WASHINGTON STATE UNIVERSITY

Pharmacogenomics of Cardiovascular Diseases

Interprofessional Clinical Pharmacogenomics Certificate Program

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WSU

Conflict of Interest Disclosure

- Teresa T. Ho has no real or potential conflicts of interest related to the subject matter of this presentation

Learning Objectives

- Determine the impact of genetic variation on drug pharmacokinetics, pharmacodynamics, and drug response
- Interpret pharmacogenomic test results by identifying clinically actionable drug-gene pairs using high-quality, evidence-based pharmacogenomic databases and guidelines to formulate therapeutic recommendations
- Recommend pharmacogenomic testing when appropriate
- Summarize main findings from the literature supporting the use of pharmacogenomics-guided treatment in cardiology
- Demonstrate clinical application of pharmacogenomic testing results in cardiology through case examples

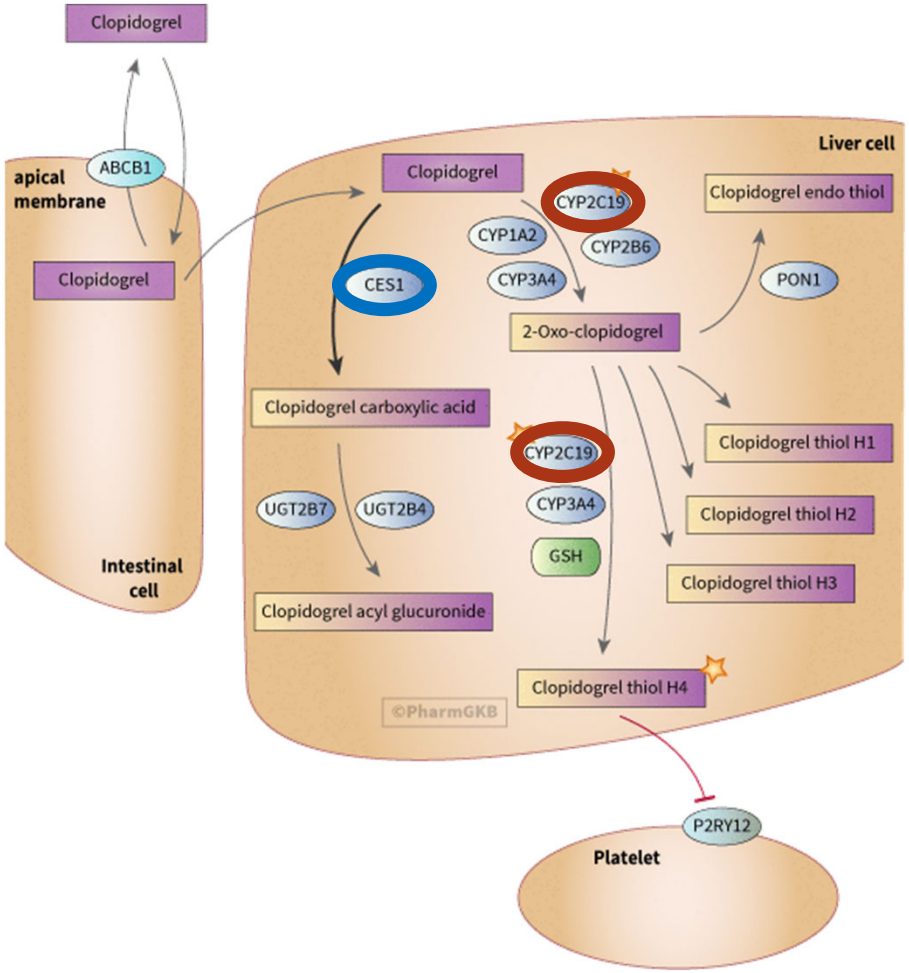
Pharmacogenomic-guided antiplatelet therapy

Clopidogrel

- Indications
  - Acute coronary syndrome +/- percutaneous coronary intervention
  - Recent myocardial infarction
  - Recent stroke
  - Peripheral artery disease

- Significant inter-patient variability in response to clopidogrel

Clopidogrel Metabolism



https://www.pharmgkb.org/pathway/PA154424674

CYP2C19 Gene

- > 35 star (*) allele haplotypes identified in the *CYP2C19 gene*

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

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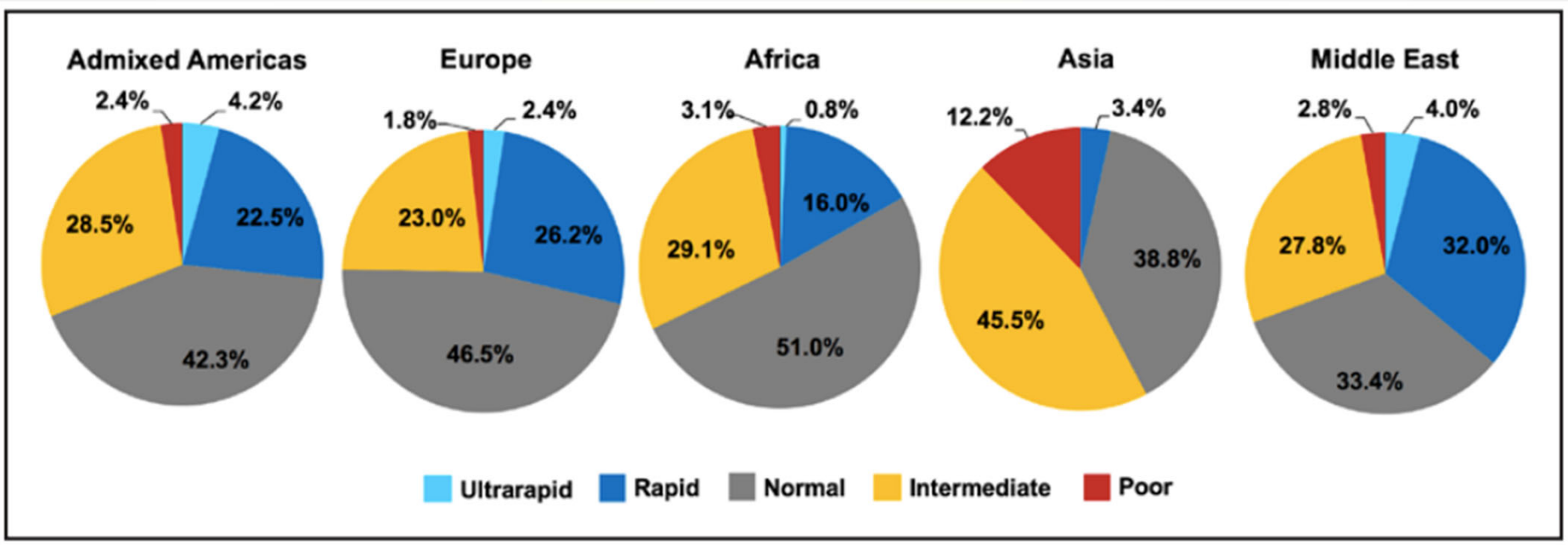
Interpreting *CYP2C19* genetic results

Phenotype	Example Genotypes
Ultra-rapid metabolizer (UM)	CYP2C19***17/*17**
Rapid metabolizer (RM)	CYP2C19***1/*17**
Normal metabolizer (NM)	CYP2C19***1/*1**
Intermediate metabolizer (IM)	CYP2C19***1/*2** or CYP2C19***1/*3**
Poor metabolizer (PM)	CYP2C19***2/*2** or CYP2C19***3/*3**

Prevalence of CYP2C19 Phenotypes



Arterioscler Thromb Vasc Biol. 2019;39:647- 652.

Impact of *CYP2C19* on Clopidogrel Response

- CYP2C19 intermediate and poor metabolizers on clopidogrel
  - Less active metabolite
  - Decreased antiplatelet effects
  - Increased risk of major adverse cardiovascular events (MACE)

Outcome	IM vs NM Risk ratio (95% CI)	PM vs NM Risk ratio (95% CI)
MACE	1.5 (1.1 – 2.1)	1.8 (1.2 – 2.5)
Stent thrombosis	2.7 (1.7 – 4.2)	4.0 (1.8 – 9.0)

MACE = major adverse CV events (CV death, MI, or stroke)
NM = normal metabolizer, IM = intermediate metabolizer, PM = poor metabolizer

Mega et al. N Engl Med 2009;360:354-62.
Mega et al. JAMA 2010;304:1821-30.

FDA-Approved Labeling for Clopidogrel

- US Food and Drug Administration (FDA) originally approved a new label for clopidogrel with a "boxed warning" in March 2010

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)**

Plavix package insert, accessed March 2022.

FDA-Approved Labeling for Clopidogrel

- Boxed warning later updated in 2016

WARNING: DIMINISHED EFFECTIVENESS ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

See full prescribing information for complete boxed warning

- Effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1, 12.3)
- Tests are available to identify a patient's who are CYP2C19 poor metabolizers(12.5)
- Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers. (5.1)

Plavix package insert, accessed March 2022.

2011 ACCF/AHA/SCAI Guidelines for PCI

6.1.2 Clopidogrel Genetic Testing: Recommendations

Class IIb: Usefulness/efficacy is well established

1. Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate plate inhibition with clopidogrel. (Level of Evidence: C)
2. When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternate P2Y12 inhibitor (e.g. prasugrel or ticagrelor) might be considered. (Level of Evidence: C)

Class III: No benefit

1. The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended. (Level of Evidence: C)

Levine GN, et al. Circulation 2011;124:e574-651.

2019 Updated Expert Consensus Statement on Genetic Testing for Guiding Antiplatelets in PCI

TABLE 5 Consensus Advice for Genotyping in Patients Undergoing Percutaneous Coronary Intervention

General advice on using genotyping in clinical practice

- Point-of-care genotyping assays are preferred over laboratory-based assays.
- Selection of assay should depend on the local site experience and availability.
- Because of in vivo bioactivation properties of the available $P2Y_{12}$ receptor inhibitors, a rationale for genotyping exists for clopidogrel-treated patients but not prasugrel- or ticagrelor-treated patients.

Patients with stable CAD (elective PCI)

- CYP2C19 genotyping in patients on clopidogrel treatment may provide useful prognostic data for cardiovascular risk prediction (for both bleeding and ischemic events) after elective PCI in stable CAD.
- CYP2C19 genotyping to escalate treatment in LoF allele carriers (especially *2 and *3) during clopidogrel treatment is not recommended as a routine but may be considered in specific clinical scenarios (heterozygous and homozygous allele carriage should be taken into account).
- CYP2C19 genotyping to screen for LoF alleles to determine the drug that would remain when DAPT de-escalation (e.g., triple treatment in which one antiplatelet agent is planned to be omitted) is being considered is not recommended.

Patients with acute coronary syndrome (NSTEMI/STEMI)

- CYP2C19 genotyping in patients on clopidogrel may provide useful prognostic data for cardiovascular risk prediction (for both bleeding and ischemic events) after PCI for ACS.
- Genotyping to escalate treatment in LoF allele carriers is not recommended, because of lack of data from dedicated studies.
- Genotyping to screen for LoF alleles when DAPT de-escalation is being considered in an individual patient is not recommended, because of lack of data from dedicated studies.

JACC Cardiovasc Interv. 2019 Aug 26;12(16):1521-1537.

2020 ESC Guidelines for ACS without STEMI

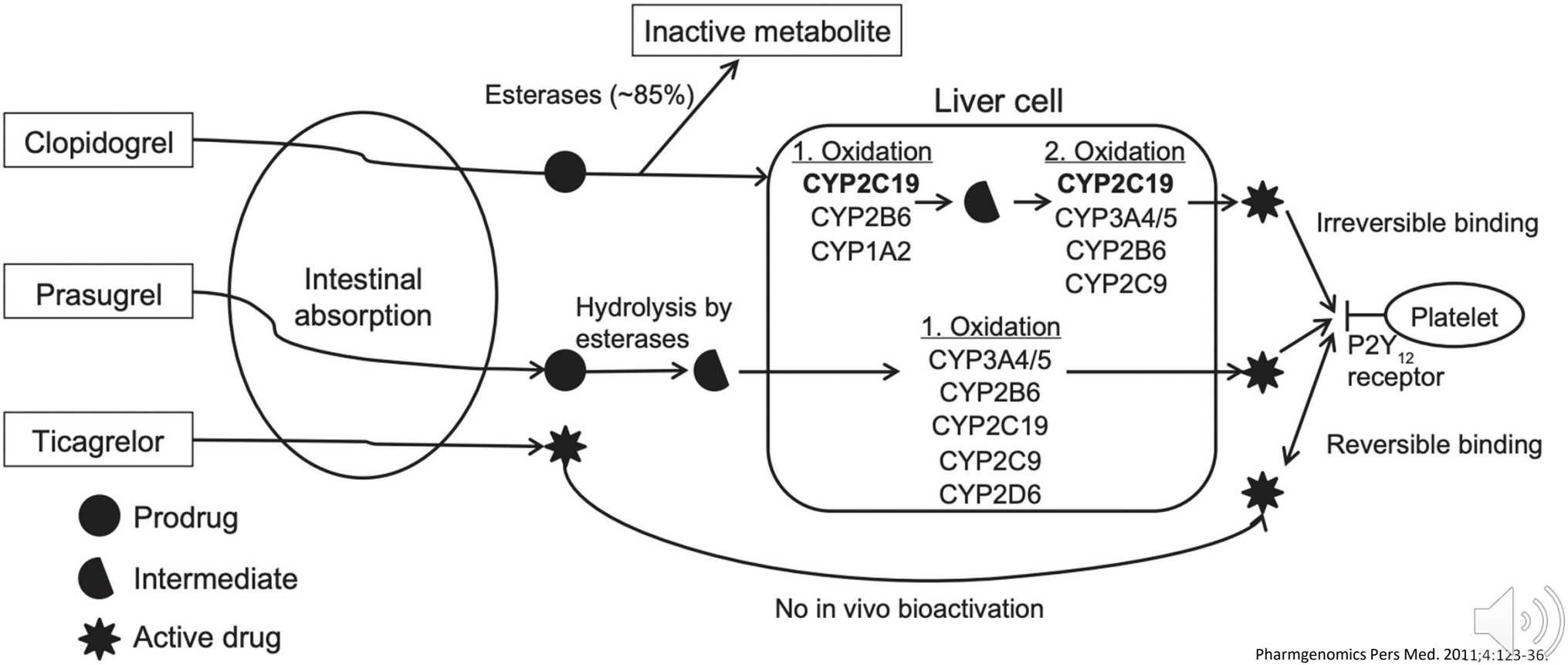
5.1.4 Post-interventional and maintenance treatment

Class IIb-A: Usefulness/efficacy is less well established by evidence/opinion (May be considered)

1. De-escalation of P2Y12 receptor inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment or guided by platelet function testing or **CYP2C19 genotyping**, depending on patient's risk profile and availability of respective assays.

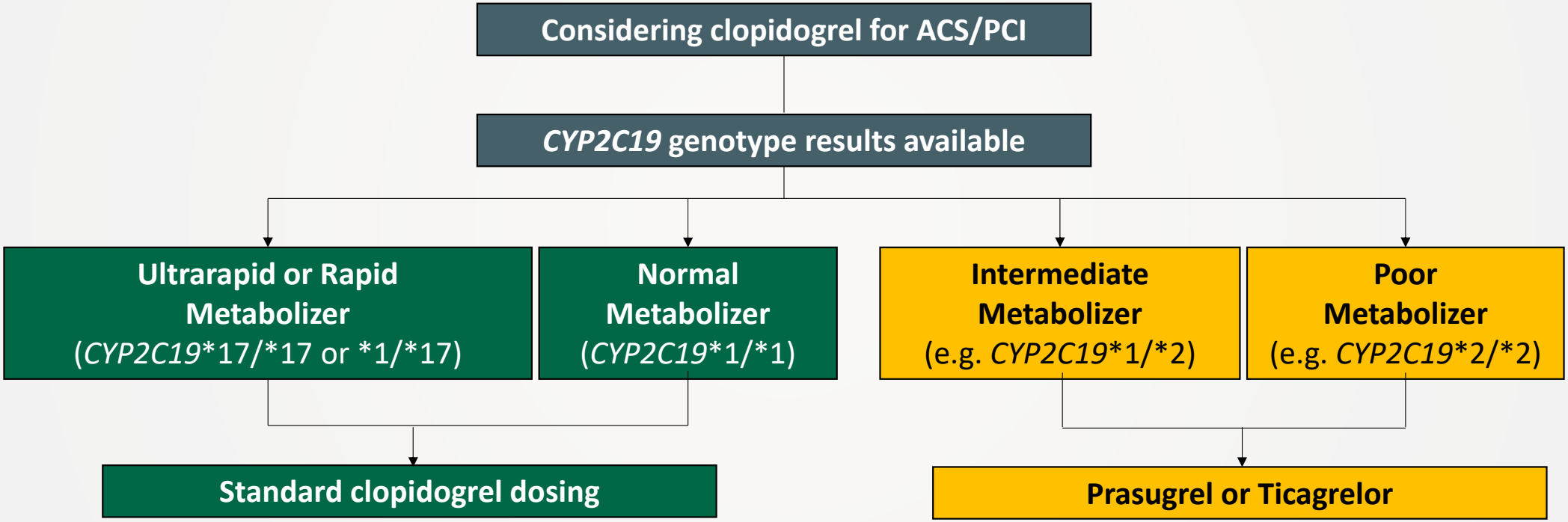
Eur Heart J. 2021 Apr 7;42(14):1289-1367.

Alternative antiplatelets



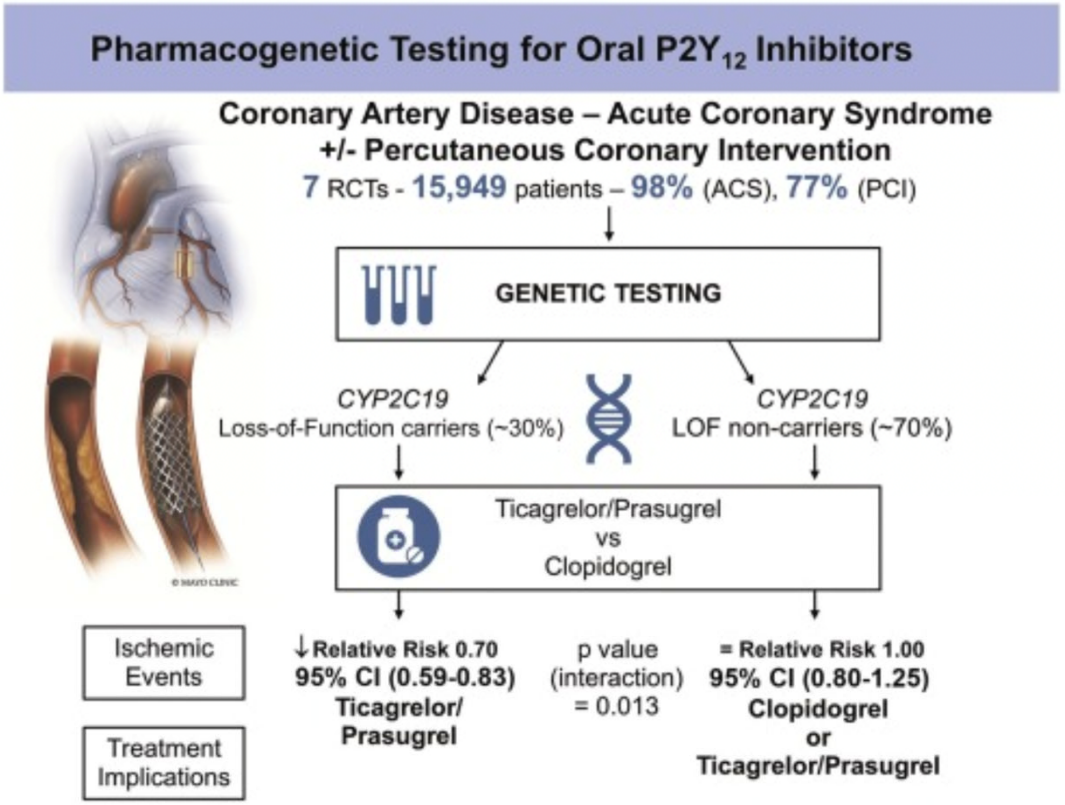
Pharmgenomics Pers Med. 2011;4:123-36.

Clinical Pharmacogenomics Implementation Consortium (CPIC) Guidelines for *CYP2C19* genotype guided clopidogrel



Clin Pharmacol Ther. 2022 Jan 16.

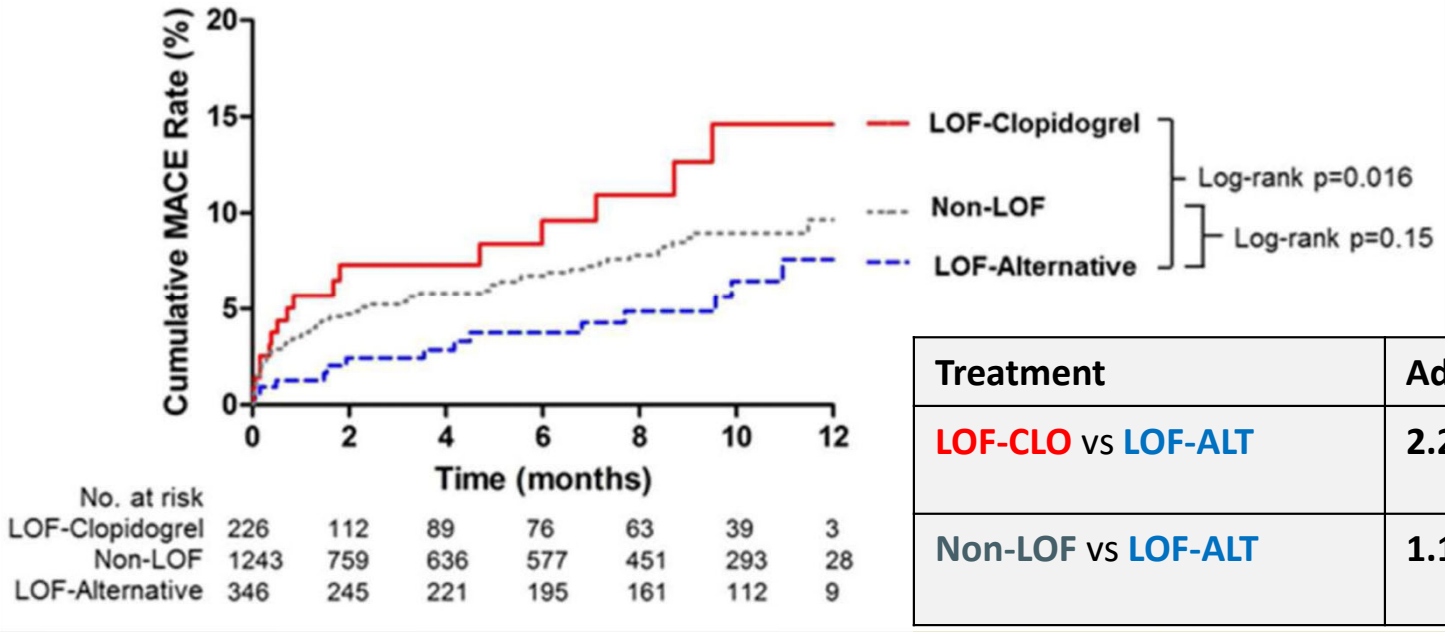
CENTRAL ILLUSTRATION: A Proposed Algorithm Using *CYP2C19* Pharmacogenetic Testing to Individualize Oral $P2Y_{12}$ Inhibitor Therapy in Patients With Coronary Artery Disease on the Basis of the Meta-Analysis Results



Pereira NL. JACC Cardiovasc Interv. 2021 Apr 12;14(7):739-750.

IGNITE Cohort: Risk of MACE

Implementing Pharmacogenomics in Practice



N = 1,815

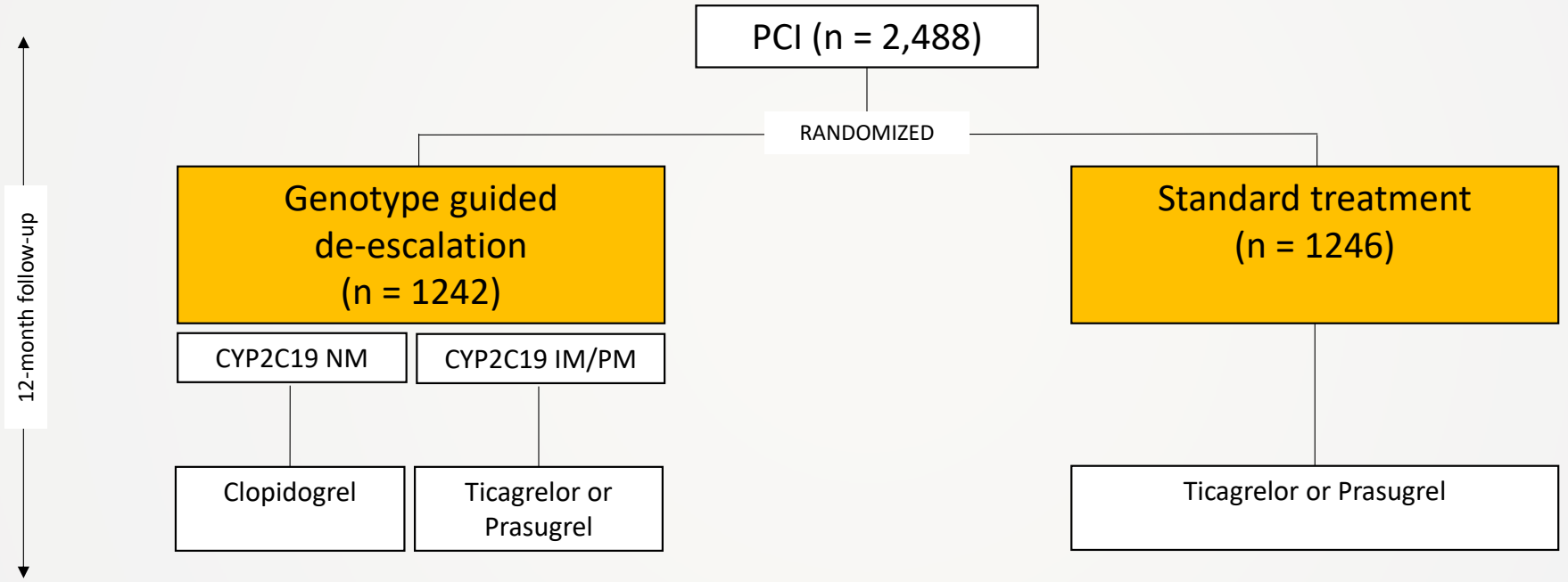
Treatment	Adjusted HR	P-value
LOF-CLO vs LOF-ALT	**2.26** (1.18 – 4.32)	0.013
Non-LOF vs LOF-ALT	**1.14** (0.69 – 1.88)	0.600

LOF = Loss of function (CYP2C19 intermediate or poor metabolizers)
CLO = Clopidogrel
ALT = Alternative antiplatelet (prasugrel or ticagrelor)
MACE = Major adverse cardiovascular events (death, MI, or ischemic stroke)

JACC Cardiovasc Interv. 2018 Jan 22;11(2):181-191.

POPular Genetics Trial

Patient Outcome after Primary PCI

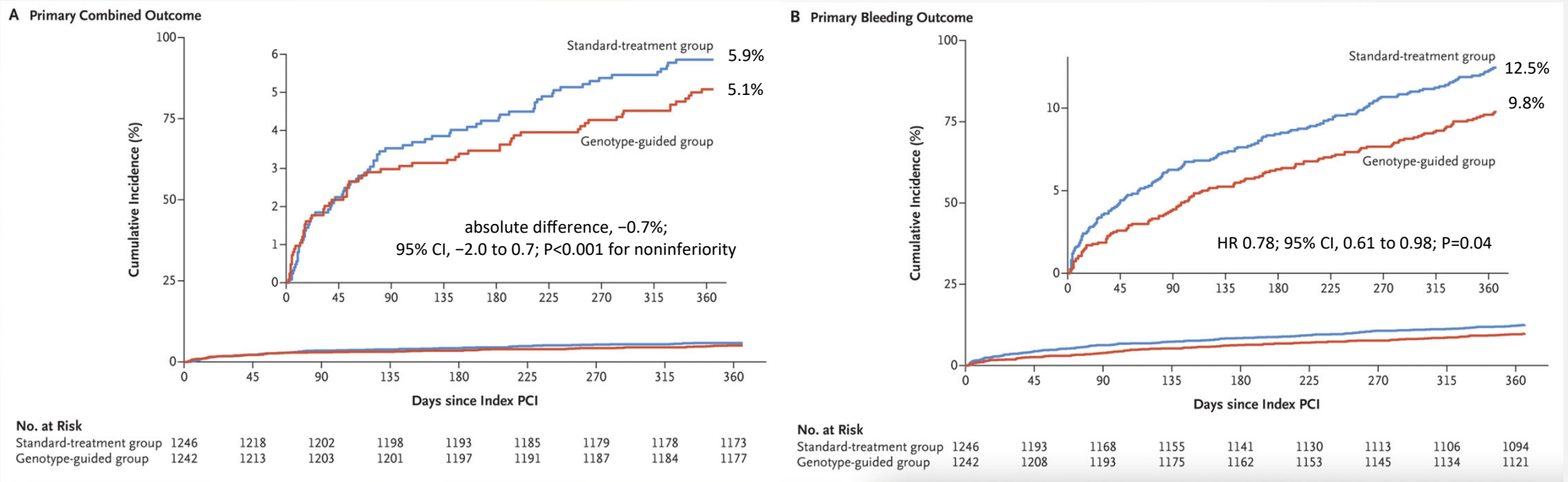


Primary outcome:

1) Net adverse clinical events (death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding)
2) PLATO major or minor bleeding

Claassens DMF. N Engl J Med. 2019 Oct 24;381(17):1621-1631.

POPular Genetics Trial

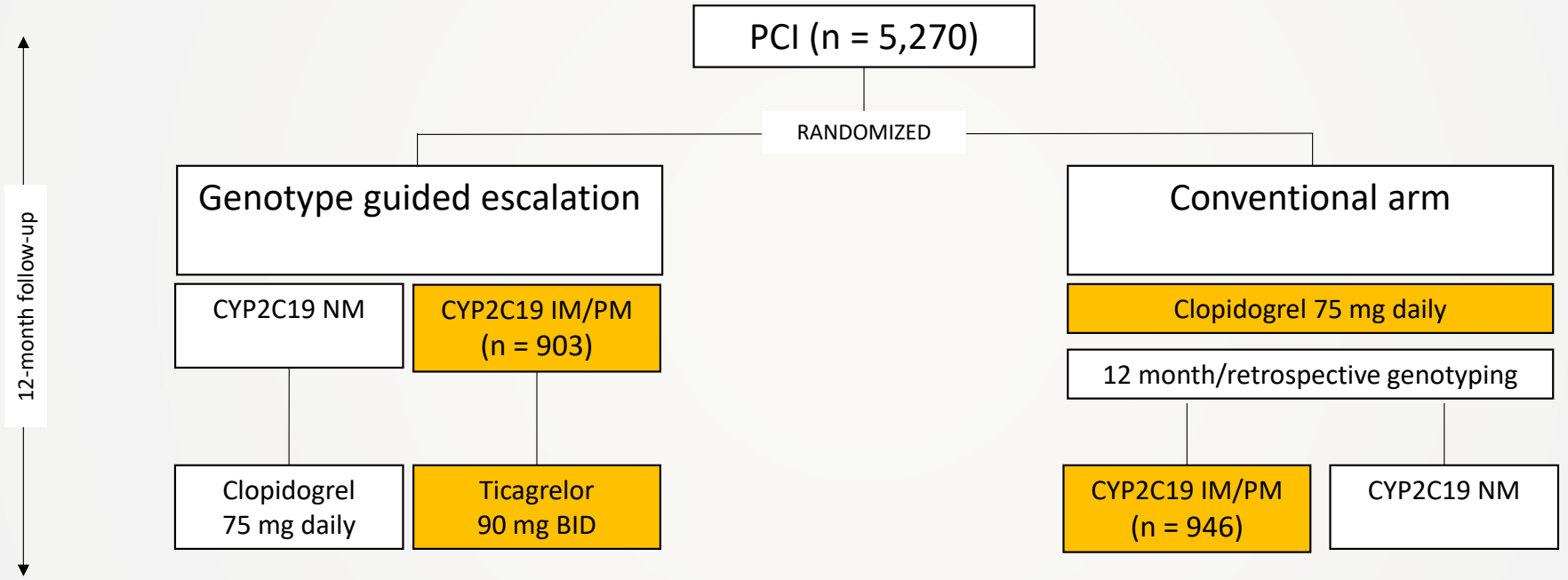


CYP2C19 genotype-guided de-escalation strategy for selection of antiplatelet therapy is noninferior to standard treatment with ticagrelor or prasugrel at 12 months and resulted in lower incidence of bleeding

Claassens DMF. N Engl J Med. 2019 Oct 24;381(17):1621-1631.

TAILOR-PCI Trial

Tailored Antiplatelet Initiation to Lessen Outcomes due to decreased clopidogrel Response after Percutaneous Coronary Intervention

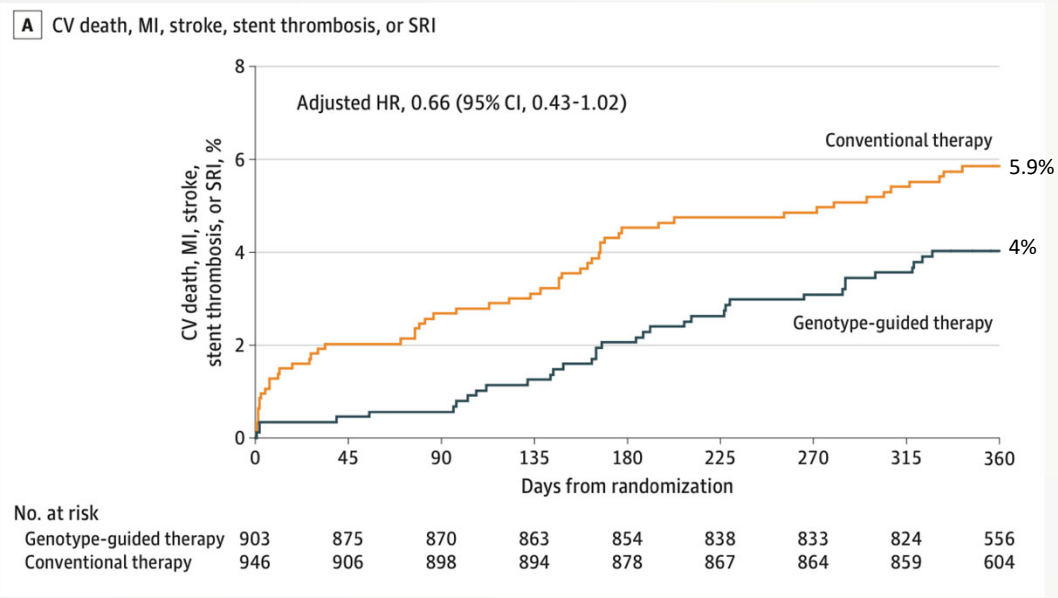


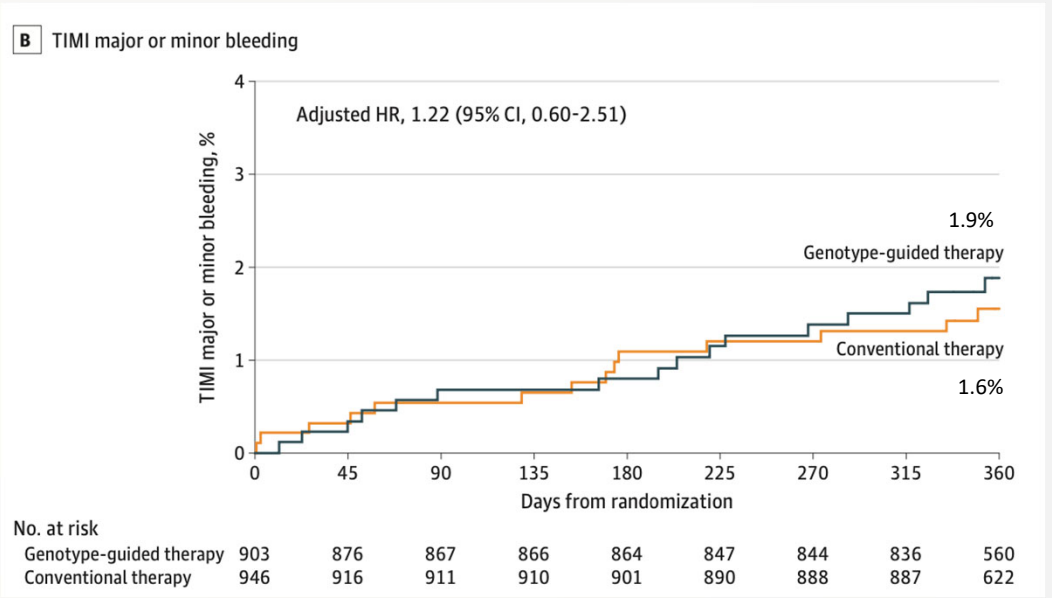
Primary outcome: CV death, MI, stroke, definite or probable stent thrombosis, and severe recurrent ischemia

JAMA. 2020 Aug 25;324(8):761-771.

TAILOR-PCI Trial

Tailored Antiplatelet Initiation to Lessen Outcomes due to decreased clopidogrel Response after Percutaneous Coronary Intervention





While TAILOR PCI fell short in finding a difference in the primary outcome for the prespecified analysis at 12 months, post-hoc analysis demonstrated potential benefit of genotype guided treatment in first 3 months after PCI (HR 0.21, 95% CI 0.08-0.54, p=0.58)

JAMA. 2020 Aug 25;324(8):761-771.

Comparison of major clinical trials

Clinical trial	N	Primary outcome				Safety outcome	ARR
TRITON-TIMI, 2006 Prasugrel vs Clopidogrel	13,608 ACS + PCI	CV death, nonfatal myocardial infarction, or nonfatal stroke				Major bleeding HR 1.32 (95% CI, 1.03-1.68; p=0.03)	2.2%
		Prasugrel 9.9%	**Clopidogrel** 12.1%	**HR (95% CI)** 0.81 (0.73-0.90)	**Pvalue** <0.001		
PLATO, 2010 Ticagrelor vs Clopidogrel	13,408 ACS	CV death, MI, or stroke				Major bleeding HR: 0.99 (95% CI, 0.89-1.10; p=0.8803)	1.7%
		Ticagrelor 9%	**Clopidogrel** 10.7%	**HR (95% CI)** 0.84 (0.75-0.94)	**Pvalue** 0.0025		
TAILOR PCI, 2020 CYP2C19 guided (85% on ticagrelor) vs Conventional (99% on clopidogrel)	1,849 ACS 82% Stb CAD 18%	CV death, MI, stroke, definite or probably stent thrombosis, severe recurrent ischemia at 12 months				TIMI major or minor bleeding HR 1.22 (95% CI: 0.60-2.51, p = 0.58)	1.9%
		CYP2C19 LOF 4%	**Conventional** 5.9%	**HR (95% CI)** 0.66 (0.43-1.02)	**Pvalue** P=0.06		

N Engl J Med. 2007 Nov 15;357(20):2001-15. Lancet. 2010 Jan 23;375(9711):283-93. JAMA. 2020 Aug 25;324(8):761-771.

CPIC Recommendations for non-ACS/PCI cardiovascular indications considering clopidogrel and CYP2C19 phenotype

CYP2C19 Phenotype	Therapeutic recommendation	Classification of recommendation ACS/PCI	Classification of recommendation non-ACS/PCI CV indications*
CYP2C19 UM	Standard dose clopidogrel	Strong	-----
CYP2C19 RM	Standard dose clopidogrel	Strong	-----
CYP2C19 NM	Standard dose clopidogrel	Strong	Strong
CYP2C19 IM	Prasugrel or ticagrelor if clinically indicated and in absence of CI	Strong	-----
CYP2C19 PM	Prasugrel or ticagrelor if clinically indicated and in absence of CI	Strong	Moderate

*Peripheral artery disease (PAD) and stable coronary artery disease (CAD) following recent MI outside setting of PCI
----- represents no recommendation

Clin Pharmacol Ther. 2022 Jan 16.

CPIC Recommendations for neurovascular indications* considering clopidogrel and CYP2C19 phenotype

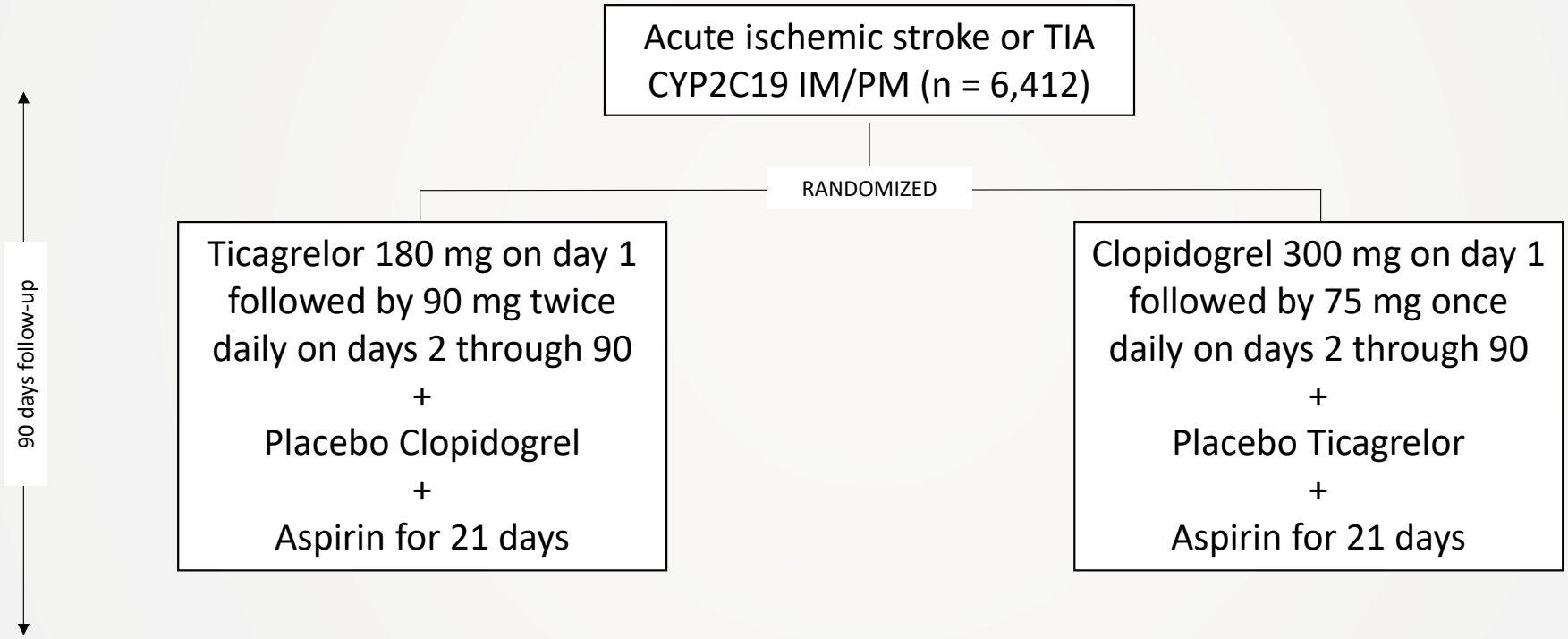
CYP2C19 Phenotype	Therapeutic recommendation	Classification of recommendation	Other considerations
CYP2C19 UM	-----	-----	-----
CYP2C19 RM	-----	-----	-----
CYP2C19 NM	Standard dose clopidogrel	Strong	-----
CYP2C19 IM	Consider alternative P2Y12 inhibitor at standard dose if clinically indicated and no contraindication	Moderate	Alternative P2Y12 inhibitors not impacted by *CYP2C19* genetic variants include ticagrelor and ticlopidine. Prasugrel is CI in patients with history of stroke/TIA.
CYP2C19 PM	Avoid clopidogrel. Consider alternative P2Y12 inhibitor at standard dose if clinically indicated and no contraindication	Moderate	

*acute ischemic stroke or TIA, secondary prevention of stroke, prevention of thromboembolic events following neurointerventional procedures
----- represents no recommendation

Clin Pharmacol Ther. 2022 Jan 16.

CHANCE-2 Trial

Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events

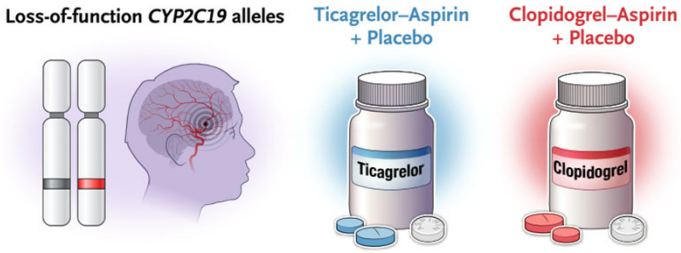


Primary efficacy outcome: new stroke
Primary safety outcome: severe or moderate bleeding

Wang Y. N Engl J Med. 2021 Dec 30;385(27):2520-2530.

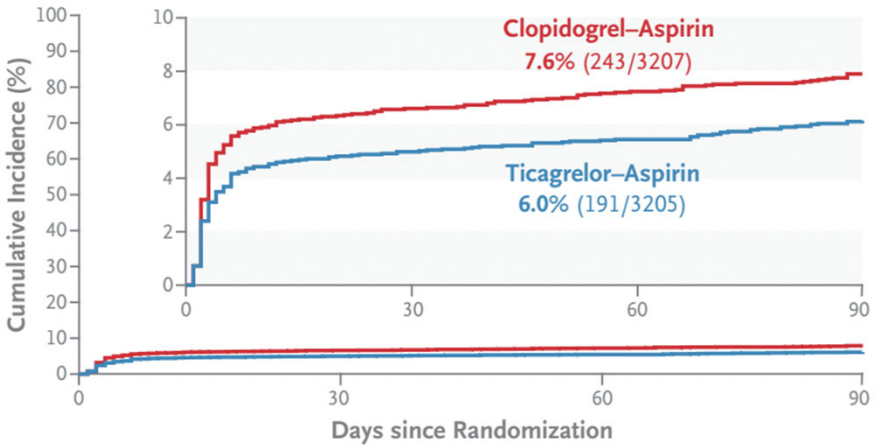
CHANCE-2 Trial

Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events



New Ischemic or Hemorrhagic Stroke at 90 Days

Hazard ratio, 0.77; 95% CI, 0.64 to 0.94; P=0.008

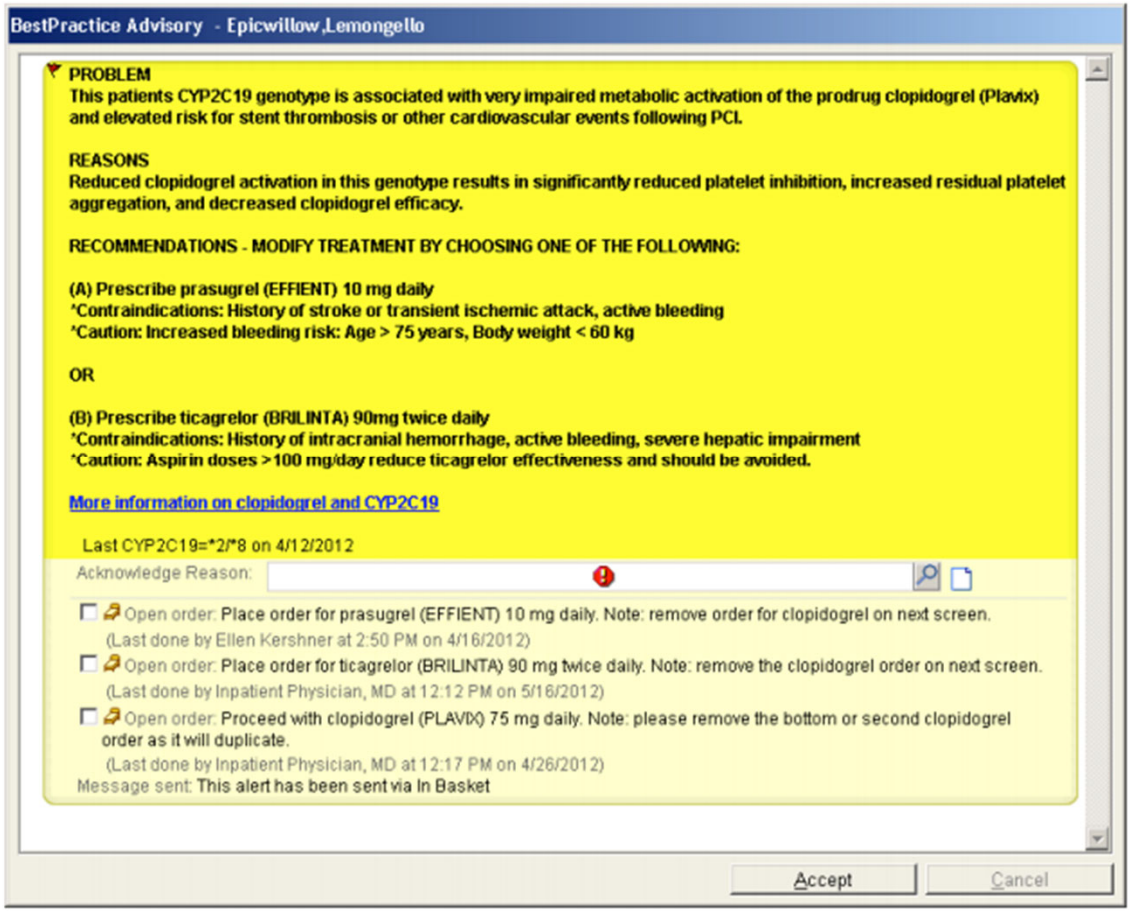


Severe or Moderate Bleeding at 90 Days

	Ticagrelor–Aspirin (N=3205)	Clopidogrel–Aspirin (N=3207)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Severe or moderate bleeding	9 (0.3)	11 (0.3)	0.82 (0.34 to 1.98)	0.66
Any bleeding	170 (5.3)	80 (2.5)	2.18 (1.66 to 2.85)	

Wang Y. N Engl J Med. 2021 Dec 30;385(27):2520-2530.

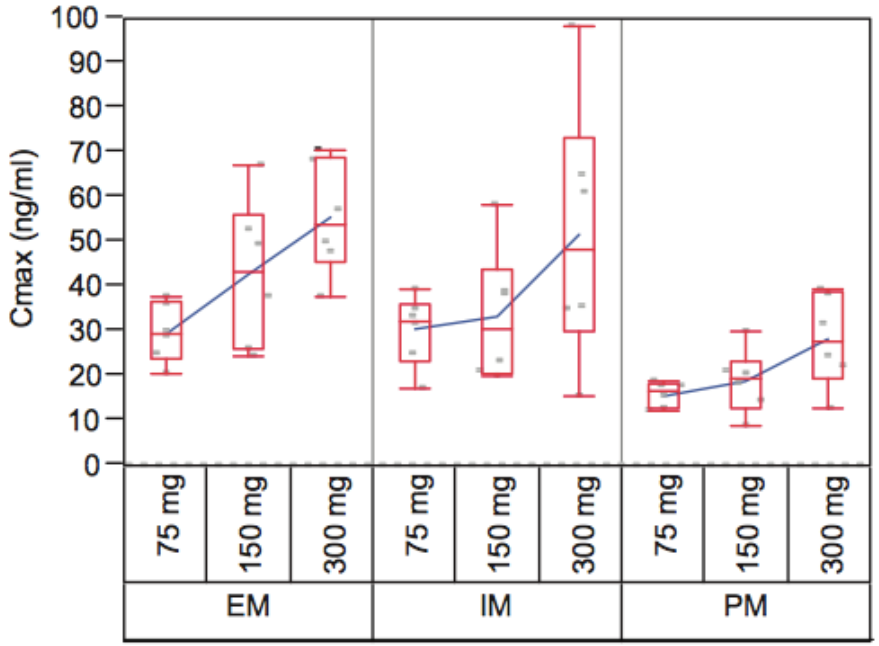
Example Clinical Decision Support Alerts

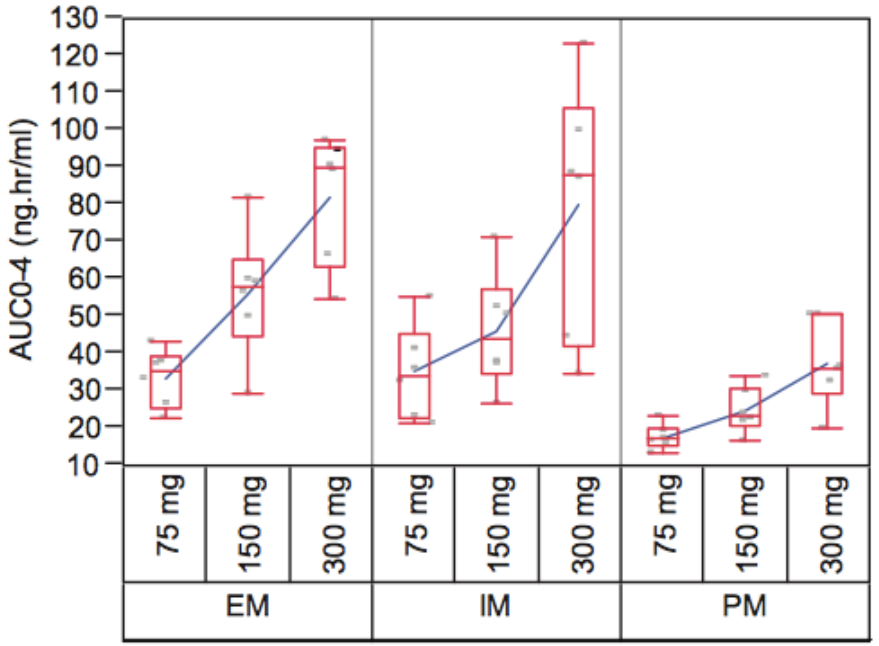


Weitzel KW, et al. Am J Med Genet C Semin Med Genet. 2014;166C(1):56-67.

Clopidogrel dose escalation

Pharmacokinetics of clopidogrel active metabolite with increasing doses of clopidogrel in EMs, IMs, and PMs



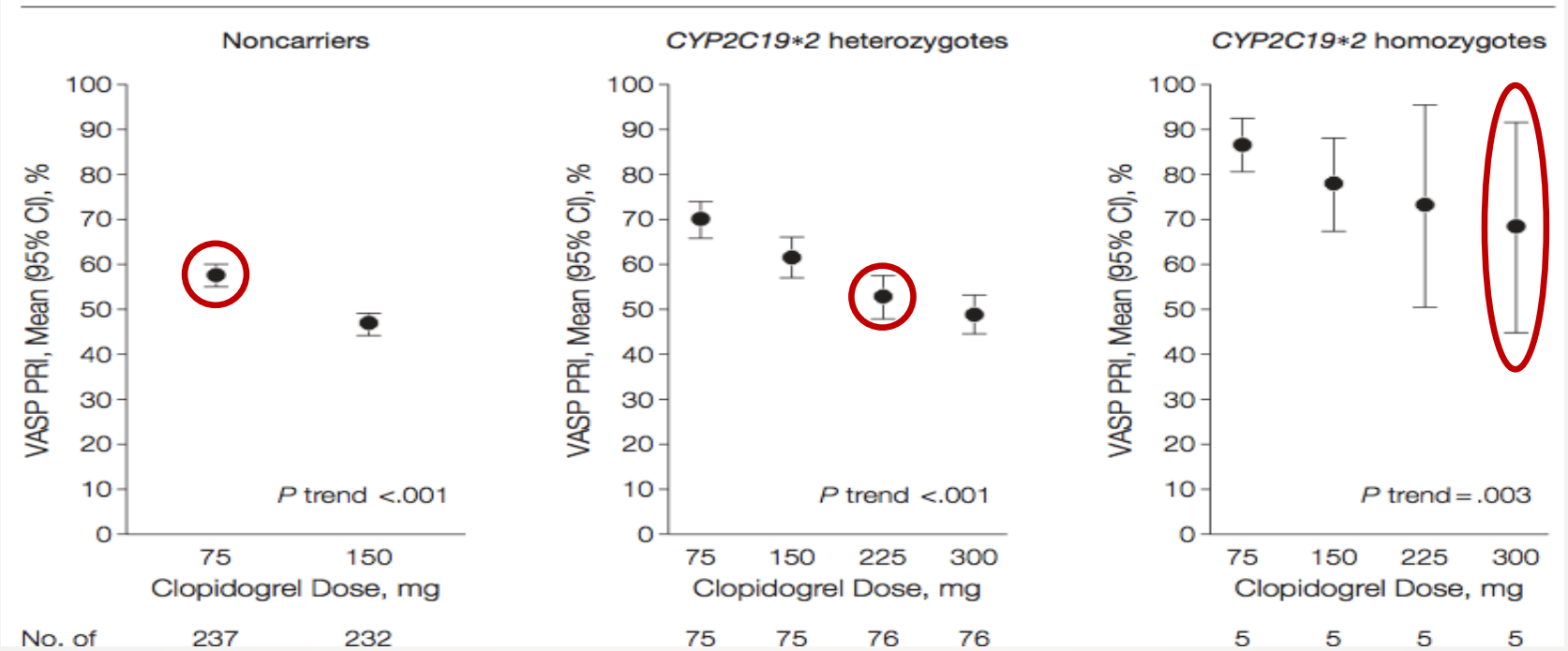


EM, extensive metabolizers (new terminology is normal metabolizers)
IM, intermediate metabolizers
PM, poor metabolizers

Horenstein RB. J Clin Pharmacol. 2014 Aug;54(8):865-73.

Clopidogrel dose escalation

Dosing Clopidogrel Based on *CYP2C19* Genotype and the Effect on Platelet Reactivity in Patients With Stable CVD



Mega JL, et al. JAMA. 2011;306(20):2221-2228.

Case study #1

GJ is a 52-year-old male with a PMH significant for HTN, TIA, and gout presents to the ED after 2 hours of progressively increasing chest pain, diagnosed as STEMI.

Patient undergoes percutaneous coronary intervention to LAD with a DES.

Indication for treatment with clopidogrel and aspirin

Pharmacogenomic results		
Gene	**Genotype**	**Phenotype**
ABCG2	c.421 C/C	Normal function
CYP2C9	*1/*2	Intermediate metabolizer
CYP2C19	*2/*2	Poor metabolizer
CYP2D6	*1/*1	Normal metabolizer
SLCO1B1	*1/*15	Decreased function

Case study #1

Pharmacogenomic results		
Gene	**Genotype**	**Phenotype**
ABCG2	c.421 C/C	Normal function
CYP2C9	*1/*2	Intermediate metabolizer
CYP2C19	*2/*2	Poor metabolizer
CYP2D6	*1/*1	Normal metabolizer
SLCO1B1	*1/*15	Decreased function

- Based on the pharmacogenomic results, what is your recommended course of action?
  A. Continue with clopidogrel 75 mg daily and aspirin 81 mg daily
  B. Change to clopidogrel 225 mg daily and aspirin 81 mg daily
  C. Change to prasugrel 10 mg daily and aspirin 81 mg daily
  D. Change to ticagrelor 90 mg twice daily and aspirin 81 mg daily

Pharmacogenomic-guided statin therapy

Statins

Reduce cholesterol

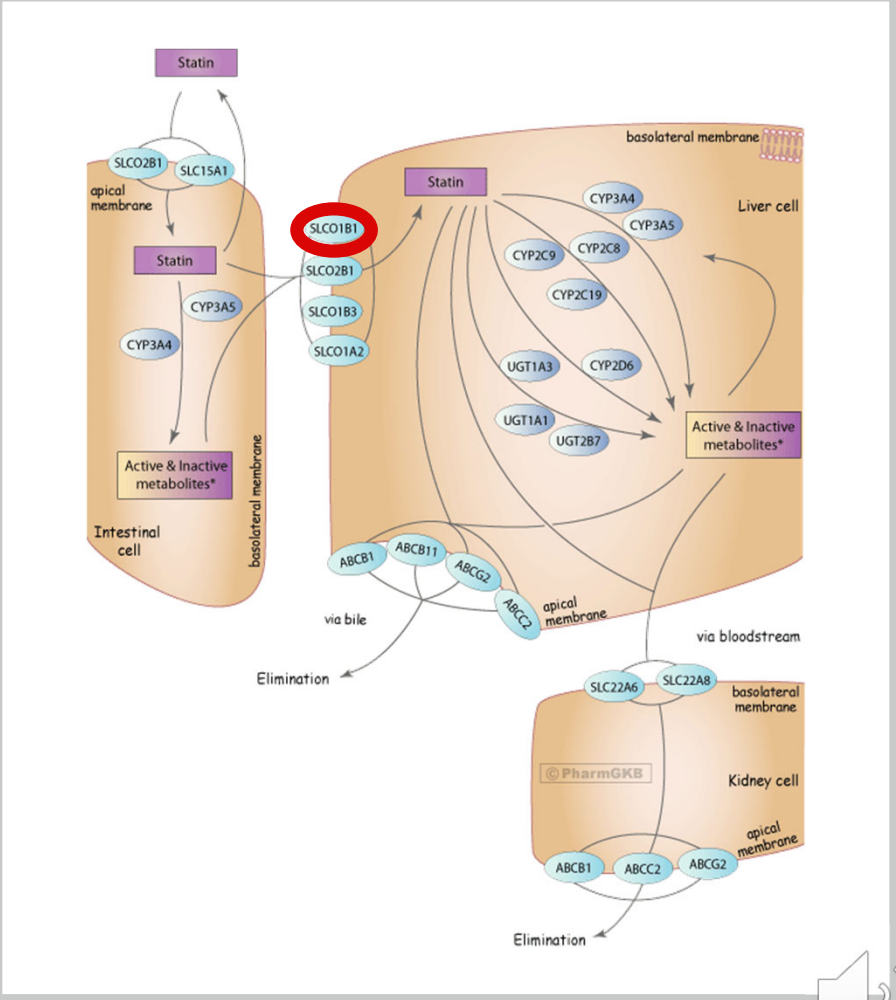
Prevent cardiovascular disease

Statin-associated musculoskeletal symptoms (SAMS)

SLCO1B1 Gene

- Encodes a transporter that facilitates the hepatic uptake of all **statins**

- Also known as OATP1B1 or OATP-C



SLCO1B1 Gene

- Most common variant studied in the *SLCO1B1* gene: **c.521T>C** (rs4149065) results in decreased transporter function

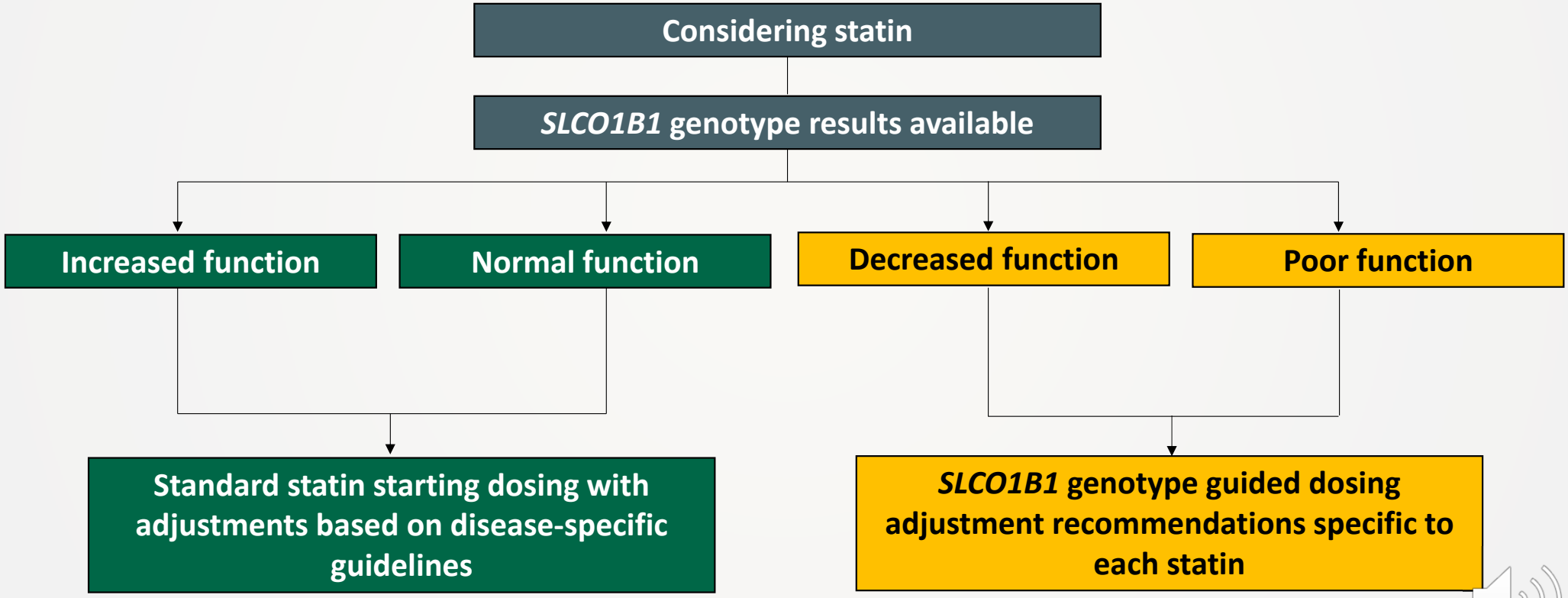
- Decreased SLCO1B1 transporter function results in increased systemic statin exposure and may lead to increased myopathy risk

Allele	SNP	SLCO1B1 Function
*1	N/A	Normal function
*5	Contains c.521T>C	No function
*15	Contains c.521T>C	No function

Interpreting *SLCO1B1* genetic results

Phenotype	Example Genotypes
Increased function	*SLCO1B1***14/*14**
Normal function	*SLCO1B1***1/*1**
Decreased function	*SLCO1B1***1/*5**, *SLCO1B1***1/*15**
Poor function	*SLCO1B1***5/*5**, *SLCO1B1***15/*15**

CPIC Recommendations for dosing STATINS based on SLCO1B1 phenotype



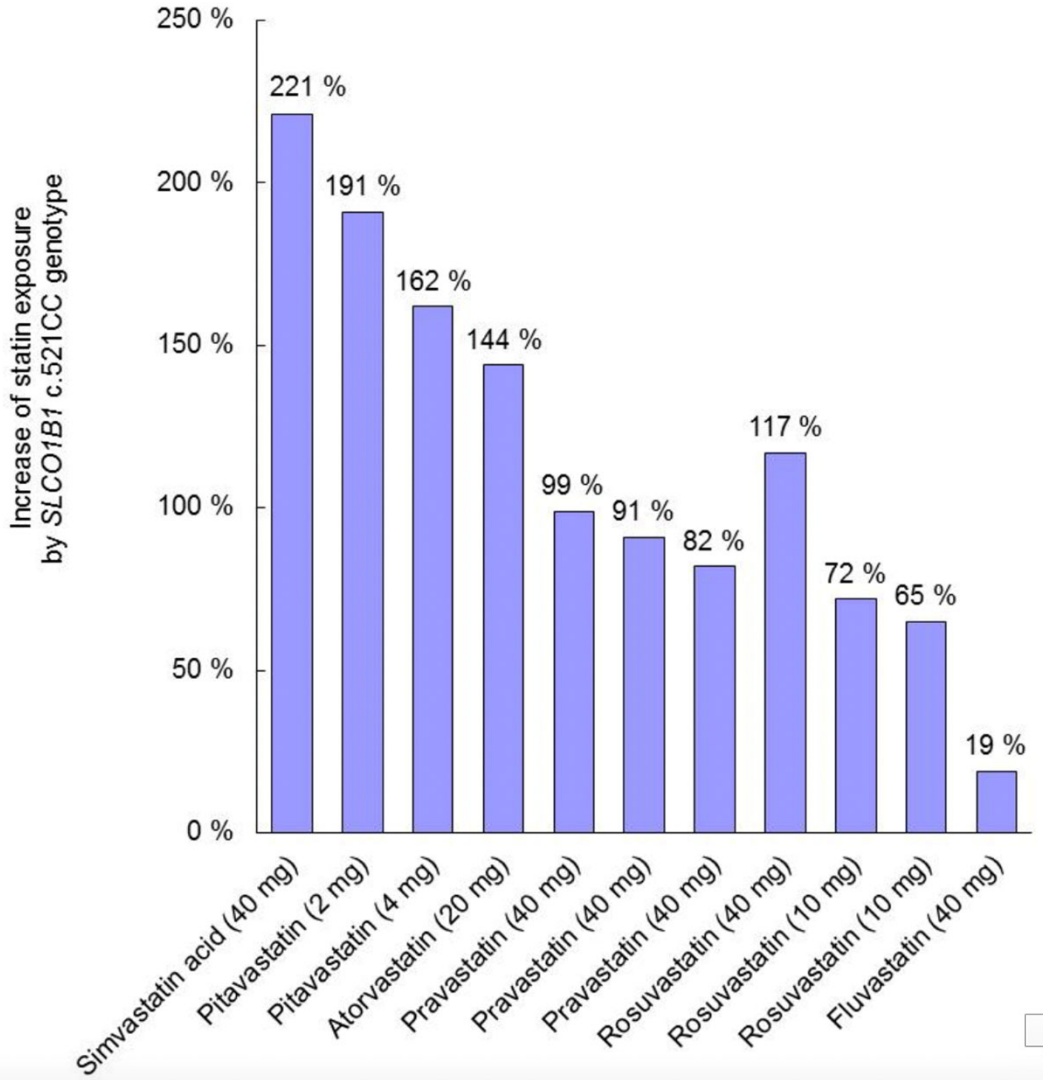
Cooper-DeHoff RM. Clin Pharmacol Ther. 2022 Feb 12. Online ahead of print.

STATIN	SLCO1B1 DECREASED FUNCTION	SLCO1B1 POOR FUNCTION
Atorvastatin	Prescribe ≤40mg as a starting dose	Prescribe ≤20mg as a starting dose
Fluvastatin	Prescribe desired starting dose; Possible ↑ risk for myopathy at doses >40mg daily	Prescribe ≤40mg per day as a starting dose
Lovastatin	Prescribe an alternative statin depending on the desired potency	Prescribe an alternative statin depending on the desired potency
Pitavastatin	Prescribe ≤ 2mg as a starting dose Possible ↑ risk for myopathy at doses >1mg daily	Prescribe ≤1mg as a starting dose
Pravastatin	Prescribe desired starting dose Possible ↑ risk for myopathy at doses >40mg daily	Prescribe ≤40mg as a starting dose
Rosuvastatin	Prescribe desired starting dose Possible ↑ risk for myopathy at doses >20mg daily	Prescribe ≤20mg as a starting dose
Simvastatin	Prescribe an alternative statin depending on the desired potency	Prescribe an alternative statin depending on the desired potency

Other considerations for dosing statins based on *SLC01B1*

- Adjust based on disease-specific guidelines
- If higher starting doses needed for desired efficacy, consider combination therapy
- Drug-drug interactions
- Dose limits based on renal and hepatic function

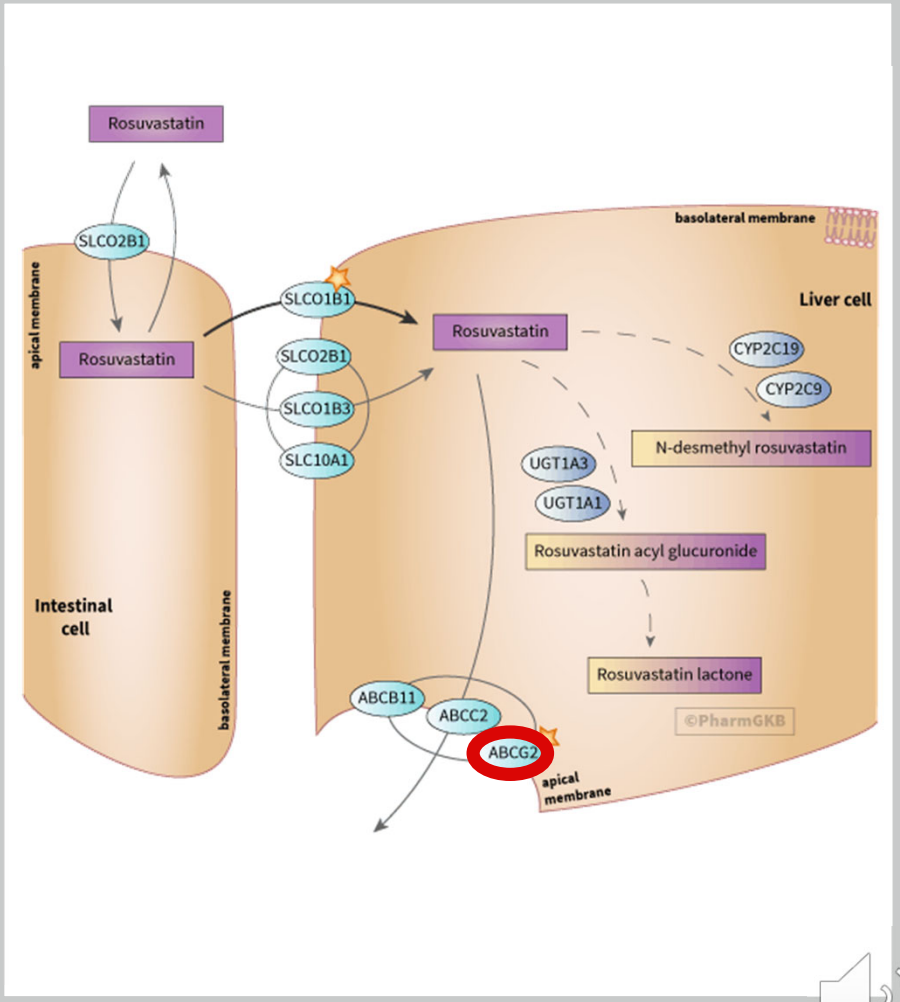
Pharmacokinetic impact of *SLCO1B1* on statins



Cooper-DeHoff RM. Clin Pharmacol Ther. 2022 Feb 12. Online ahead of print.

ABCG2 Gene

- Encodes the ATP-Binding Cassette G2 (ABCG2) efflux transporter that facilitates the export of **rosuvastatin** into the extracellular space
- Also known as BCRP
- Expressed in liver, blood-brain barrier, kidney, and intestine



https://www.pharmgkb.org/pathway/PA145011112

ABCG2 Gene

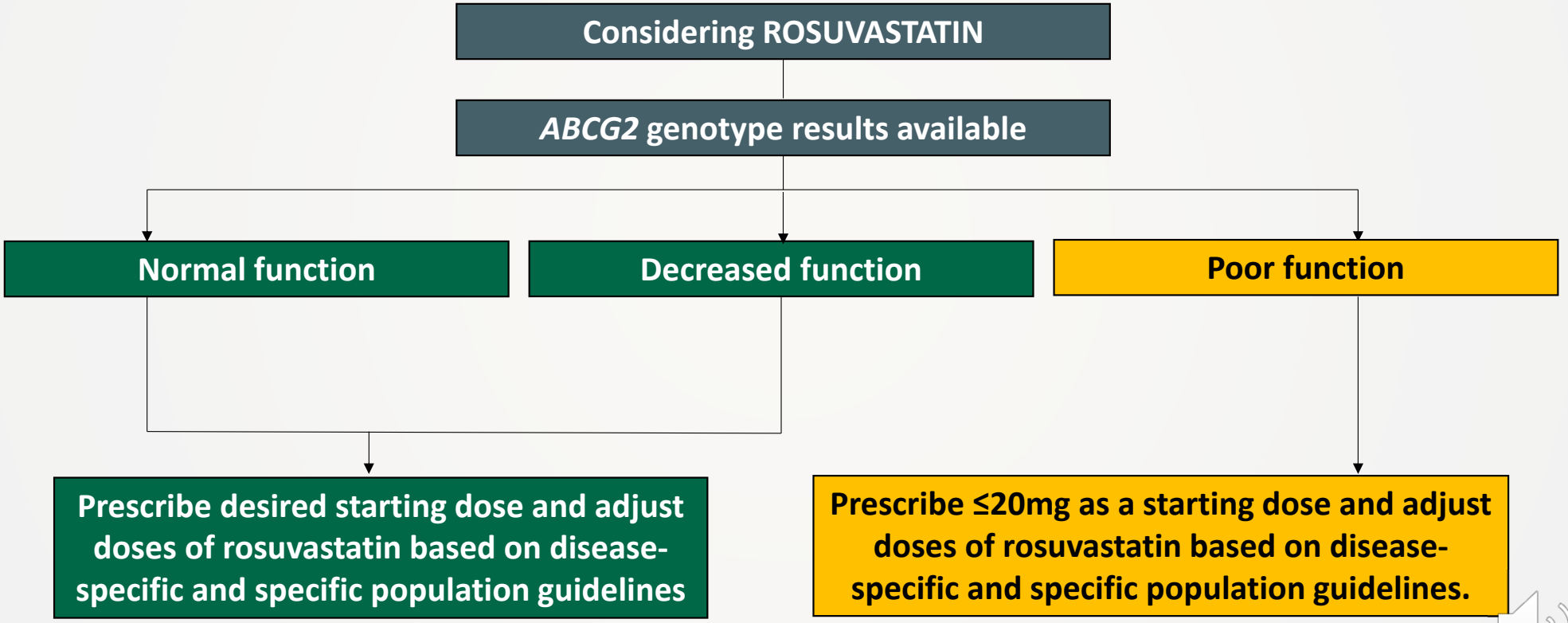
- Most common variant studied in *ABCG2:* **c.421C>A** (rs2231142)
  - ABCG2 expression reduced by 30 – 40% compared to reference allele
  - Results in increased plasma and hepatic levels of rosuvastatin
  - Myopathy risk unknown
  - Associated with improved cholesterol lowering response to rosuvastatin

Reference sequence number	SNP	ABCG2 Function
rs2231142	c.421C>A	Decreased function

Interpreting *ABCG2* genetic results

Phenotype	Example Genotypes
Normal function	*ABCG2* c.421 C/C (rs2231142)
Decreased function	*ABCG2* c.421 C/A (rs2231142)
Poor function	*ABCG2* c.421 A/A (rs2231142)

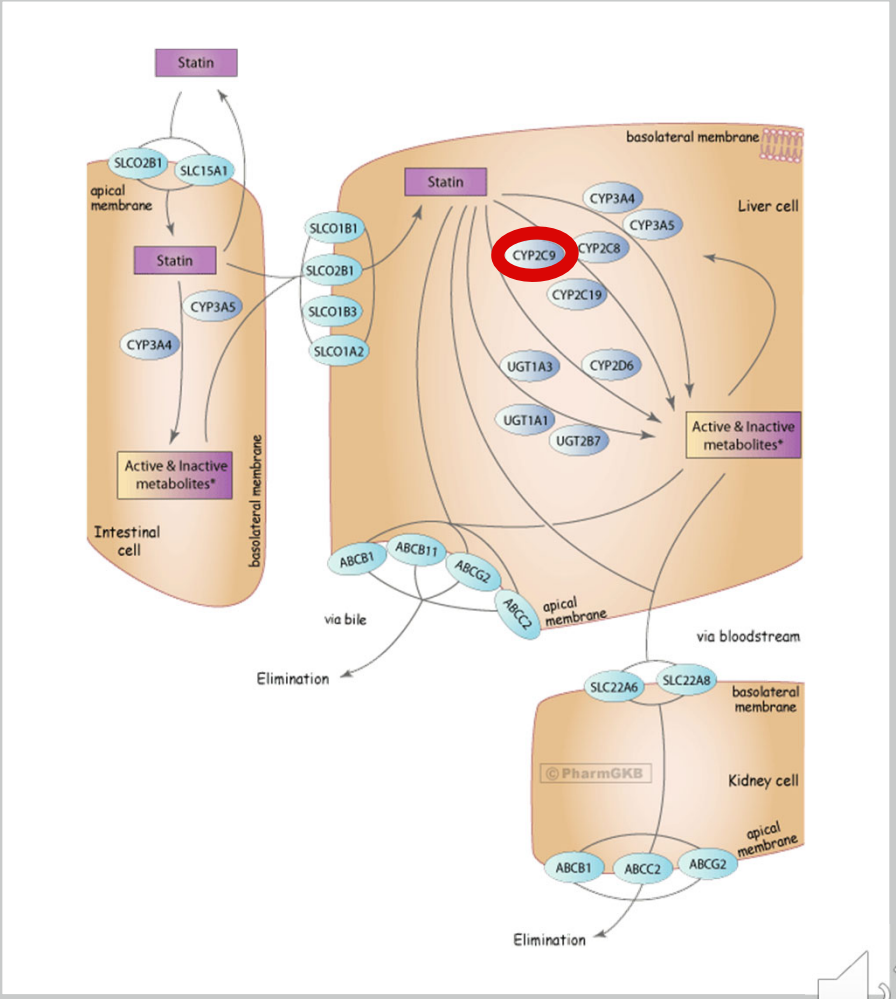
CPIC Recommendations for dosing ROSUVASTATIN based on ABCG2 phenotype



Cooper-DeHoff RM. Clin Pharmacol Ther. 2022 Feb 12. Online ahead of print.

CYP2C9 Gene

- Encodes the drug metabolizing enzyme, CYP2C9 involved in the oxidation of **fluvastatin**



CYP2C9 Gene

- > 71 variants identified in the *CYP2C9* gene
  - Increase exposure to Fluvastatin
  - Pharmacokinetics of other statins not impacted by *CYP2C9* variants

Allele	SNP	Activity score	CYP2C9 Function
*1	N/A	1	Normal function
*2	p.R144C; rs1799853	0.5	Reduced function
*3	p.I1359L; rs1057910	0	No function

CYP2C9 expression reduced by 80%

CYP2C9 expression reduced by 30 – 40%

CYP2C9 Alleles and Prevalence

CYP2C9 Allele	Enzymatic activity/ Functional status	Caucasian	African American	East Asian
*1	Normal	80%	87%	97%
*2	Decreased function	**13%**	2.3%	0.1%
*3	Decreased function	**17%**	1.2%	3.4%
*5	Decreased function	0%	**1.3%**	0%
*6	No function	0%	**0.8%**	0%
*8	Decreased function	0.1%	**6.7%**	0%
*11	Decreased function	0.2%	**1.4%**	0%

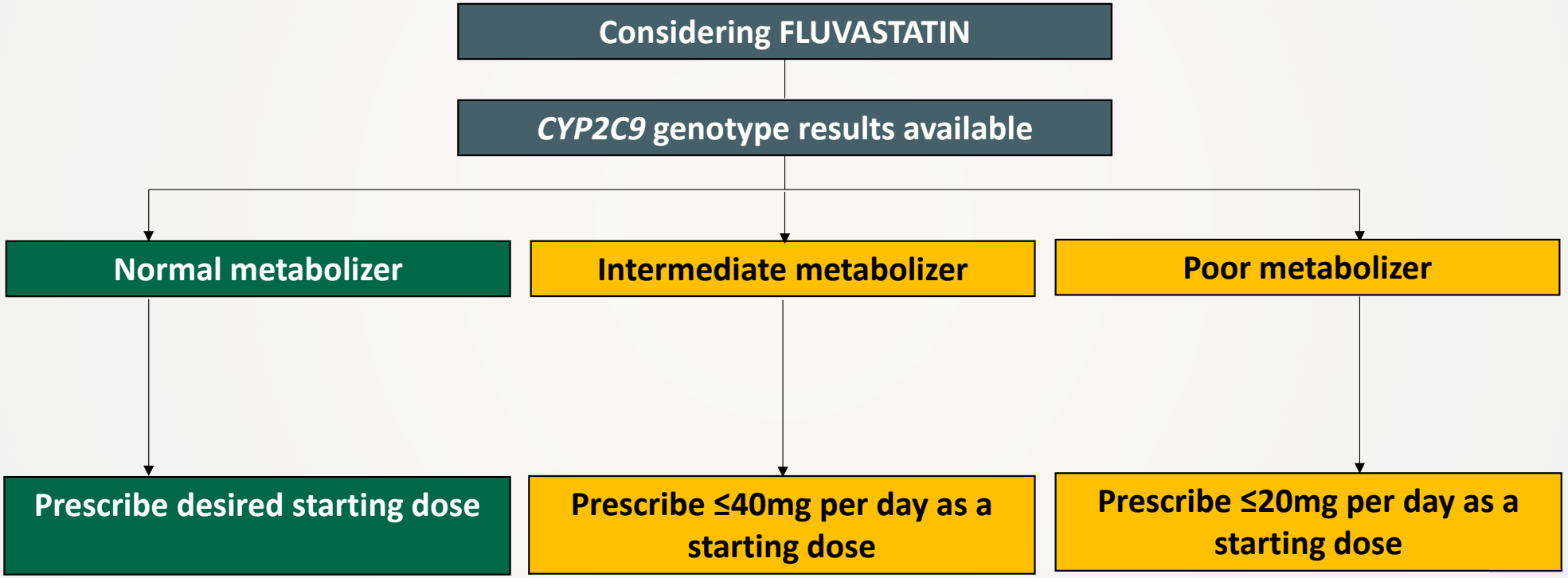
Most common actionable variants reported

Tier 1 CYP2C9 variant alleles → "must test"

Interpreting *CYP2C9* genetic results

Phenotype	Activity score	Example Genotypes
Normal metabolizer (NM)	2	CYP2C9***1/*1**
Intermediate metabolizer (IM)	1.5 1	CYP2C9***1/*2** CYP2C9***1/*3**
Poor metabolizer (PM)	0.5 0	CYP2C9***2/*3** CYP2C9***3/*3**

CPIC Recommendations for dosing FLUVASTATIN based on CYP2C9 phenotype



Cooper-DeHoff RM. Clin Pharmacol Ther. 2022 Feb 12. Online ahead of print.

Combinatorial gene-based recommendations

- CPIC Guidelines provide a table for combinatorial gene-based recommendations
  - Rosuvastatin – *SLCO1B1* and *ABCG2*
  - Fluvastatin – *SLCO1B1* and *CYP2C9*

Cooper-DeHoff RM. Clin Pharmacol Ther. 2022 Feb 12. Online ahead of print.

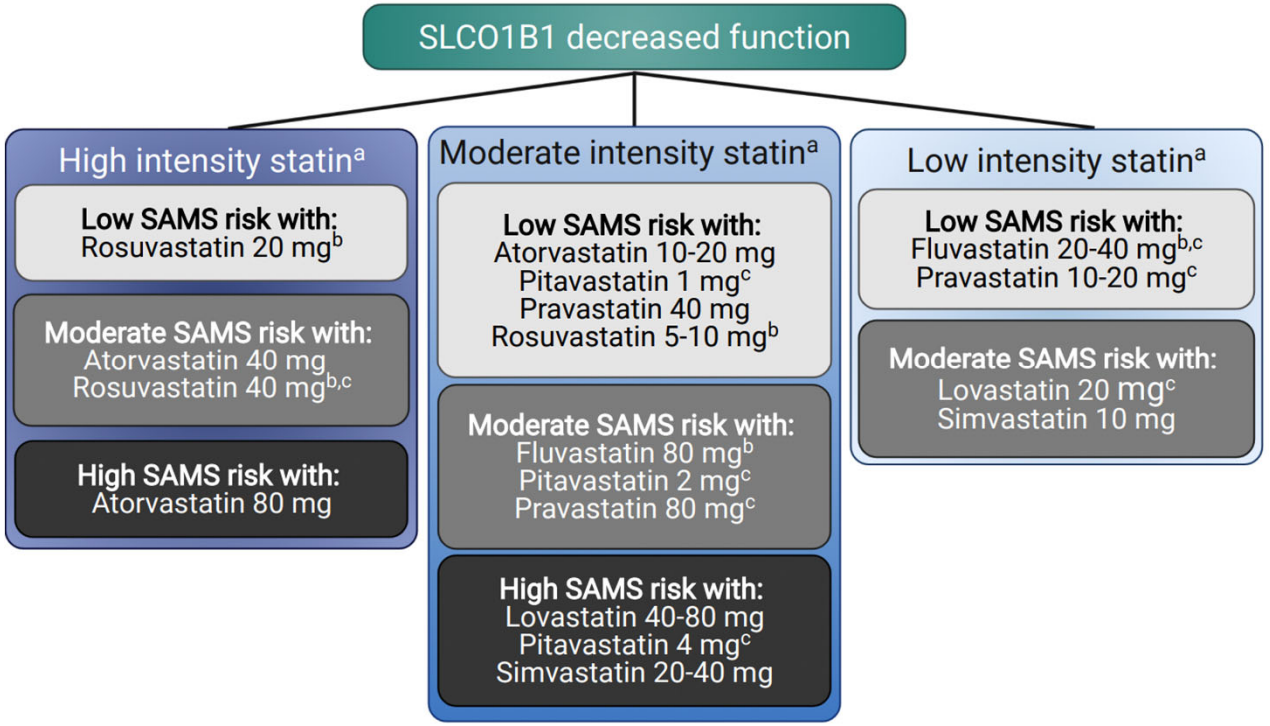
CPIC guidance for patients already on a statin with pharmacogenomic results

- On statin and *SLCO1B1* genotype predicts moderate SAMS risk
  - For ≥ 4 weeks with no SAMS → continue statin and dose long term
  - For <4 weeks, consider changing to lower SAMS risk statin/dose to prevent SAMS

- On statin and *SLCO1B1* genotype predicts high SAMS risk
  - For ≥ 1 year with no SAMS → continue statin long term
  - For <1 year, consider changing to lower SAMS risk statin/dose to reduce risk of developing SAMS

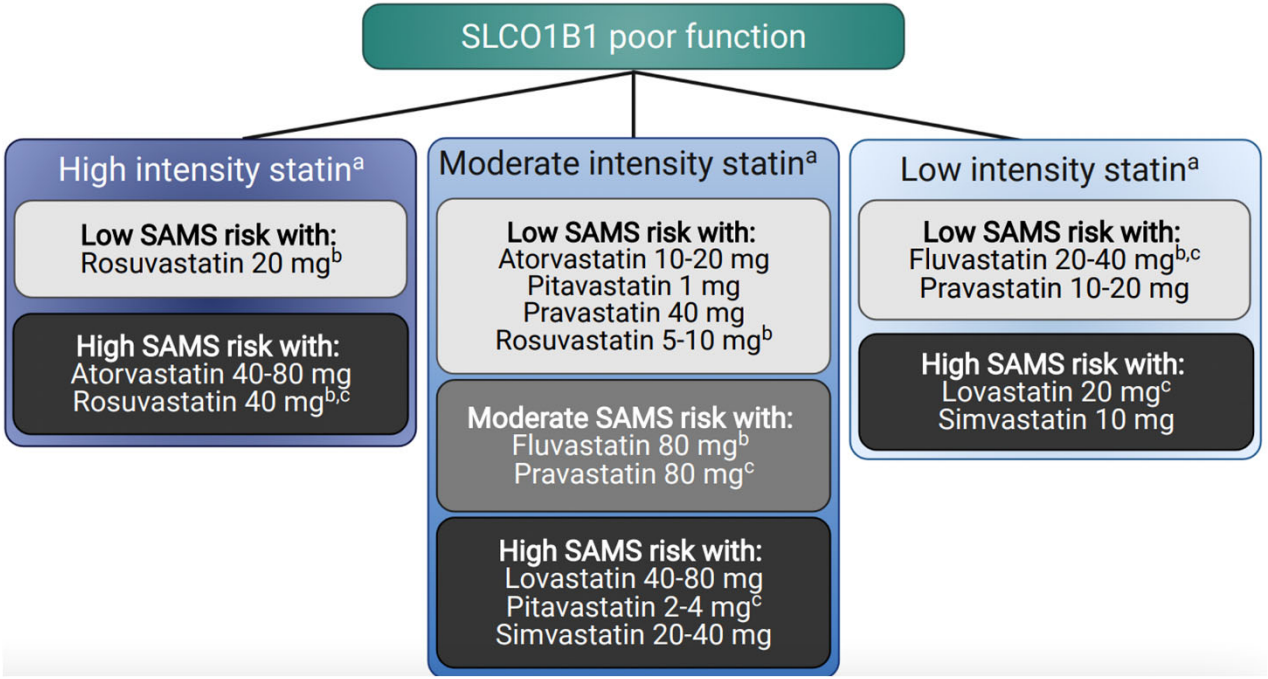
Cooper-DeHoff RM. Clin Pharmacol Ther. 2022 Feb 12. Online ahead of print.

SLCO1B1 recommendations with intensity and statin dose stratified by SLCO1B1 phenotype



Cooper-DeHoff RM. Clin Pharmacol Ther. 2022 Feb 12. Online ahead of print.

SLCO1B1 recommendations with intensity and statin dose stratified by SLCO1B1 phenotype



Cooper-DeHoff RM. Clin Pharmacol Ther. 2022 Feb 12. Online ahead of print.

Case study #2

GJ is a 52-year-old male with a PMH significant for HTN, TIA, and gout presents to the ED after 2 hours of progressively increasing chest pain, diagnosed as STEMI.

Patient undergoes percutaneous coronary intervention to LAD with a DES and will be discharged on ticagrelor and aspirin.

The cardiologist also plans to prescribe a statin for secondary ASCVD prevention on discharge.

Pharmacogenomic results		
Gene	**Genotype**	**Phenotype**
ABCG2	c.421 C/C	Normal function
CYP2C9	*1/*2	Intermediate metabolizer
CYP2C19	*2/*2	Poor metabolizer
CYP2D6	*1/*1	Normal metabolizer
SLCO1B1	*1/*15	Decreased function

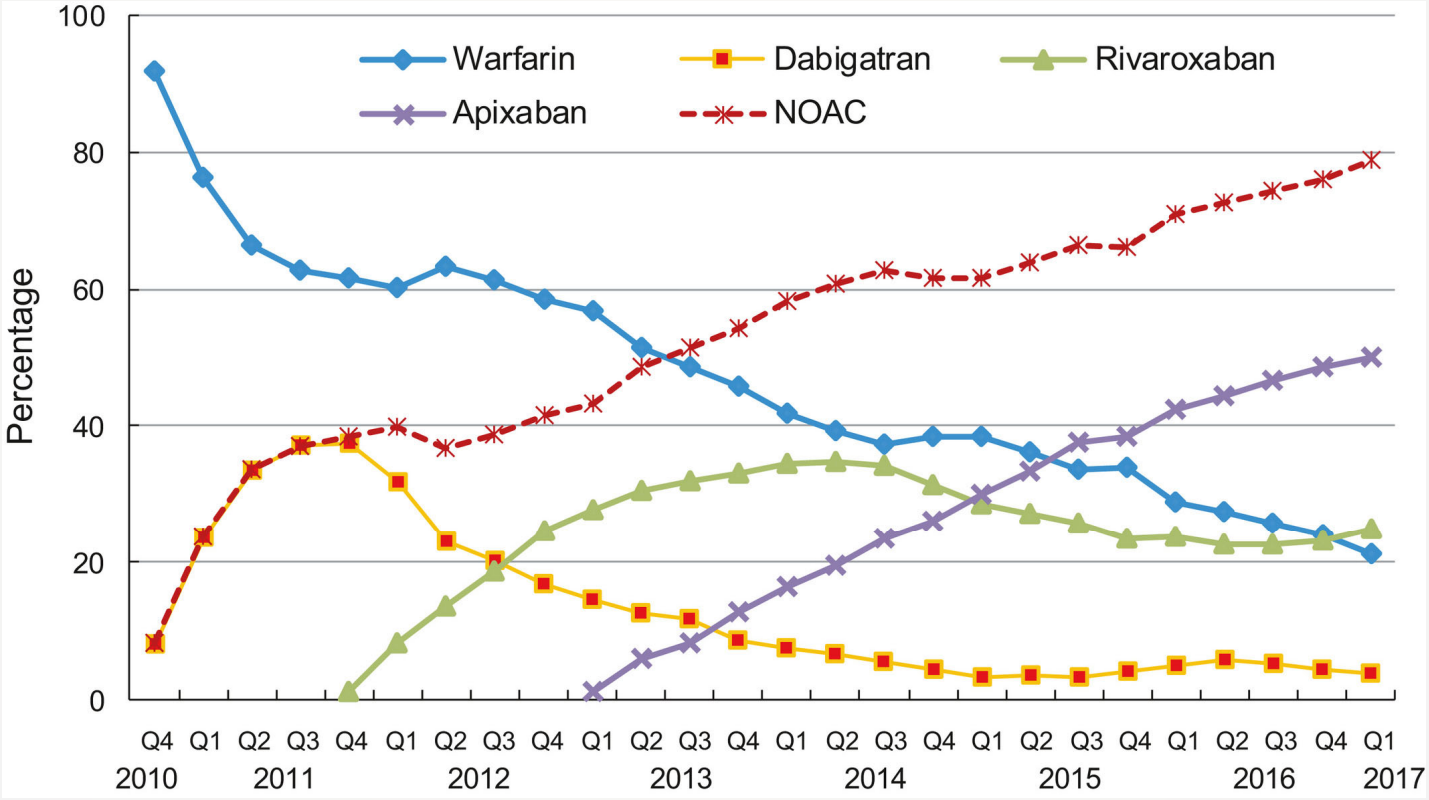
Self assessment #2

Pharmacogenomic results		
Gene	**Genotype**	**Phenotype**
ABCG2	c.421 C/C	Normal function
CYP2C9	*1/*2	Intermediate metabolizer
CYP2C19	*2/*2	Poor metabolizer
CYP2D6	*1/*1	Normal metabolizer
SLCO1B1	*1/*15	Decreased function

- Based on the pharmacogenomic results, what statin would you recommend?
  A. Rosuvastatin 20 mg daily
  B. Atorvastatin 80 mg daily
  C. Simvastatin 20 mg daily
  D. Pravastatin 40 mg daily

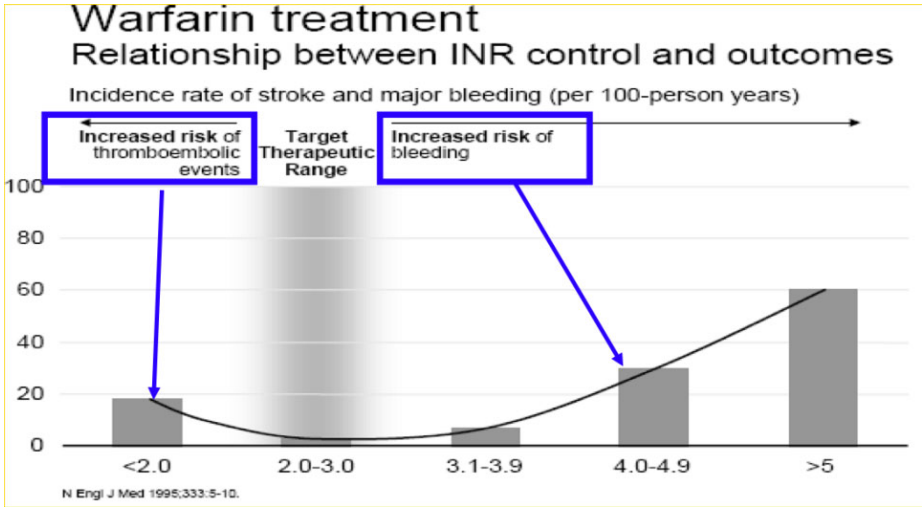
Pharmacogenomic-guided warfarin therapy

Trends in oral anticoagulant choice



Pharmacotherapy. 2018 Sep; 38(9): 907–920.

Warfarin management



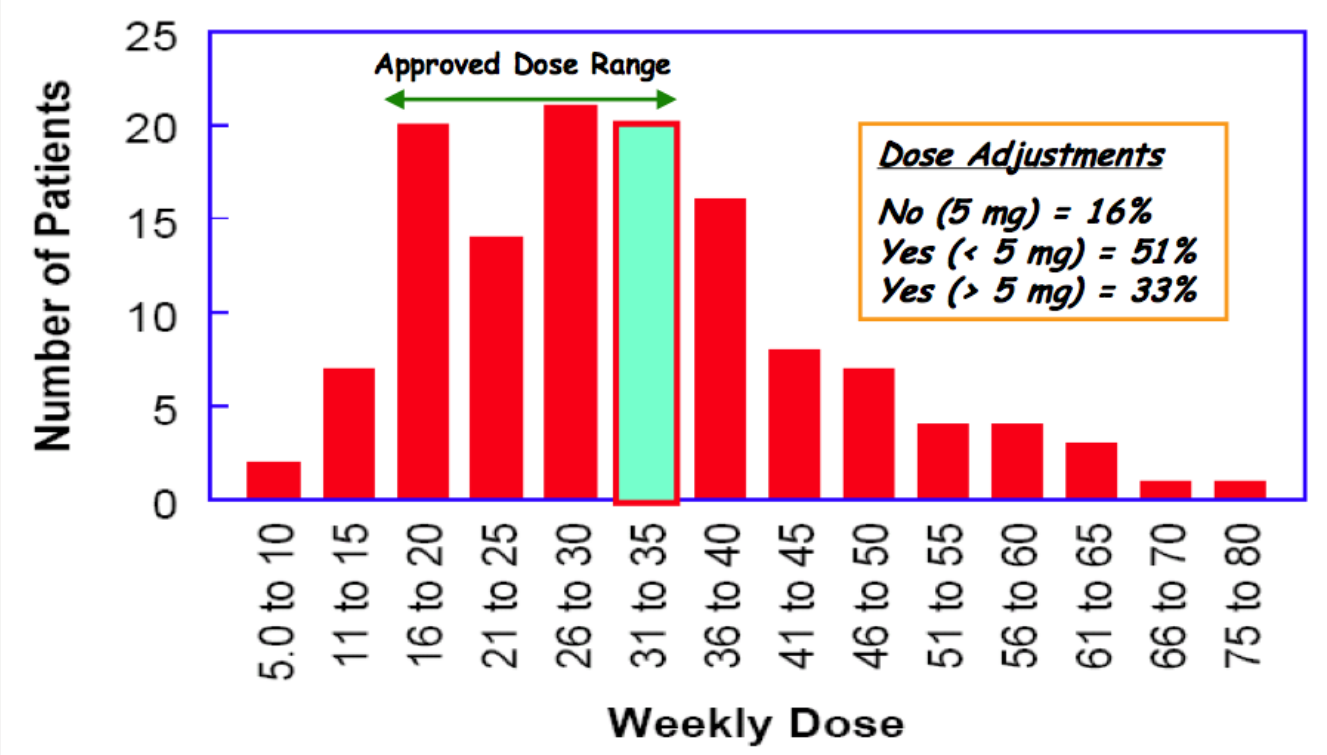
N Engl J Med 1995;333:5-10.

Table 3. US Emergency Department (ED) Visits for Adverse Drug Events (ADEs) From the Most Commonly Implicated Drug Products by Patient Age, 2013-2014[a]

Drug Product	ED Visits for ADEs	
	No. of Cases	National Estimate, % (95% CI)[b]
All Patients (N = 42 585)		
Warfarin	6179	15.1 (12.3-17.9)
Insulin	4859	10.7 (8.6-12.7)
Clopidogrel	1778	4.4 (2.9-5.9)
Amoxicillin	1780	3.8 (3.3-4.3)
Aspirin	1518	3.5 (2.2-4.9)
Sulfamethoxazole-trimethoprim	1152	3.2 (2.7-3.7)
Lisinopril	1096	2.4 (1.8-3.0)
Metformin	766	1.7 (1.4-2.1)
Ibuprofen	722	1.6 (1.3-2.0)
Rivaroxaban	526	1.3 (0.8-1.8)
Acetaminophen-hydrocodone	492	1.3 (1.0-1.6)
Cephalexin	431	1.2 (0.9-1.5)
Acetaminophen-oxycodone	459	1.1 (0.8-1.4)
Acetaminophen	479	1.0 (0.8-1.2)
Amoxicillin-clavulanate	422	1.0 (0.9-1.2)

JAMA. 2016 Nov 22;316(20):2115-2125.

Warfarin dose variability



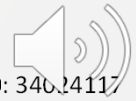
Complexity of warfarin dosing

- Age
- Sex
- Race
- Weight
- Height
- Smoking status
- Alcohol consumption
- Warfarin indication, target INR
- Drug-drug interactions
- Vitamin K intake
- Concomitant diseases (CHF, Thyroid disorders, hepatic failure)
- Adherence

Scenarios for which warfarin may be preferred

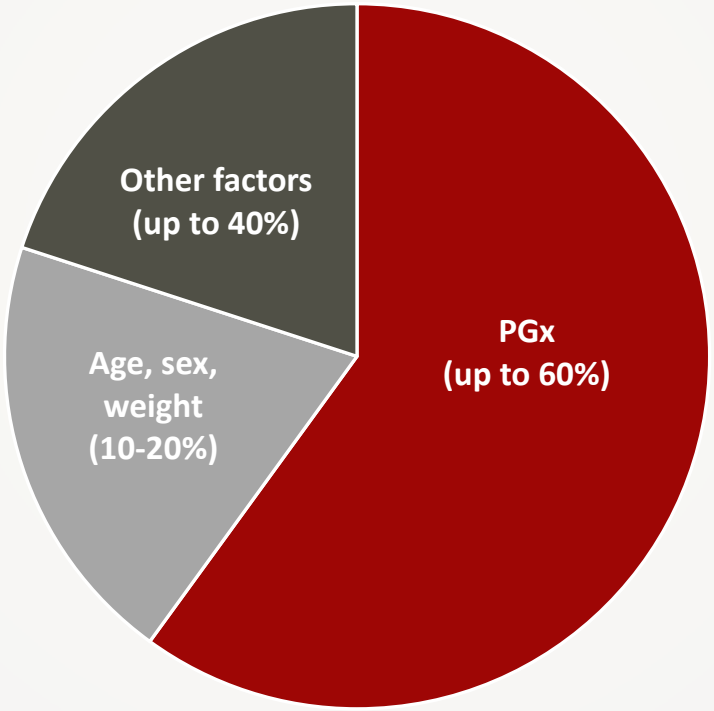
- In patients with AF and stroke or TIA who have end-stage renal disease or are on dialysis, it may be reasonable to use warfarin for anticoagulation to reduce the chance of recurrent stroke
  - Note that dose-adjusted apixaban is also an option

- In patients with ischemic stroke or TIA and valvular AF (moderate to severe mitral stenosis or any mechanical heart valve), warfarin is recommended to reduce the risk of recurrent stroke or TIA

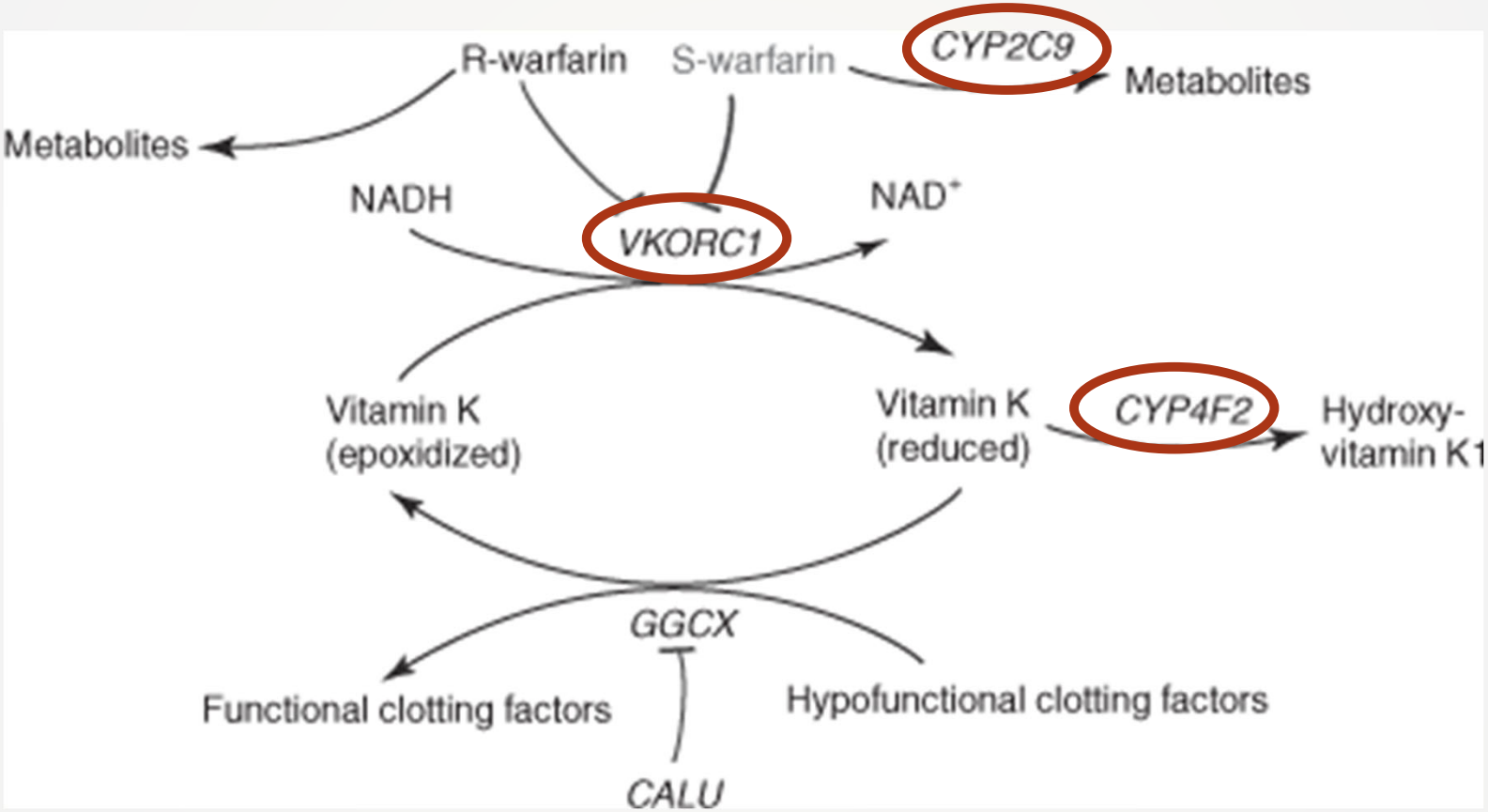


Kleindorfer DO, et al. Stroke. 2021. PMID: 34024117

Factors that correlate with warfarin dose

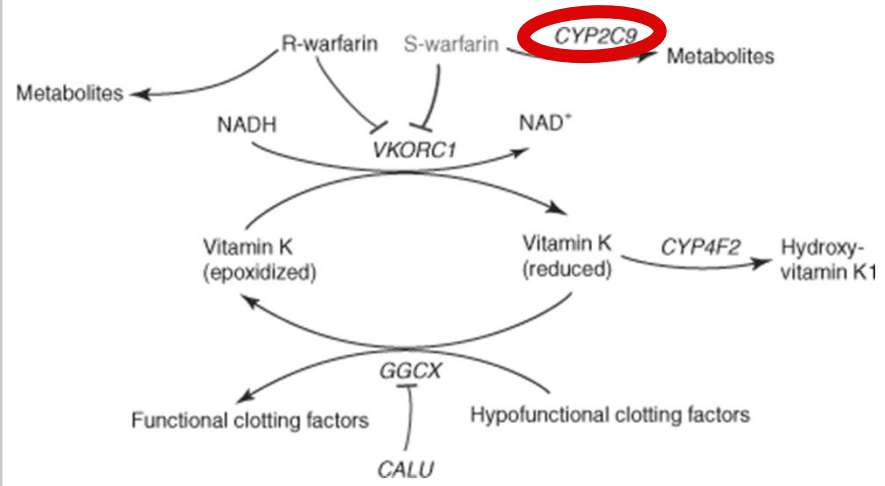


Warfarin pharmacogenomics



CYP2C9 Gene

- Encodes the drug metabolizing enzyme, CYP2C9 involved in the metabolism of warfarin



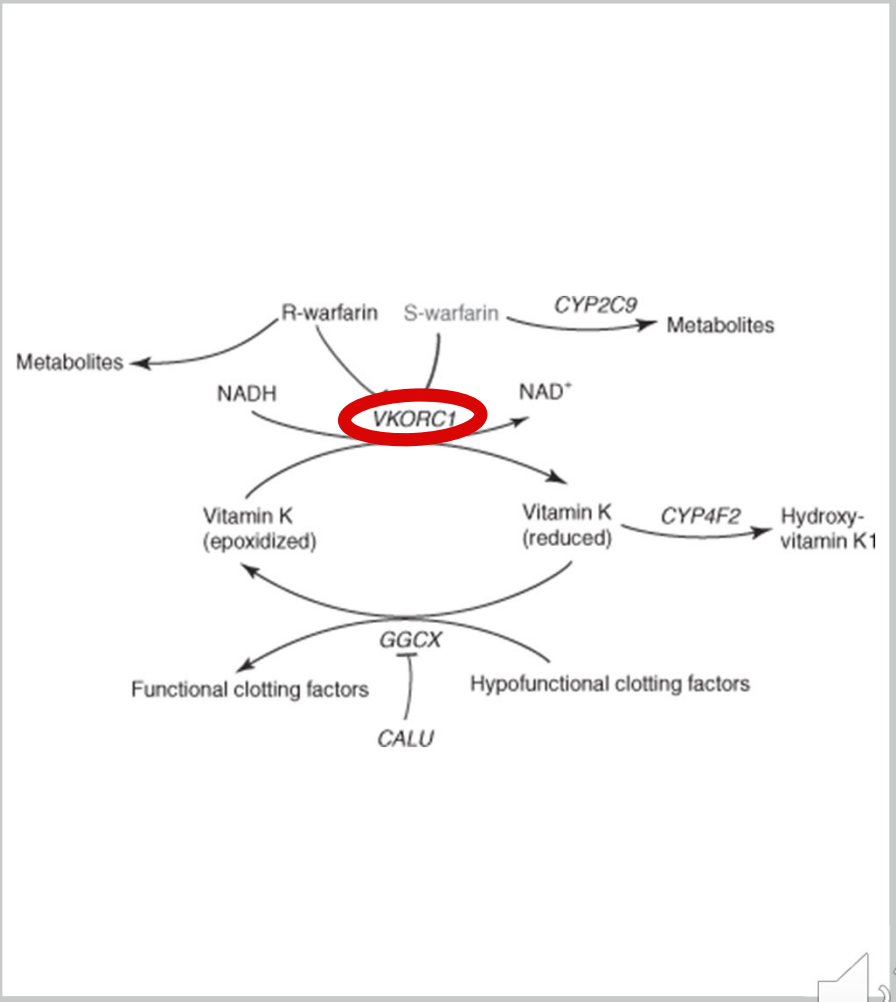
CYP2C9 Gene and Warfarin Dose

Genotype	Phenotype	Change in warfarin dose
CYP2C9*1/*1	Normal warfarin metabolism	---
CYP2C9*1/*2	Impaired warfarin metabolism	-1 mg/day
CYP2C9*1/*3	Impaired warfarin metabolism	-2 mg/day
CYP2C9*1/*5	Impaired warfarin metabolism	-15 to -30%
CYP2C9*1/*6	Impaired warfarin metabolism	-15 to -30%
CYP2C9*1/*8	Impaired warfarin metabolism	-15 to -30%
CYP2C9*1/*11	Impaired warfarin metabolism	-15 to -30%

VKORC1 Gene

- Encodes vitamin K epoxide reductase
- Most common variant upstream of *VKORC1*
  - c.-1639G>A, rs9923231

VKORC1 Allele	Caucasians	African American	East Asian
c.-1639G>A	41%	10%	88%



VKORC1 and Warfarin Dose

- VKORC1 **A/A** genotype require LOWER warfarin doses compared to VKORC1 **G/G** genotype

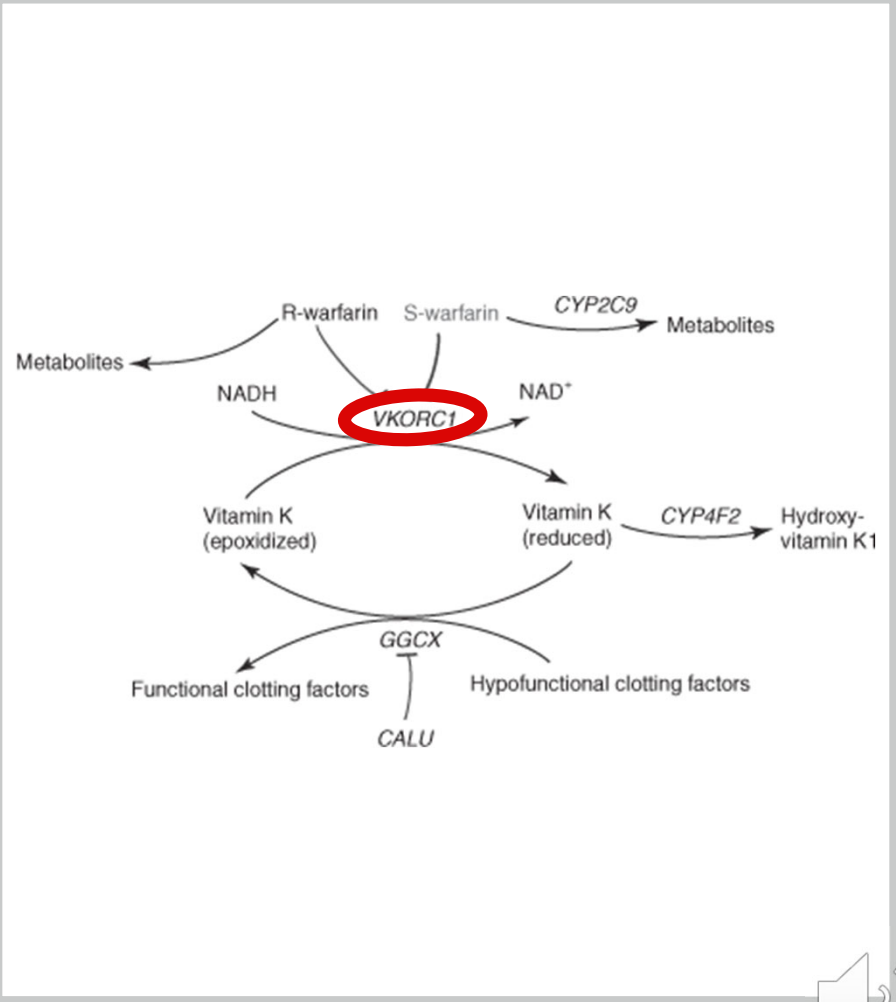
VKORC1 Allele	Functional status	Phenotype	Change in warfarin dose
G	Normal	Normal warfarin sensitivity	---
A	Decreased function	Increased warfarin sensitivity	-2 to -3 mg/day

CYP4F2 Gene

- Encodes a liver vitamin K epixodase
  - Catalyzes metabolism of vitamin K to hydroxy-vitamin K1 removing vitamin K from cycle

- Reduced functioning CYP4F2
  - CYP4F2*3 (c.1297G>A; p.Val433Met; rs2108622)

CYP4F2 Allele	Caucasian	African American	East Asian	Middle Eastern	South/ Central Asian
*3	**30%**	8%	**22%**	**43%**	**40%**



CYP4F2 and Warfarin Dose

- Warfarin dose prediction improved when CYP2C9 + VKORC1 + CYP4F2 taken into account
  - Especially in Europeans and Asians, but not for those of African ancestry

CYP4F2*3 Allele	Functional status	Phenotype	Change in warfarin dose
*1	Normal function	Normal vitamin K metabolism	---
*3	Decreased function	Decreased vitamin K metabolism	+8 to +11%

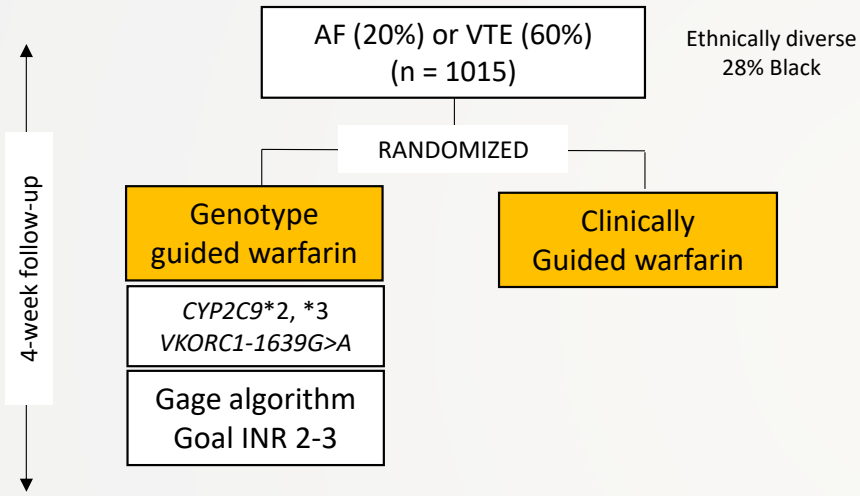
CYP2C rs12777823 (g.96405502G>A)

- rs12777823 is a SNP in the CYP2C cluster near the CYP2C18 gene on chromosome 10
- Associated with a clinically relevant effect on warfarin dose through significant alterations in warfarin clearance
- First identified in African American study cohort
- Variant has been identified in other populations, but association with warfarin dosing yet to be established (In Egyptians, rs12777823 was not predictive of warfarin dose)

CYP2C Allele	Functional status	Phenotype	Change in warfarin dose
G	Normal function	Normal metabolism	---
A	Decreased function	Decreased metabolism	-7 mg to -9 mg/week

COAG, 2013

Clarification of Optimal Anticoagulation through Genetics



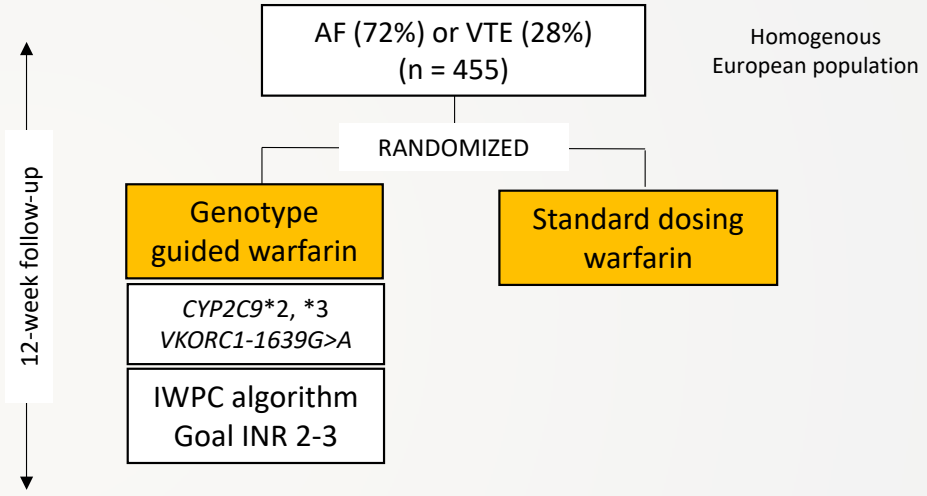
No significant difference in…

- **% TTR** (45.2% in genotype-guided and 45.4% in the clinically guided group (adjusted mean difference, −0.2; 95% CI, −3.4 to 3.1; P=0.91), **time to stable dose, # of episodes with INR >4 or <2, or bleeding risk**

African Americans in the genotype guided arm had less TTR (35.2% vs 43.5%) and more likely to have INRs above range due to lack of inclusion of *CYP2C9* alleles more commonly observed in this population.

EUPACT, 2013

European Pharmacogenetics of Anticoagulant Therapy



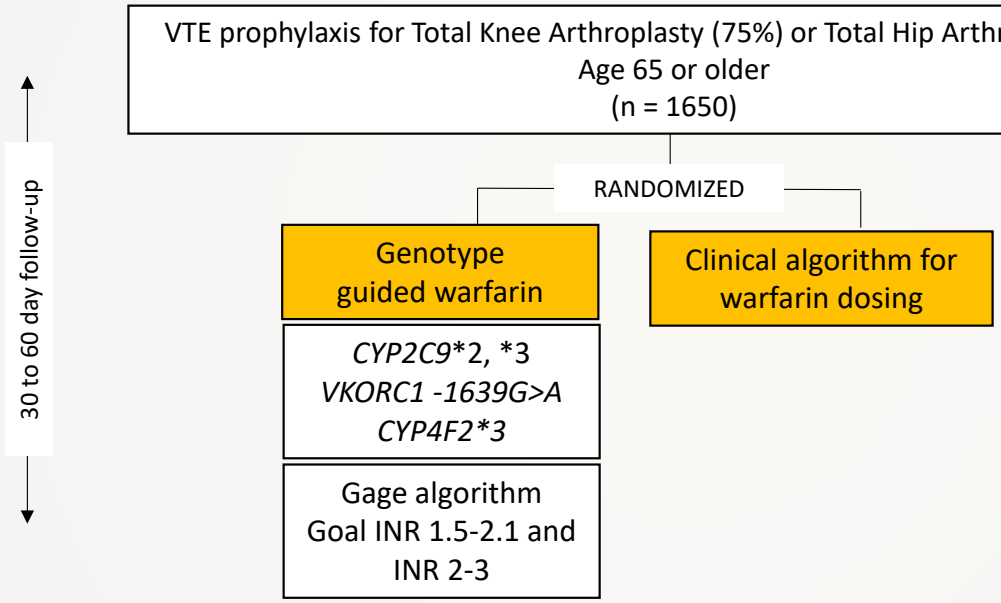
Significant difference in…

- **% TTR** (67.4% in genotype-guided and 60.3% in the standard dosing group (adjusted difference, 7.0%; 95% CI, 3.3 to 10.6; P<0.001)
- **Fewer incidences with INR >4**
- **Time to stable dose shorter** (21 vs 29 days)

N Engl J Med. 2013 Dec 12;369(24):2294-303.
N Engl J Med. 2013 Dec 12;369(24):2294-303.

GIFT, 2017

Genetic Informatics Trial (GIFT) of Warfarin to Prevent Deep Vein Thrombosis



First warfarin pharmacogenomics clinical trial to be powered for clinical outcomes!

Primary outcome: composite of the following adverse events: major bleeding within 30 days, INR of 4 or greater within 30 days, death within 30 days, and symptomatic or asymptomatic VTE confirmed by objective testing within 60 days of arthroplasty

JAMA. 2017 Sep 26;318(12):1115-1124.

GIFT, 2017

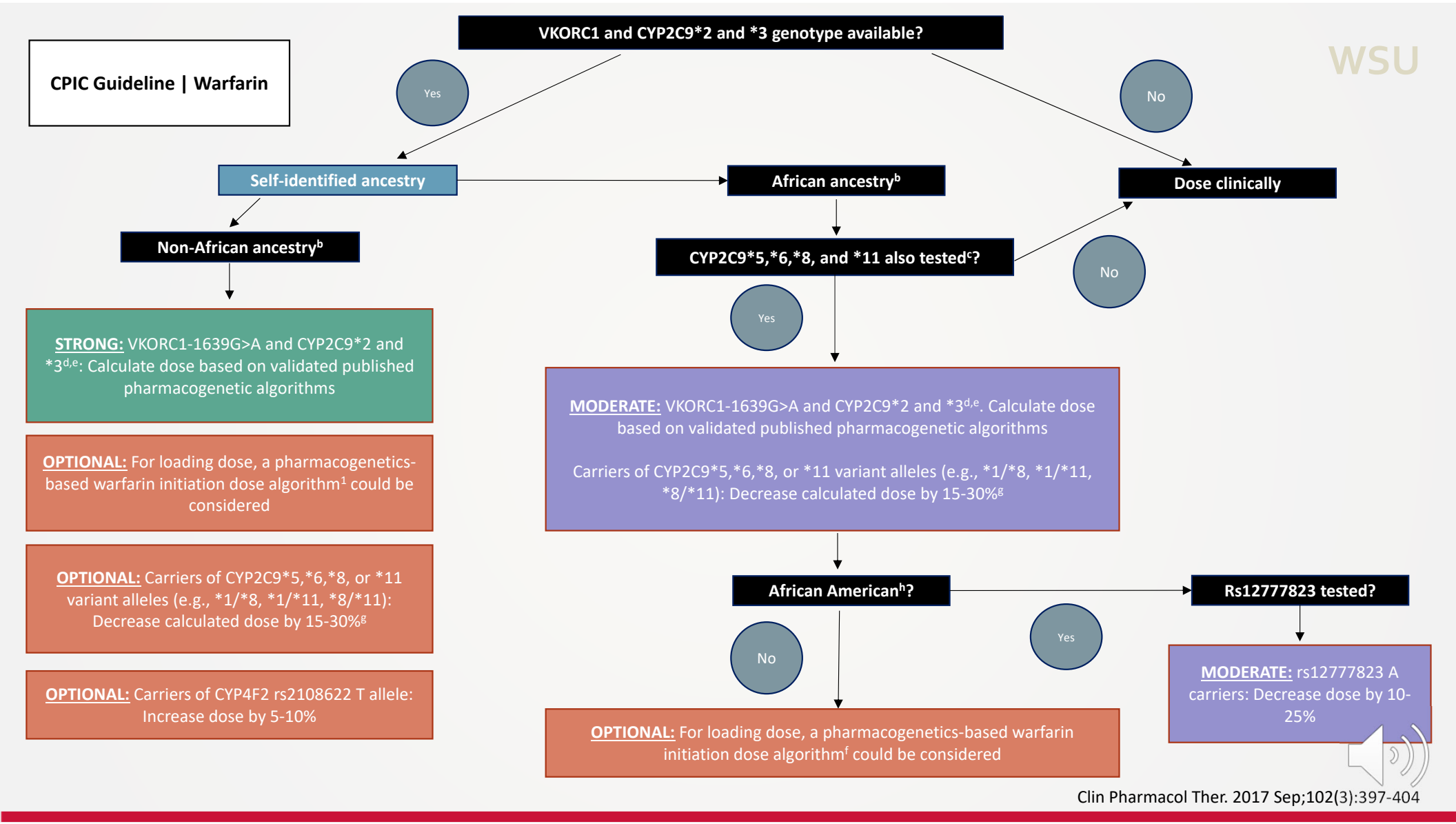
Genetic Informatics Trial (GIFT) of Warfarin to Prevent Deep Vein Thrombosis

Table 3. Components of the Composite Primary End Point[a]

	Warfarin Dosing, No. (%)				
	Genotype-Guided (n = 808)	Clinically Guided (n = 789)	Absolute Difference (95% CI), %	Relative Rate (95% CI)	*P* Value
Met ≥1 primary end point component[b]	87 (10.8)	116 (14.7)	3.9 (0.7 to 7.2)	0.73 (0.56 to 0.95)[c]	.02
Primary End Point Components					
Major bleeding on days 1-30	2 (0.2)	8 (1.0)	0.8 (-0.2 to 1.8)	0.24 (0.05 to 1.15)	.06
Plus INR <4	2 (0.2)	6 (0.8)	0.5 (-0.4 to 1.5)		
Plus INR ≥4	0	2 (0.3)	0.3 (-0.4 to 1.0)		
INR ≥4 on days 1-30	56 (6.9)	77 (9.8)	2.8 (0.1 to 5.6)	0.71 (0.51 to 0.99)	.04
Venous thromboembolism on days 1-60	33 (4.1)	38 (4.8)	0.7 (-1.3 to 2.8)	0.85 (0.54 to 1.34)	.48
PE or symptomatic DVT	10 (1.2)	15 (1.9)	0.7 (-0.7 to 2.1)		
PE	3 (0.4)	8 (1.0)	0.6 (-0.3 to 1.7)		
Death on days 1-30	0	0			

Genotype-guided warfarin dosing reduced the primary outcome (composite of major bleeding, international normalized ratio of 4 or greater, venous thromboembolism, or death) from 14.7% to 10.8%

JAMA. 2017 Sep 26;318(12):1115-1124.



Clin Pharmacol Ther. 2017 Sep;102(3):397-404

Warfarin dosing algorithms

- To minimize periods of under- and over-anticoagulation, unnecessary hospitalizations and warfarin-related adverse effects, dose-prediction algorithms incorporating nongenetic clinical factors (e.g., age, weight, height and interacting medications) and genetic factors have been developed

Gage

International Warfarin Pharmacogenetics Consortium (IWPC)

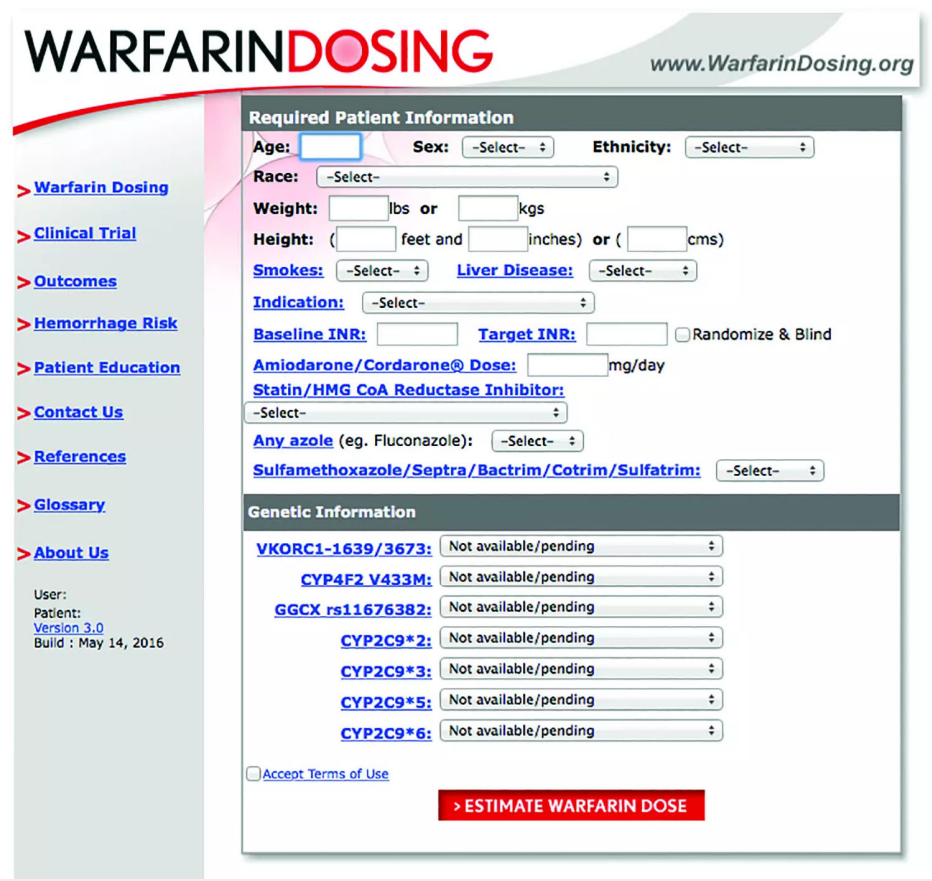
FDA label for warfarin dosing using *VKORC1* and *CYP2C9* genotype (fixed dose)

Johnson JA, Caudle KE, Gong L et al. Clin Pharmacol Ther. 2017;102(3):397-404.

Calculate warfarin dose using a published algorithm

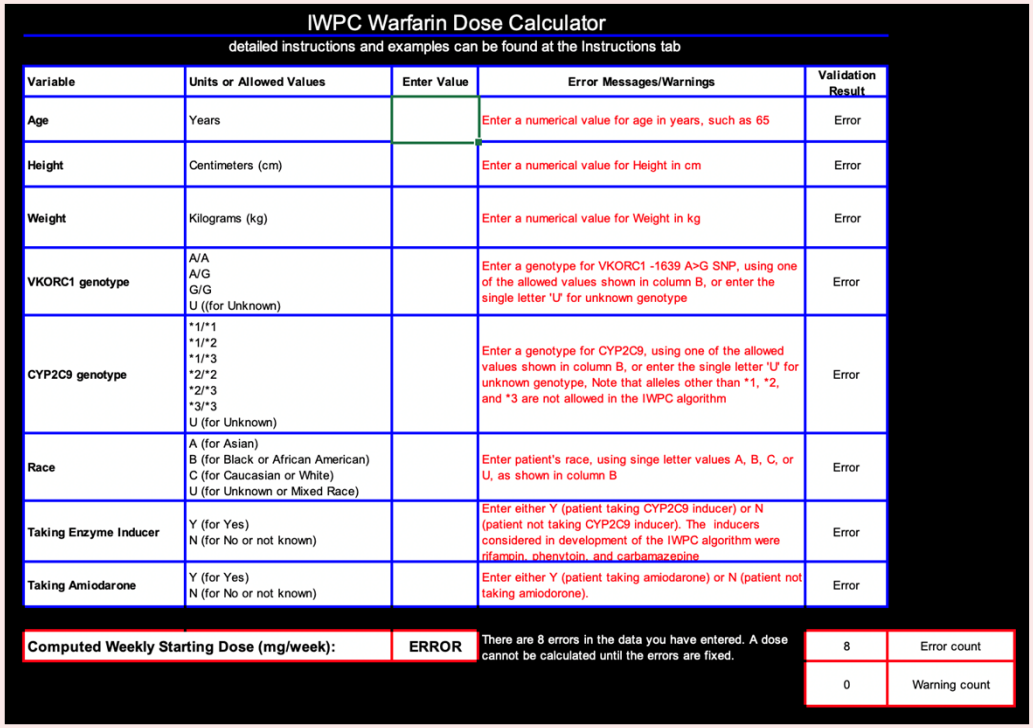
Gage

www.warfarindosing.org



International Warfarin Pharmacogenetics Consortium (IWPC)

https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/



Calculate warfarin dose using a published algorithm

Gage

www.warfarindosing.org

***Gage, et al.* (13)**

Estimated daily warfarin dose (mg/day) = Exp (0.9751 - 0.3238 x *VKOR_1639* + 0.4317 x BSA - 0.4008 x *CYP2C9*3* - 0.00745 x Age - 0.2066 x *CYP2C9*2* + 0.2029 x Target INR - 0.2538 x Amiodarone + 0.0922 x Smokes -0.0901 x AA_Race + 0.0664 x Prior_DVT_PE)
where exp is the exponential function, BSA is in m^2, the SNPs are coded 0 if absent, 1 if heterozygous, and 2 if homozygous, and race is coded as 1 if African American and 0 otherwise.

International Warfarin Pharmacogenetics Consortium (IWPC)

https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/

***IWPC warfarin pharmacogenetic dosing algorithm* (12)**

5.6044
- 0.2614 x Age in decades
+ 0.0087 x Height in cm
+ 0.0128 x Weight in kg
- 0.8677 x *VKORC1 A/G*
- 1.6974 x *VKORC1 A/A*
- 0.4854 x VKORC1 genotype unknown
- 0.5211 x *CYP2C9*1/*2*
- 0.9357 x *CYP2C9*1/*3*
- 1.0616 x *CYP2C9*2/*2*
- 1.9206 x *CYP2C9*2/*3*
- 2.3312 x *CYP2C9*3/*3*
- 0.2188 x *CYP2C9* genotype unknown
- 0.1092 x Asian race
- 0.2760 x Black or African American
- 0.1032 x Missing or Mixed race
+ 1.1816 x Enzyme inducer status
- 0.5503 x Amiodarone status
= Square root of weekly warfarin dose**

**The output of this algorithm must be squared to compute weekly dose in mg and divided by 7 to get the daily dose.

Caveats to the Gage and IWPC algorithms

- Genetics-based algorithms perform better than fixed dose algorithms

- Limitations
  - INR goal range 2-3
  - Most experience w/ European ancestry
  - Alleles most relelvant for African Americans not incorporated
  - Decreased performance in extremes (Older age, Extremely high/low doses)

- Use does not replace…
  - Clinical judgment
  - Appropriately frequent INR monitoring
  - Consideration of relevant clinical factors

Johnson JA, Caudle KE, Gong L et al. Clin Pharmacol Ther. 2017;102(3):397-404.

FDA label for warfarin dosing (Fixed dose)

VKORC1 -1639G>A	CYP2C9*1/*1	CYP2C9*1/*2	CYP2C9*1/*3	CYP2C9*2/*2	CYP2C9*2/*3	CYP2C9*3/*3
GG	5 – 7 mg	5 – 7 mg	3 – 4 mg	3 – 4 mg	3 – 4 mg	0.5 – 2 mg
GA	5 – 7 mg	3 – 4 mg	3 – 4 mg	3 – 4 mg	0.5 – 2 mg	0.5 – 2 mg
AA	3 – 4 mg	3 – 4 mg	0.5 – 2 mg	0.5 – 2 mg	0.5 – 2 mg	0.5 – 2 mg

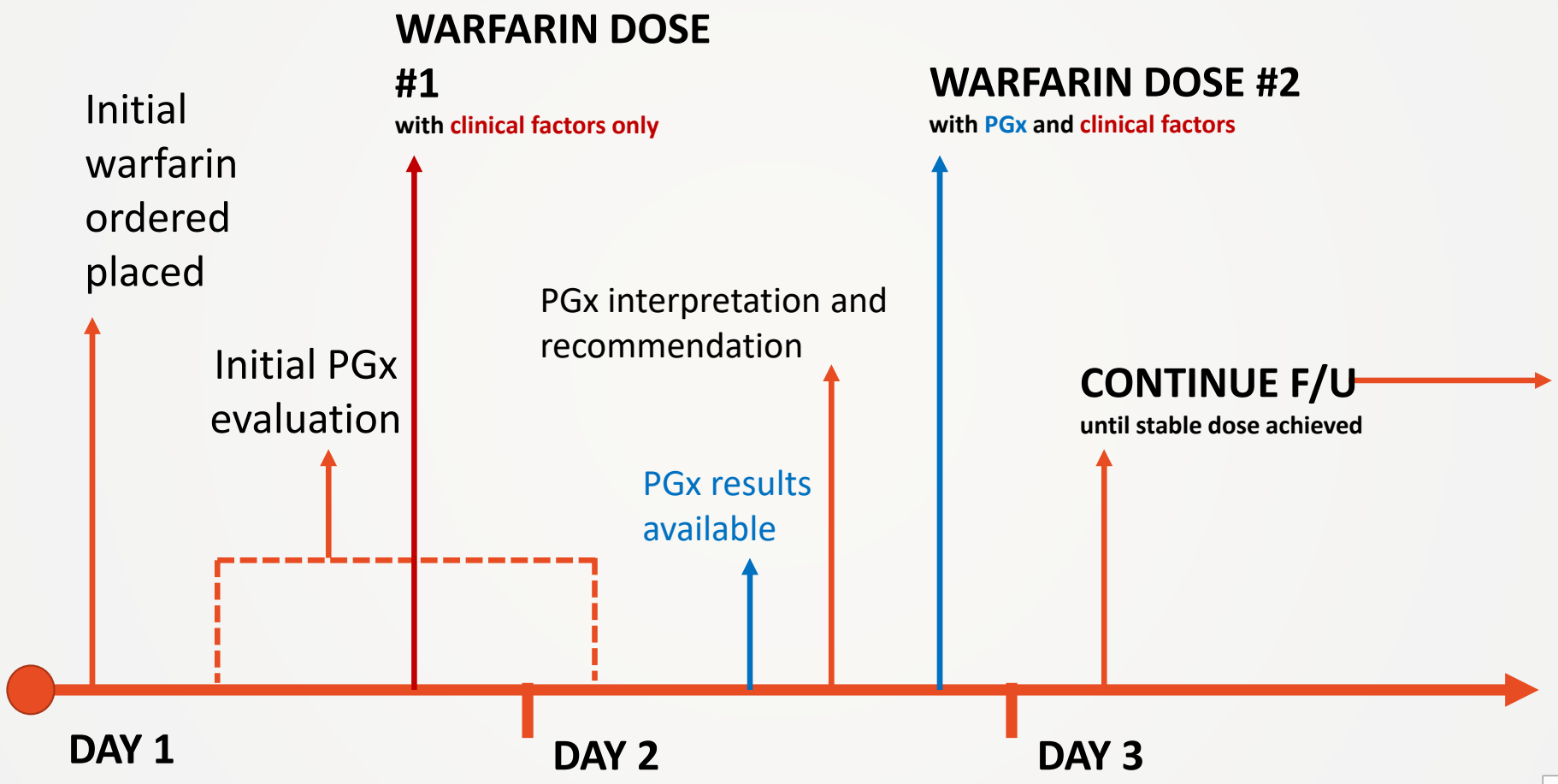
- Added to FDA labeling of warfarin in 2007 and updated 2011
- Other Pharmacogenetic-based warfarin dosing algorithms estimate dose better than FDA warfarin dosing algorithm

Coumadin. Prescribing Information. Bristol-Myers Squibb Company. New Jersey, Dec 2013.

Genotype guided warfarin considerations

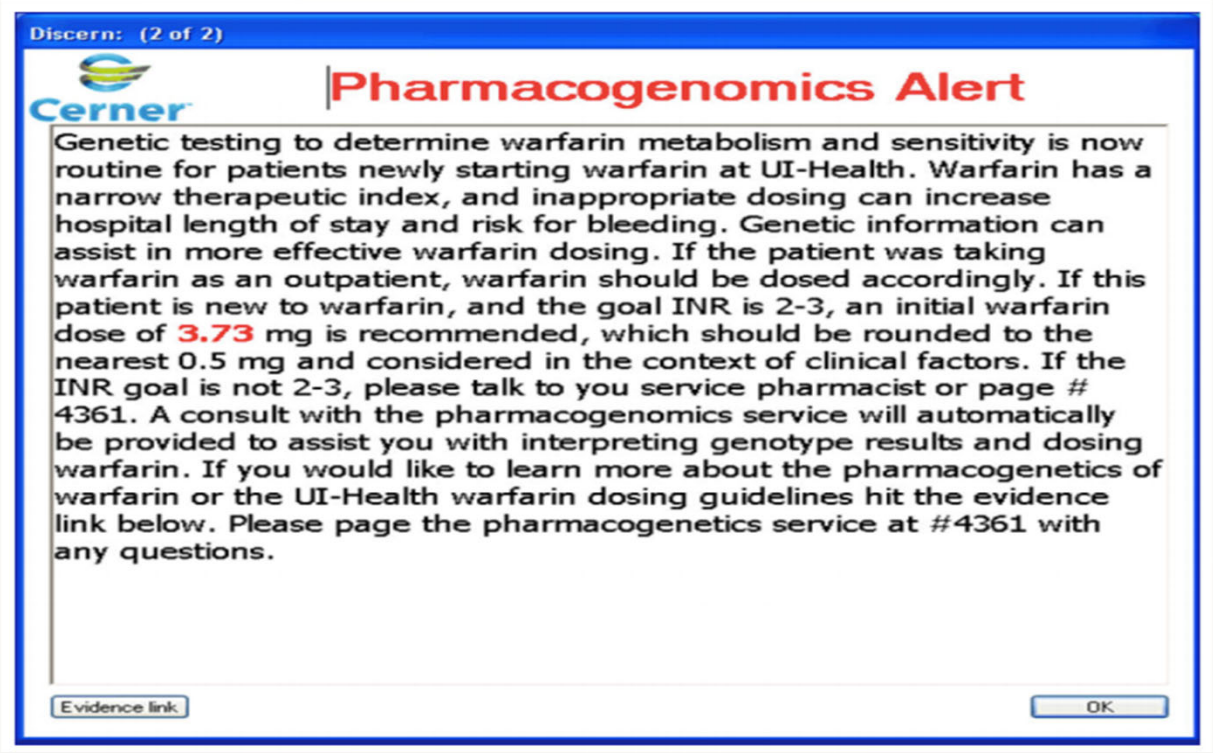
- Implementation Considerations
  - Patient population and timing are critical
  - Institution-specific oral anticoagulant prescribing trends
  - Reimbursable (Note: CMS: w/ enrollment in a clinical trial)
  - Cross-application with phenytoin (HLA-B*15:02 testing and dosing) and celecoxib

- Application Considerations
  - Rapid result turnaround time early in treatment initiation
  - SNPs relevant to race/ethnicity are interrogated
  - A published genetics-based algorithm is used to assist dose estimation



Pharmacotherapy. 2013 Nov;33(11):1156-64.

Clinical alert for PGx-guided warfarin



Pharmacotherapy. 2013 Nov;33(11):1156-64.

Case Study #3

HT is a 68-year-old African-American female who presents to the emergency department with **left lower extremity pain, swelling, and tenderness**. She denies any family history of VTE but notes that she returned home a few days ago that **involved a four-hour plane ride**. She denied shortness of breath, chest pain, and is not tachypnic upon presentation.

- Past medical history: HTN, HLD, GERD
- Social history: negative x3
- Home medications: lisinopril 5 mg daily, metoprolol succinate 25 mg daily, atorvastatin 40 mg daily, pantoprazole 40 mg daily
- Insurance: Medicare A, B, but not D, self-pays medications
- Vitals: weight 89 kg, height 172 cm, BP 148/86, pulse 108
- Labs: Hgb 11.2, Plts 298, CrCl 14 mL/min, **D-dimer (+)**, INR 1.1
- **Doppler ultrasound: (+) acutely occluded thrombus of the left femoral vein**

Case Study #3

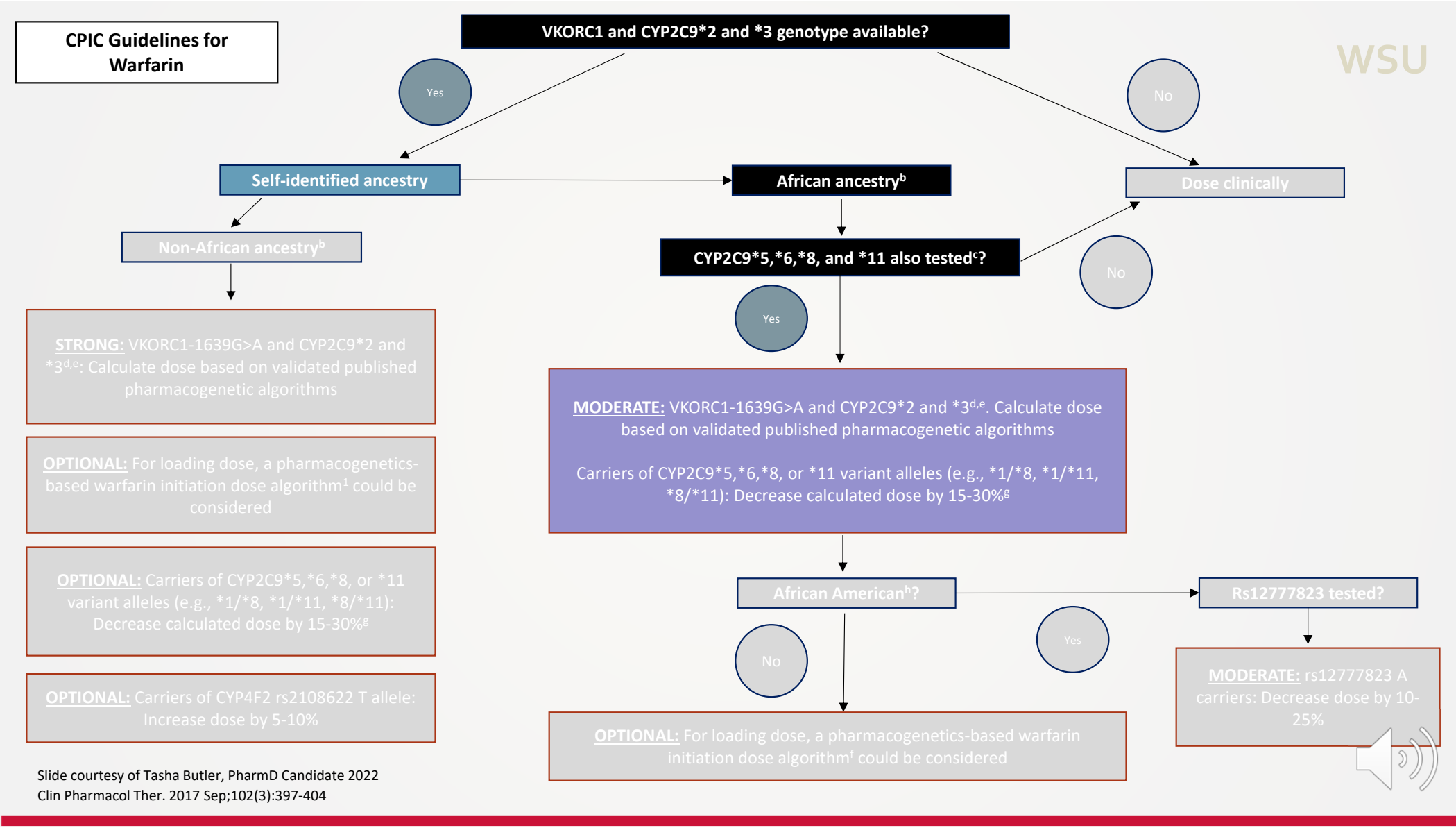
HT is diagnosed with DVT, likely provoked. Heparin is initiated with warfarin as the oral anticoagulant of choice (goal INR 2-3). Pharmacogenomic testing is performed.

PGx results:

Gene	Genotype	Alleles interrogated
CYP2C9	*1/*2	*2, *3, *5, *6, 8, *11
VKORC1	G/G	c.-1639G>A (rs9923231
CYP4F2	*1/*1	c.1297G>A (rs2108622)

Based on the pharmacogenomic results, which initial warfarin maintenance dose would you recommend?

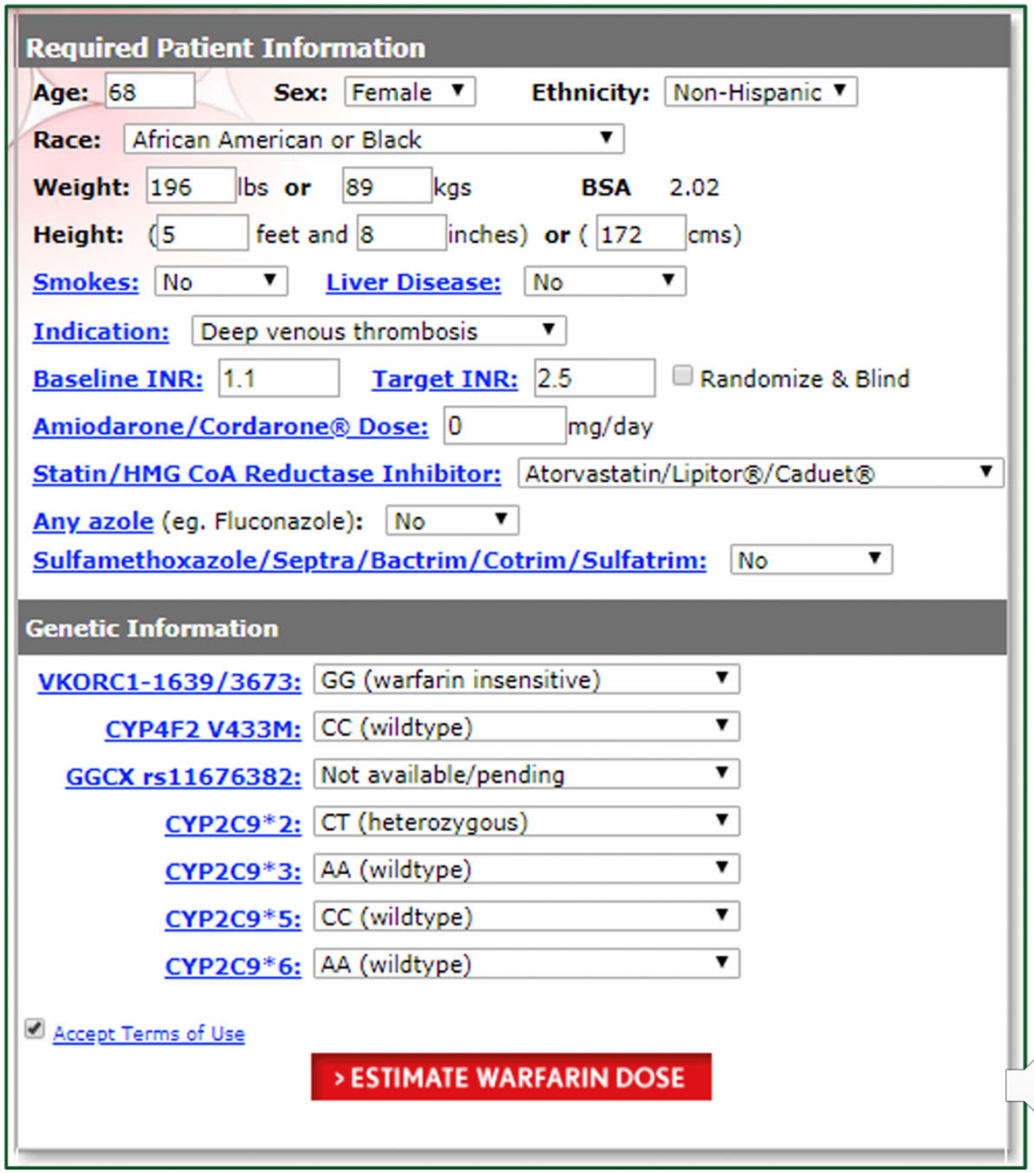
A. 2.5 mg
B. 5 mg
C. 7.5 mg
D. 15 mg



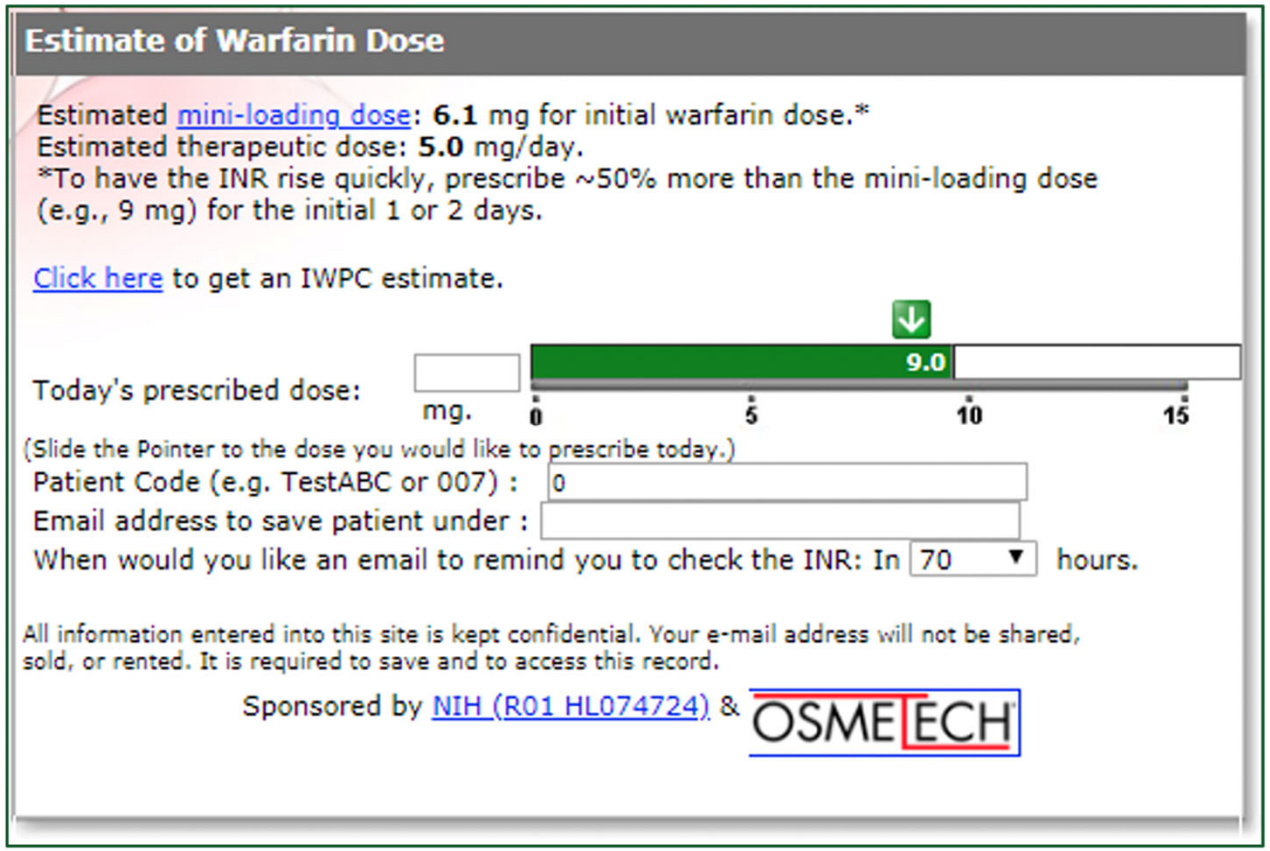
Slide courtesy of Tasha Butler, PharmD Candidate 2022

Clin Pharmacol Ther. 2017 Sep;102(3):397-404

Gage algorithm



Results of Gage algorithm



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Summary

- Clinical application of pharmacogenomics in cardiology
  - Clopidogrel and *CYP2C19*
  - Statins and SLCO1B1, ABCG2, CYP2C9
  - Warfarin and CYP2C9, CYP4F2, CYP2C cluster, VKORC1
- When pharmacogenomic results are available, the CPIC Guidelines are a great resource for interpreting and applying the results
- Implementation of pharmacogenomics in cardiology is a clinical reality and requires involvement of multiple stakeholders and an interdisciplinary team

WASHINGTON STATE UNIVERSITY

Pharmacogenomics of Cardiovascular Diseases

Interprofessional Clinical Pharmacogenomics Certificate Program

Teresa T. Ho, PharmD, BCPS

March 16, 2022