

# Drug Interactions and Prescribing Errors

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# Financial Disclosure Related to Presentation

John Horn is a partner of Hansten and Horn, LLP which publishes drug interaction reference books such as The Top 100 Drug Interactions: A Guide to Patient Management

John Horn does not currently have a financial relationship with anyone, but would certainly welcome one as he is nearing retirement.

# DDI Terminology

- Drug-drug interaction (DDI)
  - A clinically meaningful alteration in the exposure and/or response to a drug that *has occurred* as a result of the co-administration of another drug.
- Potential DDI (PODDI)
  - Co-prescription or co-administration of two drugs known to interact, and therefore a DDI *could occur* in the exposed patient.

# Definition of Terms

- Object Drug  
the drug that is being affected by the interaction
- Precipitant Drug  
the drug causing the interaction
- Interaction can either be uni-directional or bi-directional (mutual)

# Types of Drug Interactions

- Pharmacokinetic Drug Interactions

Those interactions that result in a change in the concentration-time course of active drug/ metabolites in the circulation and/or at the effector tissue or organ

- Pharmacodynamic Drug Interactions

Those interactions involving a change in the functional relationship between the degree of pharmacologic response and the drug/metabolite concentration

# Pharmacy Response to Serious DDIs

- 255 prescriptions for 1 of 5 DDIs were presented to community pharmacies by reporters from Chicago Tribune
- Primary outcome measure was verbal indication DDI identified to patient or MD
- 8 Chain pharmacies; 30 tests/chain
- 32 Independent pharmacies

# Pharmacy Response to Serious DDIs: Drug Pairs

Clarithromycin – Ergotamine

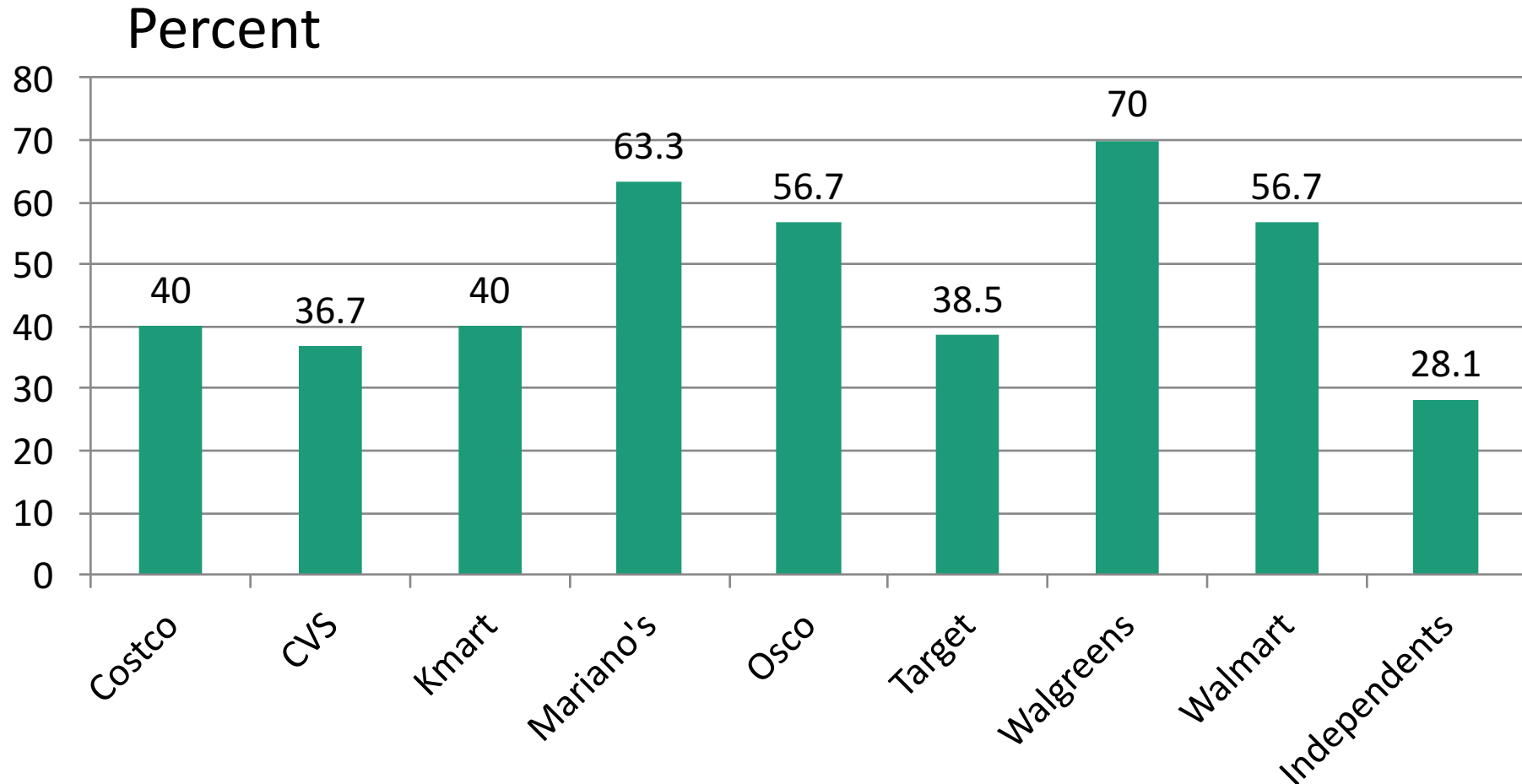
Verapamil – Colchicine

Clarithromycin – Simvastatin

Ciprofloxacin – Tizanidine

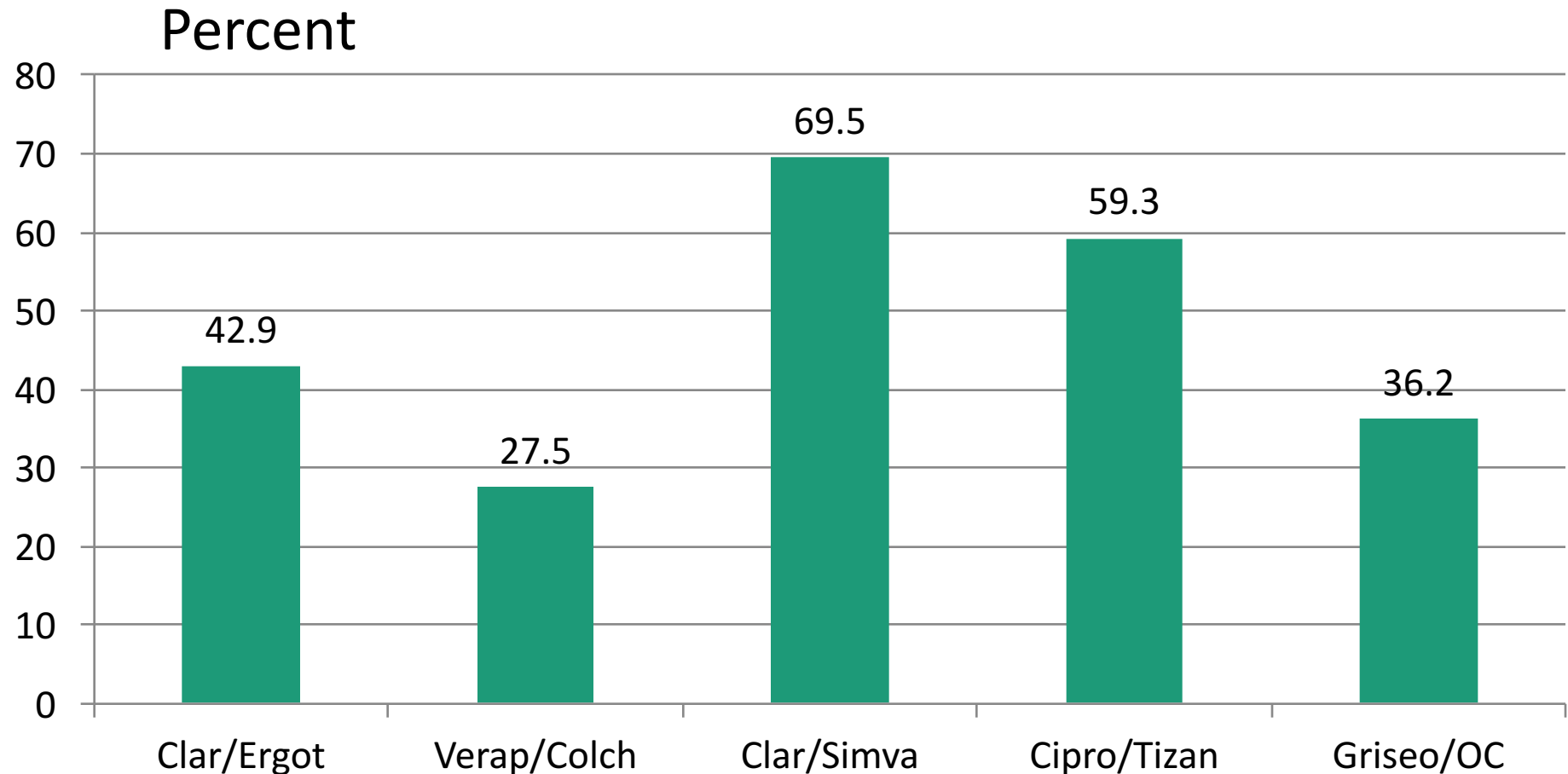
Griseofulvin – Oral Contraceptive

# Pharmacy Response to Serious DDIs: Correctly Identified by Pharmacy





# Pharmacy Response to Serious DDIs: Correctly Identified by DDI Pair



# What is the Purpose of a Drug Interaction Screening Program?

To identify potential interactions and initiate steps to prevent possible patient harm

# Prediction

“Prediction is very difficult. Especially if it’s about the future.”

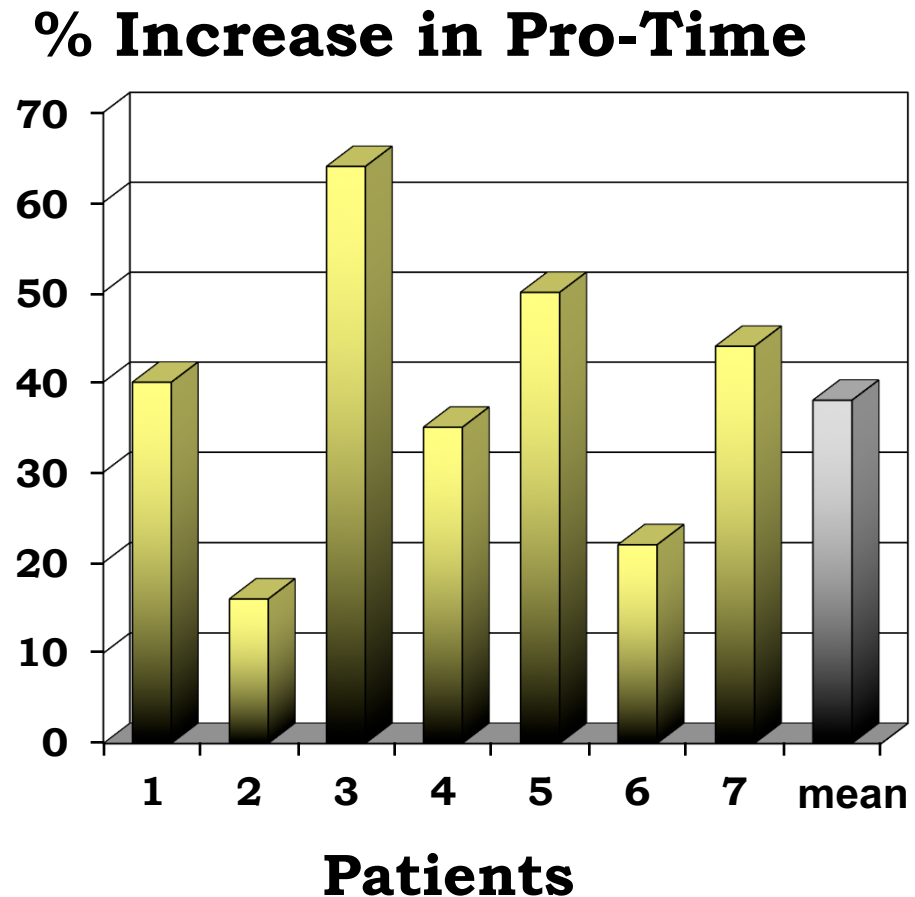
Niels Bohr

# Fluconazole (Diflucan) + Warfarin (Coumadin)

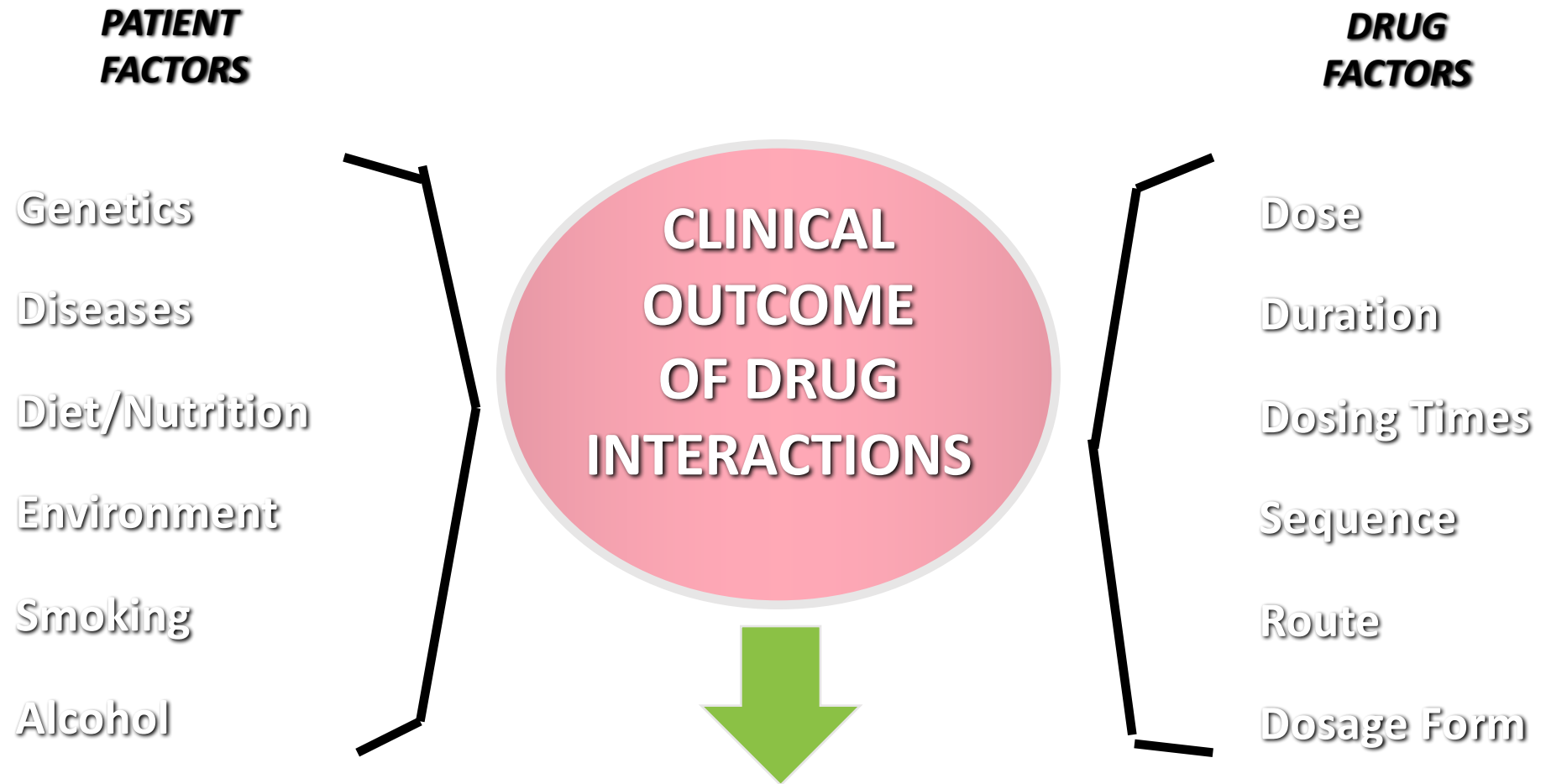
7 people on warfarin  
given fluconazole 100  
mg daily X 7 d

Marked increase in the  
PT response (but high  
variability)

No bleeding occurred



# Factors Influencing Drug Interaction Outcomes



# Computerized DI Screening: Problems

- The sheer enormity of available info
- Lack of epidemiological information
- Complexity of patients, polypharmacy
- May rely on literature reports without informed review or evaluation
- May include interactions that are 'over' classed

# Physicians Response to Computerized Drug Interaction Alerts

- 4751 DDI alerts
- 3129 separate pairs: Override rate:
  - Level 1 (Serious / substantial evidence) 89.4%
  - Level 2 (Less serious) 96.3%
  - Level 3 (Serious / some evidence) 85.4%
- MDs tried to reenter same drug pair 26% of the time

# Alert Overrides: Just a Bad Habit?

- Prescribers rarely read alerts that are overridden
- Time from alert presentation to dismissal – 8 seconds – independent of acceptance or override of alert
- More alerts = more overrides



# Problems in DDI Information Processing

- **Data Generators:** Basic and clinical scientists doing controlled studies (PK usually), case reports, “big data” mining, labeling. Huge amount of data of varying quality.
- Problem – Large volume of DDI data of varying quality.

# Cilostazol DDI: Label 1/15

## Lovastatin

Co-administration of cilostazol with lovastatin increases lovastatin and  $\beta$ -hydroxy lovastatin AUC approximately 70%. This is most likely clinically insignificant.

## Effect of Cilostazol on CYP3A4

PLETAL does not appear to cause increased blood levels of drugs metabolized by CYP3A4, as it had no effect on lovastatin, a drug with metabolism very sensitive to CYP3A4 inhibition.

# Data Mining to Identify Severe DDI ADRs

- Extract DDI-ADR pairs from FDA AERS for warfarin, clopidogrel, simvastatin
- Used Side Effect Resource (SIDER – based on package inserts) to ID ADRs associated with drugs
- Severity grades 1 (mild) to 5 (death) using common terminology criteria for ADR (CTCAE)
- Combined these sources to extract DDI pairs and the ADRs associated with them

# Data Mining to Identify Severe DDI ADRs: Simvastatin

Drug 1	Drug 2	CTCAE Grade	ADE Name
Simvastatin	Aspirin	5 Fatal	Aortic Stenosis / Coma
Simvastatin	Losartan	5	Cardiac Arrest
Simvastatin	Risiglitazone (sic)	5	LBBB / Retinopathy
Simvastatin	Tegretol	4 Life threatening	Aphasia / Arrhythmia / Dermatitis
Simvastatin	Amiodarone	4	Bone pain
Simvastatin	Aspirin	3 Severe	Dermatitis
Simvastatin	Viagra	3	Glucose tolerance impaired
Simvastatin	Ramipril	3	Intervertebral disc protrusion

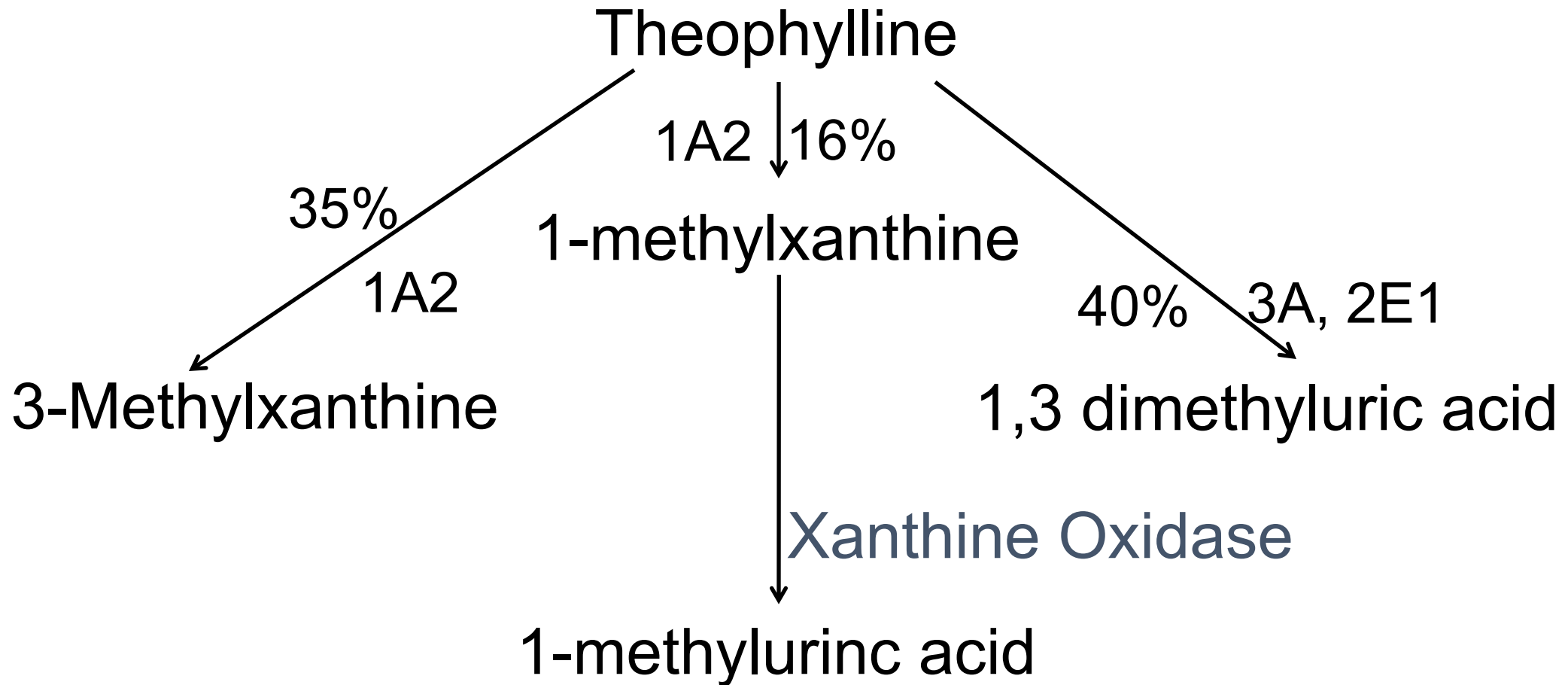
# Problems in DDI Information Processing

- **Information Analysts:** Read papers from Data Generators and write reviews, books, and electronic databases. Few specialize in DDI informatics; variability in expertise.
- **Problem –** Too few analysts with both general and specialized knowledge of DDIs.

# Theophylline – Allopurinol: A Major Drug Interaction

- Listed as highest severity in several CDS databases, including institutionally customized databases
- Two studies found no change in theo PK with allopurinol 300 mg daily x 7 days
- One study found ~ 25% increase in Theo AUC and half-life after 2 weeks of allopurinol 300 mg BID vs day 1

# Theophylline – Allopurinol: A Major Drug Interaction



# Problems in DDI Information Processing

- **Clinical Decision Support Producers:** Rely on Information Analysts' product to make CDS used by clinicians. Deciding which PODDIs and how to present them is difficult and some do a better job than others. All include PODDIs of questionable clinical importance.
- Problem – Inclusion of far too many PODDIs in CDS



# QTc Interval Prolongation in Cardiac Patients

- 900 pts admit to cardiac units
- Definitions: QTc prolonged: 470 ms / 480 ms for males / females
- QT-prolonging meds from *qtdrugs.org*
- Admission QTc ~460 ms

# QTc Interval Prolongation in Cardiac Patients

- On admission QTc prolonged in 28%; of pts on QTPD, 31.5% had prolonged QTc
- 18% admits with QTc >500 ms
- 35% of pts with QTc prolongation received QTPD
- 42% of pts with QTc >500 ms received QTPD; 57% of these had subsequent QTc increases >60 ms
- Total number of cases of TdP = ZERO

# Occurrence of QTc-Based DDIs

Reviewed all DDIs classified as Major in EMR  
DDI database: N=21,944

Identified DDIs that cite prolonged QTc as the  
basis of the DDI risk: N = 5,651

26% of all Major DDIs are due to QTc-based  
mechanisms.

# Alert Fatigue

“The much discussed phenomenon of alert fatigue suggests that there is too much information to process in the typical workflow when it comes to order prescribing. Alerts have often been considered to be duplicative, lacking in patient-specific context, or just generally spurious.”

# Causes of Alert Fatigue

- Refills
- Low specificity for clinical significance
- Based on non-clinical data
- Desire to have “complete” listing
- Legal concerns
- “It’s in the label”

# Reducing Alert Fatigue: Options

- Turn off selected DDI categories
- Do in-house review of DI database to revise existing alerts
- Knowledge base DDI program
- Patient specific DDI alerts

# What NOT To Do About Too Many DDI Alerts

Turn off selected categories (eg, all alerts not in “most severe” group) or remove “really irritating” alerts

Advantage – Very easy to do

Disadvantage – Too easy to do

# Alert Only Most Severe DDIs: What You Will NOT See

- Amiodarone / Haloperidol – PK/PD arrhythmia
- Bepridil / Clarithromycin – PK/PD arrhythmia
- Colchicine / Clarithromycin – Colchicine toxicity
- Conivaptan / Ergots – Ergotism
- Cyclosporine / Ketoconazole – Renal toxicity
- Cyclosporine / Rifampin – Organ rejection
- Simvastatin / Clarithro, Erythro, CSA – Myopathy



# What You Might Do About Too Many DDI Alerts

Do in-house review and customization of  
some or all of DDI database

Advantage – usually done by committee

Disadvantage – usually done by committee  
without adequate expertise or training in  
DDIs

# In House DDI Customization: Identified “Critical Interactions”

- CCBs (all) – BBs (all) [due to AV block]
- Digoxin - Amiodarone, Macrolides, Quinidine, Verapamil, Tetracycline (But not azole antifungals)
- SSRIs – Triptans
- Theophylline – Allopurinol, Febuxostat

# In House DDI Database Customization: Guidelines

- Start by defining what should trigger an alert
- Establish criteria for seriousness classification
- Develop criteria for assessing evidence
- Develop set of rules to guide classification and increase continuity

# In House DDI Database Customization: Where to Start?

- Review the alerts that are currently being triggered
- Start with the DDIs causing the most alerts
- Decrease seriousness of those alerts not meeting criteria
- Use previously customized database as starting point

# Customized DI Screening at University of Washington Medical Center

- In preparation for CPOE, customize DI database
- Start with DIs labeled as MAJOR
- About 8000 unique pairs in UWMC's database (2007)
- Each pair evaluated for appropriate classification in database (Major – Moderate – Minor) based on data and defined criteria

# Customized DDI Database

- Evaluation criteria was probability of patient harm and ease of avoidance
- MAJOR should only include DDIs where risk likely to exceed benefit in most patients
- MAJOR DDIs should require thought and action: change drug, adjust dose, and/or monitor

# Customized DDI Database

Hospital	Total MAJORs in Database	DIs Reduced in Severity (%)
UWMC (2007)	7970	57
Hospital 2	8404	59
Hospital 3	11727	65
Hospital 4	12268	77
UW Medicine (2016)	26040	71

# Customized DDI Database

- Reduces number of inappropriate alerts and potential for alert fatigue
- Enables selection of alerts based on institutional requirements
- Need to educate users on changes
- Need to update
- No opportunity for patient specific alerting
- Labor / expertise intensive



# Knowledge Base Drug Interaction Screening

- Does not use a simple look-up table
- Based on drug properties – PK, PD
  - Mechanism (ie, CYP450) based
  - ID substrate, inhibitor / inducer of CYP450s
  - Magnitude of effect on CYP450
  - First-Pass metabolism of object drug
  - Therapeutic window of object drug

# Mechanism-based Drug Interaction Knowledge Bases

## Advantages:

- Can predict interactions not previously reported

- Avoids “class” errors

- Predicts interactions resulting from drug withdrawal

- Supports interactions between three or more drugs

- Provides estimates of effect on Object drug

# Mechanism-based Drug Interaction Knowledge Bases

## Disadvantages:

- Mechanisms may be unknown

- PK or PD info for drugs may not be available

- Difficult to evaluate clinical risk

- Updating drug assertions in the database

- Evaluating evidence for assertions

# Patient Specific DDI Alerts

Clean up database first?

Create algorithm / decision tree with mitigating and risk factors

Apply using patient specific EMR data to decide to alert

# Common Major DDI Alerts UW Medicine

## 2016: Assessment of DDIs

Review the P'col and P'kinet properties of object and precipitant drugs

Identify modifying (Mitigating and Risky) factors

Drug: Dose, Duration, Route, Order of Administration, Co-medications

Patient: Disease, Renal function, Lab values, ECG, Pharmacogenomics, Diet, Age, Gender

# Common Major DDI Alerts UW

Medicine 2016

Amiodarone / Oxycodone

Amlodipine / Simvastatin

Ciprofloxacin / Oxycodone

Diltiazem / Oxycodone

Fluconazole / Fentanyl

Fluconazole / Oxycodone

Fluconazole / Tacrolimus

Make up 58% of Major alerts

# Dose Filters for Common Alerts

Amiodarone /  $\leq 40$  mg Oxycodone

Amlodipine /  $\leq 40$  mg Simvastatin

Ciprofloxacin /  $\leq 80$  mg Oxycodone

Diltiazem /  $\leq 80$  mg Oxycodone

Fluconazole  $\leq 200$  mg / Fentanyl

Fluconazole  $\leq 200$  mg / Oxycodone

Fluconazole  $\leq 200$  mg / Tacrolimus

# Assessment of DDIs: Fluconazole

Fluconazole CYP3A4 inhibition is dose dependent

100 mg/d – 20% incr CSA AUC

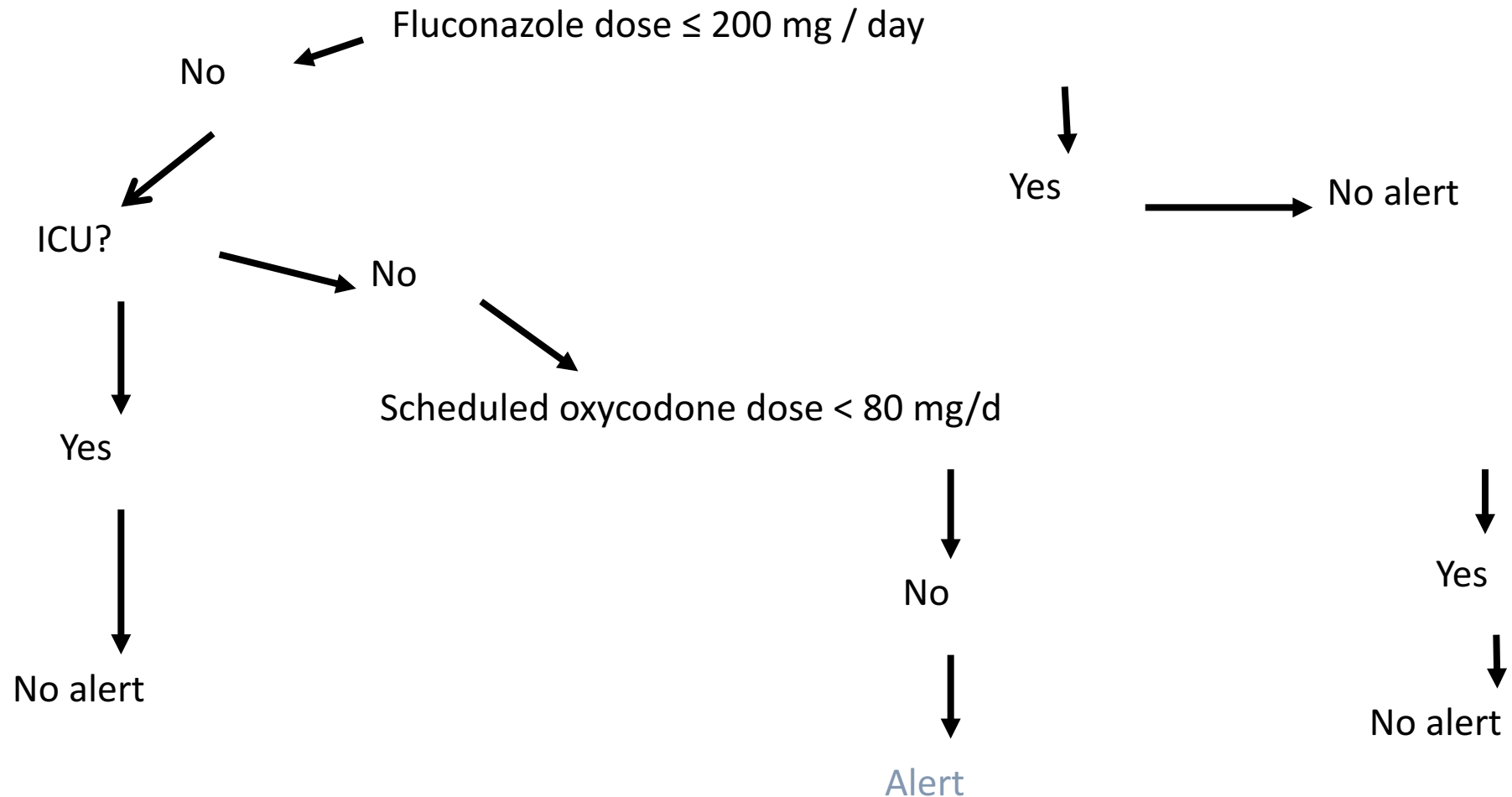
150 mg/d – 25-50% incr Midazolam AUC

100 mg/d – 2-fold incr Triazolam AUC

200 mg/d – 4-fold incr Triazolam AUC



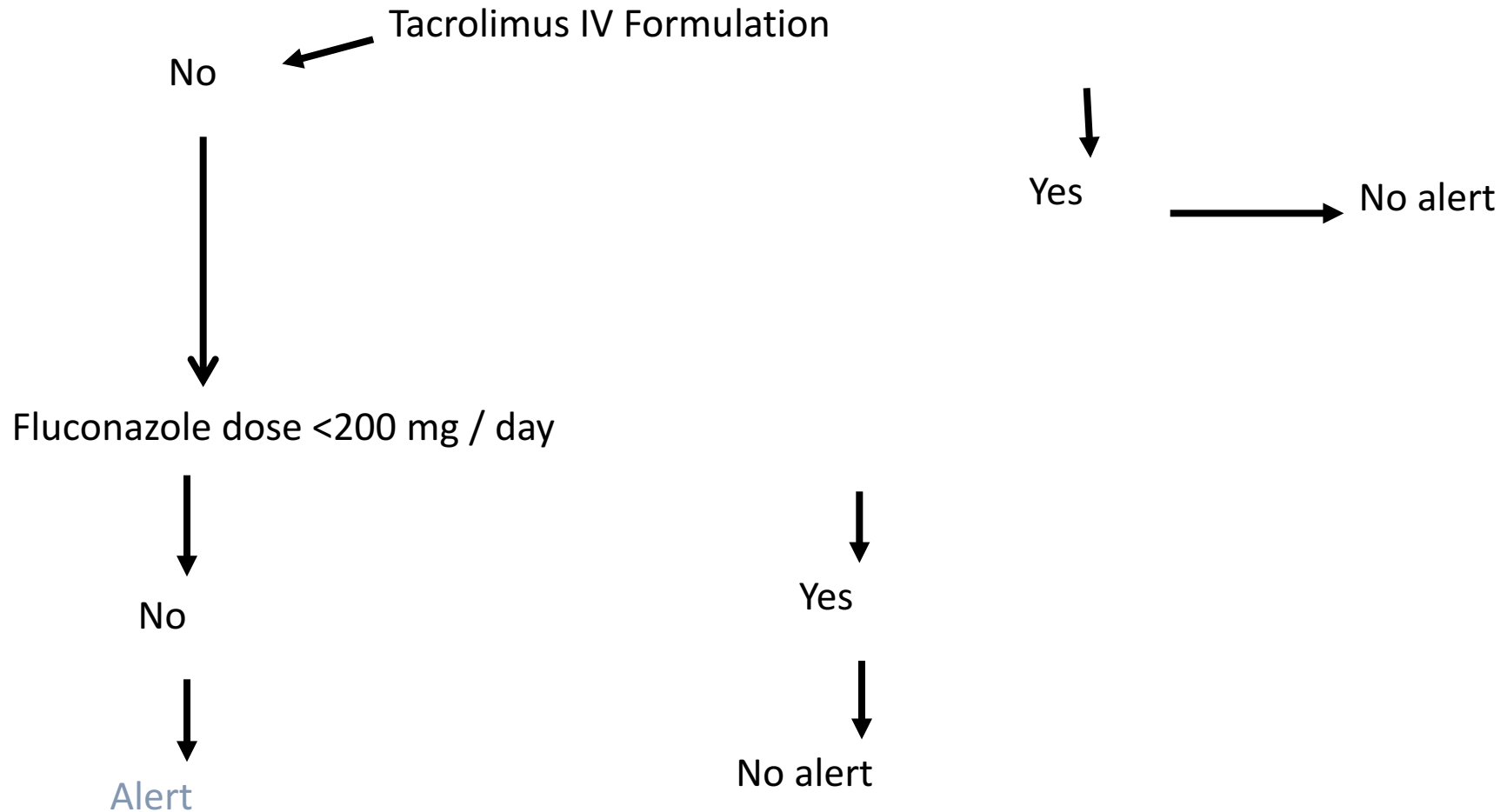
# Fluconazole / Oxycodone DDI Decision Tree



# Fluconazole / Oxycodone Decision Tree

- 242 alerts for fluconazole / oxycodone
- Flucon dose  $\leq 200$  mg/d: 169 No alert
- Flucon dose  $> 200$  mg/d: 73
- ICU: yes – 6 No alert
- ICU: no – 67
- Oxy dose  $< 80$ mg/d: 37 No alert
- Oxy dose  $> 80$  mg/d: 30 **Alert**
- ~88% reduction in alerts

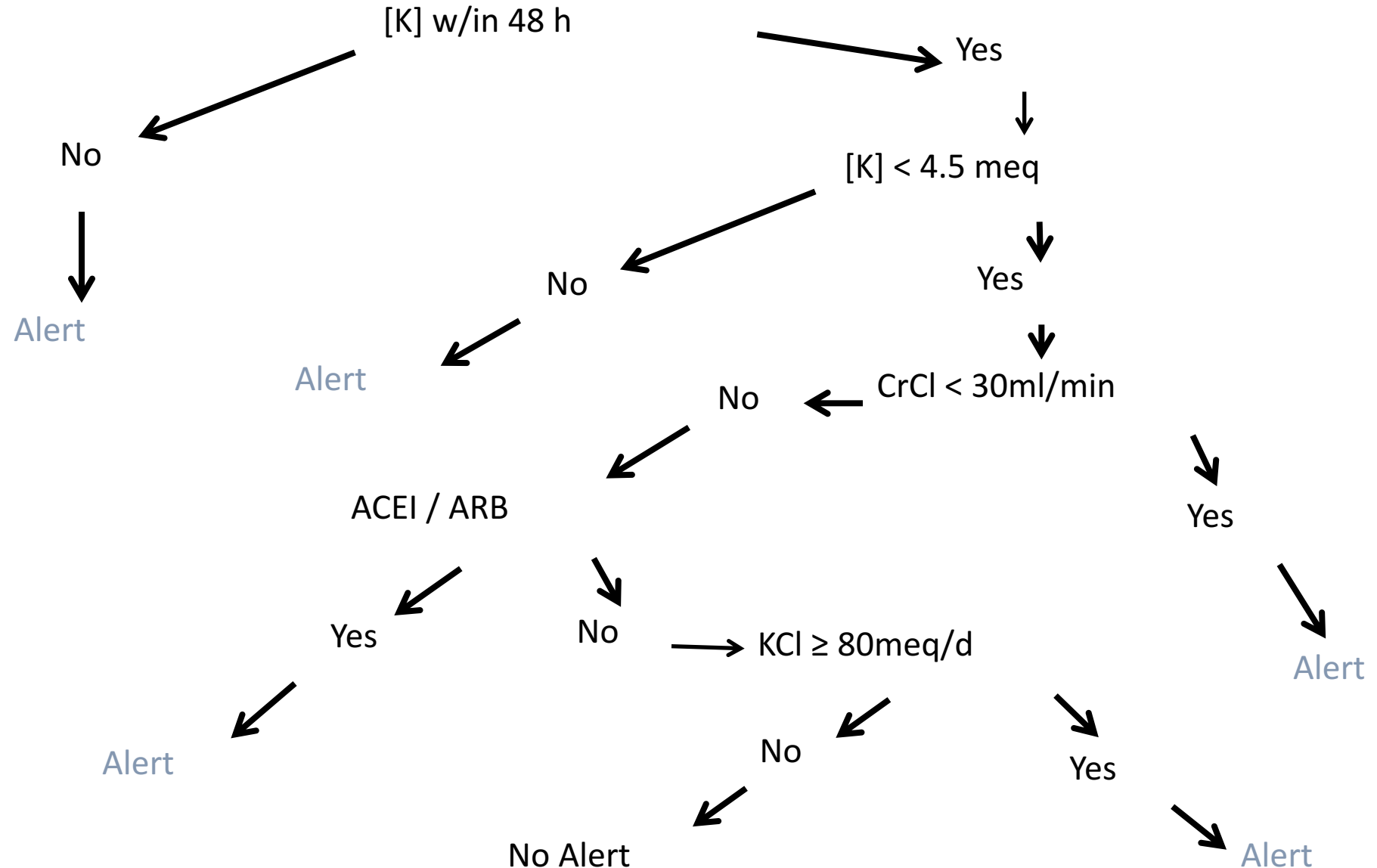
# Fluconazole / Tacrolimus DDI Decision Tree



# Fluconazole / Tacrolimus Decision Tree

- 159 alerts for fluconazole / tacrolimus
- Tacrolimus IV: 39 No alert
- Flucon dose  $< 200$  mg/d: 43 No alert
- Flucon dose  $\geq 200$  mg/d: 77 **Alert**
- ~52% reduction in alerts

# KCL / Potassium Sparing Diuretic

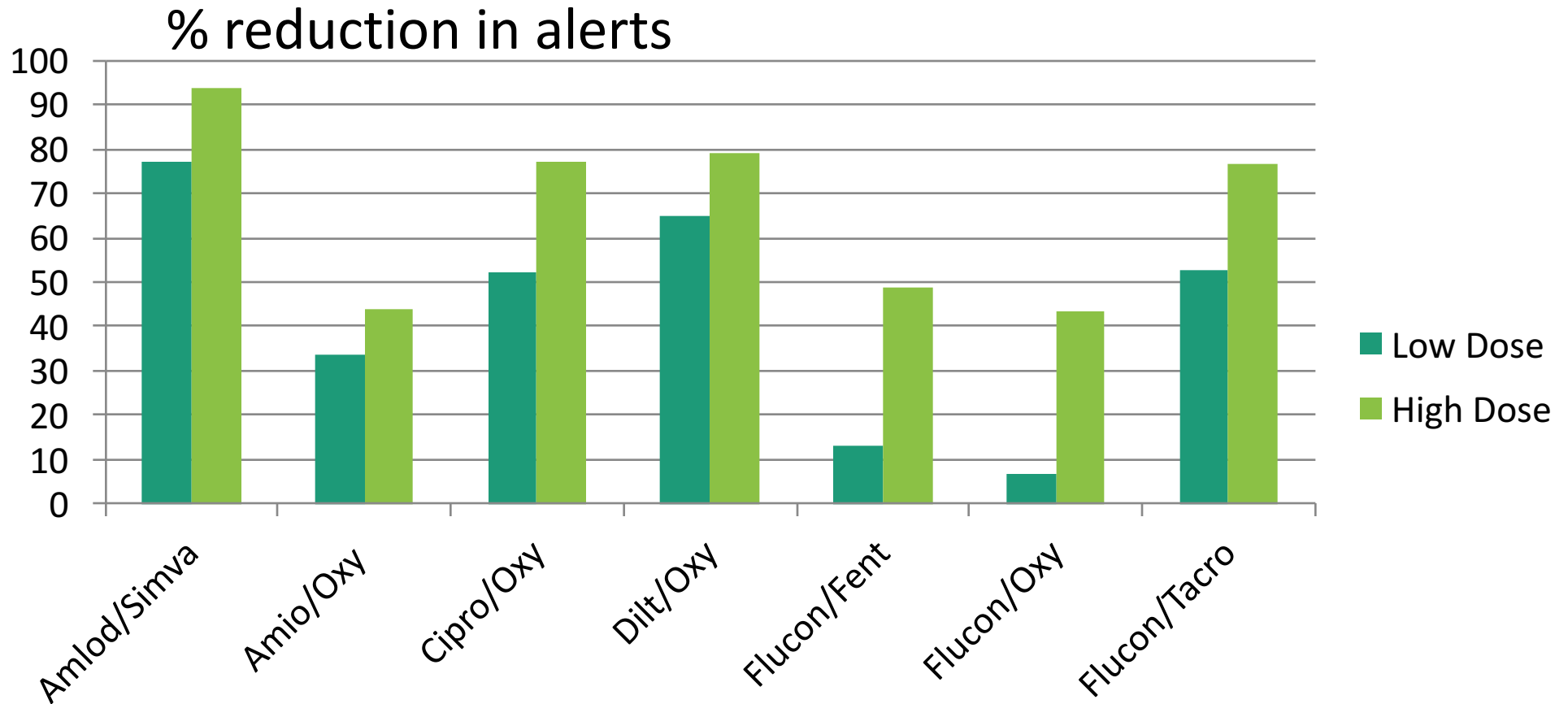


# Effect of DDI Filter on Alerts

Alert	N	Sensitivity	Specificity
K increasing DDIs; all trigger alert	6349	100	0
K > 4.0 mEq/l w/in 48 hr prior to DDI	2226	61.1	65.7
K > 4.8 mEq/l 48 hr prior and during DDI	1217	74.2	95.7

76K inpatients analyzed for DDIs resulting in K > 5.4 mEq/l

# Alert Reduction with Filter: Low / High Dose



# Drug Interaction Alerts: Problems and Solutions

## Summary and Questions



# **Drug Interaction to Avoid**

**“Never, under any circumstances, take a sleeping pill and a laxative on the same night.”**