Evaluating Outcomes with Genotype-Guided Antiplatelet Therapy

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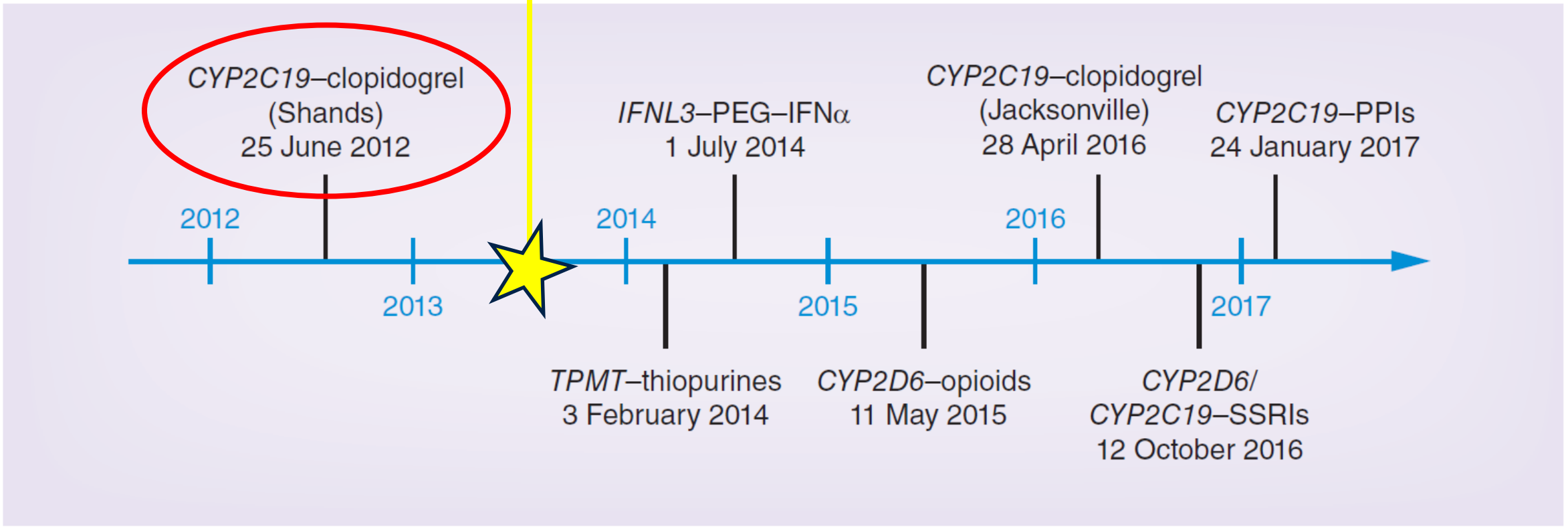
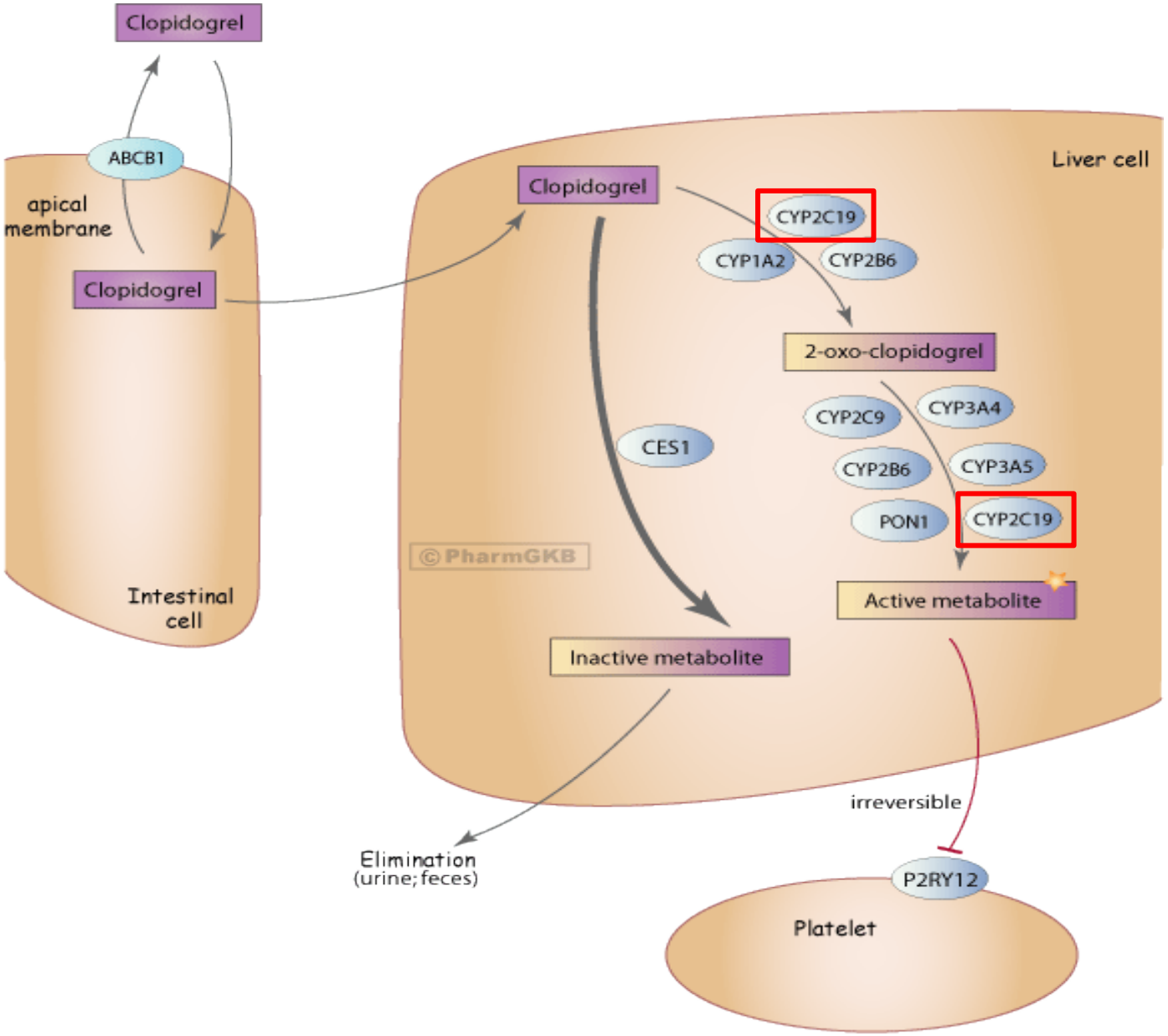


Pharmacogenomics 2017 [Epub ahead of print]. PMID: 28346068

Clopidogrel Pharmacokinetics



- *CYP2C19*2* and **3* are no-function (or loss-of-function, LOF) alleles
- Approximately 25% to 30% of Whites and Blacks and 65% of Asians have a LOF allele

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

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)

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

TAILOR-PCI

ClinicalTrials.gov Identifier: NCT01742117

Start date	5/2013
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 Implementation at UF Health

- *CYP2C19* testing
  - Genotype order is on the post-PCI order set
  - Run in UF Health Pathology Labs
  - Result placed in the electronic health record
- Recommendations for alternative therapy provided for LOF allele carriers.
- Built clinical decision support

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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 therapy, e.g. ticagrelor, prasugrel vs. clopidogrel

Circulation 2015;132:Suppl 3 A11802.

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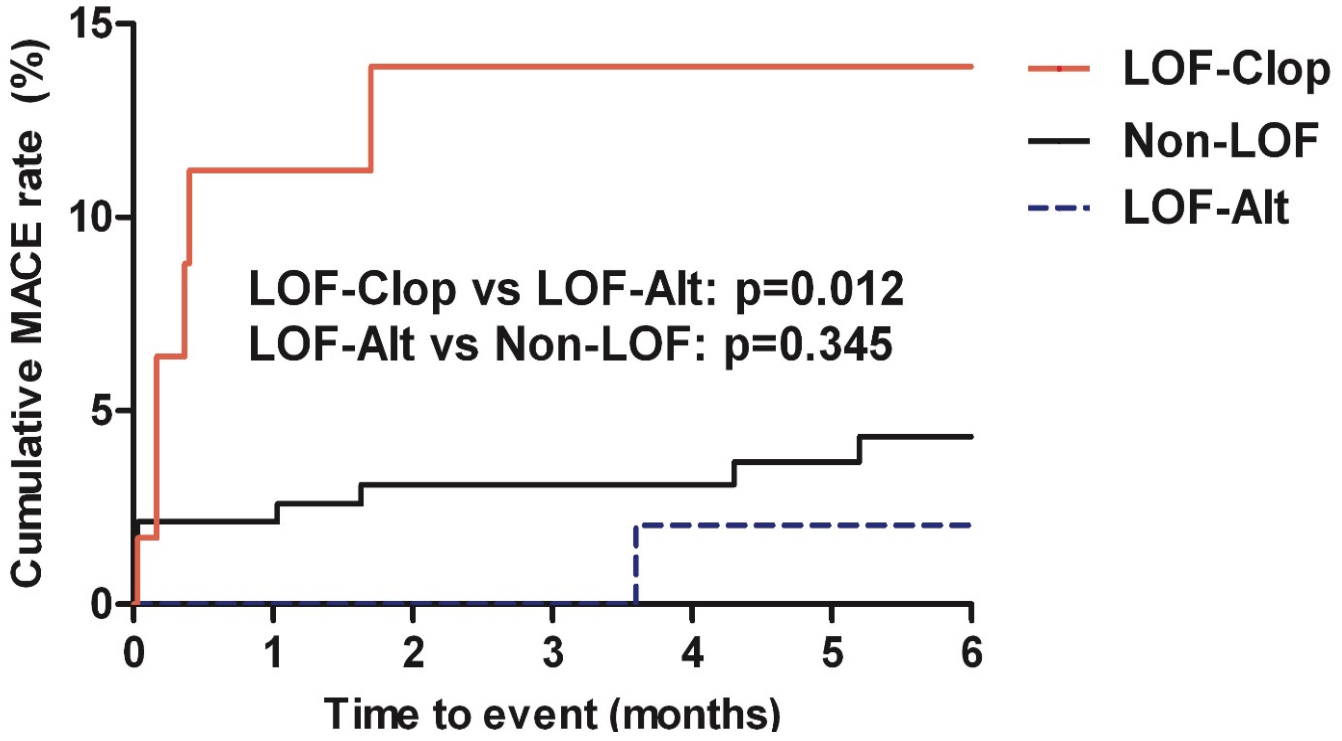
CYP2C19-Clopidogrel Outcomes at UF Health



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.

Log-rank p values shown

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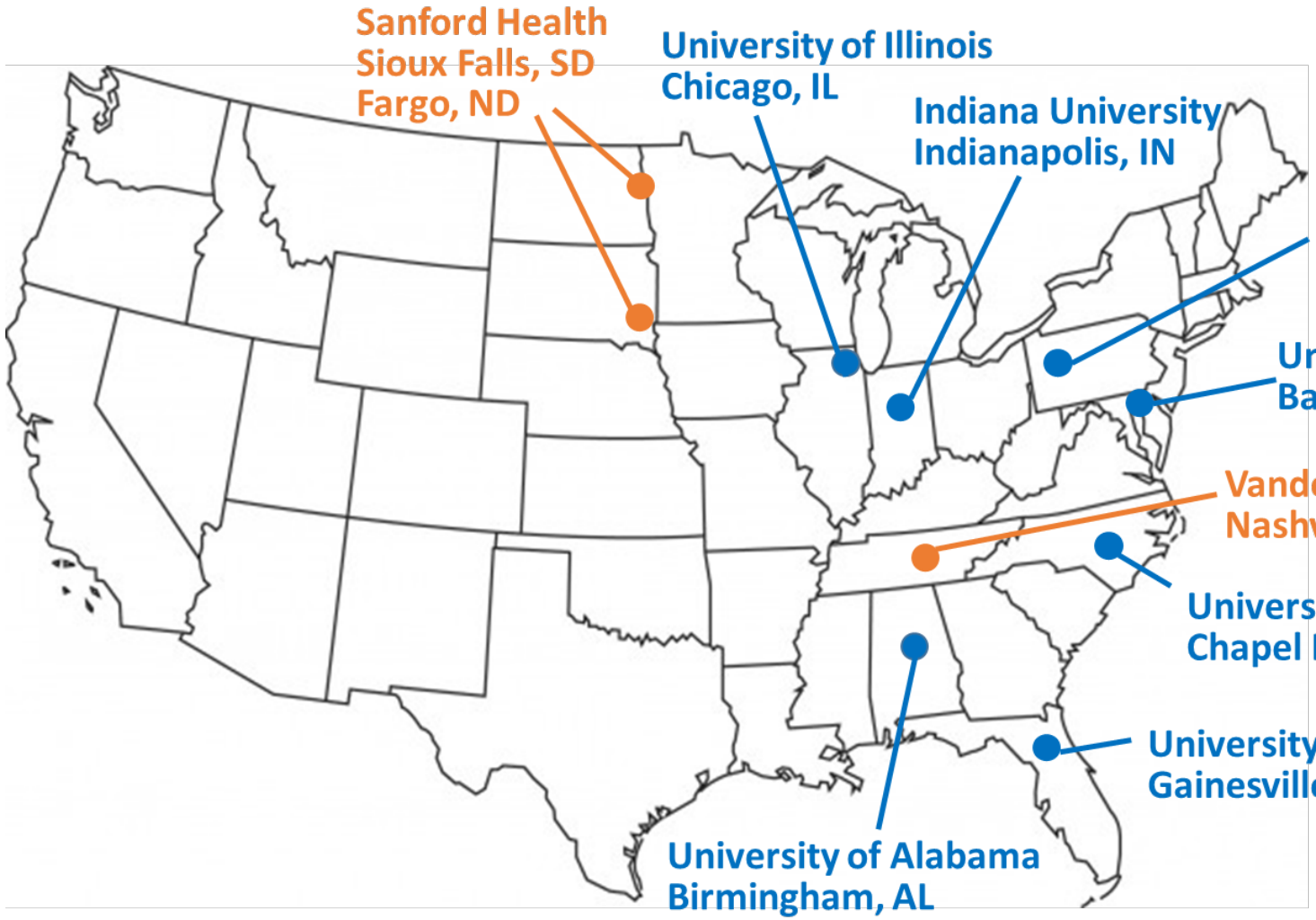

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Study Design

Multi-center pragmatic investigation of outcomes with 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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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 or ticagrelor

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Data Collection

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

Review of patient encounters

- Death or hospitalizations for cardiovascular events
- Medication use

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 ALTERNATIVE) 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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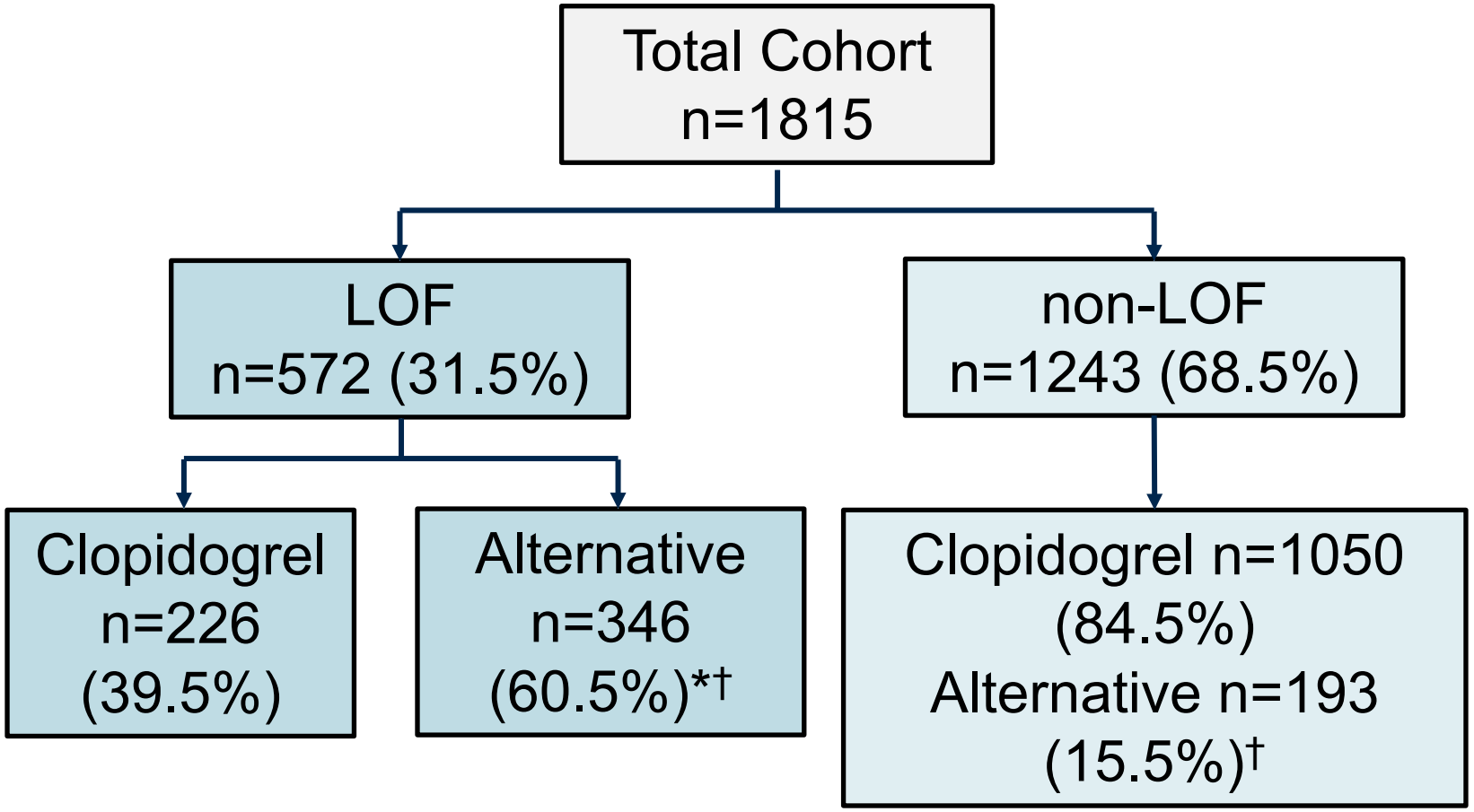
P2Y12 Inhibitor Therapy



*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 Groups

	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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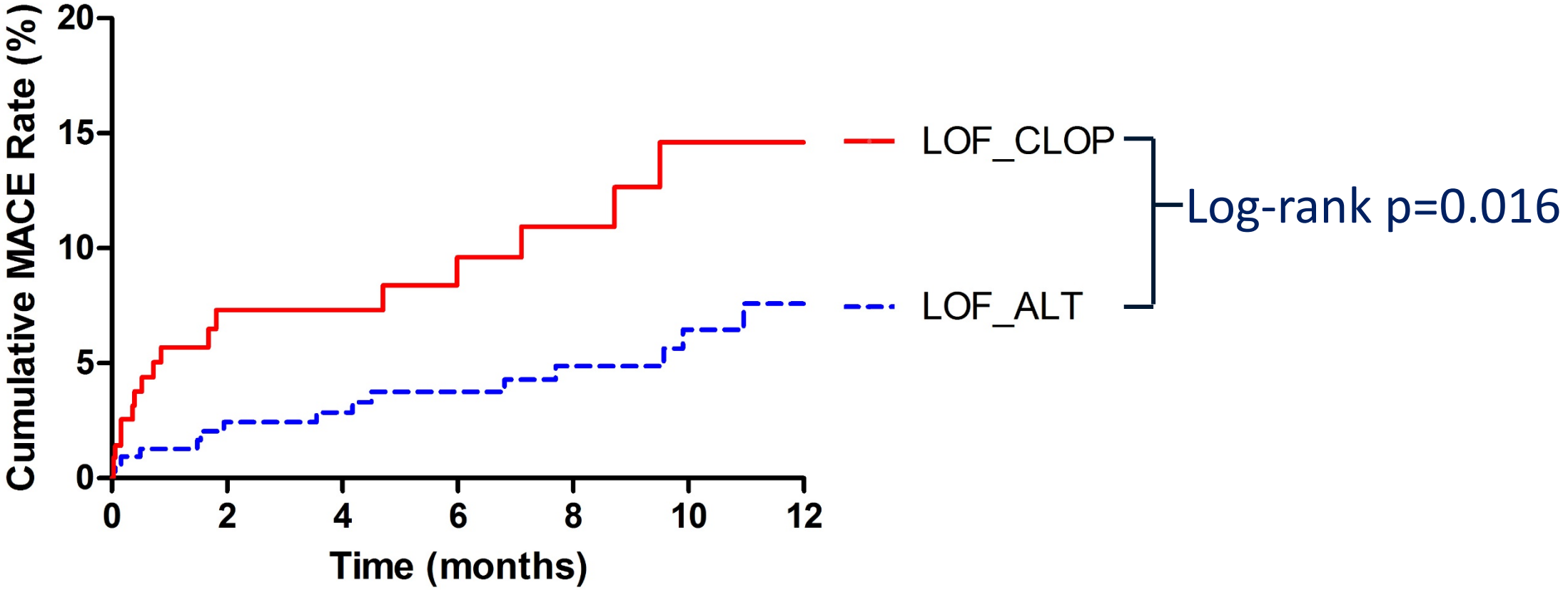
Kaplan-Meier Survival Curve

***Circulation* 2016;134:e711-12**



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

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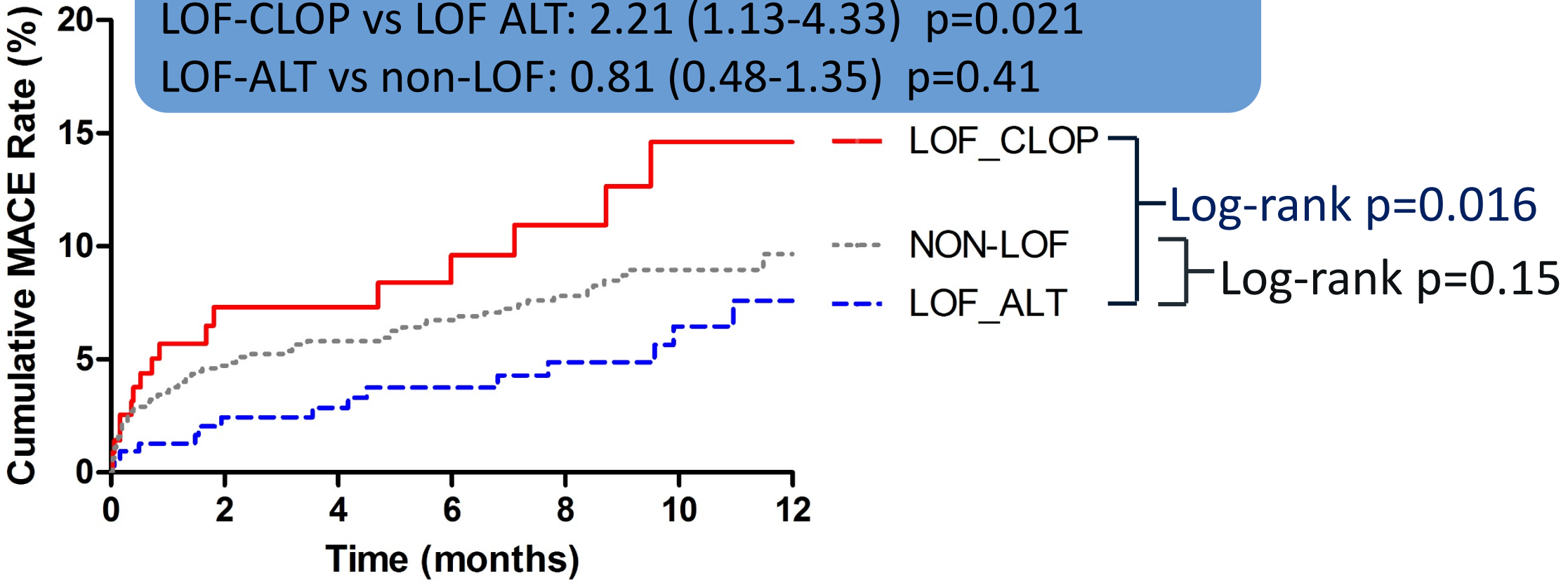
Kaplan-Meier Survival Curve

***Circulation* 2016;134:e711-12**

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

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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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