CSHP Fraser Valley Chapter CE Event 2021

Pharmacogenomics of Anti-Rejection and Cardiovascular Drugs

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Presenter Disclosure

- Presenter's Name: Dr. Tony KL Kiang
- I have no current or past relationships with commercial entities related to today's presentation.
- Speaking Fees for current program:
  - I have received a speaker's fee (i.e., standard honorarium) from Canadian Society of Hospital Pharmacists BC Branch for this learning activity

Commercial Support Disclosure

- This program has received no financial or in-kind support from any commercial or other organization

Learning objectives

By the end of this session, each learner will be able to:

- Understand warfarin, clopidogrel, tacrolimus, and mycophenolate pharmacology in relation to clinically relevant genetic polymorphisms
- Describe the Clinical Pharmacogenetics Implementation Consortium (CPIC) clinical recommendations (if available) for these agents
- Understand the clinical implications of major landmark clinical trials or emerging studies for each agent

Pre-exercise

Select the best answer(s) regarding the pharmacology of warfarin:

a) VKORC1 is responsible for the oxidation of s-warfarin
b) VKORC1 is responsible for the oxidation of r-warfarin
c) s-warfarin is inactivated by CYP2C9 to non-pharmacologically active metabolites
d) CYP2C19 genetic polymorphism significantly affects warfarin pharmacokinetics

Warfarin pharmacogenomics

Citations for the warfarin presentation

- Miklosz et al. J Physiol Pharmacol 2018; 69:1-14.
- Johnson et al. Clin Pharmacol & Ther 2017; 102:397-404.
- Johnson and Cavallari. Trends Cardiovasc Med 2015; 25:33-41.
- Kimmel. J Thromb Haemost 2015; 13 (suppl. 1): S266-271.
- Baranova et al. Expert Opin Drug Metab Toxicol 2015; 11:509-522.
- Kaye et al. Pharmacotherapy 2017; 37:1150-1163.
- Pratt et al. J Mol Diagn 2020; 22:847-859.
- Duarte and Cavallari. Nat Rev Cardiol 2021; ePUB ahead of print. https://doi.org/10.1038/s41569-021-00549-w.

Contents of this presentation based on these references

Warfarin

- Most commonly used anticoagulant
  - Therapeutic drug monitoring (TDM) via INR monitoring required due to large interpatient variability and narrow therapeutic index
  - Complications from warfarin → a common reason for ER visits
- Empiric dosing with/out loading dose
  - INR target (typically) 2-3
  - Achieved with dose 1 – 20 mg/day
  - INR TDM by “iteration” in many cases
  - INR outside target = bleeding vs. thromboembolism

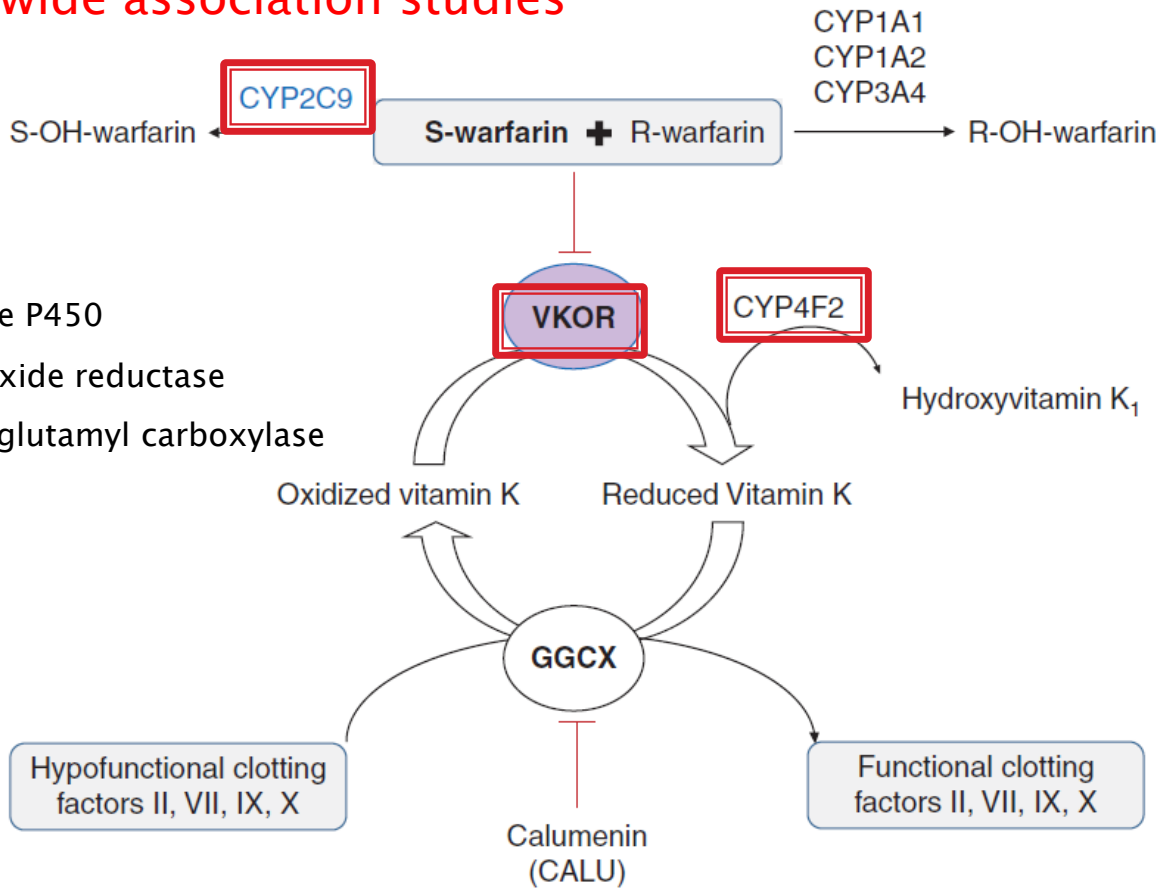
Warfarin: pharmacology

Genome wide association studies

CYP=cytochrome P450

VKOR=vit K epoxide reductase

GGCX=gamma-glutamyl carboxylase



Baranova et al. Expert Opin Drug Metab Toxicol 2015; 11:509-522

CYP2C9

- An enzyme in the cytochrome P450 superfamily
- S-warfarin hydroxylation (deactivation)
- >60 variant alleles known today
- CYP2C9*1 = wildtype allele (normal phenotype)
- CYP2C9*2, CYP2C9*3 (common in Europeans) are alleles with ↓ function
  - CYP2C9*2 ↓ warfarin hydroxylation (30 – 40%)
  - CYP2C9*3 ↓ warfarin hydroxylation (80 – 90%)
- Heterozygotes/homozygotes CYP2C9*2 or *3 ↑ bleeding
- CYP2C9*5, *6, *8, *11 (common in African Americans)
  - ↓ function

CYP2C9

Frequencies[a] of CYP2C9 alleles in biogeographical groups[b]									
CYP2C9 allele[c]	African American/Afro-Caribbean	American	Central/South Asian	East Asian	European	Latino	Near Eastern	Oceanian	Sub-Saharan African
*1[d]	0.8710	0.9119	0.7743	0.9153	0.7933	0.8636	0.7814	0.9551	0.7255
*2	0.0224	0.0334	0.1138	0.0021	0.1273	0.0763	0.1298	0.0293	0.0131
*3	0.0135	0.0301	0.1099	0.0376	0.0755	0.0402	0.0825	0.0156	0.0112
*4	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0012		0.0000
*5	0.0116	0.0015	0.0000	0.0000	0.0002	0.0087	0.0005		0.0103
*6	0.0085	0.0000	0.0000	0.0000	0.0003	0.0010	0.0000		0.0088
*7							0.0000		
*8	0.0590	0.0204	0.0010	0.0037	0.0018	0.0074	0.0006		0.0758
*9	0.0000		0.0000	0.0000			0.0000		0.1296
*10	0.0000								0.0000
*11	0.0139	0.0028	0.0010	0.0003	0.0016	0.0029	0.0000		0.0257

For each of the CYP2C9 allele, which of the race/ethnic groups have the

1) Highest allele frequency?
2) Lowest allele frequency ?

PharmGKB (Pharmacogenomics knowledgebase). Gene-specific information tables for CYP2C9. Accessed June 4 2021. Available from: https://www.pharmgkb.org/page/cyp2c9RefMaterials

VKORC1

- Encodes vitamin K epoxide reductase
- Conversion of vitamin K epoxide → vitamin K (rate limiting step)
- VKORC1 (-1639G>A, rs9923231) ↑↑ warfarin sensitivity (hence lower dose required)
- Associations with other single nucleotide polymorphisms (SNPs) not strong
- Differences in frequency of expressions of VKORC1 variants (-1639G>A) in different ethnicity → dose requirement variations b/w ethnicities

CYP4F2

- Liver vitamin K oxidase
- Metabolises vitamin K to OH-vitamin K1 (deactivation)
- CYP4F2*3 (c.1297G>A, rs2108622)
  - Higher (8 – 11%) warfarin dose requirements in A allele carriers
  - Inclusion of this polymorphism improves warfarin dose prediction

CYP2C rs12777823

- Single nucleotide polymorphism (SNP) in the CYP2C cluster near CYP2C18 gene
  - Heterozygote African Americans required ~7mg less warfarin dose per week
  - Homozygote African Americans required ~9mg less warfarin per week
  - No effects in other ethnicities?
    - WHY? Possibly NOT a functional SNP itself but a surrogate marker of other functional SNPs
    - Rs12777823 could be a shadow of “something else”, but we are not entirely sure what this “something else” is
  - ~25% of African Americans carry the polymorphic allele
- Inclusion into warfarin genomic dosing algorithm improves performance

Landmark trials

- In subjects of European ancestry, variations in CYP2C9, VKORC1, and CYP4F2 translates to 9%, 25%, and 2% of variability in warfarin dosing
- Various observational, non-randomized studies (majority in Caucasian/European population) with inconsistent findings supporting genomic-based dosing for warfarin
- Clinical Trials: Efficacy of genotype-guided warfarin dosing in randomized controlled trials
  - **EU-PACT** (Pirmohamed et al. N Engl J Med 2013; 369:2294-2303)
    - Shorter time to stable dose, improved % time in target range, reduced episodes of INR >4 compared to standard dosing
  - **COAG** (Kimmel et al. N Engl J Med 2013; 369:2283-2293)
    - No difference vs. clinical dosing algorithm
    - More diverse population

Landmark trials

- **GIFT (The Genetics-InFormatics Trial)**
  - Gage et al. JAMA 2017; 318:1115-1124
  - Randomized, controlled trial examining effectiveness and safety of genotype-guided dosing vs. clinical algorithm in orthopedic patients with a composite outcome (symptomatic and asymptomatic VTE, major hemorrhage, INR >4, and death)
  - Powered for actual clinical outcomes!
  - Genotypes: CYP2C9*2, *3; CYP4F2*3; VKORC1-1639
    - Q: which genotypes were left out? Will this affect your interpretation?
  - 27% reduction in composite outcomes in genotype dosing vs. clinical dosing

Landmark trials

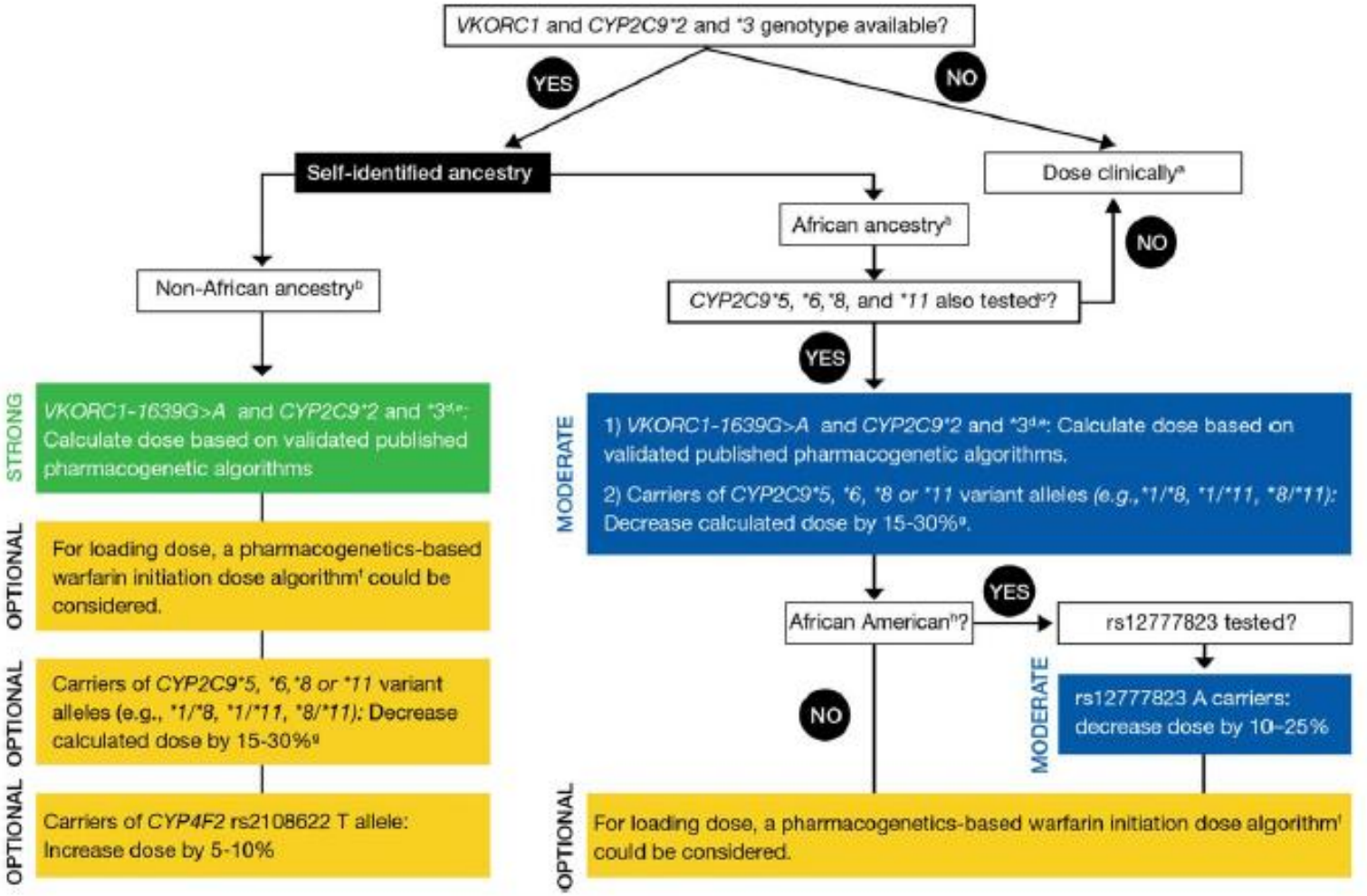
Table 3 | **Comparison of warfarin pharmacogenomic trials**

Trial	Participants	Comparator group	Genetic polymorphisms tested	Loading dose	Primary end point	Outcome	Ref.
EU-PACT (2013)	Adults from Sweden or the UK (n=455; 98.5% white) who were newly starting warfarin for atrial fibrillation or venous thromboembolism	Fixed dose of 10 mg on day 1 (or 5 mg if aged >75 years), then 5 mg on days 2 and 3, then dose guided by INR	*CYP2C9**2 and *3, *VKORC1* −1639G>A	Yes, loading dose algorithm used on days 1–3 in the genotype-guided group; 10 mg dose given on day 1 for patients aged ≤75 years in the control group	Percentage of time with an INR of 2.0–3.0 during the initial 12 weeks of warfarin therapy	Mean percentage time in INR range was 67.4% in the genotype-guided group and 60.3% in the control group (P<0.001)	89
COAG (2013)	Adults from the USA newly initiating warfarin treatment with a target INR of 2.0–3.0 (n=1,015; 27% Black, 73% non-Black)	Clinical algorithm-guided dosing	*CYP2C9**2 and *3, *VKORC1* −1639G>A	No, but *CYP2C9* variants were ignored for the initial dose in the genotype-guided group	Percentage of time with an INR of 2.0–3.0 from day 4 or 5 through to day 28 of warfarin therapy	All patients: mean percentage time in INR range was 45.2% in the genotype-guided group and 45.4% in the clinically guided group (P=0.91); Black patients: mean percentage time in INR range was 35.2% in the genotype-guided group and 43.5% in the clinically guided group (P=0.01)	122
GIFT (2017)	Patients aged ≥65 years undergoing elective total-hip or total-knee arthroplasty (n=1,650; 91% white, 6% Black)	Clinical algorithm-guided dosing	*CYP2C9**2 and *3, *VKORC1* −1639G>A, *CYP4F2**3	No, but *CYP2C9* variants were ignored for the first 2 days of therapy in the genotype-guided group	Composite of major bleeding, INR ≥4, venous thromboembolism or death	10.8% in the genotype-guided group and 14.7% in the clinically guided group had at least one end point (relative rate 0.73, 95% CI 0.56–0.95, P=0.02)	121

INR, international normalized ratio.

Duarte and Cavallari. Nat Rev Cardiol 2021; ePUB ahead of print. https://doi.org/10.1038/s41569-021-00549-w.

Decision making algorithm



Johnson et al. Clin Pharmacol Ther 2017; 102:397-404

Clopidogrel pharmacogenomics

Citations for the clopidogrel presentation

- Scott et al. Clin Pharmacol Ther 2013; 94:317-323 – most current CPIC guideline
- Rakicevic and Nestorovic. Clin Pharmacol Ther 2019; 105: 547-549
- Pereira et al. Circ Cardiovasc Interv 2019; 12:1-21
- Roden. N Engl J Med 2019; 381:1677-1678
- Moliterno et al. JAMA 2020; 324:747-475 [great commentary]
- Duarte and Cavallari. Nat Rev Cardiol 2021; ePUB ahead of print. https://doi.org/10.1038/s41569-021-00549-w.

Contents of this presentation based on these references

Clopidogrel

- One of the most widely used anti-platelet drugs in North America (~3 million prescriptions/year in US)
- Pro-drug: bioactivated by CYP2C19 to form pharmacologically active metabolites → platelet inhibition
- Selective and irreversible inhibition of P2RY12 receptor, ↓ platelet aggregation
- Pharmacological action duration ~ 10 days (life-span of typical platelet)
- Therapeutic drug monitoring (TDM) not routinely conducted
- Pharmacodynamic monitoring (platelet aggregation) not yet reliable

CYP2C19

- An enzyme in the cytochrome P450 superfamily
- Bioactivation of clopidogrel
- ~2000 variant alleles known today
- CYP2C19*1 = wildtype allele (normal phenotype)
- PK: CYP2C19*2, CYP2C19*3 are relatively more common alleles with ↓ function. CYP2C19*4-8 are also loss of function (less common)
  - ↓ Cmax or AUC of active metabolites
  - Effects of CYP2C19*3 > CYP2C19*2. Others unknown.
- PK: CYP2C19*17 with ↑ function
- PD: CYP2C19*2 → ↑residual platelet activity, stent-thrombosis,CV events
- PD: CYP2C19*17→ low residual platelet activity
- Actual clinical outcome?
  - ***Derived from patients with acute coronary syndrome with PCI (stent)
  - **POPular Genetics study** (Claassens et al. N Engl J Med 2019; 381;1621-1631)
  - **TAILOR-PCI study** (Pereira et al. JAMA 2020; 324:761-771)

CYP2C19

Frequencies[a] of CYP2C19 alleles in biogeographical groups[b]									
CYP2C19 allele[c]	African-American/Afro-Caribbean	American	Central/South Asian	East Asian	European	Latino	Near Eastern	Oceanian	Sub-Saharan African
*1[d]	0.5468	0.7725	0.5436	0.5956	0.6247	0.7148	0.6723	0.1871	0.4911
*2	0.1815	0.1216	0.2699	0.2835	0.1466	0.1027	0.1198	0.6095	0.1580
*3	0.0028	0.0000	0.0157	0.0725	0.0017	0.0009	0.0165	0.1464	0.0026
*4	0.0000	0.0000	0.0000	0.0002	0.0020	0.0006	0.0000		0.0000
*5	0.0000	0.0000	0.0000	0.0032	0.0000	0.0000	0.0000		0.0000
*6	0.0000		0.0000	0.0006	0.0003	0.0000	0.0000		0.0000
*7	0.0000		0.0000	0.0001	0.0000	0.0000			0.0000
*8	0.0011	0.0000	0.0000	0.0000	0.0034	0.0013	0.0000		0.0000
*9	0.0143			0.0001	0.0007	0.0008			0.0270
*10	0.0033			0.0001	0.0000	0.0012	0.0000		0.0000
*11				0.0000			0.0000		
*12	0.0011			0.0001	0.0000	0.0000			0.0000
*13	0.0120			0.0001	0.0022	0.0040			0.0000
*14	0.0000	0.0000		0.0001	0.0000	0.0000			0.0000
*15	0.0140			0.0014	0.0020	0.0040			0.0529
*16	0.0000			0.0000	0.0000	0.0000			
*17	0.2072	0.1059	0.1708	0.0205	0.2164	0.1697	0.1914	0.0570	0.1733

PharmGKB (Pharmacogenomics knowledgebase). Gene-specific information tables for CYP2C19. Accessed June 4 2021. Available from: https://www.pharmgkb.org/page/cyp2c19RefMaterials

Genotype → phenotype

Table 1 Assignment of likely CYP2C19 phenotypes based on genotypes

Likely phenotype	Genotypes	Examples of diplotypes
Ultrarapid metabolizer: normal or increased activity (~5–30% of patients)	An individual carrying two increased activity alleles (*17) or one functional allele (*1) plus one increased-activity allele (*17)	*1/*17, *17/*17
Extensive metabolizer: homozygous wild-type or normal activity (~35–50% of patients)	An individual carrying two functional (*1) alleles	*1/*1
Intermediate metabolizer: heterozygote or intermediate activity (~18–45% of patients)	An individual carrying one functional allele (*1) plus one loss-of-function allele (*2–*8) or one loss-of-function allele (*2–*8) plus one increased-activity allele (*17)	*1/*2, *1/*3, *2/*17
Poor metabolizer: homozygous variant, mutant, low, or deficient activity (~2–15% of patients)	An individual carrying two loss-of-function alleles (*2–*8)	*2/*2, *2/*3, *3/*3

Some rare genotype combinations have unclear predicted metabolic phenotypes; see **Supplementary Table S5** online.

Scott et al. Clin Pharmacol Ther 2013; 94:317-323– most current CPIC guideline

Dosing algorithm

Table 2 Antiplatelet therapy recommendations based on CYP2C19 status when considering clopidogrel for ACS/PCI patients

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations[a]
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation[b]	Clopidogrel: label-recommended dosage and administration	Strong
Intermediate metabolizer (*1/*2, *1/*3, *2/*17)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Moderate
Poor metabolizer (*2/*2, *2/*3, *3/*3)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Strong

[a]See **Supplementary Materials and Methods** (Strength of Therapeutic Recommendations) online. [b]The *CYP2C19*17* allele may be associated with increased bleeding risks (ref. 15). ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

Scott et al. Clin Pharmacol Ther 2013; 94:317-323 – most current CPIC guideline

POPular Genetics Study

- Randomized, open-label, multi-centre (European) trial of STEMI-PCI patients.
  - (Claassens et al. N Engl J Med 2019; 381;1621- 1631)
- CYP2C19 genotype “treatment” group vs. control group (ticagrelor or prasugrel)
  - Genotype group: CYP2C19*1/*1 (clopidogrel); carrying CYP2C19*2 or 3 alleles (ticagrelor or prasugrel)
  - Control group: ticagrelor or prasugrel
- Primary outcomes:
  - Death from any cause (MI, stent thrombosis, stroke, major bleeding) at 1 year – tested for non-inferiority
  - Bleeding outcome (major or minor bleeding)

POPular Genetics Study

- Results:
  - Death from any cause: 5.1% in genotype group vs. 5.9% in control group (absolute difference -0.7%, 95CI (-2.0 to 0.7; p<0.001)
  - Bleeding outcome: 9.8% in genotype group vs. 12.5% in control group (hazard ratio 0.78, CI 0.61 to 0.98, p=0.04)
- “CYP2C19 genotype-guided strategy for selection of oral P2Y12 inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding”

TAILOR-PCI study

- Randomized, open-label, multi-centre (North America, Asia) of patients with ACS and stable CAD undergoing PCI. (Pereira et al. JAMA; 324 2020:761-771)
- CYP2C19 genotype “treatment” group vs. control group
  - Genotype group: CYP2C19*1/*1 (clopidogrel 75mg QD); carrying CYP2C19*2 or 3 alleles (ticagrelor 90mg BID)
  - Control group: clopidogrel 75mg QD
- Primary outcomes:
  - Composite of cardiovascular death, MI, stroke, stent-thrombosis, ischemia during 1st year after PCI
- Secondary outcomes:
  - Major or minor bleeding

TAILOR-PCI study

- Results
  - Primary endpoint:
    - 4% in genotype-guided vs. 5.9% in control group (HR 0.66, 95CI 0.43-1.02; p=0.056)
    - No difference in secondary endpoints
  - “TAILOR-PCI…misses mark”
  - Due to improving standards of care (including stent technology)? Or insufficient power?

Tacrolimus & mycophenolate pharmacogenomics (quick takes)

Citations for the tacrolimus and mycophenolate presentations

- Birdwell et al. Clin Pharmacol Ther 2015; 98: 19-24 – most current CPIC guideline for tacrolimus and CYP3A5
- Brunet et al. Ther Drug Monit 2019; 41: 261-307
- Yang et al. Clin Pharmacokinet 2021; ePUB ahead of print. https://doi.org/10.1007/s40262-020-00955-2.
- Kiang TK, Ensom MH. (2017). Anti-rejection drugs. Murphy JE. Clinical Pharmacokinetics. 6th Ed: 205-220.
- Kiang TK, Ensom MHH. (2017). Immunosuppressants. Beringer P. Winter's Basic Clinical Pharmacokinetics. 6th Ed: 320-357.
- Bergan et al. Ther Drug Monit 2021; 43:150-200

Contents of this presentation based on these references

Tacrolimus

TABLE 3. Minor Allele Frequencies (by Ethnic Group) for Relevant Tacrolimus Biotransformation Enzymes and Transporters

	EUR	AFR	AMR	EAS	SAS
CYP3A5*3, rs776746	0.94	0.18	0.80	0.71	0.68
CYP3A5*6, rs10264272	<0.01	0.15	0.02	<0.01	<0.01
CYP3A4*22, rs35599367	0.05	<0.01	0.03	<0.01	<0.01
ABCB1 3435T, rs1045642	0.52	0.15	0.43	0.40	0.57
ABCB1 1199A, rs2229109	0.03	<0.01	0.02	<0.01	0.01
POR*28, rs1057868	0.30	0.17	0.28	0.37	0.35
PPAR, rs4253728	0.28	0.03	0.16	<0.01	0.10
PPAR, rs4823613	0.29	0.40	0.28	0.20	0.16

From 1000 Genomes Project data (http://www.internationalgenome.org/), all populations have been divided into 5 super populations according EUR, European; AFR, African; AMR, Ad Mixed American (Mexican, Puerto Ricans, Colombians, and Peruvians); EAS, East Asian; SAS, South Asian.

Brunet et al. Ther Drug Monit 2019; 41: 261-307

Tacrolimus

Table 1 Assignment of likely metabolism phenotypes based on *CYP3A5* diplotypes

Likely phenotype	Genotypes	Examples of diplotypes[a]
Extensive metabolizer (CYP3A5 expresser)	An individual carrying two functional alleles	*1/*1
Intermediate metabolizer (CYP3A5 expresser)	An individual carrying one functional allele and one nonfunctional allele	*1/*3, *1/*6, *1/*7
Poor metabolizer (CYP3A5 nonexpresser)	An individual carrying two nonfunctional alleles	*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7

[a]Additional rare variants, such as *CYP3A5*2*, *8, and *9 may be found, which are of unknown functional significance. However, if a copy of *1 is present, expected phenotype would be intermediate metabolizer.

Birdwell et al. Clin Pharmacol Ther 2015; 98: 19-24

Tacrolimus

Table 2 Dosing recommendations for tacrolimus based on *CYP3A5* phenotype

CYP3A5 phenotype[a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[a] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

Birdwell et al. Clin Pharmacol Ther 2015; 98: 19-24

Tacrolimus

Study or Subgroup	genotype-guided group Events	Total	conventional group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Thervet 2010	50	116	35	120	33.8%	1.48 [1.04, 2.09]	2010
Chen 2013	21	22	3	11	3.9%	3.50 [1.33, 9.23]	2013
Shuker 2016	37	104	37	99	37.3%	0.95 [0.66, 1.37]	2016
Min 2018	24	35	8	18	10.4%	1.54 [0.88, 2.71]	2018
Anutrakulchai 2019	25	62	15	63	14.6%	1.69 [0.99, 2.89]	2019
Total (95% CI)		**339**		**311**	**100.0%**	**1.40 [1.14, 1.72]**	
Total events	157		98				

Heterogeneity: Chi² = 8.46, df = 4 (P = 0.08); I² = 53%
Test for overall effect: Z = 3.22 (P = 0.001)

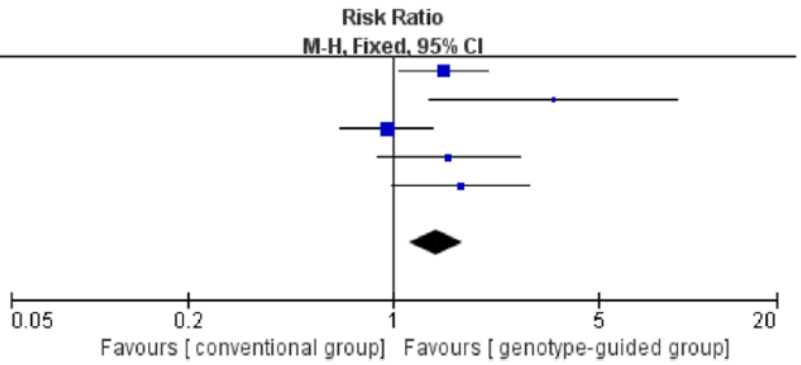


Fig. 2 Forest plot depicting the risk ratios of patients within the targeted concentration with GG versus CG. Squares indicate point estimates, and the size of the square indicates the weight of each study. *CI* confidence interval, *M-H* Mantel–Haenszel, *df* degrees of freedom, *GG* genotype-guided group, *CG* conventional group

Study or Subgroup	genotype-guided group Events	Total	conventional group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Thervet 2010	17	116	18	120	48.4%	0.98 [0.53, 1.80]	2010
Shuker 2016	6	118	5	119	13.6%	1.21 [0.38, 3.86]	2016
Anutrakulchai 2019	26	62	14	63	38.0%	1.89 [1.09, 3.26]	2019
Total (95% CI)		**296**		**302**	**100.0%**	**1.35 [0.92, 1.98]**	
Total events	49		37				

Heterogeneity: Chi² = 2.54, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 1.56 (P = 0.12)

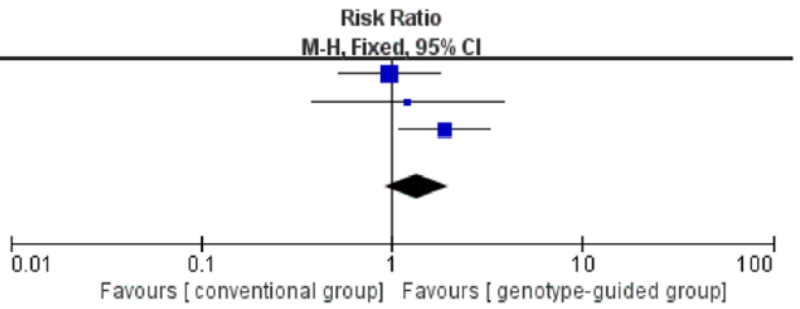
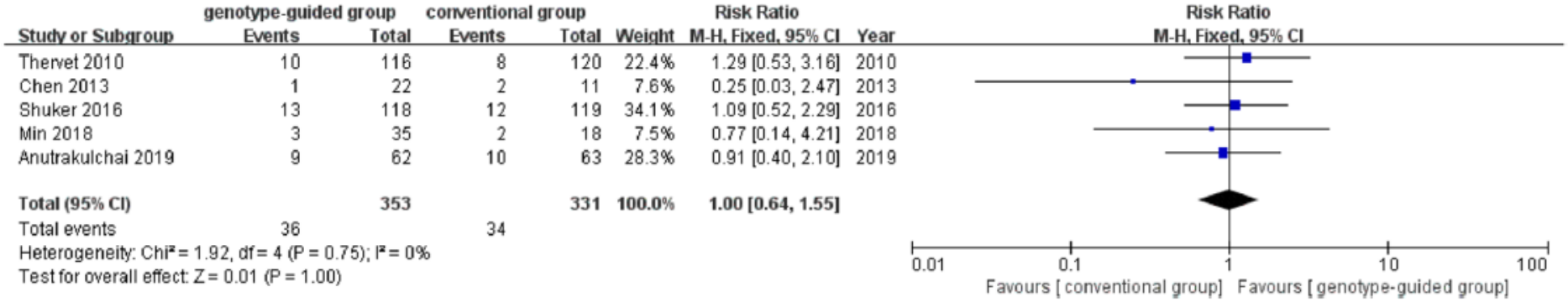


Fig. 3 Forest plot depicting the risk ratios of delayed graft function with GG versus CG. Squares indicate point estimates, and the size of the square indicates the weight of each study. *CI* confidence interval, *M-H* Mantel–Haenszel, *DF* degrees of freedom, *GG* genotype-guided group, *CG* conventional group

Yang et al. Clin Pharmacokinet 2021; ePUB ahead of print. https://doi.org/10.1007/s40262-020-00955-2.

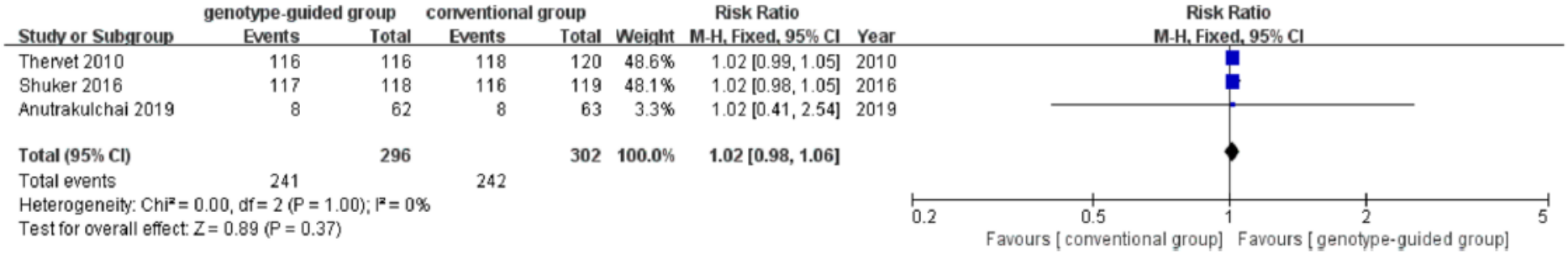
Tacrolimus



Study or Subgroup	genotype-guided group Events	Total	conventional group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Thervet 2010	10	116	8	120	22.4%	1.29 [0.53, 3.16]	2010
Chen 2013	1	22	2	11	7.6%	0.25 [0.03, 2.47]	2013
Shuker 2016	13	118	12	119	34.1%	1.09 [0.52, 2.29]	2016
Min 2018	3	35	2	18	7.5%	0.77 [0.14, 4.21]	2018
Anutrakulchai 2019	9	62	10	63	28.3%	0.91 [0.40, 2.10]	2019
Total (95% CI)		**353**		**331**	**100.0%**	**1.00 [0.64, 1.55]**	
Total events	36		34				

Heterogeneity: Chi² = 1.92, df = 4 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.01 (P = 1.00)

Fig. 4 Forest plot depicting the risk ratios of acute rejection with GG versus CG. Squares indicate point estimates, and the size of the square indicates the weight of each study. *CI* confidence interval, *M-H* Mantel–Haenszel, *df* degrees of freedom, *GG* genotype-guided group, *CG* conventional group



Study or Subgroup	genotype-guided group Events	Total	conventional group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Thervet 2010	116	116	118	120	48.6%	1.02 [0.99, 1.05]	2010
Shuker 2016	117	118	116	119	48.1%	1.02 [0.98, 1.05]	2016
Anutrakulchai 2019	8	62	8	63	3.3%	1.02 [0.41, 2.54]	2019
Total (95% CI)		**296**		**302**	**100.0%**	**1.02 [0.98, 1.06]**	
Total events	241		242				

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)

Fig. 5 Forest plot depicting the risk ratios of graft survival censored for death with GG versus CG. Squares indicate point estimates, and the size of the square indicates the weight of each study. *CI* confidence interval, *M-H* Mantel–Haenszel, *df* degrees of freedom, *GG* genotype-guided group, *CG* conventional group

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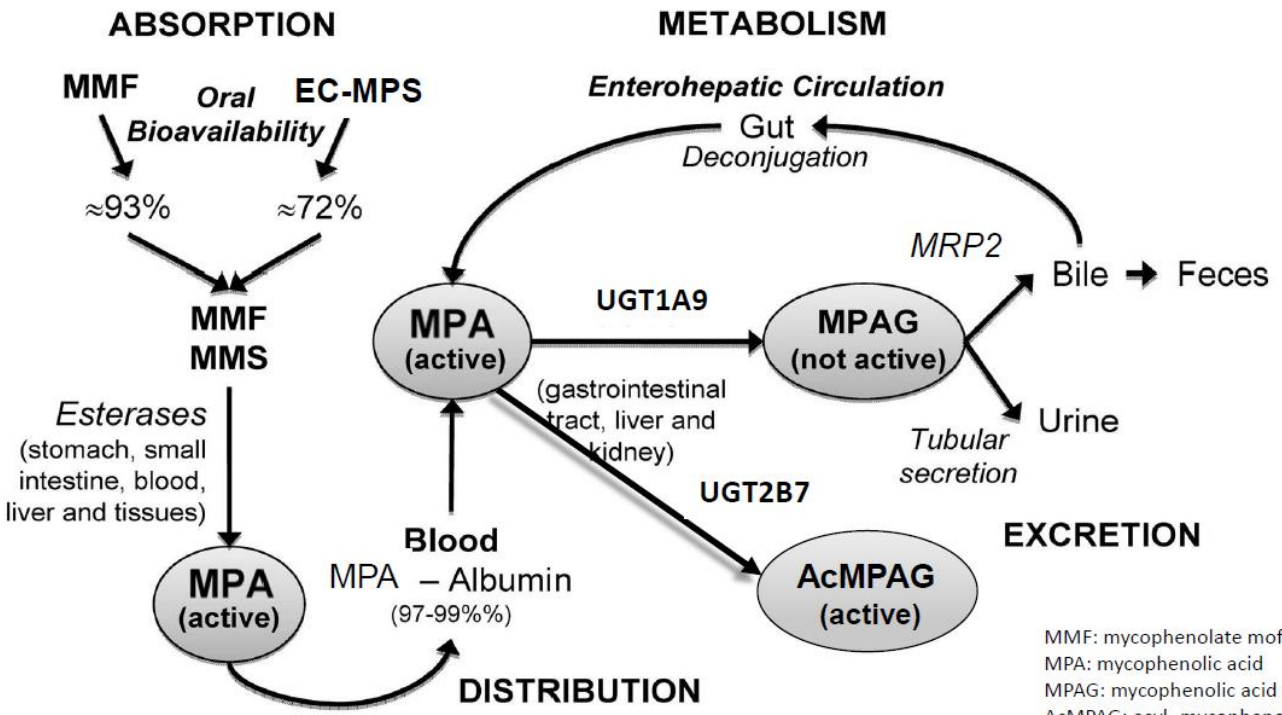
Mycophenolate



Source: http://neoreviews.aappublications.org/content/11/10/e578.figures-only

Adopted/modified from Neo Reviews. An Official Journal of the American Academy of Pediatrics. Accessed June 4 2021. Available from: https://neoreviews.aappublications.org/content/11/10/e578/F2

Mycophenolate

TABLE 5. Most Relevant Pharmacogenetic Markers by Ethnicity: Variant Allele Frequencies of Selected Genes Involved in PK and PD of MPA

Gene	Haplotype	Variant (Other Names)		rs id	Whites	African Ancestry	Asian Ancestry	Admixed Population	References
									579–582
UGT1A9	*1C	c.-2153C>T (-2152C>T)		rs17868320	0.075	0.307	0	0.06	355,361
		c.-276T>A (-275T>A)		rs6714486	0.015	0.17	0	0.06	355,361
	*3a	c.98T>C	p.Met33Thr	rs72551330	0.015–0.0158	0.0025	<0.001–0.0022	0.016–0.2	355,357,361,583
UGT2B7	*2	c.802C>T	p.Tyr268His	rs7439366	0.52–0.75	0.0085	0.27–0.4	0.5	355,361,584
		c.211G>T	p.Ala71Ser	rs12233719	NFA	0.008–0.29	0.13	0.0058	584
ABCC2		-24C>T		rs717620	0.232–0.392	0.0145	0.21–0.44	0.18	355,357,380,381
SLCO1B1	*1B	c.388A>G	p.Asn130Asp	rs2306283	0.45	0.267	0.267		355
	*5	c.521T>C	p.Val174Ala	rs4149056	0.0271	0.0084	0.0821	0.17–0.308	355,363,398
SLCO1B3		c.334T>G	p.Ser112Ala	rs4149117	0.982	0.581	0.7–0.921	0.962	355,363,381,398
IMPDH2		c.787C>T (3375C>T)	p.Leu263Phe	rs121434586	<0.01–0.104	<0.01–0.056	<0.01–0.0445		355,585
		c.-95T>G			<0.01	<0.01	<0.01		585
		c.819+10T>C (IVS7+10T>C 3757T>C)		rs11706052	0.106–0.107	0.008–0.0269	0.025–0.062		585

Frequencies are displayed as decimals.

Bergan et al. Ther Drug Monit 2021; 43:150-200

Mycophenolate

Clinical Drug Investigation (2018) 38:1011–1022
https://doi.org/10.1007/s40261-018-0694-5

ORIGINAL RESEARCH ARTICLE

Regression and Genomic Analyses on the Association Between Dose-Normalized Mycophenolic Acid Exposure and Absolute Neutrophil Count in Steroid-Free, De Novo Kidney Transplant Recipients

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Published online: 3 September 2018

Summary

- **Warfarin:** emerging, but conflicting data are available on the feasibilities of using CYP2C9, VKORC1, and CYP4F2 polymorphisms in warfarin pharmacogenomic dosing. The selection of specific polymorphic alleles should take into consideration the patients' ethnicities.
- **Clopidogrel:** emerging, but also conflicting data are available in the utilization of CYP2C19 polymorphism in clopidogrel pharmacogenomic dosing in patients undergoing PCI. Studies are ongoing in other indications.
- **Tacrolimus:** CYP3A5 expression status can help improve concentration target attainment; however, the effects of genomic doing on actual clinical outcomes (i.e. graft rejection, adverse effects) are not yet known.
- **Mycophenolate:** various genetic targets are currently being investigated. Consistent pharmacokinetic or pharmacodynamic outcomes are not yet available to support the implementation of pharmacogenomic dosing.

Contents of this presentation based on these references