Cardiovascular pharmacogenomics: ready for prime time?

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Plan of the presentation

- Overview of pharmacogenomics
- Warfarin and clopidogrel pharmacogenomics, ready for prime time?
- Conclusion
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 in the US:
  – 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 or agent

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td>Atorvastatin</td>
<td><em>LDL receptor</em></td>
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<tr>
<td>Carvedilol</td>
<td><em>CYP2D6</em></td>
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<tr>
<td>Clopidogrel</td>
<td><em>CYP2C19</em></td>
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<tr>
<td>Isosorbide dinitrate and Hydralazine</td>
<td><em>NAT1; NAT2</em></td>
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<tr>
<td>Prasugrel</td>
<td><em>CYP2C19</em></td>
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<tr>
<td>Pravastatin</td>
<td><em>ApoE2</em></td>
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<tr>
<td>Propafenone</td>
<td><em>CYP2D6</em></td>
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<tr>
<td>Propranolol</td>
<td><em>CYP2D6</em></td>
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<td>Quinidine</td>
<td><em>CYP2D6</em></td>
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<tr>
<td>Timolol</td>
<td><em>CYP2D6</em></td>
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<tr>
<td>Ticagelors</td>
<td><em>CYP2C19</em></td>
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<tr>
<td>Warfarin</td>
<td><em>CYP2C9, VKORC1</em></td>
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Pgx of clopidogrel and warfarin, ready for prime time?

• It all depends on the evidence!
Warfarin
Association of CYP2C9 and VKORC1 and warfarin

• Many clinical studies have associated CYP2C9 and VKORC1 with:
  – Warfarin dosing requirements
  – The risk for overanticoagulation and bleeding

• Nevertheless, data from randomized studies demonstrating the clinical utility of genotype-guided warfarin prescribing is limited.

**Warfarin Dosing**

**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
Clopidogrel
Clopidogrel pharmacokinetics

http://www.pharmgkb.org/do/serve?objId=PA154424674&objCls=Pathway
Patient undergoing PCI treated with clopidogrel who are carrying a reduced-function CYP2C19 allele (e.g. *2 or *3) have a higher risk of cardiovascular events, including stent thrombosis.

A meta-analysis by Mega indicated that carriers of two reduced-function allele may have a near four-fold increase in the risk of stent thrombosis.

Can we do anything about this?

- Use of high-dose clopidogrel?
  - In stable CAD patients (n = 333), clopidogrel 225-300 mg/day produced similar levels of platelet reactivity in CYP2C19*2 heterozygotes than 75 mg in non carriers.
    - But not in homozygotes!
  - 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-guided use vs unselected use of these new agents?

PgX of clopidogrel and warfarin, ready for prime time?

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

• 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.
CYP2C19 and AHA/ACC

• “Genotyping for CYP2C19 for a loss of function variant in patients with UA/NSTEMI (or after ACS with PCI) on lopidogrel therapy might be considered if results of testing may alter management (IIIB recommendation; LOI:C)”
The Clinical Pharmacogenetics Implementation Consortium of the NIH Pharmacogenomics Research Network - Clopidogrel

ACS/PCI patient population

Initiate antiplatelet therapy with standard dosing of clopidogrel

CYP2C19 testing if genotype is unknown

UM (*1/*17, *17/*17)
Standard dosing of clopidogrel
Strong

EM (*1/*1)
Standard dosing of clopidogrel
Strong

IM (*1/*2)
Prasugrel or other alternative therapy*
Moderate

PM (*2/*2)
Prasugrel or other alternative therapy*
Strong

* If not contraindicated

Warfarin pharmacogenomics and ACCP

- “For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).”

Guyatt GH et al. Chest 2012 141:2 suppl 7S-47S.
The recommendations for dosing based on genotype contained herein are rated as level A, or strong, (...) However, (...) the impact on clinical outcomes is unknown. »
If you knew one of your patients undergoing PCI with stenting was a *CYP2C9*2/*2, would you...

A. ... prescribe clopidogrel?
B. ... prescribe clopidogrel and monitor using a platelet function test?
C. ... prescribe prasugrel?
D. ... prescribe ticagrelor?
E. ... feel a bit nostalgic about the good ‘ol times and prescribe ticlopidine?
If you had access to CYP2C9 and VKORC1 genotype when you initiate warfarin in a patient, would you...

A. ... prescribe warfarin as per your usual practice
B. ... prescribe warfarin dosing based on a clinical and genetic algorithm
C. ... prescribe dabigatran
D. I’m hungry, finish already, lunch is about to be served!
Can RCTs of Pgx markers be performed?

- Yes!
  - Example: HLA-B*5701 screening for hypersensitivity to abacavir.

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)
  – Becomes a question of the cost-effectiveness of the Pgx tests
    • Would not be an issue if the information was readily available
      – Do we have RCTs of all drugs for which we adjust dosage based on renal function?
Are they always necessary?

- Different paradigms:
  - An alternative for personalizing the therapy is available
    - Monitoring of warfarin using the INR
  - The Pgx test leads to withholding treatment (or providing a less effective treatment):
    - Beta-blockers appear ineffective in heart failure patients who are *ADRB1* Gly389 carriers
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 following PCI as alternatives are available
    • Cost-effectiveness?
      – Not readily available (or low cost) as creatinine clearance or concomitant meds.
    • Availability of point-of-care tests?