CV Drug Interactions: Caution Required

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Presenter Disclosure Information

Financial Disclosure: I do not have a financial relationship with any commercial entity which may represent, in perception or reality, a conflict of interest in the context of this presentation.
Objectives

- List the types of drug interactions that may occur
- Explain the difference between a pharmacokinetic (PK) and pharmacodynamic (PD) drug-drug interaction
- Identify common CV drug interactions
Audience Question

Which of the following statements is true?

A. Drugs must physically interact with each other to cause a drug-drug interaction

B. If food slows down the rate of absorption of a drug, but not the extent, it is not considered a drug interaction

C. If a drug can worsen a patient’s comorbid medical condition, one can say a drug interaction exists
Types of Drug Interactions

- Drug-Drug
- Drug-Nutrient
- Drug-Disease
Drug-Drug Interactions

When one drug affects the pharmacokinetics, pharmacodynamics, efficacy, or toxicity of another drug

The drugs do not need to physically interact
## Types of Drug-Drug Interactions

### Pharmacokinetic
- Affects absorption, distribution, excretion, or metabolism
- Magnesium and aluminum hydroxide antacids, iron, milk, and calcium supplements all decrease absorption of ciprofloxacin
- (separate by 6 hours before or 2 after)

### Pharmacodynamic
- Modulates a drug's effect at a given plasma concentration
- ASA and clopidogrel – increased risk for bleeding (risk vs benefit)
Pharmacokinetic Interactions

Drug interactions traditionally thought to occur because of changes in hepatic metabolism

- 3A4 subfamily of cytochrome P450 (CYP-450) system
- Inhibitors include azole antifungals, macrolide antibiotics, cyclosporine, tacrolimus, and calcium channel antagonists
- Inducers include phenytoin, rifampin, St. John’s wort

Pharmacokinetic Interactions

Drug interactions also occur because of interactions with transporter proteins

Protein p-glycoprotein (P-gp)

- Intestine, P-gp acts to pump drug from columnar epithelial cells to the intestinal lumen
- When P-gp activity is inhibited, more drug is available to distribute to the systemic circulation

Multi-drug resistant protein 2

Organic anion transporting polypeptide (OATP2)

Pharmacotherapy. 2006;26(11):1601-1607
Types of Drug-Nutrient Interactions

Drugs affect nutritional status

- Alteration of nutrient absorption, metabolism, utilization, or excretion

Nutrients affect drug status

- Food, beverages, mineral/vitamin supplements can affect absorption, metabolism, utilization or excretion of drugs
Drug-Disease Interactions

- **When a drug interacts or interferes with a disease or condition the patient has**
  - Decongestants in hypertensive patients
  - Aspirin in patients with peptic ulcer disease
  - 1st generation calcium channel blockers in patients with heart failure with reduced ejection fraction
The Top 10

Derived from drug interactions that:

• Involve newer cardiovascular agents
• Can significantly affect the morbidity and/or mortality of a cardiovascular patient
• Are often not recognized or underappreciated
• Are likely to be encountered during clinical practice
Which of the following oral anticoagulants has/have a drug-nutrient interaction

I. Warfarin
II. Rivaroxaban 10mg dose
III. Rivaroxaban 20mg dose
IV. Dabigatran

A. I and II
B. I and III
C. I, II, III
D. I, III, and IV
Drug-nutrient interactions with oral anticoagulants

Warfarin
- Green Leafy Vegetables
- Vitamin K

Rivaroxaban
- Bioavailability is dose-dependent
- Doses > 10mg affected by food
- 15-20mg doses should be taken with evening meal

Dabigatran
- Take with a full glass of water
Audience Question

Of the two newer anti-hyperlipidemic agents which is a drug interaction nightmare?

A. Lomitapide
B. Mipomersen
C. Both
D. Neither
Number 9

Selected drug-drug interactions with lomitapide

**Contraindicated with strong or moderate CYP3A4 inhibitors**
- GFJ, diltiazem, verapamil, protease inhibitors

**Reduce does for weak CYP3A4 inhibitors**
- alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, ticagrelor, zileuton
Selected drug-drug and drug-nutrient interactions with lomitapide

- Reduce simvastatin (lova) dose by 50%
- Warfarin (INR increases 22%)
- Reduce dose of concomitant P-gp substrates
- Take with glass of water/avoid grapefruit
- Take on an empty stomach
- Requires daily supplementation with vitamin E, linoleic acid, ALA, EPA, DHA
Audience Question

Which of the following pose a significant drug-drug interaction when administered with ranolazine?

A. Digoxin
B. Atorvastatin
C. Verapamil
D. Digoxin and verapamil
Select drug-drug interactions with ranolazine

- Substrate of P-gp, CYP3A, CYP2D6 (lesser)
- Weak inhibitor CYP3A, moderate inhibitor of CYP2D6 and P-gp, inhibitor of OCT2
- Limit doses of simvastatin to 20mg daily
- Adjust digoxin dose if needed (increases concentrations by 50%)
- Limit ranolazine to 500mg twice daily if receiving moderate CYP3A inhibitors (e.g. diltiazem, verapamil)
Audience Question

Which of the following statements is true?

A. Carvedilol does not have a significant drug-nutrient interaction

B. Vorapaxar and prasugrel BOTH have the same drug-disease state interaction

C. Cilostazol does not have a drug-disease interaction with heart failure
Select drug interactions with carvedilol

- Drug-nutrient
  - Administer with food to reduce risk of hypotension
  - Food slows rate, but not extent, of absorption

- Drug-drug
  - Digoxin trough concentrations increase by about 15%
Drug-disease interaction with cilostazol

- Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III
- Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure
- Contraindicated in patients with heart failure of any severity (Class I-IV)
Drug-disease interaction with prasugrel

- History of prior transient ischemic attack (TIA) or stroke
- In TRITON TIMI-38 patients with a history of TIA or ischemic stroke (> 3 months) had a rate of thrombotic stroke of 4.2% and intracranial hemorrhage of 2.3% versus 1.2% on clopidogrel.
- If no history of TIA or ischemic stroke the rates were similar.
- Prasugrel is contraindicated in patients with a history of TIA or stroke and should generally have therapy discontinued if they experience one while on the drug.
Drug-disease interaction with vorapaxar (protease-activated receptor-1 antagonist)

- History of prior stroke
  - In the TRA 2P - TIMI 50 study the rate of intracranial hemorrhage was 2.4% versus 0.9% in the placebo group ($p < 0.001$)
  - Translates to a 0.8%/year absolute risk versus 0.2%/year
- Vorapaxar is contraindicated in patients with a history of TIA or stroke and should generally have therapy discontinued if they experience one while on the drug
Audience Question

Which of the following is true about amiodarone?

I. Amiodarone is a weak CYP3A4 inhibitor
II. Amiodarone is a strong CYP3A4 inhibitor
III. Amiodarone is a P-gp inhibitor

A. I only
B. II only
C. I and III
D. II and III
Selected drug-drug interactions with amiodarone (a combined P-gp and weak-moderate CYP3A4 inhibitor)

- Digoxin (reduce dose by 50%)
- Statins
  - Limit dose of simvastatin to 20mg
  - Consider non CYP3A4 metabolized statins
- Warfarin (reduce dose by up to 50%)
- Target specific oral anticoagulants?
## Selected Statin Pharmacokinetics

<table>
<thead>
<tr>
<th>Metabolism (of lactone or acid form)</th>
<th>Atorva</th>
<th>Fluva</th>
<th>Lova</th>
<th>Prava</th>
<th>Rosuva</th>
<th>Simva</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 (CYP2C8)</td>
<td>CYP3A4</td>
<td>CYP2C9</td>
<td>CYP3A4</td>
<td>Sulfation (CYP3A4)</td>
<td>CYP2C9, minor (CYP2C19)</td>
<td>CYP3A4 CYP2C8</td>
</tr>
<tr>
<td>OATP2 substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>BCRP substrate</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>P-gp (MDRP1) substrate</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes, acid</td>
</tr>
</tbody>
</table>

Audience Question

• Which of the following is correct?
  1. Entresto is not associated with any drug-drug interactions
  2. Entresto could be administered with aliskiren
  3. Entresto should not be administered to a patient with ACE inhibitor angioedema
  4. Entresto could be administered with spironolactone
Number 2

Selected drug-drug interactions with Entresto (sacubitril, valsartan)

- Avoid combo with aliskiren especially in diabetics
- Absolute contraindication in anyone with hx of angioedema (ACE I or ARB or other)
- Concomitant use with K+sparing diuretics or K+ supplement can result in hyperkalemia
- Caution with NSAID use – risk worsening renal fxn (sacubitril)
- Lithium toxicity observed (ARB)
Audience Question

Have you taken a NSAID (other than aspirin at a cardioprotective dose) in the:

A. Last 24 hours
B. Past week
C. Past month
D. Past 3 months
E. None in over 3 months
Number 1
Drug-disease interaction between NSAIDs and cardiovascular disease

- Sodium retention
- Fluid retention
- Renal toxicity
- Gastrointestinal toxicity
- Thrombotic risk
- Drug-drug interactions (diuretics, ACE inhibitors, aldosterone antagonists)
### NSAIDs and Heart Failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Death</th>
<th>CHF</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen any use</td>
<td>1.22</td>
<td>1.18</td>
<td>1.52</td>
</tr>
<tr>
<td>&lt;500 mg/day</td>
<td>0.88</td>
<td>1.18</td>
<td>1.47</td>
</tr>
<tr>
<td>&gt;500 mg/day</td>
<td>1.97</td>
<td>1.18</td>
<td>1.62</td>
</tr>
<tr>
<td>Celecoxib any use</td>
<td>1.75</td>
<td>1.24</td>
<td>1.38</td>
</tr>
<tr>
<td>&lt;200 mg/day</td>
<td>1.34</td>
<td>1.24</td>
<td>1.33</td>
</tr>
<tr>
<td>&gt;200 mg/day</td>
<td>2.72</td>
<td>1.26</td>
<td>1.50</td>
</tr>
<tr>
<td>Ibuprofen any use</td>
<td>1.31</td>
<td>1.16</td>
<td>1.33</td>
</tr>
<tr>
<td>&lt;1200 mg/day</td>
<td>0.99</td>
<td>1.16</td>
<td>1.31</td>
</tr>
<tr>
<td>&gt;1200 mg/day</td>
<td>2.83</td>
<td>1.18</td>
<td>1.47</td>
</tr>
<tr>
<td>Other NSAID</td>
<td>1.28</td>
<td>1.27</td>
<td>1.32</td>
</tr>
</tbody>
</table>

## Non-Selective NSAIDs and CV Risk

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Outcome</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Versus placebo or no treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>Vascular events</td>
<td>0.92</td>
<td>0.67–1.26</td>
</tr>
<tr>
<td>Meta-analysis of RCTs(^2)</td>
<td>CV events, mostly MI</td>
<td>0.97</td>
<td>0.87–1.07</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Vascular events</td>
<td>1.51</td>
<td>0.96–2.37</td>
</tr>
<tr>
<td>Meta-analysis of RCTs(^2)</td>
<td>CV events, mostly MI</td>
<td>1.07</td>
<td>0.97–1.18</td>
</tr>
<tr>
<td>Registry(^4)</td>
<td>Recurrent MI</td>
<td>1.25</td>
<td>1.07–1.46</td>
</tr>
<tr>
<td>Registry(^4)</td>
<td>Mortality</td>
<td>1.50</td>
<td>1.36–1.67</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Vascular events</td>
<td>1.63</td>
<td>1.12–2.37</td>
</tr>
<tr>
<td>Meta-analysis of RCTs(^2)</td>
<td>CV events, mostly MI</td>
<td>1.40</td>
<td>1.16–1.70</td>
</tr>
<tr>
<td>Registry(^4)</td>
<td>Recurrent MI</td>
<td>1.54</td>
<td>1.23–1.93</td>
</tr>
<tr>
<td>Registry(^4)</td>
<td>Mortality</td>
<td>2.40</td>
<td>2.09–2.80</td>
</tr>
<tr>
<td><strong>Versus selective COX-2 inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>Vascular events</td>
<td>0.64</td>
<td>0.49–0.83</td>
</tr>
<tr>
<td>Meta-analysis of RCTs(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any non-naproxen NSAID (primarily diclofenac or ibuprofen)</td>
<td>Vascular events</td>
<td>1.14</td>
<td>0.89–1.45</td>
</tr>
</tbody>
</table>

Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction
A Nationwide Cohort Study

Anne-Marie Schjerning Olsen, MB; Emil L. Fosbøl, MD, PhD; Jesper Lindhardsen, MD; Fredrik Folke, MD, PhD; Mette Charlot, MD; Christian Selmer, MD; Morten Lamberts, MD; Jonas Bjerring Olesen, MD; Lars Køber, MD, DMSc; Peter R. Hansen, MD, PhD, DMSc; Christian Torp-Pedersen, MD, DMSc; Gunnar H. Gislason, MD, PhD

Background—Despite the fact that nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated among patients with established cardiovascular disease, many receive NSAID treatment for a short period of time. However, little is known about the association between NSAID treatment duration and risk of cardiovascular disease. We therefore studied the duration of NSAID treatment and cardiovascular risk in a nationwide cohort of patients with prior myocardial infarction (MI).

Methods and Results—Patients ≥30 years of age who were admitted with first-time MI during 1997 to 2006 and their subsequent NSAID use were identified by individual-level linkage of nationwide registries of hospitalization and drug dispensing from pharmacies in Denmark. Risk of death and recurrent MI according to duration of NSAID treatment was analyzed by multivariable time-stratified Cox proportional-hazard models and by incidence rates per 1000 person-years. Of the 83 677 patients included, 42.3% received NSAIDs during follow-up. There were 35 257 deaths/recurrent MIs. Overall, NSAID treatment was significantly associated with an increased risk of death/recurrent MI (hazard ratio, 1.45; 95% confidence interval, 1.29 to 1.62) at the beginning of the treatment, and the risk persisted throughout the treatment course (hazard ratio, 1.55; 95% confidence interval, 1.46 to 1.64 after 90 days). Analyses of individual NSAIDs showed that the traditional NSAID diclofenac was associated with the highest risk (hazard ratio, 3.26; 95% confidence interval, 2.57 to 3.86 for death/MI at day 1 to 7 of treatment).

Conclusions—Even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent MI in patients with prior MI. Neither short- nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited from a cardiovascular safety point of view. (Circulation. 2011;123:2226-2235.)
Prescription NSAID labels will be revised to reflect the following information:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.

- The risk appears greater at higher doses.

- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.

- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.

- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.

- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.

- There is an increased risk of heart failure with NSAID use.
Conclusion

Drug interactions not only occur secondary to drug-drug interactions but also involve nutrients and interactions with comorbidities.

Not one person, or one source, is sufficient to conclude a clinically significant interaction does or does not exist.

Clinicians must remain diligent when prescribing new drugs, as well as older drugs, as some interactions may remain undiscovered for years.