Personalized Antiplatelet Therapy Possible? Not so fast…

Angioplasty Summit – TCAP Meeting 2011

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Disclosures

- I have received research support and honoraria from BMS and sanofi-aventis

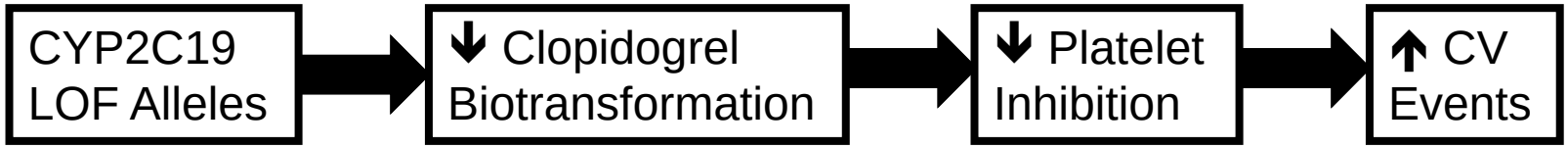
- As a geneticist, I strongly believe routine personalized medicine based on genotypes will eventually be an important component of patient care!

Outline

- Using the right outcome to assess efficacy and safety of antiplatelet therapy
- Does CYP2C19/platelet function testing (PFT) provide clinically significant prognostic value?
- Does intervention that alters the risk factor lead to clinical benefit?

Choosing the right outcome

- Neither the effect of CYP2C19 genotypes/PFT nor the causality of the association are at stake in PCI patients



- The effect of CYP2C19 genotypes and PFT varies according to outcome
  - Stent thrombosis seems particularly sensitive

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

Choosing the right outcome

- Any outcome really is a surrogate for mortality and patient well-being

- Patient outcome should be as representative of these difficult to measure endpoints
  - Need to be inclusive in our definition

- Major Adverse Cardiovascular Events best captures all types of events but…

Choosing the right outcome

MACE (11.7%)
MI (6.9%)
Death from vascular causes (5.1%)
Stent thrombosis (1.9%; definite)
Ischemic stroke (1.1%)

Major bleeding (11.2%)
Life-threatening or fatal bleeding (5.8%)
Fatal bleeding (0.3%)

Taken from the PLATO study, clopidogrel arm
Wallentin et al. NEJM 361(11) 2009: 1045-57

Does CYP2C19 testing/PFT provide clinically significant prognostic value?

- P-values alone are not representative of clinical usefulness
- Effect size matters!
  - HR of 3.0 not the same as 1.5
- Highest ORs tend to be reported by smaller studies

Does CYP2C19 testing/PFT provide clinically significant prognostic value?

- CYP2C19 effect on MACE in studies >500 individuals

Study	%PCI	Loss-of-function Carriers		No Loss-of-Function Allele		Unadj. OR (95%CI)	p
		No. Events	No. at Risk	No. Events	No. at Risk		
EXCELSIOR	100	5	243	7	554	1.65 (0.47-5.36)	0.53
TRITON	100	46	395	83	1064	1.56 (1.06-2.27)	0.03
FAST-MI	70	63	635	193	1573	0.79 (0.58-1.06)	0.12
RECLOSE	100	15	247	14	525	2.36 (1.11-5.05)	0.03
ISAR	100	55	680	119	1805	1.25 (0.89-1.73)	0.22
Intermountain	100	68	344	141	906	1.34 (0.97-1.84)	0.09
PLATO	66	149	1388	332	3516	1.15 (0.94-1.41)	0.18
CURE	15	52	651	179	1886	0.83 (0.60-1.14)	0.27
OVERALL	**73**	**453**	**4583**	**1068**	**11829**	**1.12 (0.99-1.26)**	**0.06**
OVERALL w/o CURE	**83**	**401**	**3932**	**889**	**9943**	**1.17 (1.04-1.33)**	**0.01**

Unadjusted analysis is relevant since genotypes are unlikely to be adjusted for patient characteristics to determine therapy

Does CYP2C19 testing/PFT provide clinically significant prognostic value?

- Comparing "poor metabolizers" to individuals without any LOF in studies >500 participants

Study	%PCI	Two Loss-of-function Alleles		No Loss-of-Function Allele		Unadj. OR (95%CI)	p
		No. Events	No. at Risk	No. Events	No. at Risk		
TRITON	100	4	38	83	1064	1.44 (0.41-3.73)	0.53
FAST-MI	70	10	58	193	1573	1.51 (0.71-2.91)	0.31
RECLOSE	100	2	26	14	525	3.21 (0.44-12.6)	0.17
ISAR	100	3	47	119	1805	1.01 (0.23-2.83)	1
Intermountain	100	3	14	141	906	1.53 (0.33-5.07)	0.47
CURE	15	4	61	178	1880	0.70 (0.20-1.72)	0.65
OVERALL	**73**	**26**	**244**	**728**	**7753**	**1.22 (0.80-1.85)**	**0.36**
OVERALL w/o CURE	**91**	**22**	**183**	**550**	**5873**	**1.43 (0.90-2.27)**	**0.13**

Does CYP2C19 testing/PFT provide clinically significant prognostic value?

- Similar results for PFT
  - Smaller studies report higher ORs (>6 in some cases)
  - Compounded by lack of predetermined threshold
  - HR 1.68 (95%CI 0.76-3.72; p=0.2) in GRAVITAS
  - Further complicated by entanglement of pharmacologic effect and intrinsic platelet factors on platelet reactivity

Bonello et al. JACC 56(12) 2010: 919-33
Price et al. JAMA 305(11) 2011: 1097-1105

Does intervention that alters the risk factor lead to clinical benefit?

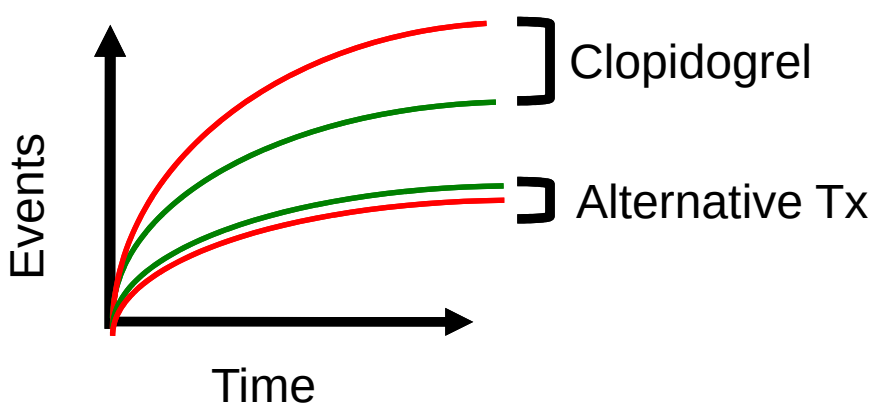
- Association of CYP2C19 genotypes with outcome is not sufficient to warrant clinical testing

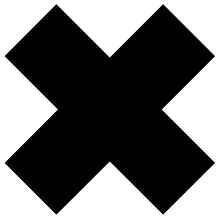
- To justify testing, there needs to be clear evidence that either:

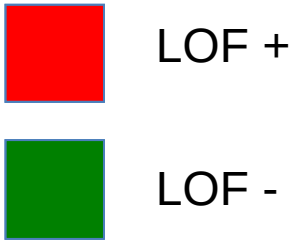
  – A group of patients will derive greater benefit from clopidogrel than the alternative antiplatelet treatment

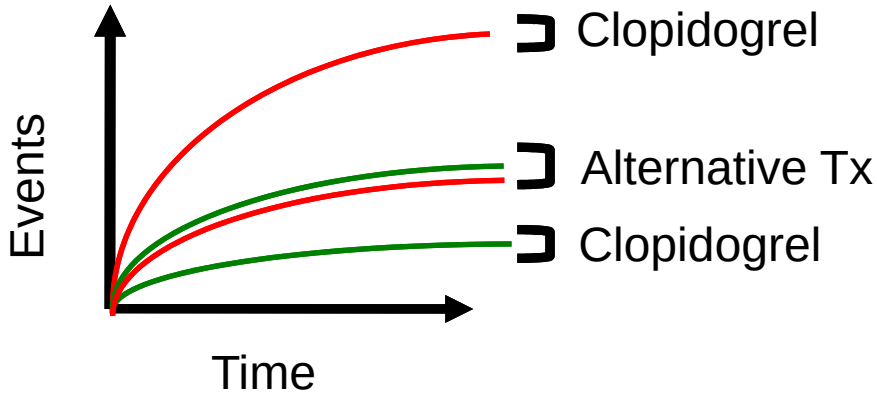
  – A group of patient will derive equal benefit from clopidogrel as the more expensive alternative

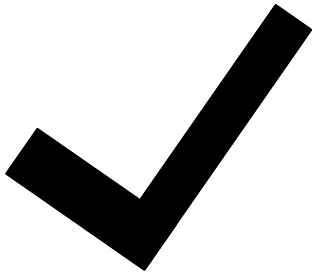
Does intervention that alters the risk factor lead to clinical benefit?











Does intervention that alters the risk factor lead to clinical benefit?

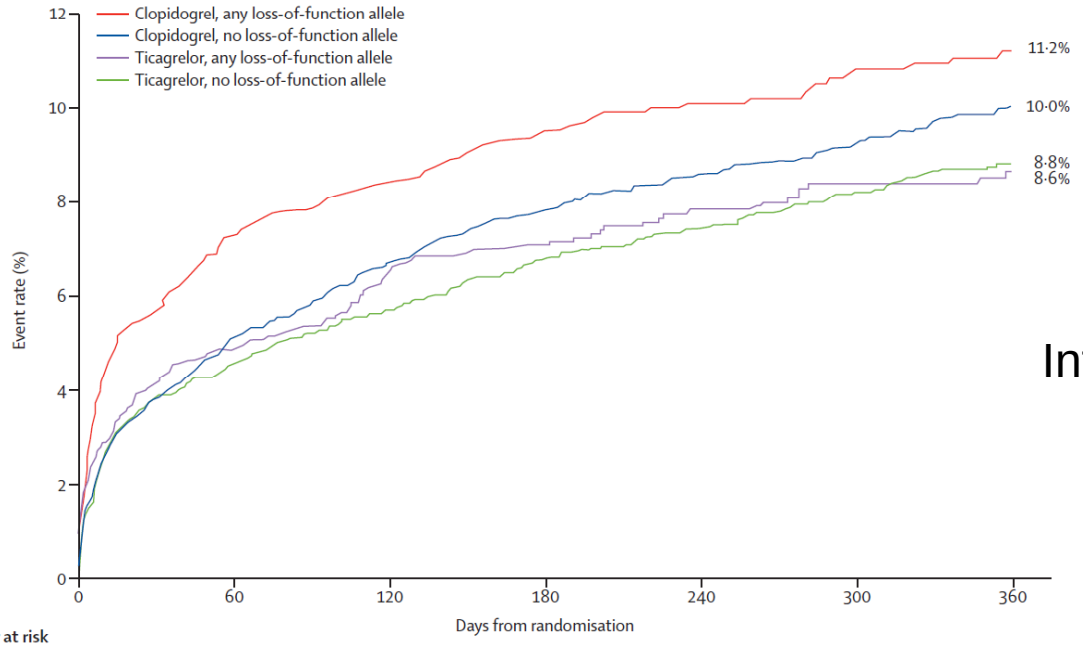
PLATO-Genetics Analysis

- 18 624 patients with or without ST-elevation ACS
  - Clopidogrel (75 mg QD) Vs ticagrelor (90 mg BID)
  - Median follow-up of 277 days
- Outcomes
  - First Primary: CV death, MI, Stroke
  - Safety: Major bleed
- 10,285 patients included in the genetic analysis

Wallentin et al. Lancet 2010; 376: 1320-8

Does intervention that alters the risk factor lead to clinical benefit?

PLATO-Genetics Analysis



Number at risk							
Clopidogrel							
Any loss-of-function allele	1388	1275	1259	1226	1027	801	658
No loss-of-function allele	3516	3321	3256	3186	2691	2123	1757
Ticagrelor							
Any loss-of-function allele	1384	1305	1274	1250	1053	834	683
No loss-of-function allele	3554	3352	3301	3222	2718	2127	1761

P=0.25

Interaction P-value = 0.46

Wallentin et al. Lancet 2010; 376: 1320-8

Does intervention that alters the risk factor lead to clinical benefit?

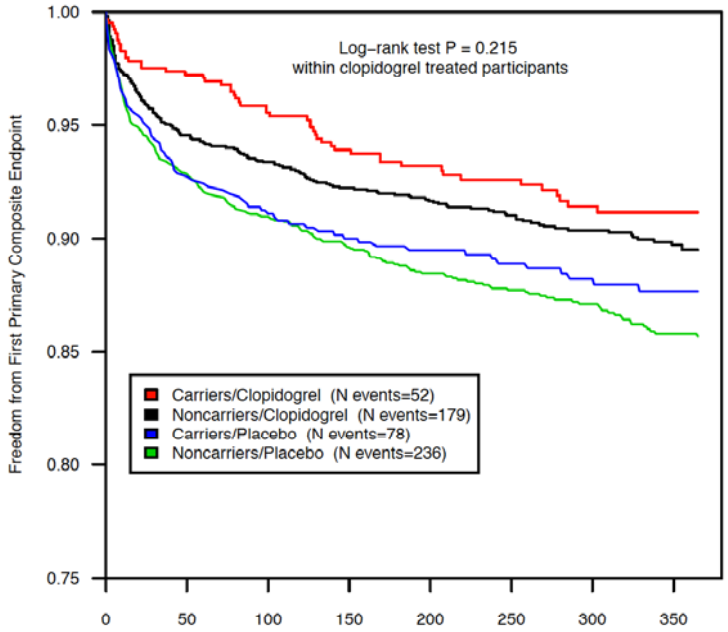
CURE-Genetics Analysis

- 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 month
- Outcomes
  - First Primary: CV death, MI, Stroke
  - Second Primary: First primary, or recurrent ischemia, or UA
  - Safety: Major bleed (life-threatening or not)
- 5,059 patients included in the genetic analysis

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

Does intervention that alters the risk factor lead to clinical benefit?

CURE-Genetics Analysis



No. at Risk								
Carriers Clopidogrel	651	632	608	545	484	425	358	297
Noncarriers Clopidogrel	1886	1778	1723	1541	1352	1191	960	804
Carriers Placebo	674	626	609	551	483	423	356	281
Noncarriers Placebo	1819	1686	1634	1456	1259	1103	922	774

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

Other considerations

- Need for further clinical studies
  - Estimates of risk in poor metabolizers versus LOF allele carriers
  - Explain differences in genetic effect between studies
  - Define the best assay and cut-off for PFT
- Need for further genetic studies
  - Heritability ~ 72% but only ~12% explained
- Cost of genetic/PFT testing as compared to alternative treatment
  - Genetic testing can cost up to 500$

Conclusion

- The impact of CYP2C19 genotypes/PFT on MACE is real but modest
- There is currently no evidence to support better outcomes from genetically-guided therapy
- Need for randomized trials evaluating genetic testing/PFT as an intervention
  - GRAVITAS, TRIGGER-PCI, ARTIC, etc.
- Future is bright for personalized therapy, but might not (yet) be ready for primetime

Thank You!


McMaster
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Population Health Research Institute
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