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Clopidogrel Pharmacogenomics: Outside the Box

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Agenda

- Response heterogeneity and CYP2C19
- Brief regulatory history and labeling
- Clinical outcomes data and meta-analyses
- Stakeholder responses
- Managing the gene-drug interaction
- Panel discussion



Discussion Questions

- When, if ever, should a drug be contraindicated (or not recommended) based solely on PK/PD data (i.e., in the absence of clinical outcome data) that a drug-drug or drug-gene interaction:
 - Reduces the serum concentration of the drug's active moiety, when the drug is used to prevent morbid events?
 - When the interaction causes toxicity
- Should clopidogrel be contraindicated (or not recommended) in patients **known to have** two loss-of-function (LOF) alleles ("poor metabolizers") for CYP2C19? Alternatively, should labeling call for universal testing for genotype?
- Should clopidogrel be contraindicated (or not recommended) in all patients whose CYP2C19 genotype is not known?
- Should clopidogrel be contraindicated in patients whose ancestry indicates they are at increased risk of having two LOF alleles (i.e., east Asians, south Asians, and Pacific Islanders) who have not been genotyped?
- Could a trial of the effect of having two LOF alleles on CV outcomes in patients being administered clopidogrel be performed? If so, can you suggest possible designs for such a trial?
- To what extent, if at all, should the clinical outcome data (with its limitations) related to the pharmacogenetic interaction be described in labeling?

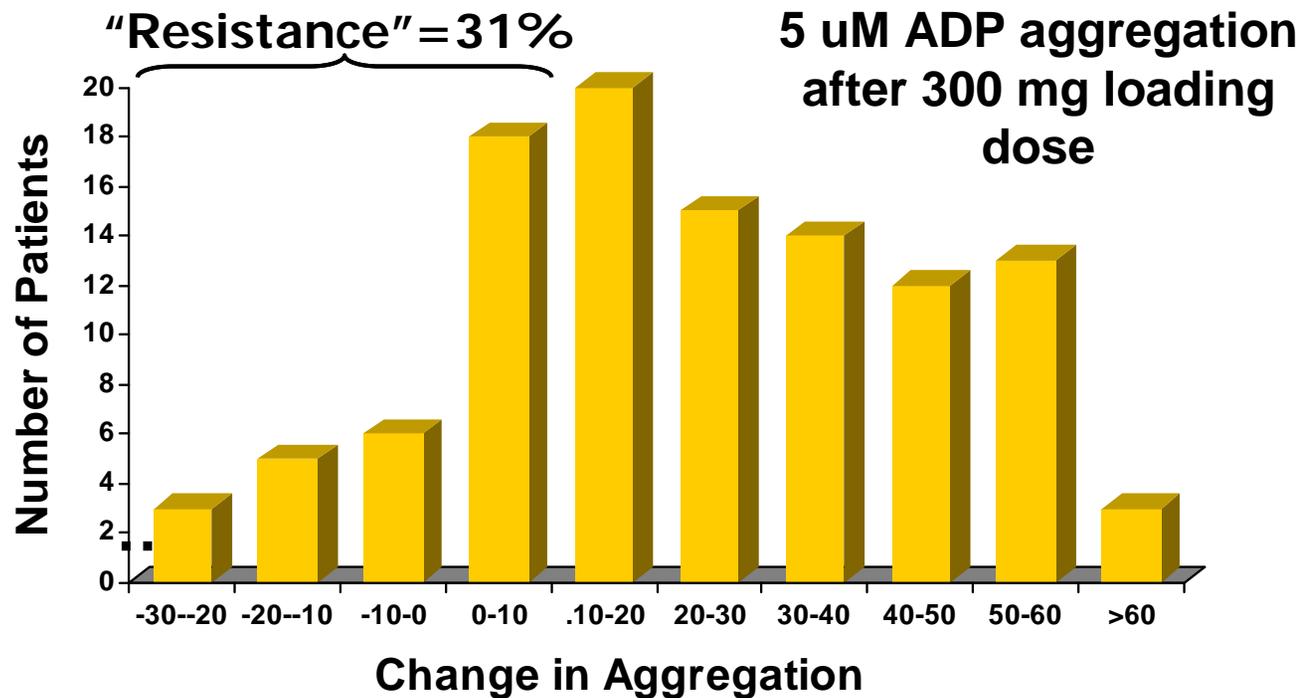


Clopidogrel Bisulfate (PLAVIX[®], sanofi aventis/BMS)

- Thienopyridine drug that irreversibly inhibits platelet aggregation via the P2Y₁₂ (ADP) receptor
- Approved in 1997, 25 million units sold in 2010 (\$4.7B)
- Indication: to reduce of the rate of death, MI, and stroke (+/- others) in patients with
 - Acute coronary syndromes (ACS; unstable angina, non-ST elevation MI, ST elevation MI)
 - Recent MI, recent stroke, or established peripheral arterial disease
- Dosing
 - Recent MI, stroke, peripheral disease: 75 mg daily
 - ACS (with aspirin): 300 mg x 1 → 75 mg daily



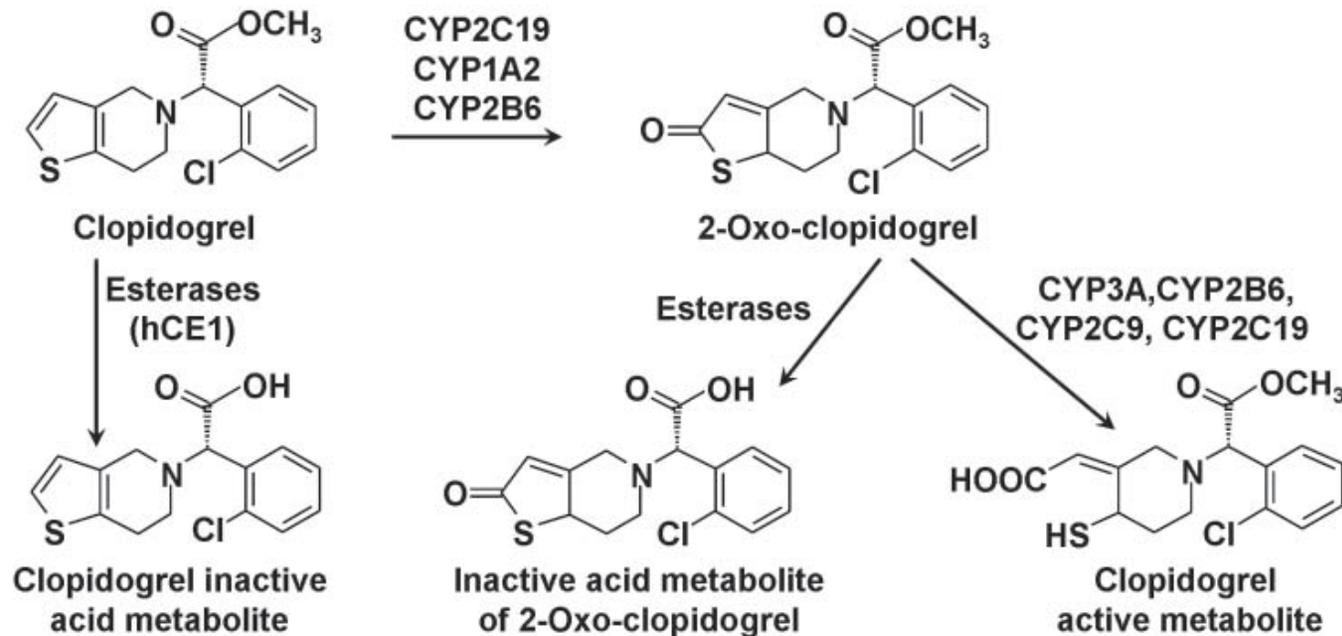
Clopidogrel Responses are Highly Variable



Clopidogrel Dosing in Practice is Variable

- Unstable Angina / Non-ST elevation MI (ACC/AHA 2012)
 - Optimum loading dose requires clinical consideration
 - 300 to 600 mg → 75 mg daily
(consider 150 mg daily for the first week)
- Percutaneous coronary intervention (PCI; ACCF/AHA/SCAI 2011)
 - 600 mg (300 mg if fibrinolytics given) → 75 mg daily
 - Duration depends on type of stent
- ST elevation MI (ACC/AHA 2009)
 - At least 300 to 600 mg should be given

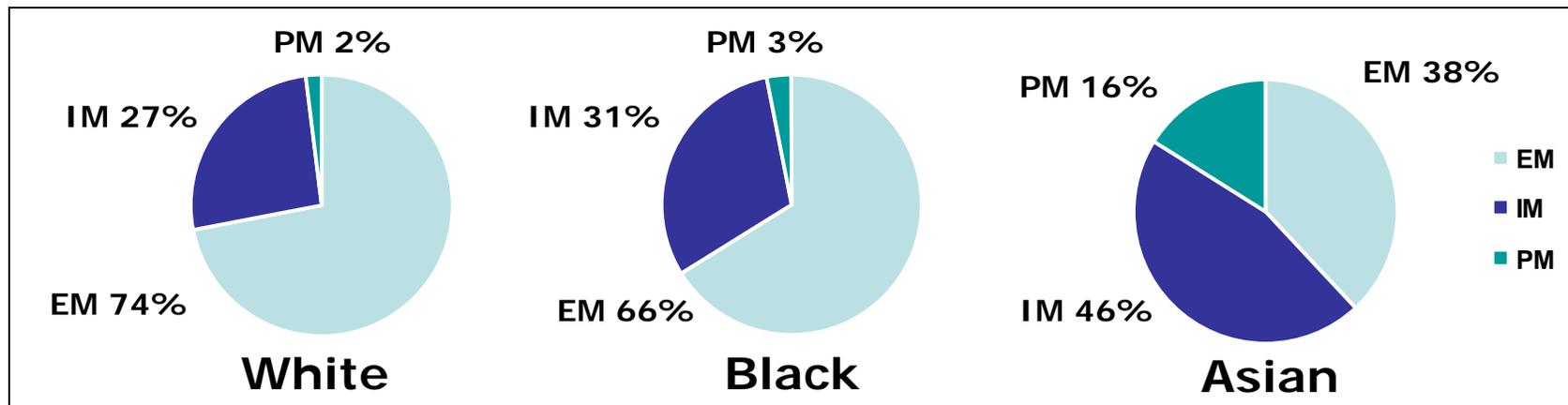
Clopidogrel is a Prodrug Activated by Polymorphic CYP450 enzymes





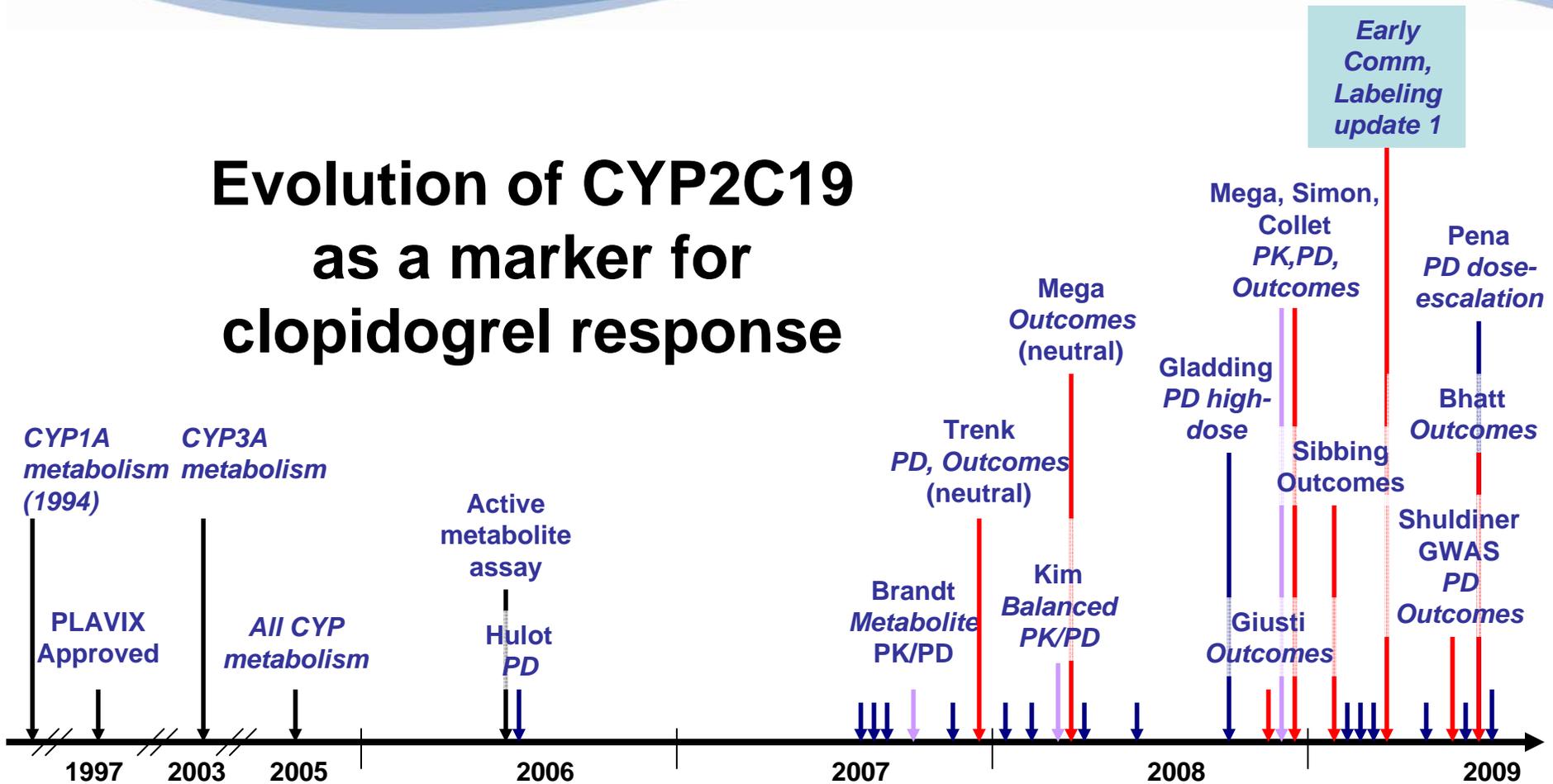
CYP2C19 Genetics

- *1 → normal
- *2 → splicing defect → no activity
- *3 → premature stop codon → no activity
- *17 → increased transcription → 'ultrarapid' metabolism





Evolution of CYP2C19 as a marker for clopidogrel response

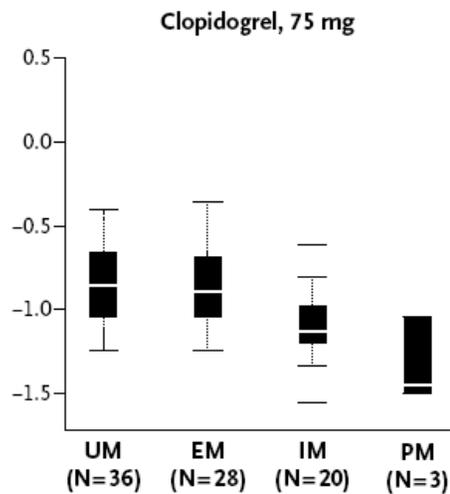


- ↓ PK (AM; N=4)
- ↓ PD (N=28)
- ↓ Outcomes (N=10)

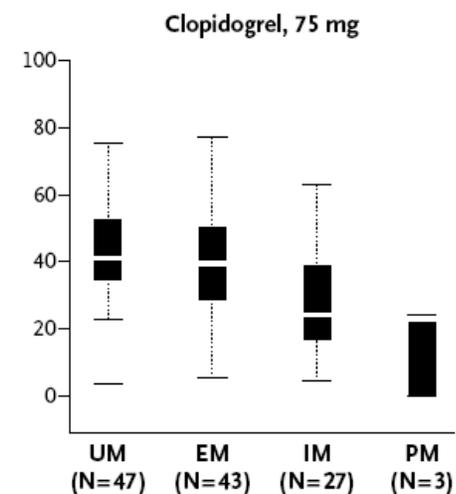


CYP2C19 Polymorphisms Influence Clopidogrel PK, PD

Drug exposure

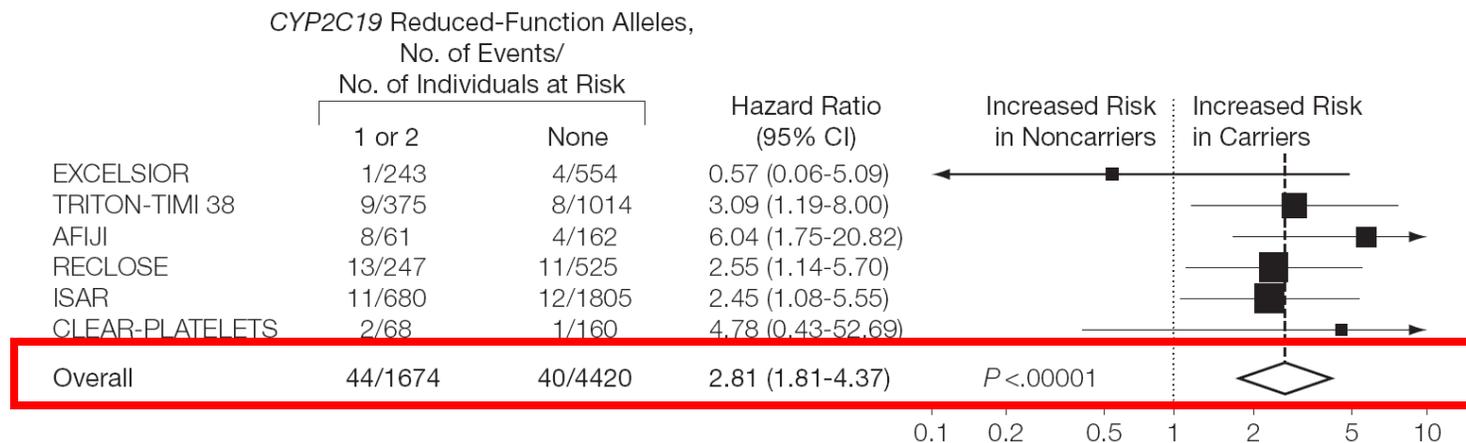


Antiplatelet response

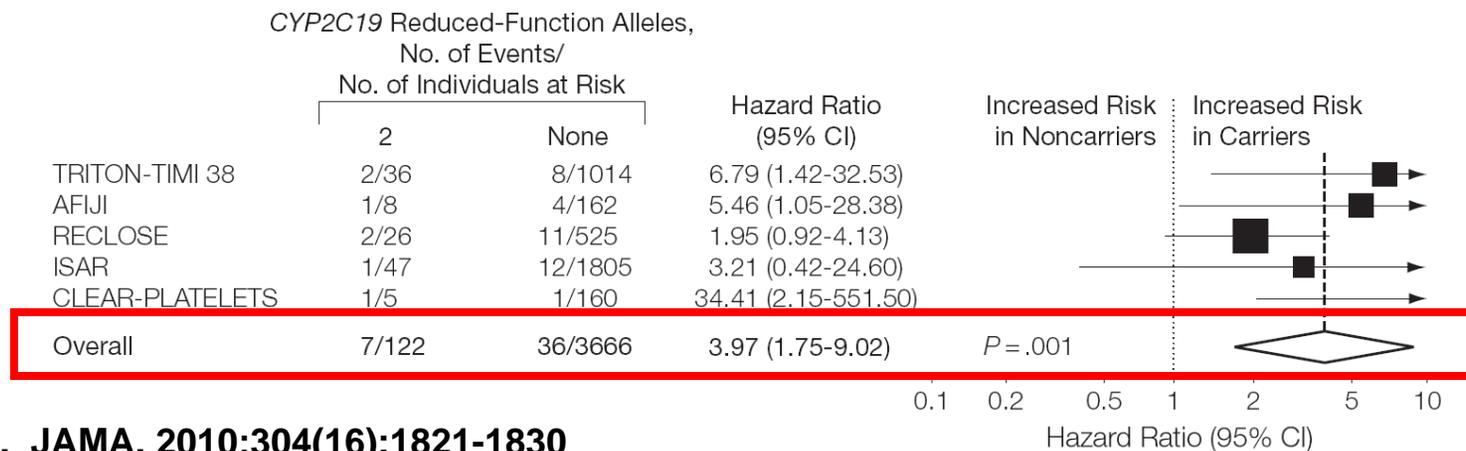


Impaired CYP2C19 Metabolism Is Associated with Higher Rates of Stent Thrombosis

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

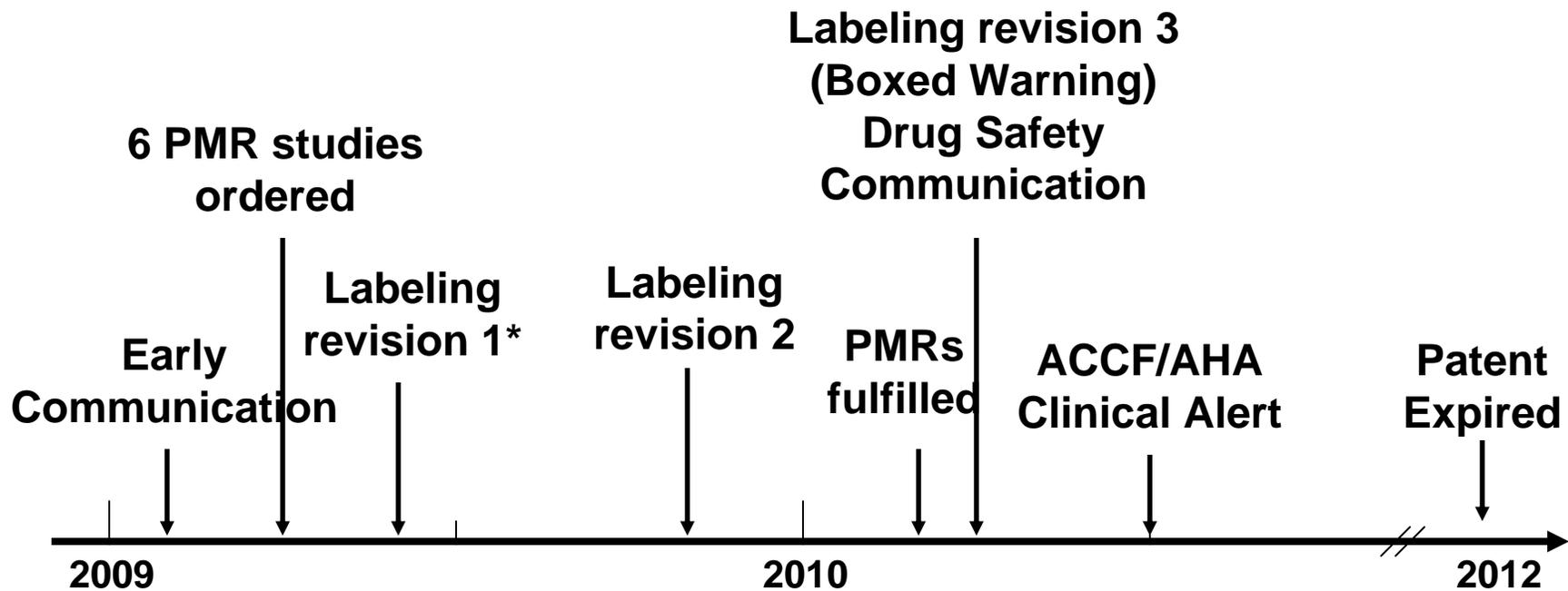


C Carriers of 2 *CYP2C19* Reduced-Function Alleles vs Noncarriers





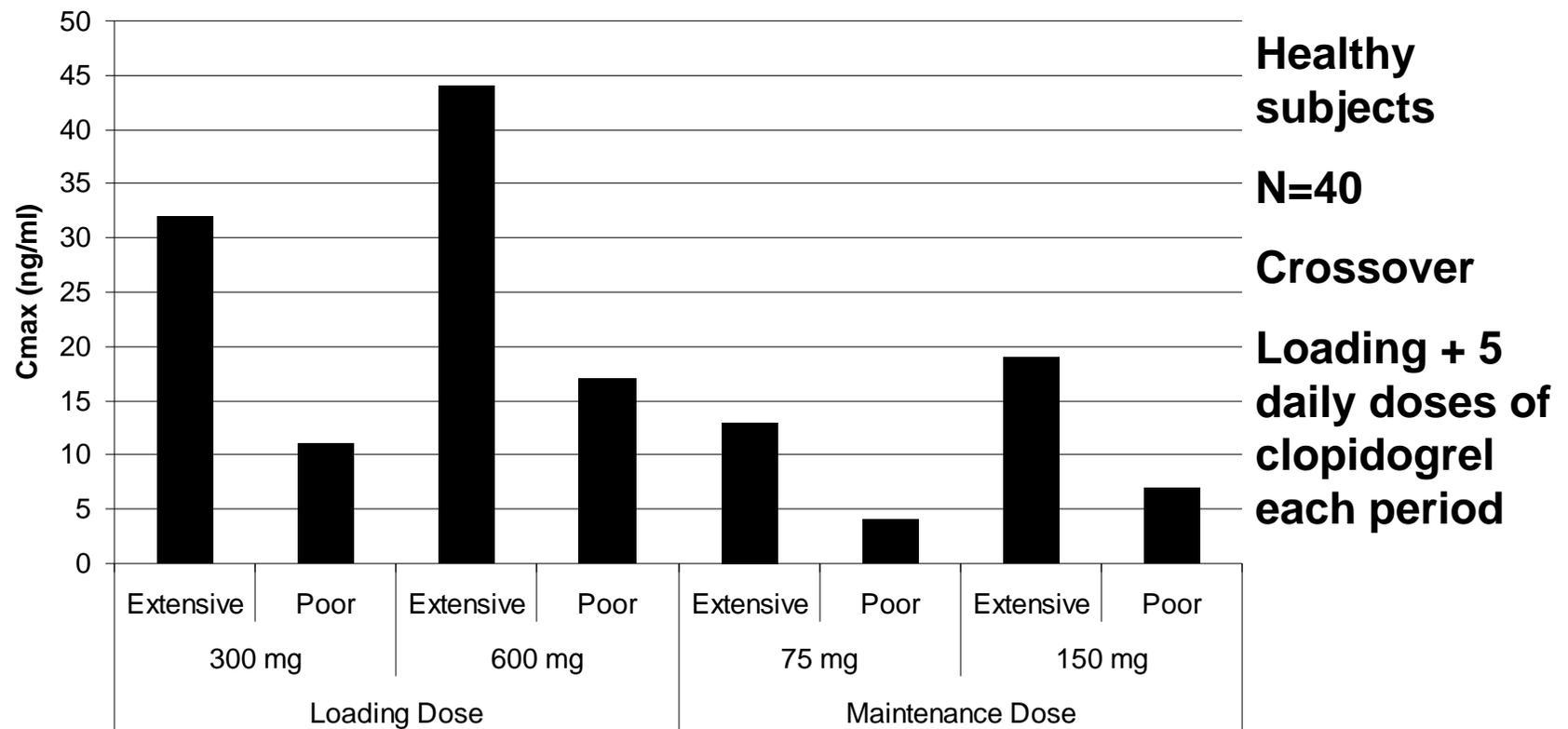
Regulatory Actions



* Warnings, Clinical Pharmacology, Dosage and Administration

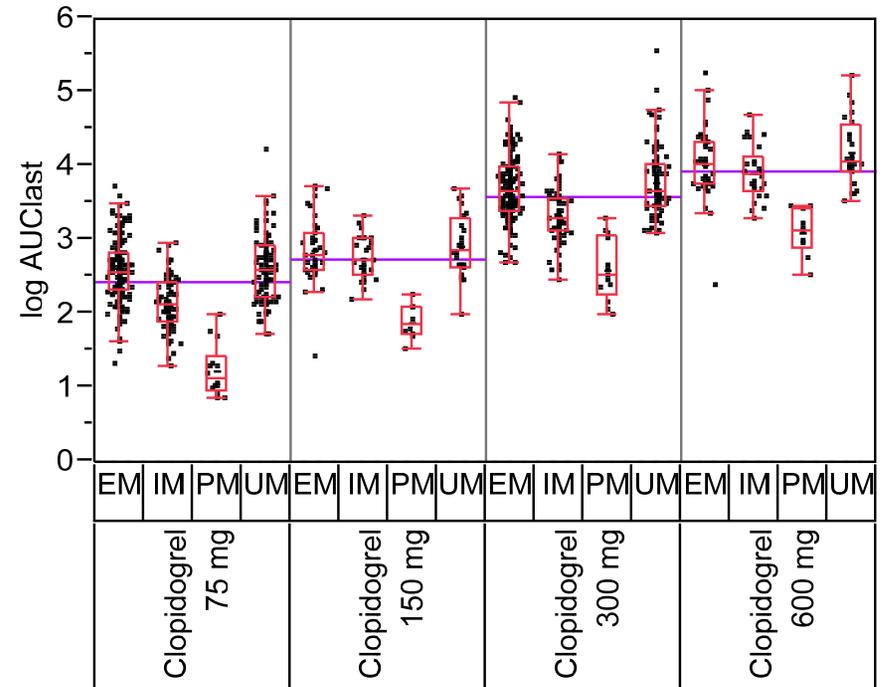
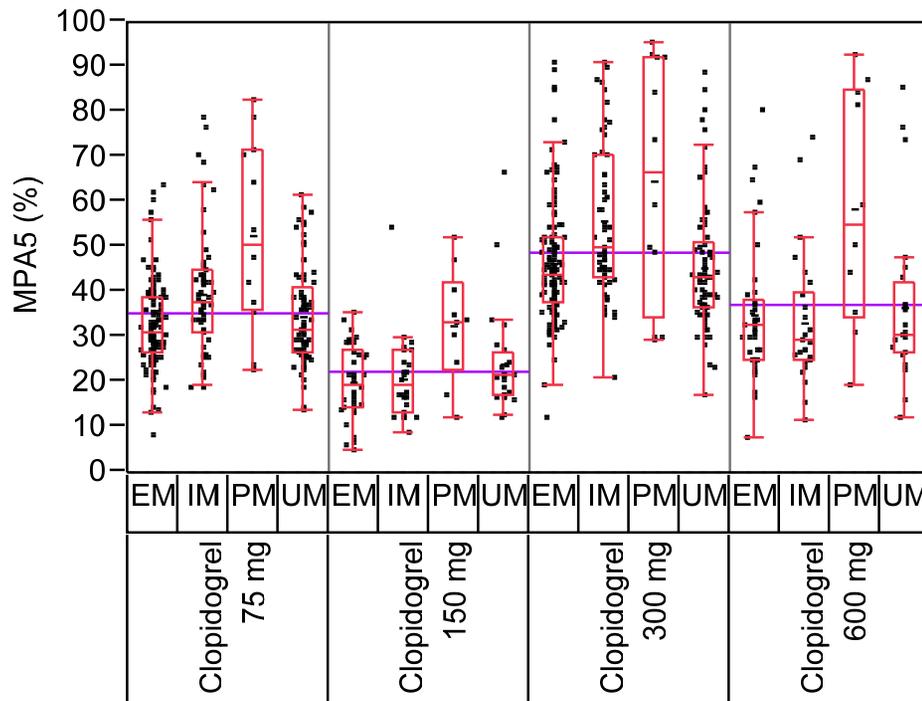


CYP2C19 Polymorphisms Influence Clopidogrel PK

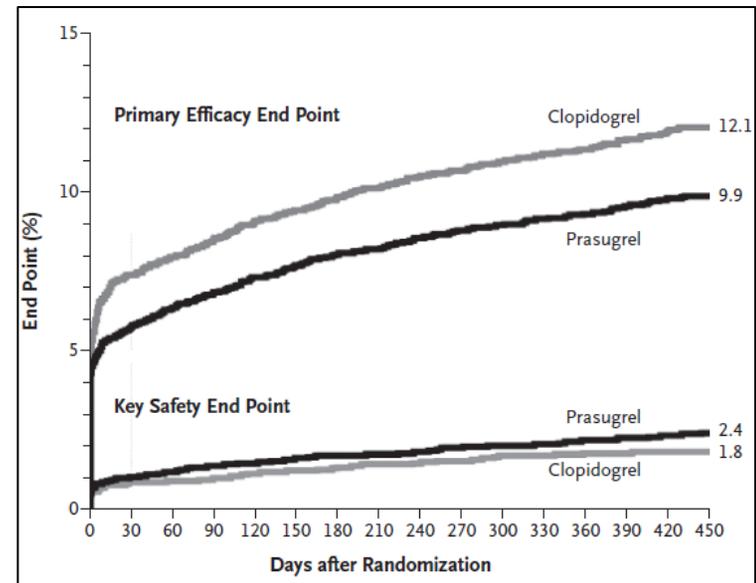
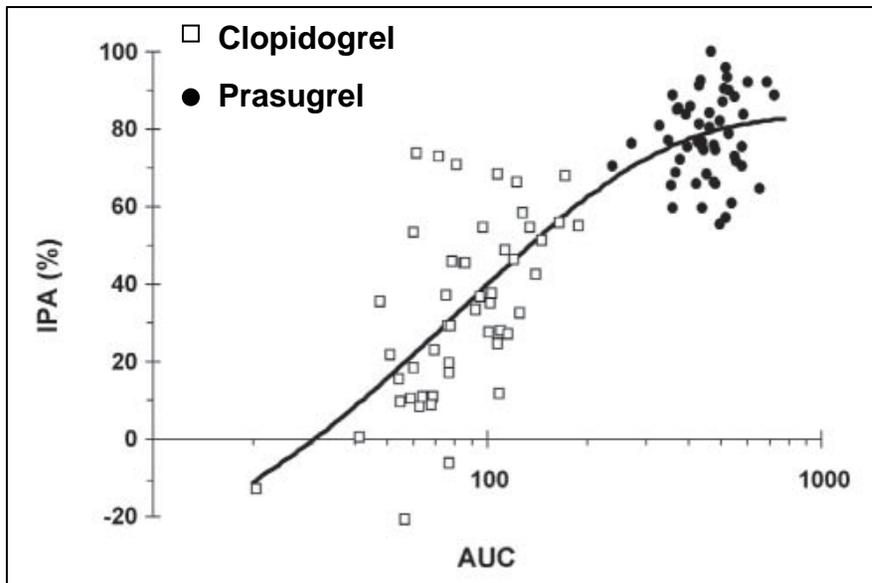




CYP2C19 Polymorphisms Influence Clopidogrel PK, PD



Clopidogrel Active Metabolite Exposure/Response Relationship





Labeling Considerations

- **21 CFR 201.57**

- “...labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association...”
- “...warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box”

- **21 CFR 314.80**

- “*Adverse experience...any failure of expected pharmacological action.*”



Labeling Deconstructed: Boxed Warning

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see *Warnings and Precautions (5.1)*]. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see *Clinical Pharmacology (12.5)*]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see *Dosage and Administration (2.3)*].

- Limited to ACS/PCI setting; data lacking for stroke/PAD
- Targeted poor metabolizers (e.g., *2/*2, *2/*3, *3/*3)
- Not prescriptive, actionable if data available



Labeling Deconstructed

- **Dosage and Administration**
 - Recognizes common practice (high LD)
 - Appropriate dose is not known
- **Warnings and Precautions**
 - Pharmacogenetic interaction analogous to pharmacologic interactions
- **Clinical Pharmacology**
 - Clopidogrel metabolic pathway and active metabolite disposition
 - Granular information on CYP2C19 and evidence



Labeling Deconstructed: Clinical Pharmacology

	Dose	Ultrarapid (n=10)	Extensive (n=10)	Intermediate (n=10)	Poor (n=10)
C _{max} (ng/mL)	300 mg (24 h)	24 (10)	32 (21)	23 (11)	11 (4)
	600 mg (24 h)	36 (13)	44 (27)	39 (23)	17 (6)
	75 mg (Day 5)	12 (6)	13 (7)	12 (5)	4 (1)
	150 mg (Day 5)	16 (9)	19 (5)	18 (7)	7 (2)
IPA (%) [*]	300 mg (24 h)	40 (21)	39 (28)	37 (21)	24 (26)
	600 mg (24 h)	51 (28)	49 (23)	56 (22)	32 (25)
	75 mg (Day 5)	56 (13)	58 (19)	60 (18)	37 (23)
	150 mg (Day 5)	68 (18)	73 (9)	74 (14)	61 (14)



Summary and Conclusions

- Clopidogrel is widely used to prevent morbid/mortal events; response cannot be routinely measured
- FDA communications and labeling revisions balanced available evidence against potential adverse outcomes
- Alternative, more effective treatments are available, but perceived safety concerns may be limiting use
- The evidence supports a strong, consistent, specific, graded, plausible, analogous and coherent effect of CYP2C19 genotype on clopidogrel exposure, response