AZIENDA OSPEDALIERA
G. RUMMO
BENEVENTO
Azienda di Rilievo Nazionale ad Alta Specializzazione

Dipartimento di CardioScienze

Unità Operativa Complessa
Cardiologia Interventistica e UTIC

Marino Scherillo

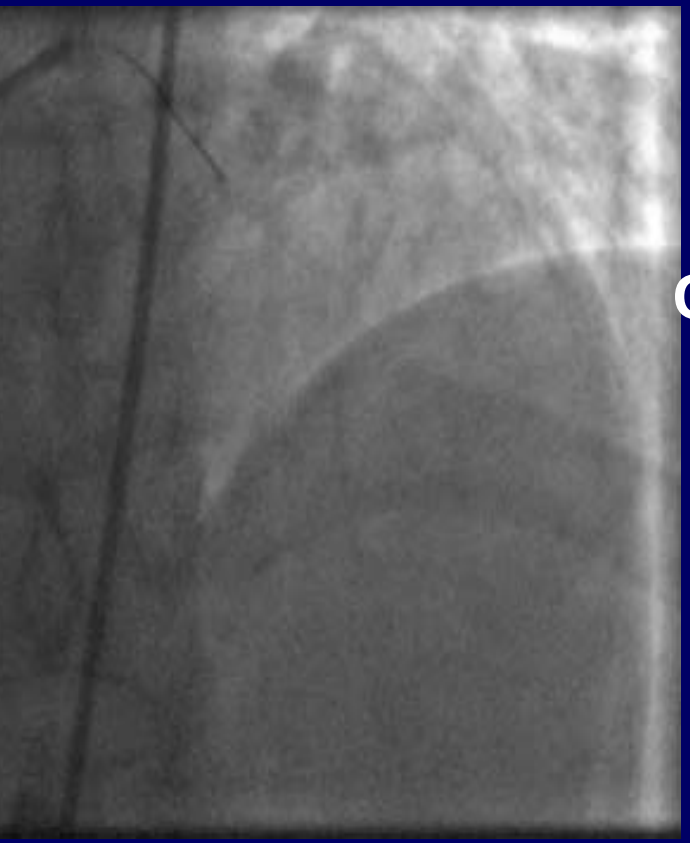
LINEE GUIDA PER L'IMPIANTO CORONARICO DI STENT E CORRETTA TERAPIA ANTIAGGREGANTE

Napoli 12-15 ottobre 2008
Mostra d'Oltremare

NSTEMI

G.F. , 52 y / male, Diabetes ,Tn I+

Strategia Farmaco-Interventistica Precoce



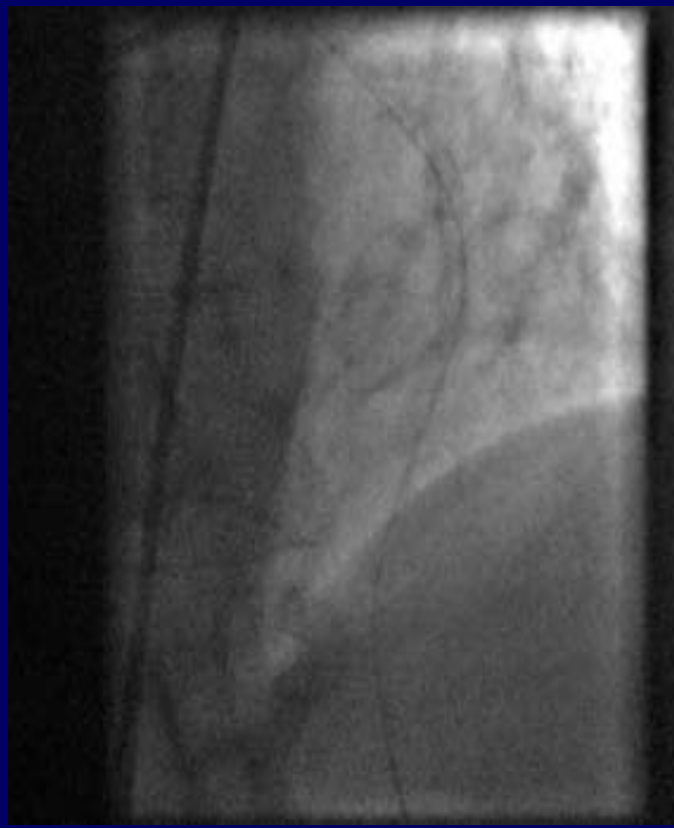
ASA

CLOPIDOGREL

LMWH

STATINA

PCI - STENT



Cardiologia Interventistica ed UTIC – A.O. G.Rummo - BENEVENTO

ESC 2007

Recommendations for Oral Antiplatelet Drugs

I	IIa	IIb	III
A			
A			
A			
A			
B			
	B		
	C		

- **Aspirin**
  - Loading dose (160 - 325 mg)
  - Maintenance (75 - 100 mg)
- **Clopidogrel**
  - Loading dose 300 mg + 75 mg
  - 12 months maintenance
  - Contraindication for Aspirin
  - 600 mg LD for PCI
  - Postpone CABG 5 days after withdrawal

Linee Guida : Verso una Definizione Operativa per la Comunità

*LG come **Bussola** per Medici e Pazienti*

“ Le LG indicano genericamente la Direzione e non lo specifico Percorso per Migliorare la Quantità e la Qualità della Vita dei Pazienti ”

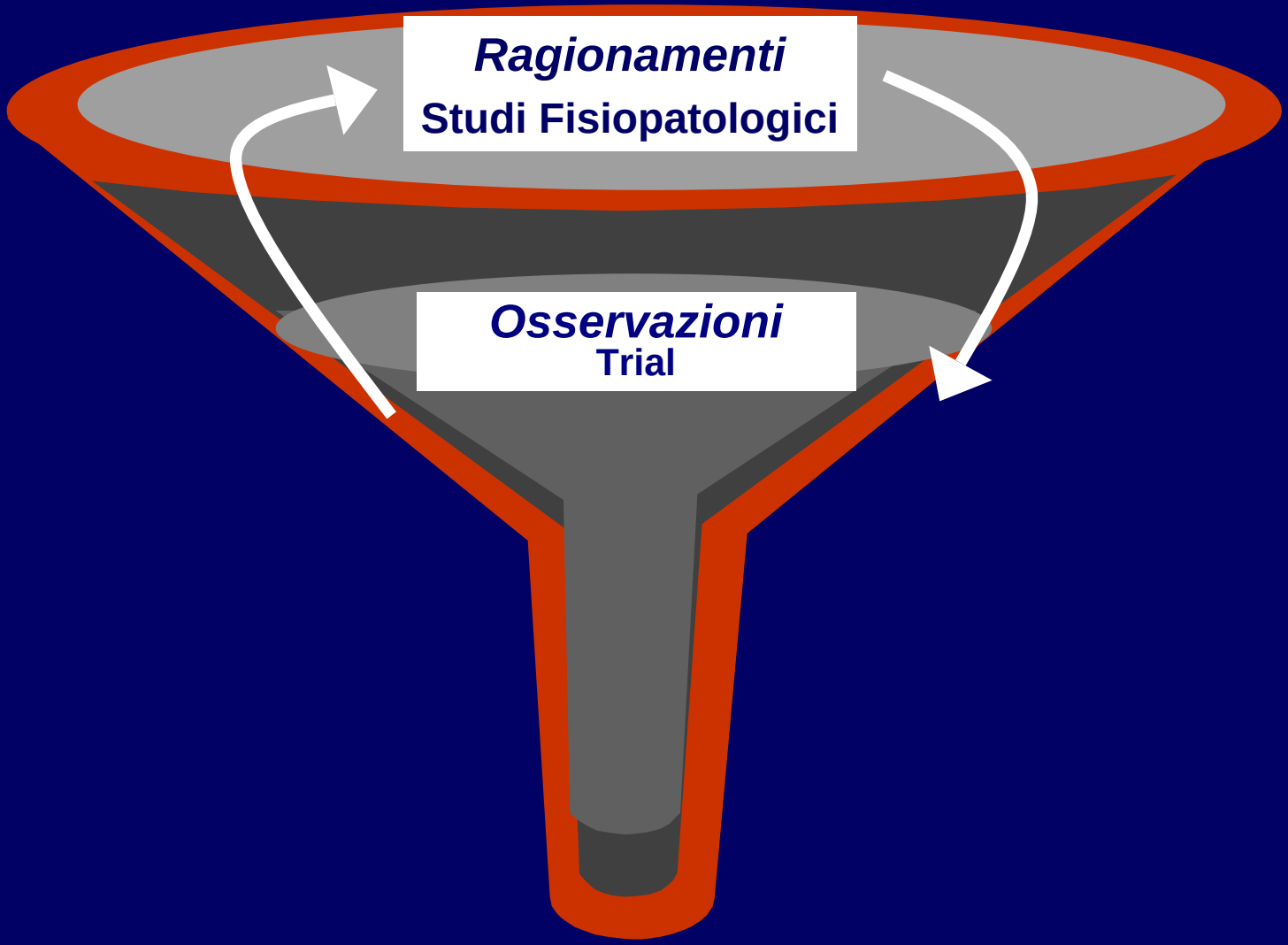
Le Linee Guida non sono il TomTom

Karl Popper

La Conoscenza non e
Sapere Certo
"Episteme" ma
Sapere Congetturale
"Doxa"
e Noi tutti siamo
Ricercatori non
Possessori della Verita

La Grappa di Popper

Linee Guida come Distillato della Verità Scientifica



Linee Guida

Trombosi Tardiva Intrastent

STEMI

9 mesi dopo

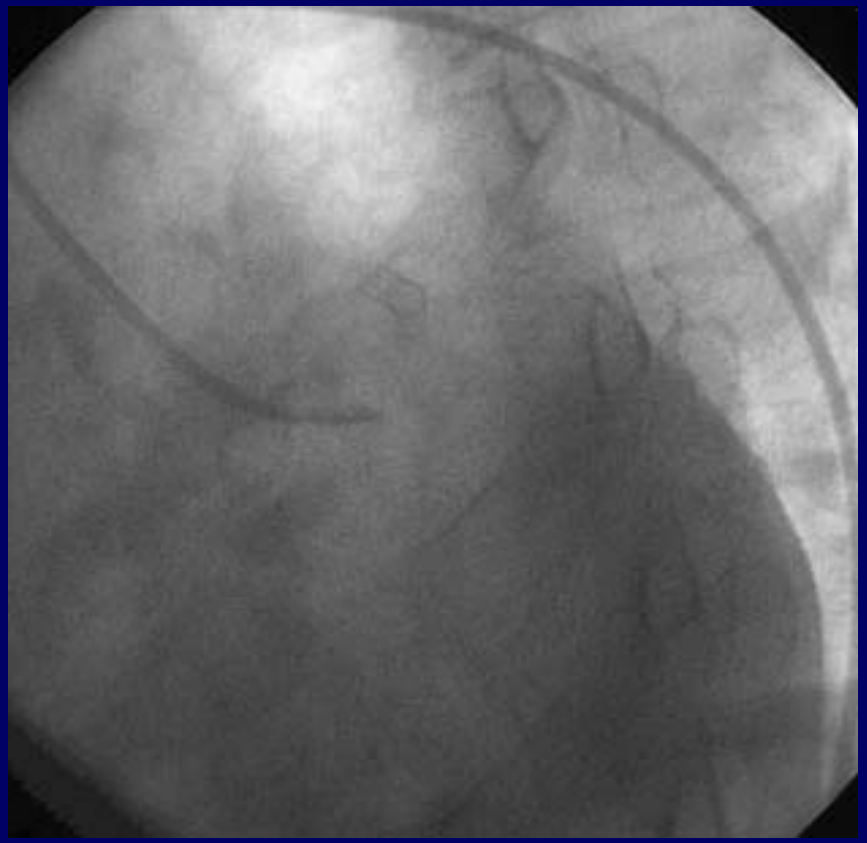
PCI - DES 3.5x15 mm

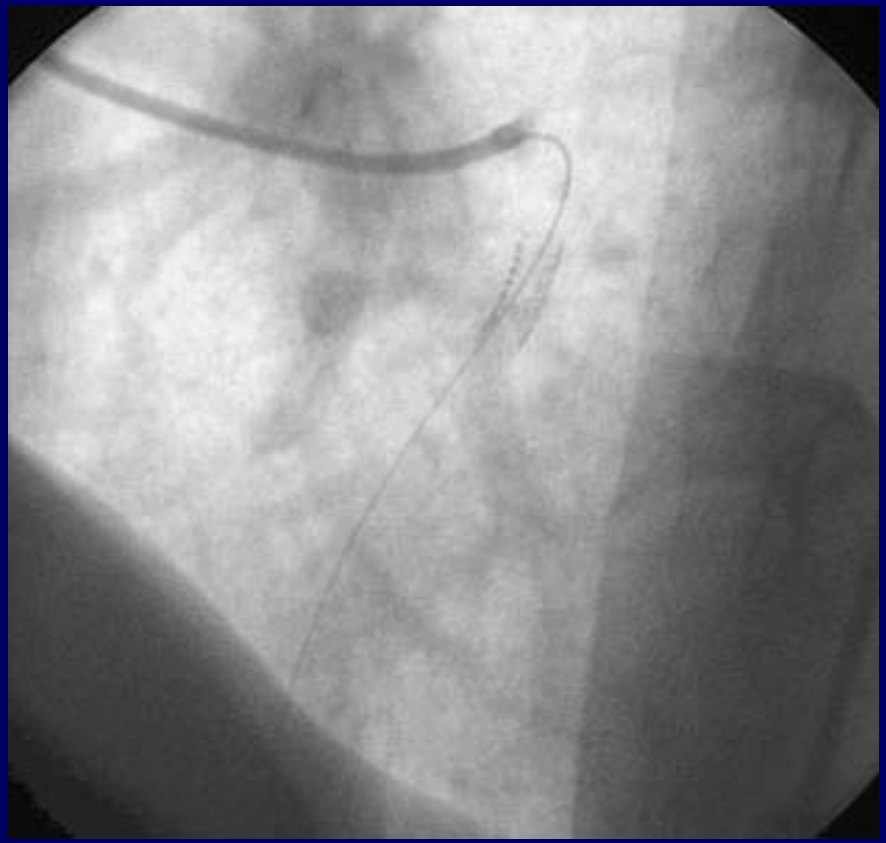
Durante ASA - CLO

PCI - BMS

3.5x18 mm

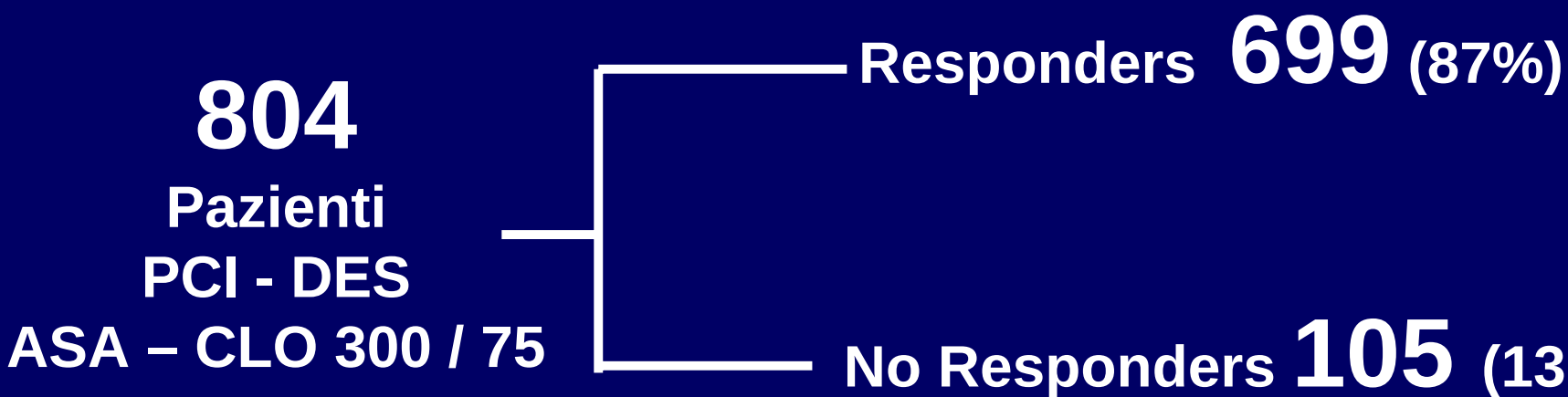
ABCXMAB





e se fosse un paziente CLOPIDOGREL Non Responder

RE-CLOSE Trial



Definizione di No Responders :

Inhibition of Platelet Aggregation

10 µM ADP > 70%

12 – 18 h dal carico di Clopidogrel 600 mg

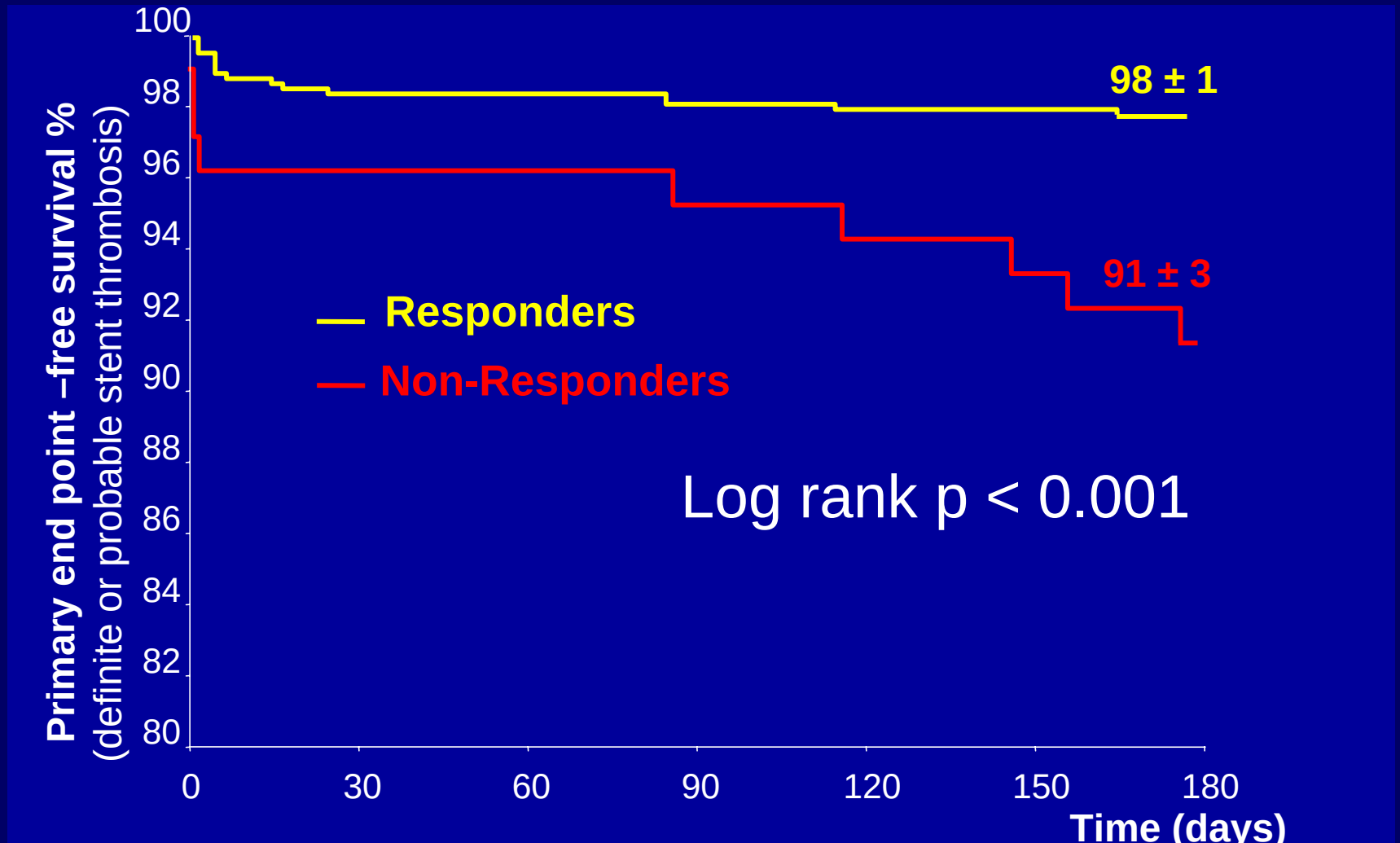
STENT THROMBOSIS

	Non - Responders 9 / 105 (8.6 %)	Responders 16 / 699 (2.3 %
AMI	3 (33%)	7 (44%
Bifurcation	5 (55%)	10 (62%
Multivessel PCI	5 (55%)	10 (62%
Stent length > 30mm	8 (89%)	8 (50%
LVEF < 30%	5 (55%)	8 (55%

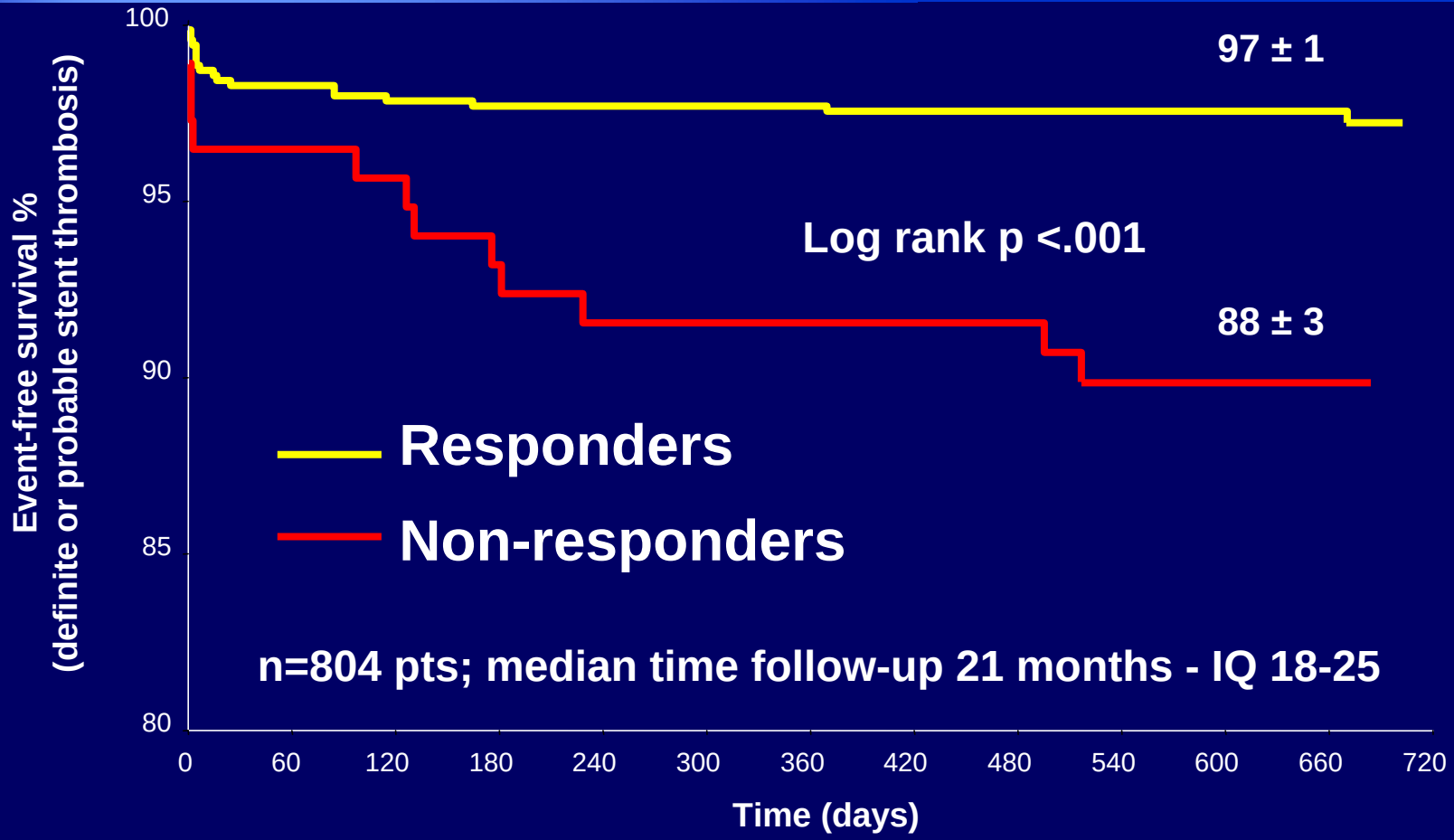
Cox multivariate analysis: Predictors of Stent Thrombosis

	HR (95% CI)	pvalue
Non-responsiveness to clopidogrel	3.08 (1.32-7.16)	0.00
Acute myocardial infarction	2.41 (1.04-5.63)	0.04
Total stent length (mm)	1.01 (1.00-1.02)	0.01
LVEF per 1 % increase	0.95 (0.92-0.98)	0.00

Definite / Probable STENT THROMBOSIS for Responders and Non - Responders to Clopidogrel (Kaplan-Meyer)



LONG - TERM SURVIVAL FOR PRIMARY END-POINT (DEFINITE OR PROBABLE STENT THROMBOSIS)



Conclusion

Non-responsiveness to CLOPIDOGREL is a strong independent predictor of stent thrombosis and mortality in patients receiving DES. Alternative revascularization strategies (BMS or CABG), or pharmacologic strategies using increasing dose of clopidogrel or other antiplatelet agents should be considered to reduce the risk of thrombotic events.

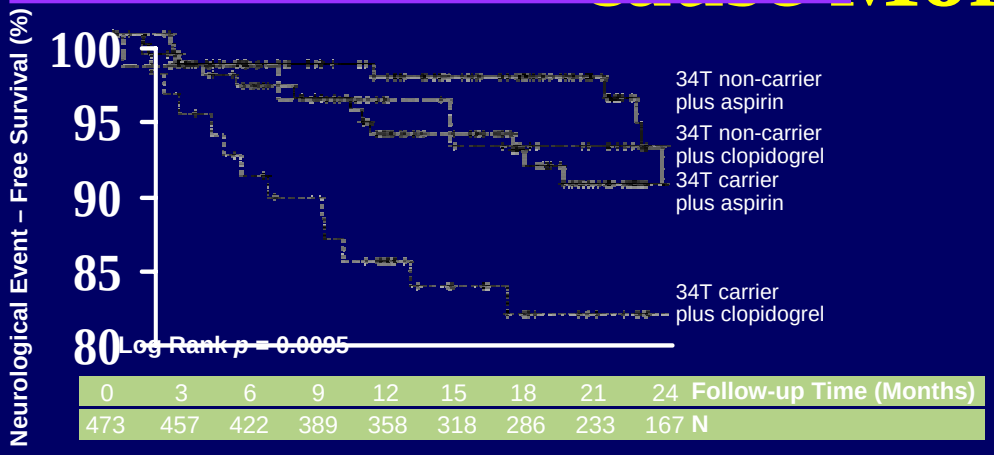
Variability Platelet Response With Antiplatelet Agents

- Genetic[1]
  - Receptors: $P2Y_{1,2}$, H2 haplotype (clopidogrel), GPIIb/IIIa, collagen, thromboxane
  - Enzymes: COX-1, COX-2, thromboxane A_2 synthetase, etc. (aspirin)
- Pharmacokinetic / Bioavailability[1]
  - Non-compliance
  - Underdosing
  - Poor absorption (e.g., enteric coated aspirin)
  - Interference: NSAIDs coadministration (aspirin); atorvastatin (clopidogrel)
- Pharmacodynamic[1]
  - Incomplete suppression of thromboxane A_2 generation (aspirin)
  - Accelerated platelet turnover, with introduction into the blood stream of newly formed, drug-unaffected platelets
  - Stress-induced COX-2 in platelets (aspirin)
  - Increased platelet sensitivity to ADP and collagen
- Environment / Concomitant disease
  - Diabetes mellitus (aspirin)[2]

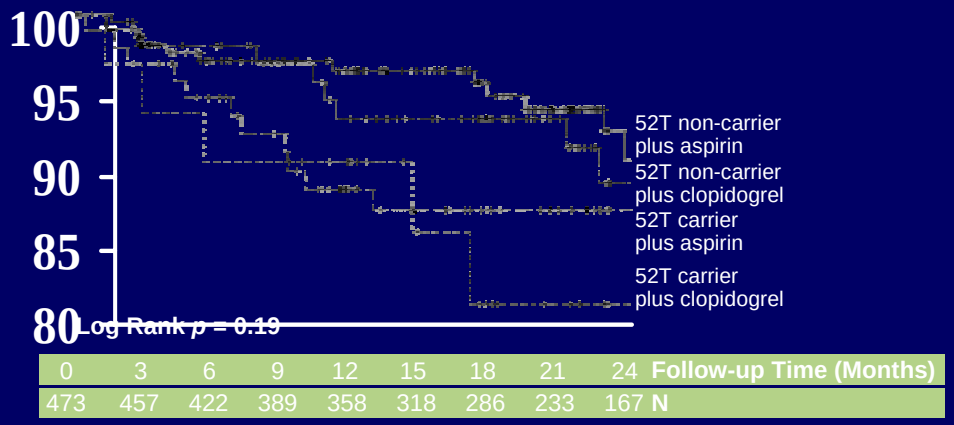
1. Michelson A. *Circulation* 2004;110:e489-93
2. Albert SG et al. *Diabetes Res Clin Pract* 2005;70:105-9

Polymorphism of the $P2Y_{12}$ Receptor is a Possible Explanation for Clopidogrel Failure, Though not Associated with All-Cause Mortality

34C>T Polymorphism



52G>T Polymorphism



Ziegler S et al. *Stroke* 2005;36:1394-9

- In PAD patients, clopidogrel variability exists, which may results in increased risk for cerebrovascular events
- Sequence alterations of the target receptor gene represent one possible mechanism for clopidogrel failure
- Genotype frequencies for mutated, heterozygous, and wild-type alleles were
  - For polymorphism 34C>T = 9%, 44%, and 47%
  - For polymorphism 52G>T = 4%, 27%, and 70%
- In clopidogrel patients, carriers of at least one 34T allele had a 4.02-fold increased adjusted risk for neurological events compared with carriers of 34C allele

Neither polymorphisms were

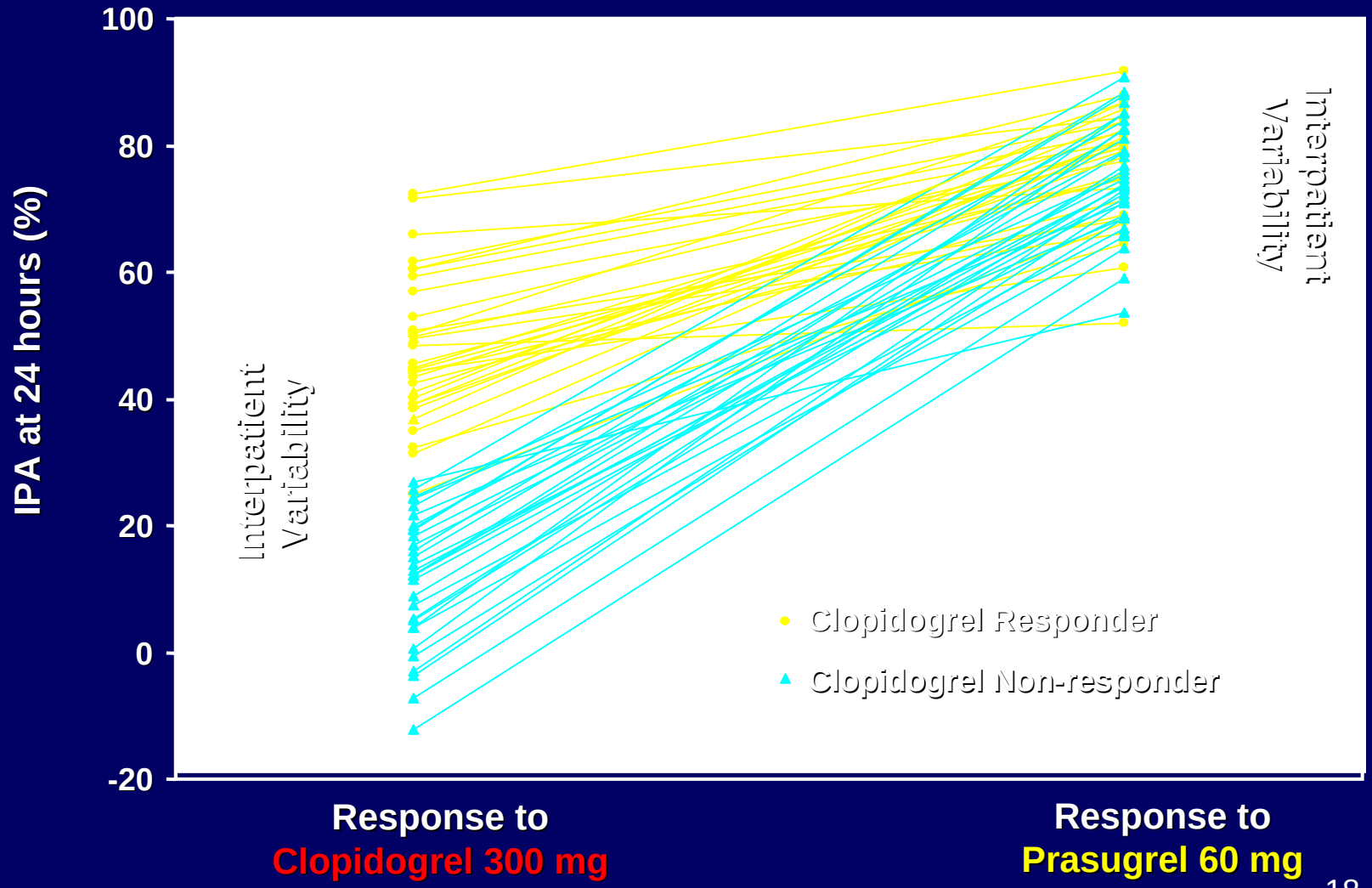
Novel ADP $P2Y_{12}$ Receptor Antagonist

Prasugrel

AZD 6140

Cangrelor

Healthy Volunteer Crossover Study

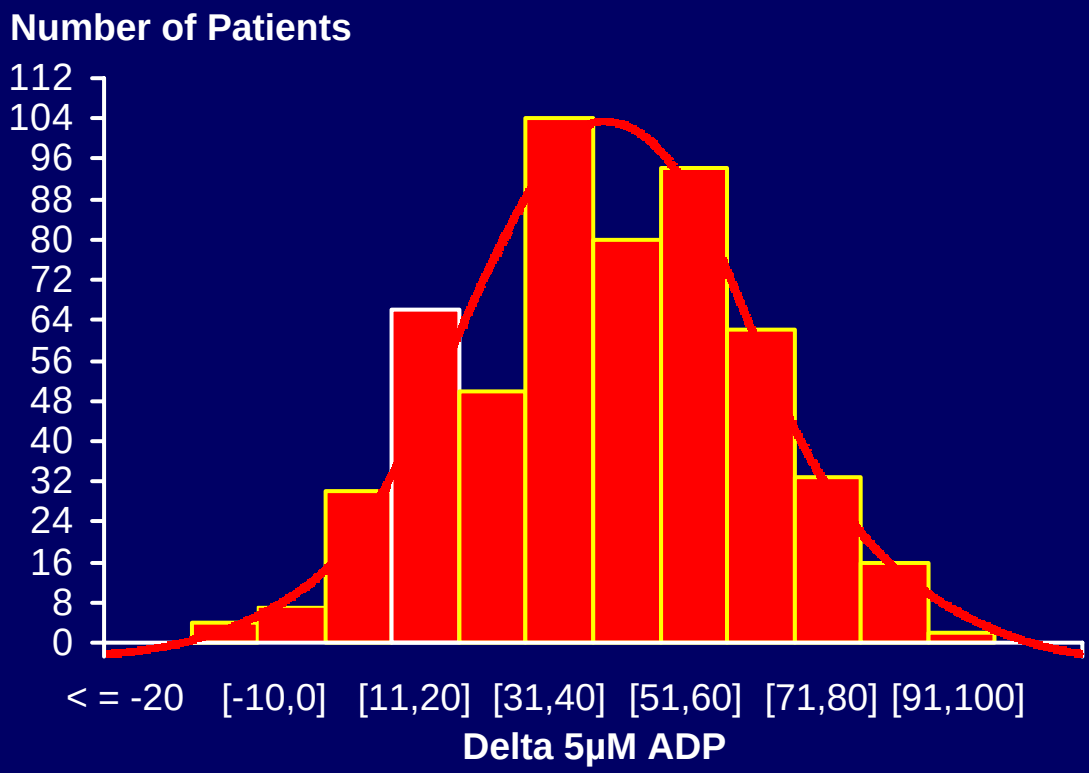


From Brandt JT AHJ 153: 66e9 2007

elevato non è necessariamente migliore perché è correlato al Rischio Emorragico

Clopidogrel Responsiveness Shows a Normal Distribution in Patients

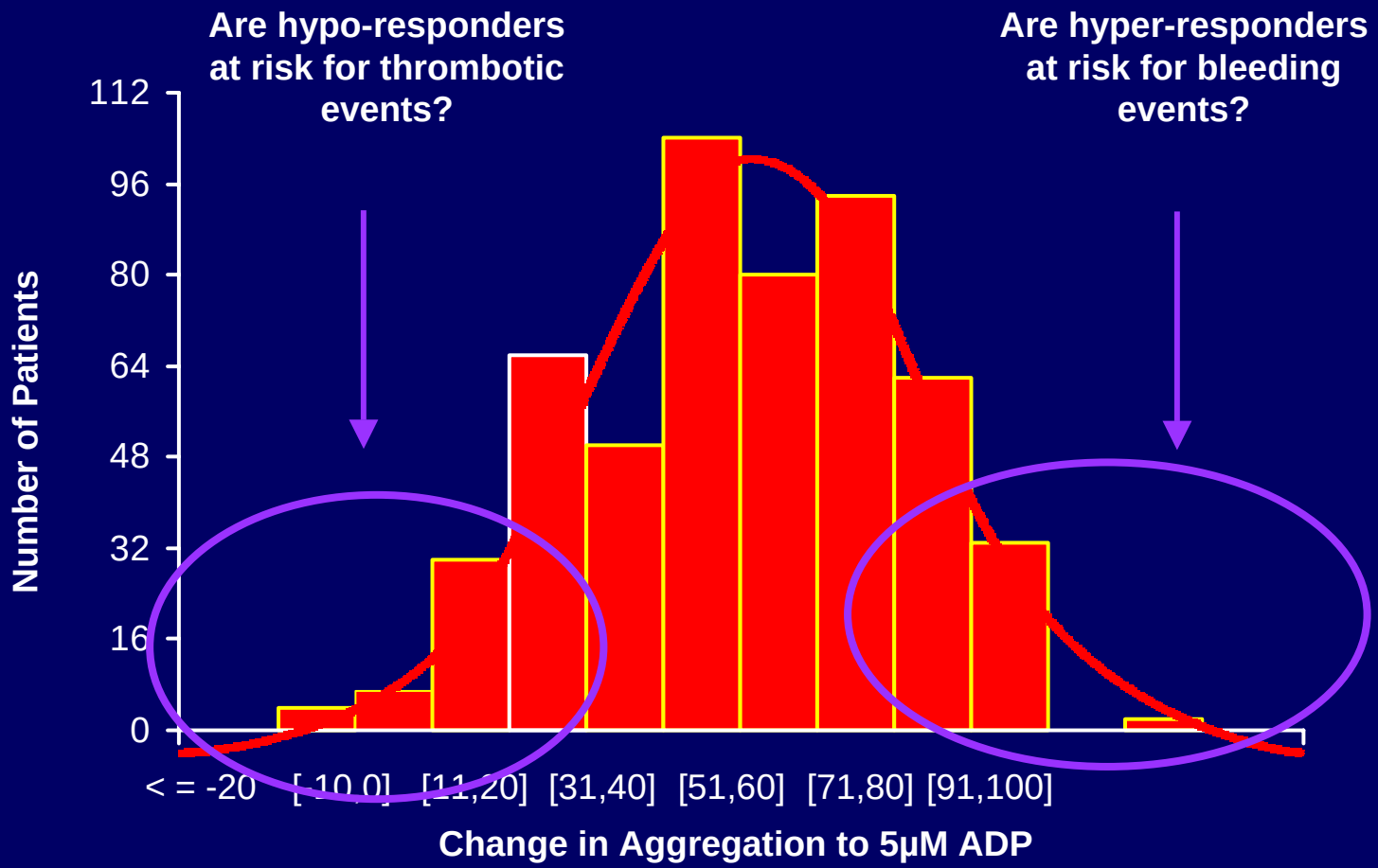
- Individuals receiving clopidogrel exhibit a wide variability in response that follows a normal distribution curve
- In this study (retrospective analysis of a dataset of different type of patients)
  - Hypo-responsive patients = 4.2%
  - Hyper-responsive patients = 4.8%
  - Defined as to be 2 standard deviation less than and greater than the mean respectively



Distribution of the changes in 5 µmol of adenosine diphosphate (ADP)-induced platelet aggregation in 544 patients after receiving clopidogrel therapy. Negative changes in aggregation values represent aggregation values after the administration of clopidogrel that were higher than the baseline readings.

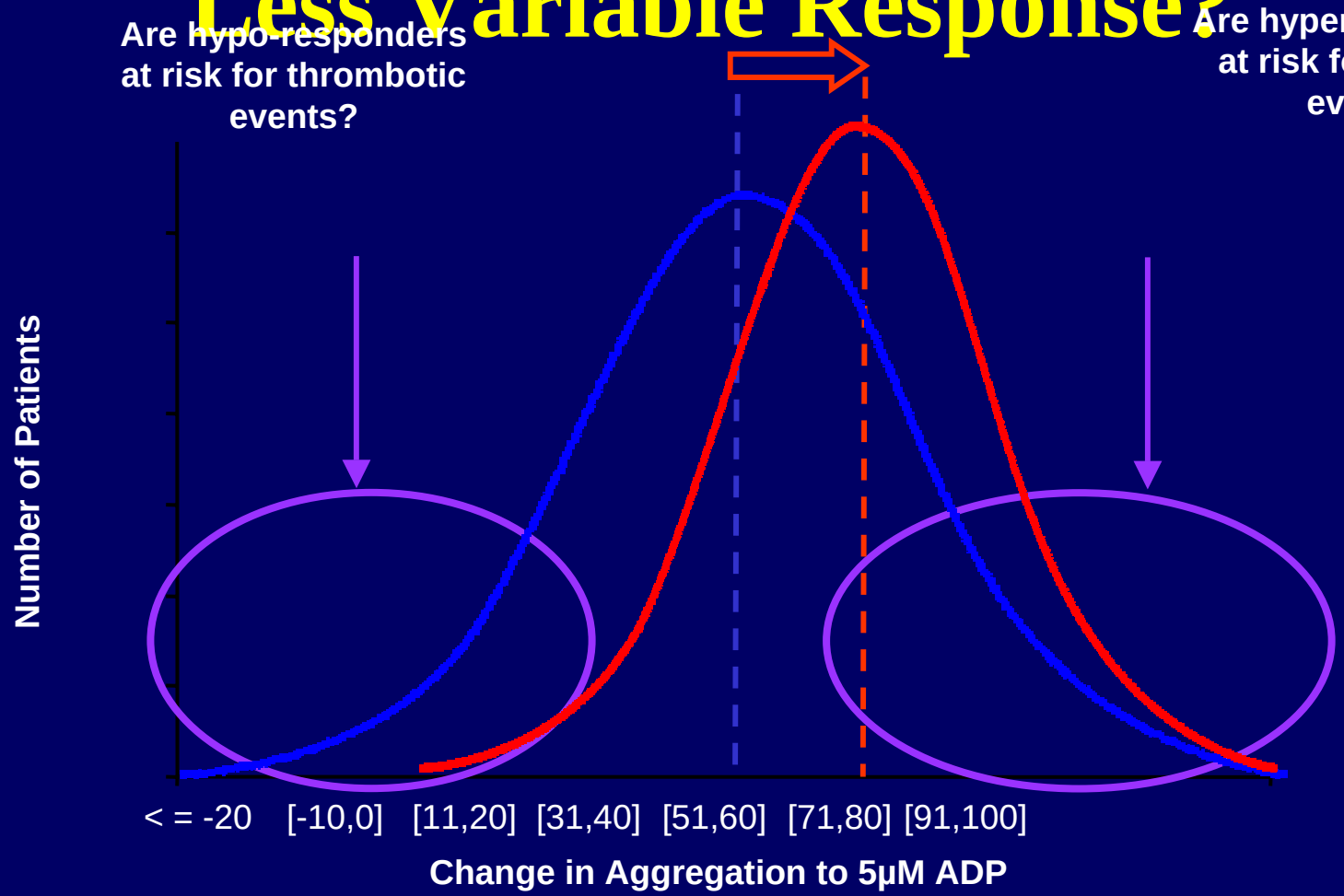
Serebruany V et al. *J Am Coll Cardiol* 2005;45:246-51

What Are the Clinical Implications?



Adapted from: Serebrauny V et al. *J Am Coll Cardiol* 2005;45:246-51

What Could be the Clinical Implications with Higher IPA and Less Variable Response?



Adapted from: Serebrauny V et al. *J Am Coll Cardiol* 2005;45:246-51

Il Bravo Cardiologo Tra Scilla e Cariddi

Scilla

Trombosi

Cariddi

Emorragia

TRITON-TIMI 38

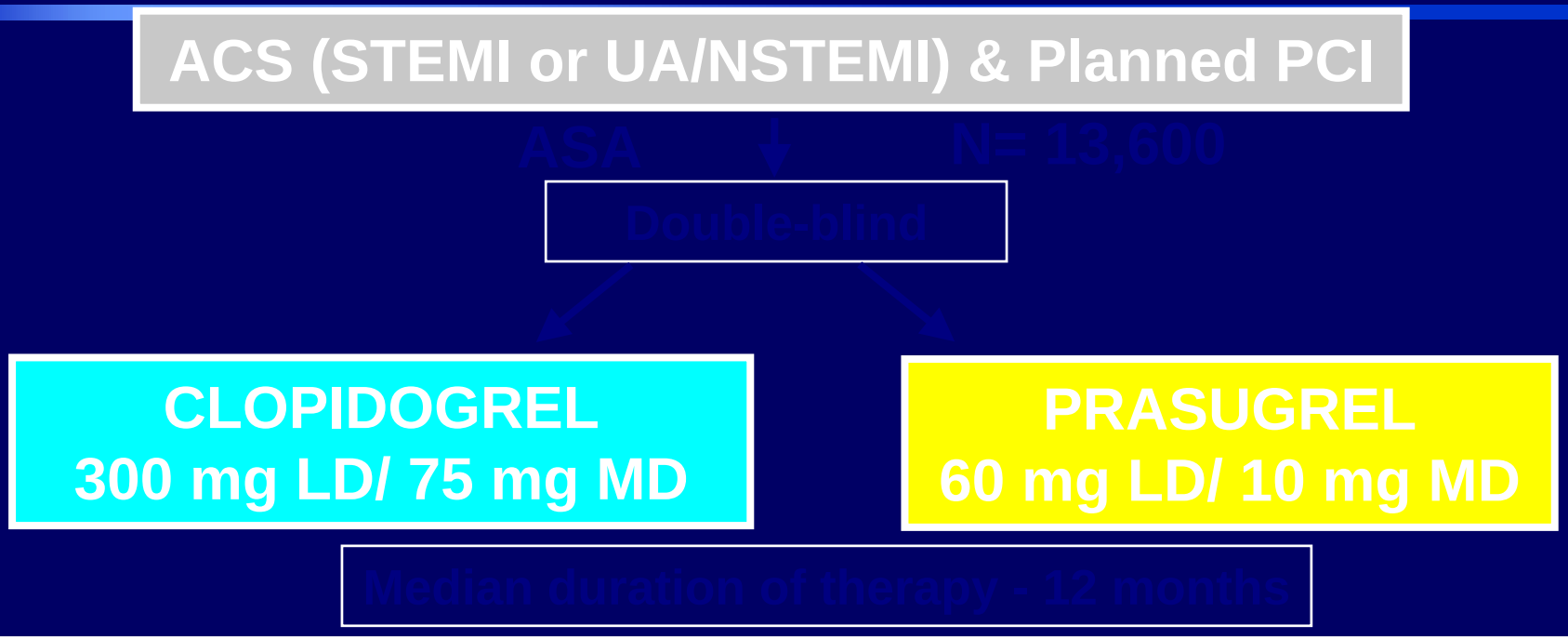
AHA 2007

Orlando, Florida

Disclosure Statement:

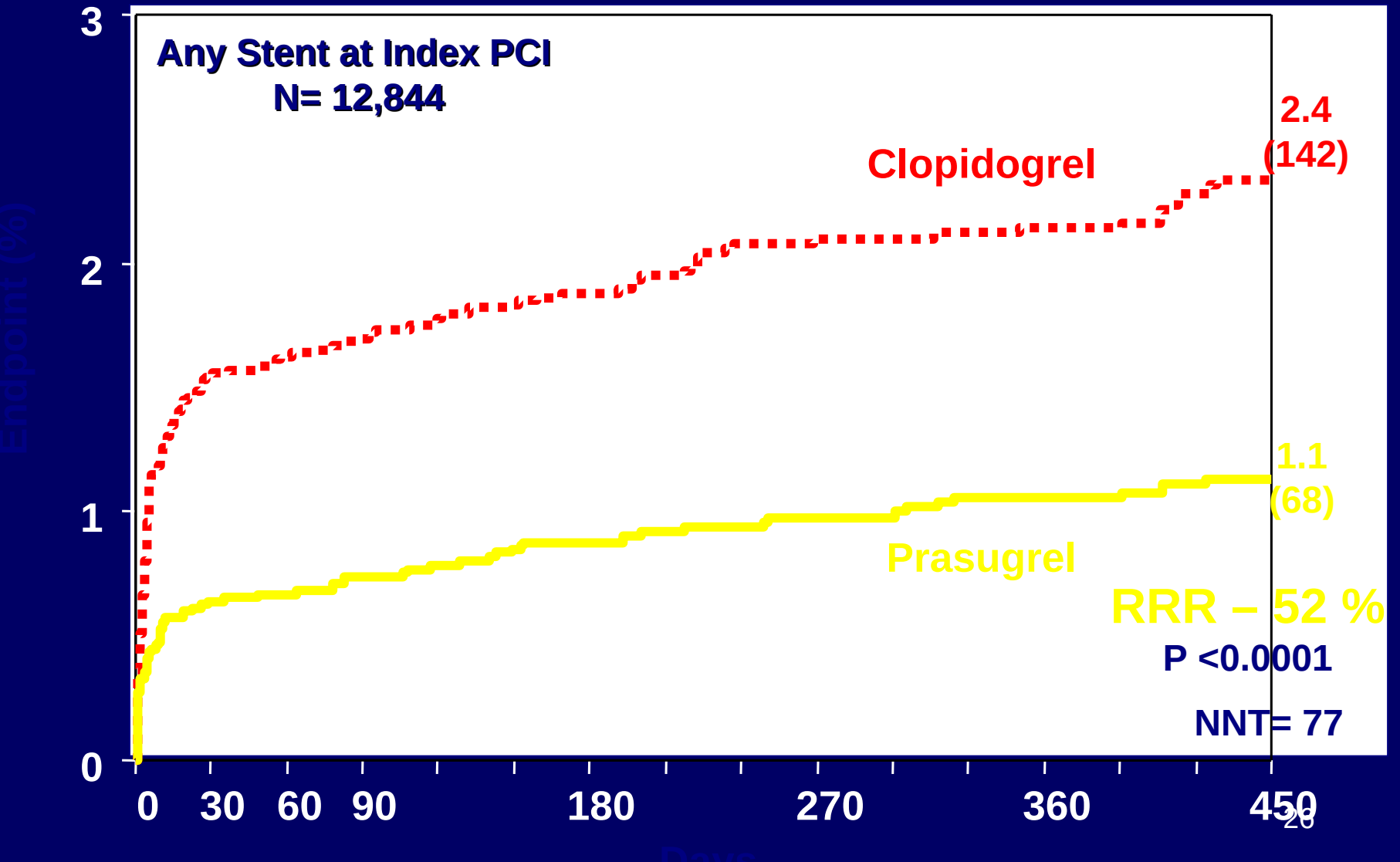
The TRITON-TIMI 38 trial was supported by a research grant to the Brigham and Women's Hospital from Daiichi Sankyo Co. Ltd and Eli Lilly & Co.

Study Design

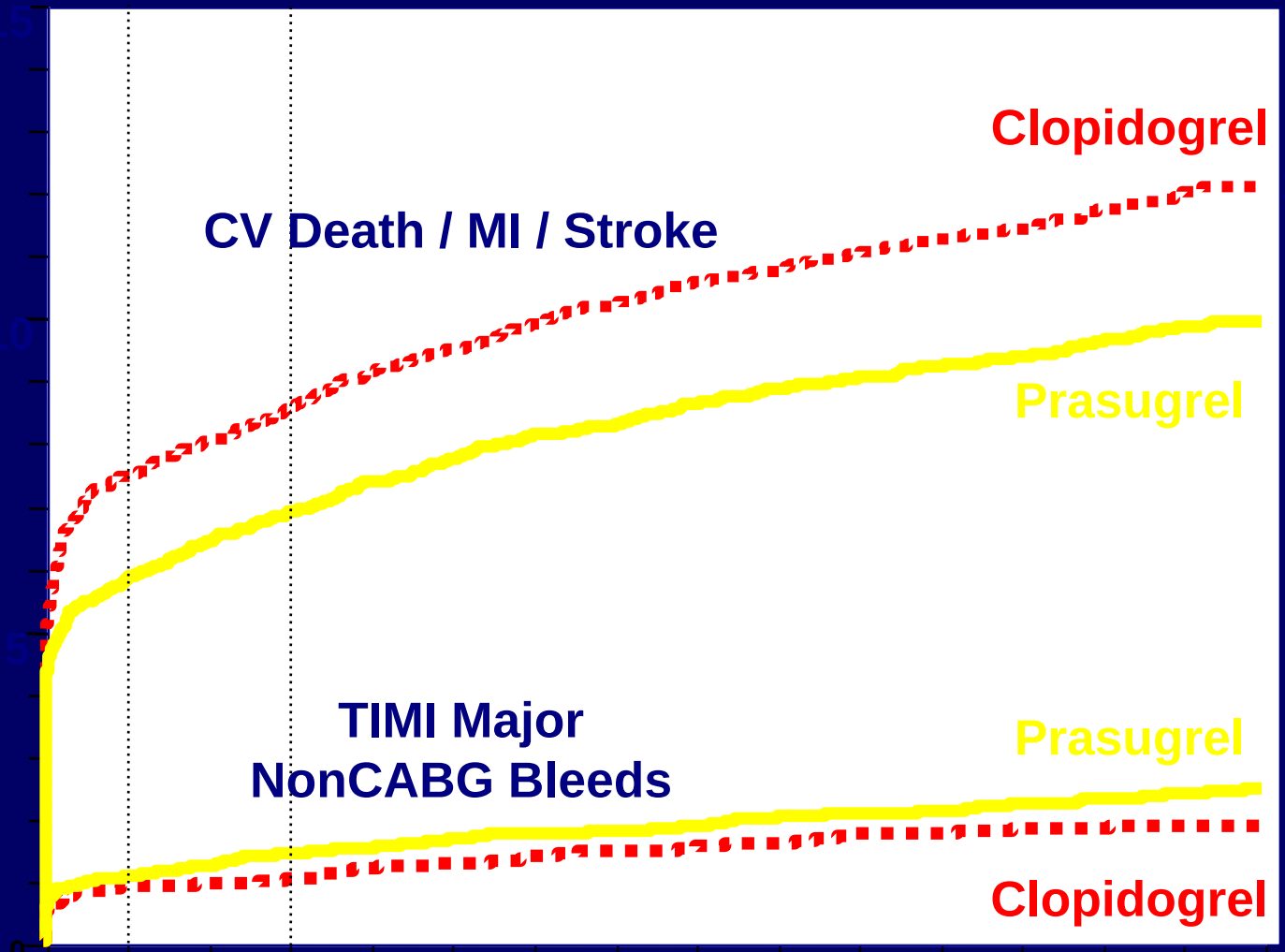


1º endpoint:	CV death, MI, Stroke
2º endpoints:	CV death, MI, Stroke, Rehosp-Rec Isch
	CV death, MI, UTVR
	Stent Thrombosis (ARC definite/prob.)
Safety endpoints:	TIMI major bleeds, Life-threatening bleeds
Key Substudies:	Pharmacokinetic, Genomic

Stent Thrombosis (ARC Definite + Probable)



Balance of Efficacy and Safety



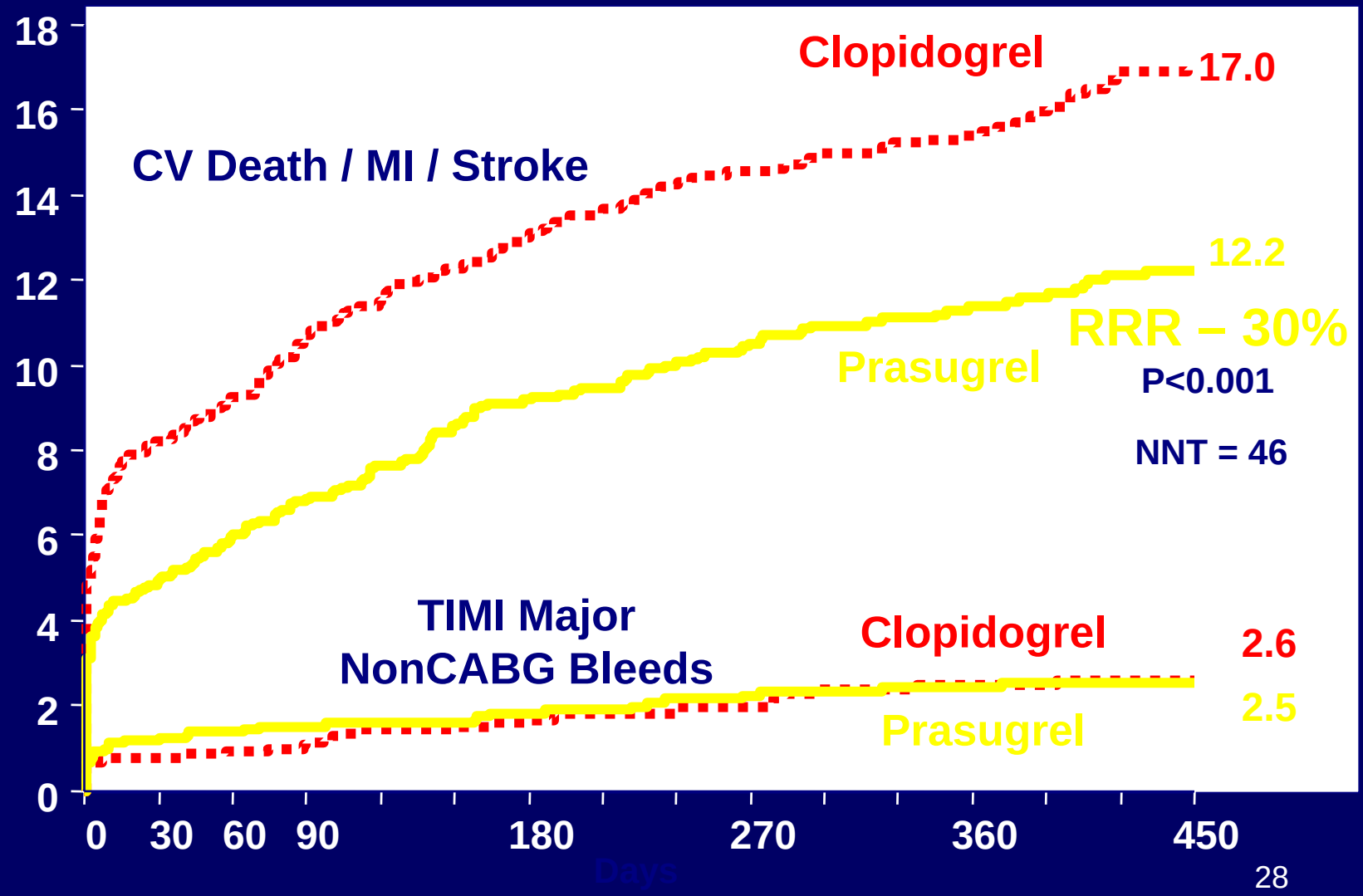
↓ 138 events

RRR – 19 %

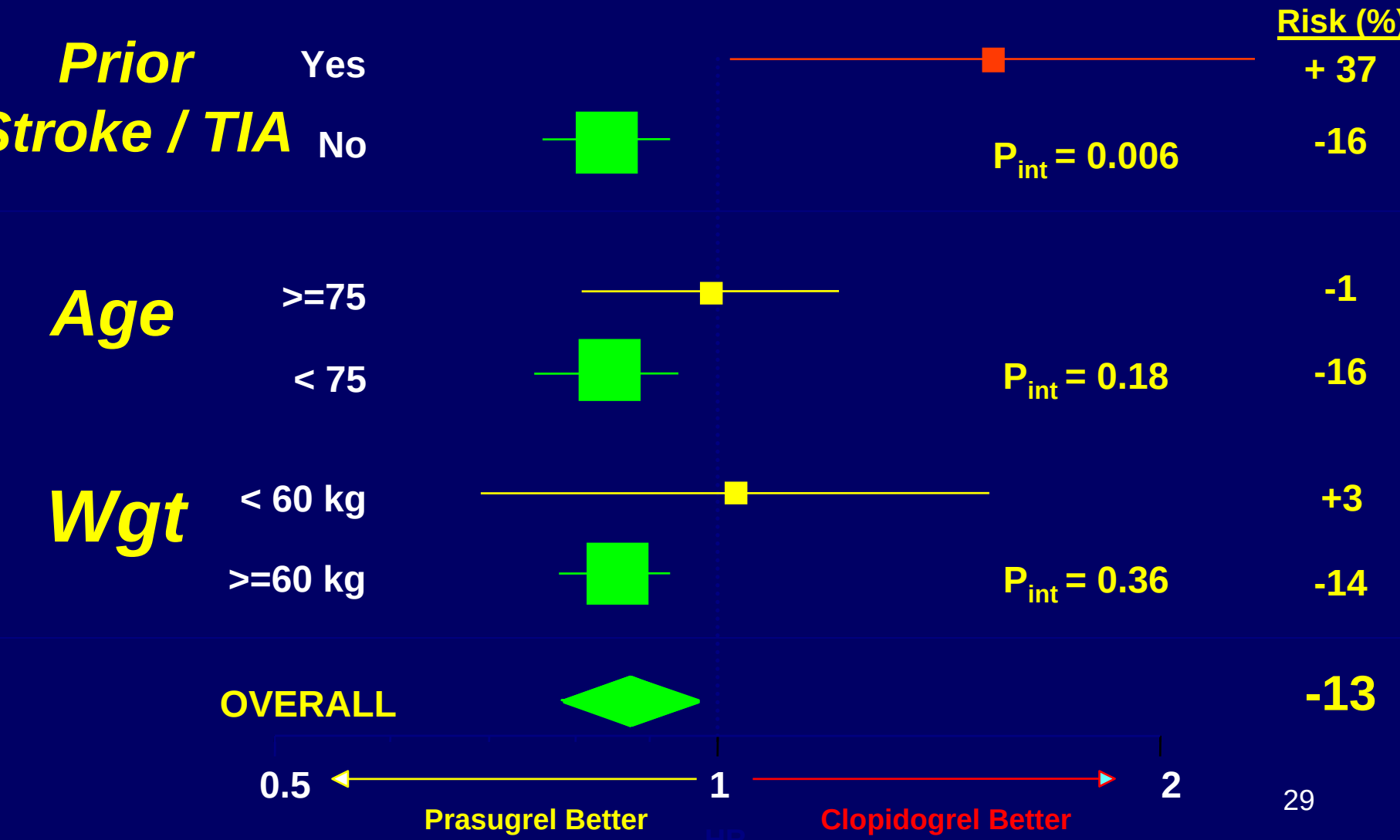
+ 32 % events

Diabetic Subgroup

N=3146

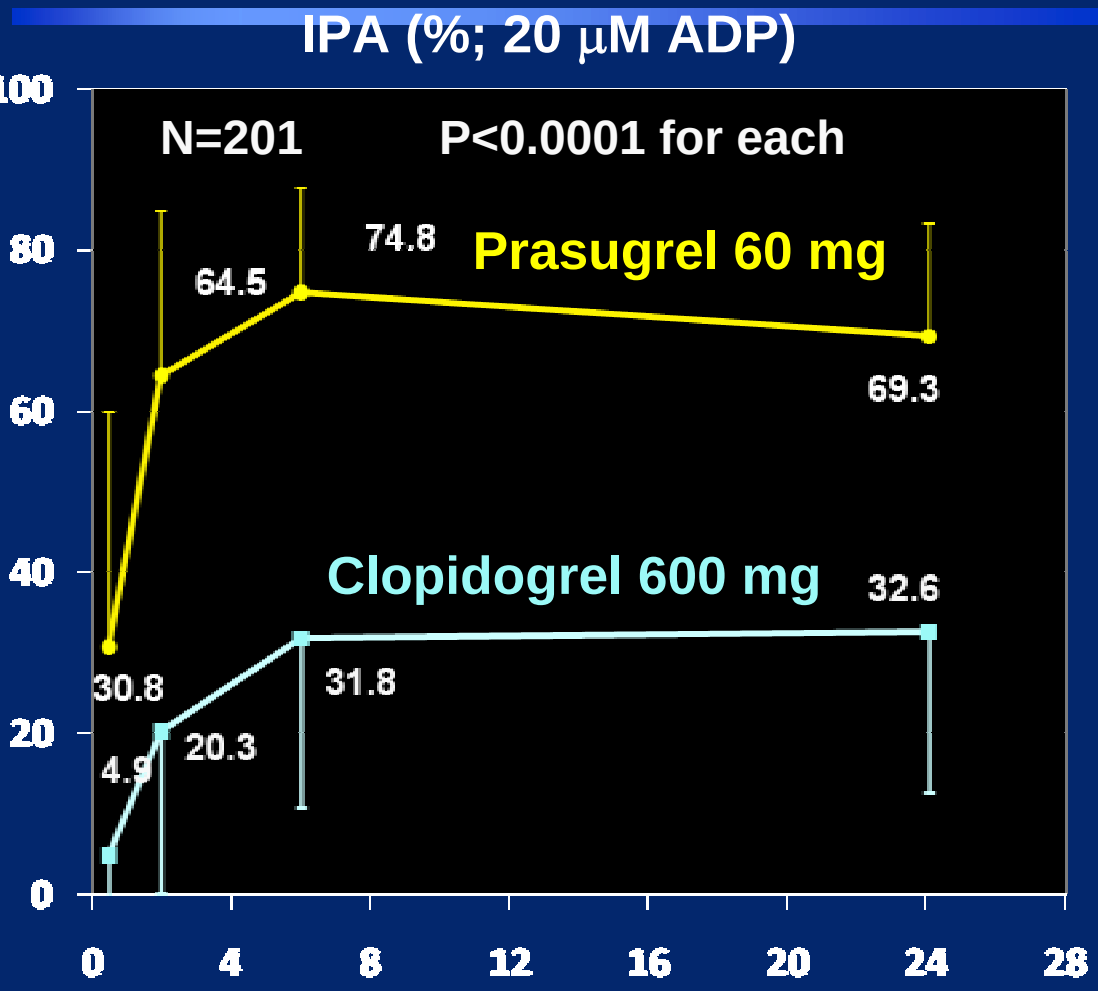


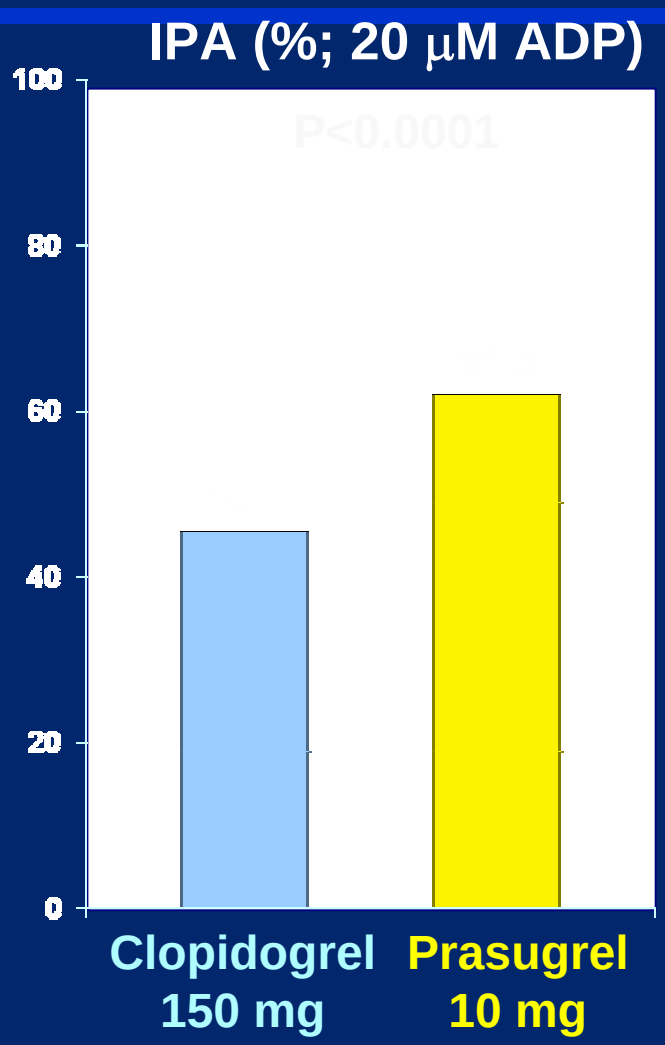
Net Clinical Benefit
Bleeding Risk Subgroups
Post-hoc analysis



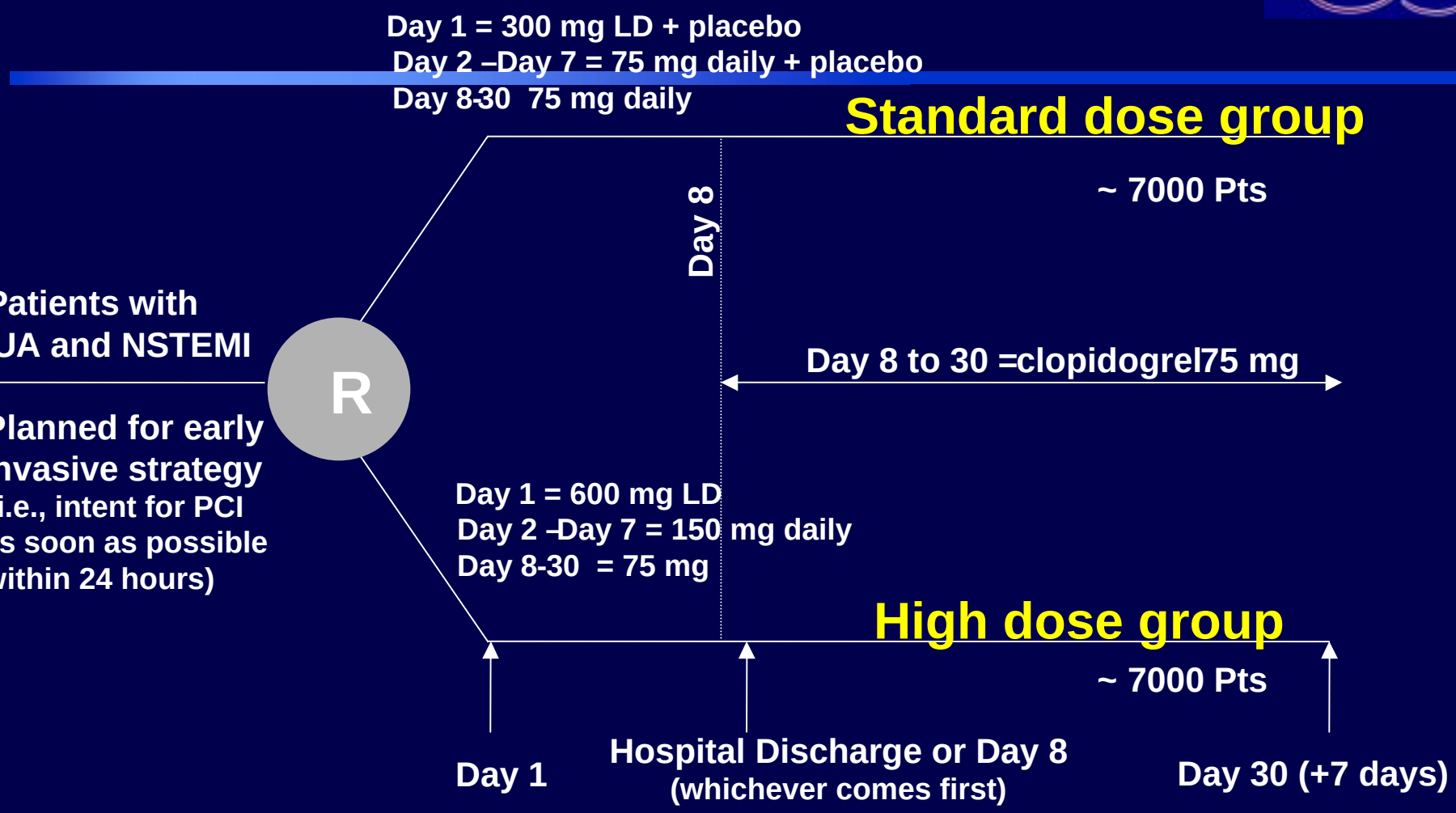
……. e se utilizzo Clopidogrel ad alte dosi (600 / 150 mg) aumento IPA senza incrementare il rischio emorragico ?

Comparison with Higher Dose Clopidogrel

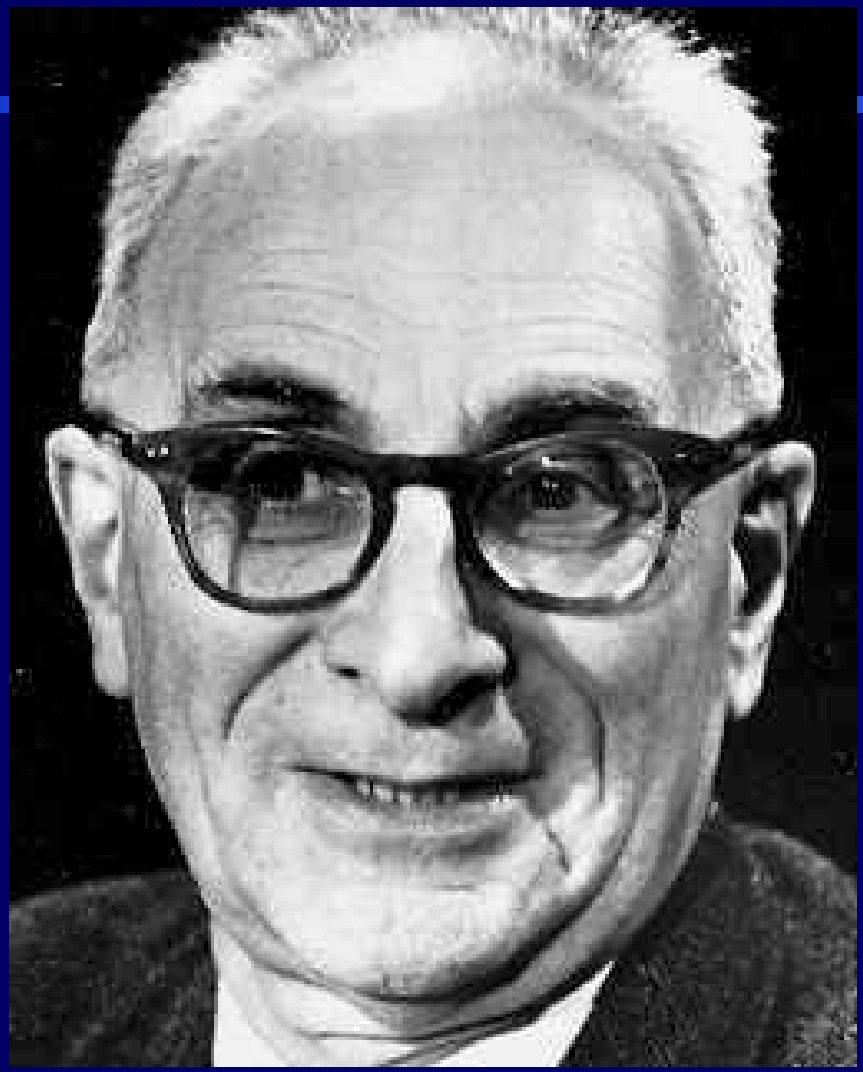




CURRENT Study Flow Chart



All patients randomized to ASA low dose (75-100 mg o.d) or high dose (300-325 mg o.d)



Claude Levi Strauss

Scienziato non é colui che sa dare le vere Risposte, ma colui che sa porre le giuste Domande