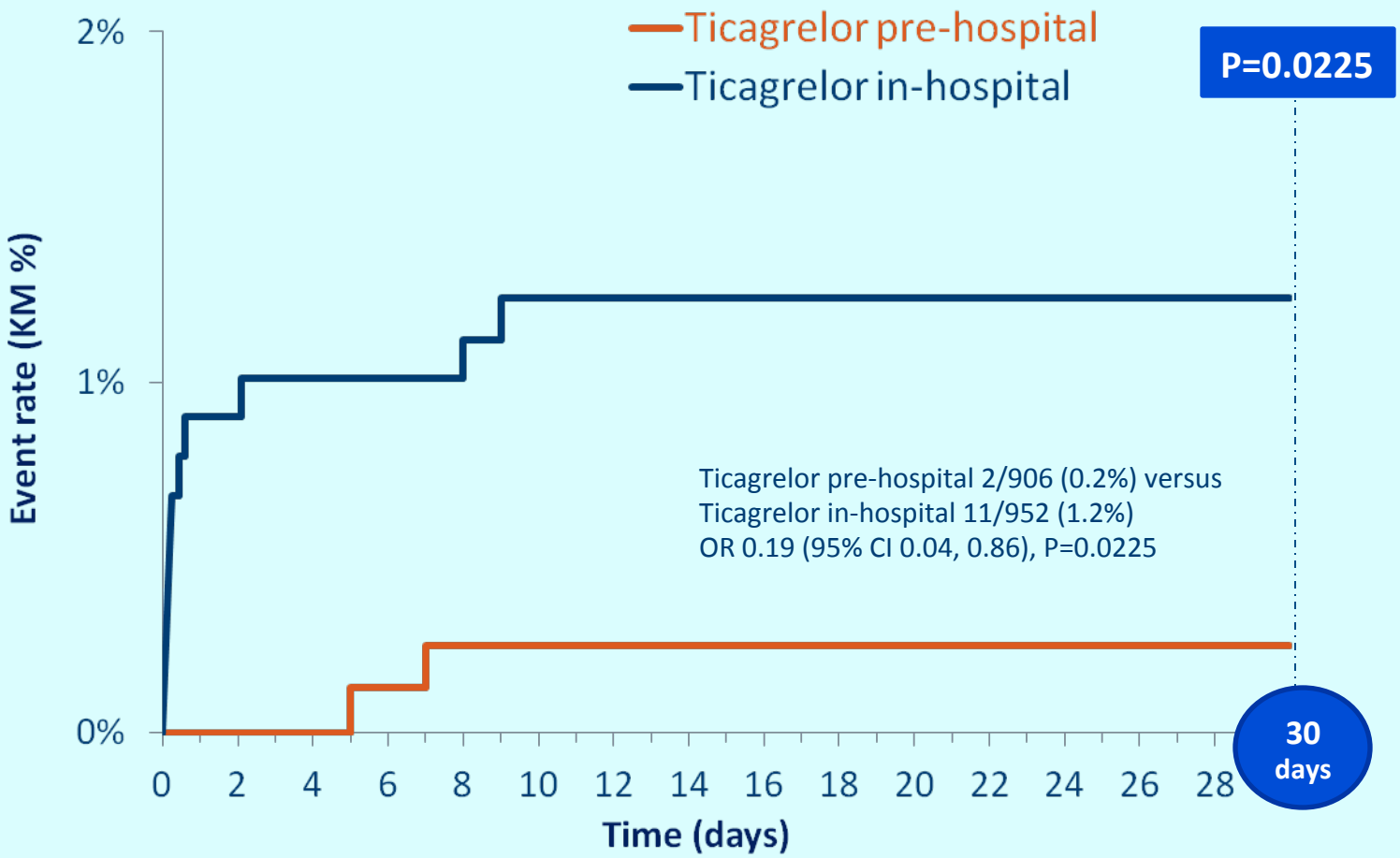
- Pre-PCI†
  - Pre-hospital n=774
  - In-hospital n=824
- Post-PCI‡
  - Pre-hospital n=713
  - In-hospital n=743

Major adverse CV events up to 30 days: Kaplan–Meier curves



Montalescot G et al. NEJM 2014

Definite stent thrombosis up to 30 days



Montalescot G et al. NEJM 2014

ATLANTIC: conclusion

- Delay too short for action before pPCI

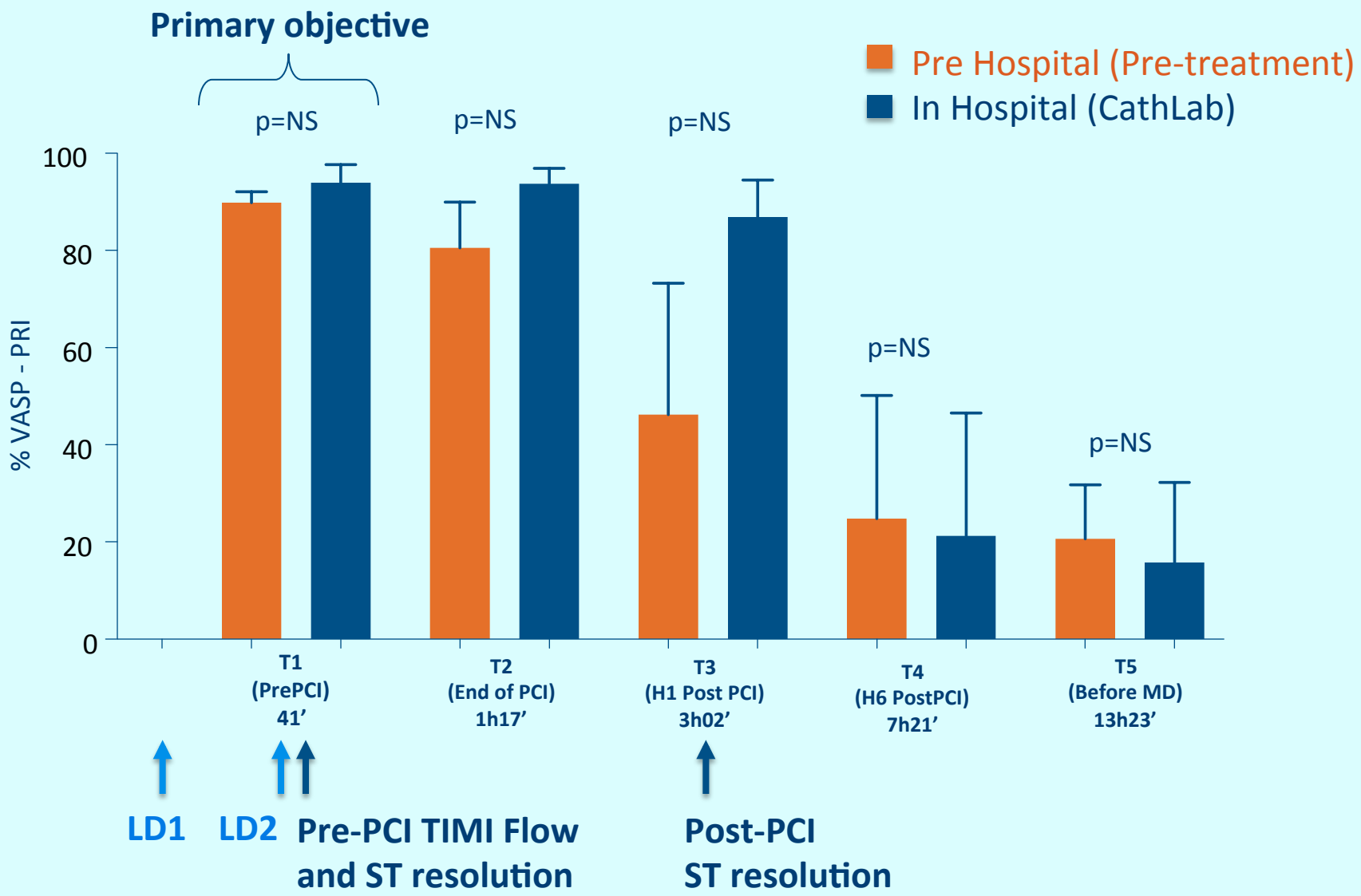
→ Primary endpoint 'neutral'

- Benefit post pPCI

→ ST resolution / Stent thrombosis

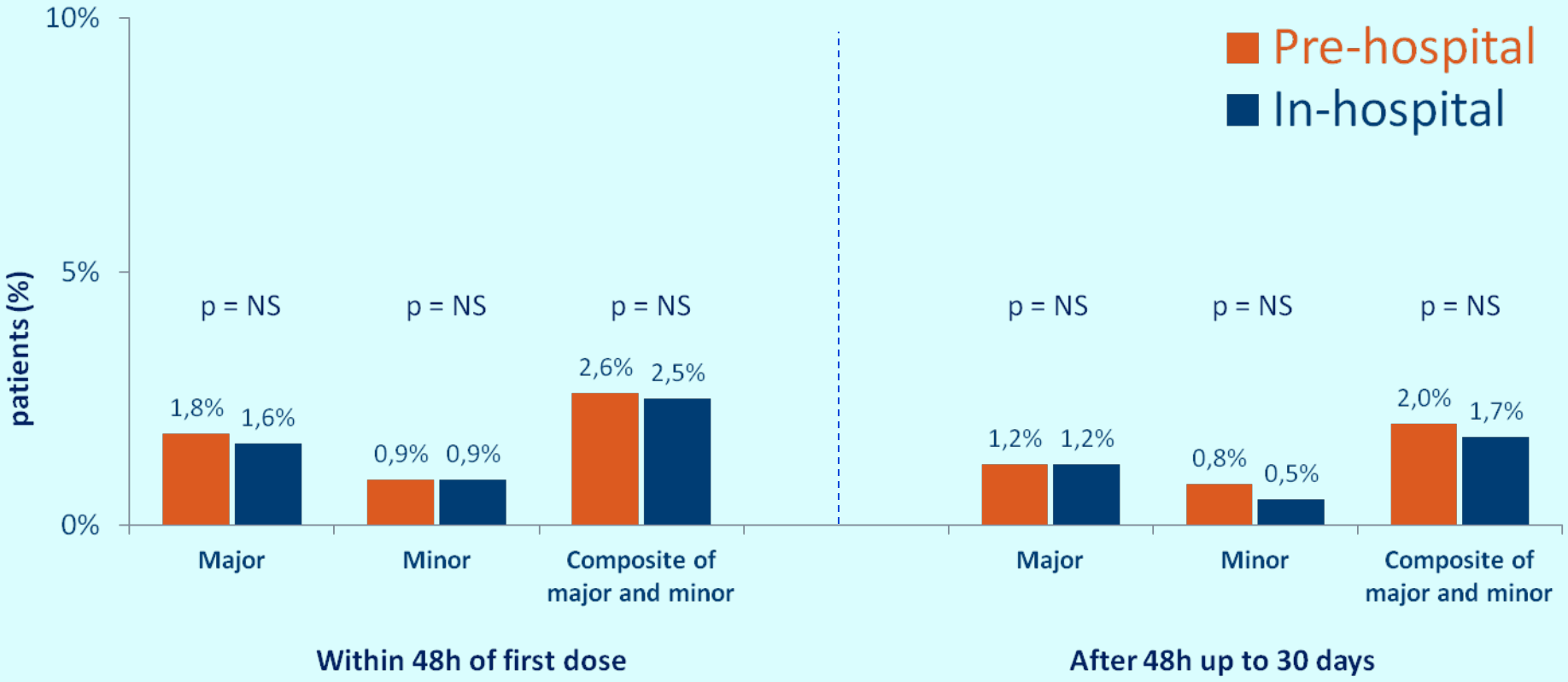
Montalescot G et al. NEJM 2014

VASP-PRI according to groups (bars)



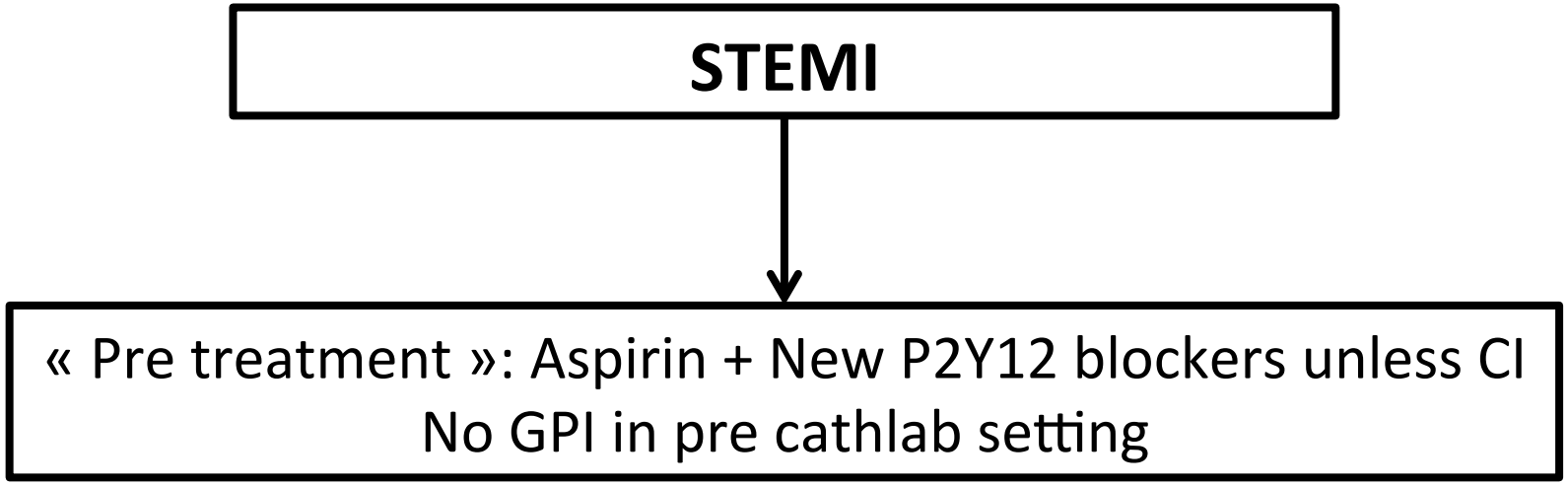
Et la Safety ?

Non-CABG-related bleeding events
(PLATO definitions) - Safety population

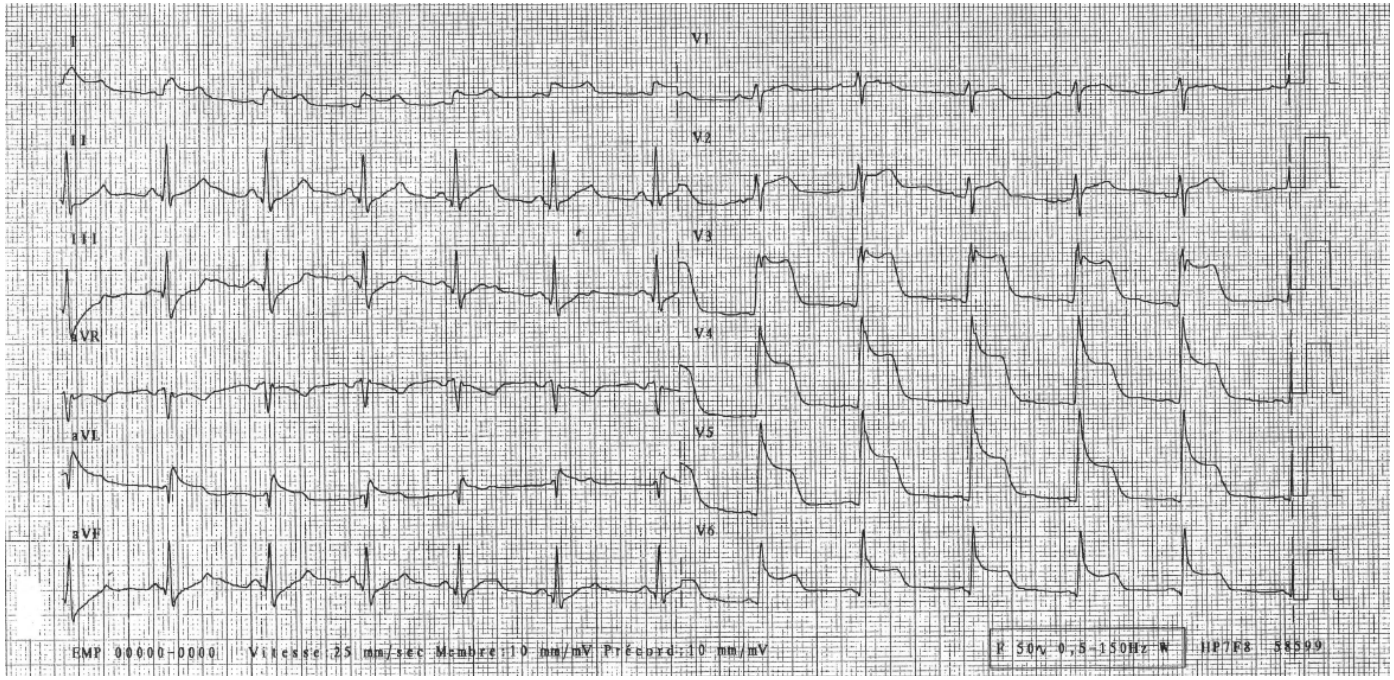


Montalescot G et al. NEJM 2014

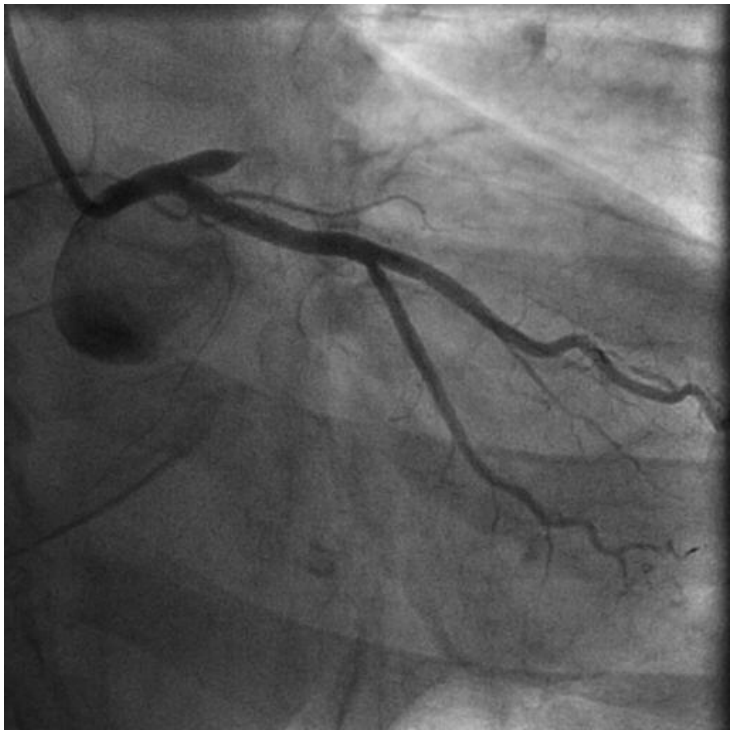
Our practice in STEMI

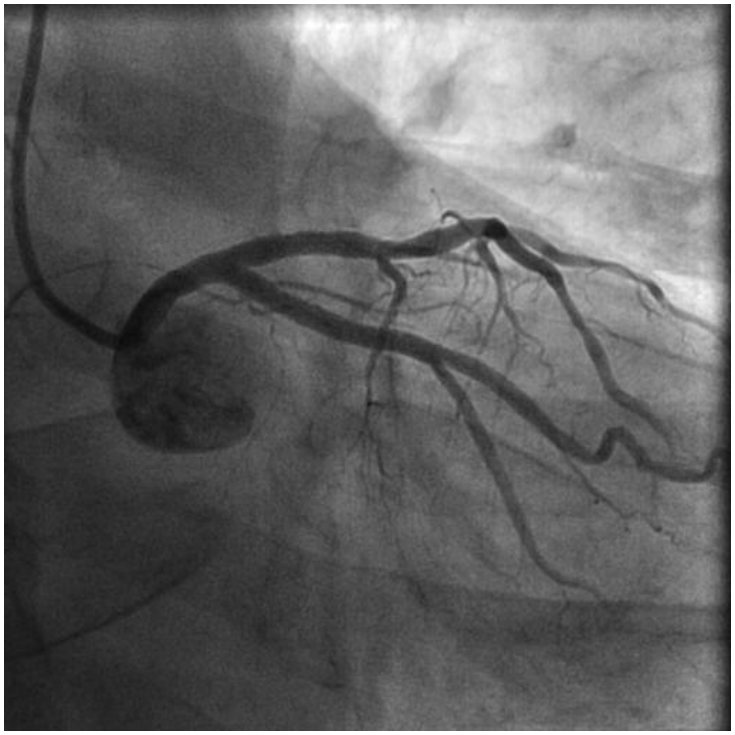


STEMI diagnosis: « easy »



PCI «always»





Thrombus burden « obvious »

Pre Cathlab with P2Y12 blockers

NSTEMI

- Diagnosis doubtful
- Thrombus burden unclear
- Rate of PCI in STEMI: 60%

↓

No pre treatment

STEMI

- Diagnosis easy
- Thrombus +++
- PCI probability > 95%

↓

« Pre treatment »

Trois grandes questions

Lequel ?

New P2Y12 blockers for which patients ?

Quand commencer ?

Pre treatment with P2Y12 blockers before cathlab ?

Quand Arrêter ?

Duration of DAPT after ACS / DES ?

Durée des AAP après SCA / Stent

1 m | 6 m | 12 m | 30 m

COURT

Thrombose

Thrombose de stent
Récidive SCA

LONG

Hémorragie

Accidents hémorragiques

Durée AAP

Indication biAAP

Pour le Stent

➔ Prévention thrombose de stent

Type (DES,BMS,BVS)

1ere, 2 ième, 3 ième G

Longueur

TCG

Bifurcation

Resténose

Amélioration technologie DES

	Taxus	Cypher	BioMatrix Nobori	Endeavor	Yukon PC	Xience Promus	Resolute	Synergy	Orsiro	Ultimaster
Platform material	SS	SS	SS	CoCr	SS	CoCr PtCr	CoCr	PtCr	CoCr	CoCr
Strut thickness (µm)	132	140	120	91	87	81	91	74	60	80
Polymer type	Durable	Durable	Biodegradable	Durable	Biodegradable	Durable	Durable	Biodegradable	Biodegradable	Biodegradable
Polymer material	SIBS	PEVA/PBMA	PDLLA	MPC/LMA/HPMA/ 3-MPMA	PDLLA	PBMA/PVDF-HFP	PBMA/PHMA/ PVP/PVA	PLGA	PLLA	PDLLA-PCL
Coating distribution	Circumferential	Circumferential	Abluminal	Circumferential	Circumferential	Circumferential	Circumferential	Abluminal	Circumferential	Abluminal
Polymer thickness (µm)	22	13	10	6	5	8	6	4	7	15
Additional coating	-	-	-	-	-	-	-	-	Silicon carbide	-
Drug released	Paclitaxel	Sirolimus	Biolimus	Zotarolimus	Sirolimus	Everolimus	Zotarolimus	Everolimus	Sirolimus	Sirolimus

Maille fine
Polymère biodégradable

→ Réduction risque thrombose ?
→ Courte biAAP possible ?

Stefanini, Taniwaki, Windecker. Heart 2013

Etudes sur durée bithérapie AAP

	n	% SCA	Ischémie	Hémorragie
DES LATE, *NEJM 2010*	2117	60%	12 Mo = >12Mo	Pas de différence
EXCELLENT, *JACC 2012*	1443	50%	6 Mo = 12Mo	Pas de différence
PRODIGY, *Circulation 2012*	2013	75%	6 Mo = 24 Mo	Plus de saignement
RESET, *JACC 2012*	2117	55%	3 Mo = 12 Mo	Pas de différence
OPTIMIZE, *JAMA 2013*	3119	30%	3 Mo = 12 Mo	Plus de saignement
ARCTIC, *Lancet 2014*	1259	25%	12 Mo = >12Mo	Plus de saignement
SECURITY, *JACC 2014*	1399	40%	6Mo = 12Mo	No difference
ISAR SAFE, *EHJ 2015*	4005	40%	6Mo = 12 Mo	Plus de saignement
ITALIC, *JACC 2014*	2031	25%	6 Mo = 24 Mo	Pas de différence
OPTIDUAL, *JACC 2015*	1385	35%	12 Mo = 48 Mo	Pas de différence

« BiAAP courte » aussi éfficace et moins de saignements

DAPT STUDY

The NEW ENGLAND JOURNAL of MEDICINE

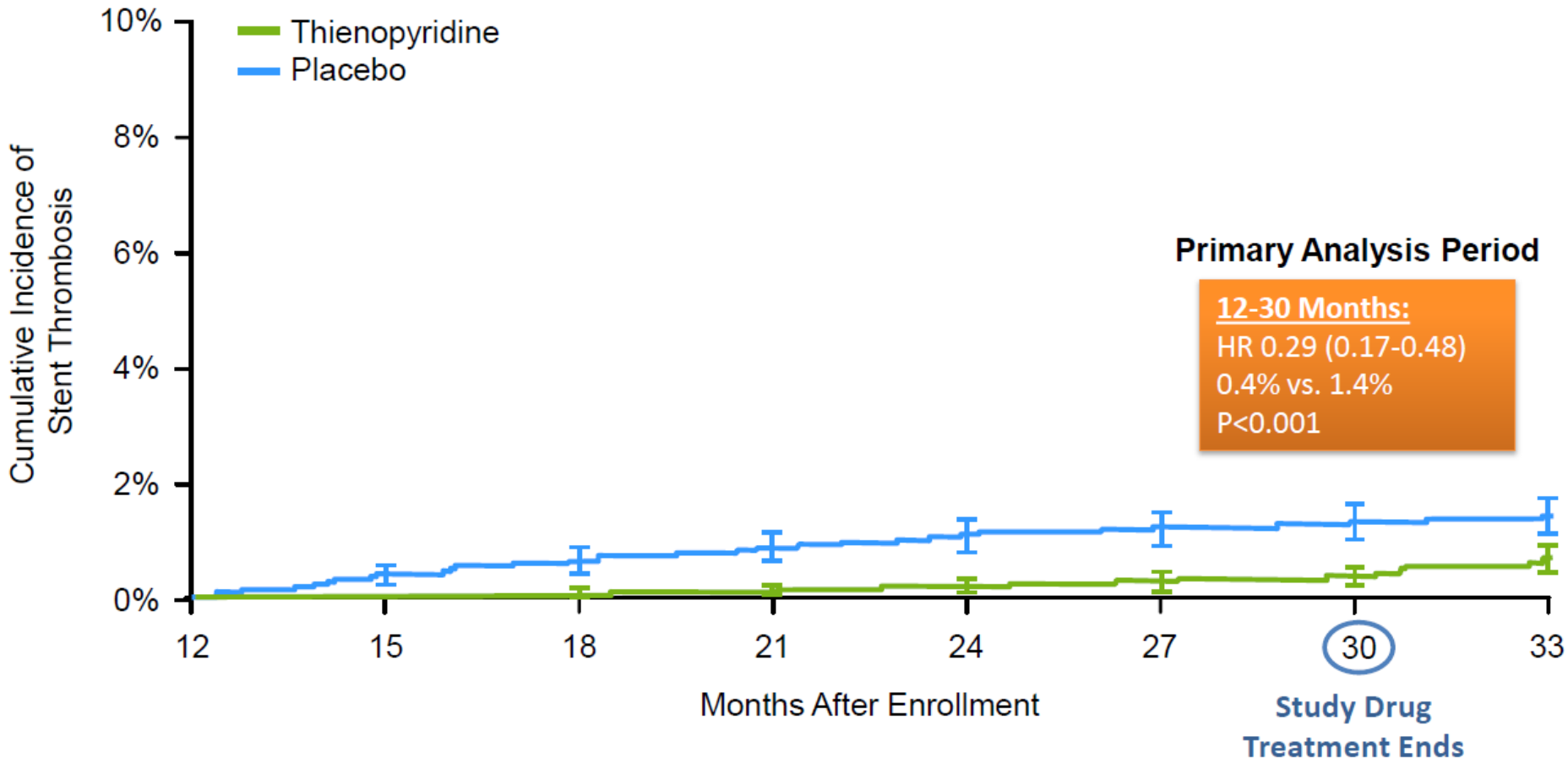
ORIGINAL ARTICLE

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massaro, Ph.D., for the DAPT Study Investigators*

Mauri et al, NEJM 2014

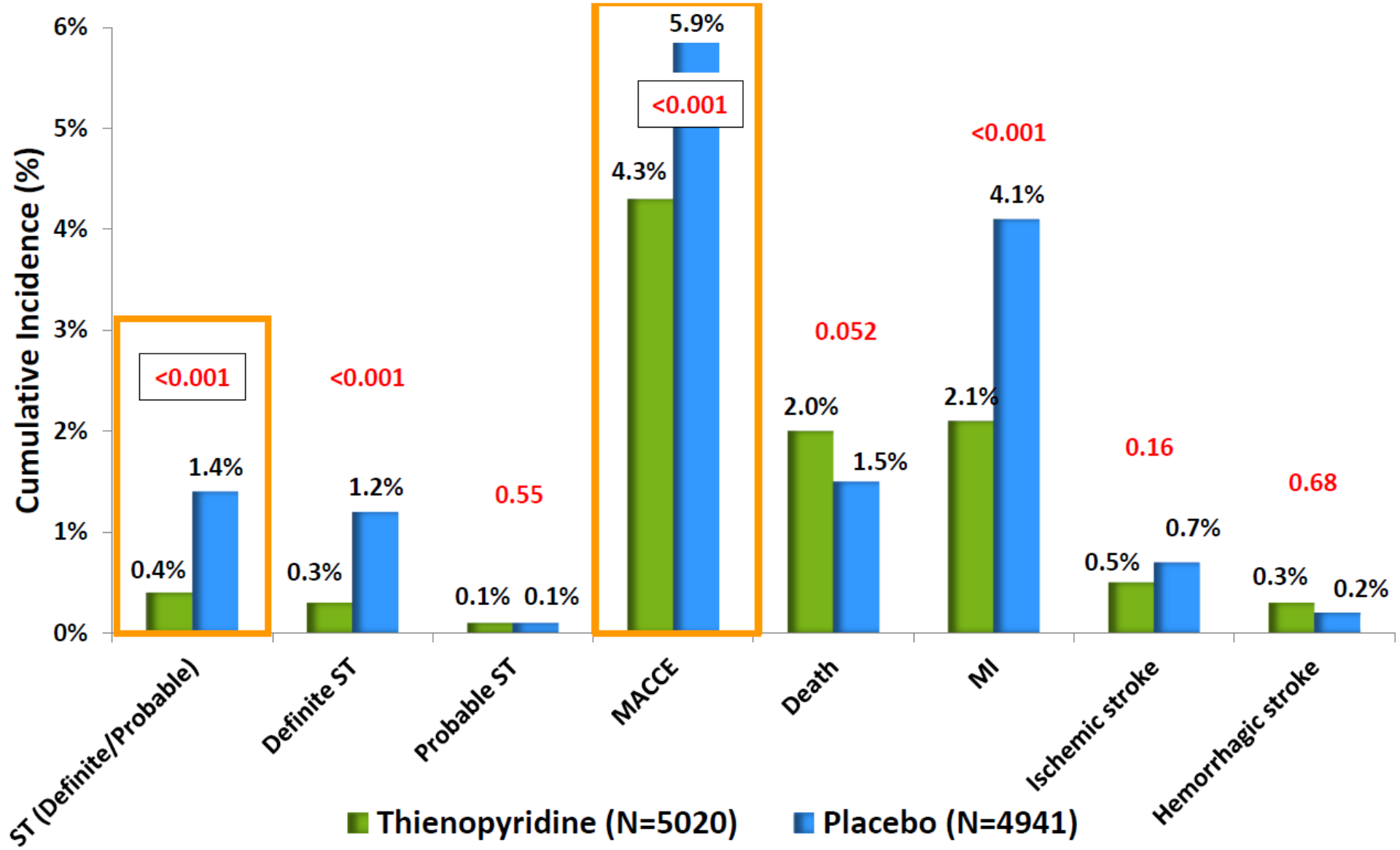
Co-Primary Effectiveness End Point Stent Thrombosis



Réduction thrombose de stent par BiAAP prolongée

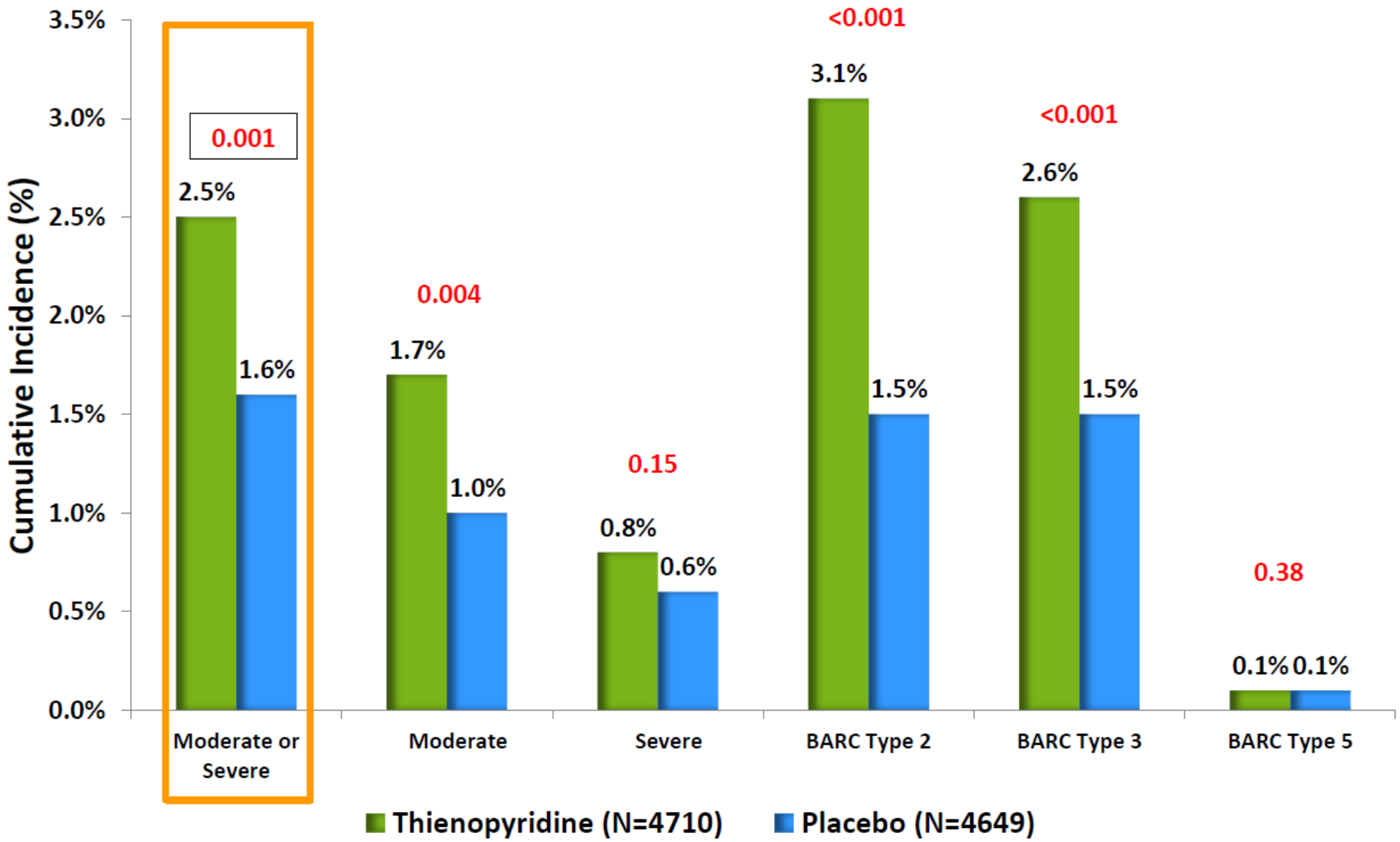
Mauri et al, NEJM 2014

Co-Primary Effectiveness End Points & Components: 12-30 Months



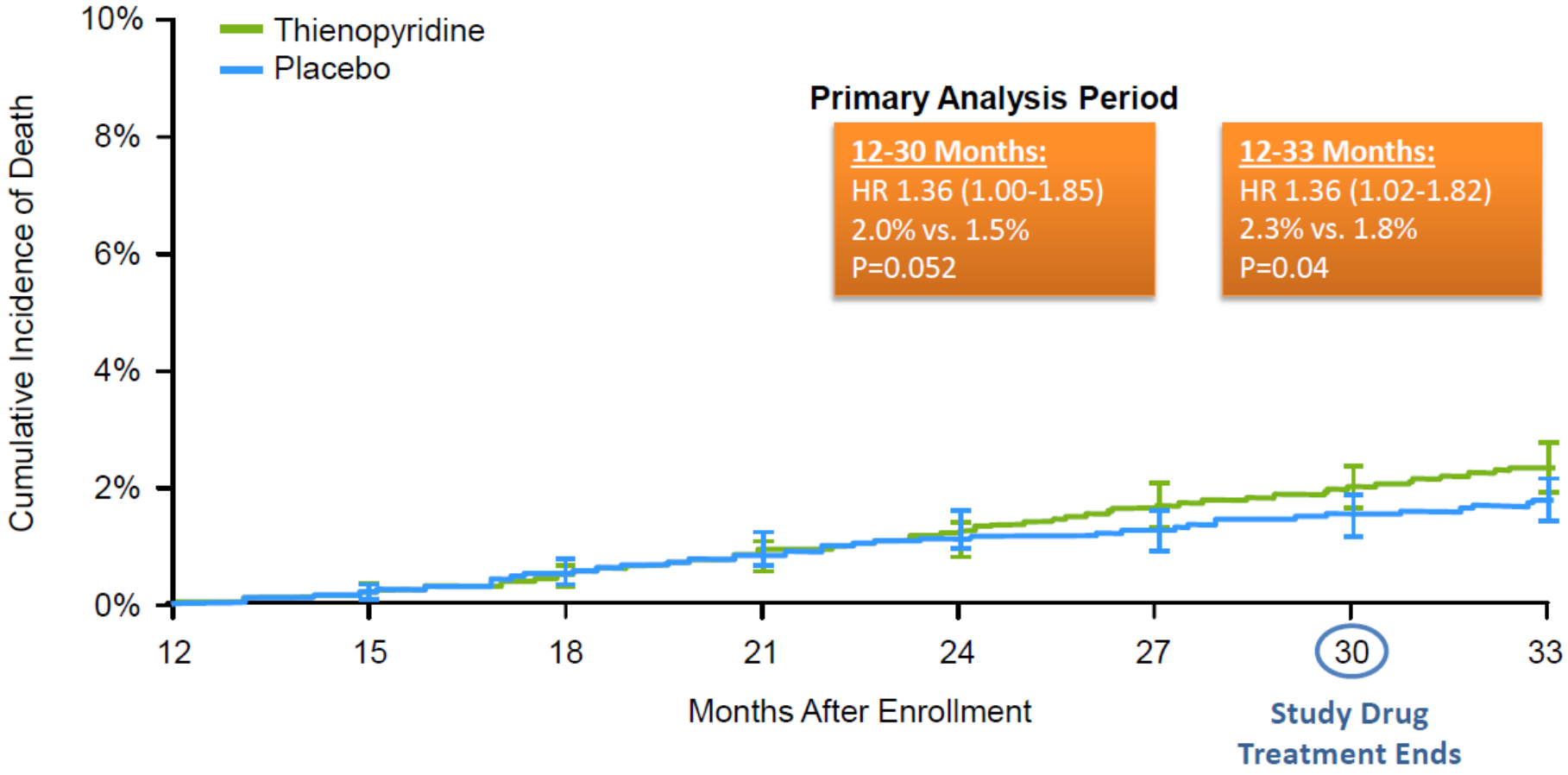
Mauri et al, NEJM 2014

Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months



Mauri et al, NEJM 2014

All-Cause Mortality



Mortalité plus élevée si BiAAP prolongée: saignement ?

Mauri et al, NEJM 2014

All-Cause Mortality

DAPT STUDY

12-30 Months				
	Thienopyridine N=5020	Placebo N=4941	P-Value	Absolute Difference
All-Cause Mortality	**98 (2.0%)**	**74 (1.5%)**	**0.052**	**24 (0.5%)**
Cardiac	45 (0.9%)	47 (1.0%)	0.98	-2 (-0.1%)
Vascular	5 (0.1%)	5 (0.1%)	0.98	0 (-)
Non-Cardiovascular	48 (1.0%)	22 (0.5%)	0.002	26 (0.5%)

Non-Cardiovascular Deaths, 12-33 Months			
Relatedness for Deaths*	Thienopyridine N=5020	Placebo N=4941	P-value
Bleeding-Related Death	11 (0.22%)	3 (0.06%)	0.057
Trauma-Related Death	9 (0.18%)	2 (0.04%)	0.07
Cancer-Related Death	31 (0.62%)	14 (0.28%)	0.02

Mauri et al, NEJM 2014

Etude DAPT: Conclusions

La question se pose chez la moitié des patients !

<u>BiAAP prolongée (30 vs 12)</u>

- Réduction MACE et thrombose de stent
- Augmentation risque hémorragique
- Mortalité totale et non CV supérieures

Mauri et al, NEJM 2014

DAPT study: Conclusions

DAPT: 30 Mo vs 12 Mo

- 1 % Thrombose de stent

Pas impact sur mortalité CV

+ 1 % Hémorragies « importantes »

Mortalité non CV *2

BiAAP prolongée chez tous ?
Pour prévenir un événement non associé à mortalité …
Et exposer à des accidents clairement reliés à mortalité

Mauri et al, NEJM 2014

Impact de présentation clinique

Effet de BiAAP prolongée	
Patients 'IDM'	Patients 'Non IDM'
MACE: - 44%	MACE: -17%
Mortalité CV: - 33%	Mortalité CV : Pas bénéfice
Mortalité non CV : Idem	Mortalité non CV : X2

BiAAP prolongée post DES

Bénéfice si patients haut risque vs.

Délétère si Patients bas risque

Yeh et al, JACC 2015

Durée AAP

Pour le Stent

➔ Prévention thrombose de stent

Type (DES,BMS,BVS)

1ere, 2 ième, 3 ième G

Longueur

TCG

Bifurcation

Resténose

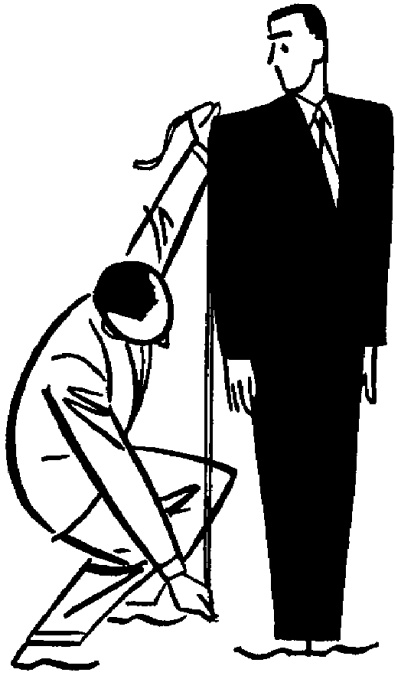
Courte !

… mais on ne soigne pas des stents !

Durée AAP

Indication biAAP

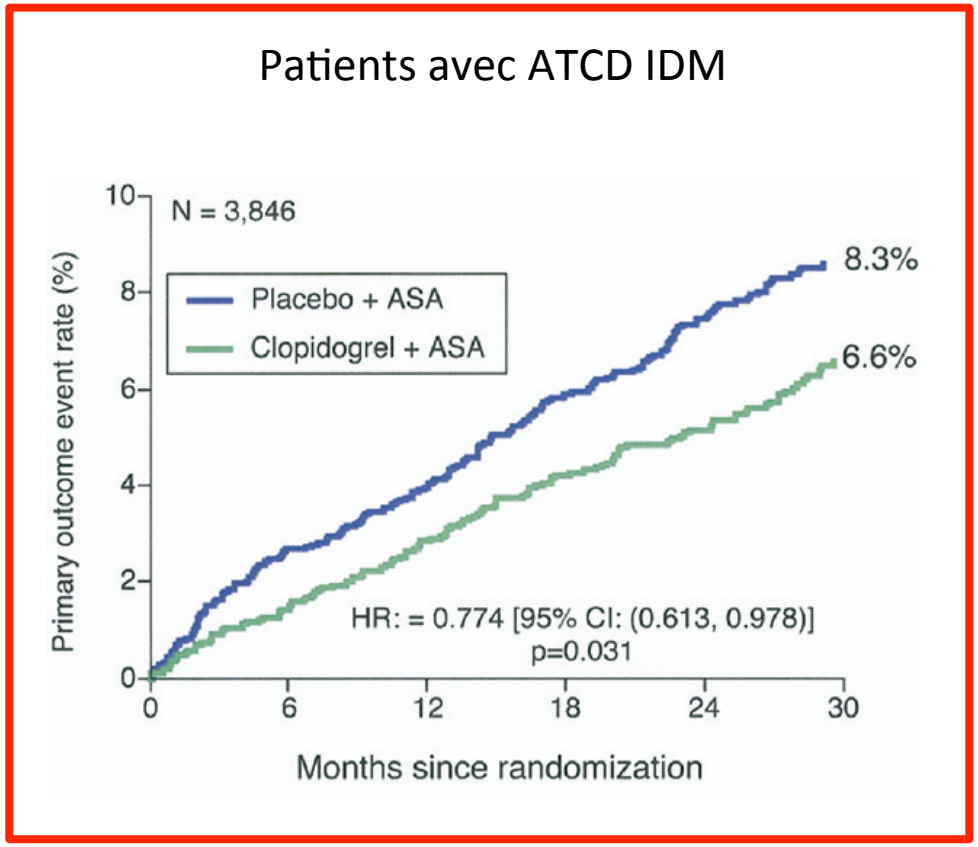
Pour le patient ?



➔ SCA

➔ Maladie coronaire stable

Post SCA: Plus de 12 mois ?

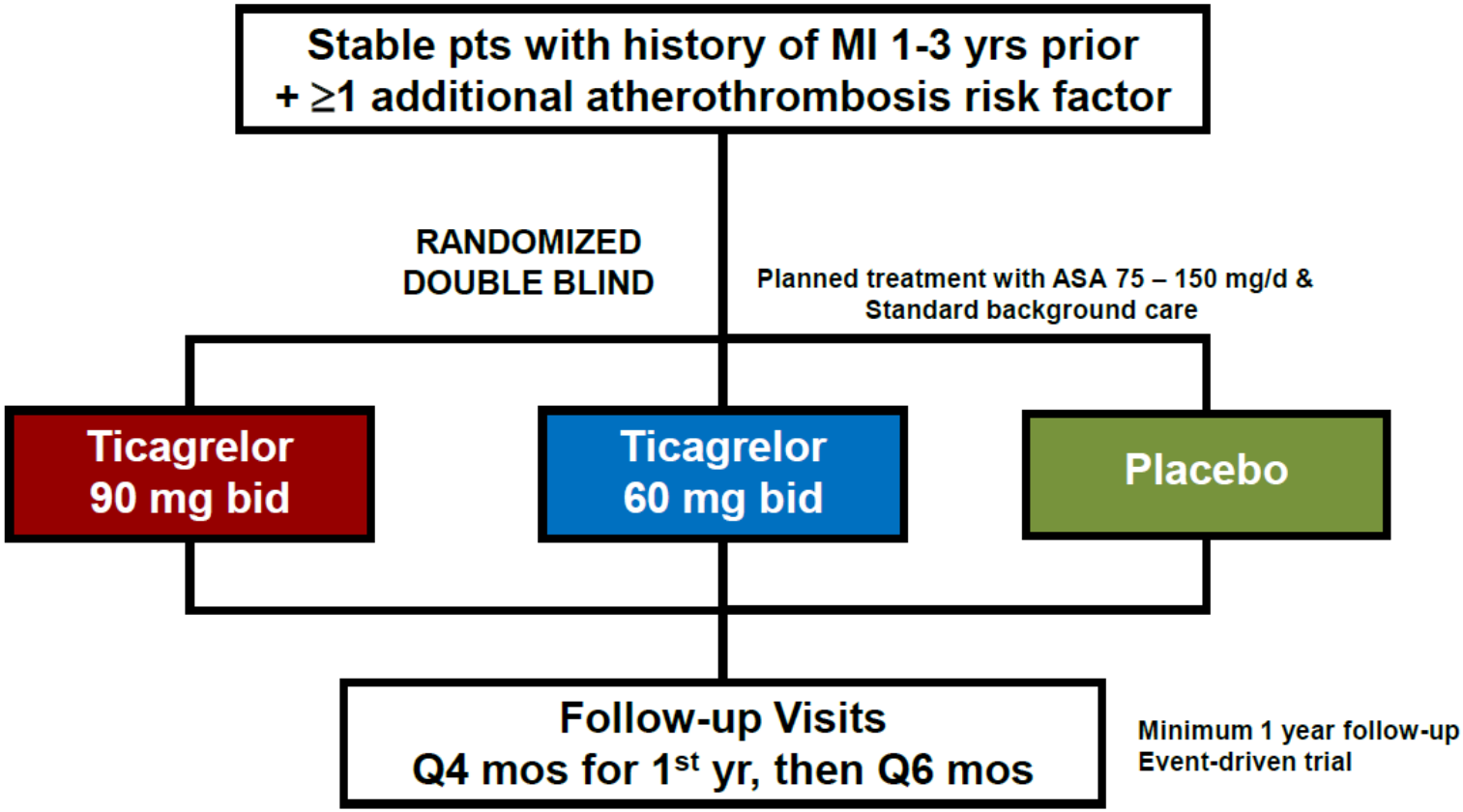


Bénéfice chez coronariens avec ATCD IDM

Etude CHARISMA

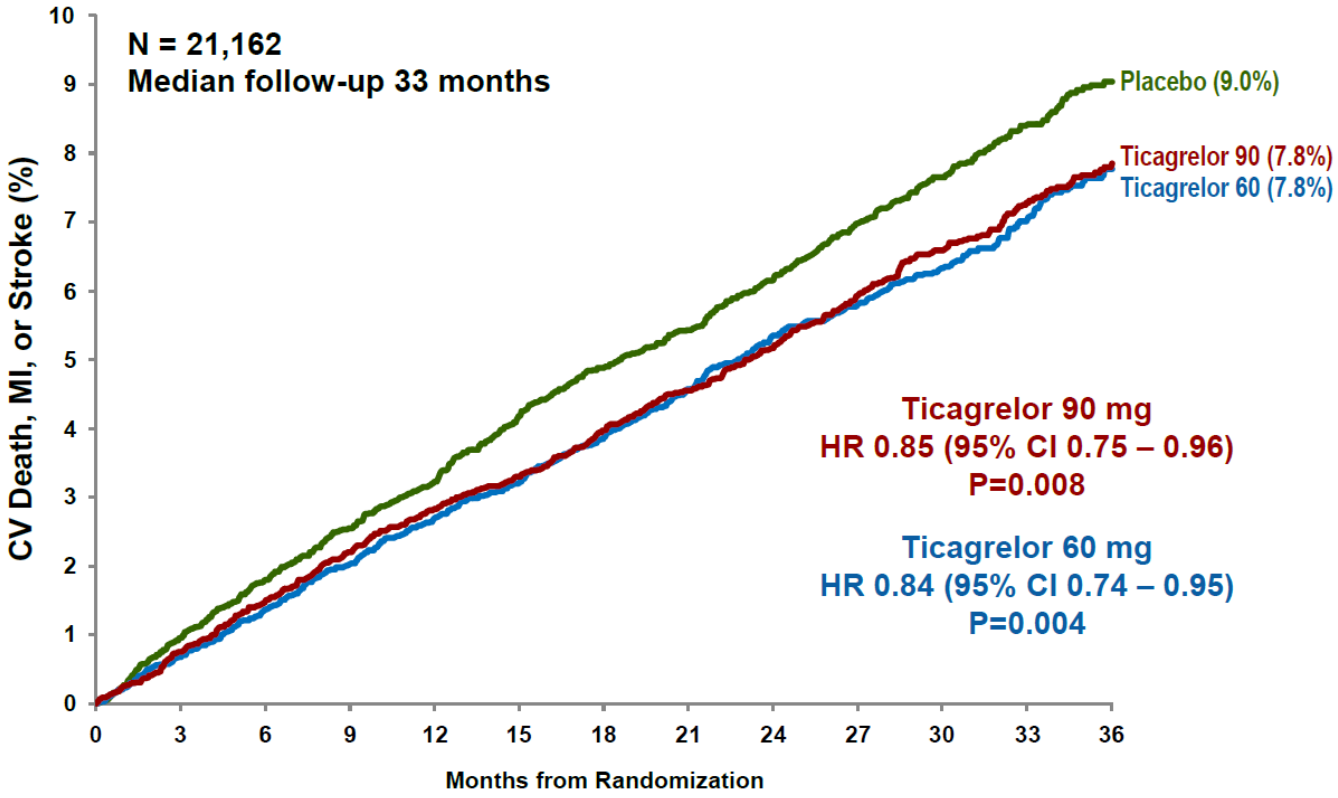
Bhatt et al, JACC 2007

Etude PEGASUS



Bonaca et al, NEJM 2015

Etude PEGASUS

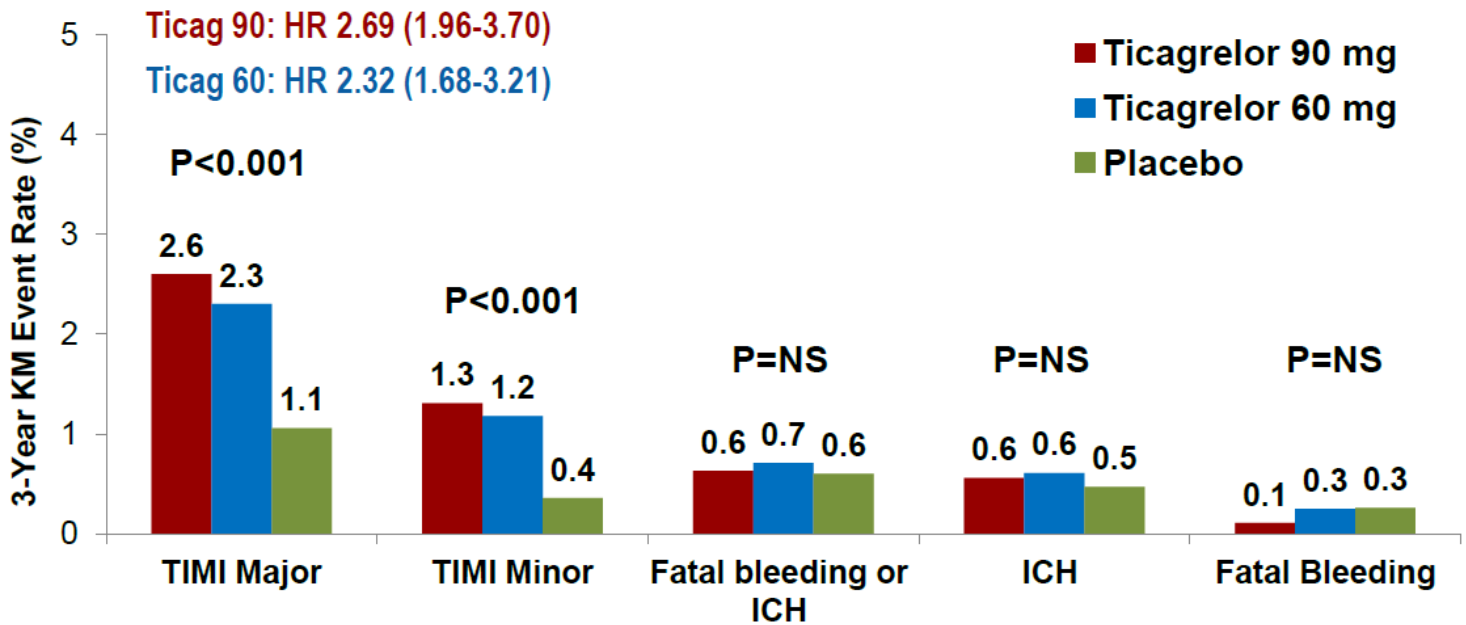


-1.2%

Bonaca et al, NEJM 2015

Etude PEGASUS

Bleeding



+1.2% 60 mg
+ 1.5% 90 mg

Bonaca et al, NEJM 2015

PEGASUS: Conclusion

Bénéfice au ticagrelor long terme avec plus de saignements

Meilleur profil efficacité / sécurité pour 60 mg

Implications ?

Sans doute assez pour fin du dogme « 1 an pour tous »

Mais pas pour un nouveau dogme « plus d'un an pour tous »

Approche individualisée

Bonaca et al, NEJM 2015

BiAAP pour **DES** chez patient stable

DES LATE, *NEJM 2010*

EXCELLENT, *JACC 2012*

PRODIGY, *Circulation 2012*

RESET, *JACC 2012*

OPTIMIZE, *JAMA 2013*

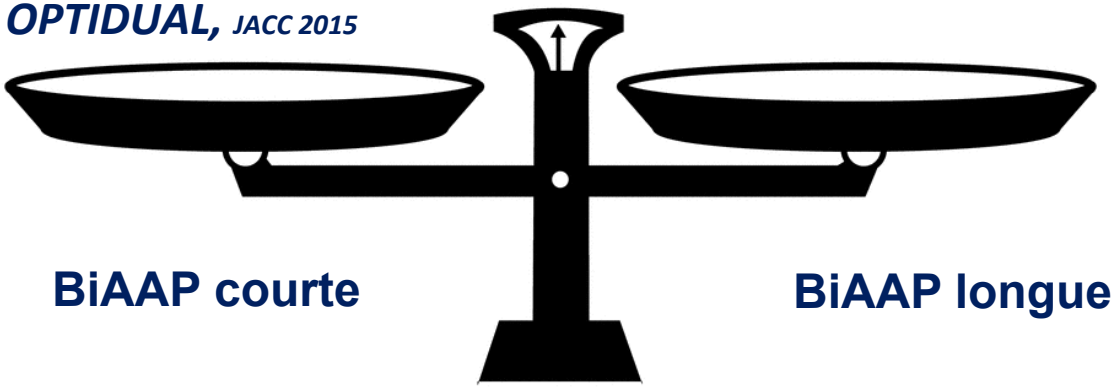
ARCTIC, *Lancet 2014*

ISAR SAFE, *EHJ 2015*

ITALIC, *JACC 2014*

« No MI » DAPT study, *NEJM 2014*

OPTIDUAL, *JACC 2015*

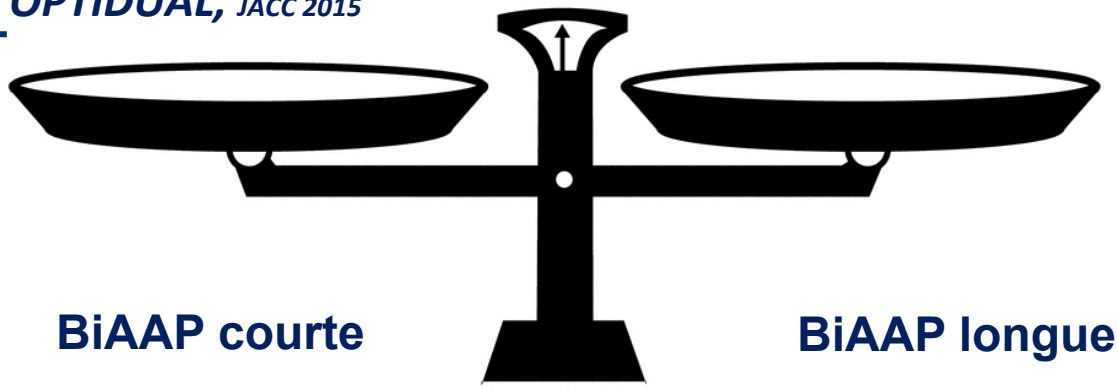


BiAAP pour patient dilaté pour **SCA**

Patients SCA
N>10,000

- ***DES LATE,*** *NEJM 2010*
- ***EXCELLENT,*** *JACC 2012*
- ***PRODIGY,*** *Circulation 2012*
- ***RESET,*** *JACC 2012*
- ***OPTIMIZE,*** *JAMA 2013*
- ***ARCTIC,*** *Lancet 2014*
- ***ISAR SAFE,*** *EHJ 2015*
- ***ITALIC,*** *JACC 2014*
- ***OPTIDUAL,*** *JACC 2015*

- ***CHARISMA II (40% ACS)*** *JACC 2007*
- ***TRILOGY,*** *NEJM 2012*
- ***« Post MI »DAPT study*** *NEJM 2014, JACC 2015*
- ***PEGASUS,*** *NEJM 2015*



BiAAP courte **BiAAP longue**

Court vs Long: comment choisir ?

Patient âgé
Risque hémorragique
Anticoagulant oral
Maladie coronaire stable

Patient jeune
Bas risque hémorragique
DES multitronculaire
ICP complexe
ATCD thrombose stent
Infarctus
SCA récidivant sous BiAAP
Diabétique
Stent 'Absorb'

Court vs Long: le patient !!

Patient jeune
Bas risque hémorragique
ATCD thrombose stent
Infarctus
SCA récidivant sous BiAAP
Diabétique
DES multitronculaire
ICP complexe
Stent 'Absorb'

Patient âgé
Risque hémorragique
Anticoagulant oral
Maladie coronaire stable

Choix durée de biAAP

Après DES

Amélioration technologie DES

Preuves que courte biAAP possible chez patients bas risque

6 mois comme règle, plus court si haut risque hémorragique

Après SCA

12 mois comme règle, plus court si haut risque hémorragique

Preuves que Patient SCA à haut risque bénéficient de

BiAAP long terme *(CHARISMA post-MI, DAPT post-MI, PEGASUS)*

Trois grandes questions: AAP et SCA

Lequel ?

Nouvelles molécules par défaut

Quand commencer ?

Avant CORO ST + / Après CORO ST-

Quand Arrêter ?

Approche individualisée / >12 mois parfois

Merci