Pharmacogenetic Debates in Antiplatelet Therapy

Angioplasty Summit – TCAP Meeting 2011

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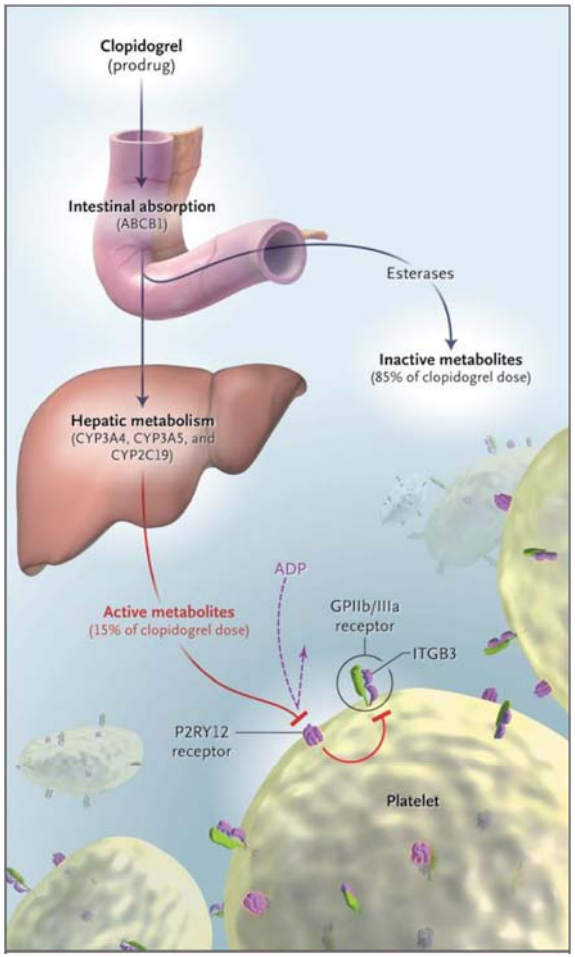
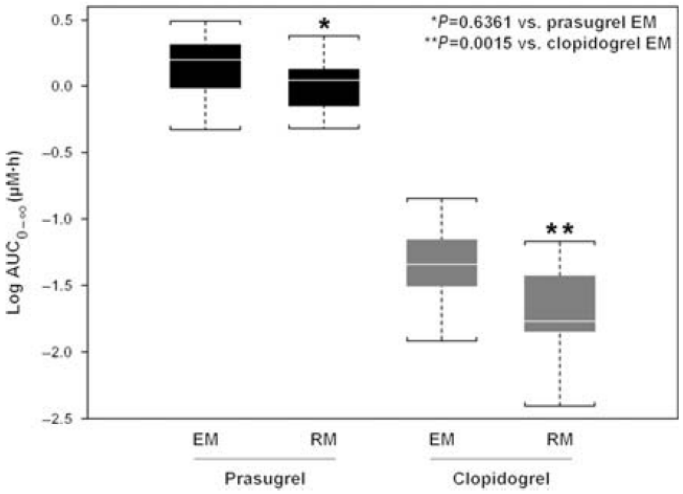
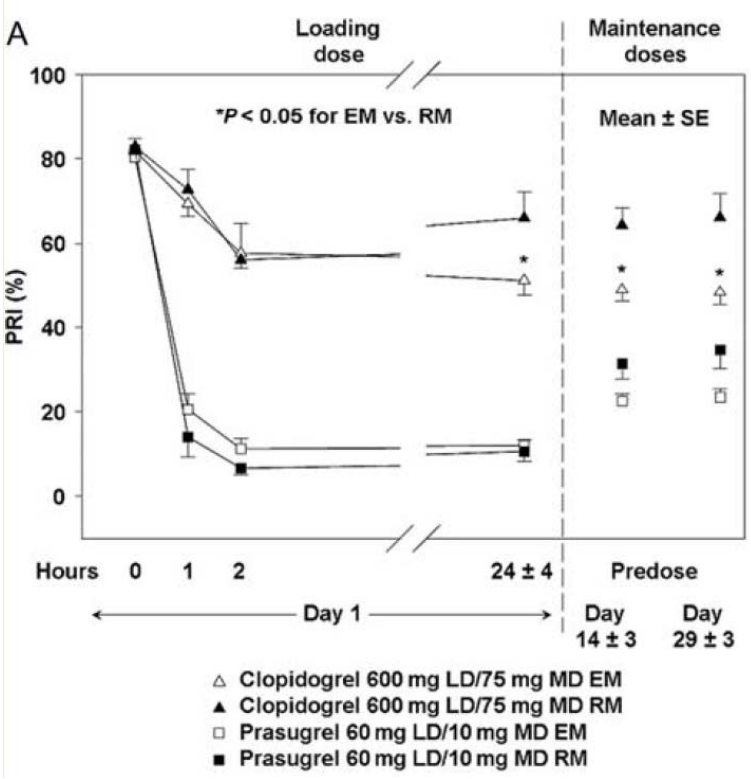
Background



Taken from Tabassome et al. NEJM 2009, 22;360(4):363-75

Effects of CYP2C19 genotypes on pharmacokinetic and pharmacodynamic



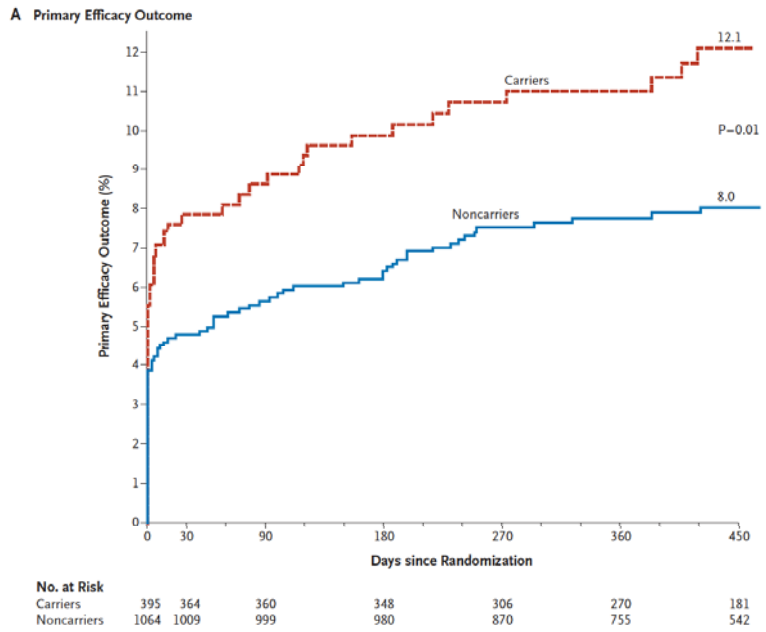


In 47 ASA-treated CAD patients

Varenhorst et al. EHJ 2009; 30: 1744-52

TRITON-TIMI 38

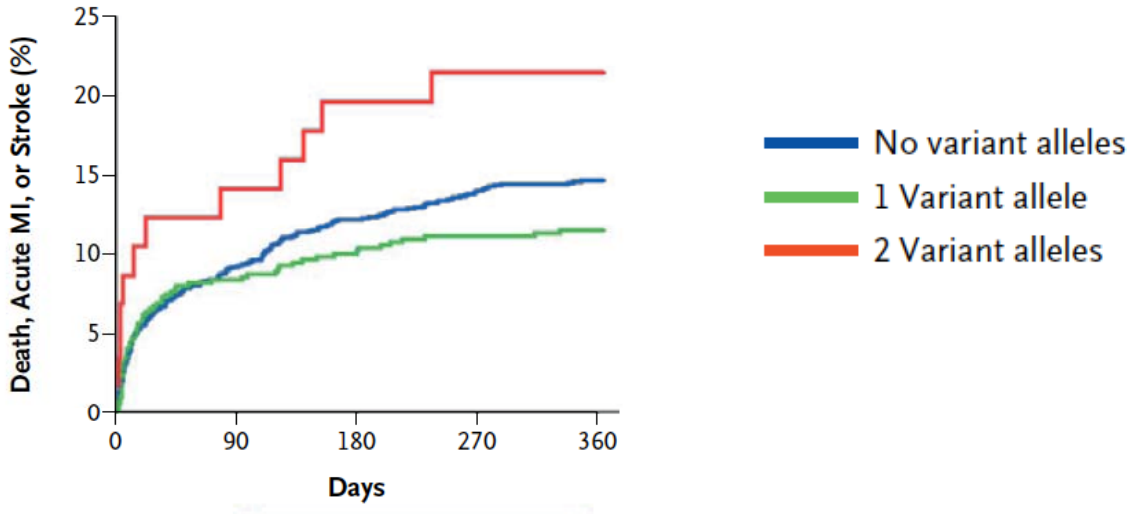
- 1477 ACS patients from TRITON-TIMI 38
  - Carriers of loss-of-function allele had 53% increase in the composite efficacy outcome
  - 46 (12.1%) Vs 83 (8.0%) events (HR=1.53 95%CI 1.07-2.19)



Mega et al. NEJM 2009; 360: 354-62

FAST-MI

- 2208 AMI patients receiving clopidogrel from a national registry
  - Carriers of two loss-of-function alleles had 98% increase in cardiovascular events
  - 12 (21.5%) Vs 282 (13.3%) events (HR=1.98 95%CI 1.10-3.58)



Simon et al. NEJM 2009; 360: 363-75

FDA “Boxed Warning”

- Assumption that CYP2C19 poor metabolizers do not convert the pro-drug into the active metabolite and thus do not derive clinical benefit of treatment

- “Box warning” from FDA of reduced effectiveness of clopidogrel in patients who are poor metabolizers
  - Use of a higher dose of clopidogrel
  - Use of an alternative antiplatelet agent

Three Key Controversies

- What is the “at risk” genotype?
  - “Poor metabolizers” only Vs. all LOF allele carriers
- Which patient populations should be targeted for genotyping?
  - All patients on clopidogrel Vs. PCI patients only
- Should other genes be included?

What is the “at risk” genotype?

3 allele classes

- “Wild type” (*1): 63%
- Loss-of-function (*2, *3): 13%
- Gain-of-function (*17): 24%

5 metabolizer phenotypes

- Poor: 2 loss-of-function alleles (2%)
- Intermediate: 1 loss-of-function and 1wild type alleles (16%)
- Extensive: 2 wild types alleles (39%)
- Ultra: 1 or 2 gain-of-function alleles (37%)
- Unknown: 1 gain-of-function and 1 loss-of-function alleles (6%)

2 carrier status

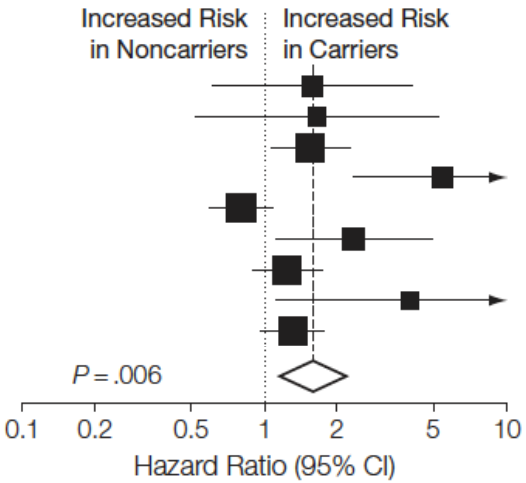
- Loss-of-function carriers (1 or more *2, *3): 24%
- Gain-of-function carriers (1 or more *17): 41%

What is the “at risk” genotype?

- Cardiovascular Death, Myocardial infarction, or Ischemic Stroke

A Carriers of 1 or 2 *CYP2C19* Reduced-Function Alleles vs Noncarriers

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



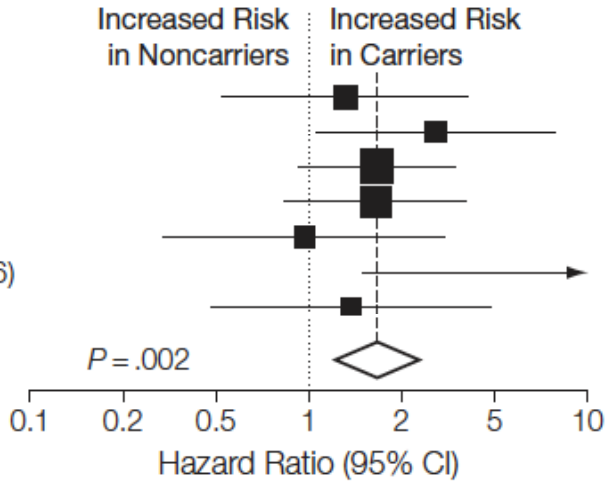
Mega et al. JAMA 304(16): 1821-30

What is the “at risk” genotype?

- Cardiovascular Death, Myocardial infarction, or Ischemic Stroke

C Carriers of 2 *CYP2C19* Reduced-Function Alleles vs Noncarriers

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



Mega et al. JAMA 304(16): 1821-30

What is the “at risk” genotype?

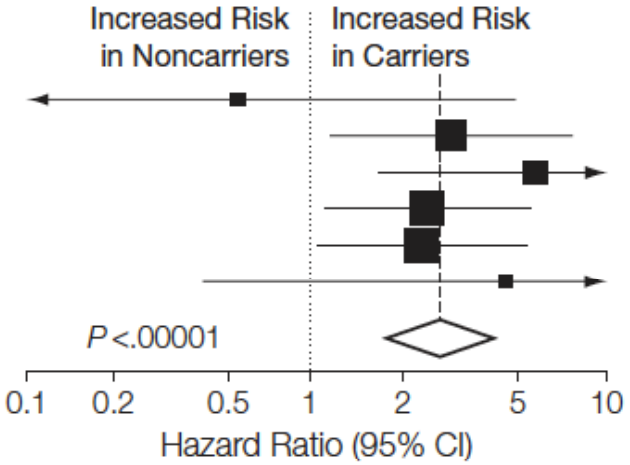
- Both “loss-of-function carriers” and “poor metabolizers” are at risk
- Dose-response relationship
- Implications for Asian populations
- Role of gain-of-function allele (?)

Which patient populations should be targeted for genotyping?

- Most early studies in stent PCI patients
- Genetic effect appears stronger for stent thrombosis

A Carriers of 1 or 2 *CYP2C19* Reduced-Function Alleles vs Noncarriers

	CYP2C19 Reduced-Function Alleles, No. of Events/ No. of Individuals at Risk		Hazard Ratio (95% CI)
	1 or 2	None	
EXCELSIOR	1/243	4/554	0.57 (0.06-5.09)
TRITON-TIMI 38	9/375	8/1014	3.09 (1.19-8.00)
AFIJI	8/61	4/162	6.04 (1.75-20.82)
RECLOSE	13/247	11/525	2.55 (1.14-5.70)
ISAR	11/680	12/1805	2.45 (1.08-5.55)
CLEAR-PLATELETS	2/68	1/160	4.78 (0.43-52.69)
Overall	**44/1674**	**40/4420**	**2.81 (1.81-4.37)**



Mega et al. JAMA 304(16): 1821-30

CURE Trial

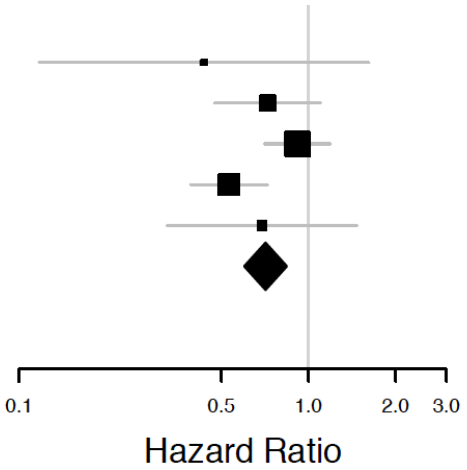
- 12,562 ACS patients without ST-segment elevation
  - Randomized to Clopidogrel (75mg) or Placebo
  - On a background of ASA (75 mg to 325 mg)
  - Average follow-up of 9 months
- Only 14.5% underwent stent PCI
- Outcomes
  - First Primary: CV death, MI, Stroke
  - Second Primary: First primary, or recurrent ischemia, or UA
  - Safety: Major bleed (life-threatening or not)

Yusuf et al. NEJM 2001; 345: 494-502

CURE – Metabolizer Phenotypes

- First primary composite outcome

Metabolizer Phenotype	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)
Poor	10.9% (6/55)	6.6% (4/61)	0.44 (0.12–1.61)
Intermediate	12.2% (54/442)	8.5% (37/437)	0.72 (0.48–1.10)
Extensive	12.3% (121/987)	10.8% (112/1033)	0.92 (0.71–1.19)
Ultra	13.6% (112/826)	7.8% (66/847)	0.53 (0.39–0.72)
Unknown	10.2% (18/176)	7.2% (11/152)	0.69 (0.33–1.47)
Total	**12.5% (311/2486)**	**9.1% (230/2530)**	**0.71 (0.60–0.84)**

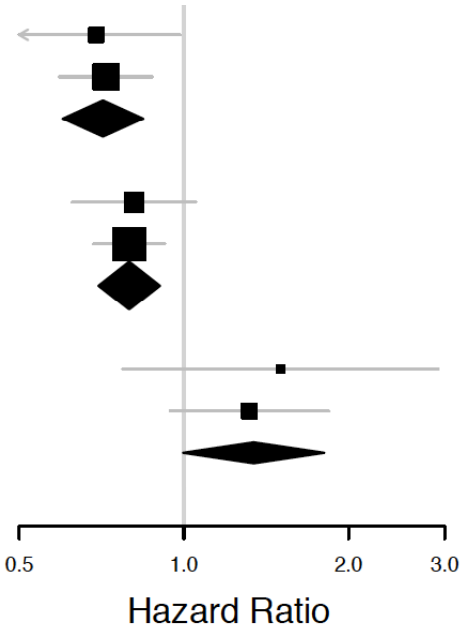


Heterogeneity P-value = 0.12

Pare et al. NEJM 2010 363(18): 1704-14

CURE – Loss-of-Function Carrier Status

Outcome	Carrier Status	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)
First Primary Composite	Carriers	11.6% (78/674)	8.0% (52/651)	0.69 (0.49–0.98)
	Noncarriers	13.0% (236/1819)	9.5% (179/1886)	0.72 (0.59–0.87)
	Total	**12.6% (314/2493)**	**9.1% (231/2537)**	**0.71 (0.60–0.84)**
Second Primary Composite	Carriers	19.0% (128/674)	15.7% (102/651)	0.81 (0.63–1.05)
	Noncarriers	20.7% (376/1819)	16.8% (317/1886)	0.79 (0.68–0.92)
	Total	**20.2% (504/2493)**	**16.5% (419/2537)**	**0.79 (0.70–0.90)**
Major Bleed	Carriers	2.2% (15/674)	3.2% (21/651)	1.50 (0.77–2.92)
	Noncarriers	3.3% (60/1819)	4.3% (81/1886)	1.32 (0.94–1.84)
	Total	**3.0% (75/2493)**	**4.0% (102/2537)**	**1.34 (1.00–1.81)**



No heterogeneity for the first primary (P=0.84), second primary (P=0.87) or safety (P=0.74) endpoint

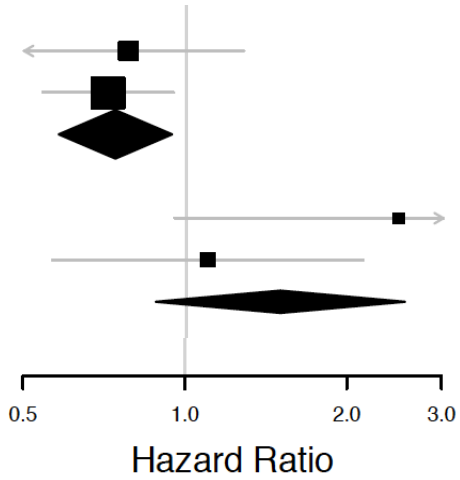
ACTIVE-A Trial

- 7,554 high-risk AF patients ineligible to warfarin randomized to clopidogrel (75mg) or Placebo on a background of ASA (75-100 mg)
- Median follow-up 3.6 years
- Primary efficacy: Stroke, MI, non-CNS embolism, CV Death

Connolly et al. NEJM 2009; 360: 2066-78

ACTIVE – Loss-of-Function Carrier Status

Outcome	Carrier Status	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)
First Primary Composite	Carriers	25.0% (35/140)	20.9% (29/139)	0.78 (0.48–1.28)
	Noncarriers	26.9% (118/438)	19.9% (84/422)	0.72 (0.54–0.95)
	Total	**26.5% (153/578)**	**20.1% (113/561)**	**0.74 (0.58–0.94)**
Major Bleed	Carriers	4.3% (6/140)	10.1% (14/139)	2.48 (0.95–6.47)
	Noncarriers	3.9% (17/438)	4.3% (18/422)	1.10 (0.56–2.13)
	Total	**4.0% (23/578)**	**5.7% (32/561)**	**1.49 (0.88–2.55)**



No heterogeneity for the primary (P=0.73) or safety (P=0.16) endpoints.

Pare et al. NEJM 2010 363(18): 1704-14

Which patient populations should be targeted for genotyping?

- From CURE and ACTIVE, no need to genotype in patients on chronic clopidogrel therapy
- Also lack of association in CHARISMA
- CYP2C19 genotypes appears to be a concern mosly for stent PCI patients

Should other genes be included?

- Heritability of platelet response to clopidogrel is estimated at ~72%
- CYP2C19 only explains ~12% of the variance in platelet response
- Where is the “missing heritability”?

Should other genes be included?

- ABCB1 association
  - P-glycoprotein efflux protein
  - ABCB1 3435C→T polymorphism associated with increased CV events in TT vs CC/CT (HR 1.72 CI 1.22-2.44)

- PON1 association
  - PON1 involved in clopidogrel bioactivation
  - PON1 Q192R polymorphism associated with increased stent thrombosis in QQ vs RR/QR (OR=3.6 CI 1.6-7.9)

Lancet 2010; 376: 1320-8. Mega et al.
Nat Med. 2011 Jan;17(1):110-6. Bouman et al.

Should other genes be included?

- Need for further replication of these novel genetic associations
- Need to integrate with known CYP2C19 variants in multiple studies
- New genetic determinants of response to clopidogrel will undoubtedly be discovered

Conclusion

- “Poor metabolizers” at highest risk but LOF carriers are also at increased risk
- CYP2C19 genotypes is mostly a concern for stent PCI patients
- Too early to include other genes, but the future looks bright!

Should we genotype patients in real life?
“Antiplatelet controversies” Thursday 12:12, Main Arena

Thanks!

CURE/ACTIVE Genetics Team

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