Current Concepts:
The Application of Cardiovascular Pharmacogenomics in Clinical Practice

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Learning Objectives

1. Evaluate the results of pharmacogenomic tests and apply the results to a cardiovascular patient case.

2. Given a case, use evidence-based guidelines and literature to formulate a cardiovascular patient-specific medication regimen plan based on pharmacogenomic test results and other patient-specific factors.

3. Recommend strategies for the implementation of pharmacogenomics in cardiovascular pharmacy practice.

The Era of Precision Medicine

- **Precision medicine:** An approach to disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person
  - Also known as "personalized medicine" or "precision health"

- **Precision pharmacotherapy:** Customizing medications for subgroups of patients categorized by shared molecular and cellular biomarkers to improve treatment outcomes

Pharmacogenomics (PGx)

- Component of precision and personalized medicine

- The study of how genetic variation contributes to interindividual variability in drug disposition, response, and toxicity

- Clinical application of PGx: Use of genetic information to guide drug selection and dosing to maximize efficacy and minimize adverse effects

Cardiovascular PGx

- During this session, we will take a close look at the application of <u>actionable</u> drug-gene pairs in cardiovascular pharmacy practice

  ❖ Clopidogrel and *CYP2C19*

  ❖ Warfarin and *CYP2C9*, *VKORC1*, and *CYP4F2*

  ❖ Simvastatin and *SLCO1B1*

- We will evaluate factors such as evidence, clinical utility, and strategies for clinical implementation

What is Your Experience with PGx in Clinical Practice?

- Briefly share with your neighbor your practice-based experiences

- If you have not used PGx, please share your insights about barriers in your practice setting

Clopidogrel Case

JB is a 76-year-old, 58-kg Asian woman who presents with "heavy" chest pain, shortness of breath, nausea, and diaphoresis. She has a past medical history significant for hypertension, hyperlipidemia, and depression. She has no known drug allergies and takes lisinopril, simvastatin, and paroxetine. Based on ECG findings and cardiac markers, she is diagnosed with ST-elevation MI (STEMI) and is sent for coronary angiography and percutaneous coronary intervention (PCI).

PCI reveals that JB has 95% occlusion of her left anterior descending artery, and a drug-eluting stent is deployed. After a few days, JB is discharged on clopidogrel 75 mg daily, aspirin 81 mg daily, lisinopril 20 mg daily, metoprolol succinate 25 mg daily, simvastatin 40 mg daily, and paroxetine 20 mg daily.

During her admission, JB's blood was sent to an external lab for *CYP2C19* genotyping.

Question 1:

Which of following *CYP2C19* genotypes is associated with the highest risk of major adverse cardiovascular events (MACE) and stent thrombosis in patients like JB who are treated with clopidogrel?

    A.   *1/*1
    B.   *2/*2
    C.   *1/*3
    D.   *17/*17

Note: MACE is often defined as MI, stroke, or death

Clopidogrel Clinical Pharmacology

- Clopidogrel undergoes a two-step bioactivation process mediated predominantly by CYP2C19
  - Active thiol metabolite irreversibly binds to P2Y12 receptors, thereby inhibiting ADP-induced platelet aggregation

- The *CYP2C19* gene has functional (*1), no function (*2,*3), and increased function (*17) alleles

- Combinations of these alleles give rise to five different CYP2C19 metabolizing enzyme phenotypes in the population:
  - Ultrarapid metabolizers (UM)   *17/*17
  - Rapid metabolizers (RM)   *1/*17
  - Normal metabolizers (NM)   *1/*1
  - Intermediate metabolizers (IM)   *1/*2, *1/*3
  - Poor metabolizers (PM)   *2/*2, *2/*3, *3/*3

- Plasma exposure of the active thiol metabolite: PM < IM < NM < RM < UM

Scott SA et al. *Clin Pharmacol Ther.* 2013; 94:317-323.

Alternative Antiplatelet Agents

- Prasugrel and ticagrelor are superior to clopidogrel in terms of platelet inhibition and reduction of MACE in patients with acute coronary syndromes (ACS) undergoing PCI

- Prasugrel and ticagrelor pharmacokinetics, pharmacodynamics, and clinical outcomes are not affected by *CYP2C19* genetic variation

- Clopidogrel continues to be widely used due to its low cost and lower risk of serious bleeding compared with prasugrel and ticagrelor
  - Ticagrelor is also associated with adverse effects, such as dyspnea and bradycardia, that increase the risk of discontinuation

Scott SA et al. *Clin Pharmacol Ther.* 2013; 94:317-323.

Question 2:

JB's *CYP2C19* results return a few days after discharge and indicate that she has the *2/*2 genotype. Based on this result, what is the best recommendation for JB's long-term antiplatelet therapy regimen?

    A. Continue clopidogrel 75 mg daily

    B. Discontinue clopidogrel and start prasugrel 10 mg daily

    C. Discontinue clopidogrel and start ticagrelor 90 mg twice daily

    D. Increase clopidogrel to 150 mg daily

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines

CPIC antiplatelet therapy recommendations are based on CYP2C19 status when considering clopidogrel for patients with ACS undergoing PCI

- <u>UM, RM, NM</u>: Administer clopidogrel at standard dosage (classification -strong)

- <u>IM</u>: Consider alternative antiplatelet therapy, e.g., prasugrel or ticagrelor, if no contraindications (classification - moderate)

- <u>PM</u>: Consider alternative antiplatelet therapy, e.g., prasugrel or ticagrelor, if no contraindications (classification - strong)

Prasugrel contraindications or warnings: active pathological bleeding (contraindication); history of transient ischemic attack or stroke (contraindication); ≥ 75 years of age (warning); patients likely to undergo urgent coronary artery bypass graft (CABG) surgery (warning); or additional risk factors for bleeding (e.g., body weight <60 kg, warning)

Ticagrelor contraindications and warnings: history of intracranial hemorrhage (contraindication); active pathological bleeding (contraindication); severe hepatic impairment (warning); or patients undergoing urgent CABG surgery (warning)

Scott SA et al. *Clin Pharmacol Ther* 2013; 94:317-323.

Clinical Caveats

- CPIC recommendations are indication-specific (i.e., patients with ACS undergoing PCI)
  - Do NOT apply to the use of clopidogrel for medically-managed ACS, stroke, or peripheral artery disease

- Other clinical considerations: racial differences in variant allele frequencies, presence of diabetes, age, body mass index, interacting medications
  - For example, potent CYP2C19 inhibitors may turn genetically-mediated CYP2C19 EM/IMs into PMs

- Data are inconsistent regarding the relationship between *CYP2C19*17* and increased risk of bleeding in clopidogrel-treated patients

Clinical Caveats

- Data do not support the use of increased clopidogrel dosages in CYP2C19 IM/PMs

- PCI guidelines from the American College of Cardiology Foundation/American Heart Association state that genetic testing might be considered in high-risk patients, but presently, the evidence base does not warrant routine genetic testing in patients undergoing PCI

- FDA boxed warning in clopidogrel prescribing information: Diminished antiplatelet effect in CYP2C19 PMs
    - Tests are available to identify patients who are CYP2C19 PMs
    - Consider use of another P2Y12 inhibitor in CYP2C19 PMs

Supporting Evidence

- Several retrospective analyses of large clinical trials have shown that the risk for MACE and stent thrombosis after PCI is significantly higher in clopidogrel-treated CYP2C19 IM/PMs than UM/RM/NMs

- Some prospective international studies have shown that *CYP2C19* genotype-guided selection of antiplatelet therapy in IM/PMs is associated with significant reductions in the incidence of MACE compared with standard therapy/no genotyping

Supporting Evidence

- In a multicenter, prospective pragmatic trial of PCI patients (N=1815), the risk for MACE was higher in CYP2C19 IM/PMs treated with clopidogrel versus alternative therapy* (HR 2.26, 95% CI 1.18-4.32)
  - *Ticagrelor, prasugrel, or high-dose clopidogrel

- In a single-center, observational study of PCI patients (N=1193), the risk for MACE was higher in CYP2C19 IM/PMs treated with clopidogrel versus alternative therapy* (HR 4.65, 95% CI 2.22-10)
  - *Ticagrelor or prasugrel

- In both studies, the effects were more pronounced in high-risk patients (PCI for ACS)
  - No significant difference in the incidence of MACE was observed in CYP2C19 UM/RM/NMs treated with clopidogrel vs. alternative therapy

Cavallari LH et al. *JACC Cardiovasc Pharmacol.* 2018; 11:181-191.

Lee CR et al. *Circ Genom Precis Med.* 2018; 11(4):e002069.

Unresolved Questions

- Is genotype-guided antiplatelet drug selection better than conventional therapy?
    - TAILOR-PCI: large, prospective trial of PCI patients randomized to receive conventional therapy (i.e., clopidogrel/no genotyping) versus *CYP2C19* genotype-guided antiplatelet selection (i.e., ticagrelor in CYP2C19 IM/PMs or clopidogrel in CYP2C19 UM/RM/NMs)

- For those already on antiplatelet therapy, is genotype-guided de-escalation of antiplatelet therapy noninferior to standard treatment?
    - CYP2C19 UM/RM/NM: change from more potent (prasugrel/ticagrelor) to less potent (clopidogrel) antiplatelet therapy

- What is the role of genotype-guided antiplatelet therapy for indications other than patients with ACS undergoing PCI?

Tailored Antiplatelet Therapy Following PCI (TAILOR-PCI).
https://clinicaltrials.gov/ct2/show/NCT01742117.

Question 3:

Warfarin Case: KG is a 66-year-old, non-Hispanic, African-American man (85 kg, 185 cm) with atrial fibrillation, hyperlipidemia, and gout. He is a nonsmoker and has no liver disease. His medications include atorvastatin 20 mg daily and allopurinol 100 mg daily. KG is being initiated on warfarin, with target INR of 2.5 (baseline INR=1.1). His genotyping results are as follows:

- – VKORC1 -1639 = A/G
- – CYP2C9*2 = C/C
- – CYP2C9*3 = A/A
- – CYP4F2*3 (V433M) = C/C

_____

Using the calculator available on www.warfarindosing.org, which of the following is the most appropriate estimated <u>therapeutic dose</u> of warfarin for this patient?
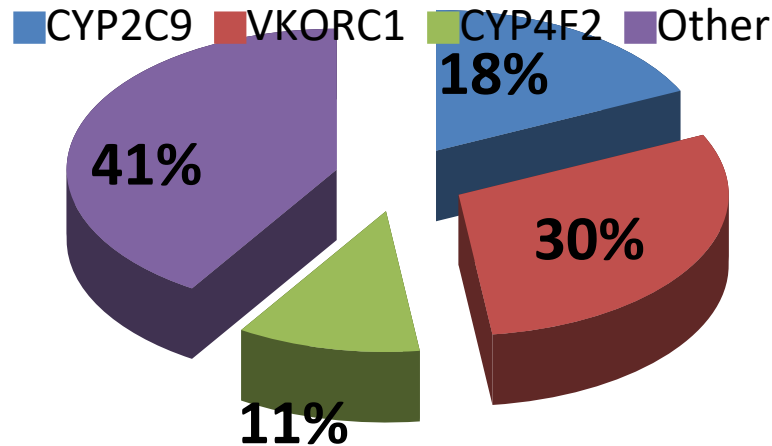
- A. 3 mg per day
- B. 4 mg per day
- C. 5 mg per day
- D. 6 mg per day

Question 3: Debrief

- Electronic warfarin dosing algorithms are available that include genetic and non-genetic variables
  - Example:
    www.warfarindosing.org

WARFARINDOSING www.WarfarinDosing.org

> Warfarin Dosing
> Clinical Trial
> Outcomes
> Hemorrhage Risk
> Patient Education
> Contact Us
> References
> Glossary
> About Us

User:
Patient: 0
Version 3.0
Build : May 14, 2016

Required Patient Information

Age: 66   Sex: Male ▼   Ethnicity: Non-Hispanic ▼
Race: African American or Black ▼
Weight: 187 lbs or 85 kgs   BSA 2.09
Height: (6 feet and 1 inches) or (185 cms)
Smokes: No ▼   Liver Disease: No ▼
Indication: Atrial fibrillation ▼
Baseline INR: 1.1   Target INR: 2.5   ☐ Randomize & Blind
Amiodarone/Cordarone® Dose: 0 mg/day
Statin/HMG CoA Reductase Inhibitor:
Atorvastatin/Lipitor®/Caduet® ▼
Any azole (eg. Fluconazole): No ▼
Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim: No ▼

Genetic Information

VKORC1-1639/3673: AG ▼
CYP4F2 V433M: CC (wildtype) ▼
GGCX rs11676382: Not available/pending ▼
CYP2C9*2: CC (wildtype) ▼
CYP2C9*3: AA (wildtype) ▼
CYP2C9*5: Not available/pending ▼
CYP2C9*6: Not available/pending ▼

☑ Accept Terms of Use

> ESTIMATE WARFARIN DOSE

Permission for use of this website graphic granted by Dr. Brian Gage (www.warfarindosing.org).

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Genetic Contribution to Warfarin Dose Variability

Other factors : age, weight, drug interactions, diet, smoking, race, concomitant diseases, other genetic factors

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

Warfarin Clinical Pharmacology

- **CYP2C9** metabolizes S-warfarin, the pharmacologically more active enantiomer of warfarin
  - CYP2C9*2 and CYP2C9*3 (decreased activity alleles) are associated with decreased warfarin metabolism, increased warfarin plasma exposure, and decreased warfarin dose requirements

- Warfarin inhibits **vitamin K epoxide reductase (VKOR)**. By inhibiting VKOR, warfarin prevents vitamin K recycling and prevents the production of functional vitamin K-dependent coagulation factors II, VII, IX and X
  - *VKORC1* variants (e.g., -1639G>A) are associated with decreased VKOR quantity and function, resulting in decreased warfarin dose requirements

- **CYP4F2** catalyzes the metabolism of vitamin K to an inactive form, thus removing it from the vitamin K cycle
  - CYP4F2*3 is associated with reduced CYP4F2 enzyme levels, reduced vitamin K metabolism, increased hepatic vitamin K levels, and higher warfarin dose requirements

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

Considerations for Persons of African Ancestry

- Frequencies of the CYP2C9*2, CYP2C9*3, and VKORC1 -1639A alleles are <u>LOW</u> in African Americans

- **CYP2C9*5, *6, *8, and *11** occur almost exclusively in persons of African descent
  - These variants are associated with decreased warfarin dose requirements
  - Combined frequency of 15-20% in African Americans

- **rs12777823 G>A**, located in the CYP2C cluster near the CYP2C18 gene, is also a predictor of lower warfarin dose requirements in African Americans
  - Frequency of >40% in African Americans

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

Does Genotyping Improve Outcomes?

- **COAG Trial:** Prospective trial of *CYP2C9*/*VKORC1* genotype-guided warfarin dosing vs. conventional dosing
  - No significant difference between groups for the primary endpoint, % time in therapeutic range over 30 days
  - Subgroup analysis showed African-Americans did worse with genotype-guided dosing

- **EU-PACT:** Prospective trial of *CYP2C9*/*VKORC1* genotype-guided warfarin dosing vs. conventional dosing
  - Compared with conventional dosing, genotype-guided dosing was significantly associated with:
    - Greater % time in therapeutic range
    - Fewer occurrences of INR ≥ 4
    - Shorter time to therapeutic INR

Kimmel SE et al. *N Engl J Med.* 2013; 369:2283-93.
Pirmohamed M et al. *N Engl J Med.* 2013; 369:2294-303.

Why the Discrepancy Between Studies?

- Different study designs
  - For example, no loading dose in COAG vs. loading dose in EU-PACT

- Different race/ethnic makeups
  - For example, COAG was more racially heterogeneous than EU-PACT

- Warfarin dosing algorithms used in these studies were derived mainly from European populations

- Variants common in Caucasians were the ones primarily genotyped in both studies
  - Can lead to overestimation of warfarin doses in African Americans

The Age of Algorithms

- If genetic information is available, warfarin dosing should be estimated using a PGx dosing algorithm

- Gage algorithm (www.warfarindosing.org)
    - Does not include *CYP2C9*8*, *CYP2C9*11* , or rs12777823

- International Warfarin Pharmacogenetics Consortium (IWPC) algorithm (https://www.pharmgkb.org/guideline/PA166104949)
    - Does not include *CYP4F2; CYP2C9*5*, **6*, **8*, or **11;* or rs12777823

- If you can't access an algorithm, a warfarin dosing table that includes genotype is superior to other approaches that ignore genetic information.
    - Example: Dosing table available in warfarin prescribing information

Gage BF et al. *Clin Pharmacol Ther.* 2008; 84:326-31.
International Warfarin Pharmacogenetics Consortium. *N Engl J Med.* 2009; 360:753-64.
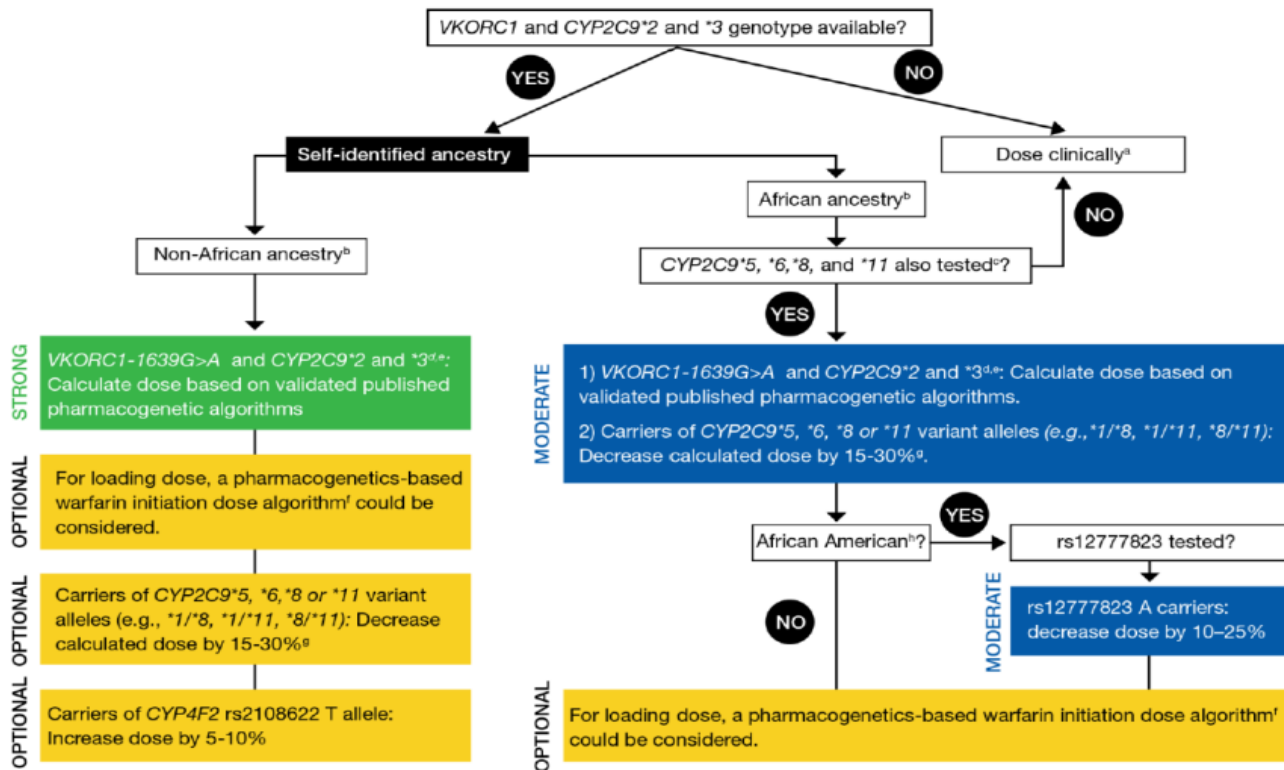
CPIC Recommendations: Warfarin

Figure used with permission from the Clinical Pharmacogenetics Implementation Consortium:
https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/.

Mind the Footnotes

A. "Dose clinically" means to dose without genetic information, which may include use of a clinical dosing algorithm or standard dose approach

B. Data strongest for European and East Asian ancestry populations and consistent in other populations

C. 45-50% of individuals with self-reported African ancestry carry *CYP2C9*5*, **6*, **8*, **11*, or rs12777823. If *CYP2C9*5*, **6*, **8*, and **11* were NOT tested, dose warfarin clinically. Note: these data are derived primarily from African Americans, who are largely from West Africa. It is unknown if the same associations are present for those from other parts of Africa.

D. Most algorithms are developed for the target INR 2-3

E. Consider an alternative agent in individuals with genotypes associated with CYP2C9 poor metabolism (*CYP2C9*3/*3*, **2/*3*, **3/*3*) or both increased sensitivity (*VKORC1 A/G* or *A/A*) and CYP2C9 poor metabolism

F. See the EU-PACT trial for PGx-based warfarin initiation (loading) dose algorithm with the caveat that the loading dose PGX algorithm has not been specifically tested or validated in populations of African ancestry

G. Larger dose reduction might be needed in variant homozygotes (i.e., 20-40%)

H. African American refers to individuals mainly originating from West Africa

Question 4:

Warfarin Case Continued: Our patient (KG) was also genotyped for the *CYP2C9*5, *6, *8*, and *11* alleles. He is homozygous wild-type for all of the variants with the exception of *8, for which his genotype is *1/*8. Based on this information, what is the best recommendation regarding warfarin dosing in this patient?

    A.   Use previous algorithm-calculated dose
    B.   Decrease algorithm-calculated dose by 15-30%
    C.   Decrease algorithm-calculated dose by 30-50%
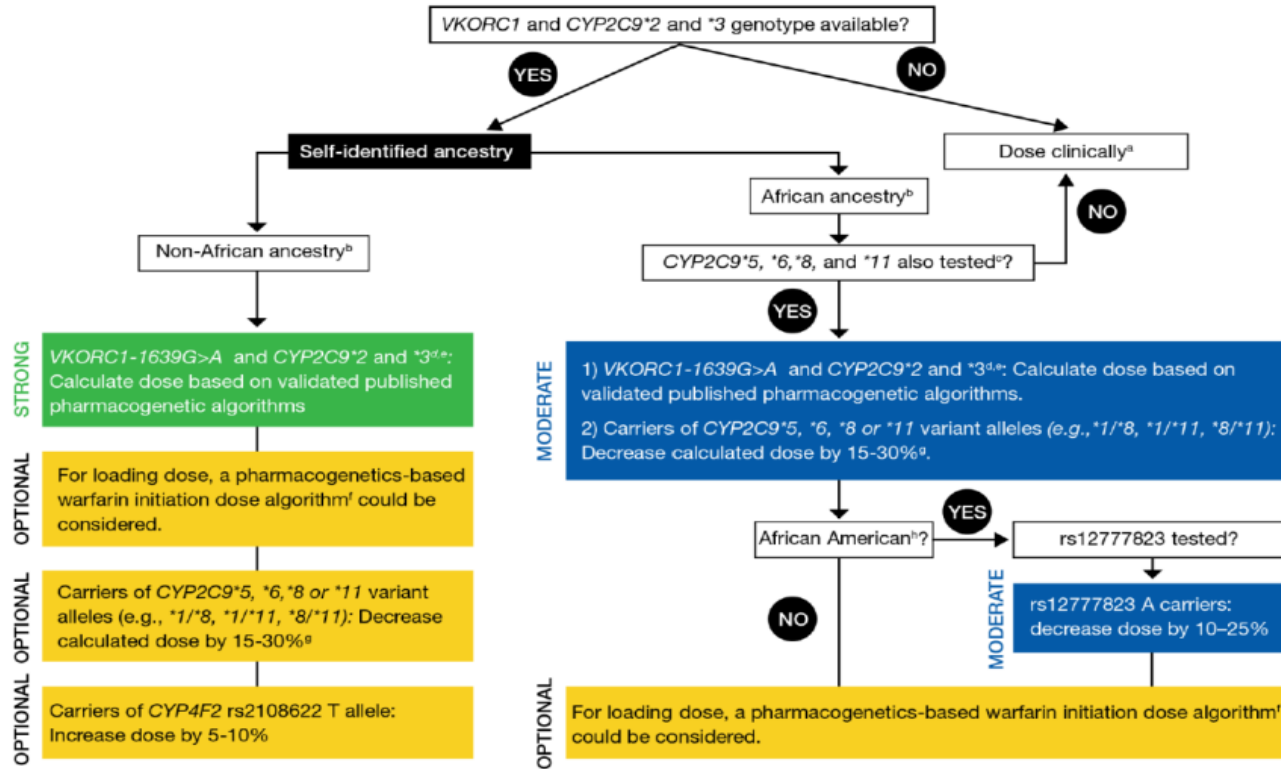   D.   Increase algorithm-calculated dose by 5-10%

Warfarin Case - Debrief

Figure used with permission from the Clinical Pharmacogenetics Implementation Consortium:
https://cpicpgx.org/guidelines/guideline-for-warfarin-and-cyp2c9-and-vkorc1/.

The GIFT Trial

- Prospective, randomized trial of older adults undergoing hip or knee arthroplasty to determine whether the use of genotype-guided instead of clinically-guided warfarin dosing during days 1-11 of therapy reduces adverse effects

- Used warfarindosing.org and genotyped for VKORC1, CYP2C9*2, CYP2C9*3, and CYP4F2*3 polymorphisms

- Primary composite endpoint of major bleeding, INR ≥ 4, venous thromboembolism, or death

- Genotype-guided dosing was associated with a 27% reduction in the risk of the primary composite endpoint compared with clinically-guided dosing (HR 0.73, 95%CI 0.56 to 0.95)
  - Differences driven primarily by improved INR control in the genotype-guided group

- Results provided promising evidence to support genotype-guided warfarin dosing
  - Twenty-six patients would need to be genotyped to prevent 1 "event," most commonly INR ≥ 4

Gage BF et a. *JAMA.* 2017; 318:1115-1124.

What's Next for Warfarin PGx?

- Cost-effectiveness studies

- Adaptation of PGx dosing algorithms to include African-specific *CYP2C9* alleles, *CYP4F2*, and rs12777823

- Continual evaluation and testing of the algorithms in other racial groups (e.g., North or East Africans)

- Implementation studies focusing on the integration of warfarin dosing algorithms, which include genetic and clinical factors, in the electronic health record (EHR)

Question 5:

Simvastatin Case: TA is a 52-year-old man recently diagnosed with hyperlipidemia (LDL=210 mg/dL). He has been taking simvastatin 40 mg daily for 3 months without any problems (current LDL is at goal). The patient recently had his DNA genotyped using a comprehensive PGx panel and his *SLCO1B1* genotype is *1A/*5. Based on this information, what is the best recommendation regarding statin therapy in this patient?

- A. Continue simvastatin 40 mg daily
- B. Decrease simvastatin to 20 mg daily
- C. Discontinue simvastatin and start pravastatin 40 mg daily
- D. Discontinue simvastatin and start fluvastatin 20 mg daily

Simvastatin

- *SLCO1B1* encodes the OATP1B1 transporter. OATP1B1 is located on the basolateral surface of hepatocytes and it facilitates drug uptake into the liver

- *SLCO1B1* c.521 T>C (p.V174A, rs4149056) is associated with decreased OATP1B1 function
  - c.521 C is contained within several <u>decreased function</u> haplotypes: *5, *15, and *17
  - Normal function alleles are designated as *1A or *1B

- *SLCO1B1* c.521C results in decreased simvastatin uptake in the liver and increased simvastatin concentrations in the plasma
  - Increased risk of concentration-dependent adverse effects, e.g., **myopathy**
  - In patients treated with simvastatin 80 mg/day, those with the polymorphic C/C genotype had 16.9 greater odds of myopathy than those with the reference T/T genotype (95% CI 4.7-61.1)

Link E et al. *N Engl J Med.* 2008; 359:789-99.

CPIC Guidelines

Dosing recommendations for **simvastatin** based on *SLCO1B1* genetics:

- Normal *SLCO1B1* function (2 normal function alleles, e.g., *1A/*1A)
  - Use desired simvastatin starting dose and adjust doses based on disease-specific guidelines [classification – strong]

- Decreased *SLCO1B1* function (1 normal function allele and 1 decreased function allele, e.g., *1A/*5)
  - Prescribe a lower simvastatin dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine creatine kinase (CK) surveillance [classification – strong]

- Poor *SLCO1B1* function (2 decreased function alleles, e.g., *5/*5)
  - Prescribe a lower simvastatin dose or consider an alternative statin (e.g., pravastatin or rosuvastatin); consider routine CK surveillance [classification – strong]

Note: FDA recommends against use of simvastatin 80 mg/day, unless already tolerated for 12 months

Clinical Pharmacogenetics Implementation Consortium:
https://cpicpgx.org/guidelines/guideline-for-simvastatin-and-slco1b1/.

Do the CPIC Guidelines Apply to Other Statins?

- Not all statins are transported by OATP1B1 to the same extent as simvastatin
  - Fluvastatin < rosuvastatin < pravastatin < atorvastatin < pitavastatin < simvastatin

- Some data suggest a relationship between rs4149056 and risk of myopathy for other statins, but generally the data are not as strong or consistent as for simvastatin

- Consider other factors in clinical decision making
  - For example: age, body weight, drug-drug interactions

- If a moderate-to-strong CYP3A4 inhibitor was prescribed to TA, it would be appropriate to consider a lower simvastatin dose or prescribe an alternative statin

Strategies for Clinical PGx Testing in Cardiology Practice

- Type of testing:
  - Single gene/few variants: e.g., CYP2C19*2, *3, *17
  - Multiple-gene/multiple-variant panel: e.g., 30 genes, 120 variants

- Timing of testing:
  - Reactive ("just-in-time"): conduct genetic testing when a medication is prescribed
  - Preemptive ("just-in-case"): conduct genetic testing months or years before it may be needed and store the information electronically for future use

- Location of testing:
  - Internal laboratory
  - External/commercial laboratory

- EHR considerations:
  - Ability to integrate genetic results into the EHR in a structured way
  - Availability of clinical decision support (CDS) tools

Strategies for Clinical PGx Testing in Cardiology Practice

- **Audience poll – what kind of testing do you do?**

- Reactive testing, particularly of only a few variants, is more straightforward
  - Turnaround time may be long; high per-variant cost
  - Ideally, results need to be integrated into the EHR so they can be used for other relevant drug-gene pairs

- Preemptive multiple-gene/multiple-variant panels are attractive for many cardiology applications because they obviate turnaround time issues
  - Need an EHR capable of housing the information
  - Need CDS tools to provide genetic results and recommendations to the provider at the time a relevant drug is prescribed
  - Cost per-variant is lower than for reactive testing, but often not reimbursed by insurers

Question 6:

A reactive PGx testing strategy would be most appropriate in which of the following patients?

A. A patient with peripheral arterial disease contemplating use of clopidogrel 75 mg daily
B. A patient taking warfarin 10 mg/day for two years with INR in goal range, prior to initiation of amiodarone
C. A heart transplant patient taking pravastatin 40 mg daily, prior to initiation of diltiazem
D. A patient six months post-PCI for STEMI who is nonadherent to ticagrelor 90 mg twice daily

KEY TAKEAWAYS

1) **KEY TAKEAWAY**
   Several clinically-actionable drug-gene pairs should be considered in cardiology practice – clopidogrel, warfarin, & simvastatin

2) **KEY TAKEAWAY**
   Pharmacists play an integral role in the application of PGx in cardiovascular clinical practice settings

3) **KEY TAKEAWAY**
   PharmGKB and CPIC are excellent resources for PGx information and its application in clinical practice guidelines

Questions?