

An abstract graphic featuring a human silhouette composed of DNA base pairs (A, T, C, G) and various genomic elements. The background is a collage of colorful geometric shapes, including triangles and circles, overlaid with DNA sequences and chromosome maps. The text is presented in a clean, sans-serif font on a blue background.

# Clinical Care Implementation of Guidelines for Genomic Testing

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# Disclosures

- ▶ Funding
  - ▶ NHLBI
  - ▶ Mayo Clinic



# Clinicians follow professional society guidelines



# ACC/ AHA Guidelines – Class of Recommendation

- ▶ Benefits versus Risk
- ▶ Recommendations
  - ▶ Class 1 – Is recommended
  - ▶ Class 2a – Is reasonable
  - ▶ Class 2b – May/might be reasonable
  - ▶ Class 3a – Is not recommended
  - ▶ Class 3b – Potentially harmful or causes harm



# ACC/ AHA Guidelines – Level of Evidence

- ▶ RCTs
- ▶ Meta-analyses of high quality RCTs
- ▶ Well-designed, well-executed nonrandomized studies, observational, or registry studies
- ▶ Meta-analyses of such studies



# Clinicians follow professional society guidelines

**Pharmacogenomics as an example**



# Background

## CLOPIDOGREL

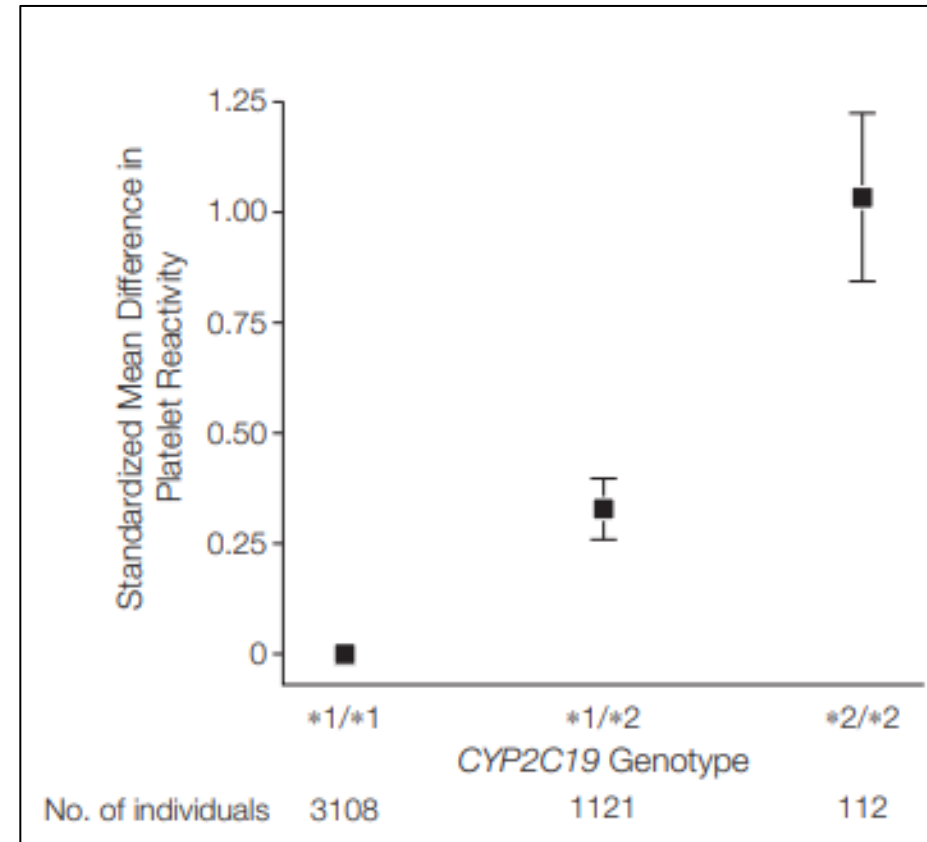
Prodrug  $\xrightarrow{\text{CYP2C19}}$  Active metabolite

*CYP2C19* LOF carriers



## CYP2C19 LOF carriers

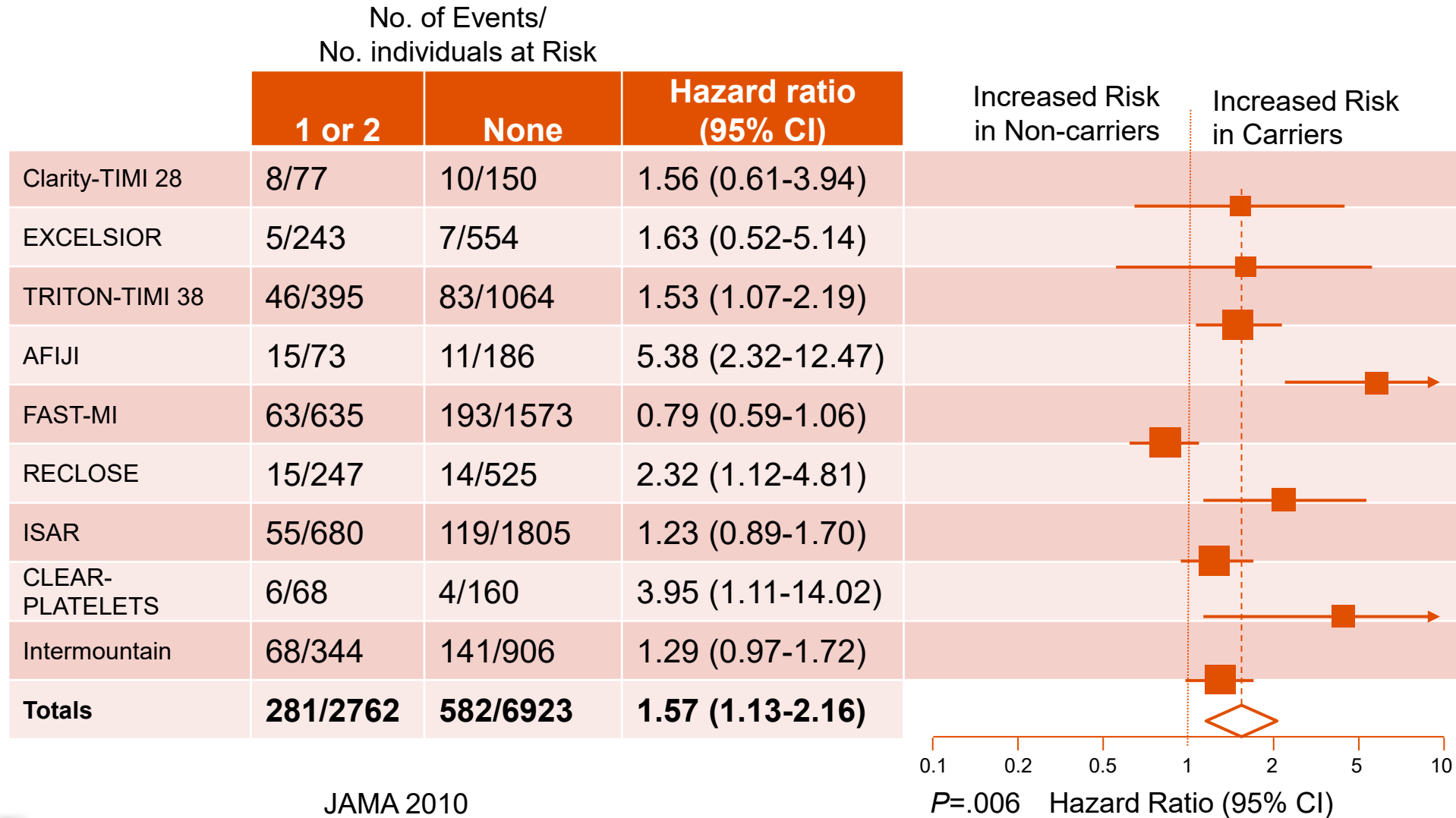
- ▶ 1 in 3 individuals may be LOF carriers
- ▶  $AUC_{0-24}$  is up to 46% and  $C_{max}$  up to 40% lower than that of non-carriers for the active metabolite





# CYP2C19 LOF carriers vs Non-carriers

## Risk of CV death, MI, or stroke



JAMA 2010

# Clopidogrel: Black-box warning

PLAVIX<sup>®</sup> (clopidogrel bisulfate) tablets  
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR  
METABOLIZERS

*See full prescribing information for complete boxed warning.*

- Effectiveness of Plavix depends on activation to an active

BLACK BOX WARNING:

- *IDENTIFY*
- *ALTERNATIVE THERAPY*

- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

March 12, 2010



In addition, there are other genetic polymorphisms such as ABCB1 that may also contribute to variation in the response of individual patients to clopidogrel.

Information about the predictive value of pharmacogenomic testing is very limited, but is the focus of multiple ongoing studies. The design of such studies in terms of specific tests and patient populations (eg, acute care versus chronic care settings) will have major implications for the role of testing. A related issue is whether the risk from a given individual's genomic profile changes over time, depending on the specific clinical scenario (eg, ACS versus stable angina pectoris, PCI versus medical therapy, small vessel versus large artery, atherosclerotic ischemic stroke, or carotid stenting versus medical therapy), is relevant. This question has yet to be resolved.

4. The answer to the specific question of the role of genotyping in everyday practice remains unknown at the present time. Although the boxed warning does not mandate testing, proponents would argue that there are common genetic

wide variety of situations. New agents such as prasugrel and ticagrelor, which are not affected by CYP2C19 genetic variants, have been found to be more effective than standard-dose clopidogrel. This relates to the PK characteristics of these newer agents. In very high-risk clinical circumstances (eg, prior stent thrombosis) such agents may be considered alternatives to standard ACCF/AHA and AHA Stroke Council Guideline therapy. This is particularly important in any patient suspected of treatment failure to standard-dose clopidogrel. Other treatment strategies are also being tested, including increased clopidogrel dosing or the addition of a third drug such as cilostazol to aspirin and clopidogrel. In the setting of stroke or transient ischemic neurologic symptoms, the combination of aspirin and extended release dipyridamole and aspirin monotherapy are alternatives recommended by the AHA Stroke Council guidelines for secondary prevention of stroke.<sup>66</sup>

## 6.2. Recommendations for Practice

The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients.

CYP2C19\*2 or \*3 (poor metabolizers), or be extended to other variants including the gain-of-function CYP2C19\*17 variant (hyper-rapid or ultrarapid metabolizers). As part of this argument, opponents note that the predictive performance of CYP2C19 variant is low, ranging from 12% to 20%, and raise the question of what to do when variant genotype information is identified in patients with no clinical events. Finally, they would note that there are no point-of-care genotyping tests, which severely limits the usefulness of these data in the acute care setting. Currently, there are studies underway or in the planning stages that will address these issues to varying degrees. Despite the gaps in current knowledge, both clinicians and patients need to be aware of genetic polymorphisms that may modulate clopidogrel responsiveness and cause MACE. It is important to emphasize again that in the most recent labeling for clopidogrel, the FDA only informs physicians and patients that genetic testing is available; it neither mandates, requires, nor recommends genetic testing, thereby allowing for flexibility in clinical decisions.

5. Given the concerns about the mortality and morbidity that may be attributable to an inadequate response to antiplatelet therapy, there are a number of alternative approaches to standard guideline-based care with clopidogrel. New agents and new strategies have been used clinically and tested in a

phisms on clinical outcome remains to be determined (eg, the importance of CYP2C19\*2 versus \*3 or \*4 for a specific patient), and the frequency of genetic variability differs among ethnic groups. This has particular relevance related to the frequency of homozygotes, which occurs in approximately 2% of the population, versus heterozygotes, which occurs in approximately 30% of the population, both of whom may have increased risk.

4. Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. The selection of the specific test, as well as the issue of reimbursement, are both important additional considerations.

The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. In addition, the clinical course of the majority of patients treated with clopidogrel without either genetic testing or functional testing is excellent. Clinical judgment is required to assess clinical risk and variability in patients considered to be at increased risk. Genetic testing to determine if a patient is predisposed to poor clopidogrel metabolism ("poor metabolizers") may be considered before starting clopidogrel

Circulation  
2010



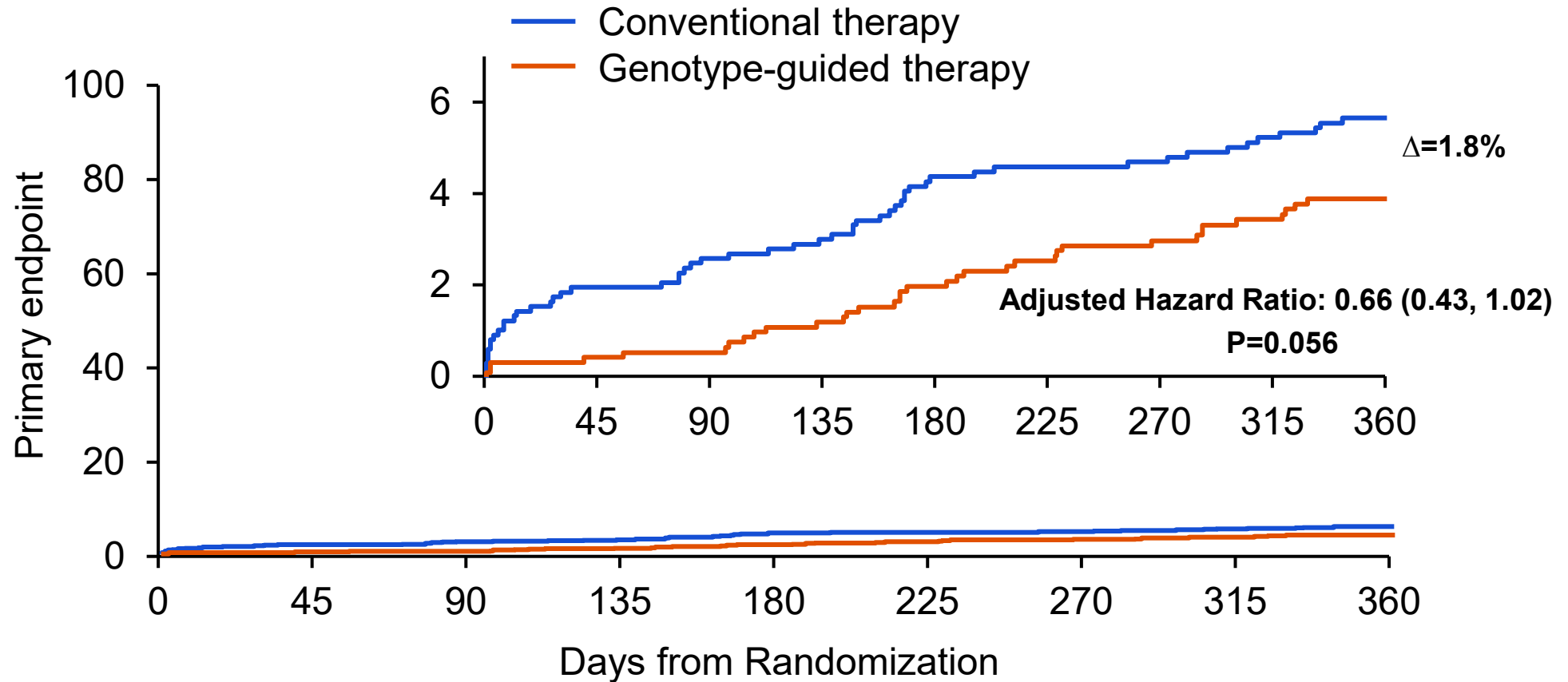
# Genotype-based Clinical Trials

- Allele frequency
- Number of homozygotes
- Effect size
- Trial design complexity and sample size
- Ethics
- Regulations and FDA



# Primary Endpoint

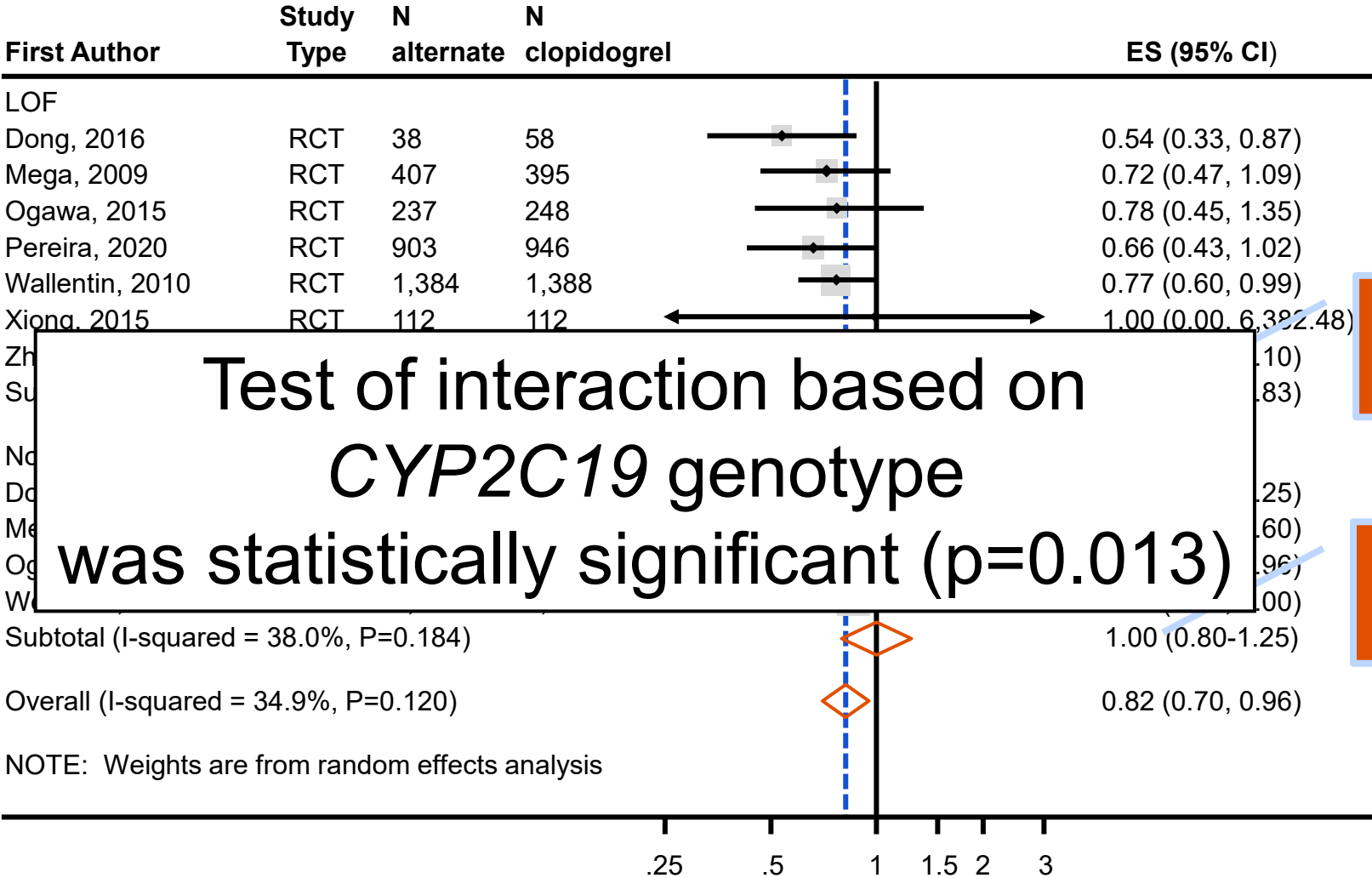
Composite of CV death, MI, stroke, stent thrombosis, severe recurrent ischemia



|                         |     |     |     |     |     |     |     |     |     |
|-------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Conventional therapy    | 946 | 906 | 898 | 894 | 876 | 867 | 864 | 859 | 604 |
| Genotype-guided therapy | 903 | 875 | 870 | 863 | 854 | 838 | 833 | 824 | 556 |



# CYP2C19 Genetic Testing – Meta-Analysis



**LOF carriers  
HR 0.70**

**Non-carriers  
HR1.0**



# Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis

*Mattia Galli, Stefano Benenati, Davide Capodanno, Francesco Franchi, Fabiana Rollini, Domenico D'Amario, Italo Porto, Dominick J Angiolillo*

- ▶ ↓ Major Cardiovascular Events (RR 0.78, 95% CI 0.63-0.95,  $p=0.015$ )
- ▶ ↓ Cardiovascular Death (RR 0.77, 95% CI 0.50-1.00,  $p=0.049$ )
- ▶ ↓ MI (RR 0.76, 95% CI 0.60-0.96,  $p=0.021$ )
- ▶ ↓ Stent Thrombosis (RR 0.64, 95% CI 0.46-0.89,  $p=0.011$ )
- ▶ ↓ Stroke (RR 0.66, 95% CI 0.48-0.91,  $p=0.010$ )
- ▶ ↓ Minor Bleeding (RR 0.78, 95% CI 0.67-0.92,  $p=0.0030$ )

**Funding** None.





**AHA SCIENTIFIC STATEMENT**

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# *CYP2C19* Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement From the American Heart Association

Naveen L. Pereira, MD, FAHA, Chair; Sharon Cresci, MD, FAHA, Vice Chair; Dominick J. Angiolillo, MD, PhD; Wayne Batchelor, MD, MHS; Quinn Capers IV, MD; Larisa H. Cavallari, PharmD; Dana Leifer, MD, FAHA; Jasmine A. Luzum, PharmD, PhD, FAHA; Dan M. Roden, MD, FAHA; Konstantinos Stellos, MD, FAHA; Stephanie L. Turrise, PhD, RN, FAHA; Sony Tuteja, PharmD, MS, FAHA; on behalf of the American Heart Association Professional/Public Education and Publications Committee of the Council on Genomic and Precision Medicine; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Peripheral Vascular Disease; and Stroke Council





# Clinicians follow professional society guidelines

## Clopidogrel - *CYP2C19* yet to be addressed

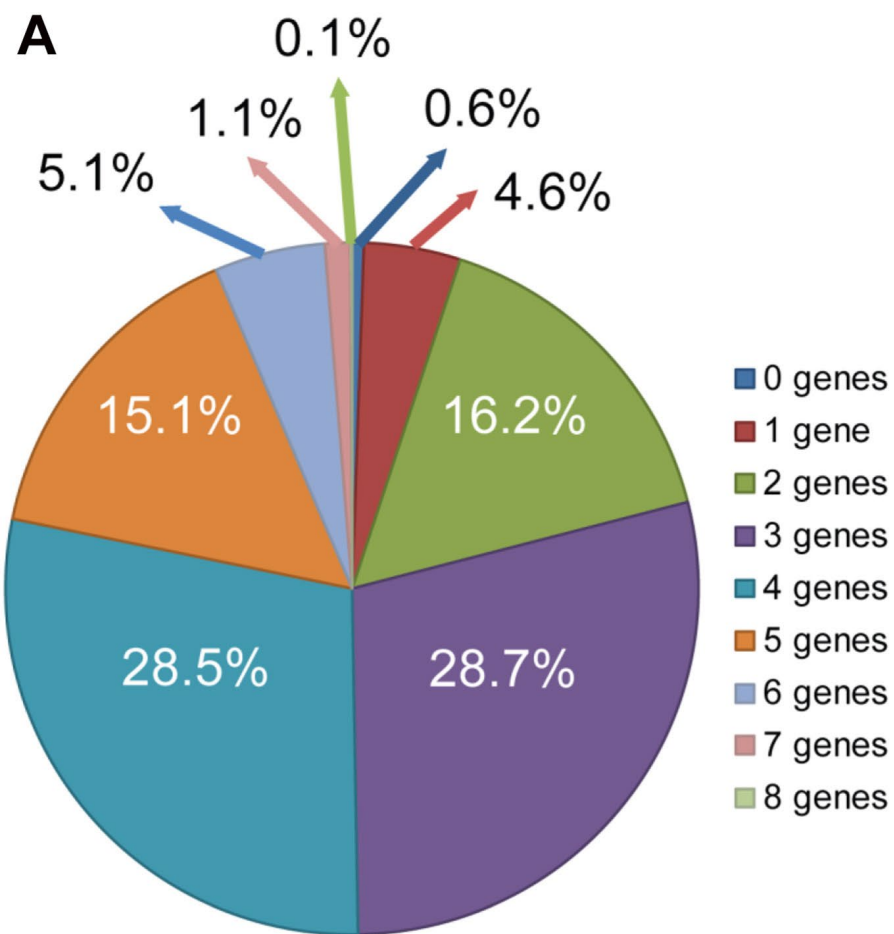


# Challenges to Clinical Implementation

- ▶ Evidence of clinical utility
- ▶ Objective practice guidelines
- ▶ Availability of rapid turn-around genotyping performed in a CLIA-approved environment
- ▶ Incorporation of genotype data in an electronic medical record
- ▶ EHR “alerts” at the point of care
- ▶ Education of clinicians – patients
- ▶ User friendly decision support software/tools
- ▶ Insurance coverage and cost
- ▶ Clinician and patient perceptions



# Preemptive genetic testing Mayo-Baylor RIGHT 10K Study

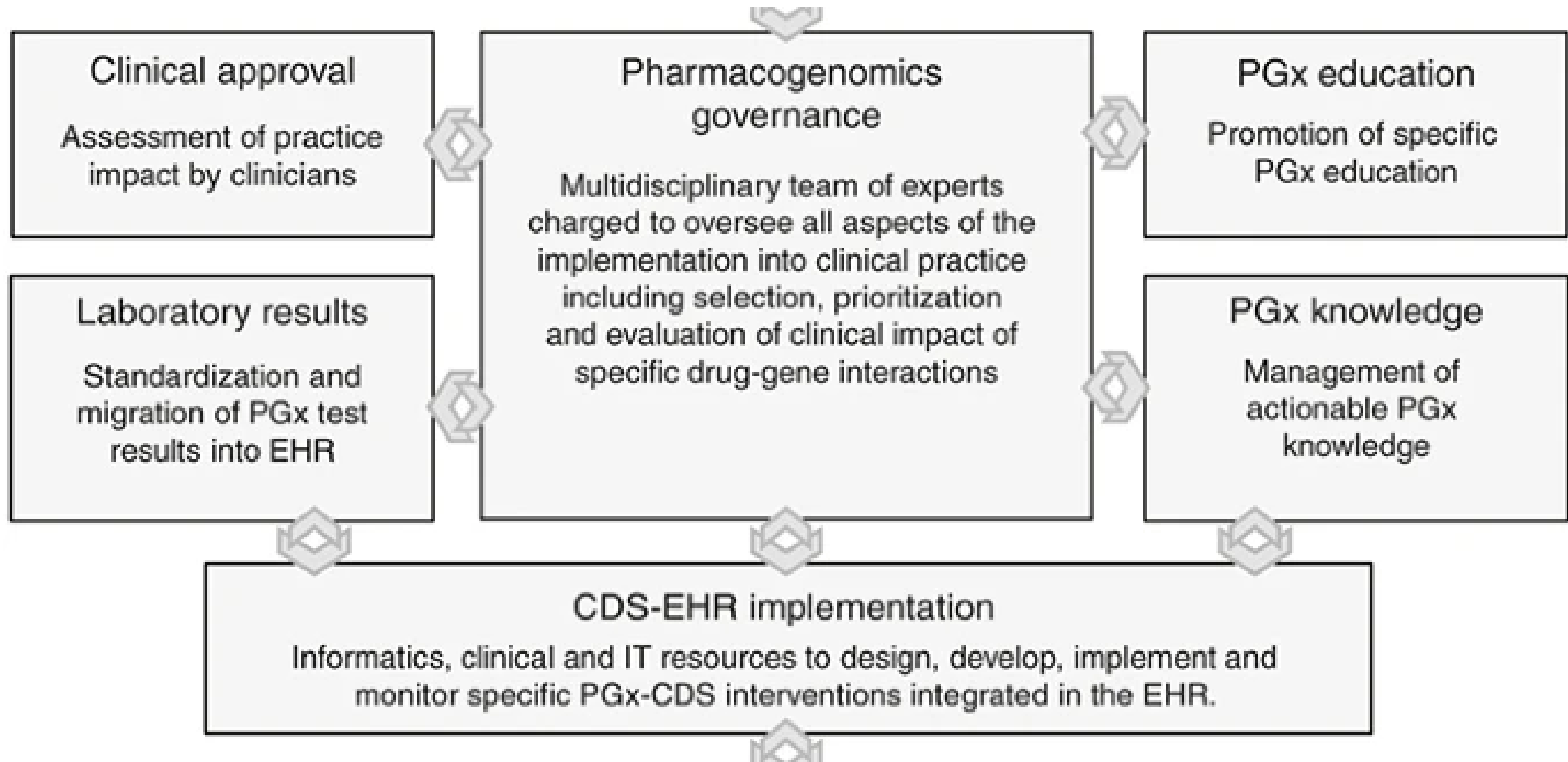


**B**

| Number of Genes | Number of Subjects | % of Subjects |
|-----------------|--------------------|---------------|
| 0               | 59                 | 0.6%          |
| 1               | 465                | 4.6%          |
| 2               | 1636               | 16.2%         |
| 3               | 2893               | 28.7%         |
| 4               | 2869               | 28.5%         |
| 5               | 1521               | 15.1%         |
| 6               | 514                | 5.1%          |
| 7               | 111                | 1.1%          |
| 8               | 9                  | 0.1%          |






# Operational Model to Implement Genetic Testing *at Point of Care*



# Genetic Test Reporting – Decreasing Complexity

BestPractice Advisory - Cdstesting,Adt


High Priority (1) 


 **PHARMACOGENOMICS ALERT:** This patient is a CYP2D6 Ultra Rapid metabolizer. Avoid codeine due to potential for toxicity. 


Remove the following orders? \_\_\_\_\_

Remove

Keep

 butalbital-aspirin-caff-codeine 30-50-325-40 mg per capsule 1 capsule (FIORINAL WITH CODEINE)  
1 capsule, oral, Every 4 hours PRN, headaches, Starting Today at 1714

Genomic Indicators 

For more information go to AskMayoExpert (codeine) 

Acknowledge Reason \_\_\_\_\_


Benefit outweighs risk

Patient previously tolerated

Therapeutically appropriate

Will cancel order

Other reason

 **Accept**





Department of Cardiovascular Medicine

## Dilated Cardiomyopathy (DCM) Genetic Testing

**Only 13% of eligible patients undergo genetic testing**



# DCM Genetic Testing Process

## Genetic testing and clinical workflows

- @ point of clinical care
- Pre-emptive identification of eligible patients and opt-out option
- Use existing clinical resources
- Automate genetic counseling
- Transparency regarding cost
- Virtual engagement to provide results



# DCM Genetic Testing: Mayo Clinic Experience

- ▶ Genetic counseling pre-INT vs post-INT (14.8% vs 33.5%, OR 2.9,  $P < .0001$ )
- ▶ Genetic testing pre-INT vs post-INT (13% vs 27.3%, OR 2.5,  $P = .001$ )
- ▶ Likely pathogenic or pathogenic DCM related genetic variants detection increased from 2 pre to 6 post-intervention





# Take home points

- ▶ Clinicians follow professional society guidelines
- ▶ Guidelines are primarily driven by results of clinical trials but maybe biased when totality of data should be assessed
- ▶ Developing and conducting genotype-based clinical trials is complex
- ▶ Availability of genetic testing and results at the point of care is essential
- ▶ Institutional support and multidisciplinary teams involving clinicians, the laboratory, informatics, and IT resources are required
- ▶ Incorporating genetic testing within existing workflows including engaging clinicians, patients with insurance approvals/payments increases its adoption





**Questions?**  
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