Torino

15 ottobre 2009

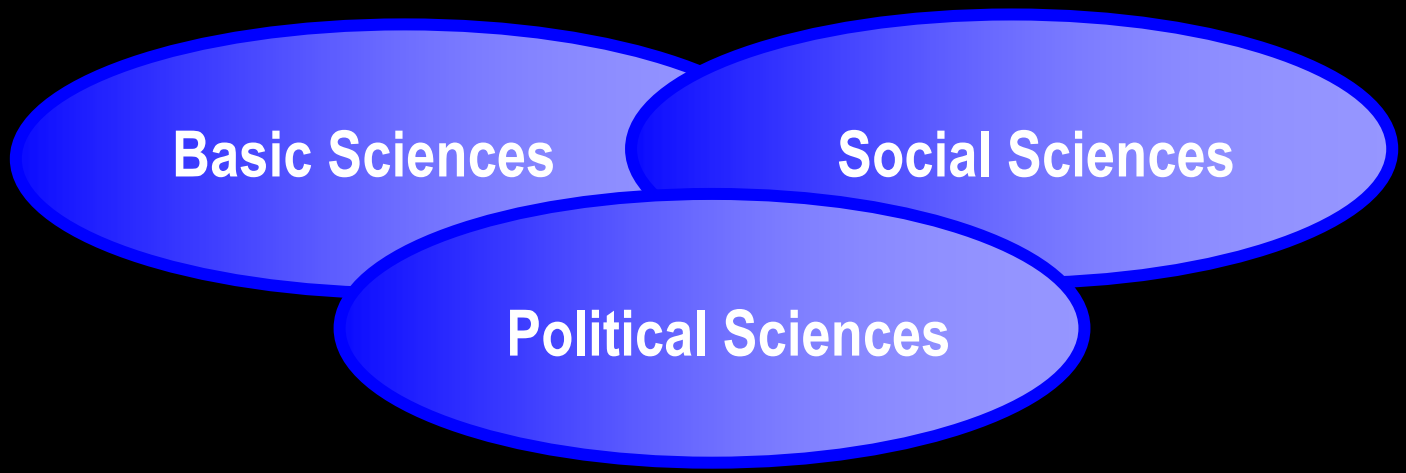
GREAT INNOVATIONS IN CARDIOLOGY

From bench to bedside: should the clinical cardiologist listen more attentively to the basic scientist?

Diego Ardissino

Parma

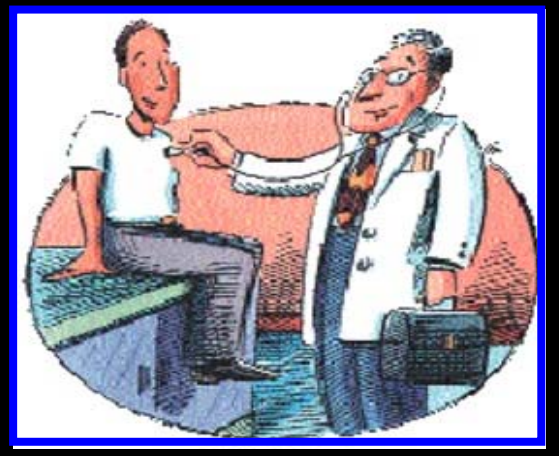
Translational Medicine



Optimization patients care and preventive measures

Translational research

A two-way road



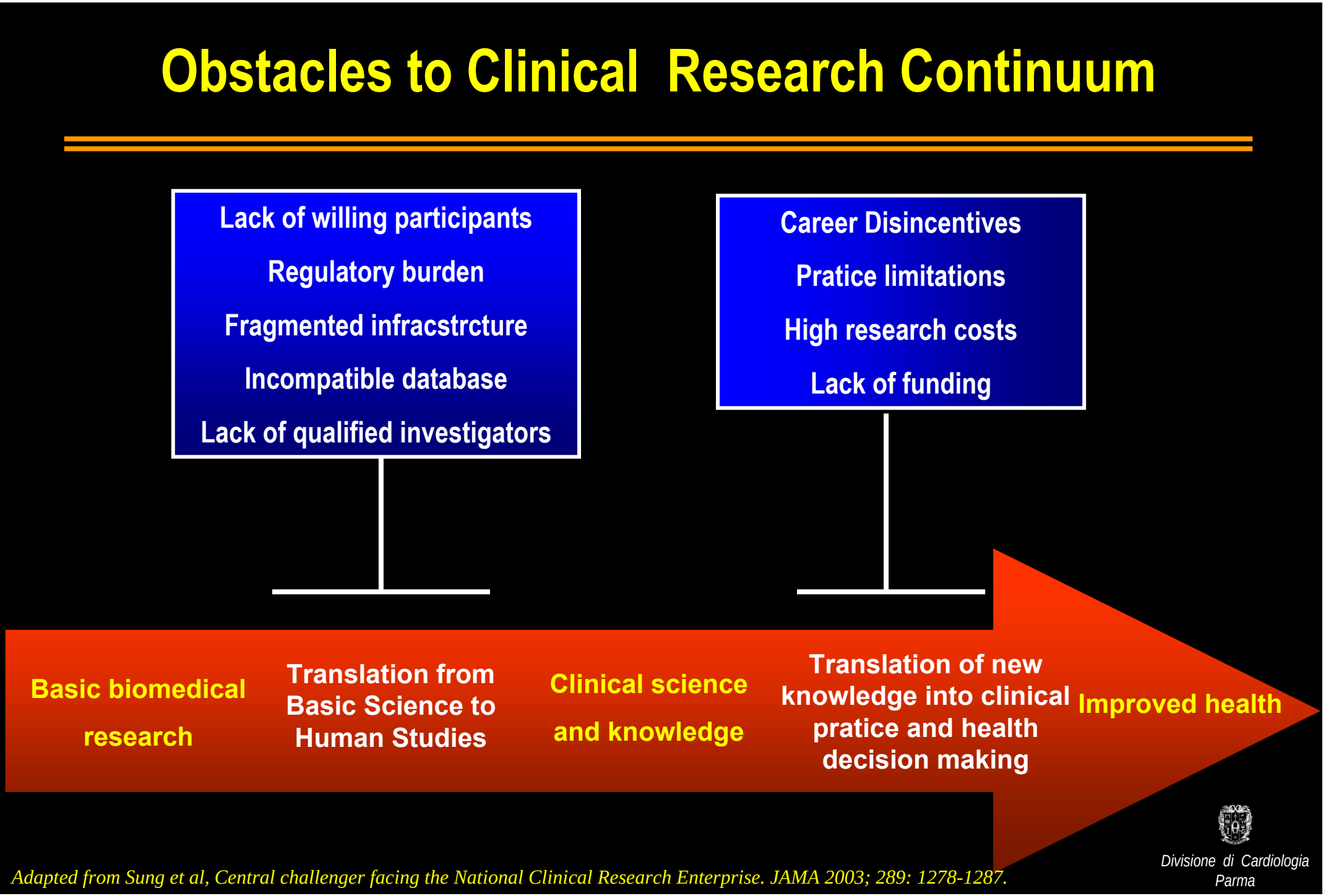
Basic

biomedical research

Clinical science

and knowledge

Obstacles to Clinical Research Continuum

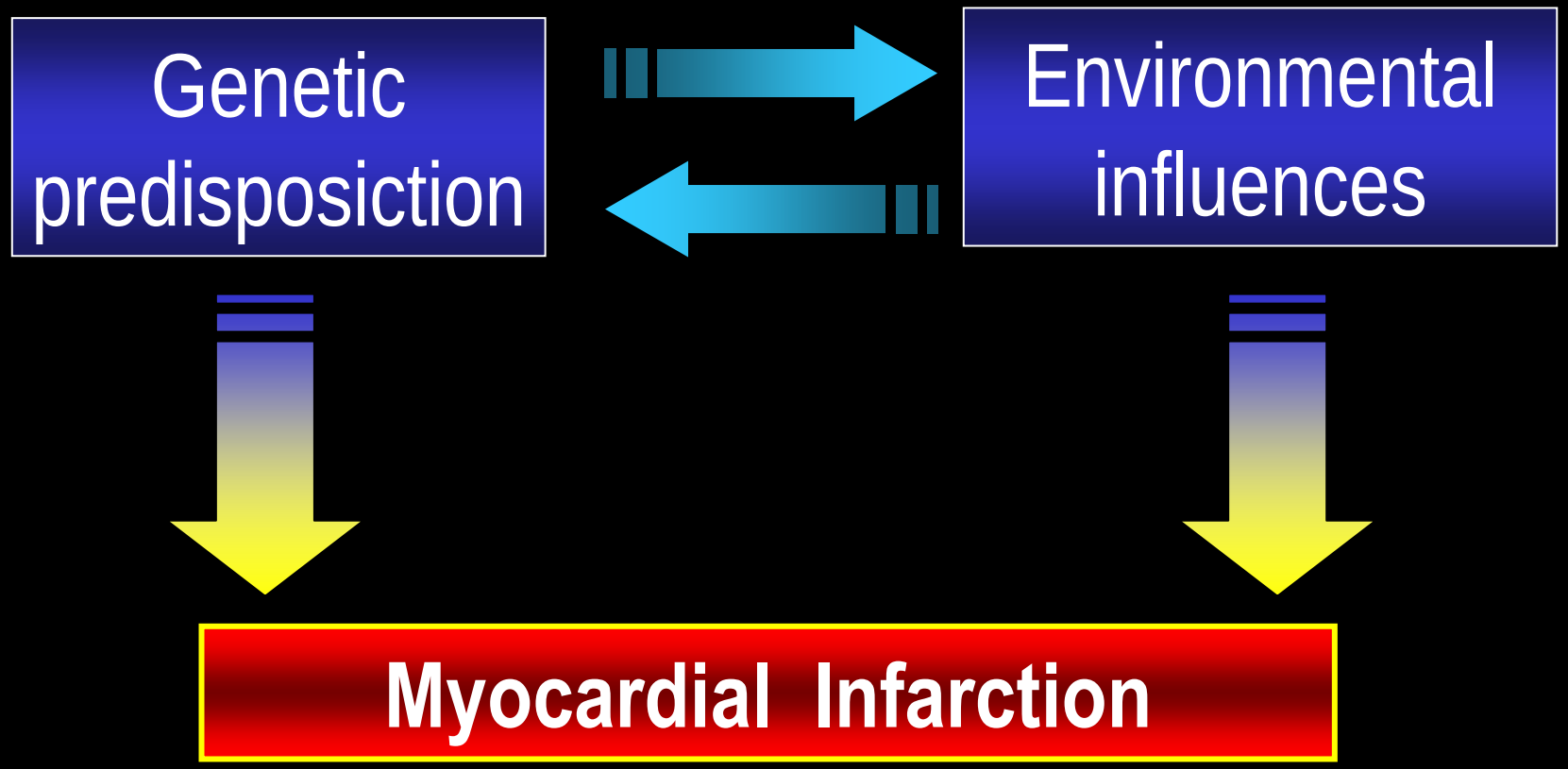


Adapted from Sung et al, Central challenger facing the National Clinical Research Enterprise. JAMA 2003; 289: 1278-1287.

Bench-to-Bedside Model to Speed Translational Research

JAMA 2006;295(13):1506-7

Individual Risk



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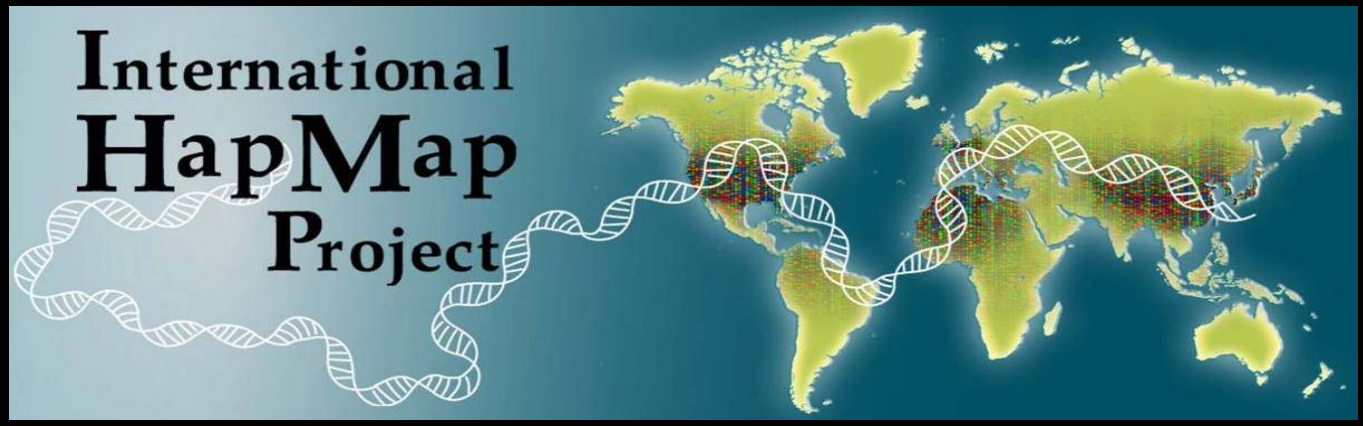
HapMap



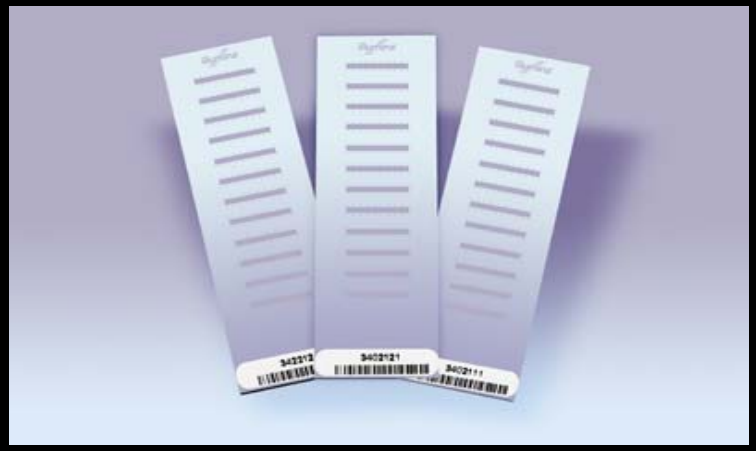
270 samples

Four population groups (CEU, CHB, JPT, YRI)

Successfully genotyped >3,300,000 SNPs

Correlation structure (linkage disequilibrium [LD]) among SNPs

Whole-genome genotyping platforms



Illumina

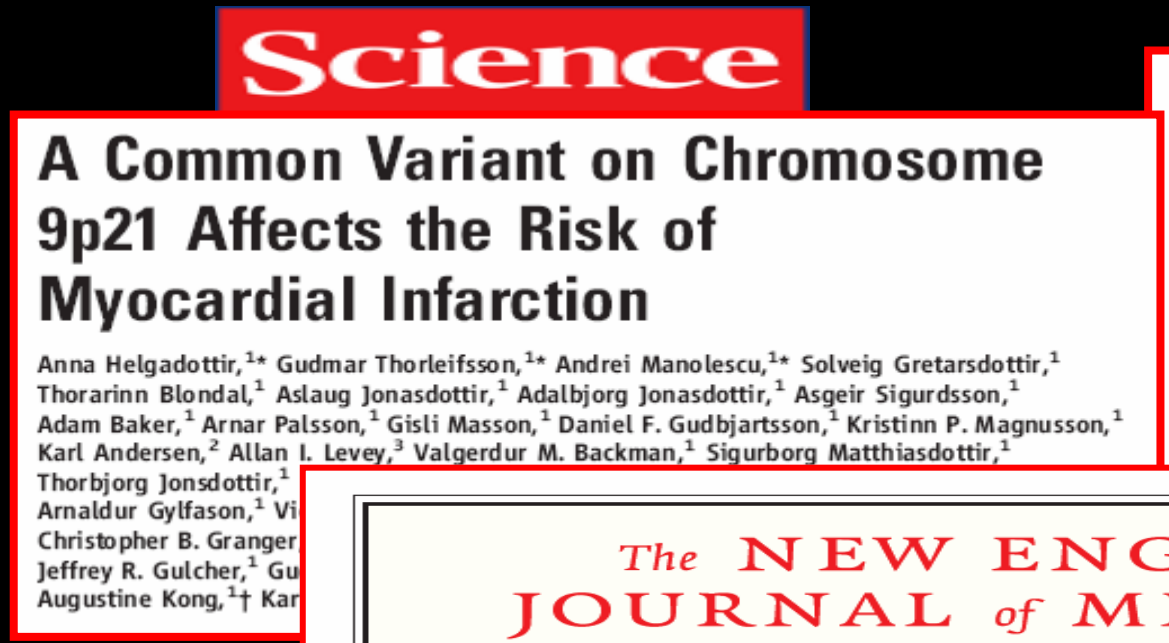
317,000 SNPs

Affymetrix

1,000,000 SNPs

Genome wide association study

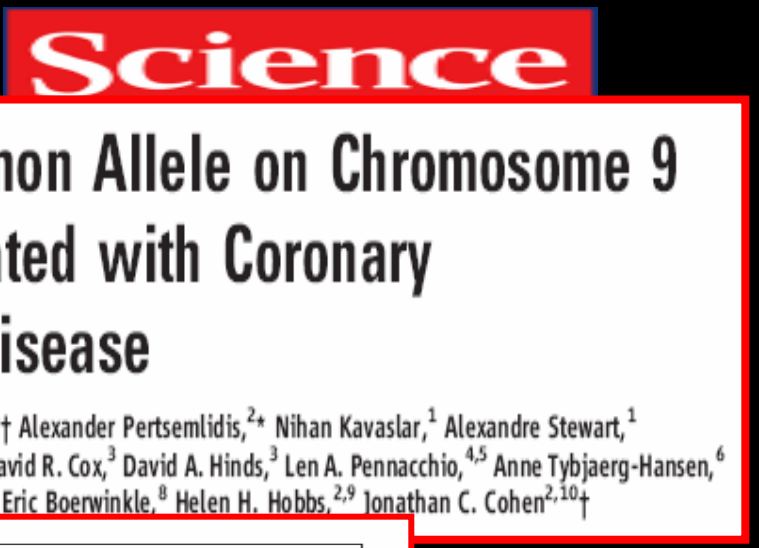
Chr 9 genetic variants and risk of MI



Science

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

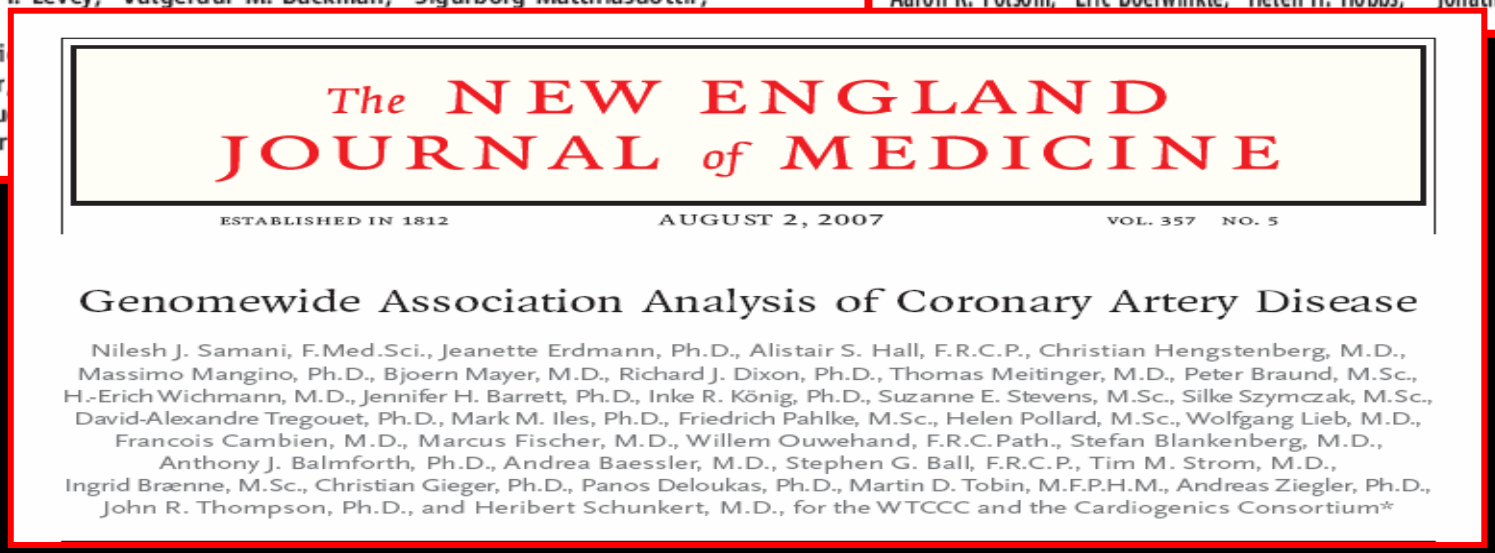
Anna Helgadottir,[1*] Gudmar Thorleifsson,[1*] Andrei Manolescu,[1*] Solveig Gretarsdottir,[1] Thorarinn Blondal,[1] Aslaug Jonasdottir,[1] Adalbjorg Jonasdottir,[1] Asgeir Sigurdsson,[1] Adam Baker,[1] Arnar Palsson,[1] Gisli Masson,[1] Daniel F. Gudbjartsson,[1] Kristinn P. Magnusson,[1] Karl Andersen,[2] Allan I. Levey,[3] Valgerdur M. Backman,[1] Sigurborg Matthiasdottir,[1] Thorbjorg Jonsdottir,[1] Arnaldur Gylfason,[1] Vi
Christopher B. Granger
Jeffrey R. Gulcher,[1] Gu
Augustine Kong,[1†] Kar



Science

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,[1*†] Alexander Pertsemlidis,[2*] Nihan Kavaslar,[1] Alexandre Stewart,[1] Robert Roberts,[1] David R. Cox,[3] David A. Hinds,[3] Len A. Pennacchio,[4,5] Anne Tybjaerg-Hansen,[6] Aaron R. Folsom,[7] Eric Boerwinkle,[8] Helen H. Hobbs,[2,9] Jonathan C. Cohen[2,10†]



The NEW ENGLAND JOURNAL of MEDICINE

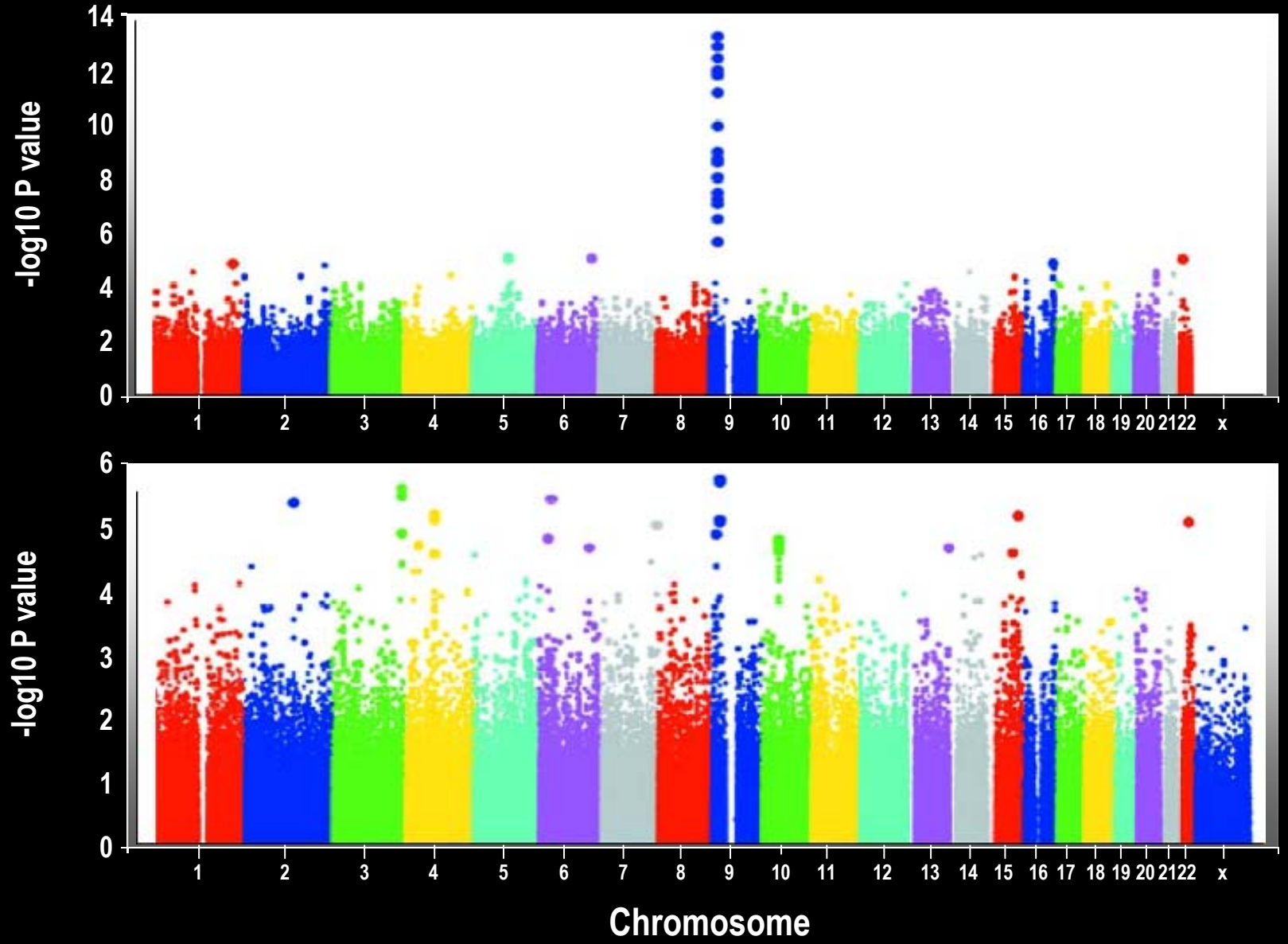
ESTABLISHED IN 1812 AUGUST 2, 2007 VOL. 357 NO. 5

Genomewide Association Analysis of Coronary Artery Disease

Nilesh J. Samani, F.Med.Sci., Jeanette Erdmann, Ph.D., Alistair S. Hall, F.R.C.P., Christian Hengstenberg, M.D., Massimo Mangino, Ph.D., Bjoern Mayer, M.D., Richard J. Dixon, Ph.D., Thomas Meitinger, M.D., Peter Braund, M.Sc., H.-Erich Wichmann, M.D., Jennifer H. Barrett, Ph.D., Inke R. König, Ph.D., Suzanne E. Stevens, M.Sc., Silke Szymczak, M.Sc., David-Alexandre Tregouet, Ph.D., Mark M. Iles, Ph.D., Friedrich Pahlke, M.Sc., Helen Pollard, M.Sc., Wolfgang Lieb, M.D., Francois Cambien, M.D., Marcus Fischer, M.D., Willem Ouwehand, F.R.C.Path., Stefan Blankenberg, M.D., Anthony J. Balmforth, Ph.D., Andrea Baessler, M.D., Stephen G. Ball, F.R.C.P., Tim M. Strom, M.D., Ingrid Brænne, M.Sc., Christian Gieger, Ph.D., Panos Deloukas, Ph.D., Martin D. Tobin, M.F.P.H.M., Andreas Ziegler, Ph.D., John R. Thompson, Ph.D., and Heribert Schunkert, M.D., for the WTCCC and the Cardiogenics Consortium*

Genome wide association study

Chr 9 genetic variants and risk of MI

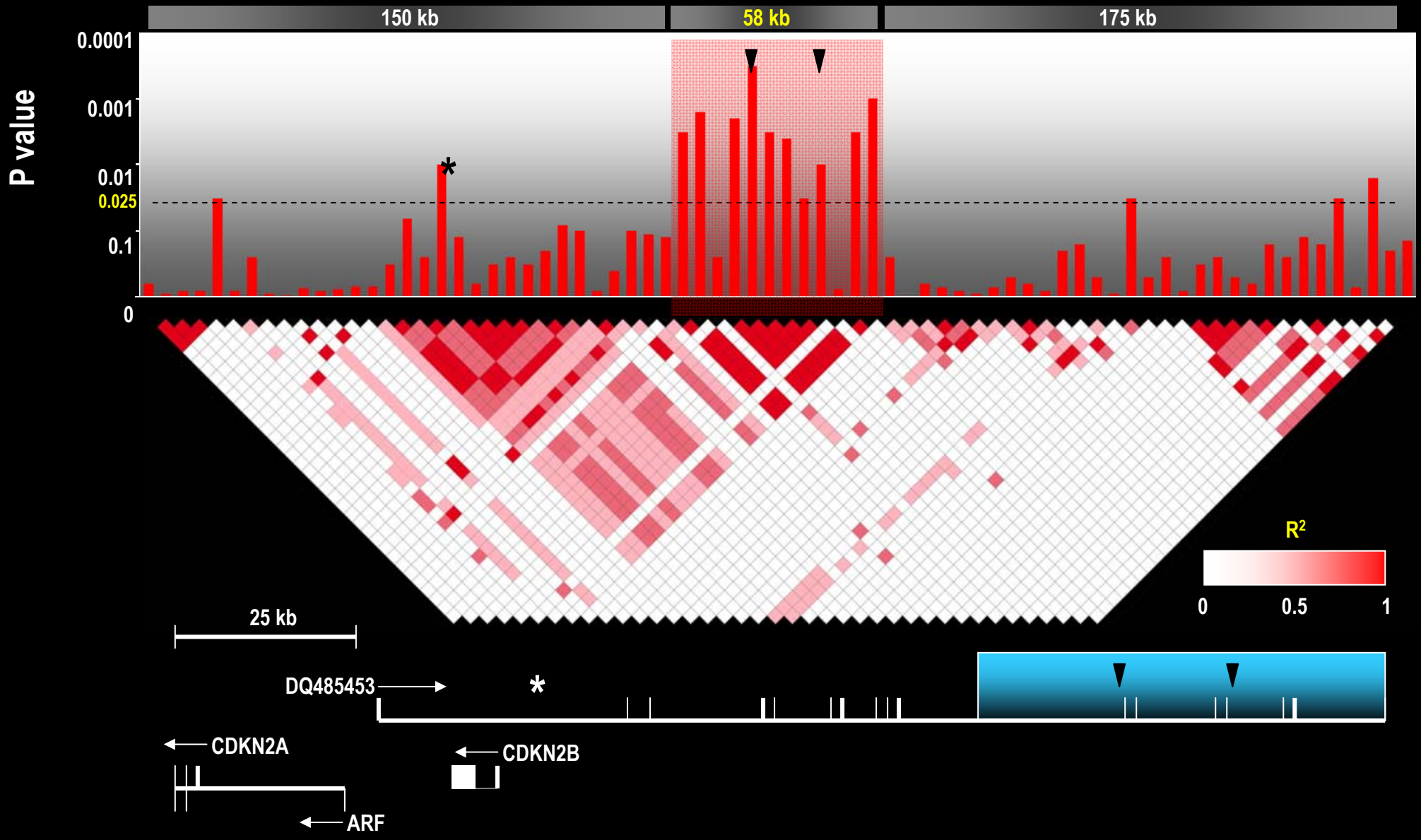


A
WTCCC study

B
German MI Family study

Samani N J et al. N Engl J Med 2007; 357:443-53

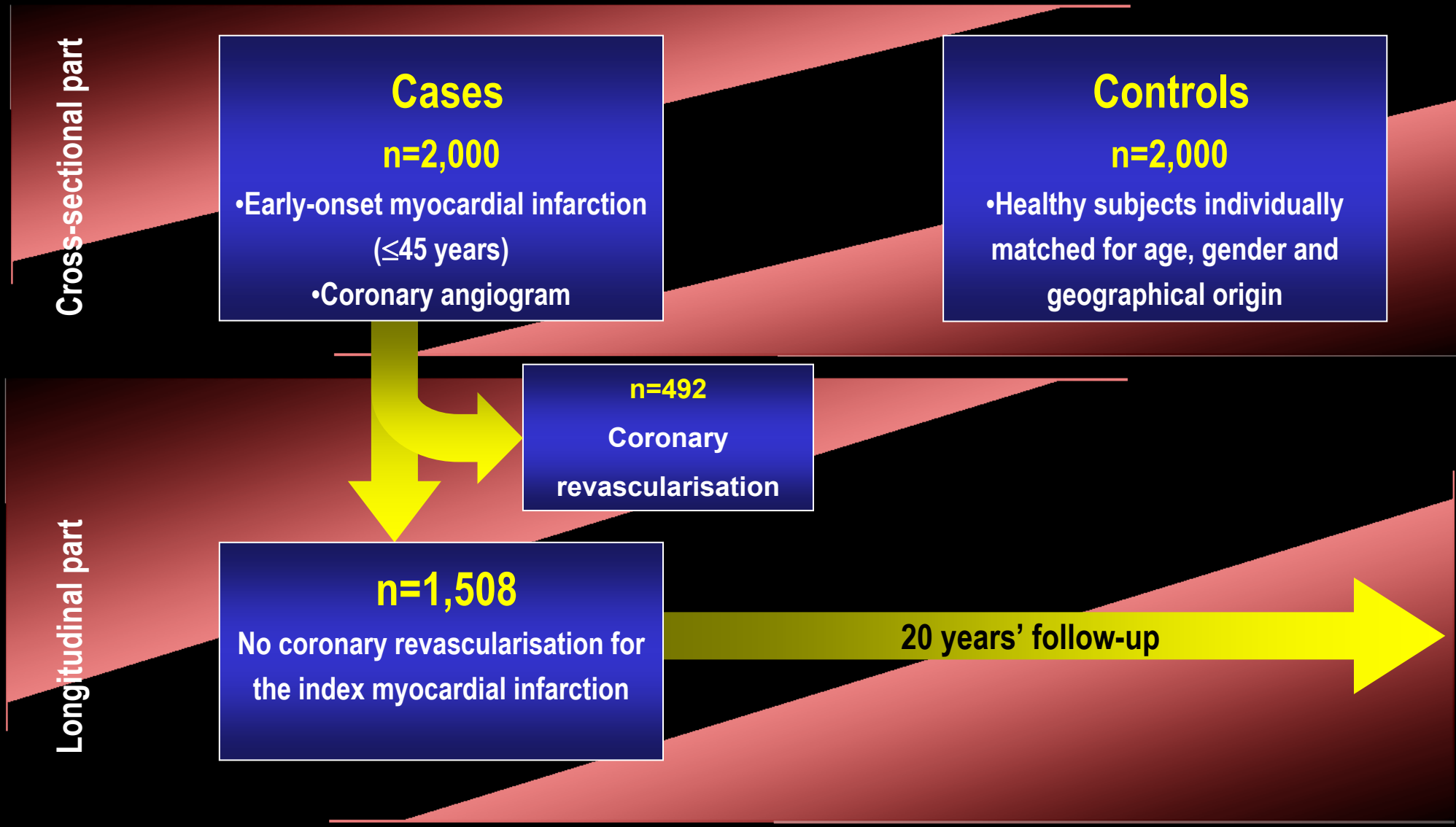
9p21.3 genetic variants in early-onset myocardial infarction *Background*



McPherson R. et al. Science 2007; 316: 1488-9

Italian Genetic Study in Early-Onset Myocardial Infarction

Study population



9p21.3 genetic variants in early-onset myocardial infarction

Multivariate analysis

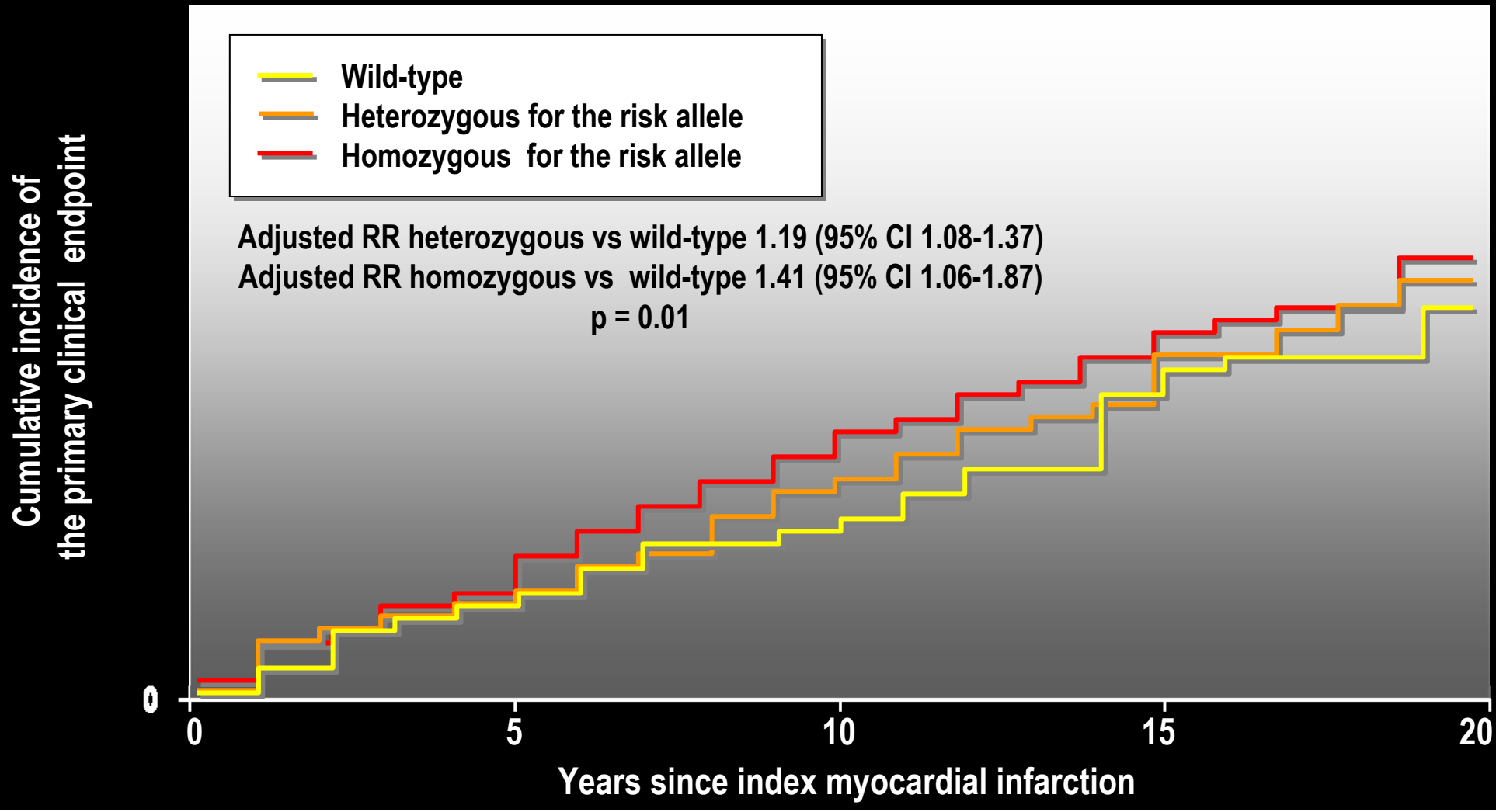
1,508 patients with early-onset myocardial infarction

Explanatory variable	Odds Ratio	95% Confidence Interval	*p* value
Diabetes Mellitus (Yes/No)	7.45	3.39-16.37	0.00000005
Smoking (Yes or former/No)	6.62	5.08-8.63	$1e^{-54}$
Hypertension (Yes/No)	3.36	2.46-4.62	0.000000000000006
rs1333040 (per allele)	1.43	1.22-1.66	0.0000093
Body mass index (pre-obese or obese/ normal)	1.55	1.33-1.82	0.000000021
Hypercholesterolemia (Yes/No)	1.38	1.12-1.69	0.0025

9p21.3 genetic variants in early-onset myocardial infarction

Primary clinical endpoint

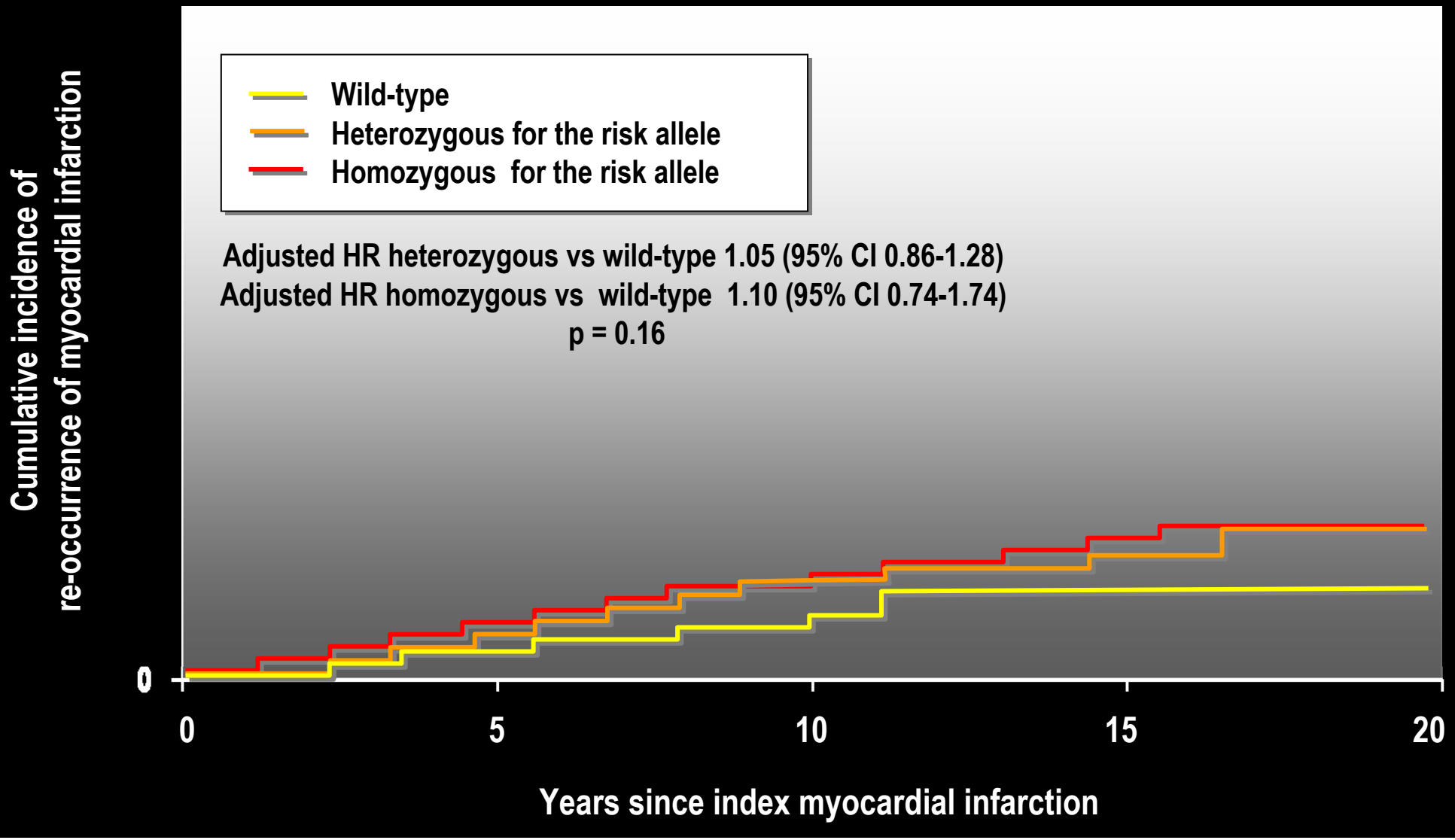
rs1333040



9p21.3 genetic variants in early-onset myocardial infarction

Reoccurrence of myocardial infarction

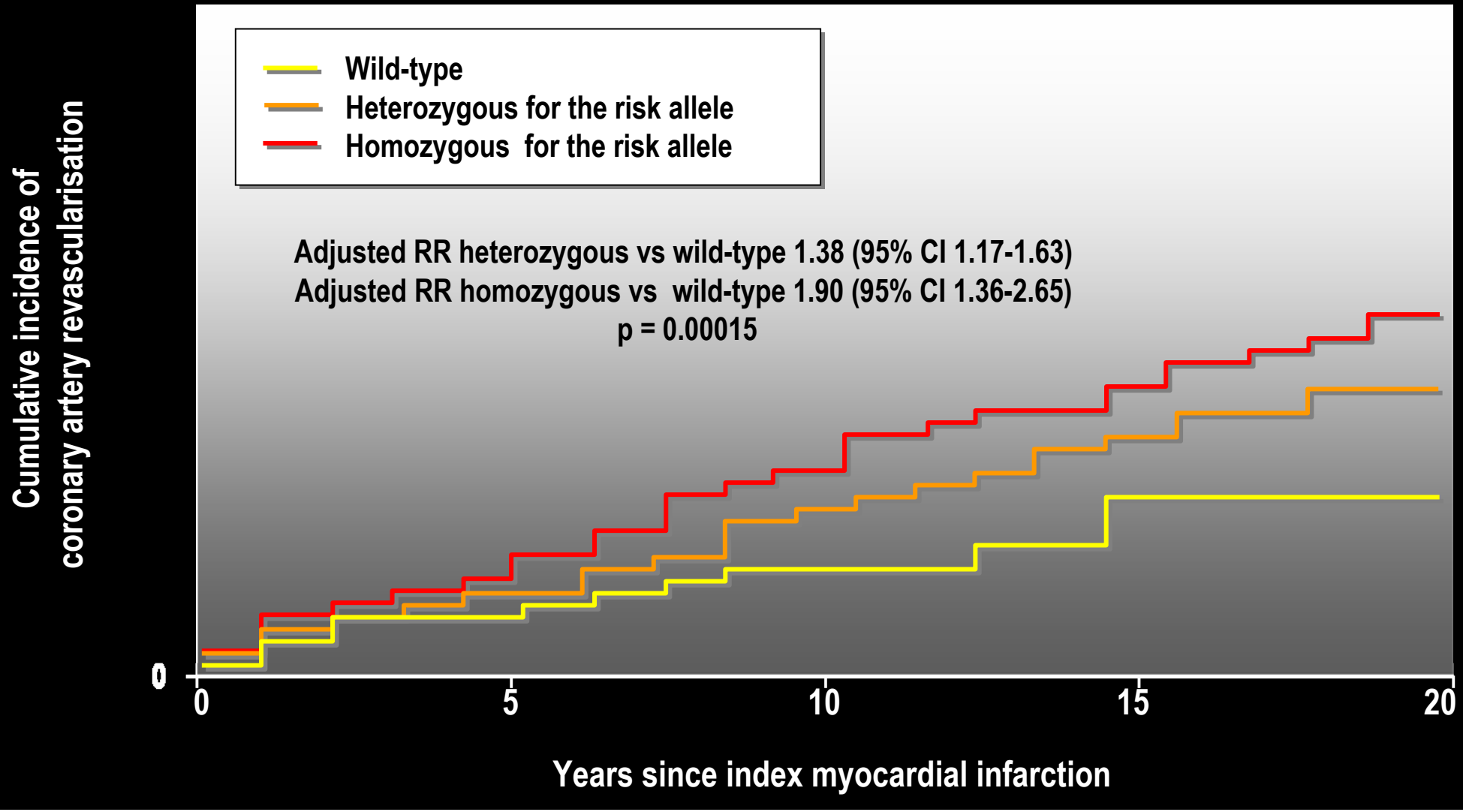
rs1333040



9p21.3 genetic variants in early-onset myocardial infarction

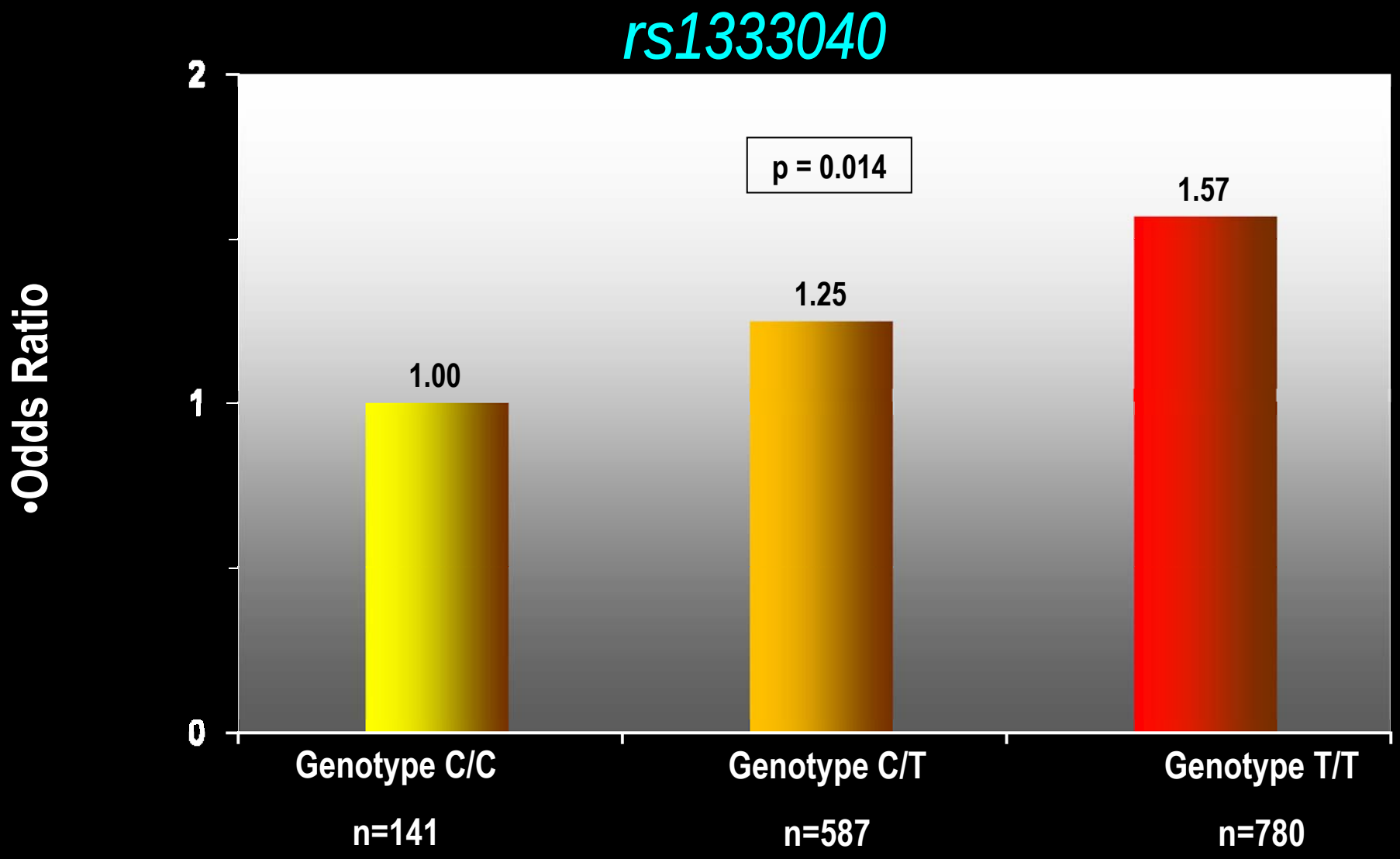
Coronary artery revascularisation

rs1333040



9p21.3 genetic variants in early-onset myocardial infarction

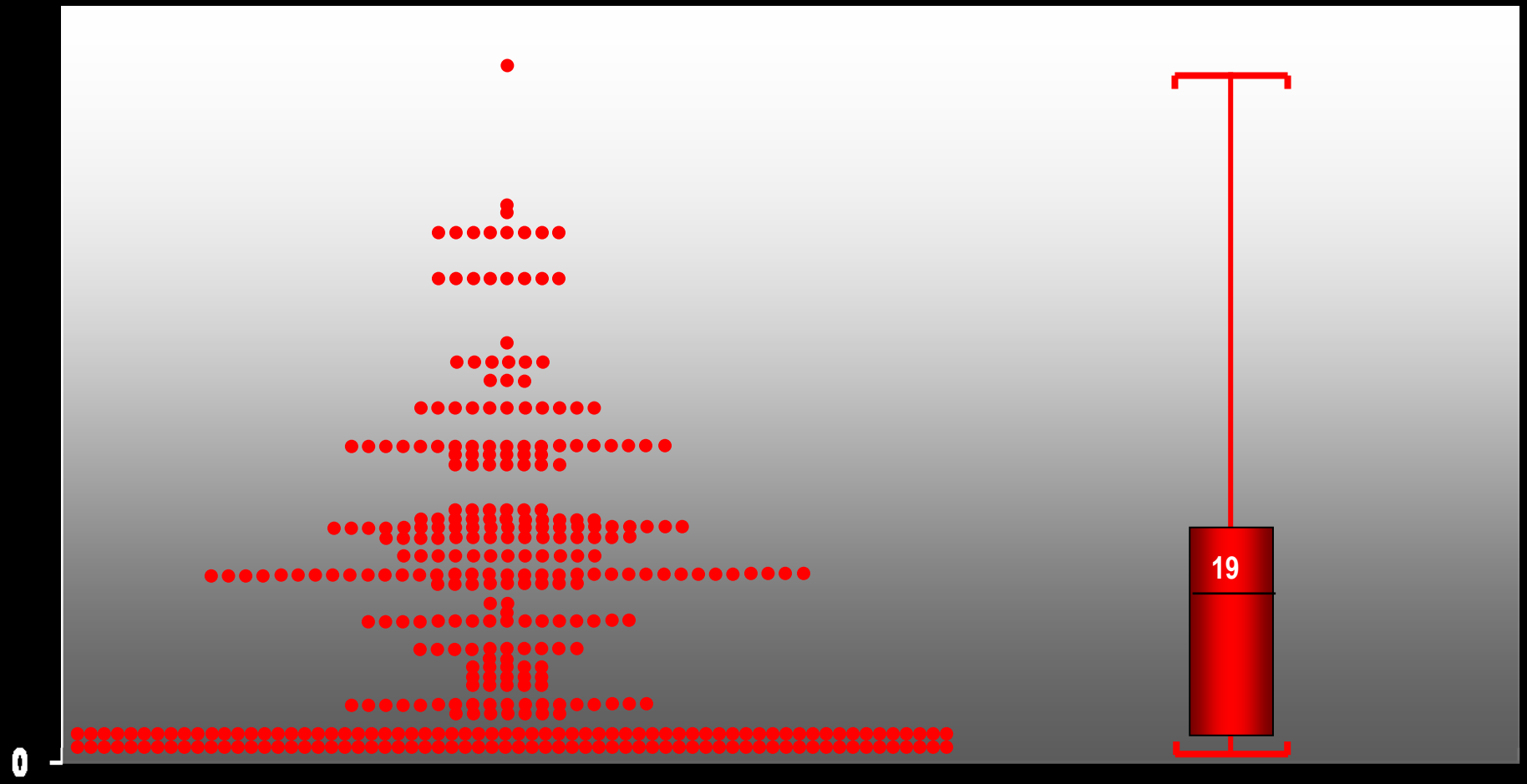
Significant coronary artery disease



9p21.3 genetic variants in early-onset myocardial infarction

Definition of angiographic endpoint

405 patients underwent at least one repeat coronary angiography

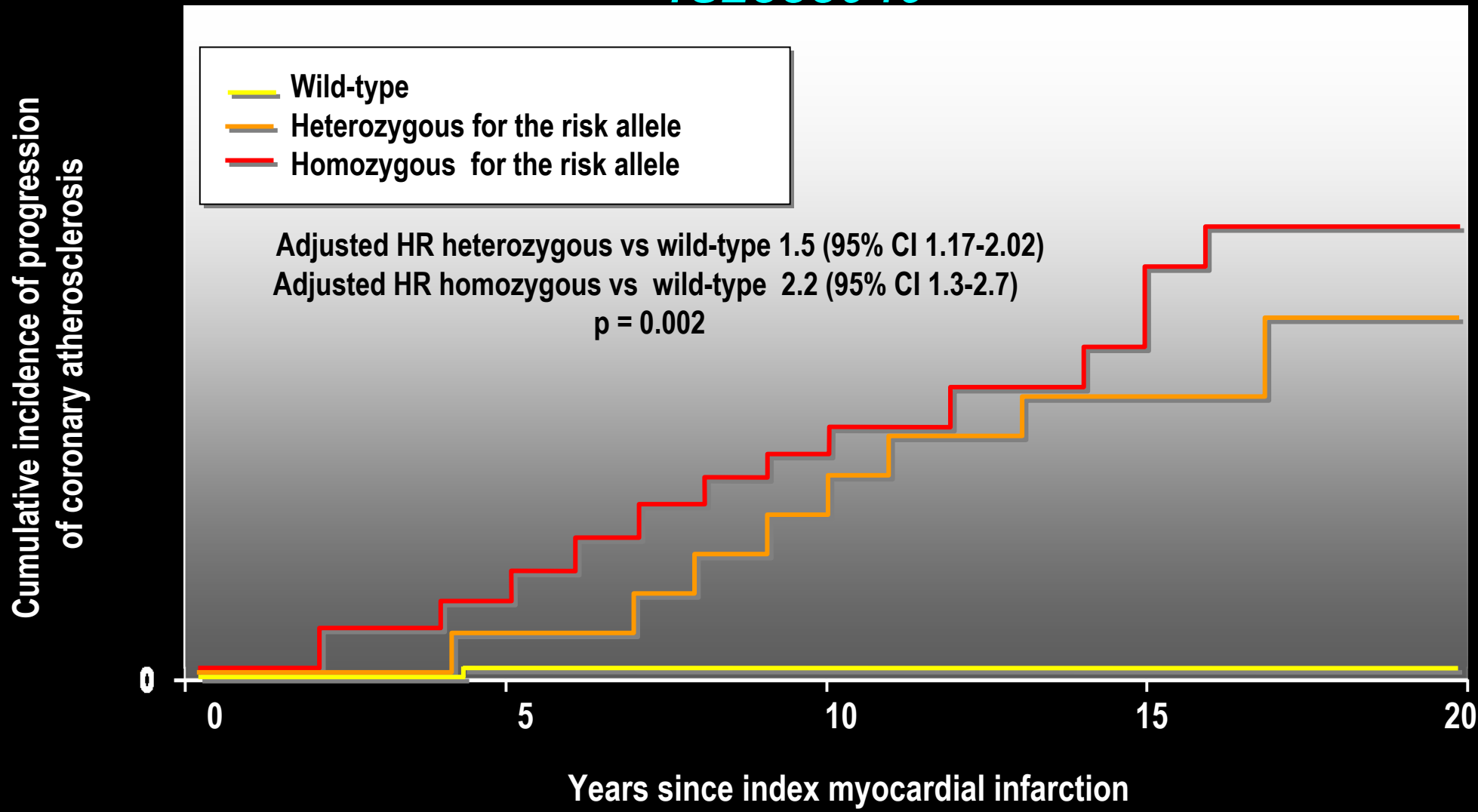


Angiographic progression of coronary atherosclerosis was defined as changes in the Duke Coronary Artery Disease Index greater than the median change in the sample

9p21.3 genetic variants in early-onset myocardial infarction

Angiographic endpoint

rs1333040



Genome-wide association study of early-onset myocardial infarction

The MIGen Consortium

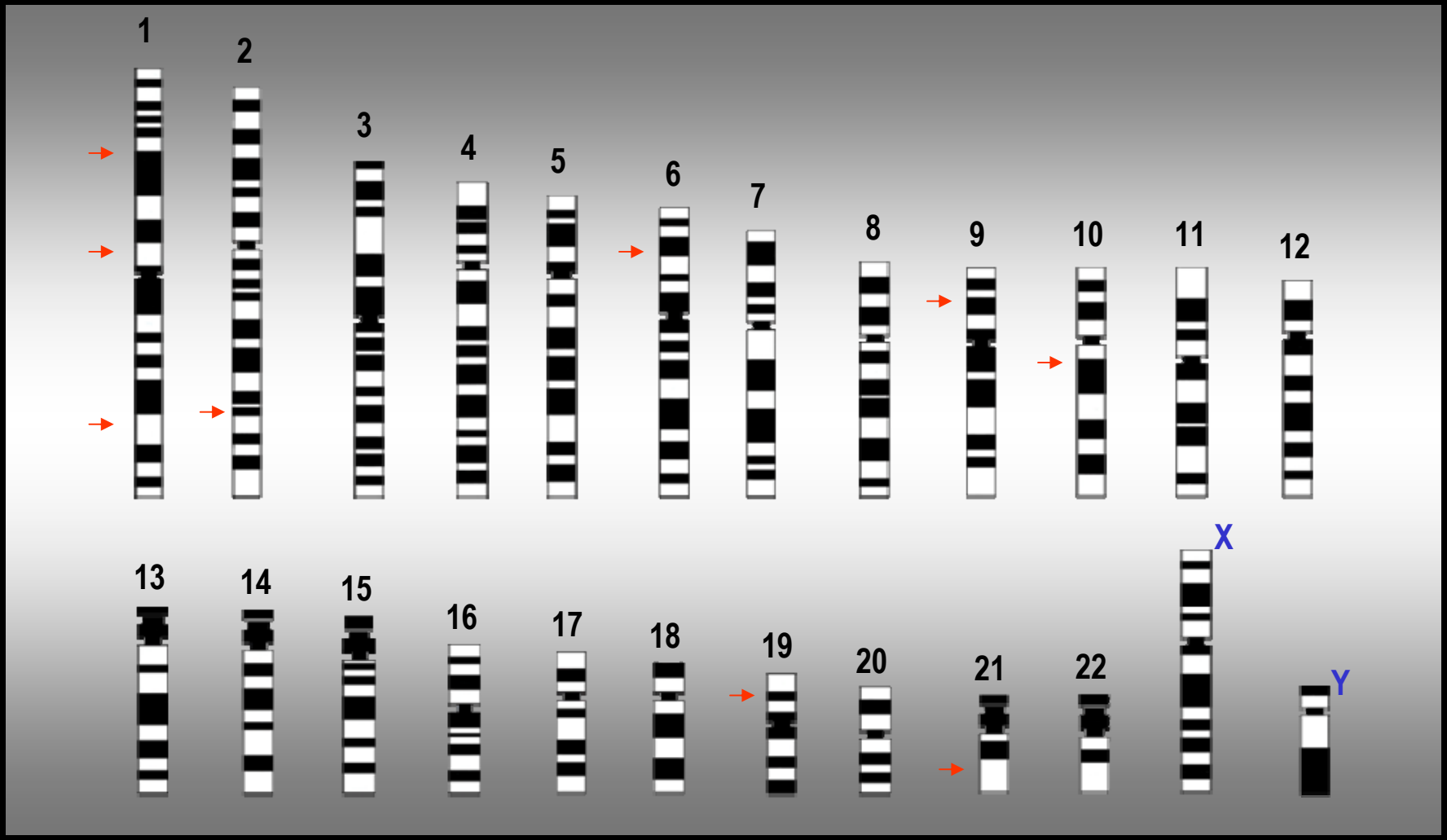
SNPs	Chromosome	OR (95% CI)	*p* value
rs6725887	2q33	1.17 (1.11-1.23)	1.3×10^{-8}
rs12526453	6p24	1.12 (1.08-1.17)	1.3×10^{-9}
rs9982601	21q22	1.20 (1.14-1.27)	6.4×10^{-11}
rs1122608	19p13	1.15 (1.10-1.20)	1.9×10^{-9}
rs11206510	1p32	1.15 (1.10-1.21)	9.6×10^{-9}
rs1746048	10q11	1.17 (1.11-1.24)	7.4×10^{-9}
rs17465637	1q41	1.14 (1.10-1.19)	1.4×10^{-9}
rs4977574	9p21	1.29 (1.25-1.34)	2.7×10^{-44}
rs646776	1p13	1.19 (1.13-1.26)	7.9×10^{-12}

MIGen Consortium, Nat Genet 2009; 41: 334-41

Chromosomal location of coronary artery disease genes

Data from the MIGEN consortium

Ideogram of human karyotype.
Human loci associated withearly ontset myocardial infarction identified by Migen Genome Wide Association Study



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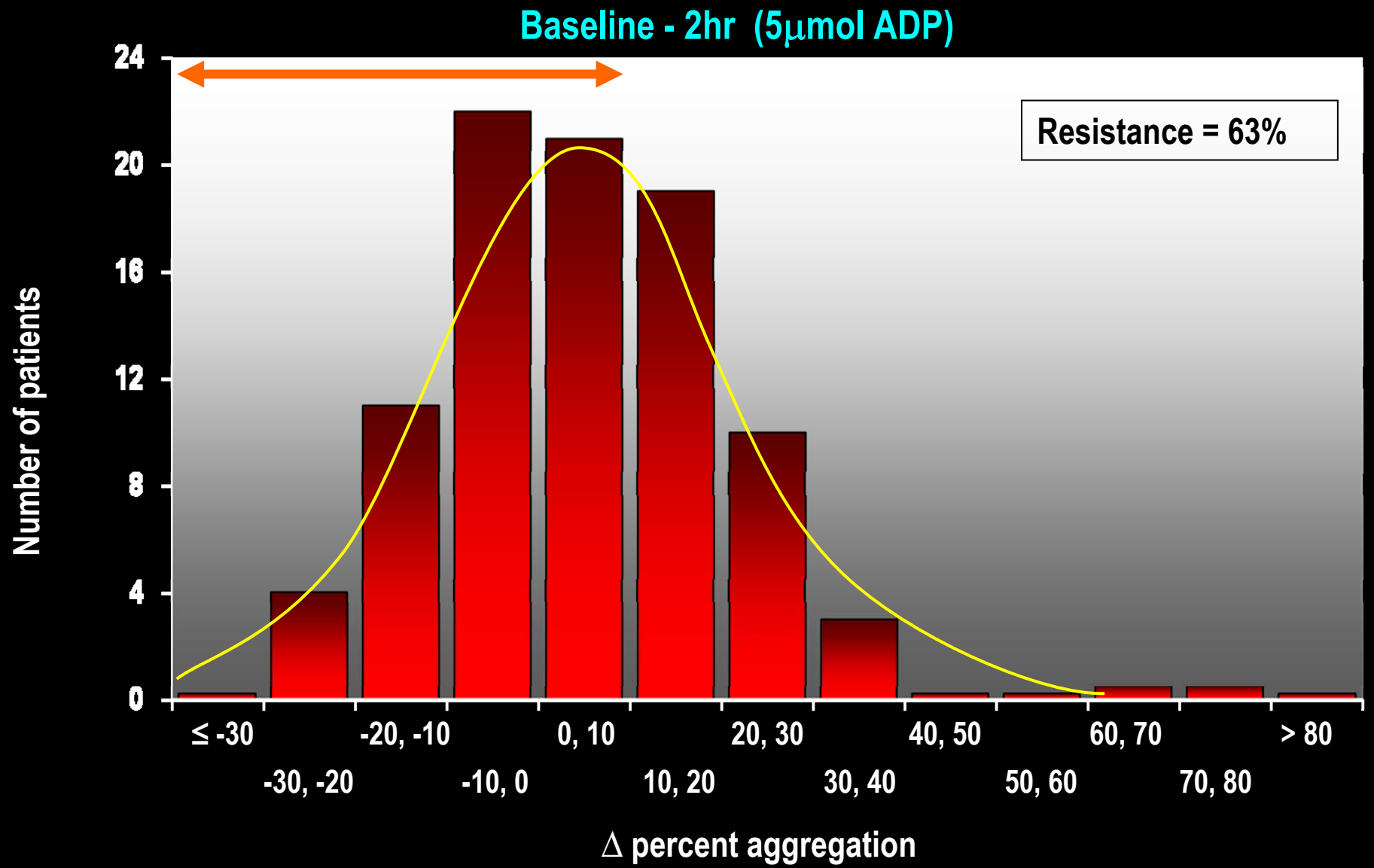
Bench-to-Bedside Model to Speed Translational Research

JAMA 2006;295(13):1506-7


nature
REVIEWS
DRUG DISCOVERY

Clopidogrel Response Variability



Gurbel PA et al. Circulation 2003; 107:2908

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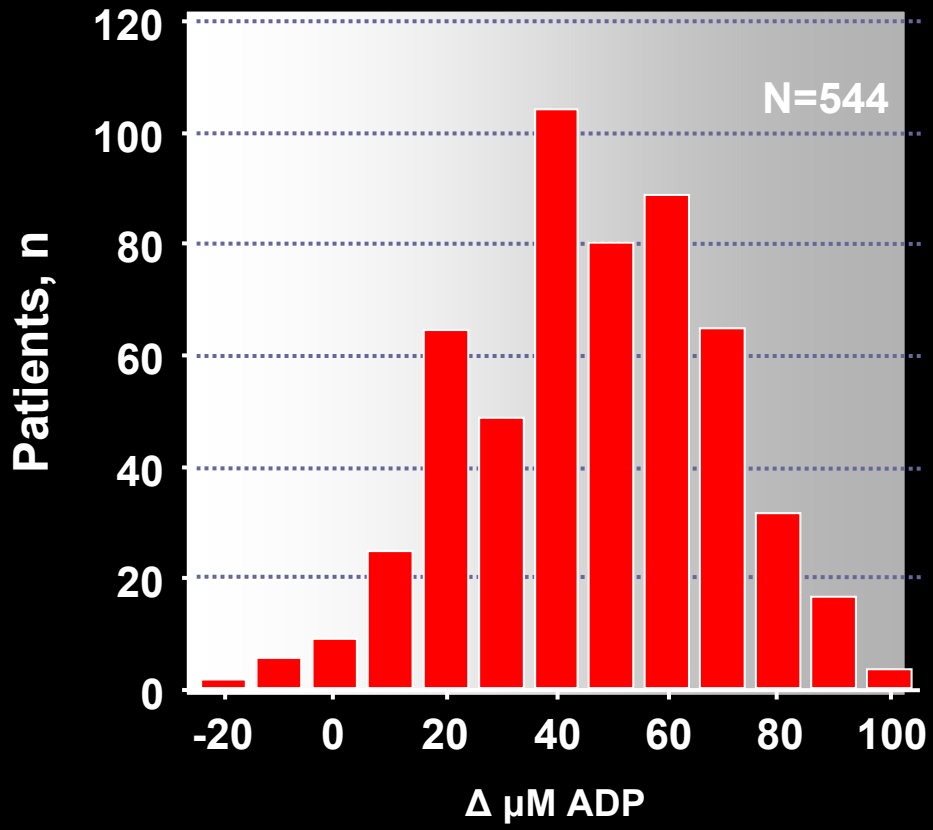
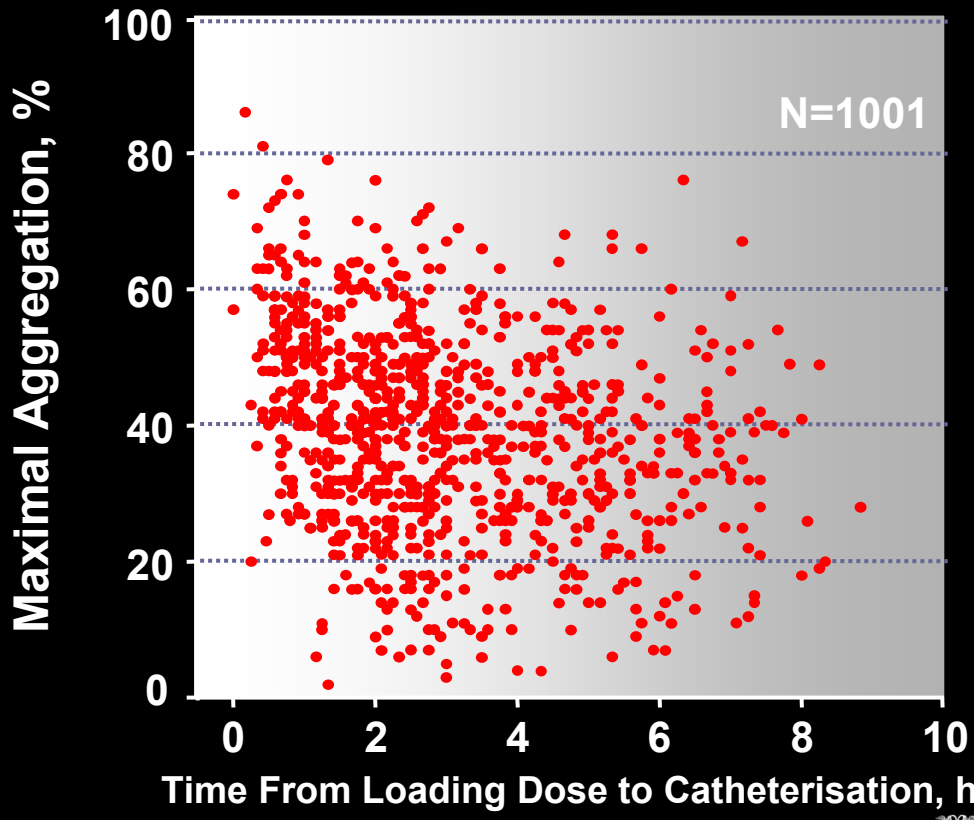
Variability in Clopidogrel response

Change in ADP-Induced Platelet Aggregation: 75 mg Chronic Dosing



Serebruany VL, et al. *J Am Coll Cardiol*. 2005;45:246-251.

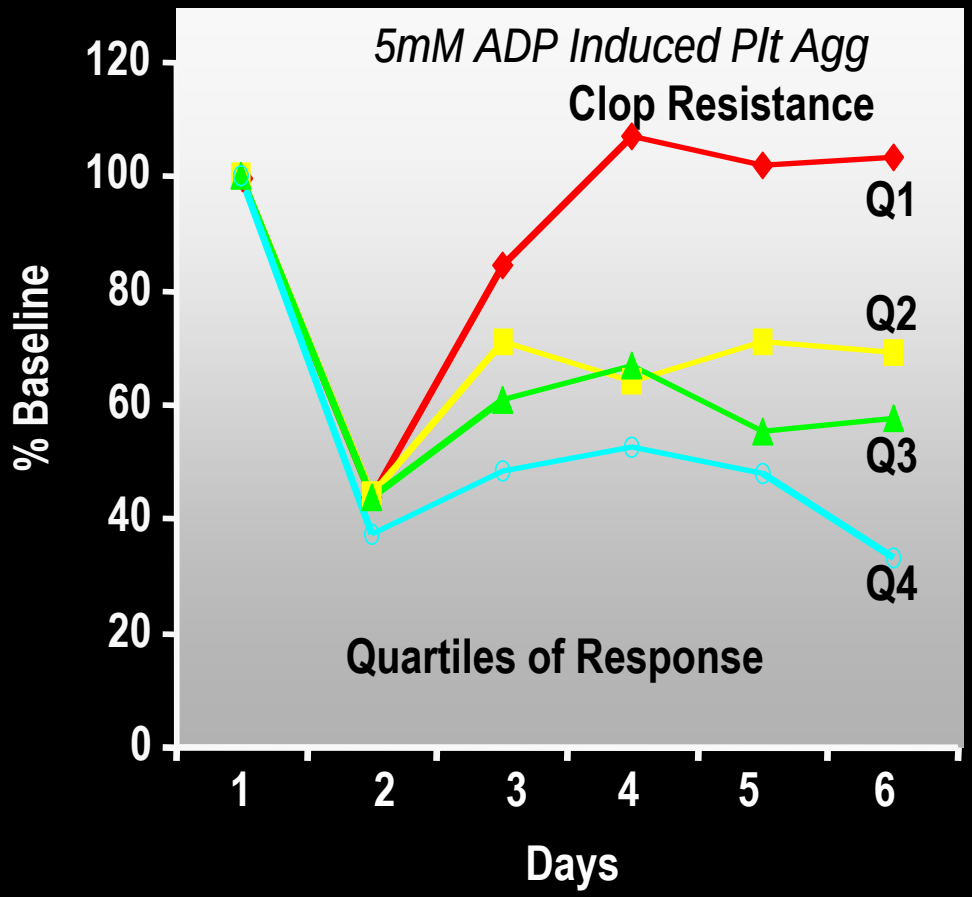
% Maximal Aggregation: 5 µmol/L ADP Following 600-mg Loading Dose

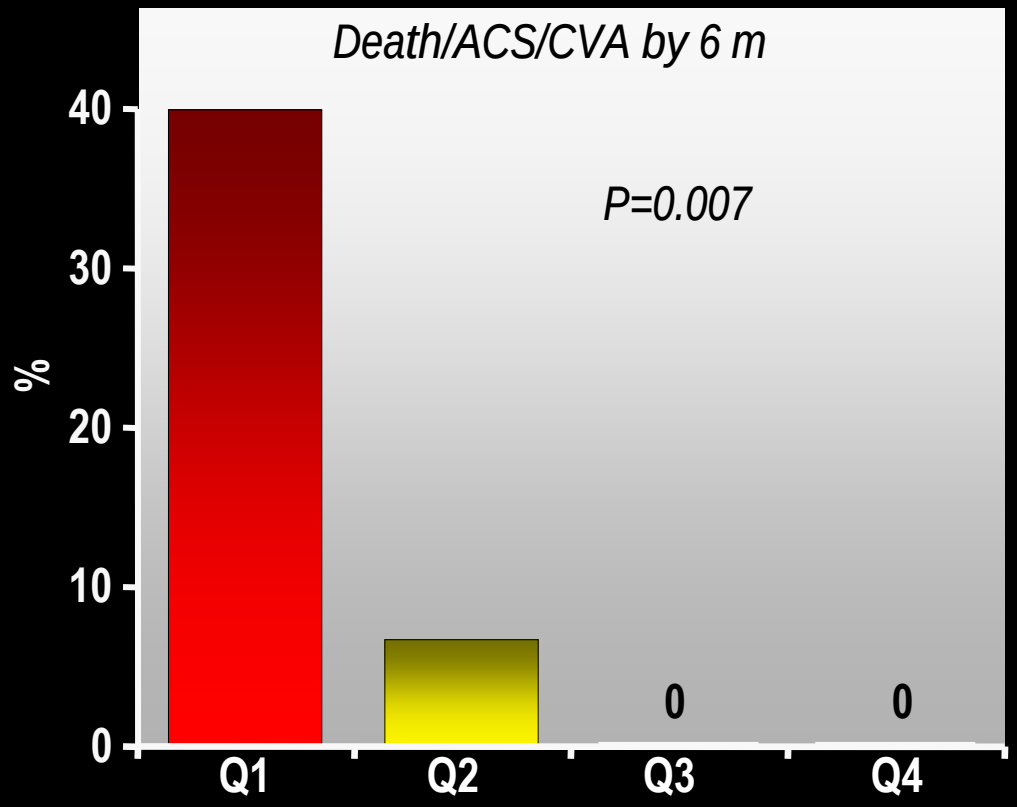


Hochholzer W, et al. *Circulation*. 2005;111:2560-2564.

Clopidogrel Resistance and Risk of Ischemic Events

N = 60 Primary PCI for STEMI





Matetzky et al. Circ 109: 3171 2004
Wiviott + Antman Circ 109: 3064,2004

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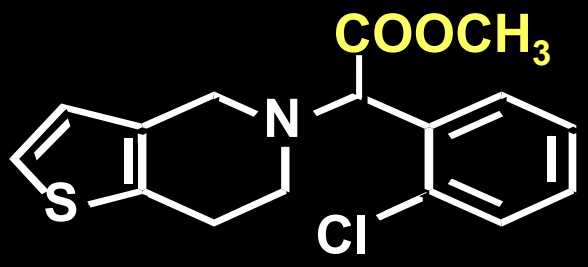
Genetic targets potentially modulating Clopidogrel induced antiplatelet effects



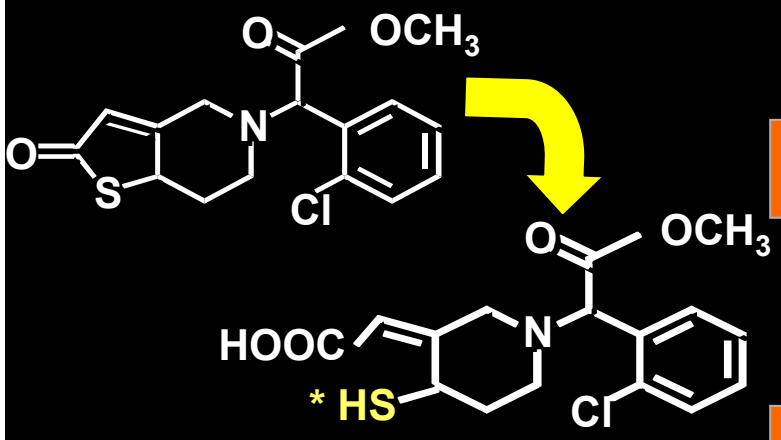
Clopidogrel

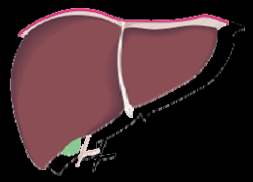
Pro-drug

Pre-hepatic metabolism

Esterases in blood (Small Intestine)

MDR-1





Hepatic Metabolism

1 step:
CYP1A2
CYP2C19
CYP2B6

2 step:
CYP3A
CYP2C9
CYP2C19
CYP2B6

Platelet inhibition

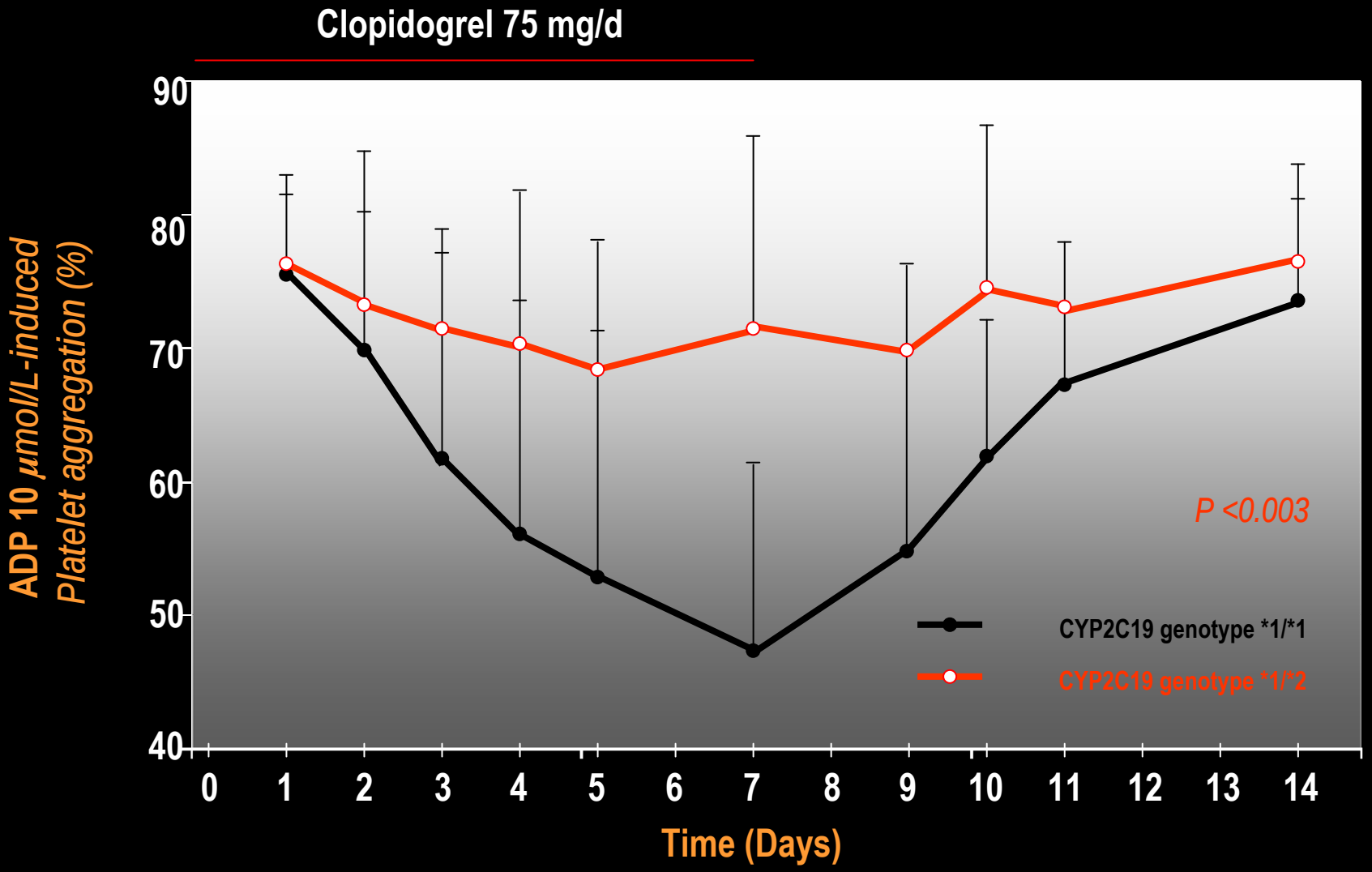
Platelet membrane receptors

P2Y12, GP IIb/IIIa, GPIa

Marin et al, JACC 2009, 54: 1041-1057

Cytochrome P450 2C 19 polymorphism

Time course of ex-vivo platelet aggregation in response to 10 μM ADP



Hulot et al. Blood 2006; 108:2244-47

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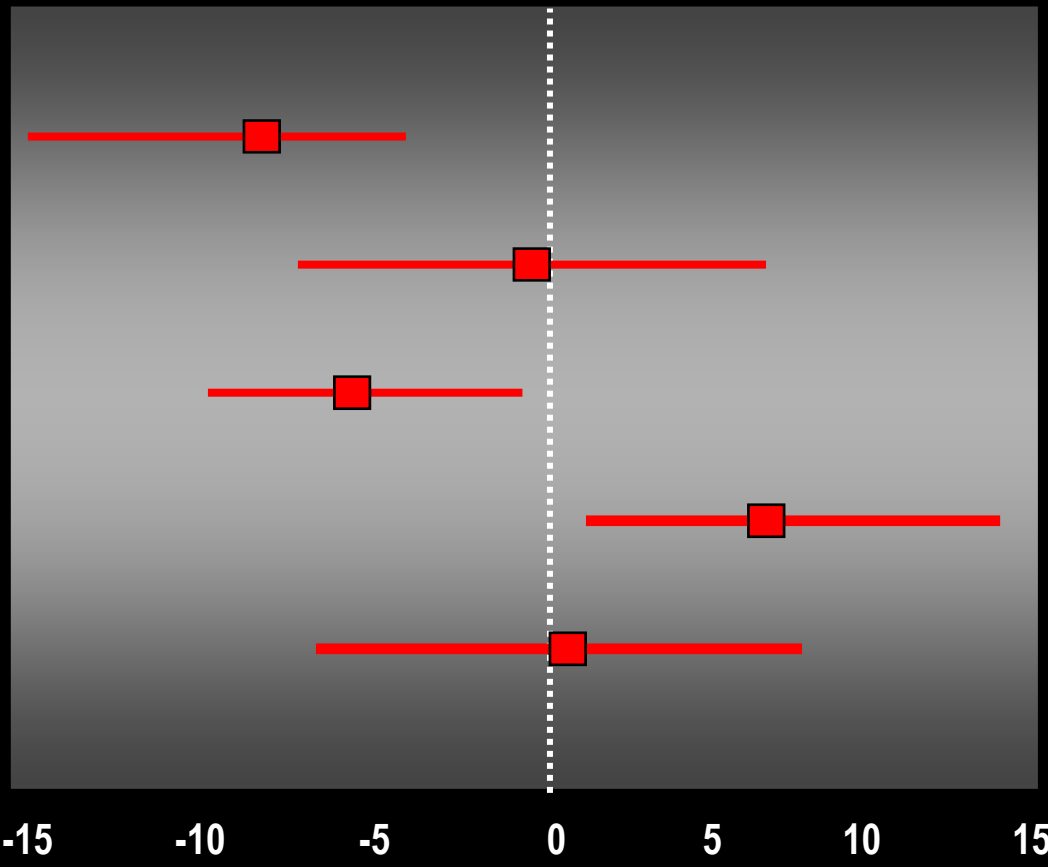
Genetic effects on pharmacodynamic responses to clopidogrel

162 healthy subjects



	Percent difference in ΔMPA	p value
CYP2C19	-9.0	<0.001
CYP2C9	-0.6	0.86
CYP2B6	-5.7	0.012
CYP3A5	7.5	0.012
CYP1A2	0.5	0.90

Mega J L et al, N Engll J Med 2009; 360: 354-62

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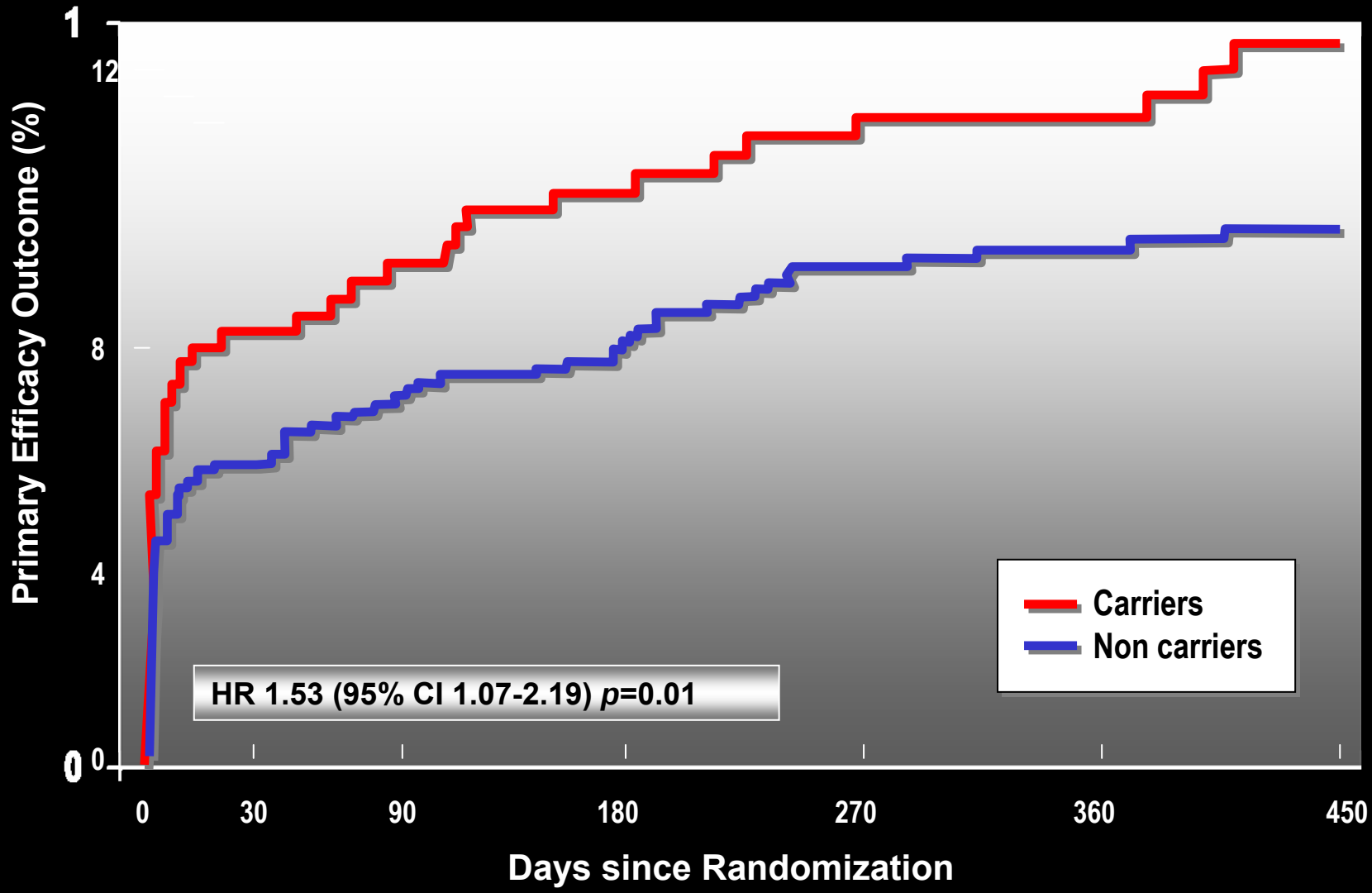
Association between CYP2C19*2 risk allele and outcome (death from CV cause, MI, or stroke) in subjects receiving clopidogrel

TRITON TIMI-38 study population (n=1477)



Mega J L et al, N Engll J Med 2009; 360: 354-62

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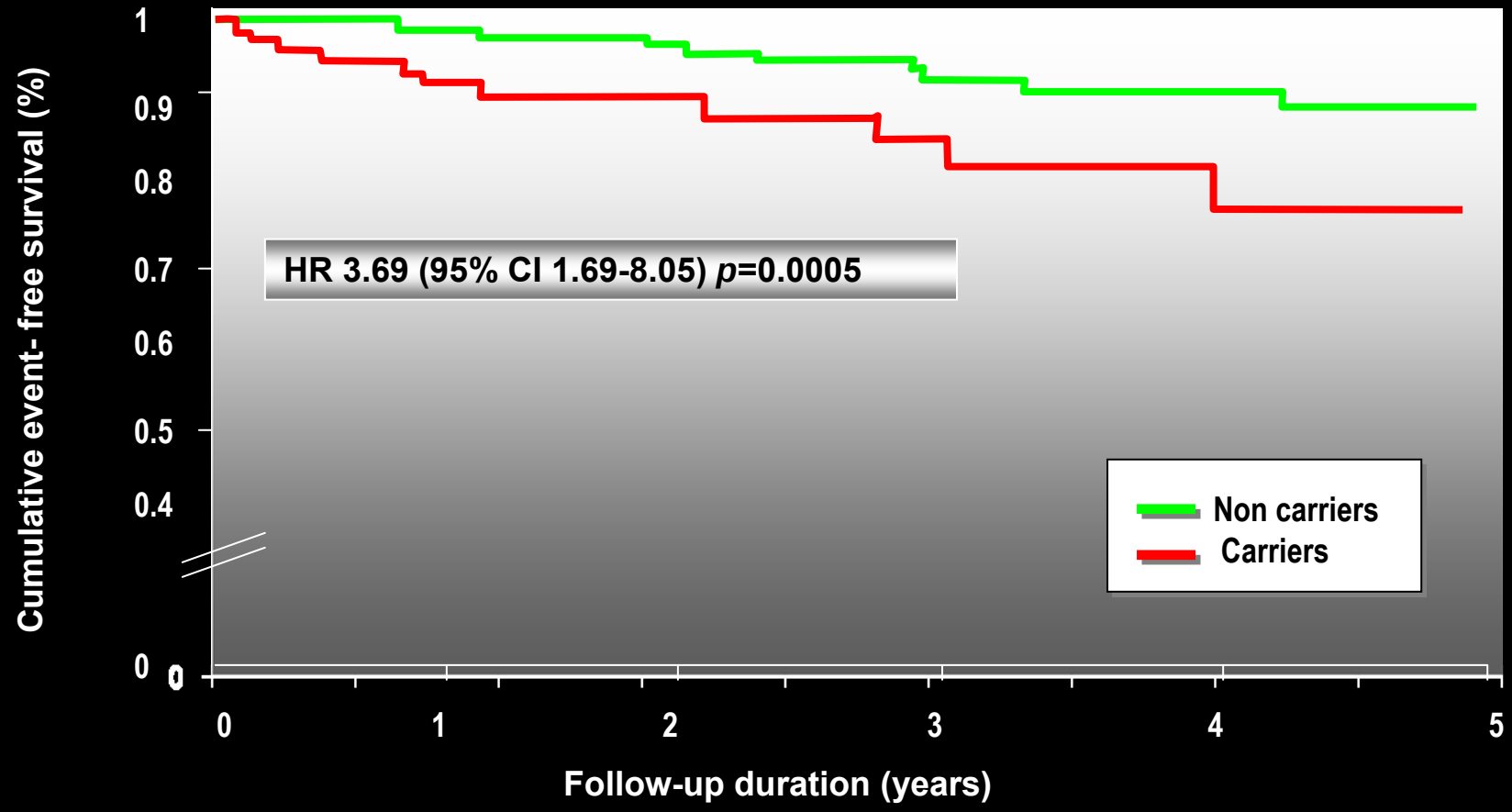
Outcome after MI according to CYP2C19 genotype

The AFIJI Multicentre Registry (n= 259)

Kaplan Maier estimates of the rates of first cardiovascular event at 5y follow-up



Collet JP, et al, Lancet 2009; 373: 309-17

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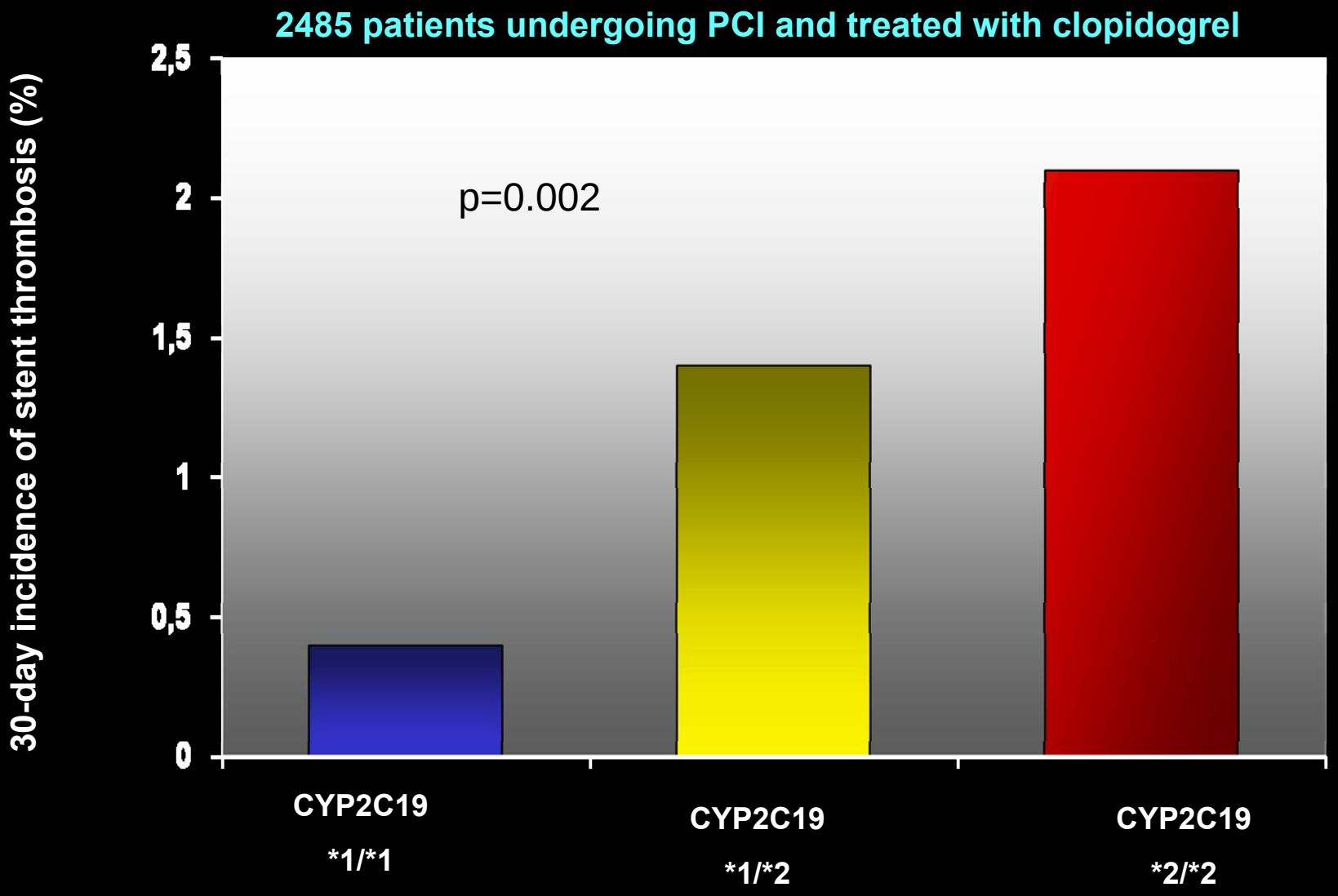
Cytochrome P450 2C19 polymorphism and stent thrombosis



Sibbing et al, Eur Heart Journal 2009; 30: 916-922

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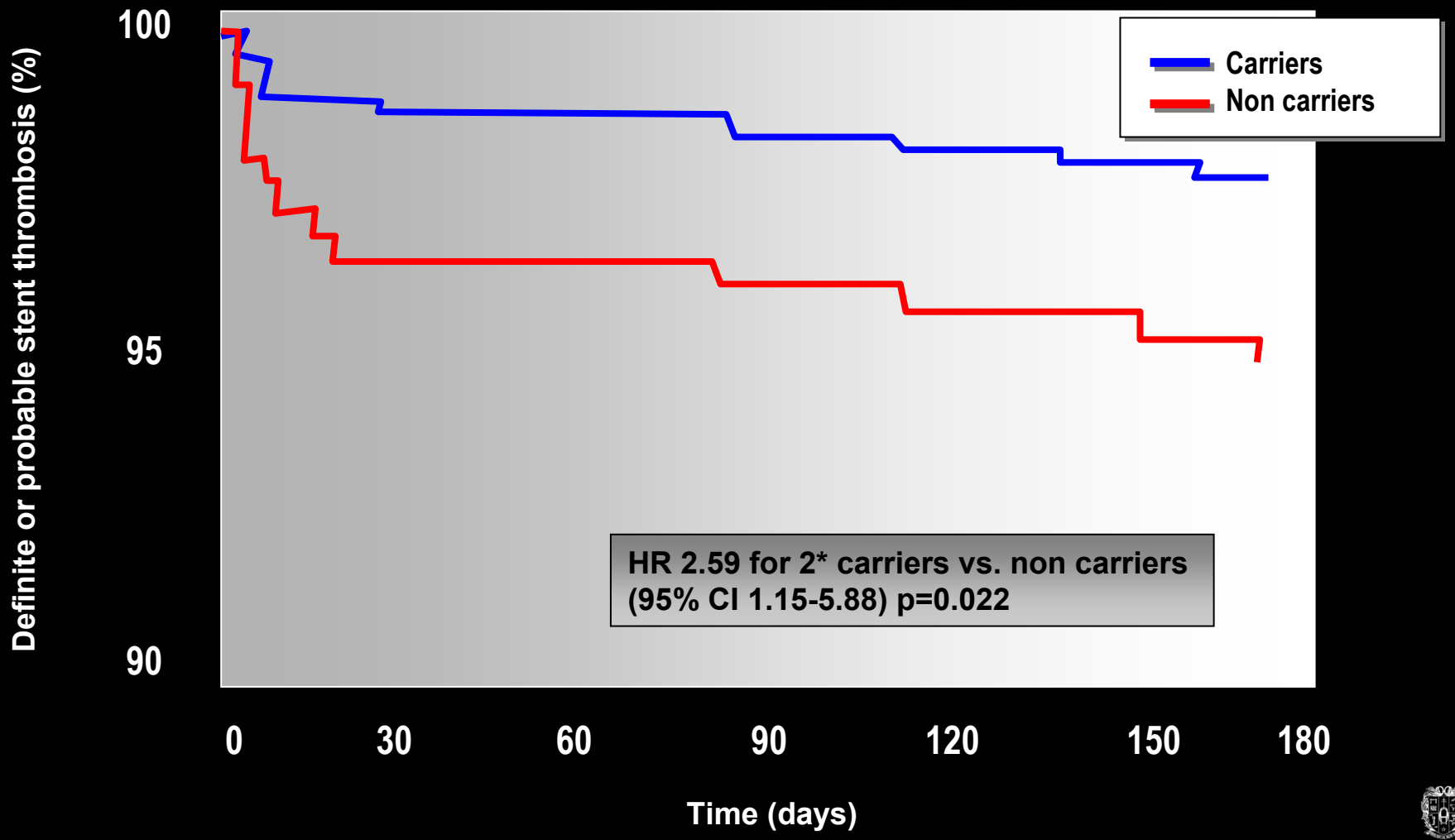
CYP2C19 and stent thrombosis

RECLOSE trial

772 patients undergoing PCI and treated with clopiogrel



Giusti B et al, Am J Cardiol 2009; 103:806-11

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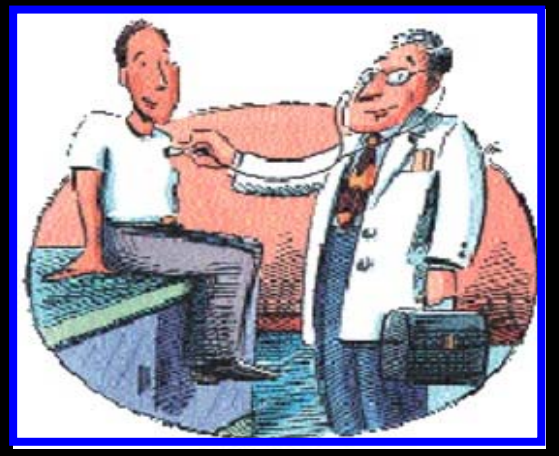
Bench-to-Bedside Model to Speed Translational Research

JAMA 2006;295(13):1506-7

Translational research

A two-way road



Basic

biomedical research

Clinical science

and knowledge

Limits of dual antiplatelet therapy

Pharmacokinetics

-pre-epatic metabolism (esterases)

-hepatic metabolisn (prodrug)

-pharmacogenomic

-slow onset of action and slow elimination

-drug interference

Pharmacodynamic

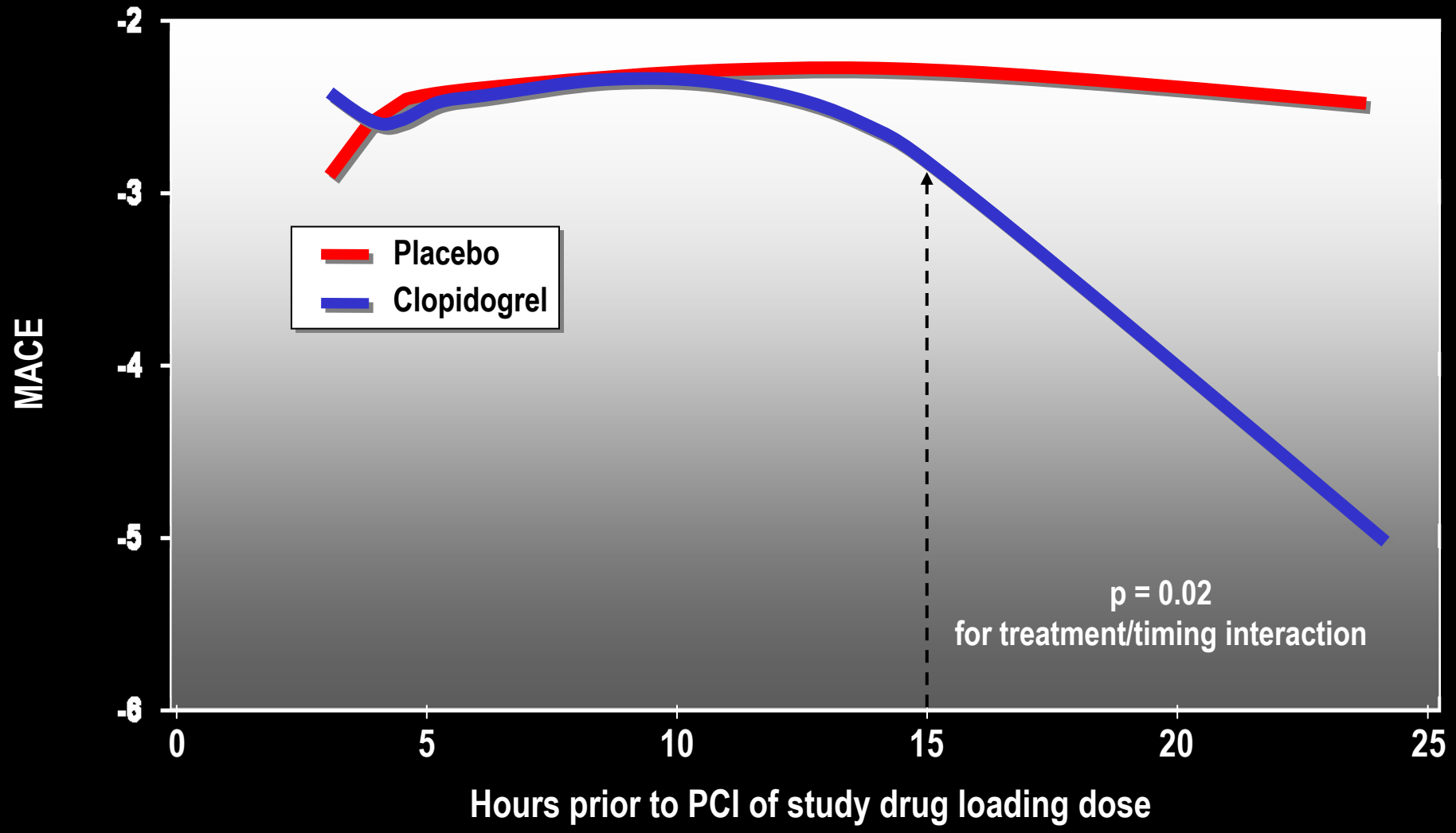
-pathways of inhibition of platelet aggregation

-only 20% relative risk reduction of major adverse cardiovascular events

-increase in bleeding risk

Prevention of Myocardial Infarction During PCI

Effect of Clopidogrel 300 mg Loading Dose



Steirhubl SR et al Circulation 2003;108:374

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Complications During CABG
Effect of Clopidogrel

	Clopidogrel (n=59)	No Clopidogrel (n=165)	p Value
Reoperation for bleeding	6.8 %	0.6 %	0.018 %
Severe low cardiac output	6.8 %	3.6 %	0.296 %
Mortality†	1.7 %	3.6 %	0.678 %
MI‡	0 %	3.6 %	0.344 %
CVA	3.4 %	4.8 %	1.000 %
Atrial fibrillation	44.1 %	34.5 %	0.211 %
Deep sternal wound infection	1.7 %	1.2 %	1.000 %
Intubation ≤ 8 h	54.2 %	75.8 %	0.002 %
Postop length of stay ≤ 5 days	33.9 %	46.7 %	0.094 %

Hongo et al JACC 2002; 40: 231-237

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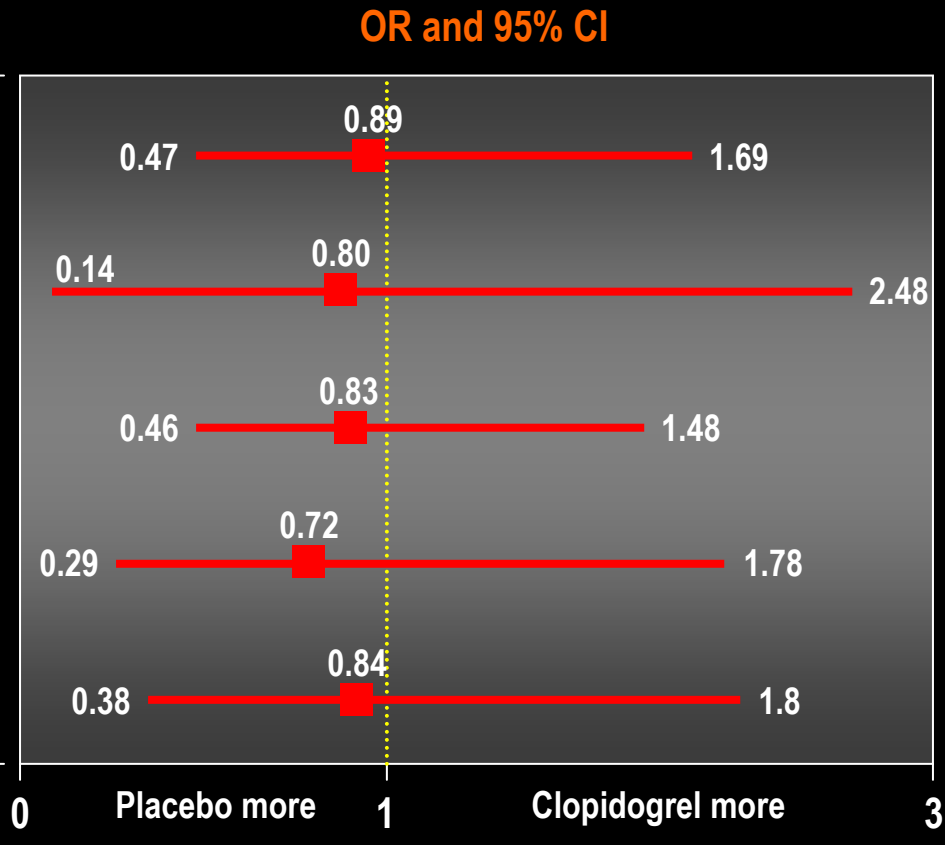
Cure Trial

Bleeding Within 7 Days After CABG Surgery

Drug stopped > 5 days prior to CABG

Life threatening	4.2	3.7
Other major	1.1	0.7
Life threatening or major	5.3	4.4
TIMI major	2.4	1.8
GUSTO severe/life-threatening	2.9	2.4



Fox KAA, et al. Circulation 2004; 110: 1202-8

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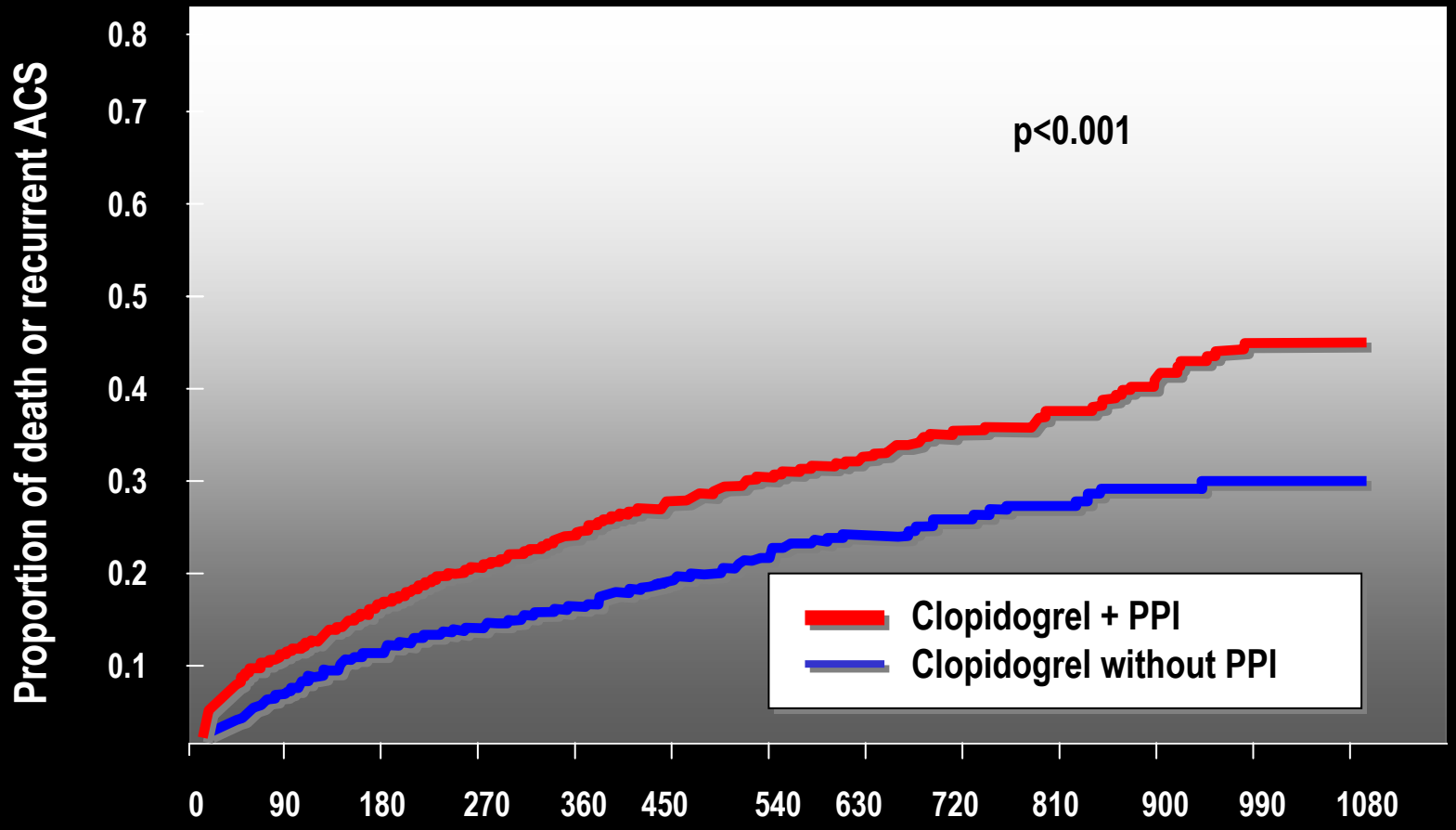
Clopidogrel and Proton Pump Inhibitors

Cumulative risk of all-cause mortality and recurrent acute coronary syndrome



Clopidogrel without PPI	2425	1878	1179	620	362	147	78
Clopidogrel + PPI	3931	2490	1577	891	494	214	102

Michael P. et al, JAMA 2009; 301:937-944

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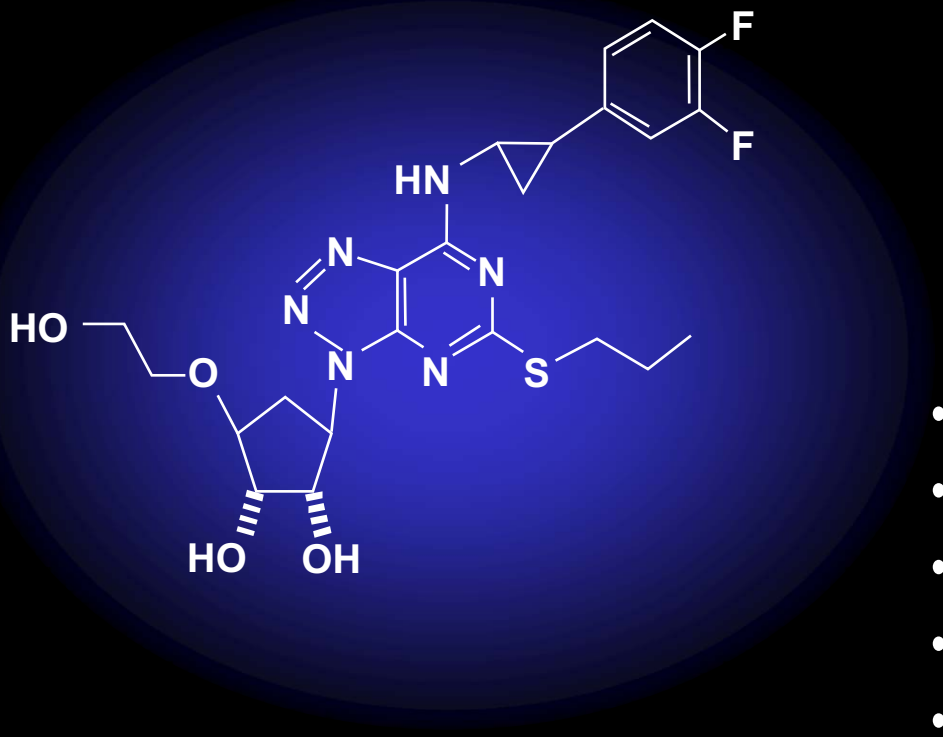
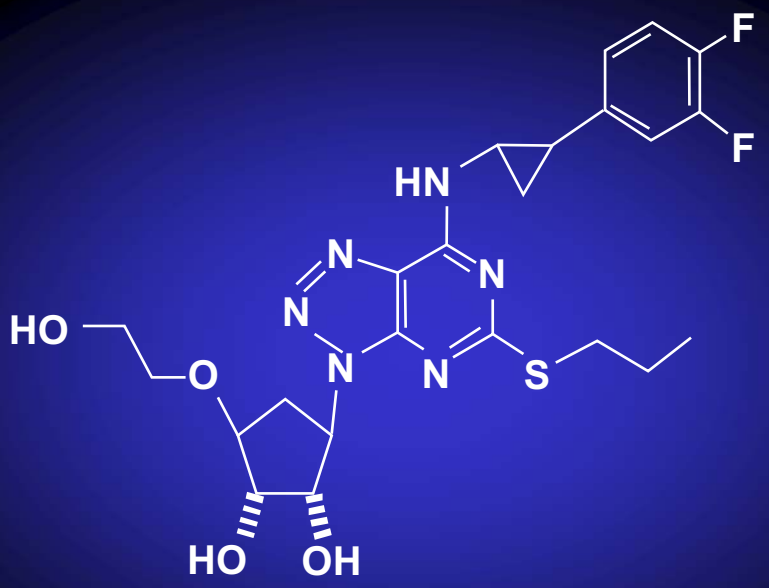
AZ6140
Characteristics

A new and selective oral reversible platelet ADP P2Y12 receptor antagonist



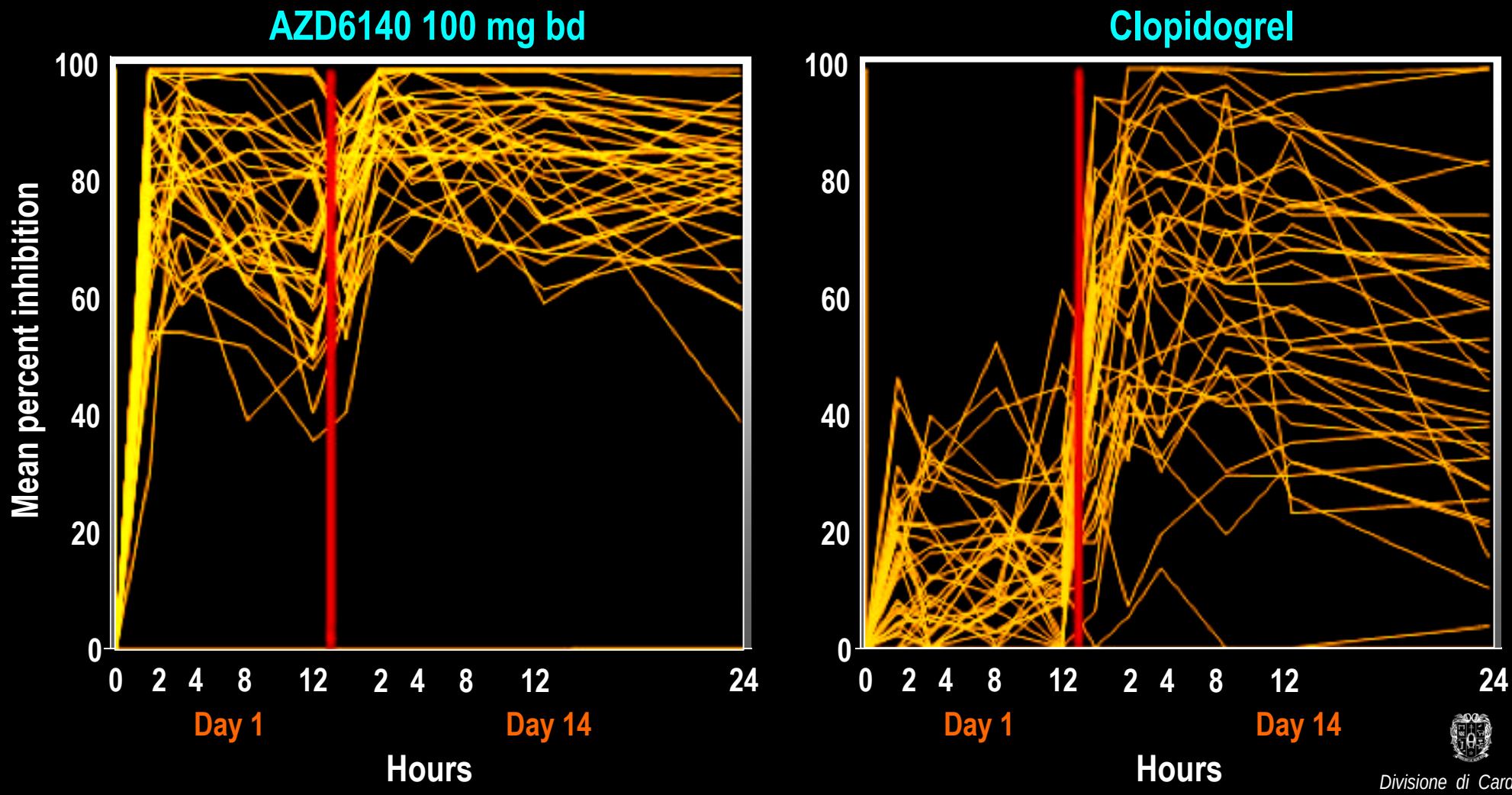
- Rapid onset of antiplatelet effect
- No resistance or variability in response
- Higher level of inhibition >80%
- Direct acting
- Reversible can be stopped for CABG procedures

Ticangrelor
Mechanism of action



Greater and More Consistent IPA with AZD6140 (ticangrelor) than Clopidogrel

Final Extent



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PLATO *Study design*

UA / NSTEMI (moderate to high risk)
STEMI (if primary PCI)
All receiving ASA; clopidogrel-treated or -naïve;
randomised within 24 h of index event

(*n* = 18,000)
Event driven

Clopidogrel
300 mg loading dose,
then 75 mg od maintenance;
(additional 300 mg allowed pre-PCI)

AZD 6140
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

12-month maximum exposure
(Minimum 6-month exposure of last included patient)

Primary endpoint: • CVD / MI / stroke

Secondary endpoint: • CVD / MI / stroke in patients with intent for inv. management
• CVD / MI / stroke / recurrent ischaemia / TIA / other arterial thrombotic events

Recruitment October 2006 – July 2008

bid, twice daily; CVD, cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; od, once daily; TIA, transient ischaemic attack.

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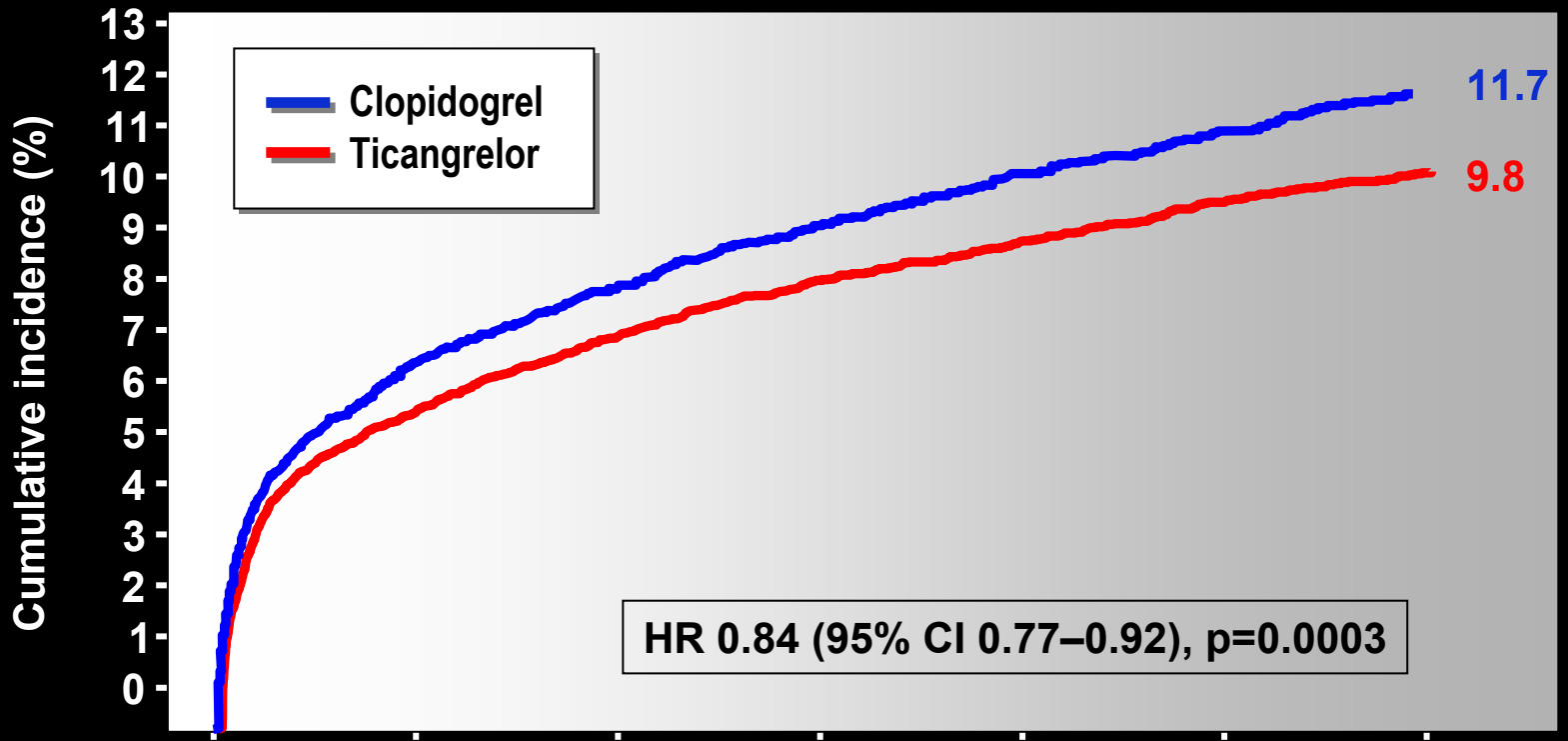
PLATO trial

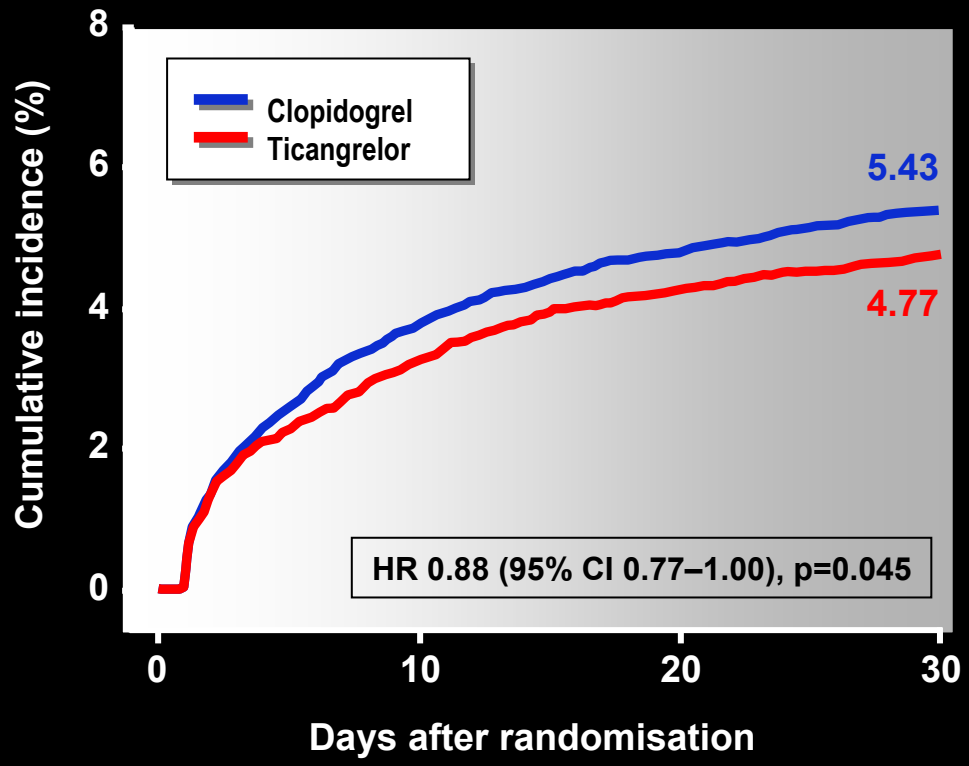
K-M estimate of time to first primary efficacy event

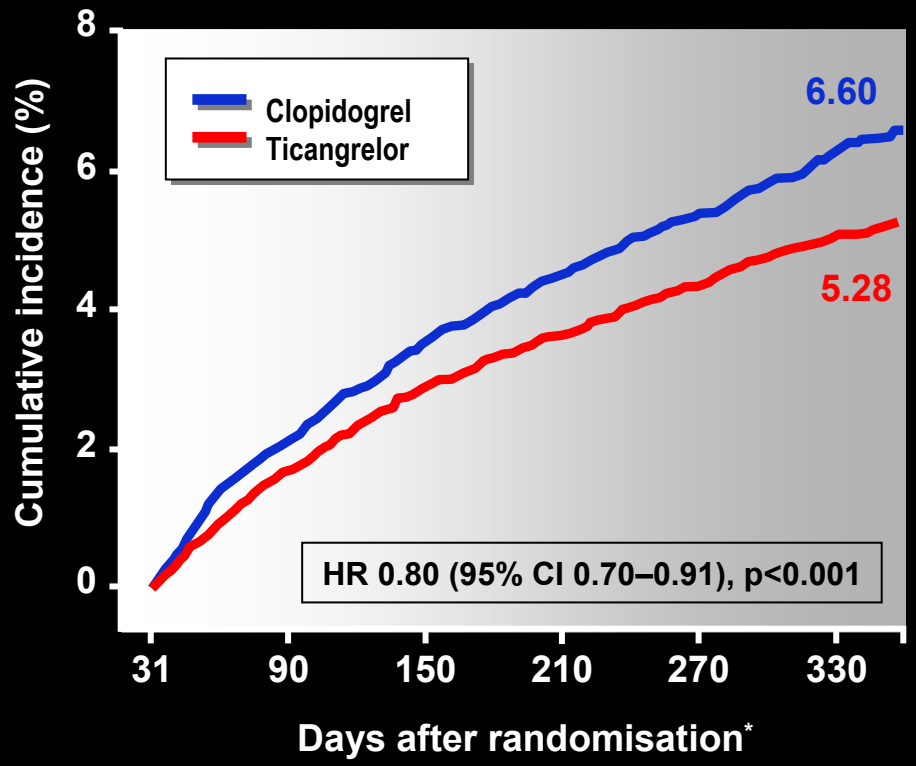


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

PLATO trial

Primary efficacy endpoint over time (composite of CV death, MI or stroke)





No. at risk										
Ticagrelor	9,333	8,942	8,827	8,763	8,673	8,543	8,397	7,028	6,480	4,822
Clopidogrel	9,291	8,875	8,763	8,688	8,688	8,437	8,286	6,945	6,379	4,751

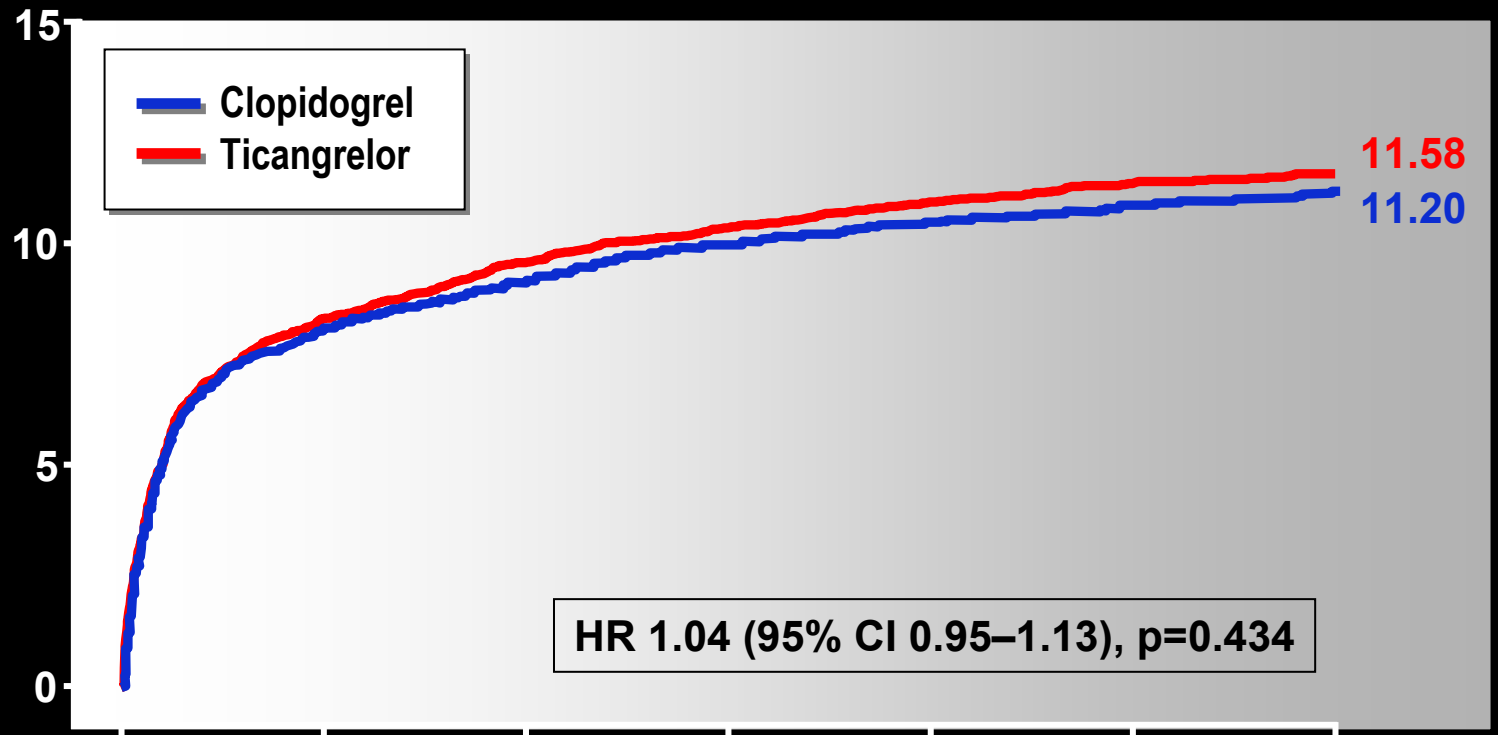
PLATO trial

Major efficacy end-point

All patients	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value
Primary objective, n (%)				
CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Secondary objectives, n (%)				
Total death + MI + stroke	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	<0.001
CV death + MI + stroke + ischaemia + TIA + arterial thrombotic events	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22
Total death	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

PLATO trial

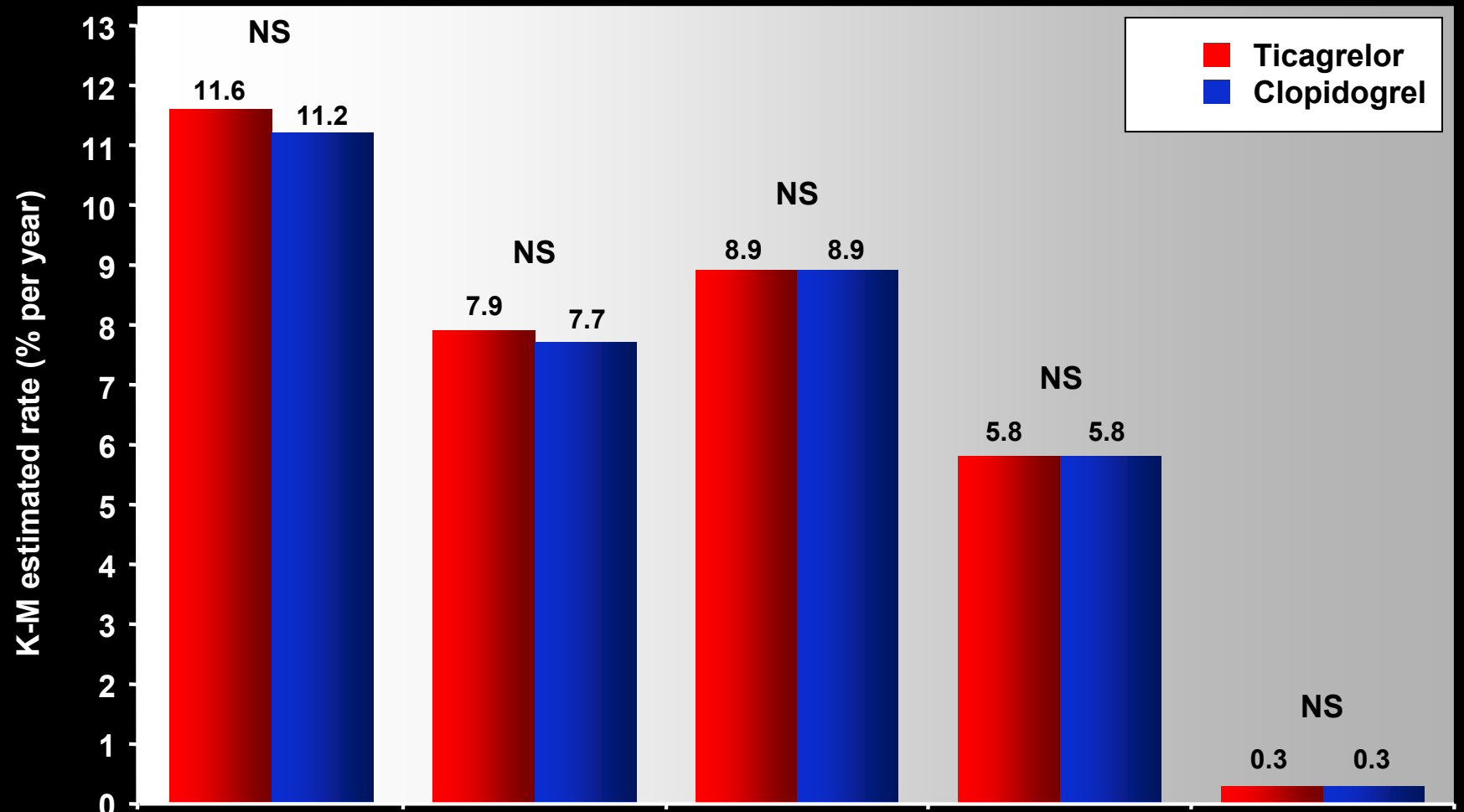
Time to major bleeding – primary safety event



No. at risk							
Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

PLATO trial

Total major bleeding



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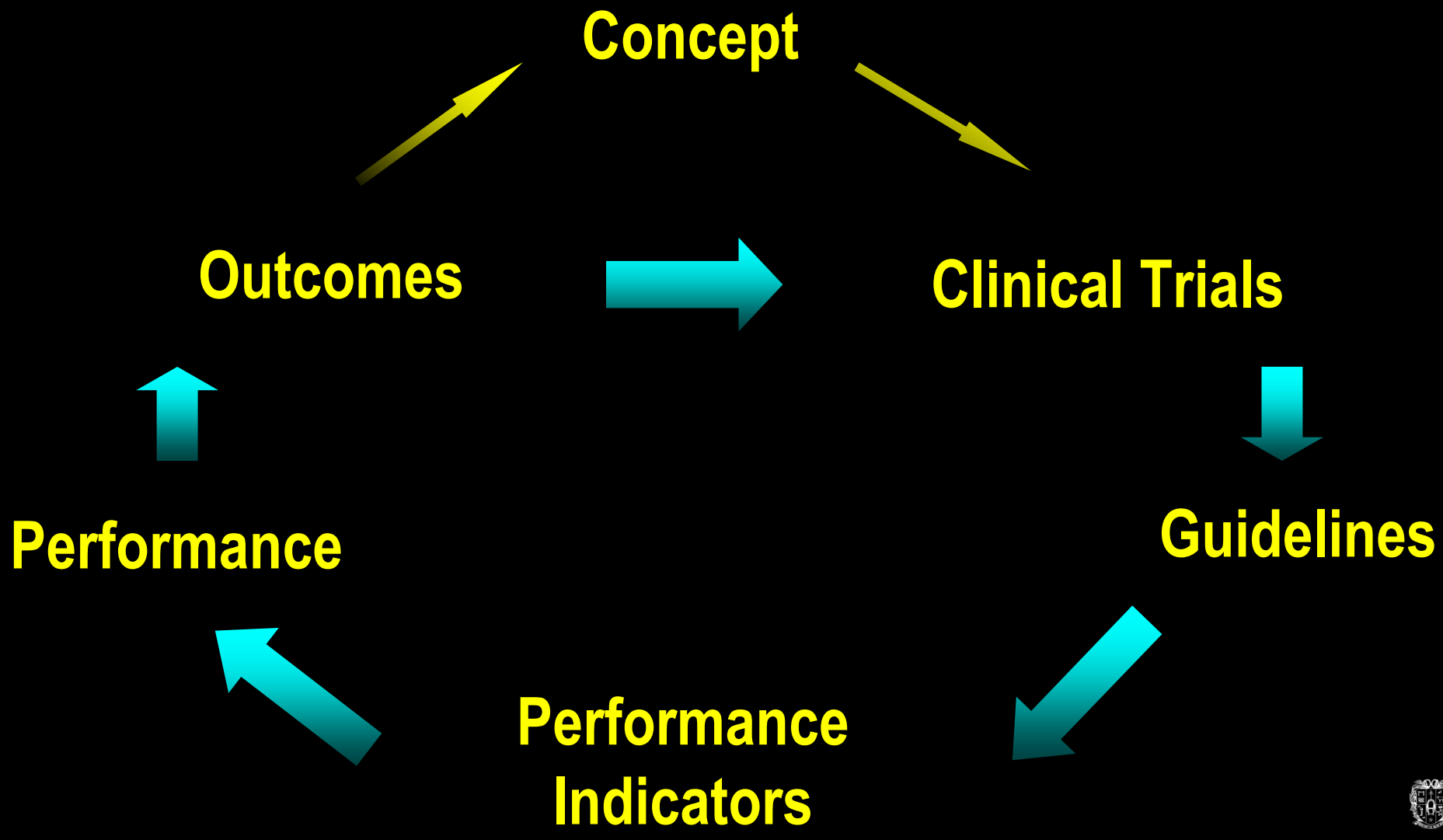
The cycle of continuous quality improvement



Califf RM et al. JACC 2002;40:1895-901

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