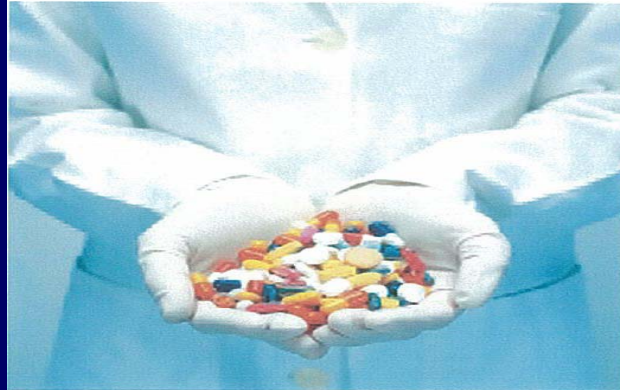


UPDATES IN CARDIOLOGY

DECEMBER 4, 2009

Drug-Drug Interactions

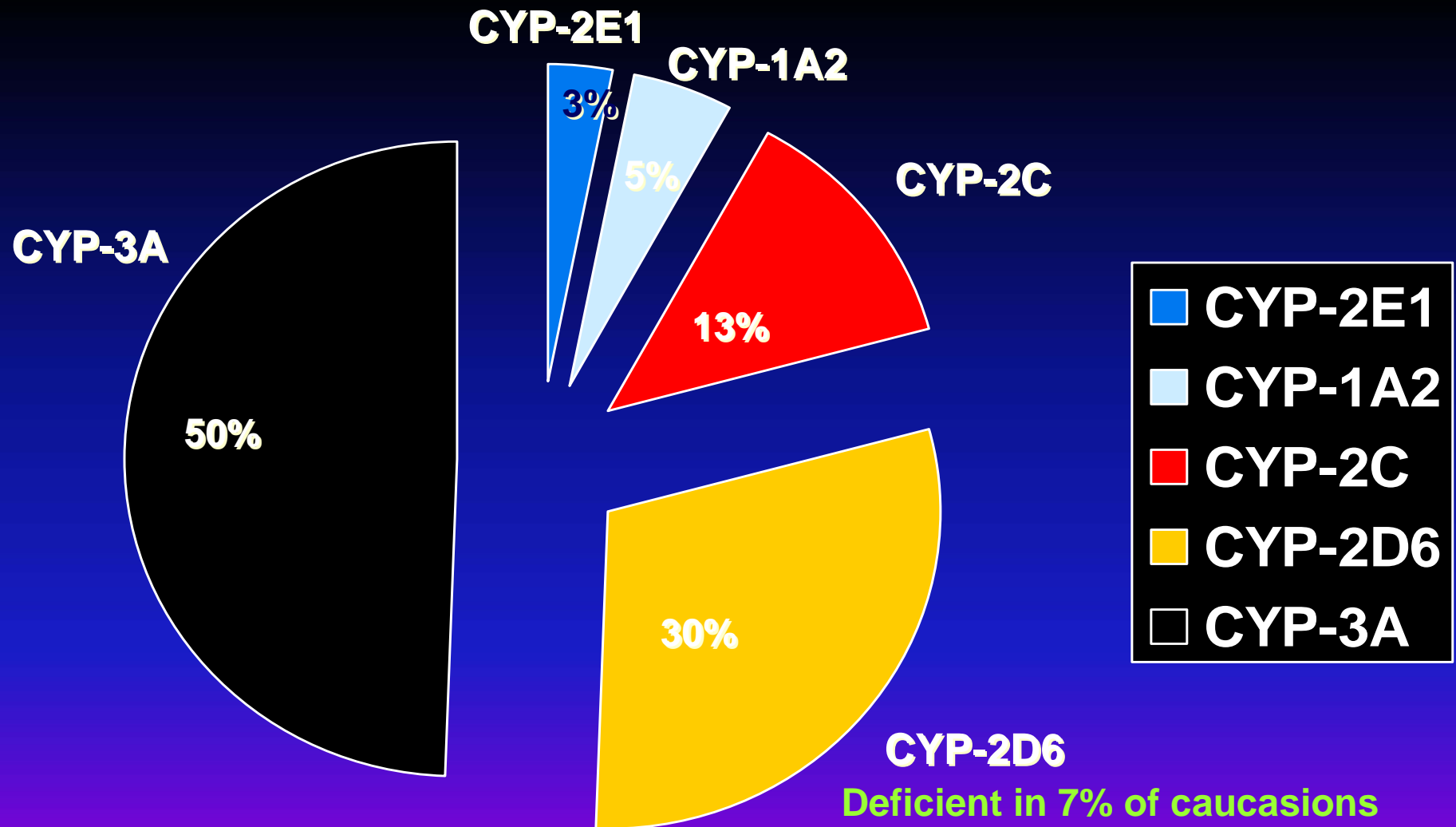


Scott Freeland, Pharm.D.

Drug Interactions

- **Pharmacodynamics (PD):**
 - What the *drug* does to the *body*
- **Pharmacokinetics (PK):**
 - What the *body* does to the *drug*
- **Primary source for drug interactions**
 - PK >> PD

CYP-450 Enzymes



Adapted from Pharmacotherapy 15:848-998, 1995

Clopidogrel and Proton Pump Inhibitors (PPI's)

- **> 100 million combined prescriptions /yr**
 - 2008 ACC/AHA/ACG Clinical Expert Consensus Document
 - 2007 ACC/AHA Unstable Angina/NESTMI Guidelines
- **Clopidogrel – “Prodrug”**
 - Converted to its active form by metabolic enzymes (CYP450-2C19) within the GI tract
- **PPI's**
 - Inhibits the activity of CYP-450 (2C19) enzyme
 - Reduced activity/efficacy of clopidogrel
 - Platelet Inhibition Reactivity (PRI) – lab assay
 - Higher platelet activity compared with clopidogrel use alone
 - Higher observed rates of MACE (AMI; Stent thrombosis; ACS; TVR)

Clopidogrel + PPI's

- Initial “Evidence”:
 - 2006: Letter to the Editor
 - 2008:
 - OCLA study
 - AETNA insurance retrospective review
 - MEDCO Outcomes Study
- Recent Findings (Nov 2009)
 - COGENT trial – No difference in clinical events when combining PPI's and clopidogrel
 - CREDO / TRITON (TIMI 38) / PLATO

Clopidogrel + PPI's

- Class Effect?
 - Proton Pump Inhibitors –
 - Omeprazole ~ esomeprazole >>> pantoprazole > lansoprazole > rabeprazole
- Recommendations
 - FDA recommendations: Nov 17, 2009
 - Avoid omeprazole with clopidogrel
 - H₂ antagonists if appropriate
 - PPI: Pantoprazole / Lansoprazole / Rabeprazole
 - Alternate dosing schedules ?
 - has not proven to be effective

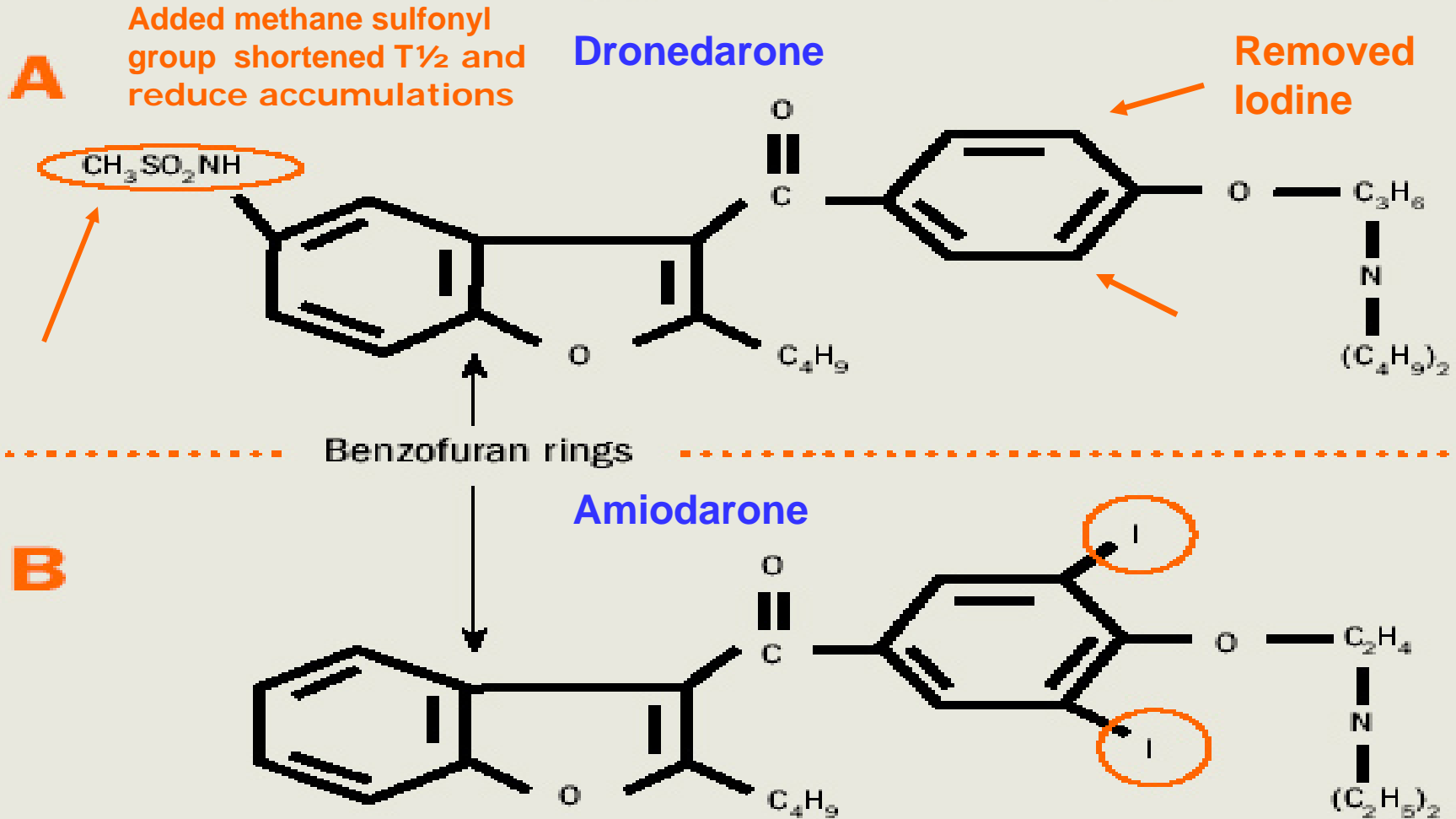
Prasugrel (Effiant[®]) and PPI's

- Metabolism:
 - Prodrug—requires activation
 - Dual metabolic activation
 - ▣ CYP (3A4 / 2B6) >>>> CYP(2C9) and CYP (2C19)
- 2009: Prasugrel studies
 - TRITON – TIMI 38
- Conclusions: not affected by concurrent PPI's
- Ticagrelor (Investigational) – Not affected

DRONEDARONE (Multaq®)

■ Figure 1

Chemical structures of (A) dronedarone and (B) amiodarone^a



^a Circles depict location of sulfonamide group on dronedarone (A) and iodine groups on amiodarone (B).

Dronedarone (Multaq[®])

- **Digoxin**
 - Dronedarone increases digoxin exposure by 2.5 fold
 - Follow similar dosing guidelines as amiodarone when combining dronedarone with digoxin
- **Warfarin**
 - Dronedarone increased S-warfarin isomer by 1.2 fold
 - No change in R-warfarin isomer
 - No observed excess risk of bleeding when dronedarone was administered with warfarin
 - **No dosage adjustment of warfarin required**
- **Simvastatin**
 - Dronedarone ↑ simvastatin exposure by 4 fold
 - Recommend following same guidelines as amiodarone
 - max dose of simvastatin at 20mg

STATINS

Not a Class Effect

Lipophilic

Higher rate of Drug Interactions

- Lovastatin
- Fluvastatin
- Simvastatin
- Atorvastatin

Hydrophilic

Lower rate of Drug Interactions

Use if potential drug interactions due to CYP-450 metabolism

- Pravastatin
- Rosuvastatin

ED drugs and Nitrates

PDE ₅	Concurrent Drug	Findings	RECOMMENDATION
Sildenafil (<i>Viagra</i> [®]) (<i>Revatio</i> [®]) Tadalafil (<i>Cialis</i> [®])	Nitrates Nitroprusside Alpha₁ Blocker (Cardura, Hytrin)	<u>Nitrates + PDE₅</u> Increased hypotensive effects due to increased levels of cyclic guanosine monophosphate (cGMP)	Combination - contraindicated The length of time required between discontinuation of nitroglycerin therapy and safe administration of sildenafil, etc. is not known. <u>Recommendations:</u> Sildenafil (T _{1/2} 4hr) > 24hrs Tadalafil (T _{1/2} 17hr) > 24 hrs Vardenafil (T _{1/2} 4hr) > 24 ?
	CYP- 450(3A4) (INHIBITORS) ▪ Erythromycin ▪ Antifungal	Prolonged hypotensive effects with Nitrates	Anticipate prolonged effects of PDE ₅ drugs if need to start Nitrates

Thank You