Therapeutic Substitution: Implications for Cardiovascular Therapy

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The interchange of one agent in the same therapeutic class for another. They are not identical compounds, but may be used for similar clinical effects.

This compares to *generic substitution* which allows for the exchange of one agent which is the same chemical as another.
Used as a measure of drug safety, the therapeutic index is the difference in doses needed for the desired effect and the dose that produces unwanted and possibly dangerous side effects. This relationship, termed the therapeutic index, is defined as the ratio $LD_{50} : ED_{50}$. In general, the narrower this margin, the more likely it is that the drug will produce unwanted effects. Classic examples are digitalis and warfarin.
Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Systematic Review and Meta-analysis

…it is reasonable for physicians and patients to rely on FDA bioequivalence rating as a proxy for clinical equivalence among a number of important cardiovascular drugs, even in higher-risk contexts such as warfarin. These findings also support the use of formulary designs aimed at stimulating appropriate generic drug use.

Figure 2. Drug Class and Aggregate Meta-analyses of Trials Comparing Generic and Brand-Name Drugs Used in Cardiovascular Disease

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>No. Studies</th>
<th>Subjects</th>
<th>Effect Size (95% CI)</th>
<th>Favors Generic</th>
<th>Favors Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>6</td>
<td>135</td>
<td>0.00 (-0.24 to 0.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>10</td>
<td>135</td>
<td>-0.03 (-0.28 to 0.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>4</td>
<td>242</td>
<td>0.00 (-0.53 to 0.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>2</td>
<td>50</td>
<td>0.21 (-0.19 to 0.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>1</td>
<td>23</td>
<td>-0.09 (-0.68 to 0.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>2</td>
<td>71</td>
<td>-0.25 (-0.62 to 0.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α-Blockers</td>
<td>1</td>
<td>43</td>
<td>0.06 (-0.37 to 0.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>4</td>
<td>138</td>
<td>-0.09 (-0.33 to 0.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>30</td>
<td>837</td>
<td>-0.03 (-0.15 to 0.08)</td>
<td></td>
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</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; CI, confidence interval.

*Heterogeneous agents in a class
Challenges of therapeutic substitution of drugs for economic reasons: focus on CVD prevention

Although population studies support therapeutic substitution in principle, there is evidence that substitution may not always result in therapeutic equivalence in individual patients, with the consequent potential for greater risks of decreased efficacy and/or increased safety concerns.

Table 1. The relationship between a reference formulation (A) and potential substitutions (B and C).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bioavailability</th>
<th>% Ratio to A</th>
<th>% Ratio to B</th>
<th>% Ratio to C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>100%</td>
<td>125%</td>
<td>83%</td>
</tr>
<tr>
<td>B</td>
<td>80</td>
<td>80%</td>
<td>100%</td>
<td>67%</td>
</tr>
<tr>
<td>C</td>
<td>120</td>
<td>120%</td>
<td>150%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Examples: Is 10mg oral timolol = 10mg propranolol? Is hydrochlorothiazide an acceptable alternative to lasix?
...there are 9 different calcium channel blockers that are approved for clinical use in the United States...

Based on specific Ca++ channels, these are broken down into sub-classes known as dihydropyridines phenylalkylamines and benzothiazepines

...Any attempt to lump all calcium channel blockers into a single class is an oversimplification and obscures important observations with therapeutic consequences...

_Circulation_. 2003;108:2604 –2607
Case Study: Lipid Management

Patient A present with a history of heart disease and multiple risk factors. We need to manage their lipids.

Lipid-modifying agents include 7 statins, cholestryamine, niacin, ezetimibe, gemfibrozil, fenofibrate, colesevelam, omega 3 fatty acids (fish oils) all which various effects on LDL-C, HDL-C, and Triglycerides

How do we proceed clinically?
EBM: Levels of evidence

Benefit of Treatment

Class I: Conditions for which there is evidence and/or general agreement that a given treatment is useful and effective

Class II: Conditions for which there is evidence and/or a divergence of opinion about the usefulness/efficacy of a treatment

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy

Strength of evidence

Level A: data derived from multiple randomized controlled trials

Level B: data derived from single randomized or non-randomized studies

Level C: data derived from expert opinion

Adapted from AHA/ACC
http://www.emedmag.com/images/038100020c.jpg
Focus on LDL-Cholesterol as a CV risk determines the emphasis on a statin drug followed by resin, colesevalam, ezetimibe, 

How about HDL-C? The HDL-C value impacts the intensity of LDL-C treatment. 

Triglycerides add complexity to the treatment and the choices of: omega 3 fatty acids (fish oil), niacin, or a fibrate.
Focus on LDL-Cholesterol as a CV risk determines the emphasis on a statin drug\textsuperscript{1a} followed by resin\textsuperscript{1b}, colesevelam\textsuperscript{1c}, ezetimibe\textsuperscript{1c},

Unless high triglycerides add to the profile, then the choices are

omega 3 fatty acids\textsuperscript{2a} (fish oil), niacin\textsuperscript{2b}, or a fibrate\textsuperscript{2}

\textsuperscript{1} = evidence based ranking scores
...the practice of therapeutic substitution is both more challenging and less scientifically sound...

...“extrapolations are not accepted by regulatory agencies” (ie, the US Food and Drug Administration). Why should extrapolations be accepted by hospital or health plan pharmacy and therapeutic committees?

*Circulation* 2003;108;2611-2612
The AAFP strongly opposes any legislative or regulatory effort at the state or federal level to permit therapeutic substitution, that is the substitution of a therapeutic alternate, a drug product containing a different pharmaceutical moiety but which is of the same therapeutic or pharmacologic class. (1988) (2008)