Association between CYP2C19 Genotype and Adverse Clinical Outcomes Among PCI Patients: A Meta-analysis

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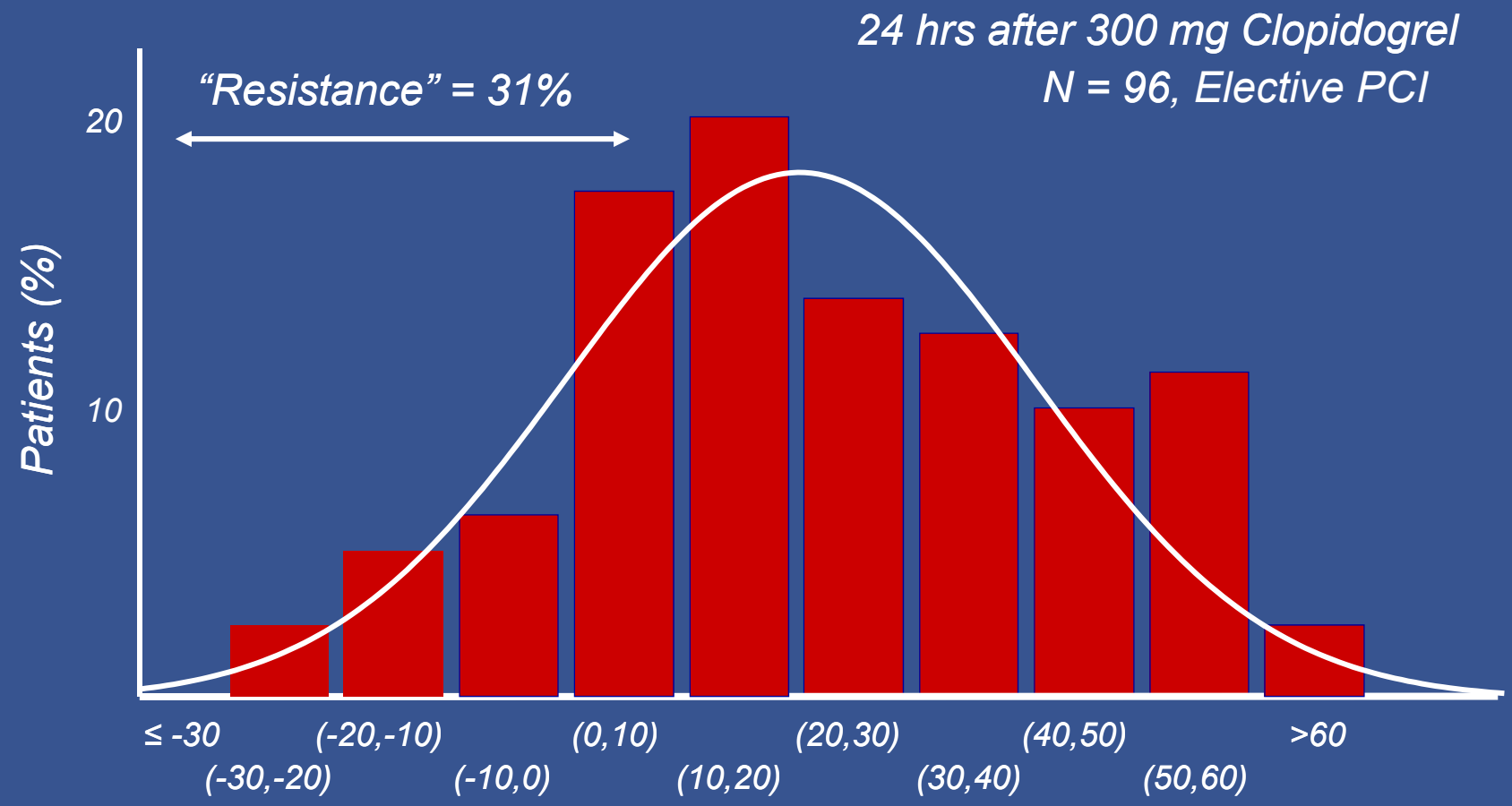
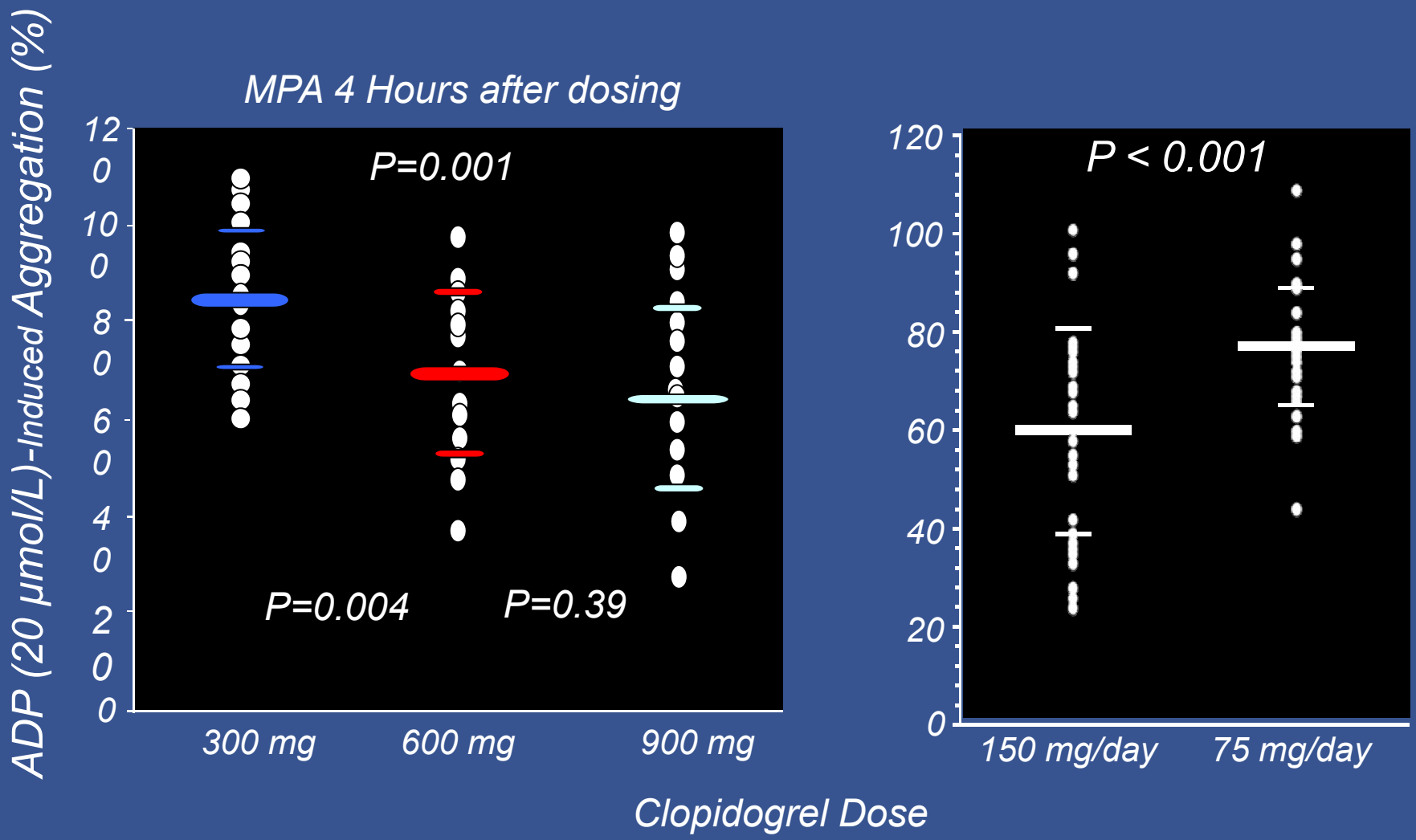
Variable Response to Clopidogrel



"Resistance" = ≤ 10% Δ platelet aggregation

Gurbel PA et al. Circulation 2003; 107: 2908-2913

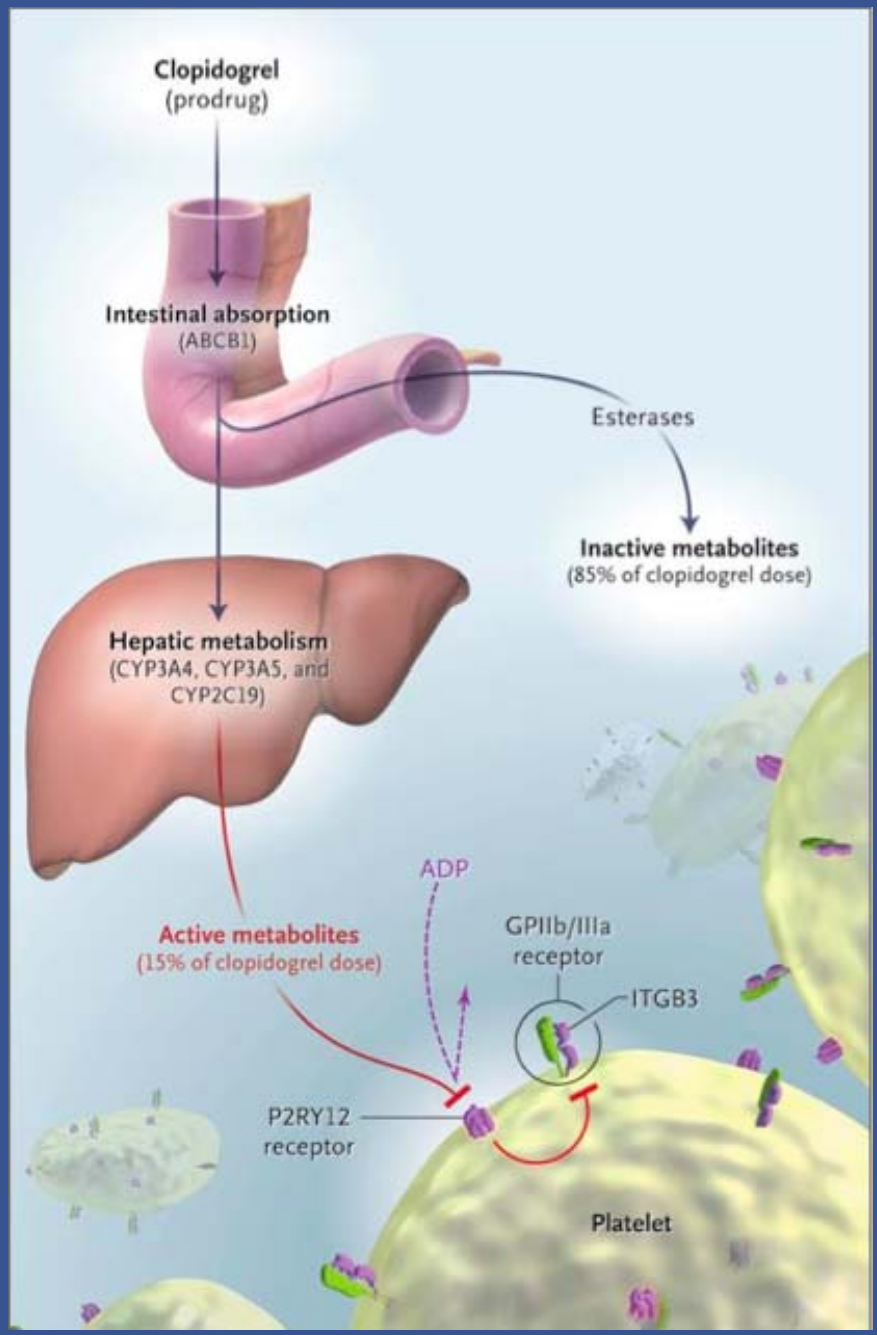
Persistent Variability in Platelet Inhibition (MPA) With High Dose Clopidogrel



MPA=Maximum Platelet Aggregation

von Beckerath N, et al. Circulation 2005;112(19):2946-2950

Metabolism of Clopidogrel



Investigating Variation in CYP450 Enzymes

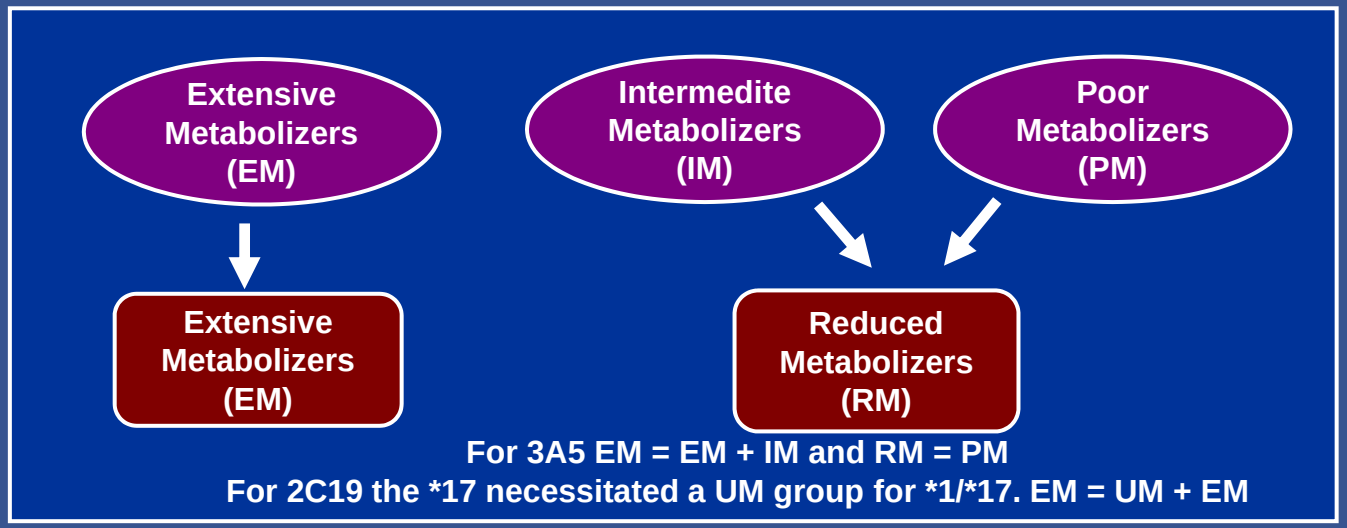
5 Genes: CYP 3A5, 2B6, 2C19, 2C9, 1A2
Genetic Variation: SNPs, in/del, STR

48 DNA Variants

Translation into Star Allele Nomenclature
eg. CYP2C19 *2
54 Different Allele ("normal" by default)

Predicted Genetic Functional Group

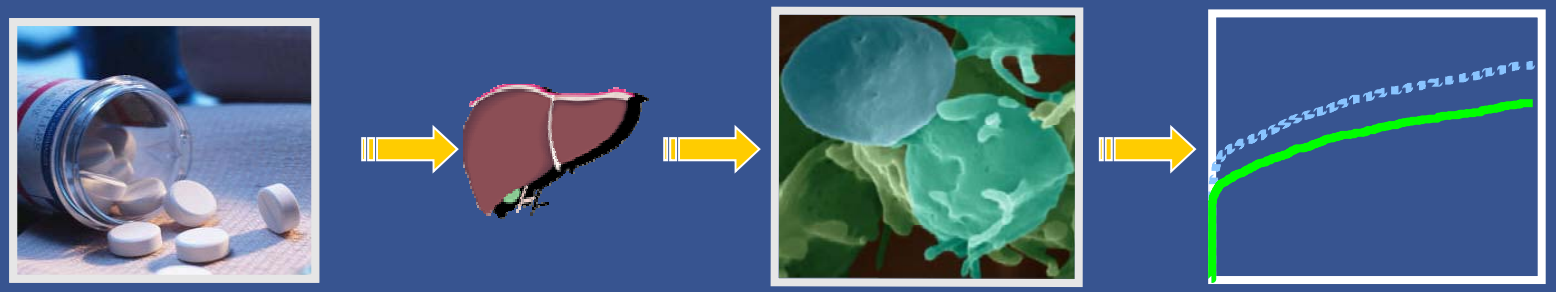
Comparison by predicted metabolic function



Daly TM et al. *Clin Chem* 2007;53(7):1222-1230

Close SL et al. *Eur Heart J* 2008;29(S1):759

Genetic Hypothesis



Prodrug

Conversion to active metabolite (PK)

Platelet response (PD)

Clinical response

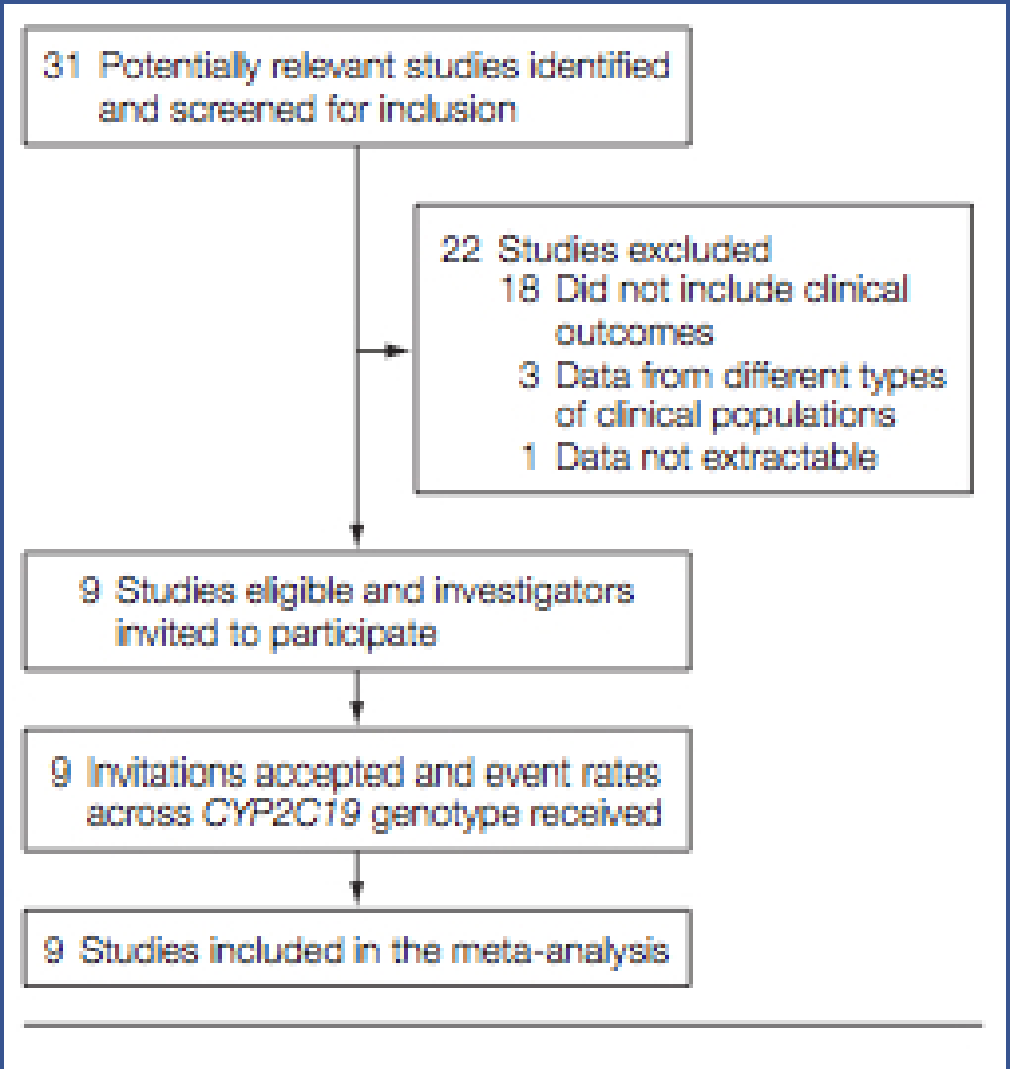
CYP Genotypes

Questions:

- Does the carrier of reduced function allele (e.g, CYP 2C19*2, 95% reduced function allele) have worse cardiovascular outcome after PCI?

- If worse outcome is observed, does it require the presence of 2 reduced function alleles (present in approx. 2% of the population) or only 1 reduced function allele (present in approx. 26% of white or 40% of Asian populations)?

Meta-ananlysis
Mega JL, et al. JAMA 2010;304(16):1821-1830



CYP2C19 Reduced-Function Alleles by Individual Study

	CLARITY-TIMI 28[4]	EXCELSIOR[5]	TRITON-TIMI 38[6]	AFIJI[7]	FAST-MI[8]
***CYP2C19* Reduced-Function Alleles**					
None (n)	150	554	1,064	186	1,573
One (n)	73	226	357	64	577
Two (n)	4	17	38	9	58

	RECLOSE[9]	ISAR[10]	CLEAR-PLATELETS[11]	INTER MOUNTAIN[12]	Total
None (n)	525	1,805	160	906	6,923 (71.5%)
One (n)	221	633	63	330	2,544 (26.3%)
Two (n)	26	47	5	14	218 (2.2%)

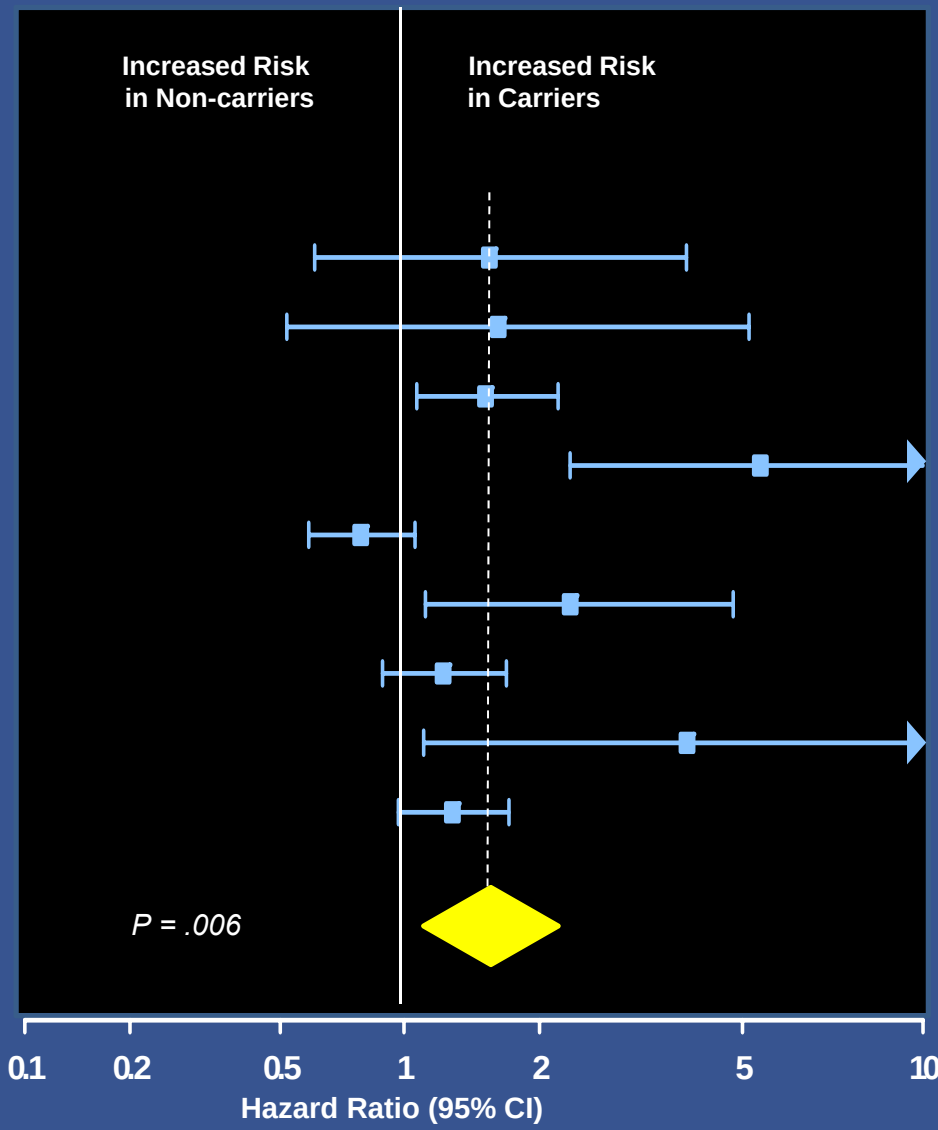
[4]Mega JL, et al.*J Am Coll Cardiol* 2008;51(suppl A):206A
[5]Trenk D, et al. *J Am Coll Cardiol* 2008;51(20):1925-1934
[6]Mega JL, et al. *N Engl J Med* 2009;360(4):354-362
[7]Collet JP, et al. *Lancet* 2009;373(9660):309-317
[8]Simon T, et al. *N Engl J Med* 2009;360(4):363-375
[9]Giusti B, et al. *Am J Cardiol* 2009;103(6):806-811
[10]Sibbing D, et al. *Eur Heart J* 2009;30(8):916-922
[11]Shuldiner AR, et al. *JAMA* 2009;302(8):849-857
[12]Anderson JL, et al. *J Am Coll Cardiol* 2009;53(10 suppl A):A27

Mega JL, et al. JAMA 2010;304(16):1821-1830

Cardiovascular Death, Myocardial Infarction, or Stroke by *CYP2C19* Genotype

	CYP2C19 Reduced-Function Alleles No. of Events/ No. of Individuals at Risk		
	1 or 2	None	HR (95% CI)
CLARITY-TIMI 28[4]	8/77	10/150	1.56 (0.61-3.94)
EXCELSIOR[5]	5/243	7/554	1.63 (0.52-5.14)
TRITON-TIMI 38[6]	46/395	83/1064	1.53 (1.07-2.19)
AFIJI[7]	15/73	11/186	5.38 (2.32-12.47)
FAST-MI[8]	63/635	193/1573	0.79 (0.59-1.06)
RECLOSE[9]	15/247	14/525	2.32 (1.12-4.81)
ISAR[10]	55/680	119/1805	1.23 (0.89-1.70)
C- PLATELETS[11]	6/68	4/160	3.95 (1.11-14.02)
INTERMOUNTAIN[12]	68/344	141/906	1.29 (0.97-1.72)
OVERALL	281/2762	582/6923	1.57 (1.13-2.16)

CI, confidence interval; HR, hazard ratio



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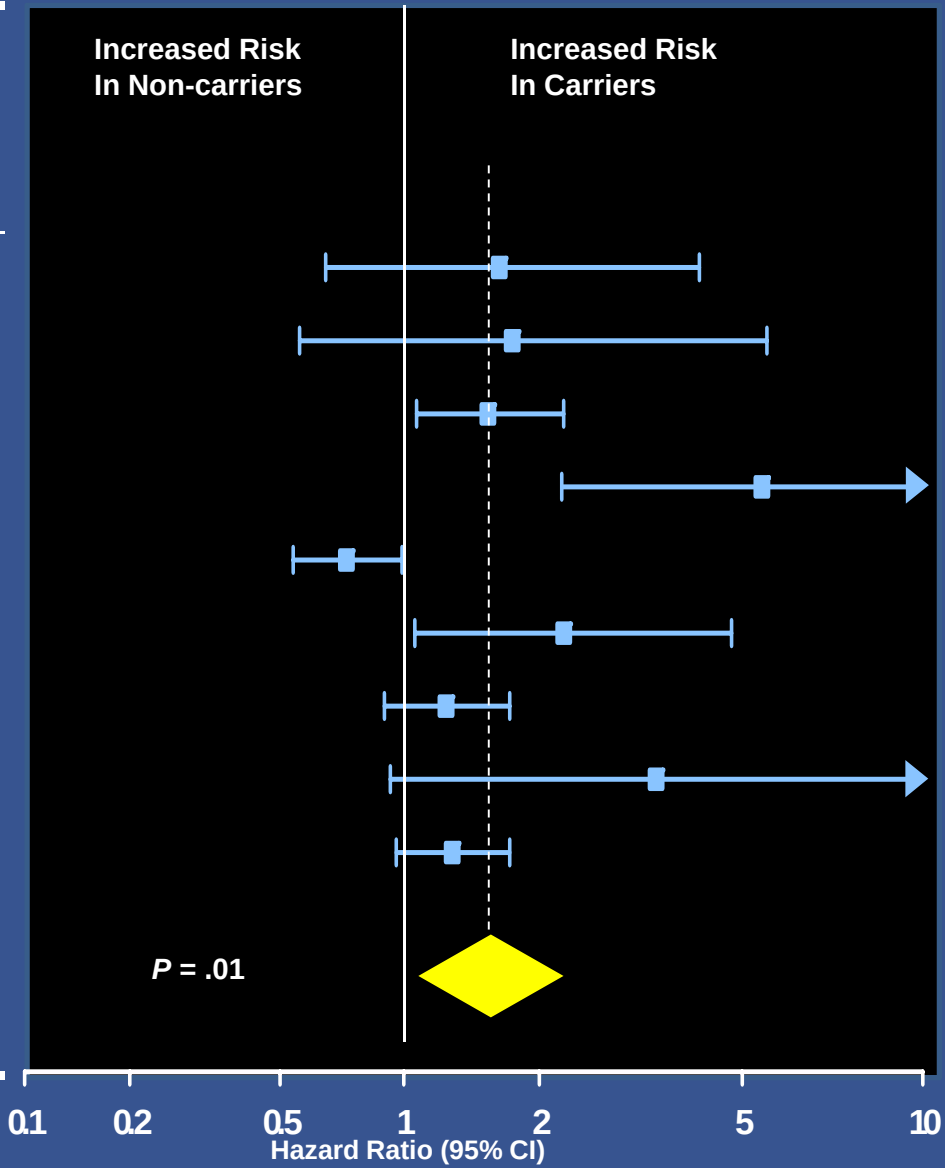
Cardiovascular Death, Myocardial Infarction, or Stroke by *CYP2C19* Genotype

	CYP2C19 Reduced-Function Alleles No. of Events/ No. of Individuals at Risk		
	1	None	HR (95% CI)
CLARITY-TIMI 28[4]	8/73	10/150	1.64 (0.65-4.17)
EXCELSIOR[5]	5/226	7/554	1.75 (0.56-5.53)
TRITON-TIMI 38[6]	42/357	83/1064	1.55 (1.07-2.25)
AFIJI[7]	13/64	11/186	5.42 (2.23-13.18)
FAST-MI[8]	53/577	193/1573	0.73 (0.54-0.99)
RECLOSE[9]	13/221	14/525	2.25 (1.06-4.78)
ISAR[10]	52/633	119/1805	1.25 (0.90-1.73)
CLEAR-PLATELETS[11]	5/63	4/160	3.45 (0.93-12.89)
INTERMOUNTAIN[12]	65/330	141/906	1.29 (0.96-1.73)
OVERALL	256/2544	582/6923	1.55 (1.11-2.17)

CI, confidence interval; HR, hazard ratio



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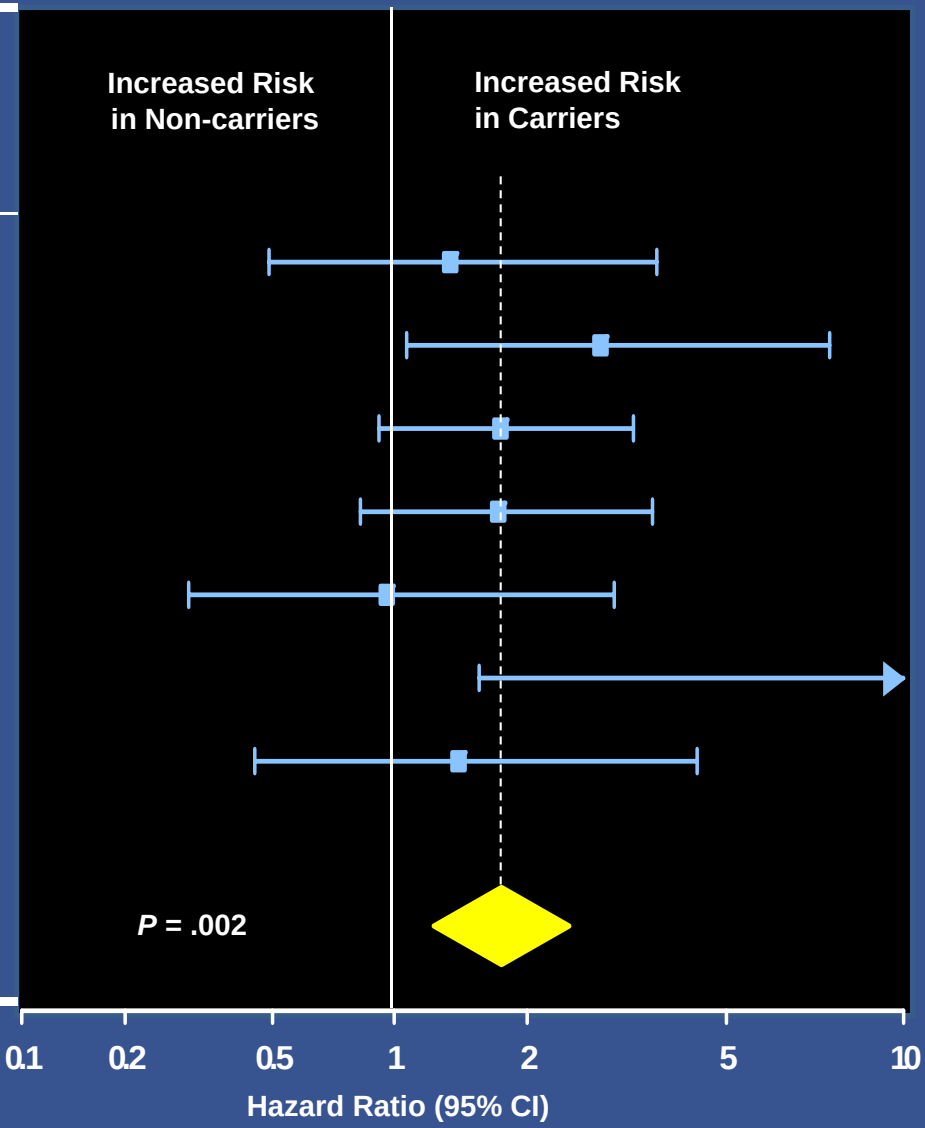
Cardiovascular Death, Myocardial Infarction, or Stroke by *CYP2C19* Genotype

	CYP2C19 Reduced-Function Alleles No. of Events/No. of Individuals at Risk		
	2*	None	HR (95% CI)
TRITON-TIMI 38[6]	4/38	83/1064	1.35 (0.49-3.69)
AFIJI[7]	2/9	11/186	2.85 (1.07-7.59)
FAST-MI[8]	10/58	193/1573	1.75 (0.92-3.32)
RECLOSE[9]	2/26	14/525	1.73 (0.83-3.62)
ISAR[10]	3/47	119/1805	0.96 (0.30-3.04)
CLEAR-PLATELETS[11]	1/5	4/160	14.27 (1.57-129.46)
INTERMOUNTAIN[12]	3/14	141/906	1.41 (0.45-4.41)
OVERALL	25/197	565/6219	1.76 (1.24-2.50)



CI, confidence interval; HR, hazard ratio

*Studies with no adverse cardiovascular events among carriers of 2 reduced-function *CYP2C19* alleles were not included.

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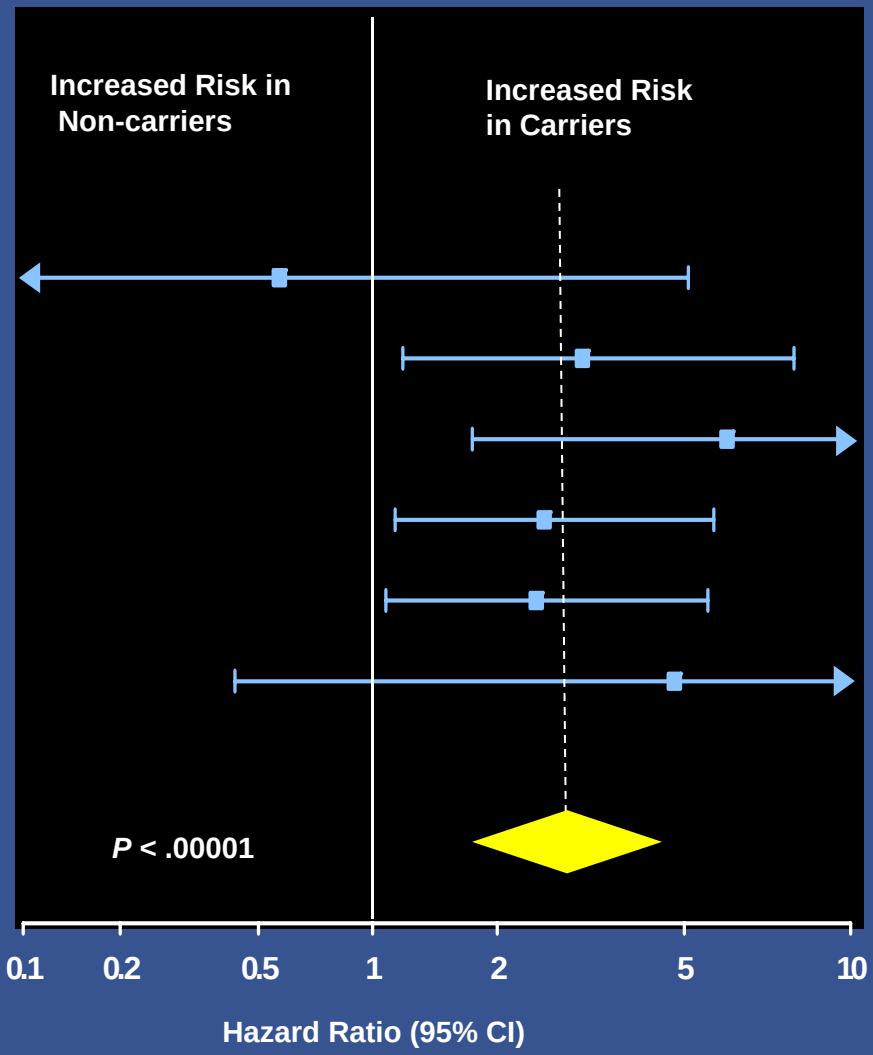
Stent Thrombosis by *CYP2C19* Genotype*

	CYP2C19 Reduced-Function Alleles No. of Events/No. of Individuals at Risk		
	One or Two	None	HR (95% CI)
EXCELSIOR[5]	1/243	4/554	0.57 (0.06-5.09)
TRITON-TIMI 38[6]	9/375	8/1014	3.09 (1.19-8.00)
AFIJI[7]	8/61	4/162	6.04 (1.75-20.82)
RECLOSE[9]	13/247	11/525	2.55 (1.14-5.70)
ISAR[10]	11/680	12/1805	2.45 (1.08-5.55)
CLEAR-PLATELETS[11]	2/68	1/160	4.78 (0.43-52.69)
OVERALL	44/1674	40/4220	2.81 (1.81-4.37)

CI, confidence interval; HR, hazard ratio



***Six studies included stent thrombosis as an end point.**

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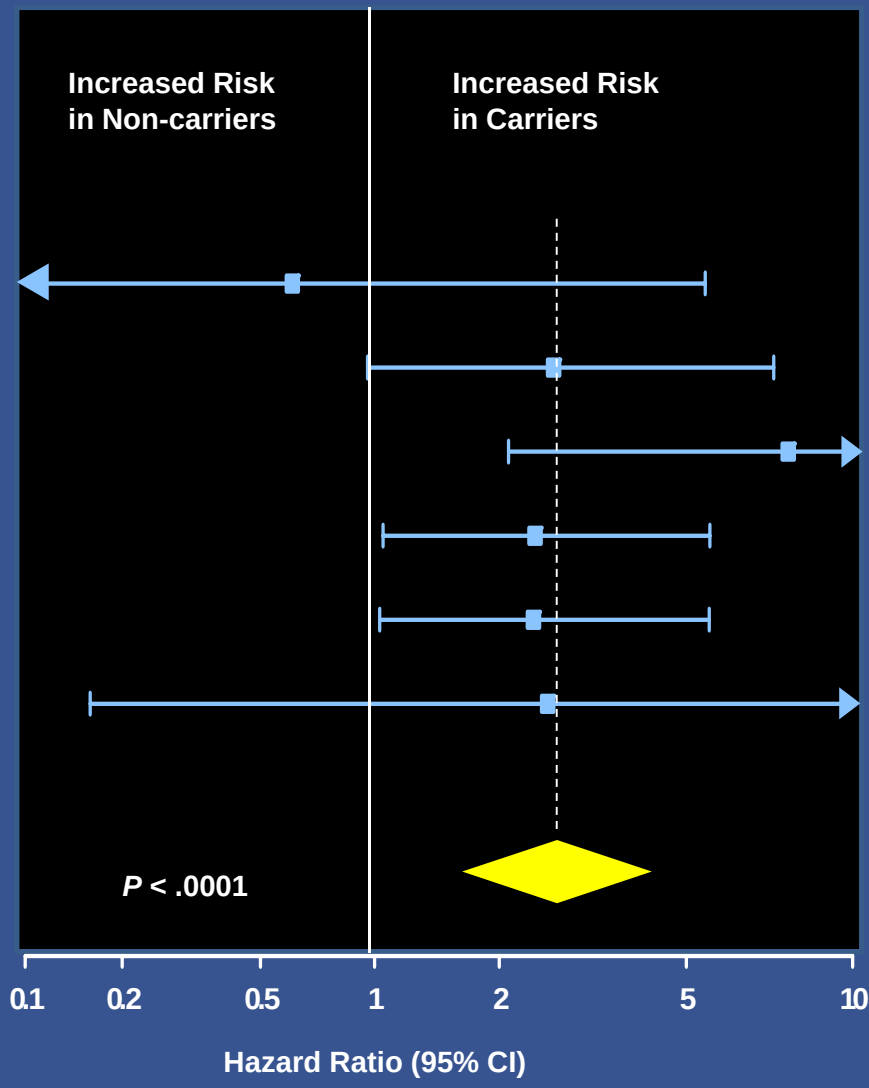
Stent Thrombosis by *CYP2C19* Genotype*

	CYP2C19 Reduced-Function Alleles No. of Events/No. of Individuals at Risk		
	One	None	HR (95% CI)
EXCELSIOR[5]	1/226	4/554	0.61 (0.07-5.44)
TRITON-TIMI 38[6]	7/339	8/1014	2.65 (0.96-7.30)
AFIJI[7]	7/53	4/162	7.75 (2.10-28.60)
RECLOSE[9]	11/221	11/525	2.41 (1.05-5.55)
ISAR[10]	10/633	12/1805	2.39 (1.03-5.54)
CLEAR-PLATELETS[11]	1/63	1/160	2.57 (0.16-40.99)
OVERALL	37/1535	40/4220	2.67 (1.69-4.22)

CI, confidence interval; HR, hazard ratio



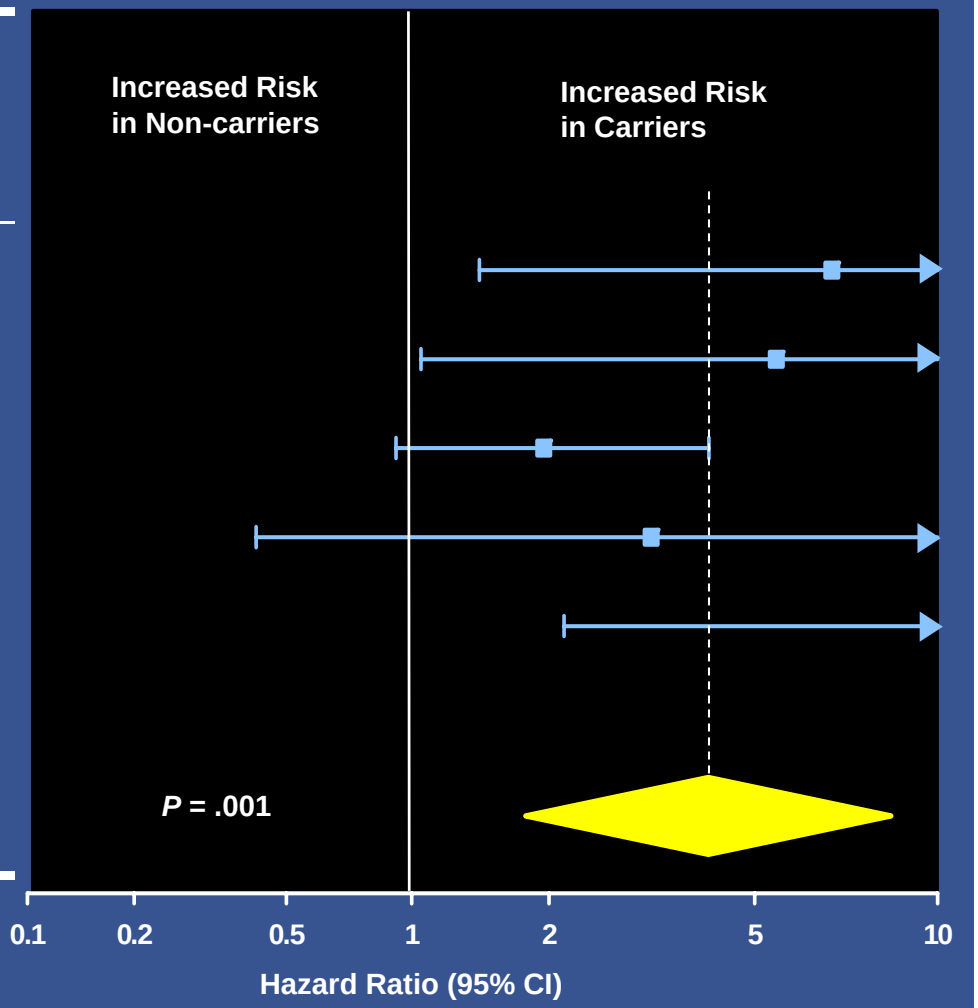
*Six studies included stent thrombosis as an end point.

Mega JL, et al. JAMA 2010;304(16):1821-1830

Stent Thrombosis by *CYP2C19* Genotype*

	CYP2C19 Reduced-Function Alleles No. of Events/No. of Individuals at Risk		
	Two	None	HR (95% CI)
TRITON-TIMI 38[6]	2/36	8/1014	6.79 (1.42-32.53)
AFIJI[7]	1/8	4/162	5.46 (1.05-28.38)
RECLOSE[9]	2/26	11/525	1.95 (0.92-4.13)
ISAR[10]	1/47	12/1805	3.21 (0.42-24.60)
CLEAR-PLATELETS[11]	1/5	1/160	34.41 (2.15-551.50)
OVERALL	7/122	36/3666	3.97 (1.75-9.02)

CI, confidence interval; HR, hazard ratio



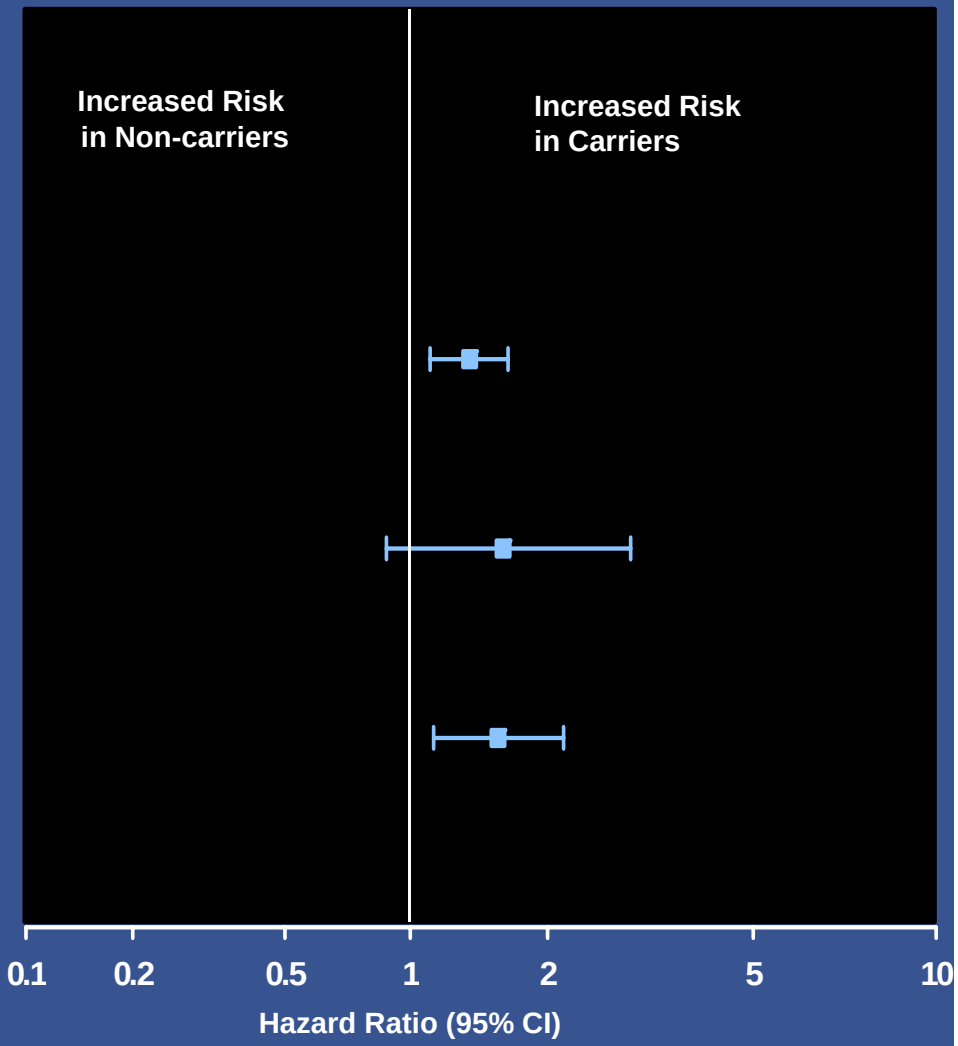
***Six studies included stent thrombosis as an end point. Studies that had no stent thrombosis among carriers of 2 reduced-function CYP2C19 alleles were not included.**

Mega JL, et al. JAMA 2010;304(16):1821-1830

Timing of Events for Cardiovascular Death, Myocardial Infarction, or Stroke

	CYP2C19 Reduced-Function Alleles No. of Events/ No. of Individuals at Risk			
	1 or 2	None	HR (95% CI)	Overall *P*-Value
0 to 30 Days	183/2762	348/6923	1.36 (1.11-1.65)	.003
31 Days to End of Follow-up	113/1712	246/4316	1.61 (0.88-2.94)	.123
0 Days to End of Follow-up	281/2762	582/6923	1.57 (1.13-2.16)	.006

CI, confidence interval; HR, hazard ratio



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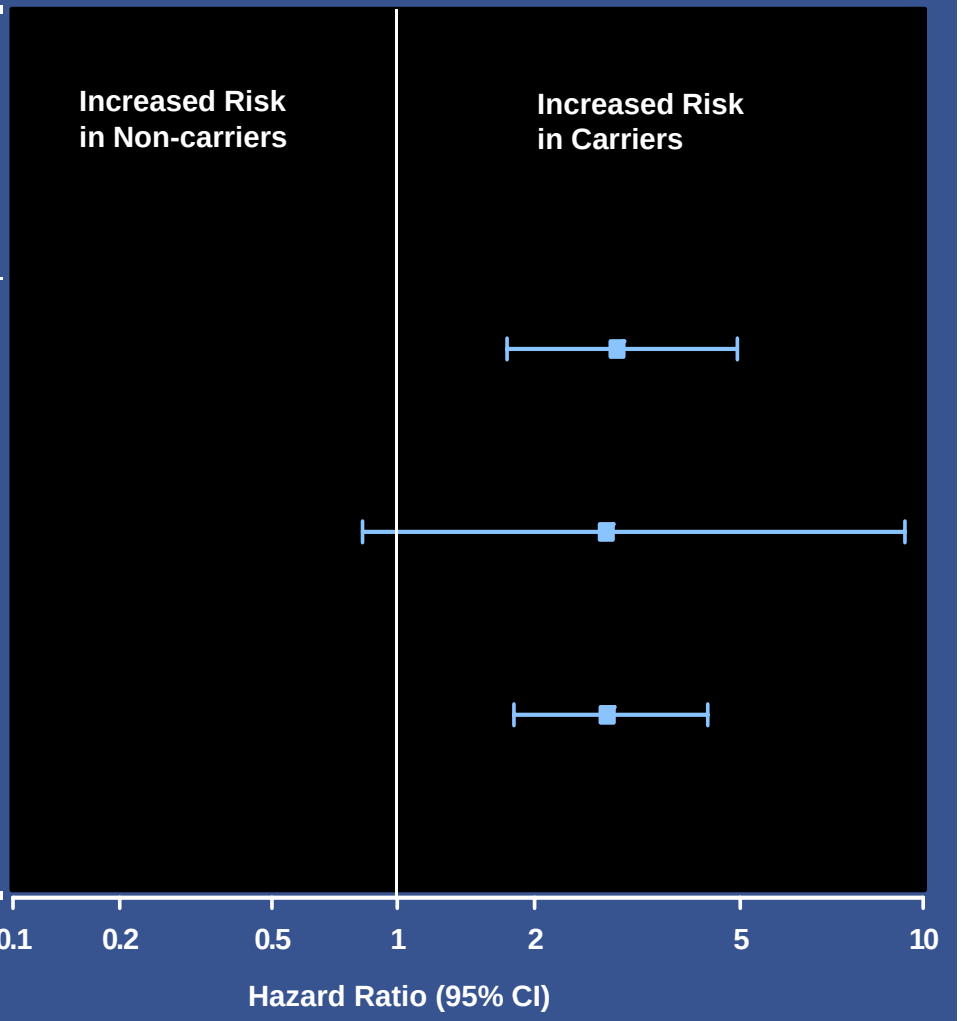
Timing of Events for Stent Thrombosis

	CYP2C19 Reduced-Function Alleles No. of Events/ No. of Individuals at Risk			
	1 or 2	None	HR (95% CI)	Overall *P*-Value
0 to 30 Days	32/1674	28/4220	2.94 (1.75-4.94)	<.0001
31 Days to End of Follow-up	12/820	13/2023	2.80 (0.83-9.38)	.096
0 Days to End of Follow-up	44/1674	40/4220	2.81 (1.81-4.37)	<.00001

CI, confidence interval; HR, hazard ratio



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Heterogeneity:

- Two studies carried the heterogeneity for death/MI/CVA: FAST-MI and AFIJI.

- No clear difference in design or outcome

- No other heterogeneity

Summary:

- 30% of the population have one reduced function allele and are at increased risk of CV event after PCI

- 2% of white, 4% of blacks and 14% of Chinese populations have 2 reduced function alleles. They have significantly higher risk. Though this meta-analysis included 95.8% white population.

- Only CYP2C19*2 is counted as a reduced function allele, all others are counted as non-carriers.

Implications:

- In patients undergoing PCI, one reduced function allele can impact significant increase risk.

- In an ACS population treated with PCI, the positive predictive value of testing for CYP2C19*2 is low, in range of 12-20%.

- More studies are on the way (e.g. GIANT, TARGET PCI are on the way).