Outcomes with *CYP2C19* Genotyping for Clopidogrel Response: An Update from the IGNITE Network

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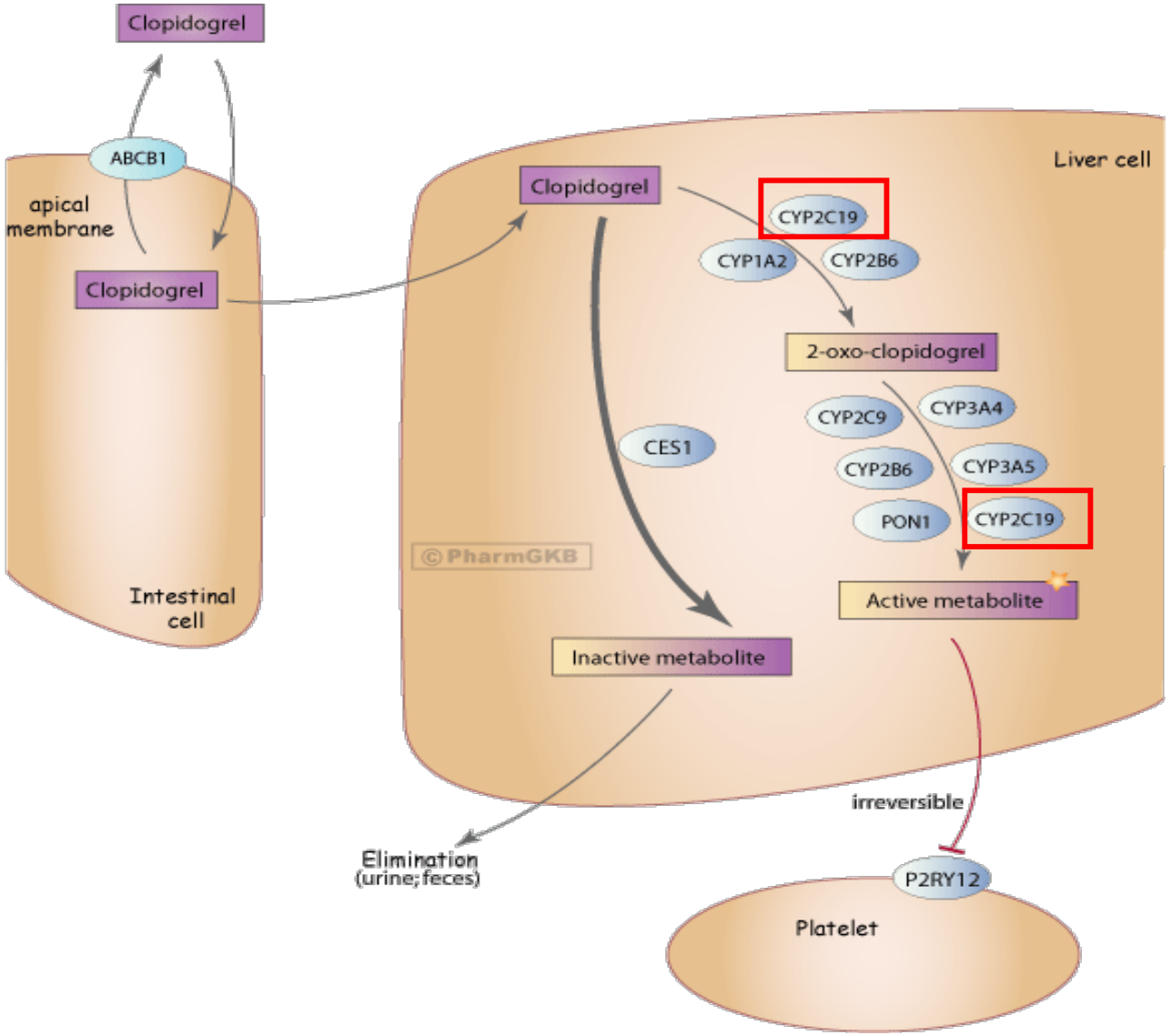
Clopidogrel Pharmacokinetics



Sangkuhl K et al. "Clopidogrel pathway" *Pharmacogenet Genomics* (2010). Copyright to PharmGKB.

CYP2C19

Gene alleles

Allele	SNP	CYP2C19 Function
*1	N/A	Normal function
*2	681G>A	No function/loss of function
*3	636G>A	No function/loss of function
*17	-808C>T	Increased function

Phenotype

Genotype	Phenotype
*1/*1	Normal Metabolizer (NM)
*1/*2, *1/*3	Intermediate Metabolizer (IM)
*2/*2, *2/*3	Poor Metabolizer (PM)
*1/*17	Rapid Metabolizer (RM)
*17/*17	Ultra-rapid Metabolizer (UM)

Outcomes Based on RCT and Registry Post-Hoc Analyses

Meta-analysis of 9 trials and 9685 clopidogrel-treated high risk patients

Outcome	LOF vs no LOF
MACE*	HR 1.57 (1.13-2.16)
Stent Thrombosis	HR 2.81 (1.81-4.37)

*Major adverse cardiovascular events (CV death, MI, or stroke)

LOF = Loss of function

Mega JL, et al. *JAMA* 2010;304:1821-30.

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Outcomes Based on Post-Hoc Analyses or TRITON-TIMI 38 and PLATO Trials

Occurrence of MACE

CYP2C19 Genotype	Prasugrel	Ticagrelor
LOF	8.5%	8.6%
No LOF	9.6%	8.8%

Sorich et al. *J Thromb Haemost* 2010;8:1678-84.
Wallentin, et al. *Lancet* 2010;376:1320-8.

LOF = Loss of function

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FDA-Approved Clopidogrel Label

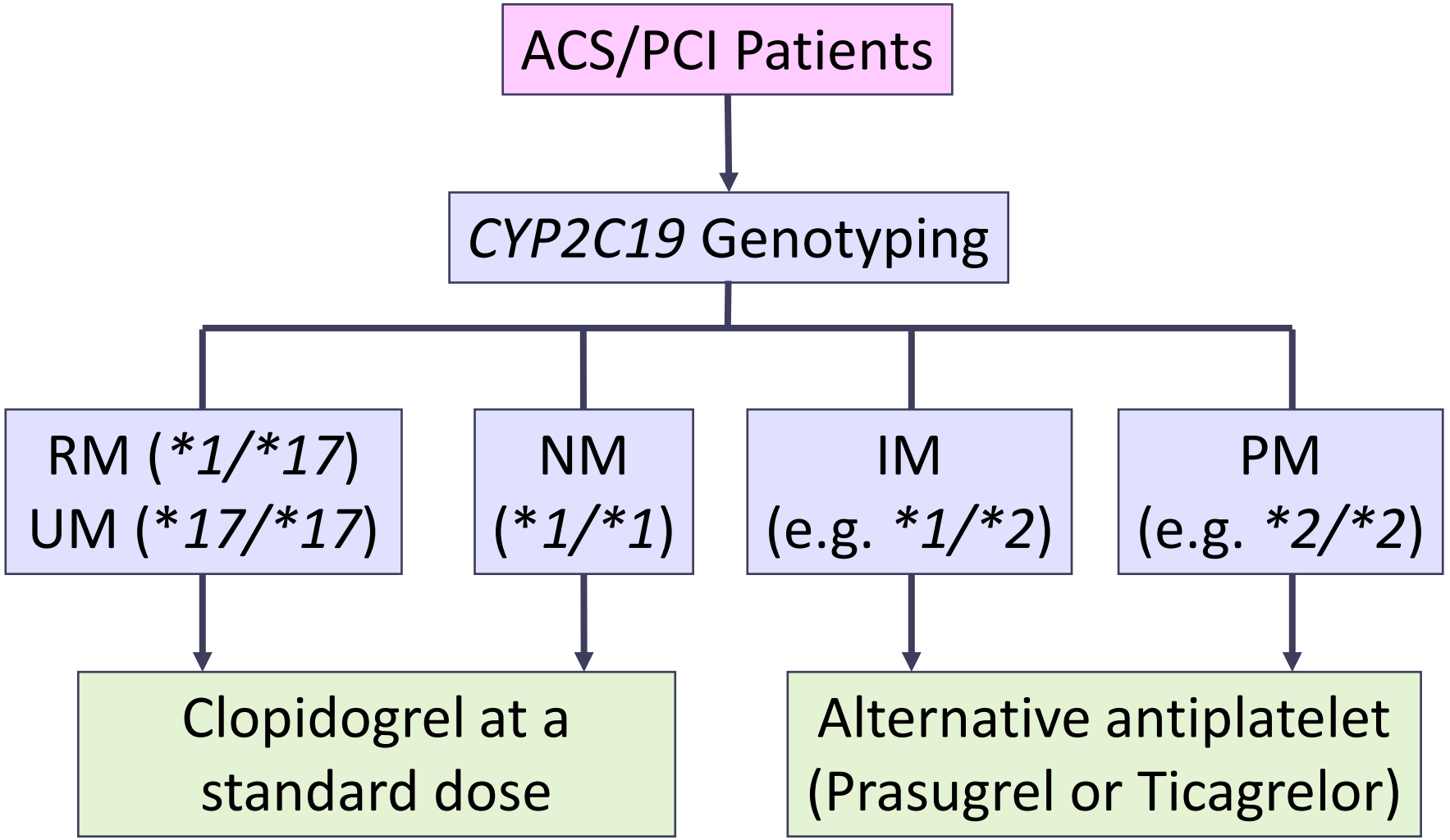
WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- 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)

CPIC Guidelines for Clopidogrel

Scott SA et al. *Clin Pharmacol Ther* 2013;94:317-23.



CYP2C19-Clopidogrel Implementation at UF Health

- Implemented in June 2012 as part of routine clinical practice
  - Test added to standard order set
  - Run in UF Health Pathology Labs
  - *CYP2C19* genotype placed in the electronic medical record
- Recommendations for alternative therapy provided for no-function/LOF allele carriers.
- Built clinical decision support.

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TAILOR-PCI

ClinicalTrials.gov Identifier: NCT01742117

Est. enrollment	5,270
Inclusion criteria	PCI
Arms	Genotype-guided strategy (Ticagrelor for *CYP2C19*2* or **3* allele) versus clopidogrel
Outcomes	MACE at 1 year
Est. completion	3/2020

- TAILOR-PCI: Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention

CYP2C19-Clopidogrel Outcomes at UF Health

- Reviewed medical records for patients who underwent PCI and genotyping in first 2 years of program
- Collected data on Major Adverse Cardiovascular Events (MACE) through 6 months after PCI
  - Composite of cardiovascular death, myocardial infarction, stroke, or stent thrombosis
  - Compared between patients with a LOF allele treated with alternative antiplatelet, e.g. ticagrelor, prasugrel vs. clopidogrel

Circulation 2015;132:Suppl 3 A11802.

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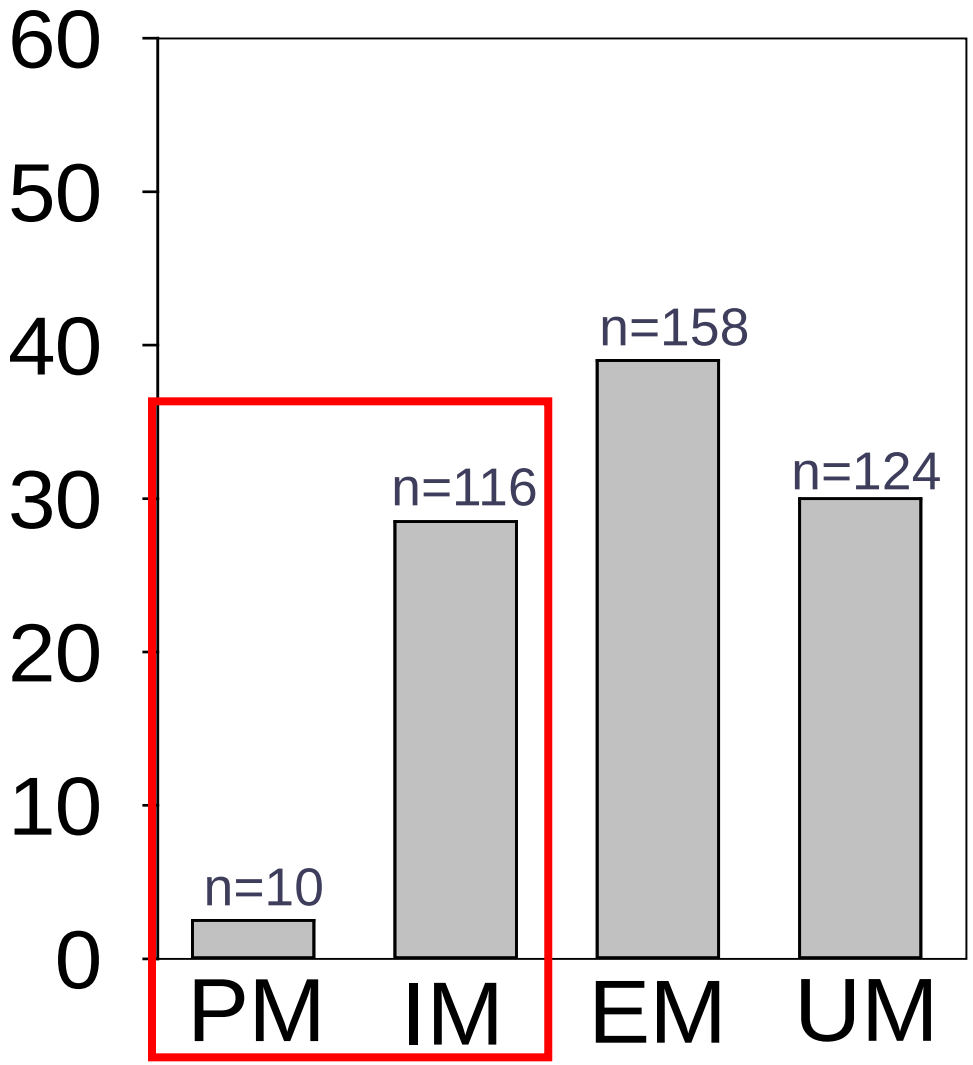
CYP2C19-Clopidogrel Outcomes at UF Health



- n=408 total patients
  - n=126 (31%) with LOF allele
    - n=68 (54%) with LOF allele on alternative therapy

Circulation 2015;132:Suppl 3 A11802.

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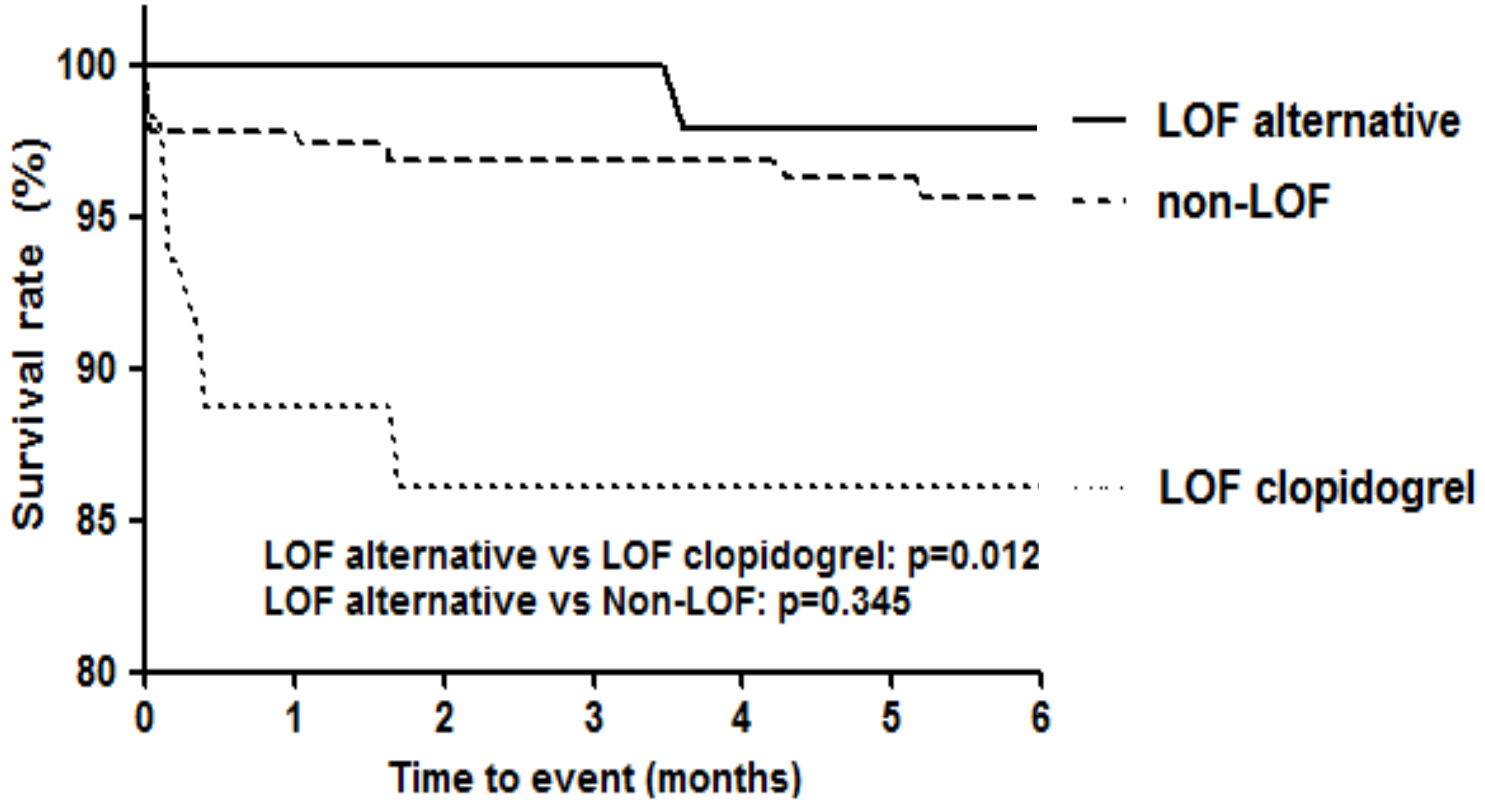
CYP2C19-Clopidogrel Outcomes at UF Health



Number at risk							
LOF alternative	68	59	54	51	47	45	40
Non-LOF	282	213	191	181	167	153	144
LOF clopidogrel	58	37	32	29	26	24	22
Total	408	309	277	261	240	222	206

Circulation 2015;132:Suppl 3 A11802.

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IGNITE Pharmacogenetics Working Group

- Part of the NIH-funded Implementing GeNomics In pracTicE (IGNITE) network
- Purpose
  - Engage institutions implementing pharmacogenetic testing into practice to collectively disseminate data on healthcare-related outcomes, utilization, and cost with genotype-guided drug therapy

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Prospective Clinical Implementation of *CYP2C19* Genotype Guided Antiplatelet Therapy After PCI: a Multi Site Investigation of MACE Outcomes in a Real-World Setting

Presented at the American Heart Association Scientific Sessions, New Orleans, LA, November 15, 2016.

Circulation 2016;134:e711-712 (abstract #21050)

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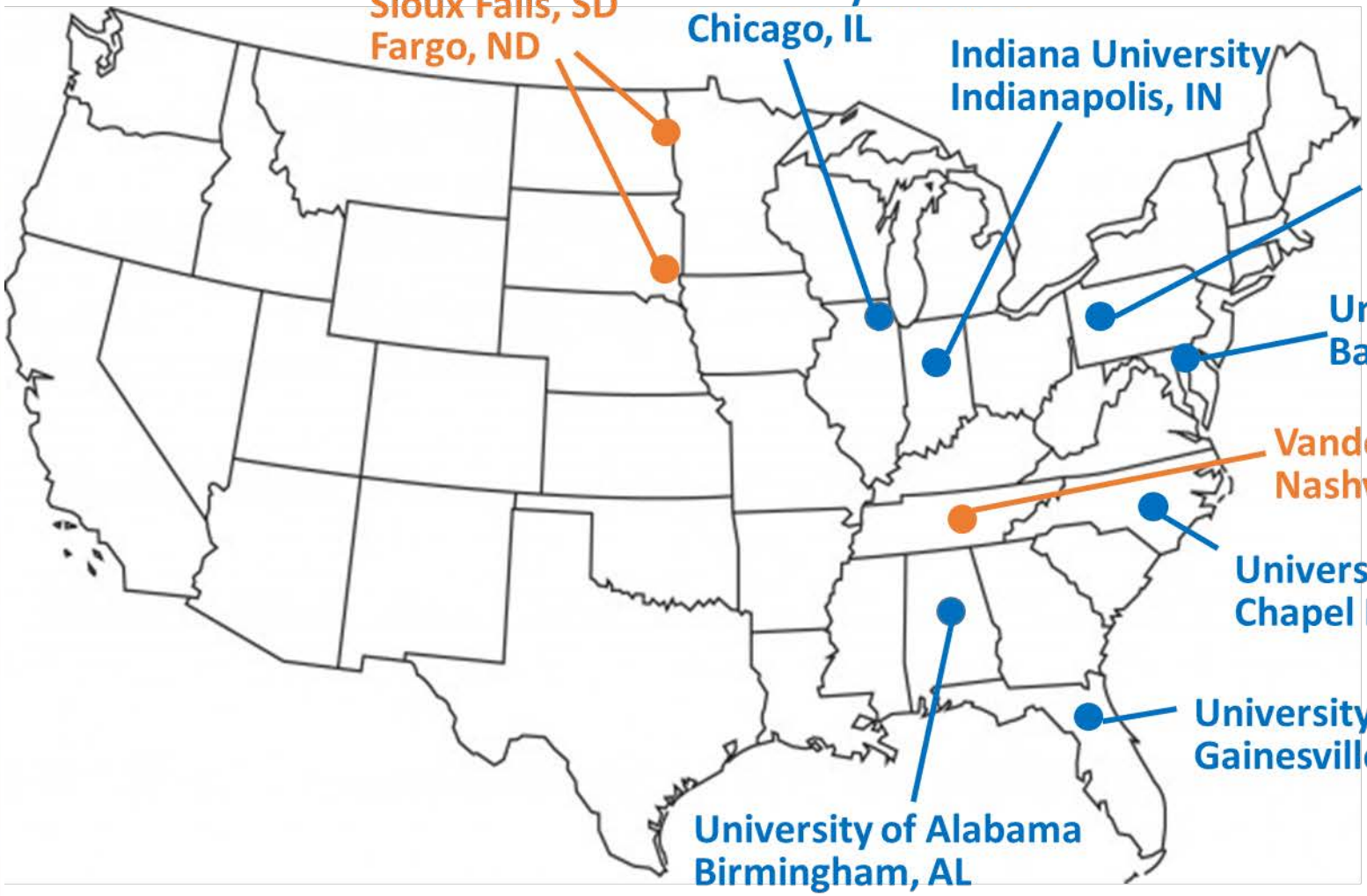
NIH IGNITE Pharmacogenetics Working Group



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Specific Aims

In patients undergoing *CYP2C19*-guided antiplatelet therapy post-PCI, compare risk for major adverse cardiovascular events (MACE)

Aim 1

LOF-ALTERNATIVE (LOF on alternative therapy)* *vs*
LOF-CLOPIDOGREL (LOF on clopidogrel 75 mg/day

Aim 2

LOF-ALTERNATIVE *vs* non-LOF (no LOF allele)

*Prasugrel, ticagrelor, high dose clopidogrel
LOF = Loss of function

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Study Design

Prospective multi-center investigation of clinical *CYP2C19* genotype-guided antiplatelet therapy post-PCI

- Alternative antiplatelet therapy recommended in *CYP2C19* LOF
- No genotype-guided recommendations in NON-LOF
- 7 sites contributed data on patients who underwent PCI and genotyping for primary analysis

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Data Collection

Data manually abstracted from the electronic medical record using a common data collection tool

Review of patient encounters

- Death or hospitalizations for cardiovascular events

Data curated at University of Florida

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Primary Endpoint

Major Adverse Cardiac Events (MACE)

- Death, myocardial infarction, or stroke within 12 months following index PCI

Antiplatelet therapy (CLOP or ALT) assessed at time of event or last encounter

Patients without MACE were censored at the time of last encounter

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Statistical Analysis

Kaplan-Meier analysis to compare time to MACE

- LOF-ALTERNATIVE vs LOF-CLOPIDOGREL
- LOF-ALTERNATIVE vs NON-LOF

Logistic regression to build exposure propensity score

Cox proportional hazard model with propensity score adjustment

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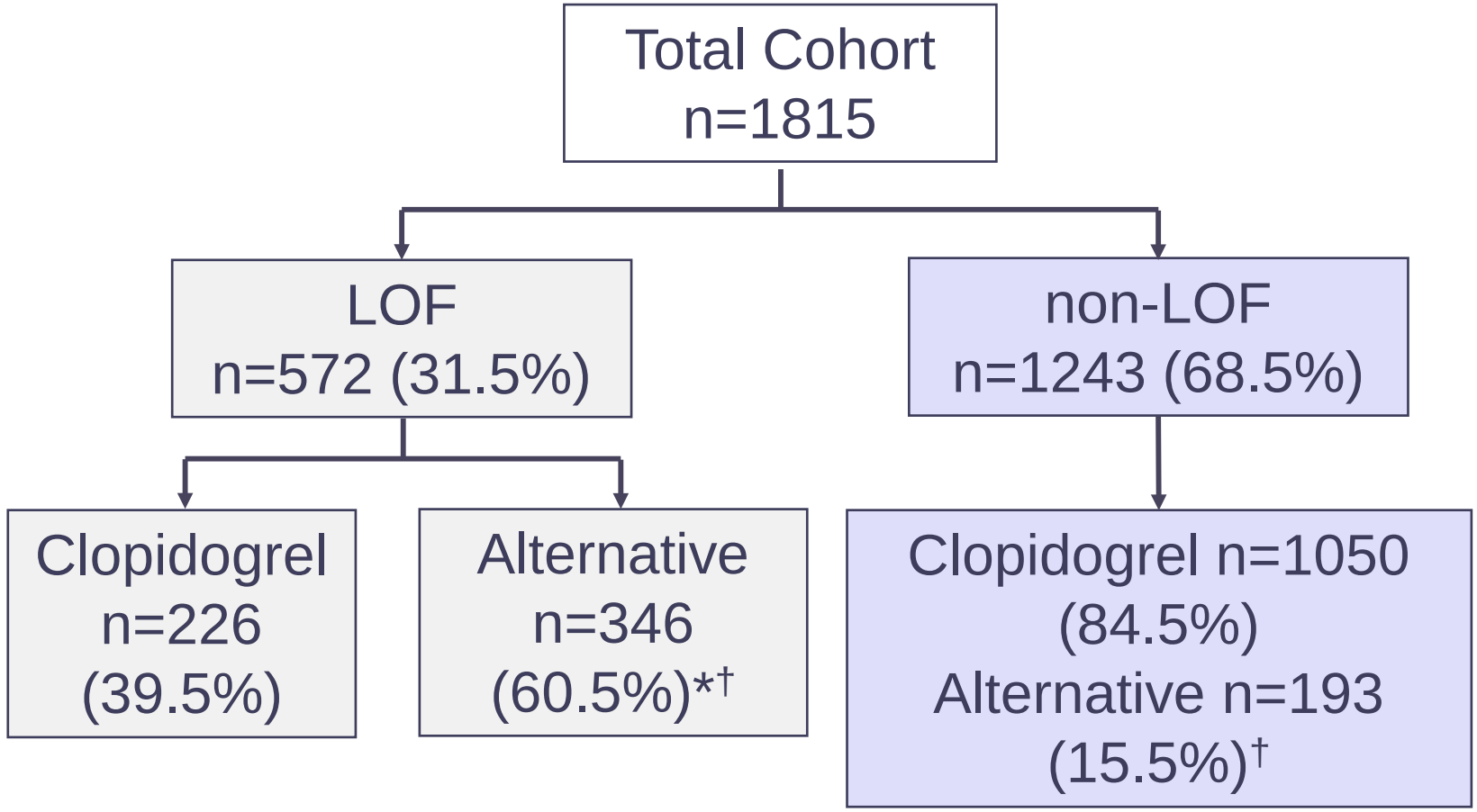
P2Y12 Inhibitor Therapy



*p<0.0001 for ALTERNATIVE between LOF and NON-LOF groups

†Prasugrel comprised >60% of ALTERNATIVE therapy

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Patient Characteristics (n=1,815)

	LOF-ALT (n=346)	LOF-CLOP (n=226)	Non-LOF (n=1243)
Age, yrs, mean±SD	61±11	64±12*	63±12*
Male (%)	71	66	67
White (%)	77	76	79*
Diabetes (%)	32	41*	39*
Prior MI (%)	25	30	25
Stroke or TIA (%)	7	16*	10
PCI indication (%)			
STEMI	22	15	20
Non-STEMI	28	32	28
Unstable angina	19	18	19
Stable disease	29	31	31
Other/unknown	2	4	2

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Implementation Metrics in LOF

	n=572
Time to genotype results, median (IQR)	1 (1-3) day
Time to alternative therapy, median (IQR)*	1 (1-6) day

*Data available for all but 4 patients

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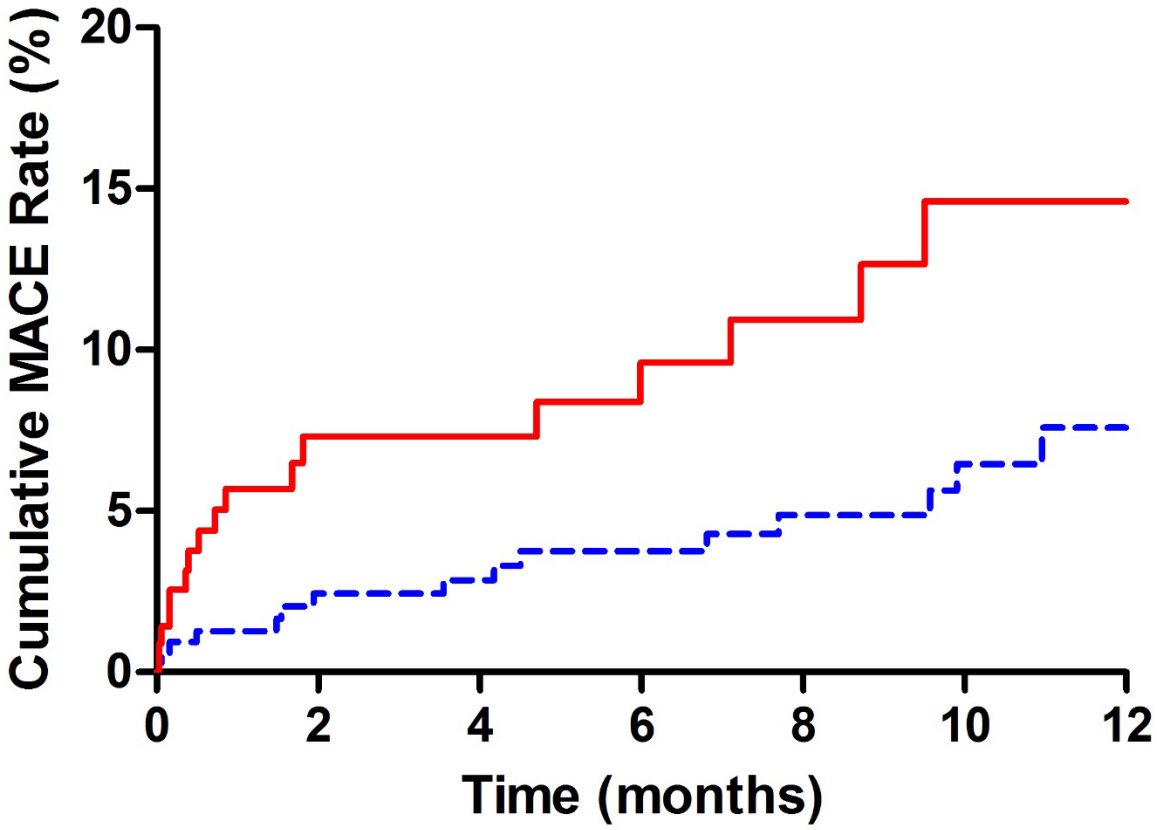
Kaplan-Meier Survival Curve



NO. at risk							
LOF_CLOP	226	112	89	76	63	39	3
LOF_ALT	346	245	221	195	161	112	9

LOF = Loss of function

Circulation 2016;134:e711-712

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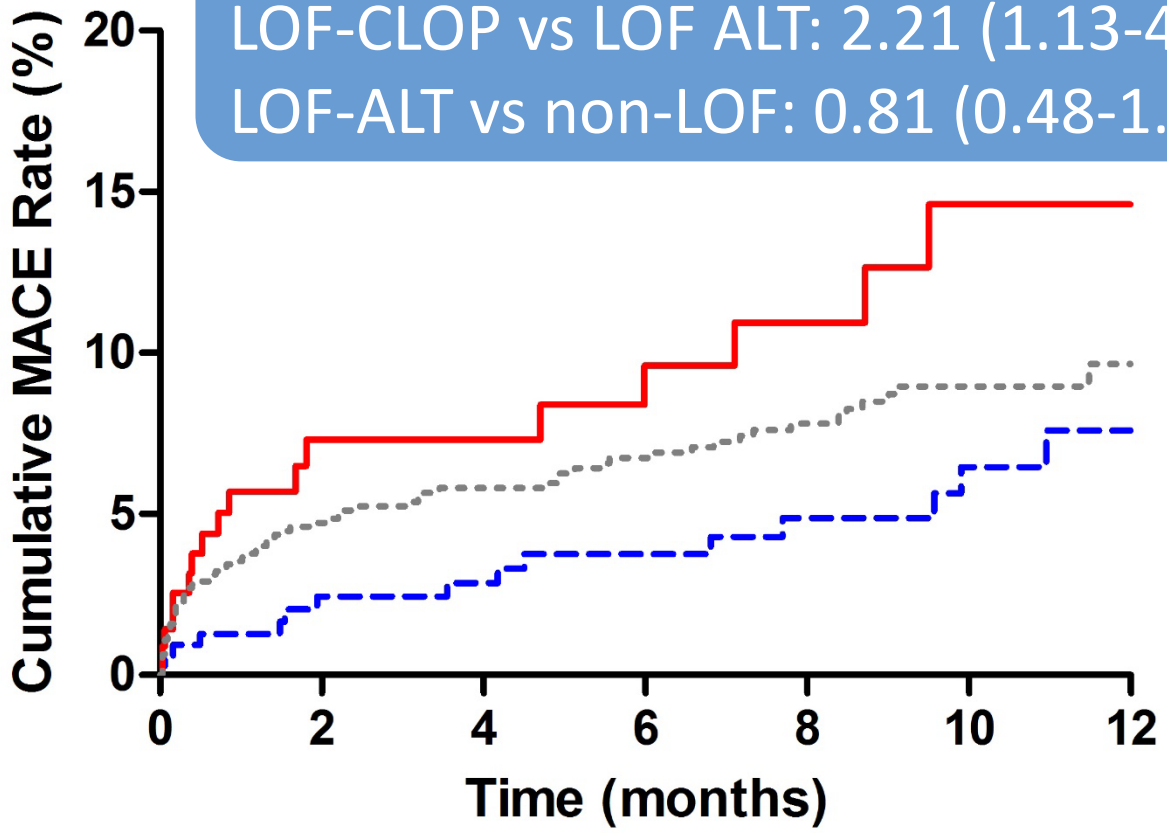
Kaplan-Meier Survival Curve

Adjusted Hazard Ratio
LOF-CLOP vs LOF ALT: 2.21 (1.13-4.33) p=0.021
LOF-ALT vs non-LOF: 0.81 (0.48-1.35) p=0.41



NO. at risk							
LOF_CLOP	226	112	89	76	63	39	3
NON-LOF	1243	759	636	577	451	293	28
LOF_ALT	346	245	221	195	161	112	9

Circulation 2016;134:e711-712

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Summary

In data collected in a real-world setting with *CYP2C19* genotyping as part of clinical care, higher risk for MACE in *CYP2C19* LOF who were prescribed clopidogrel versus alternative antiplatelet therapy

Validation of findings at 2 additional sites is underway

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Conclusion

Genotype-guided approach to antiplatelet therapy in the real world is feasible

In patients with *CYP2C19* LOF, CV outcomes can be improved when clinical genotype made available and alternative therapy prescribed early after PCI

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Next Steps

Economic analysis based on outcomes data.

Manuscript describing implementation strategies across sites.

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