A 60-year-old male with a history of carotid artery stenosis comes to the physician because of a 5-day history of nausea, fatigue and shortness of breath. Six months ago, treatment with aspirin and clopidogrel was initiated after coronary angioplasty. Omeprazole, a PPI inhibitor, was also prescribed to reduce the risk of GI bleeding from the antiplatelet drugs. Today, physical examination stress echocardiography indicates coronary artery disease. What is the cause of this patient’s angina relapse?
Cytochrome P450

The super-family of cytochrome P450 enzymes (CYP) has a crucial role in the metabolism of dietary and xenobiotic agents

This can reduce the bioavailability of a drug OR can result in formation of an active metabolite.

Cytochrome P450 1A2

- Induced by:
  - smoking tobacco
  - carbamazepine, phenobarbital
  - rifampin
- Catalyzes primary metabolism of:
  - caffeine, theophylline
  - tizanidine
  - R-warfarin
- Inhibited by:
  - amiodarone
  - cimetidine
  - ciprofloxacin
  - fluvoxamine
Cytochrome P450 2C9

- Absent in 1% Caucasians and African-Americans
- Induced by:
  - carbamazepine, phenobarbital, phenytoin
  - rifampin
- Catalyzes primary metabolism of:
  - angiotensin receptor blockers
  - carvedilol
  - fluvastatin
  - S-warfarin
- Inhibited by:
  - amiodarone
  - fluoxetine
  - metronidazole, trimethoprim-sulfamethoxazole

Cytochrome P450 2C19

- Absent in 20-30% of Asians, 3-5% Caucasians
- Induced by:
  - carbamazepine, phenytoin
  - rifampin
- Catalyzes primary metabolism of:
  - clopidogrel
  - omeprazole
  - phenobarbital, phenytoin
- Inhibited by:
  - fluvoxamine
  - isoniazid
  - ritonavir
Cytochrome P450 2D6

- Absent in 7% of Caucasians, 1-2% non-Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes primary metabolism of:
  - amitriptyline
  - codeine
  - carvedilol, metoprolol
- Inhibited by:
  - amiodarone
  - cimetidine
  - diphenhydramine
  - fluoxetine
  - ritonavir

Cytochrome P450 2E1

- Induced by:
  - alcohol
  - isoniazid
- Catalyzes primary metabolism of
  - acetaminophen
- Inhibited by:
  - disulfiram
Cytochrome P450 3A4 Inducers

- carbamazepine
- phenobarbital
- phenytoin
- rifampin
- St. John’s wort
Cytochrome P450 3A4 Inhibitors
- clarithromycin
- diltiazem
- erythromycin
- ketoconazole
- ritonavir
- verapamil
- And grapefruit juice

Cytochrome P450 3A4 Substrates
- amiodarone
- calcium channel blockers
- estradiol-contraceptives
- prednisone
- saquinavir
- statins
- R-warfarin
- zolpidem
Inhibition of CYP, ↑ Drug Levels

- grapefruit juice + statins
- tizanidine + ciprofloxacin
- metronidazole + warfarin
Inhibition of CYP, ↓ Drug Levels

- omeprazole + clopidogrel

Induction of CYP, ↓ Drug Levels

- carbamazepine
  - metabolic tolerance
- carbamazepine + warfarin
  - reduced drug levels
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