Effects of CYP2C19 genotype on clopidogrel treatment in the CURE and ACTIVE trials

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

Background

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

- “Black 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

Key Questions

- Do CYP2C19 genetic associations extend to the CURE and ACTIVE population?
- Will an effect be detected in the placebo group?
- Are “poor metabolizers” or “LOF allele carriers” at risk?
- What is the impact of the gain-of-function allele?

CYP2C19 Alleles

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%

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

- 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 Genetics Baseline Characteristics

- The benefit of clopidogrel treatment on the first primary composite efficacy outcome was similar to the parent study:

CURE Overall: 582 events, 9.3 % versus 719 events, 11.4%; HR=0.80 95% CI 0.72-0.90, P<0.001
CURE-Genetics: 231 events, 9.1% versus 316 events, 12.6%; HR=0.71 95% CI 0.60-0.84, P<0.001

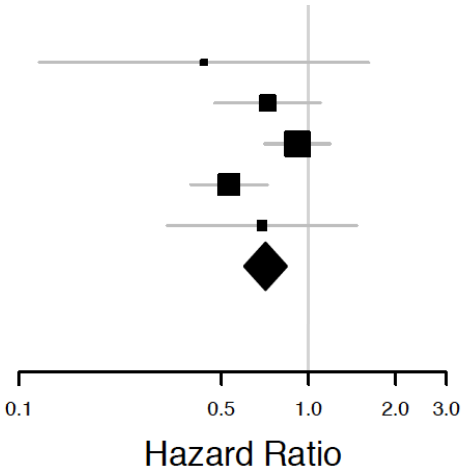
Characteristic	OVERALL			CURE-Genetics		
	Placebo	Clopidogrel	Total	Placebo	Clopidogrel	Total
N	6303	6259	12562	2510	2549	5059
Female (%)	38.3	38.7	38.5	40.9	41.2	41.0
Age	64.2 (11.3)	64.2 (11.3)	64.2 (11.3)	63.9 (11.1)	63.8 (11.0)	63.8 (11.0)
BMI	27.4 (4.1)	27.4 (4.1)	27.4 (4.1)	27.6 (4.1)	27.7 (4.2)	27.6 (4.2)
Diabetes (%)	22.8	22.4	22.6	21.5	20.7	21.1
Smoking (%)	22.7	23.4	23.0	21.6	23.1	22.4
SBP	134.1 (22.0)	134.4 (22.5)	134.2 (22.2)	134.6 (22.0)	135.5 (22.3)	135.0 (22.1)
PCI without stent	4.0	3.7	3.9	3.9	3.2	3.5
PCI with stent	17.3	17.3	17.3	13.5	15.5	14.5
CABG	16.8	16.2	16.5	16.3	15.9	16.1

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

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)**

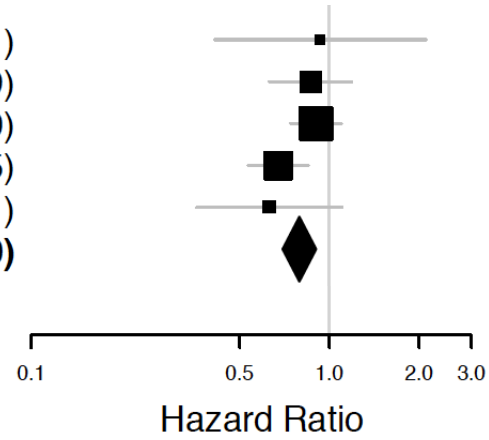


Heterogeneity P-value = 0.12

CURE – Metabolizer Phenotypes

- Second primary composite outcome

Metabolizer Phenotype	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)
Poor	20.0% (11/55)	21.3% (13/61)	0.93 (0.41–2.11)
Intermediate	19.0% (84/442)	16.0% (70/437)	0.87 (0.63–1.19)
Extensive	20.9% (206/987)	18.7% (193/1033)	0.90 (0.74–1.10)
Ultra	20.2% (167/826)	14.5% (123/847)	0.68 (0.53–0.85)
Unknown	19.3% (34/176)	12.5% (19/152)	0.63 (0.36–1.11)
Total	**20.2% (502/2486)**	**16.5% (418/2530)**	**0.79 (0.70–0.90)**

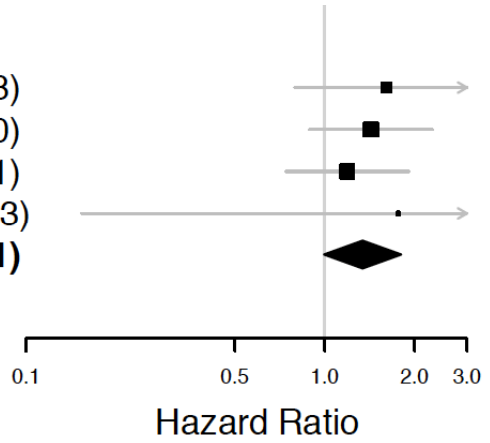


Heterogeneity P-value = 0.29

CURE – Metabolizer Phenotypes

- Major bleed

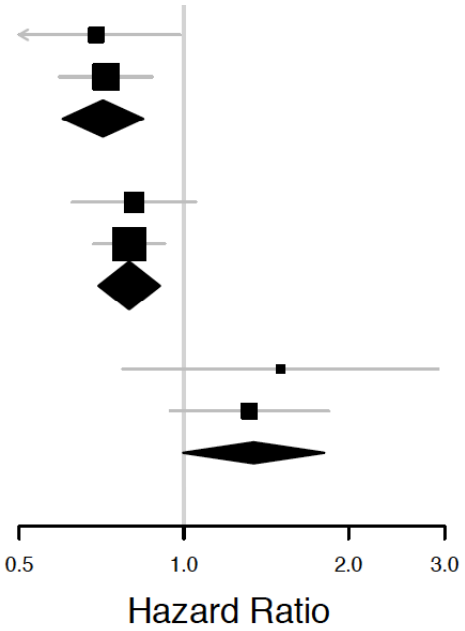
Metabolizer Phenotype	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)
Poor	1.8% (1/55)	0.0% (0/61)	N/A
Intermediate	2.9% (13/442)	4.3% (19/437)	1.61 (0.79–3.28)
Extensive	2.9% (29/987)	4.1% (42/1033)	1.43 (0.89–2.30)
Ultra	3.8% (31/826)	4.6% (39/847)	1.19 (0.74–1.91)
Unknown	0.6% (1/176)	1.3% (2/152)	1.77 (0.15–20.33)
Total	**3.0% (75/2486)**	**4.0% (102/2530)**	**1.34 (1.00–1.81)**



Heterogeneity P-value = 0.64

CURE – Loss-of-Function Carrier Status

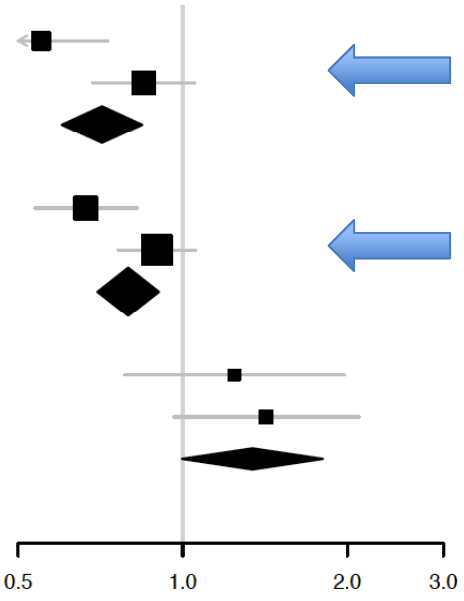
Outcome	Carrier Status	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)
First Primary Composite	Carriers	11.6% (78/674)	8.0% (52/651)	0.69 (0.49–0.98)
	Noncarriers	13.0% (236/1819)	9.5% (179/1886)	0.72 (0.59–0.87)
	Total	**12.6% (314/2493)**	**9.1% (231/2537)**	**0.71 (0.60–0.84)**
Second 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

CURE – Gain-of-Function Carrier Status

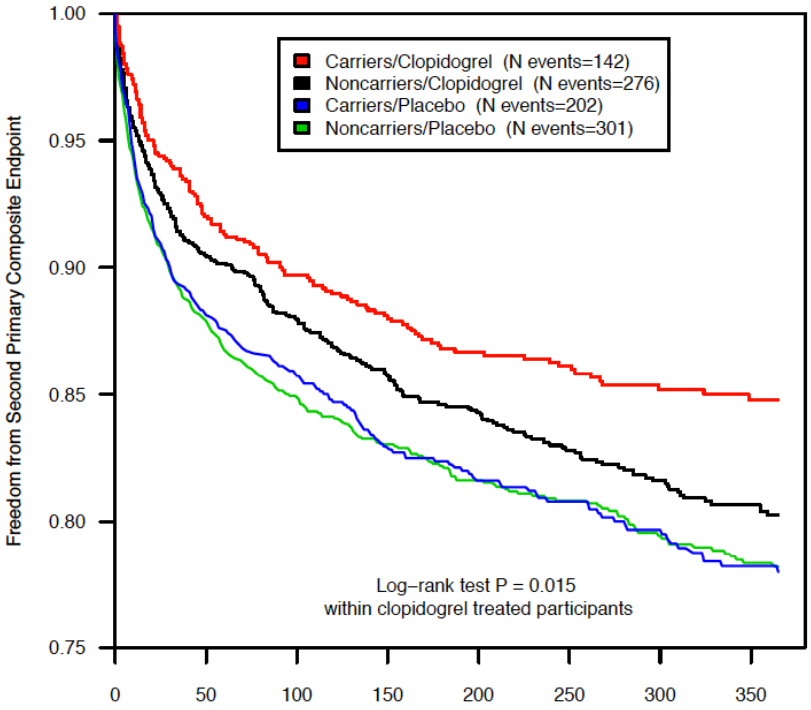
Outcome	Carrier Status	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)
First Primary Composite	Carriers	13.0% (131/1004)	7.7% (77/1001)	0.55 (0.42–0.73)
	Noncarriers	12.2% (181/1489)	10.0% (153/1536)	0.85 (0.68–1.05)
	Total	**12.5% (312/2493)**	**9.1% (230/2537)**	**0.71 (0.60–0.84)**
Second Primary Composite	Carriers	20.1% (202/1004)	14.2% (142/1001)	0.66 (0.54–0.82)
	Noncarriers	20.2% (301/1489)	18.0% (276/1536)	0.90 (0.76–1.06)
	Total	**20.2% (503/2493)**	**16.5% (418/2537)**	**0.79 (0.70–0.90)**
Major Bleed	Carriers	3.2% (32/1004)	4.1% (41/1001)	1.24 (0.78–1.97)
	Noncarriers	2.9% (43/1489)	4.0% (61/1536)	1.42 (0.96–2.10)
	Total	**3.0% (75/2493)**	**4.0% (102/2537)**	**1.34 (1.00–1.81)**



Significant heterogeneity for the first (P=0.02) and second (P=0.03) primary endpoints

No heterogeneity for the safety (P=0.66) endpoint

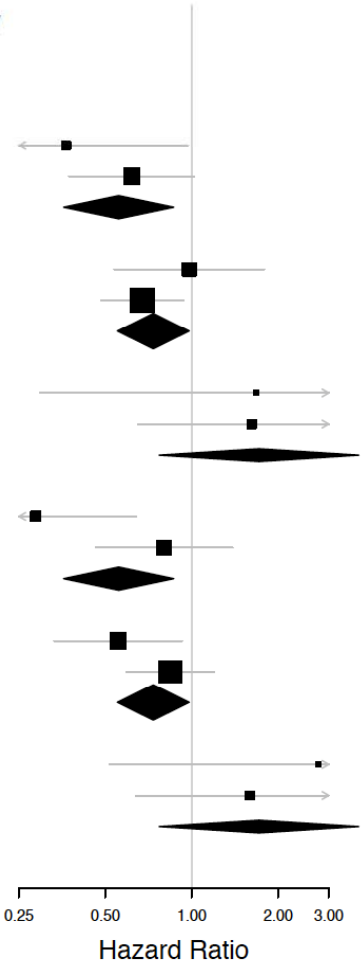
CURE – Freedom From Second Primary Endpoint According to GOF Carrier Status



No. at Risk								
Carriers Clopidogrel	1001	919	882	780	664	592	467	390
Noncarriers Clopidogrel	1536	1386	1319	1174	1035	897	736	612
Carriers Placebo	1004	883	851	740	629	551	453	374
Noncarriers Placebo	1489	1310	1251	1122	970	842	701	572

CURE – Sub-Group Analysis
736 patients with stent PCI

Carrier Type	Outcome	Carrier Status	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)	Heterogeneity P Value
Loss–of–Function	First Primary Composite	Carriers	16.9% (14/83)	6.2% (6/97)	0.37 (0.14–0.96)	
		Noncarriers	13.6% (35/257)	9.1% (27/298)	0.62 (0.37–1.02)	
		Total	**14.4% (49/340)**	**8.4% (33/395)**	**0.56 (0.36–0.87)**	**0.37**
	Second Primary Composite	Carriers	25.3% (21/83)	23.7% (23/97)	0.98 (0.54–1.79)	
		Noncarriers	30.0% (77/257)	21.8% (65/298)	0.67 (0.48–0.93)	
		Total	**28.8% (98/340)**	**22.3% (88/395)**	**0.73 (0.55–0.98)**	**0.28**
	Major Bleed	Carriers	2.4% (2/83)	4.1% (4/97)	1.68 (0.30–9.55)	
		Noncarriers	2.7% (7/257)	4.7% (14/298)	1.61 (0.65–4.01)	
		Total	**2.6% (9/340)**	**4.6% (18/395)**	**1.71 (0.77–3.82)**	**0.85**
Gain–of–Function	First Primary Composite	Carriers	17.6% (23/131)	5.6% (8/143)	0.29 (0.13–0.64)	
		Noncarriers	12.4% (26/209)	9.9% (25/253)	0.80 (0.46–1.39)	
		Total	**14.4% (49/340)**	**8.3% (33/396)**	**0.56 (0.36–0.87)**	**0.03**
	Second Primary Composite	Carriers	27.5% (36/131)	17.5% (25/143)	0.55 (0.33–0.92)	
		Noncarriers	29.7% (62/209)	24.9% (63/253)	0.84 (0.59–1.19)	
		Total	**28.8% (98/340)**	**22.2% (88/396)**	**0.73 (0.55–0.98)**	**0.21**
	Major Bleed	Carriers	1.5% (2/131)	3.5% (5/143)	2.75 (0.52–14.64)	
		Noncarriers	3.3% (7/209)	5.1% (13/253)	1.60 (0.64–4.01)	
		Total	**2.6% (9/340)**	**4.5% (18/396)**	**1.71 (0.77–3.82)**	**0.74**



ACTIVE-A Trial

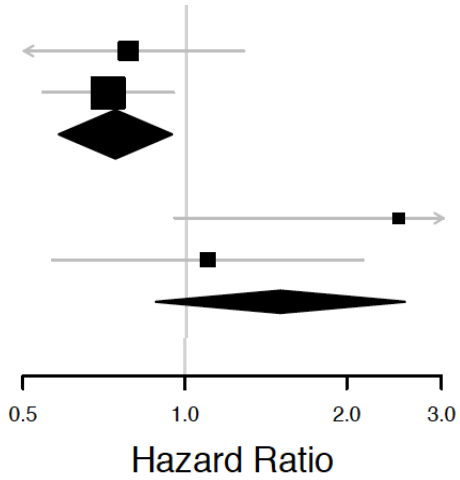
- 7,554 high-risk AF patients ineligibles to warfarin randomized to clopidogrel (75mg) or Placebo on a background of ASA (75-100 mg)
- Median follow-up 3.6 years
- Primary efficacy: Stroke, MI, non-CNS embolism, CV Death
- 1156 patients included in ACTIVE-Genetics, with similar characteristics as in the main study
- Similar benefit of clopidogrel treatment in ACTIVE-Genetics as in the parent study

ACTIVE Overall: 832 events, 22.1 % versus 924 events, 24.4%; HR=0.89 95% CI 0.81-0.98, P=0.01
ACTIVE-Genetics: 114 events, 20.0% versus 154 events, 26.3%; HR=0.74 95% CI 0.58-0.94, P=0.01

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

ACTIVE – Loss-of-Function Carrier Status

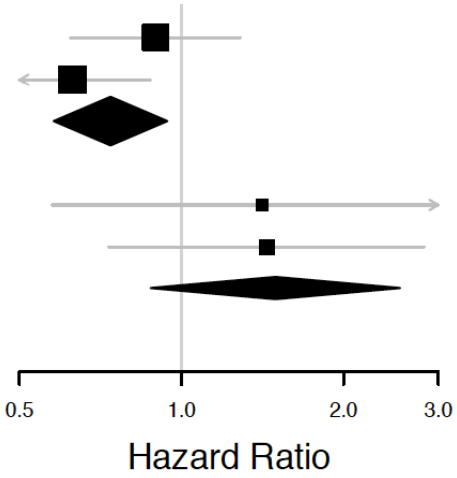
Outcome	Carrier Status	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)
First Primary Composite	Carriers	25.0% (35/140)	20.9% (29/139)	0.78 (0.48–1.28)
	Noncarriers	26.9% (118/438)	19.9% (84/422)	0.72 (0.54–0.95)
	Total	**26.5% (153/578)**	**20.1% (113/561)**	**0.74 (0.58–0.94)**
Major 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) endpoint

ACTIVE – Gain-of-Function Carrier Status

Outcome	Carrier Status	Placebo Event Rate	Clopidogrel Event Rate	Hazard Ratio (95% CI)
First Primary Composite	Carriers	25.8% (61/236)	21.8% (57/261)	0.90 (0.62–1.29)
	Noncarriers	27.2% (93/342)	18.4% (56/305)	0.63 (0.45–0.88)
	Total	**26.6% (154/578)**	**20.0% (113/566)**	**0.74 (0.58–0.94)**
Major Bleed	Carriers	3.4% (8/236)	4.6% (12/261)	1.41 (0.57–3.46)
	Noncarriers	4.4% (15/342)	6.6% (20/305)	1.44 (0.73–2.82)
	Total	**4.0% (23/578)**	**5.7% (32/566)**	**1.49 (0.88–2.55)**



No heterogeneity for the primary (P=0.17) or safety (P=0.96) endpoint

Conclusion

- No effect of CYP2C19 loss-of-function alleles on efficacy and safety in CURE and ACTIVE
- Suggests there is no need for genotyping in patients on chronic clopidogrel therapy
- No effect observed in the placebo group
- Effect of gain-of-function allele on efficacy endpoints observed in CURE participants

Thanks!

CURE/ACTIVE Genetics Team

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