FROM MOLECULE TO PATIENT

CYP2C19 Genotype-Guided Escalation and De-Escalation Switching of Antiplatelet Therapy After Percutaneous Coronary Intervention in a Real-World Setting

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ANTIPLATELET THERAPY AND SWITCHING

FROM MOLECULE TO PATIENT

Percutaneous Coronary Intervention (PCI)

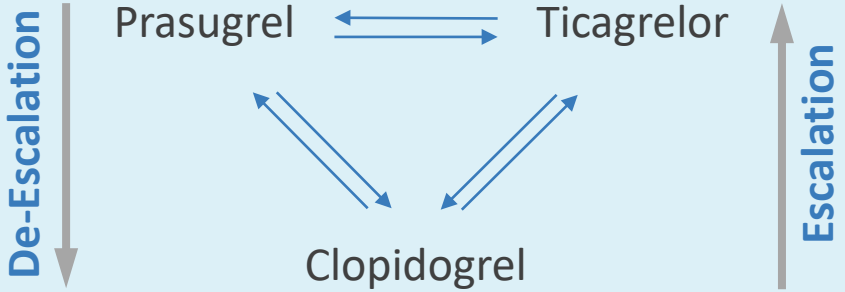
600K per year

Dual Antiplatelet Therapy (DAPT)

Aspirin + $P2Y_{12}$ Inhibitor

- **Benefit**: Reduce Ischemic Events
- **Risk**: Increase Bleeding Events

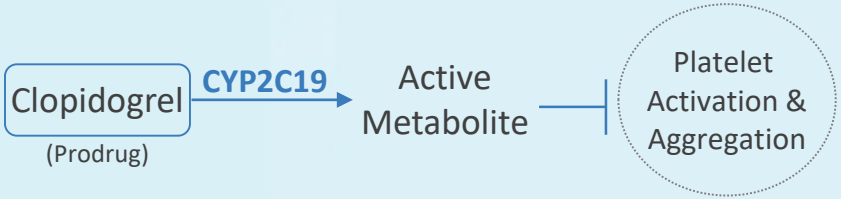
$P2Y_{12}$ Inhibitor **Switching** After PCI is Common



CLOPIDOGREL & NONFUNCTIONAL CYP2C19

FROM MOLECULE TO PATIENT

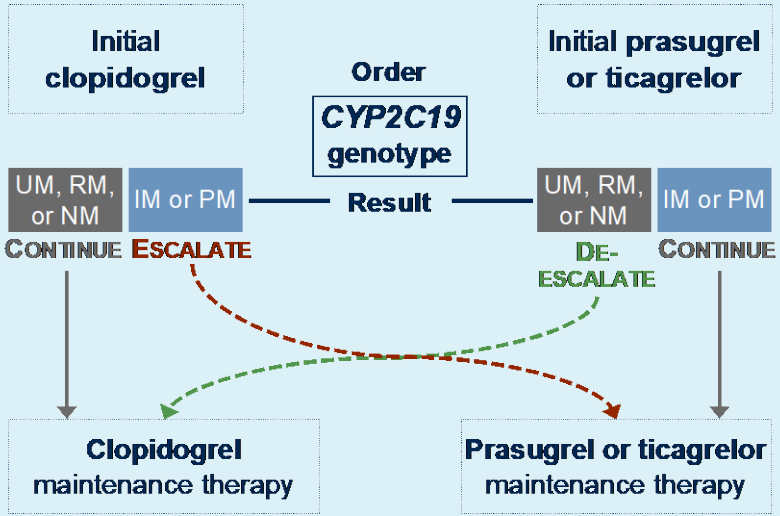
CYP2C19-Mediated Activation



1 in **3** patients are
CYP2C19 nonfunctional allele carriers

Genotype		Phenotype
Nonfunctional Allele Carriers	IM/PM	
Any *2 or *3 allele	Intermediate/poor metabolizer	
No Nonfunctional Alleles	UM/RM/NM	
*1 and *17 genotypes	Ultrarapid/rapid/normal metabolizer	

UNC Genotype-Guided Algorithm



CPIC guidelines for *CYP2C19* genotype and clopidogrel therapy
Scott et al. *Clin Pharmacol Ther*. 2013

STUDY AIMS AND METHODS

FROM MOLECULE TO PATIENT

AIM	METHODS	
1 Describe **frequency and timing** of switches between $P2Y_{12}$ inhibitors	DESIGN	Single-center, retrospective cohort of 1,063 genotyped patients who underwent PCI and received DAPT at UNC between 2012 and 2014
2 Evaluate **impact of *CYP2C19* results** on escalation and de-escalation	ENDPOINT	Switch: change in $P2Y_{12}$ inhibitor after initial therapy Clinical Outcome: MACCE* or clinically significant bleeding event†
3 Examine the relationship between escalation and de-escalation, *CYP2C19* status, & **clinical outcomes** post-PCI	ANALYSIS	Demographic/Clinical Factors: t-test, chi-square, or Fisher's exact Time-to-Switch: Wilcoxon signed rank test Time-to-Event: Cox proportional hazards regression in patients with follow-up after PCI (N=928), following stratification by initial antiplatelet therapy and adjusting for covariates. $p<0.05$ significant

* MACCE: major adverse cardiovascular or cerebrovascular event. Composite of death, MI, stent thrombosis, hospitalization for ACS/UA, ischemic stroke, or TIA
† Clinically significant bleeding: GUSTO moderate or severe/life-threatening

STUDY POPULATION (N=1063)

FROM MOLECULE TO PATIENT

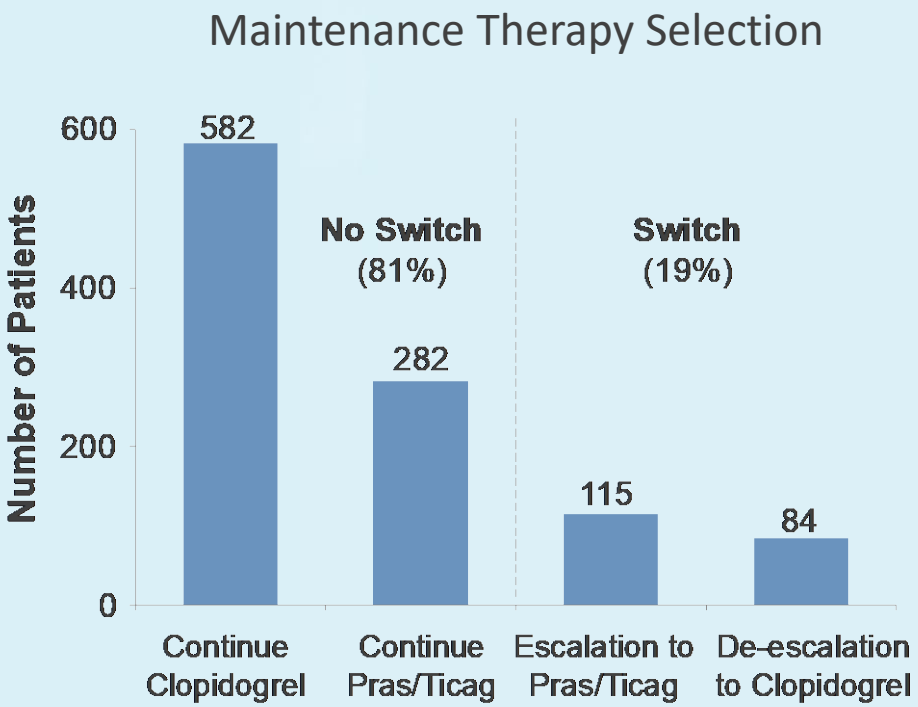
Demographics	
Age, year (mean ± SD)	62 ± 12
Male	720 (68%)
African-American	204 (19%)
Comorbidities	
Current smoker	313 (29%)
Hypertension	867 (82%)
Diabetes	429 (40%)
Peripheral vascular disease	117 (11%)
Atrial fibrillation	94 (9%)
Clinical Characteristics	
Previous myocardial infarction	286 (27%)
Previous coronary artery stent	384 (36%)
Elevated bleeding risk*	390 (37%)
Clopidogrel on admission	220 (21%)
Prasugrel/Ticagrelor on admission	31 (3%)

Indication for PCI	
Stable angina	428 (40%)
Acute coronary syndrome	635 (60%)
Unstable angina	182 (17%)
NSTEMI	291 (27%)
STEMI	162 (15%)
Stent Placement at Index PCI	
Drug-eluting stent	896 (84%)
Multiple vessels stented	141 (13%)
Initial $P2Y_{12}$ Therapy	
Clopidogrel	697 (66%)
Prasugrel/Ticagrelor	366 (34%)
Prasugrel	355 (33%)
Ticagrelor	11 (1%)

In the overall population, patients are primarily male, white, and older, with multiple comorbidities. ACS makes up over half of index PCI indication. Two-thirds of patients were initiated on clopidogrel.

* Elevated bleeding risk: composite defined as one or more of: age ≥75 yrs; wt <60 kg; hx TIA or stroke; hx significant bleeding; current end-stage renal disease requiring dialysis; or, anticoagulant prescribed at discharge.

SWITCH FREQUENCY & TIMING



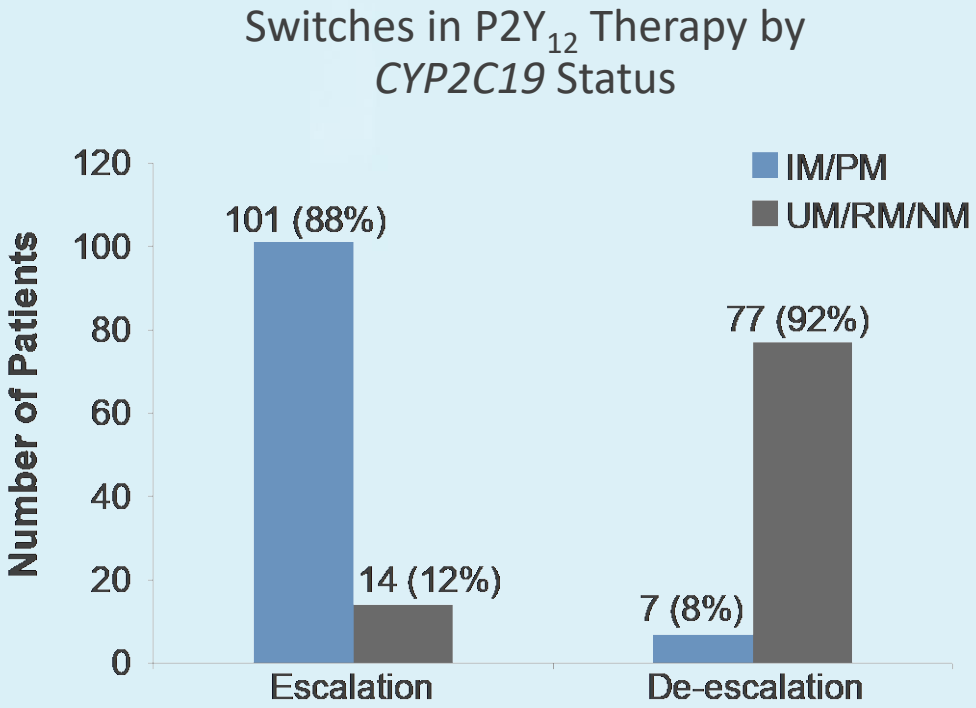
	Escalation		De-escalation
Median [IQR] Time-to-Switch	4 [2-17] days	vs.*	20 [2-39] days

*p=0.001

CYP2C19-guided switching was common, observed in approximately 1 in 5 patients.

De-escalation occurred significantly later after PCI on average than escalation.

IMPACT OF *CYP2C19*

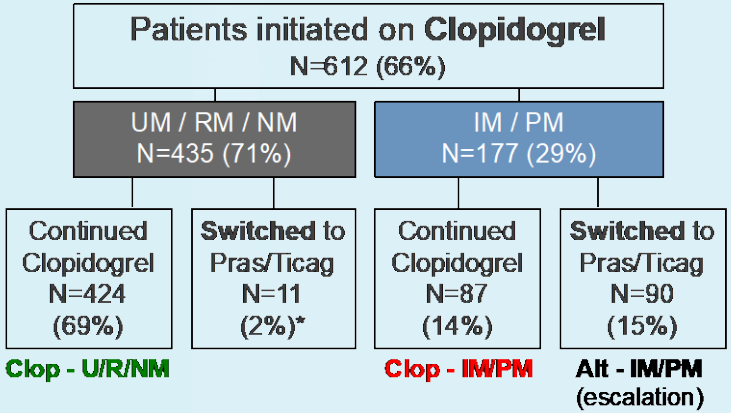


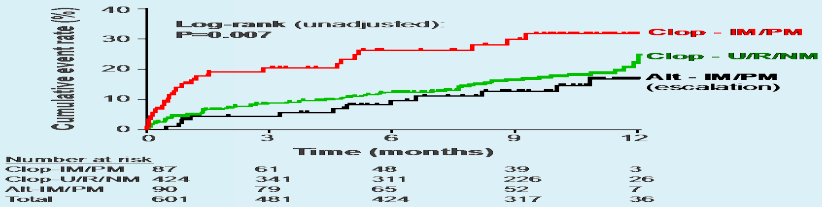
1. Among **IM/PMs** initiated on clopidogrel, 101 (**51%**) were escalated to prasugrel or ticagrelor

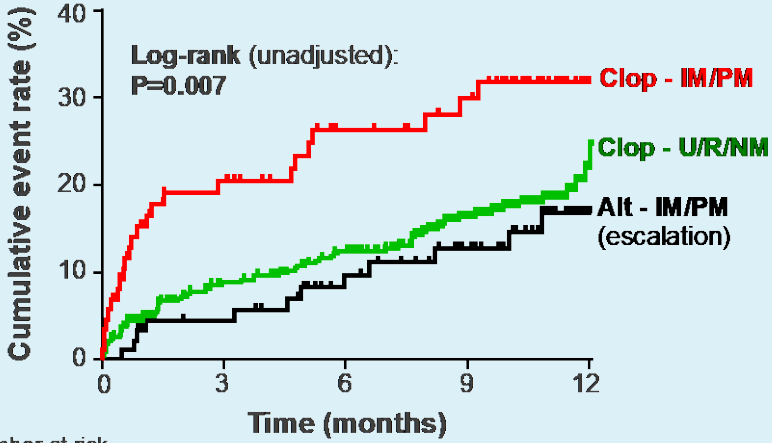
2. Among **UM/RM/NMs** initiated on prasugrel/ticagrelor, 77 (**33%**) were de-escalated to clopidogrel

Consistent with genotype-guided prescribing, escalations occurred almost exclusively in IM/PMs and de-escalations occurred primarily in UM/RM/NMs

CLINICAL OUTCOMES – INITIAL CLOPIDOGREL





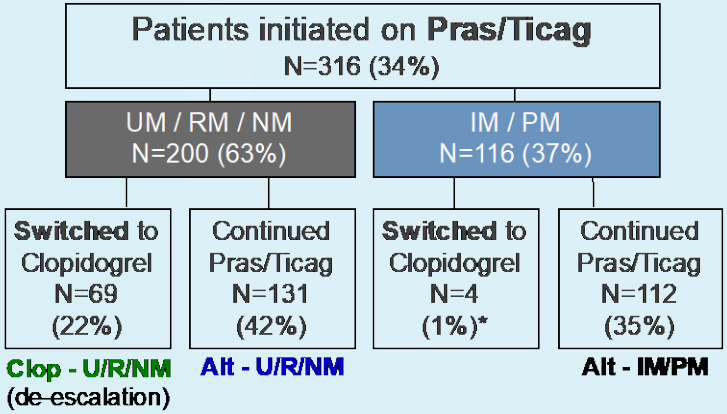


Number at risk

Clop-IM/PM	87	61	48	39	3
Clop-U/R/NM	424	341	311	226	26
Alt-IM/PM	90	79	65	52	7
Total	601	481	424	317	36

*Due to rare occurrence, UM/RM/NMs escalated to prasugrel or ticagrelor were not included in the analysis.

CLINICAL OUTCOMES – INITIAL PRAS/ TICAG



Group	Events No. (%)	Event Rate (per 100 pt-yrs)	Adjusted HR (95% CI)	P-value
Clop- U/R/NM	10 (15%)	21	1.1 (0.5 - 2.3)	0.75
Alt- U/R/NM	17 (13%)	20	Reference	
Alt- IM/PM	13 (12%)	18		

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Alt- U/R/NM	17 (13%)	20	Reference	
Alt- IM/PM	13 (12%)	18		

*Due to rare occurrence, IMs de-escalated to clopidogrel were not included in the analysis.

SUMMARY AND CLINICAL PERSPECTIVE

FROM MOLECULE TO PATIENT

- FREQUENCY: *CYP2C19*-guided switching was common, observed in approximately 1 in 5 patients
- IMPACT OF GENOTYPE & TIMING: escalation primarily in *CYP2C19* nonfunctional allele carriers (88%), while de-escalation significantly later and primarily in patients without a nonfunctional allele (92%)

CLINICAL PERSPECTIVE

1. genotype-guided escalation to prasugrel or ticagrelor mitigates the risk of adverse cardiovascular outcomes conferred by clopidogrel use in *CYP2C19* nonfunctional allele carriers
2. use of genotype to selectively guide de-escalation to clopidogrel in patients without a *CYP2C19* nonfunctional allele appeared safe and effective

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