Cardiovascular pharmacogenomics: ready for prime time?

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Researcher, Pharmacist, Montreal Heart Institute
April 17th 2011
Genetic Variation

What is a SNP?
Single Nucleotide Polymorphism
- can be rare or common in specific populations

Patient 1

Patient 2

Patient 3

Patient 4

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>A</th>
<th>C</th>
<th>T</th>
<th>G</th>
<th>A</th>
<th>C</th>
<th>T</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 2</td>
<td>A</td>
<td>C</td>
<td>T</td>
<td>G</td>
<td>C</td>
<td>C</td>
<td>T</td>
<td>G</td>
</tr>
<tr>
<td>Patient 3</td>
<td>A</td>
<td>C</td>
<td>T</td>
<td>G</td>
<td>A</td>
<td>C</td>
<td>T</td>
<td>G</td>
</tr>
<tr>
<td>Patient 4</td>
<td>A</td>
<td>C</td>
<td>T</td>
<td>G</td>
<td>A</td>
<td>C</td>
<td>T</td>
<td>G</td>
</tr>
</tbody>
</table>
Allele to Genotype

• An allele represents one of two or more versions of a genetic sequence at a particular location in the genome.

• The term **genotype** refers to the two **alleles** inherited for a particular gene.

Why personalized medicine?

- Variable response to CV drugs
- Adverse drug reactions
  - 4th to 6th cause of death
  - 2 million hospitalisations/year
  - Up to $160 billion/year
- The annual cost of CV medications in Canada surpassed $5 billion in 2006

Potential of Pharmacogenomics

All patients with same diagnosis

1. Non-responders and toxic responders
   - Treat with alternative dose

2. Responders and patients not predisposed to toxicity
   - Treat with conventional drug or dose
Cardiovascular drugs with Pgx information in their labels

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use PLAVIX safely and effectively. See full prescribing information for PLAVIX.

The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose. Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants. Consider these ranges in choosing the initial dose.

In all patients, subsequent dosage adjustments must be made based on the results of PT/INR determinations.17,18

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
<th>Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
<td>*1/*2</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
<td>3-4 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

†Ranges are derived from multiple published clinical studies. Other clinical factors (eg, age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1 -1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

CYP2C19 poor metabolizers. (2.3, 5.1)
Pgx of clopidogrel and warfarin, ready for prime time?

- It all depends on the evidence!
Warfarin
Warfarin: Narrow therapeutic window

Warfarin Metabolism and Activation Pathway

Candidate proteins in the pathway

- CYP1A1
- CYP1A2
- CYP3A4
- CYP2C9

Vitamin K Reductase

Warfarin

Oxidized Vitamin K → Reduced Vitamin K

CO₂ → O₂

γ-glutamyl carboxylase

Hypofunctional F. II, VII, IX, X
Protein C, S, Z

Functional F. II, VII, IX, X
Proteins C, S, Z

Gage et al. 2005
Association of CYP2C9 and VKORC1 and warfarin dosing

N = 369

$P < 0.001$


Coumarin derivatives and excessive anticoagulation


Required Patient Information

Age: [ ]  Sex: [Select-]  Ethnicity: [Select-]

Race: [Select-]

Weight: [ ] lbs  or  [ ] kgs

Height: [ ] feet and [ ] inches  or  [ ] cms

Smokes: [Select-]  Liver Disease: [Select-]

Indication: [Select-]

Baseline INR: [ ]  Target INR: [ ]  Randomize & Blind

Amiodarone/Cordarone® Dose: [ ] mg/day

Statin/HMG CoA Reductase Inhibitor: [Select-]

Anyazole (eg. Fluconazole): [Select-]

Sulfamethoxazole/Septra/Bactrim/Cotrim/Sulfatrim: [Select-]

Genetic Information

VKORC1-1639/3673: Not available/pending

CYP4F2 V433M: Not available/pending

GGCX rs11676382: Not available/pending

CYP2C9*2: Not available/pending

CYP2C9*3: Not available/pending

CYP2C9*5: Not available/pending

CYP2C9*6: Not available/pending
Results: Unadjusted 6 mo. hospitalization rates >=1 hospitalization per 100 patients/6months

Historical control (n=2688)
- 28% ↓
- 25.52

Intervention group (n=896)
- 27% ↓
- 18.45

All cause
- p-value <0.001

Bleed or thromboembolism
- 8.13
- 5.97
- 0.039

Intention to treat (ITT)

Randomized Trial of Genotype-Guided Versus Standard Warfarin Dosing in Patients Initiating Oral Anticoagulation

Jeffrey L. Anderson, MD; Benjamin D. Horne, PhD, MPH; Scott M. Stevens, MD; Amanda S. Grove, BS; Stephanie Barton, PharmD; Zachery P. Nicholas, BS; Samera F.S. Kahn, BS; Heidi T. May, MSPH; Kent M. Samuelson, MD; Joseph B. Muhlestein, MD; John F. Carlquist, PhD; for the Couma-Gen Investigators

Background—Pharmacogenetic-guided dosing of warfarin is a promising application of “personalized medicine” but has not been adequately tested in randomized trials.

Methods and Results—Consenting patients (n=206) being initiated on warfarin were randomized to pharmacogenetic-guided or standard dosing. Buccal swab DNA was genotyped for CYP2C9 *2 and CYP2C9 *3 and VKORCI C1173T with a rapid assay. Standard dosing followed an empirical protocol, whereas pharmacogenetic-guided dosing followed a regression equation including the 3 genetic variants and age, sex, and weight. Prothrombin time international normalized ratio (INR) was measured routinely on days 0, 3, 5, 8, 21, 60, and 90. A research pharmacist unblinded to treatment strategy managed dose adjustments. Patients were followed up for up to 3 months. Pharmacogenetic-guided predicted doses more accurately approximated stable doses (P<0.001), resulting in smaller (P=0.002) and fewer (P=0.03) dosing changes and INRs (P=0.06). However, percent out-of-range INRs (pharmacogenetic=30.7%, standard=33.1%), the primary end point, did not differ significantly between arms. Despite this, when restricted to wild-type patients (who required larger doses; P=0.001) and multiple variant carriers (who required smaller doses; P<0.001) in exploratory analyses, results (pharmacogenetic=29%, standard=39%) achieved nominal significance (P=0.03). Multiple variant allele carriers were at increased risk of an INR of ≥4 (P=0.03).

Conclusions—An algorithm guided by pharmacogenetic and clinical factors improved the accuracy and efficiency of warfarin dose initiation. Despite this, the primary end point of a reduction in out-of-range INRs was not achieved. In subset analyses, pharmacogenetic guidance showed promise for wild-type and multiple variant genotypes. (Circulation. 2007;116:2563-2570.)

Key Words: anticoagulation ■ clinical trial ■ genetics ■ pharmacogenetics ■ warfarin

Clopidogrel
Clopidogrel pharmacokinetics

http://www.pharmgkb.org/do/serve?objId=PA154424674&objCls=Pathway
Cytochrome P-450 Polymorphisms and Response to Clopidogrel

Balance of Efficacy and Safety

CV Death / MI / Stroke

- **Clopidogrel**
  - HR 0.81 (0.73-0.90)
  - **P=0.0004**
  - **NNT = 46**

- **Prasugrel**
  - HR 1.32 (1.03-1.68)
  - **P=0.03**
  - **NNH = 167**

TIMI Major

- **Clopidogrel**
  - Event rate: 12.1\%
- **Prasugrel**
  - Event rate: 9.9\%

NonCABG Bleeds

- **Clopidogrel**
  - Event rate: 1.8\%
- **Prasugrel**
  - Event rate: 2.4\%

Primary end point according to CYP2C19 genotype in patients receiving clopidogrel

Risk of stent thrombosis according to CYP2C19 genotype in patients receiving clopidogrel


![Graph showing the risk of stent thrombosis in carriers and noncarriers of the CYP2C19 genotype among patients receiving clopidogrel. The graph illustrates the cumulative incidence of stent thrombosis over time, with a significant difference between carriers and noncarriers (P=0.02).]
Replication???
Reduced-Function CYP2C19 Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI
A Meta-analysis

Mehilli, and

Department of Cardiology, Deutsches Herzzentrum and 1. Medizinische Klinik rechts der Isar, Technische Universität München, Munich, Germany

Received 3 October 2008; revised 16 December 2008; accepted 12 January 2009; online publish-ahead-of-print 4 February 2009
Can we do anything about this?

- Use of high-dose clopidogrel?
  - No Pgx data available from CURRENT-OASIS 7
  - Limited data from GRAVITAS study.
    - No improvement in reduced function CYP2C19 alleles
- Alternatives?
  - The effects of prasugrel and ticagrelor are independent of CYP2C19 genotype.
    - Genotype-guided use vs unselected use of these new agents in all patients?

Pgx of clopidogrel and warfarin, ready for prime time?

• It all depends on the evidence!
• … and your definition of “evidence”
« Evidence » - based medicine

- Marked differences in the evaluation of the “evidence”
  - American Heart Association, American College of Chest Physician
    - RCTs are at the center of the evaluation process.
  - Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
    - One (Level 2) or two (level 1) RCTs are required to provide convincing evidence of clinical utility.
  - Clinical Pharmacogenetics Implementation Consortium of the NIH’s Pharmacogenomics Research Network:
    - Level 1 evidence: the evidence includes consistent results from well-designed, well-conducted studies.
Pharmacology and Management of the Vitamin K Antagonists*

American College of Chest Physicians
Evidence-Based Clinical Practice Guidelines
(8th Edition)

Jack Ansell, MD; Jack Hirsh, MD; Elaine Hylek, MD, MPH; Alan Jacobson, MD; Mark Crowther, MD; and Cualtiero Palareti, MD

(CHEST 2008; 133:1605–1985)

At the present time, for patients beginning VKA therapy, without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing (Grade 2C).

Can RCTs of Pgx markers be performed?

- Yes!

Are they always necessary?

• No, not always.
• We use « markers » to personalize our selection of drugs, in the absence of RCTs:
  – Choice of an antibiotic in a patient treated with digoxin or warfarin (clarithromycin vs cefuroxime)
  – Choice of a beta-blocker in a patient with severe renal dysfunction (atenolol vs metoprolol)
Are they always necessary?

- Clopidogrel
  - RCTs not necessary when alternatives exist for a specific indication (prasugrel or ticagrelor in non-ST elevation ACS undergoing a PCI)
  - How ethical are such RCTs?
  - Becomes a question of the cost-effectiveness of the Pgx tests

- Would not be an issue if the information was readily available

2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction
Circulation – online before print
Are they always necessary?

- Different paradigms:
  - An alternative for personalizing the therapy is available
  - Monitoring of warfarin using the INR

**Statistical design of personalized medicine interventions: The Clarification of Optimal Anticoagulation through Genetics (COAG) trial**

Benjamin French, Jungnam Joo, Nancy L Geller, Stephen E Kimmel, Yves Rosenberg, Jeffrey L Anderson, Brian F Gage, Julie A Johnson, Jonas H Ellenberg, the COAG (Clarification of Optimal Anticoagulation through Genetics) Investigators
Cardiovascular pharmacogenomics: ready for prime time?

- For most CV drugs, no.
- **Warfarin**
  - Extensive data
  - RCTs are required to determine whether genotype-guided therapy is superior to INR-guided
- **Clopidogrel**
  - Testing for CYP2C19 should be considered for specific indications where alternatives are available
    - Cost-effectiveness?
    - Availability of point-of-care tests?
The future...

Clinical assessment incorporating a personal genome


« Prediction is very difficult, especially about the future. »

Niels Bohr, Danish physicist.
Summary

• Many Pgx associations reported in CV diseases
  – Few replicated associations with clinical outcomes (clopidogrel and warfarin)
  – The definition of « Evidence-based practice » in Pgx remains an issue of discussion
    • “Personalized evaluation of the evidence”
Is this clinically relevant?

Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease

Christoph Varenhorst¹*, Stefan James¹, David Erlinge², John T. Brandt³, Oscar Ö. Braun², Michael Man³, Agneta Siegbahn⁴, Joseph Walker⁵, Lars Wallentin¹, Kenneth J. Winters³, and Sandra L. Close³

¹Uppsala Clinical Research Center and Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden; ²Department of Cardiology, Lund University, Lund, Sweden; ³Eli Lilly and Company, Indianapolis, IN, USA; ⁴Coagulation Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden; and ⁵Daiichi Sankyo, Inc., Parsippany, NJ, USA

Received 26 September 2008; revised 12 March 2009; accepted 19 March 2009
TRITON – TIMI 38 Genex treatment interaction

# TRITON-TIMI 38 - Pgx of clopidogrel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Carriers of Reduced-Function Allele</th>
<th>Noncarriers of Reduced-Function Allele</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite primary efficacy outcome†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>46/395 (12.1)</td>
<td>83/1064 (8.0)</td>
<td>1.53 (1.07–2.19)</td>
<td>0.01</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>22/230 (10.0)</td>
<td>107/1226 (9.0)</td>
<td>1.09 (0.69–1.73)</td>
<td>0.41</td>
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<tr>
<td>CYP2B6</td>
<td>36/370 (10.0)</td>
<td>68/777 (9.0)</td>
<td>1.11 (0.74–1.67)</td>
<td>0.78</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>95/1130 (8.7)</td>
<td>14/151 (9.5)</td>
<td>0.89 (0.51–1.57)</td>
<td>0.69</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>5/59 (8.5)</td>
<td>95/1099 (8.9)</td>
<td>0.97 (0.40–2.39)</td>
<td>0.96</td>
</tr>
<tr>
<td>Major or minor bleeding‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>11/393 (2.9)</td>
<td>30/1061 (3.0)</td>
<td>1.01 (0.51–2.01)</td>
<td>0.98</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>7/229 (3.4)</td>
<td>34/1222 (2.9)</td>
<td>1.07 (0.47–2.40)</td>
<td>0.88</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>12/370 (3.3)</td>
<td>22/773 (3.1)</td>
<td>1.08 (0.53–2.18)</td>
<td>0.84</td>
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<tr>
<td>CYP3A5</td>
<td>31/1125 (3.0)</td>
<td>5/151 (3.3)</td>
<td>0.77 (0.30–1.97)</td>
<td>0.58</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>2/59 (3.4)</td>
<td>31/1094 (3.0)</td>
<td>1.29 (0.31–5.38)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Other biomarkers in CV diseases

• B-type natriuretic peptide (BNP) and NT-proBNP
  – Established diagnostic and prognostic markers of heart failure
    • Commonly used to enrich clinical
      – Others: Left ventricular ejection fraction, QRS duration
    • Cannot distinguish « responders » from « non responders », only low vs high-risk
  – Still no convincing data regarding BNP-guided therapy.
SNP (pronounce snip!), *is*...

A) One of the 3 Rice Krispies® characters (SNP, Crackle et Pop!)
B) A rap band from the 90’s
C) The abbreviation of *Single Nucleotide Polymorphisms*
Association Studies

Uses:
- Unrelated individuals
- Case and Controls
- Reconstruct ancestral haplotypes

Cardon and Bell, *Nature Reviews: Genetics*, 2001
Maladies mendéliennes vs maladies complexes

Maladies mendéliennes (ex: Fibrose kystique)

- Gène 1

L’expression de la maladie est sous le contrôle d’un gène à forte pénétrance

Maladies complexes
(ex: hypertension)

- Gène 1
- Gène 2
- Gène 3
- Gène 4
- Gène 5

Environnement

Plusieurs facteurs génétiques et environnementaux conférant un faible risque sont impliqués.
GWAS of clopidogrel PD

Figure 2. Genome-Wide Association Study of Adenosine Diphosphate–Stimulated Platelet Aggregation in Response to Clopidogrel

CYP2C18-CYP2C19-CYP2C9-CYP2C8 cluster
Is this clinically relevant?

Cytochrome P450 Genetic Polymorphisms and the Response to Prasugrel
Relationship to Pharmacokinetic, Pharmacodynamic, and Clinical Outcomes

Jessica L. Mega, MD, MPH; Sandra L. Close, PhD; Stephen D. Wiviott, MD; Lei Shen, PhD; Richard D. Hockett, MD; John T. Brandt, MD; Joseph R. Walker, PharmD; Elliott M. Antman, MD; William L. Macias, MD, PhD; Eugene Braunwald, MD; Marc S. Sabatine, MD, MPH

Background—Both clopidogrel and prasugrel require biotransformation to active metabolites by cytochrome P450 (CYP) enzymes. Among persons treated with clopidogrel, carriers of reduced-function CYP2C19 alleles have significantly lower levels of active metabolite, diminished platelet inhibition, and higher rates of adverse cardiovascular events. The effect of CYP polymorphisms on the clinical outcomes in patients treated with prasugrel remains unknown.

Methods and Results—The associations between functional variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to prasugrel were tested in 238 healthy subjects. We then examined the association of these genetic variants with cardiovascular outcomes in a cohort of 1466 patients with acute coronary syndromes allocated to treatment with prasugrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38 trial. Among the healthy subjects, no significant attenuation of the pharmacokinetic or the pharmacodynamic response to prasugrel was observed in carriers versus noncarriers of at least 1 reduced-function allele for any of the CYP genes tested (CYP2C19, CYP2C9, CYP2B6, CYP3A5, and CYP1A2). Consistent with these findings, in subjects with acute coronary syndromes treated with prasugrel, no significant associations were found between any of the tested CYP genotypes and risk of cardiovascular death, myocardial infarction, or stroke.

Conclusions—Common functional CYP genetic variants do not affect active drug metabolite levels, inhibition of platelet aggregation, or clinical cardiovascular event rates in persons treated with prasugrel. These pharmacogenetic findings are in contrast to observations with clopidogrel, which may explain, in part, the different pharmacological and clinical responses to the 2 medications. (Circulation. 2009;119:2553-2560.)
Clopidogrel and the Reduced-Function CYP2C19 Genetic Variant
A Limited Piece of the Overall Therapeutic Puzzle

Valentin Fuster, MD, PhD
Joseph M. Sweeney, MD

JAMA. 2010;304:1839-1840.

translate into clinical practice. Based on the most recent information, 4 critical issues require careful attention. First, CYP219*2 and CYP2C19*3 are reduced-function alleles
Plan of the presentation

- Genetics 101
- Do we need personalized medicine?
- Selected examples:
  - Warfarin
  - Clopidogrel
- Ready for prime time?
- Summary and conclusions
“Oh, I forgot,.... here's my genome ...”
Variant alleles frequencies differ significantly between populations.

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Variant alleles</th>
<th>Alteration in function</th>
<th>White</th>
<th>Black</th>
<th>Asian</th>
<th>Chinese</th>
<th>Japanese</th>
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<tbody>
<tr>
<td>CYP2C8 (refs. 21,22)</td>
<td>Repaglinide</td>
<td>*2</td>
<td>0.4</td>
<td>18</td>
<td>—</td>
<td>—</td>
<td>0</td>
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<tr>
<td></td>
<td>Paclitaxel</td>
<td>*3</td>
<td>13;15</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*4</td>
<td>7.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>CYP2C9 (refs. 22–24)</td>
<td>Warfarin</td>
<td>*2</td>
<td>10;13.3;8–14.9</td>
<td>3;1–3.6</td>
<td>Absent or rare</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Tolbutamide</td>
<td>*3</td>
<td>5.6;8;3.3–15.3</td>
<td>1;0.5–2</td>
<td>—</td>
<td>2.5;1.7–4.9</td>
<td>3.5b;1.1–6.8</td>
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<tr>
<td></td>
<td></td>
<td>*5</td>
<td>0</td>
<td>3</td>
<td>0a</td>
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<td></td>
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<tr>
<td>CYP2C19 (refs. 23,24)</td>
<td>Meprazole</td>
<td>*2</td>
<td>Nonfunctional</td>
<td>13.6;15</td>
<td>17</td>
<td>—</td>
<td>29.7</td>
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<tr>
<td></td>
<td>Diazepam</td>
<td>*3</td>
<td>Nonfunctional</td>
<td>0;&lt;1</td>
<td>&lt;1</td>
<td>—</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*17</td>
<td>Increased</td>
<td>20.1</td>
<td>—</td>
<td>—</td>
<td>0.5</td>
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<td>CYP2D6c (ref. 25)</td>
<td>Atomoxetine</td>
<td>PM</td>
<td>Nonfunctional</td>
<td>7.7</td>
<td>1.9–7.3</td>
<td>0–4.8</td>
<td>&lt;1.0</td>
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<tr>
<td></td>
<td>Codeine</td>
<td>IM</td>
<td>Decreased</td>
<td>1–2</td>
<td>—</td>
<td>51</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>UM</td>
<td>Increased</td>
<td>4.3</td>
<td>4.9</td>
<td>—</td>
<td>0.9</td>
</tr>
</tbody>
</table>

The Treatment of CV diseases;
"A One Size Fits All Approach"

• The efficacy and safety of drugs are established in populations.
• In practice, we treat individuals.


Pharmacogenomics is complex (genetics)