VANDERBILT UNIVERSITY

Using Real World Data to Fill Evidence Gaps for Precision Dosing

Sara Van Driest, MD, PhD

Assistant Professor of Pediatrics and Medicine

Monroe Carell Jr. Children's Hospital at Vanderbilt

Disclosure

- I will present Real World Data extracted from electronic health records on drugs including statins, antibiotics, antipsychotics, and analgesics. Exposure data may include off-label use, by age or indication, for these drugs.
- I have received an honorarium as an invited speaker to Merck.

Objective

- Discuss examples of using clinically generated data to better understand drug-drug interactions, drug-gene interactions, and the clinical factors that influence drug response in specific populations.
- Appraise the utility and limitations to using clinically generated data to perform precision dosing research.

Outline

- Drug-Drug Interactions
  - Statin-daptomycin
  - Vancomycin-piperacillin/tazobactam
- Dose-Response
  - Statin
- Pharmacogenomics
  - Risperidone (adverse drug events)
  - Fentanyl (population PK)

Outline

- Drug-Drug Interactions
  - Statin-daptomycin
  - Vancomycin-piperacillin/ta
- Dose-Response
  - Statin
- Pharmacogenomics
  - Risperidone (adverse drug
  - Fentanyl (population PK)

Clinical Infectious Diseases

MAJOR ARTICLE

Effect of Statin Coadministration on the Risk of Daptomycin-Associated Myopathy

Ryan K. Dare,[1] Chad Tewell,[2] Bryan Harris,[3] Patty W. Wright,[3] Sara L. Van Driest,[4,5] Eric Farber-Eger,[6] George E. Nelson,[3] and Thomas R. Talbot[3]

[1]Division of Infectious Diseases, Department of Medicine, University of Arkansas for Medical Sciences, Little Rock; [2]St Vincent Health, Indianapolis, Indiana; and [3]Division of Infectious Diseases, Department of Medicine, [4]Division of General Pediatrics, Department of Pediatrics, [5]Division of Clinical Pharmacology, Department of Medicine, and [6]Vanderbilt Institute for Clinical and Translational Research, Vanderbilt University Medical Center, Nashville, Tennessee

Background. Daptomycin-associated myopathy has been identified in 2%–14% of patients, and rhabdomyolysis is a known adverse effect. Although risk factors for daptomycin-associated myopathy are poorly defined, creatine phosphokinase (CPK) monitoring and temporary discontinuation of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or "statins," has been recommended.

Methods. We conducted a single-center, retrospective, matched case-control risk factor analysis in adult and pediatric patients from 2004 to 2015. Patients in whom myopathy (defined as CPK values above the upper limit of normal) developed during daptomycin treatment were matched 1:1 to no-myopathy controls with at least the same duration of therapy. Risk factors independently associated with myopathy were determined using multivariable conditional logistic regression. Secondary analysis was performed in patients with rhabdomyolysis, defined as CPK values ≥10 times the upper limit of normal.

Results. Of 3042 patients reviewed, 128 (4.2%) were identified as having daptomycin-associated myopathy, 25 (0.8%) of whom had rhabdomyolysis; 121 (95%) of the 128 were adults, and the mean duration of therapy before CPK elevation was 16.7 days (range, 1–58 days). In multivariate analysis, deep abscess treatment (odds ratio, 2.80; $P = .03$), antihistamine coadministration (3.50; $P = .03$), and statin coadministration (2.60; $P = .03$) were independent risk factors for myopathy. Obesity (odds ratio, 3.28; $P = .03$) and statin coadministration (4.67; $P = .03$) were found to be independent risk factors for rhabdomyolysis, and older age was associated with reduced risk (0.97; $P = .05$).

Conclusions. Statin coadministration with daptomycin was independently associated with myopathy and rhabdomyolysis. This is the first study to provide strong evidence supporting this association. During coadministration, we recommend twice-weekly CPK monitoring and consideration of withholding statins.

Keywords. daptomycin; myopathy; rhabdomyolysis; statin; drug-drug interaction.

Dare et al, *Clin Infect Dis.* 2018

Background

- Daptomycin
  - Used for *Staph, Strep,* and *Ent*
    infections
  - Associated with myopathy (2-1
    rhabdomyolysis (up to 5%)
- Statin Drugs
  - 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors
  - Lipid lowering agents
  - Associated with myopathy (5-10%) and rhabdomyolysis (<0.1%)

7 DRUG INTERACTIONS

7.1 HMG-CoA Reductase Inhibitors

In healthy adult subjects, concomitant administration of daptomycin for injection and simvastatin had no effect on plasma trough concentrations of simvastatin, and there were no reports of skeletal myopathy [see Clinical Pharmacology (12.3)].

However, inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of creatine phosphokinase (CPK). In the adult Phase 3 S. aureus bacteremia/endocarditis trial, some patients who received prior or concomitant treatment with an HMG-CoA reductase inhibitor developed elevated CPK [see Adverse Reactions (6.1)]. Experience with the coadministration of HMG-CoA reductase inhibitors and daptomycin for injection in patients is limited; therefore, consideration should be given to suspending use of HMG-CoA reductase inhibitors temporarily in patients receiving daptomycin for injection.

MICs, suggesting possible cross-resistance [45, 47, 48]. Elevations in creatinine phosphokinase (CPK), which are rarely treatment limiting, have occurred in patients receiving 6 mg/kg/day but not in those receiving 4 mg/kg/day of daptomycin [49, 50]. Patients should be observed for development of muscle pain or weakness and have weekly CPK levels determined, with more frequent monitoring in those with renal insufficiency or who are receiving concomitant statin therapy. Several case reports of daptomycin-induced eosinophilic pneumonia have been described [51]. The pharmacokinetics, safety, and efficacy of daptomycin in children have not been established and are under investigation [52].

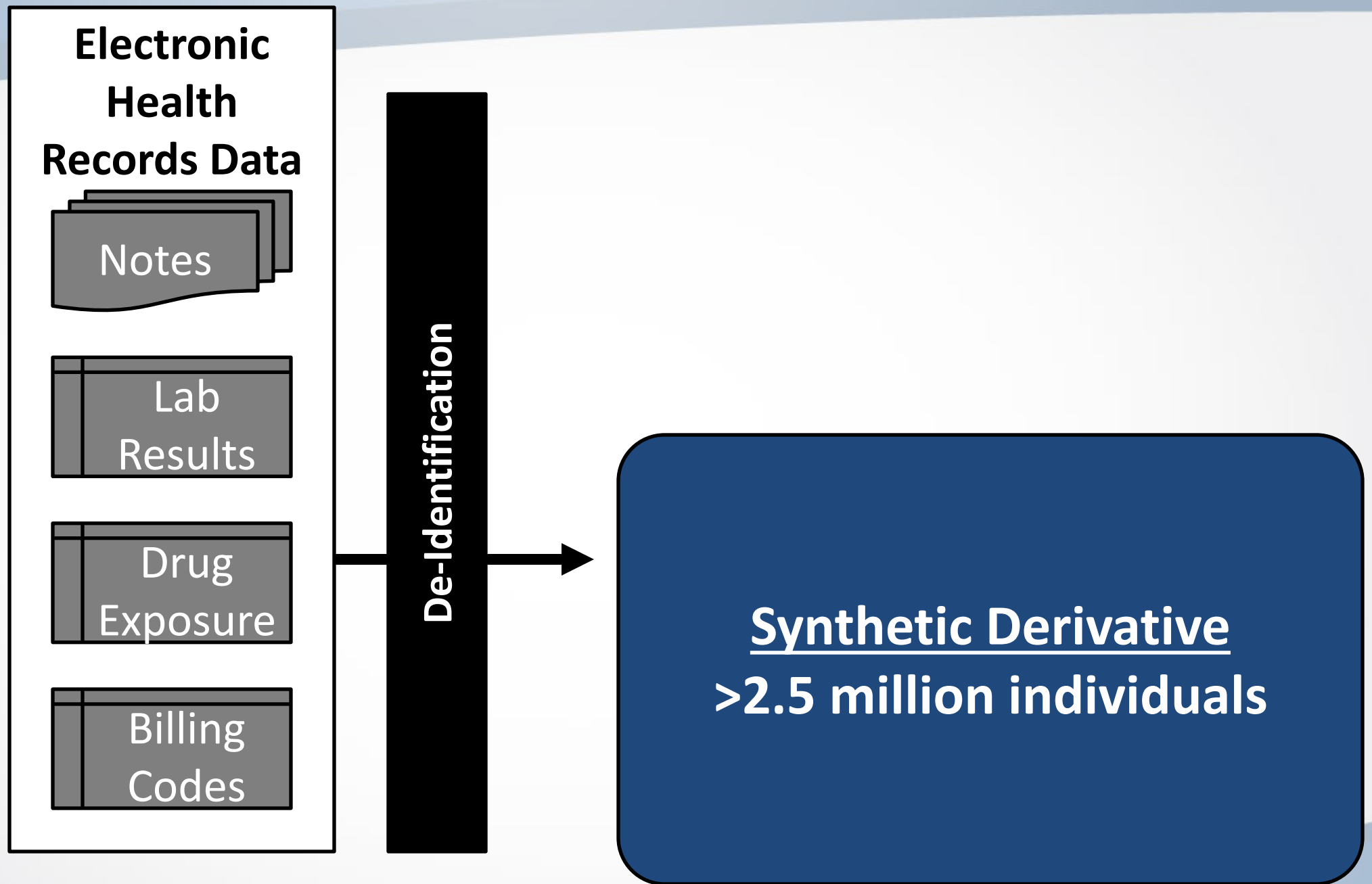
https://dailymed.nlm.nih.gov/dailymed/, Daptomycin injection
Liu et al. *Clin Infect J.* 2011

Methods

- Retrospective (1990-2015) case control risk factor analysis
- Study cohort from Vanderbilt Synthetic Derivative
  - ≥72h of daptomycin exposure
  - Normal CPK at initiation of therapy
  - No surgery in first 7 days of therapy
- Cases:
  - CPK >200 U/L during therapy
  - No alternate causes of CPK elevation on manual review
- Controls:
  - At least 1x normal CPK during therapy
  - Matched 1:1 for duration of therapy

Dare et al, *Clin Infect Dis.* 2018

Synthetic Derivative



Demographics and Comorbid Conditions of Cases and Matched Controls

Characteristic or Condition	Controls (n = 128)	Case Patients (n = 128)	OR	*P* Value
Demographics				
Age, y, mean (SD)	53.2 (18.2)	48.2 (17.1)	0.99	.04[b]
Female sex	50 (39)	57 (45)	1.30	.35
White race	106 (83)	98 (77)	0.97	.82
BMI >30 kg/m^2	45 (35)	61 (48)	1.84	.03[b]
Comorbid conditions				
CHF	13 (10)	17 (13)	1.36	.44
Cirrhosis	8 (6)	1 (1)	0.13	.05[b]
CKD	21 (16)	22 (17)	1.06	.87
Dialysis	17 (13)	8 (6)	0.40	.06[b]
COPD	11 (9)	14 (11)	1.33	.51
DM	38 (30)	44 (34)	1.26	.41
HIV infection	3 (2)	1 (1)	0.33	.34
Cancer	33 (26)	22 (17)	0.58	.09[b]
BMT	9 (7.0)	11 (9)	1.22	.66
Thyroid disease	14 (11)	14 (11)	1.00	>.99
Paraplegia	4 (3)	8 (6)	2.00	.60
Tobacco use	33 (6)	25 (20)	0.67	.21
Alcohol abuse	11 (9)	3 (2)	0.20	.04[b]

[a]Data represent No. (%) of patients unless otherwise specified.

[b]Significant at $P < .10$.

Dare et al, *Clin Infect Dis.* 2018

Results of Multivariable Analysis

Risk Factor	OR	*P* Value
Age	0.99	.16
BMI >30 kg/m^2	1.48	.25
Cirrhosis	0.16	.10
Dialysis	0.39	.14
Cancer	0.55	.16
Bacteremia	1.28	.53
Osteomyelitis	1.74	.11
Deep abscess	2.80	.03[a]
Antihistamine coadministration	3.50	.03[a]
Statin coadministration	2.60	.03[a]

Abbreviations: BMI, body mass index; OR, odds ratio.

[a]Significant at $P \leq .05$.

Dare et al, *Clin Infect Dis.* 2018

Summary and Recommendations from Manuscript

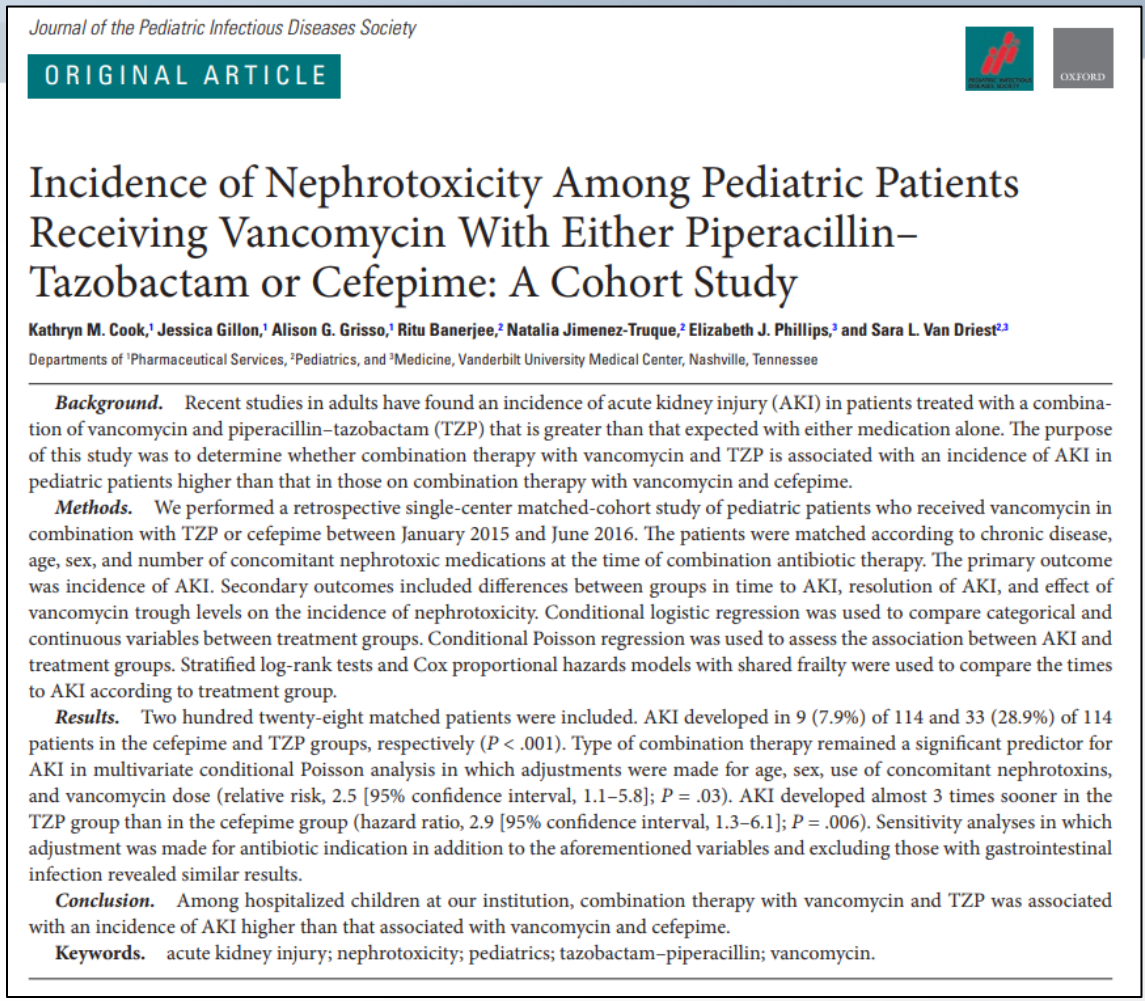
- In this dataset, statin coadministration is associated with increased risk of myopathy
- **Discontinue statins while on daptomycin**
- Assure compliance with CPK monitoring
- Consider twice weekly CPK and Creatinine monitoring in high risk patients

- **LIMITATIONS**: Retrospective (ascertainment bias, no causality, data limited to clinical documentation); Small sample size; Single center.

Dare et al, *Clin Infect Dis.* 2018

Outline

- Drug-Drug Interactions
  - Statin-daptomycin
  - Vancomycin-piperacillin/tazobactam
- Dose-Response
  - Statin
- Pharmacogenomics
  - Risperidone (adverse drug events)
  - Fentanyl (population PK)



Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE

Incidence of Nephrotoxicity Among Pediatric Patients Receiving Vancomycin With Either Piperacillin–Tazobactam or Cefepime: A Cohort Study

Kathryn M. Cook,[1] Jessica Gillon,[1] Alison G. Grisso,[1] Ritu Banerjee,[2] Natalia Jimenez-Truque,[2] Elizabeth J. Phillips,[3] and Sara L. Van Driest[2,3]

Departments of [1]Pharmaceutical Services, [2]Pediatrics, and [3]Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

Background. Recent studies in adults have found an incidence of acute kidney injury (AKI) in patients treated with a combination of vancomycin and piperacillin–tazobactam (TZP) that is greater than that expected with either medication alone. The purpose of this study was to determine whether combination therapy with vancomycin and TZP is associated with an incidence of AKI in pediatric patients higher than that in those on combination therapy with vancomycin and cefepime.

Methods. We performed a retrospective single-center matched-cohort study of pediatric patients who received vancomycin in combination with TZP or cefepime between January 2015 and June 2016. The patients were matched according to chronic disease, age, sex, and number of concomitant nephrotoxic medications at the time of combination antibiotic therapy. The primary outcome was incidence of AKI. Secondary outcomes included differences between groups in time to AKI, resolution of AKI, and effect of vancomycin trough levels on the incidence of nephrotoxicity. Conditional logistic regression was used to compare categorical and continuous variables between treatment groups. Conditional Poisson regression was used to assess the association between AKI and treatment groups. Stratified log-rank tests and Cox proportional hazards models with shared frailty were used to compare the times to AKI according to treatment group.

Results. Two hundred twenty-eight matched patients were included. AKI developed in 9 (7.9%) of 114 and 33 (28.9%) of 114 patients in the cefepime and TZP groups, respectively ($P < .001$). Type of combination therapy remained a significant predictor for AKI in multivariate conditional Poisson analysis in which adjustments were made for age, sex, use of concomitant nephrotoxins, and vancomycin dose (relative risk, 2.5 [95% confidence interval, 1.1–5.8]; $P = .03$). AKI developed almost 3 times sooner in the TZP group than in the cefepime group (hazard ratio, 2.9 [95% confidence interval, 1.3–6.1]; $P = .006$). Sensitivity analyses in which adjustment was made for antibiotic indication in addition to the aforementioned variables and excluding those with gastrointestinal infection revealed similar results.

Conclusion. Among hospitalized children at our institution, combination therapy with vancomycin and TZP was associated with an incidence of AKI higher than that associated with vancomycin and cefepime.

Keywords. acute kidney injury; nephrotoxicity; pediatrics; tazobactam–piperacillin; vancomycin.

Cook et al, *J Pediatric Infect Dis Soc.* 2018

Background and Methods

JAMA Pediatrics | Original Investigation

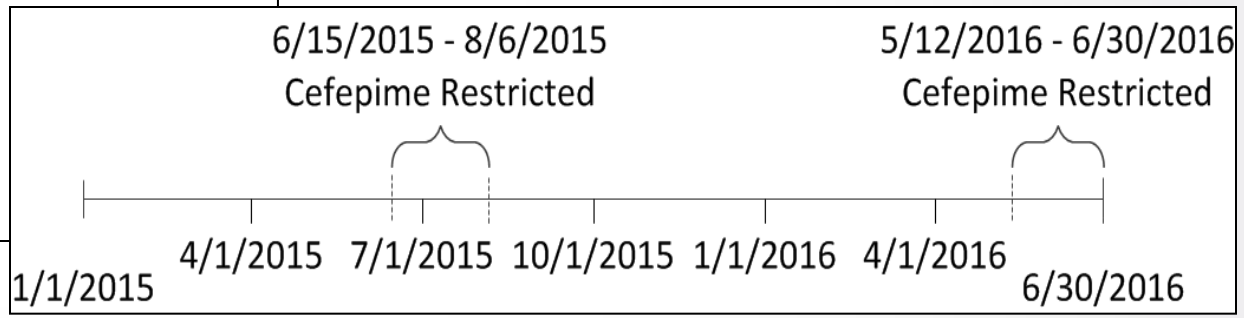
Association of Acute Kidney Injury With Concomitant Vancomycin and Piperacillin/Tazobactam Treatment Among Hospitalized Children

Kevin J. Downes, MD; Carter Cowden, MPH; Benjamin L. Laskin, MD, MS; Yuan-Shung Huang, MS; Wu Gong, MS, MPH; Matthew Bryan, PhD; Brian T. Fisher, DO, MPH, MSCE; Stuart L. Goldstein, MD; Theoklis E. Zaoutis, MD, MSCE

Supplemental content

IMPORTANCE β-Lactam antibiotics are often coadministered with intravenous (IV) vancomycin hydrochloride for children with suspected serious infections. For adults, the combination of IV vancomycin plus piperacillin sodium/tazobactam sodium is associated with a higher risk of acute kidney injury (AKI) compared with vancomycin plus 1 other β-lactam antibiotic. However, few studies have evaluated the safety of this combination for children.

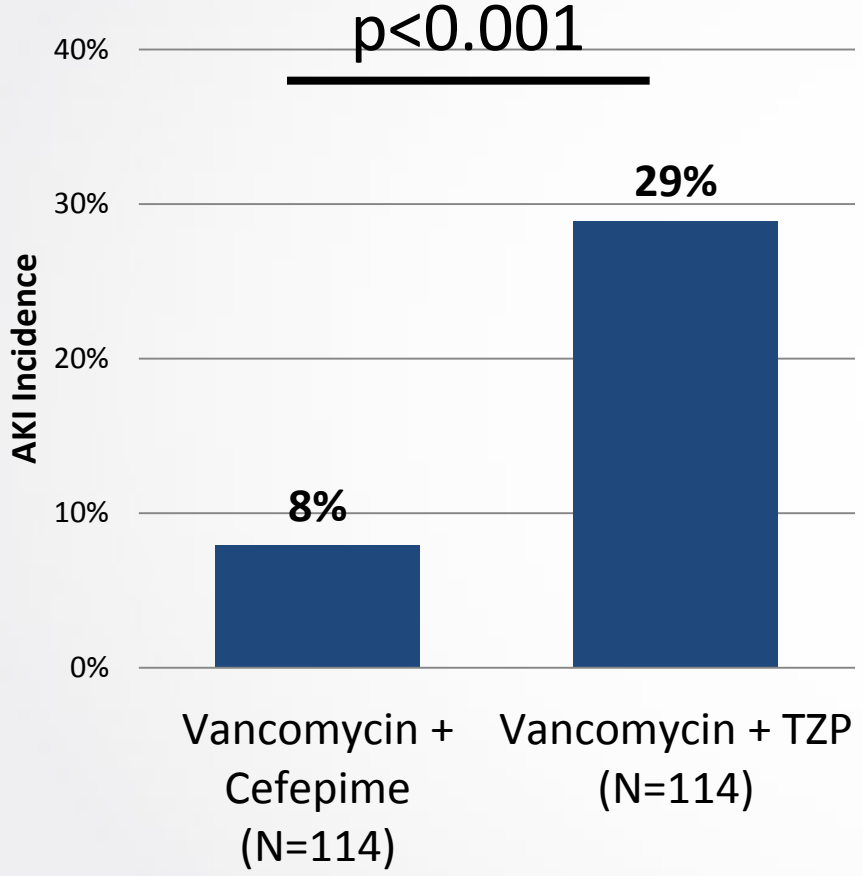
OBJECTIVE To assess the risk of AKI in children during concomitant therapy with vancomycin and 1 antipseudomonal β-lactam antibiotic throughout the first week of hospitalization.



Downes et al, *JAMA Pediatrics.* 2017
Cook et al, *J Pediatric Infect Dis Soc.* 2018

Results and Recommendations

Univariate Analysis of AKI in 228 Matched Children



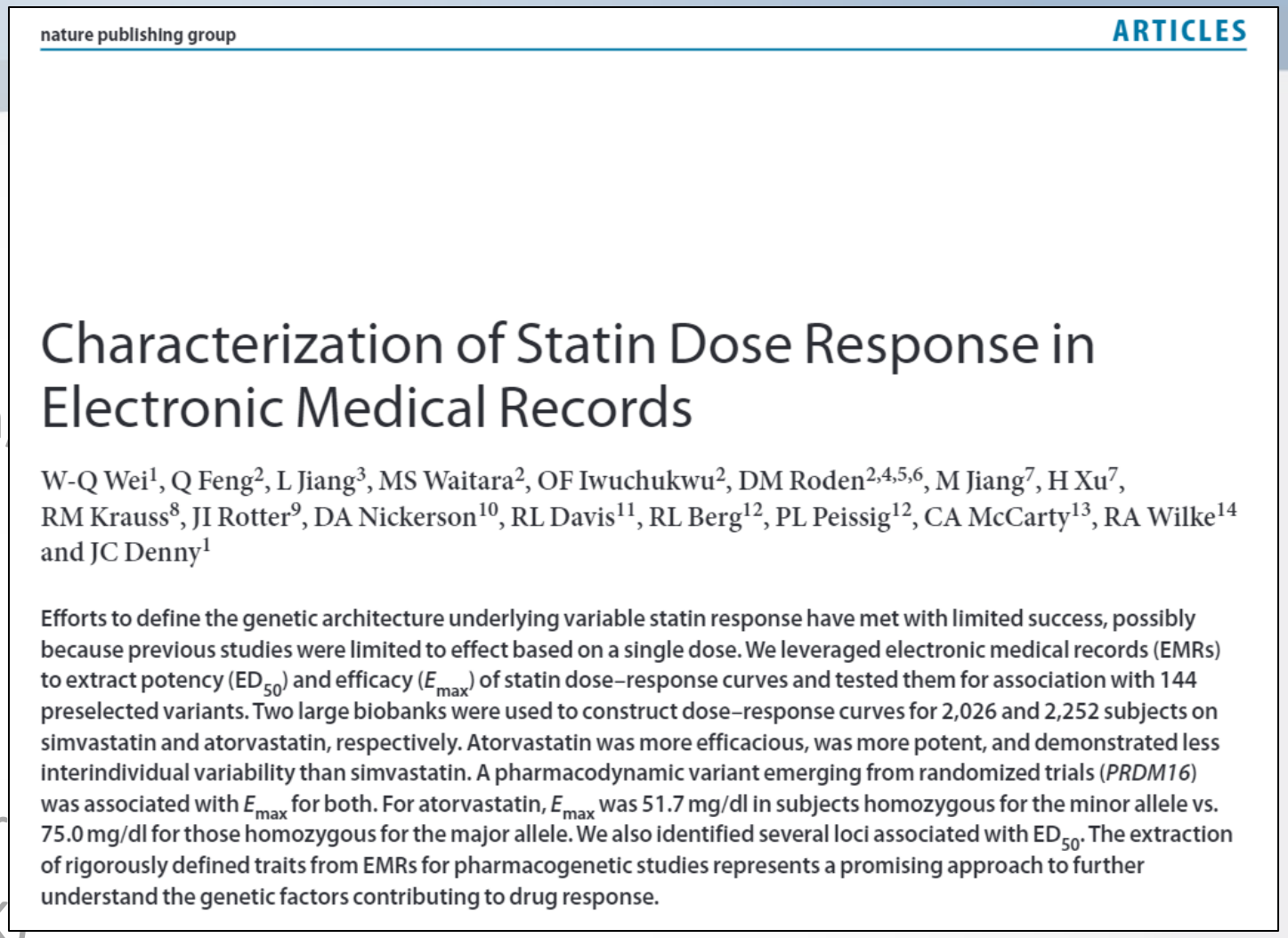
Adjusted Analysis of AKI in 228 Matched Children		
	Odds Ratio [95% CI]	**p-value**
Vancomycin + Cefepime	Reference	
Vancomycin + TZP	2.5 [1.1-5.8]	0.03
Adjusted for age, sex, nephrotoxins, and vancomycin dose		

- ✓ Monitor
- ✓ De-escalate
- ✓ Drug shortages affect patients

Cook et al, *J Pediatric Infect Dis Soc.* 2018

Outline

- Drug-Drug Interactions
  - Statin-daptomycin
  - Vancomycin-piperacillin
- Dose-Response
  - Statin
- Pharmacogenomics
  - Risperidone (adverse dr
  - Fentanyl (population PK)



nature publishing group ARTICLES

Characterization of Statin Dose Response in Electronic Medical Records

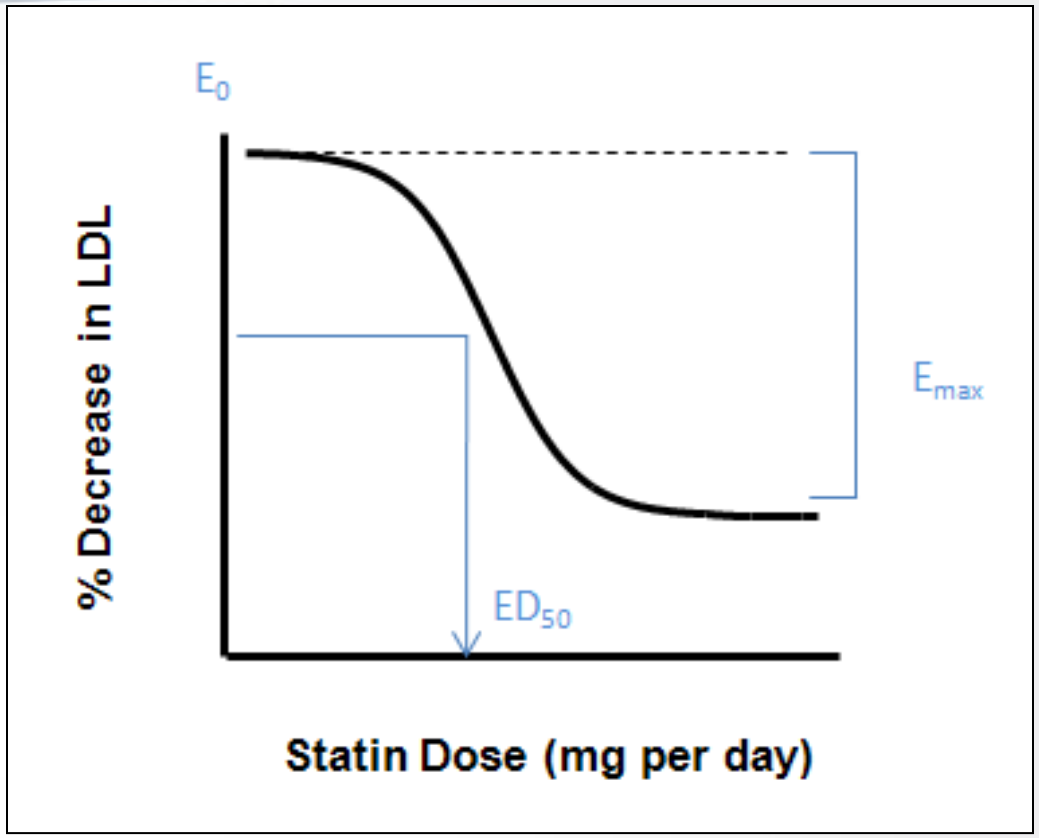
W-Q Wei[1], Q Feng[2], L Jiang[3], MS Waitara[2], OF Iwuchukwu[2], DM Roden[2,4,5,6], M Jiang[7], H Xu[7], RM Krauss[8], JI Rotter[9], DA Nickerson[10], RL Davis[11], RL Berg[12], PL Peissig[12], CA McCarty[13], RA Wilke[14] and JC Denny[1]

Efforts to define the genetic architecture underlying variable statin response have met with limited success, possibly because previous studies were limited to effect based on a single dose. We leveraged electronic medical records (EMRs) to extract potency (ED_{50}) and efficacy (E_{max}) of statin dose–response curves and tested them for association with 144 preselected variants. Two large biobanks were used to construct dose–response curves for 2,026 and 2,252 subjects on simvastatin and atorvastatin, respectively. Atorvastatin was more efficacious, was more potent, and demonstrated less interindividual variability than simvastatin. A pharmacodynamic variant emerging from randomized trials (*PRDM16*) was associated with E_{max} for both. For atorvastatin, E_{max} was 51.7 mg/dl in subjects homozygous for the minor allele vs. 75.0 mg/dl for those homozygous for the major allele. We also identified several loci associated with ED_{50}. The extraction of rigorously defined traits from EMRs for pharmacogenetic studies represents a promising approach to further understand the genetic factors contributing to drug response.

Wei et al, *Clin Pharm Ther.* 2014

Background and Methods

- Simvastatin and atorvastatin
  - Commonly used lipid-lowering drugs
  - RCTs identified potential pharmacogenomic associations
- Use longitudinal EHR data
  - Individuals with multiple dosing regimens
  - Serial lipid measurements
  - Candidate genetic variants



$$\mathrm{LDL_{Dose}} = \mathrm{E_0} - \frac{\mathrm{E_{max}} \times \mathrm{Dose}}{\mathrm{ED_{50}} + \mathrm{Dose}}$$

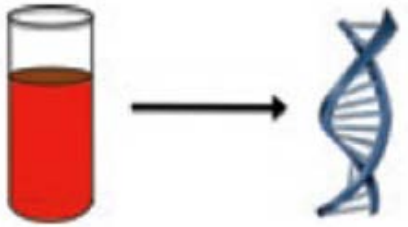
Wei et al, *Clin Pharm Ther.* 2014

The BioVU Resource

Electronic Health Records Data

- Notes
- Lab Results
- Drug Exposure
- Billing Codes

De-Identification



DNA from Discarded Blood Samples

Synthetic Derivative

>2.5 million individuals

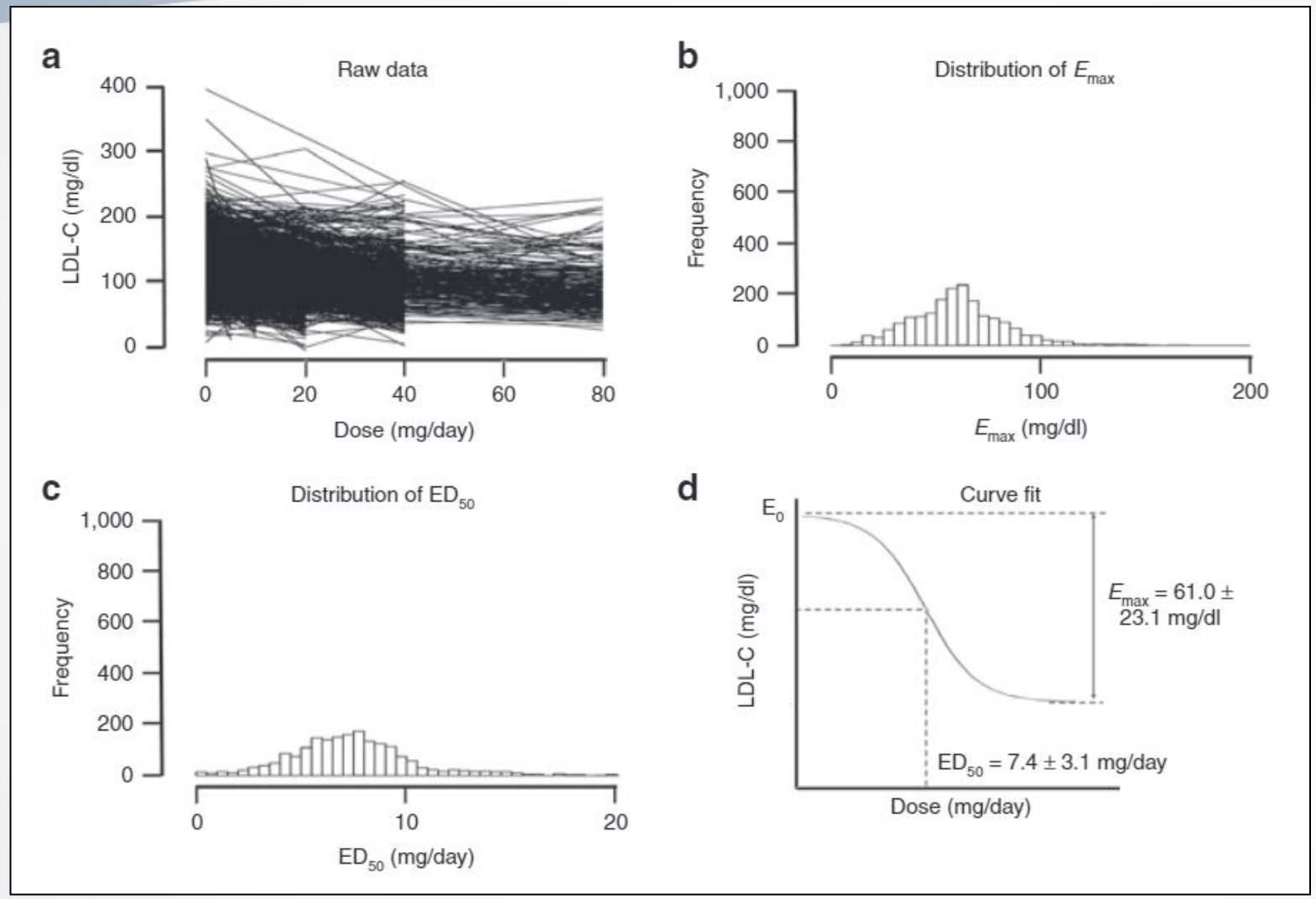
BioVU

>240,000 DNA samples

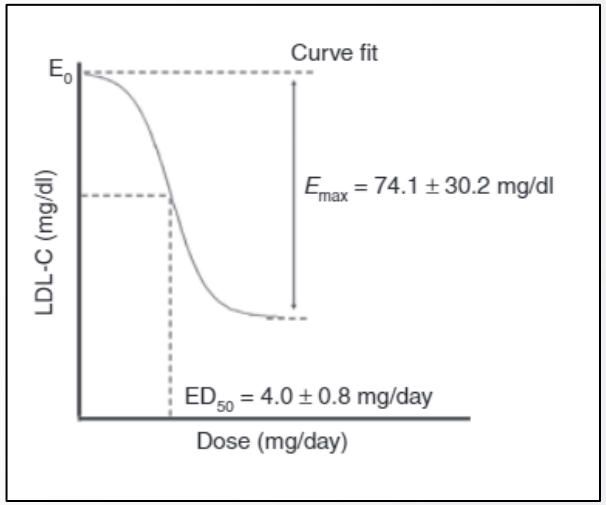
>30,000 pediatric

Results

Simvastatin



Atorvastatin



Wei et al, *Clin Pharm Ther.* 2014

Results

Variants associated with response to SIMVASTATIN

	SNP	Effect Size			*P* Value	Gene
		M/M	M/m	m/m		
EMAX (Efficacy)	rs6588480	61.86±24.38	57.40±21.14	59.46±17.88	0.0022	GLIS1
	rs776746	61.22±23.72	60.06±22.21	55.71±21.70	0.0065	CYP3A5
	rs7564379	61.00±23.44	59.92±22.07	56.53±27.90	0.0090	DGUOK
	rs17091962	59.97±23.01	64.01±25.09	66.51±22.13	0.0127	NEGR1
	rs1800961	60.16±23.26	66.71±23.62	58.76±26.03	0.0141	HNF4A
	rs2740574	61.07±23.65	58.87±20.73	57.12±23.93	0.0316	CYP3A4
	rs11807862	**60.92±23.34**	**59.50±23.02**	**53.23±23.51**	**0.0443**	**PRDM16**
ED50 (Potency)	rs1555926	7.63±3.27	7.00±2.82	7.08±2.86	0.0004	ZNF217
	rs17645290	7.33±2.99	7.57±3.47	8.53±3.63	0.0029	USP8
	rs4149056	7.55±3.20	7.12±3.02	7.06±2.30	0.0153	SLCO1B1
	rs35599367	7.49±3.18	6.78±2.69	10.15±0.00	0.0178	CYP3A4
	rs6495228	7.54±3.15	7.16±3.16	6.96±2.66	0.0202	RYR3
	rs8014194	7.34±3.08	7.40±2.95	8.04±4.11	0.0327	CLMN
	rs4438302	7.31±2.92	7.41±3.18	7.88±3.61	0.0343	LOC729913
	rs6029526	7.54±3.40	7.53±2.97	7.10±3.10	0.0432	PRO0628

M/M = homozygous major allele, M/m = heterozygous, m/m = homozygous minor allele

Wei et al, *Clin Pharm Ther.* 2014

Summary and Recommendations from Manuscript

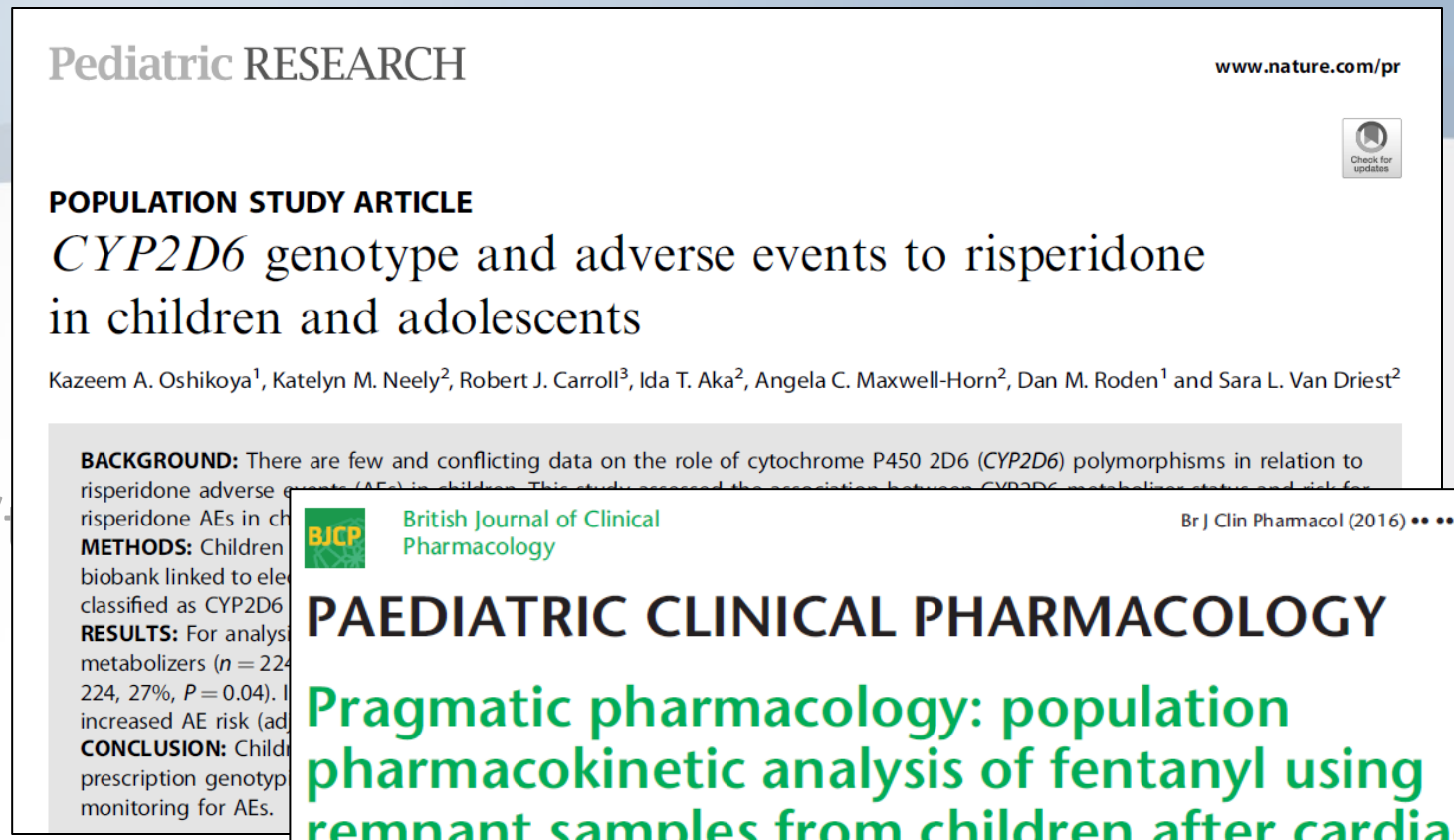
- Atorvastatin is more efficacious, more potent, less individual variability than simvastatin
- Identified drug-gene interactions: Patients genetically predisposed to low potency of simvastatin may need a more potent statin

- **LIMITATIONS**: Selection bias; No replication of genetic findings; Compliance unknown

Wei et al, *Clin Pharm Ther.* 2014

Outline

- Drug-Drug Interactions
  - Statin-daptomycin
  - Vancomycin-piperacillin/
- Dose-Response
  - Statin
- Pharmacogenomics
  - Risperidone (adverse drug events)
  - Fentanyl (population PK)



Pediatric RESEARCH

www.nature.com/pr

POPULATION STUDY ARTICLE

CYP2D6 genotype and adverse events to risperidone in children and adolescents

Kazeem A. Oshikoya[1], Katelyn M. Neely[2], Robert J. Carroll[3], Ida T. Aka[2], Angela C. Maxwell-Horn[2], Dan M. Roden[1] and Sara L. Van Driest[2]

BACKGROUND: There are few and conflicting data on the role of cytochrome P450 2D6 (*CYP2D6*) polymorphisms in relation to risperidone adverse

risperidone AEs in ch

METHODS: Children

biobank linked to ele

classified as CYP2D6

RESULTS: For analysi

metabolizers ($n = 224$

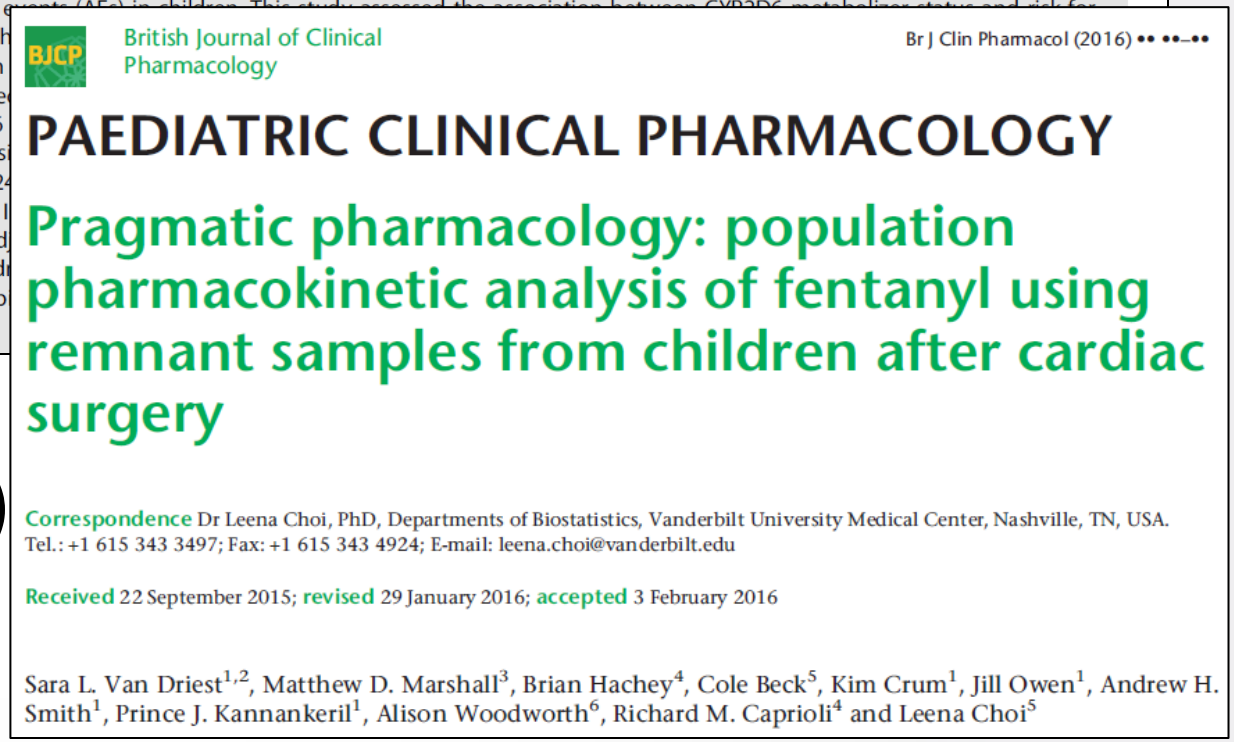
224, 27%, $P = 0.04$). I

increased AE risk (ad

CONCLUSION: Child

prescription genotyp

monitoring for AEs.



BJCP British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) •• ••–••

PAEDIATRIC CLINICAL PHARMACOLOGY

Pragmatic pharmacology: population pharmacokinetic analysis of fentanyl using remnant samples from children after cardiac surgery

Correspondence Dr Leena Choi, PhD, Departments of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA. Tel.: +1 615 343 3497; Fax: +1 615 343 4924; E-mail: leena.choi@vanderbilt.edu

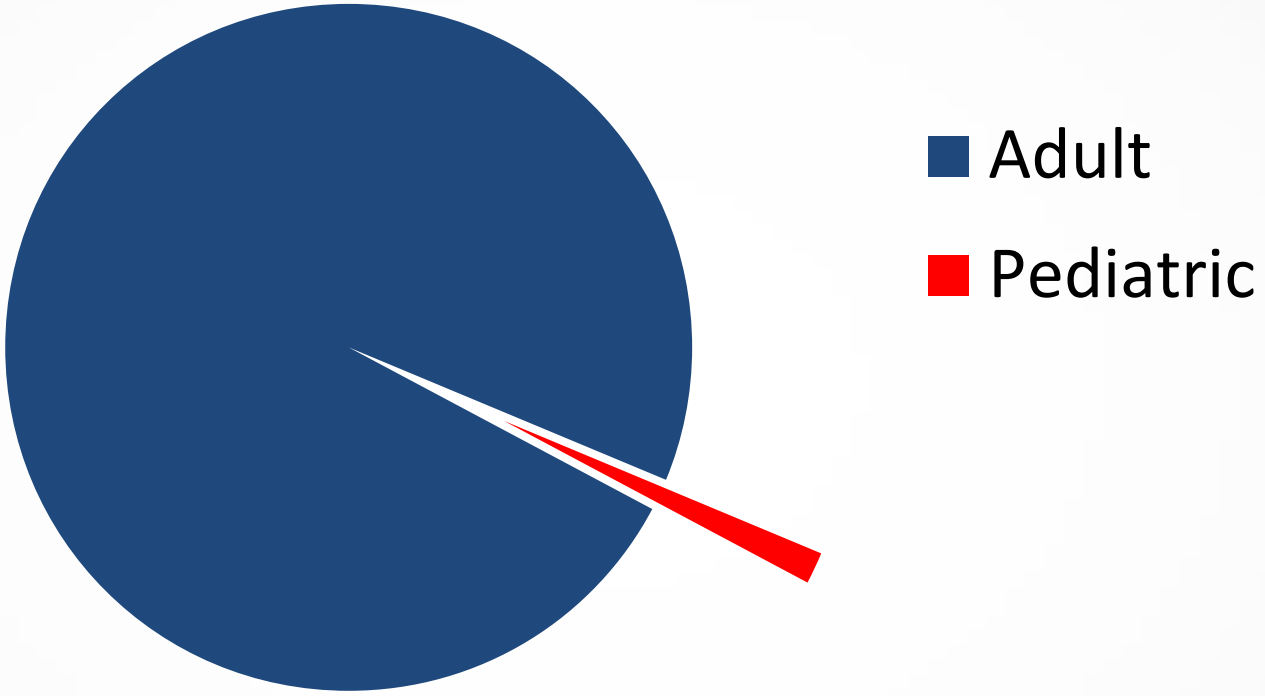
Received 22 September 2015; revised 29 January 2016; accepted 3 February 2016

Sara L. Van Driest[1,2], Matthew D. Marshall[3], Brian Hachey[4], Cole Beck[5], Kim Crum[1], Jill Owen[1], Andrew H. Smith[1], Prince J. Kannankeril[1], Alison Woodworth[6], Richard M. Caprioli[4] and Leena Choi[5]

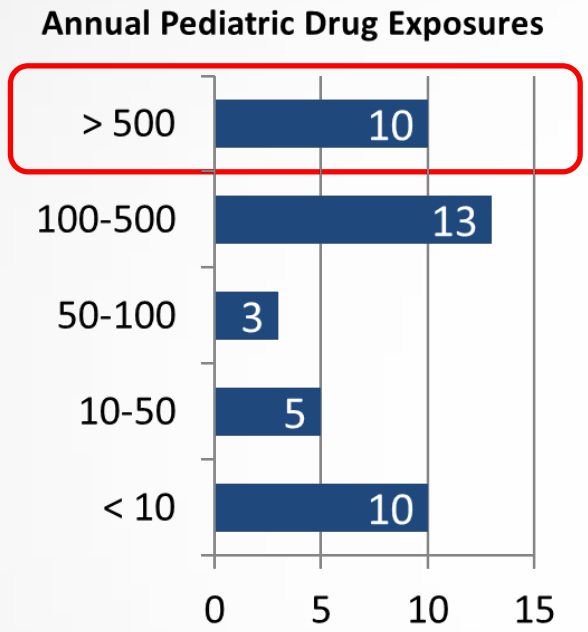
Oshikoya et al, *Peds Res.* 2019

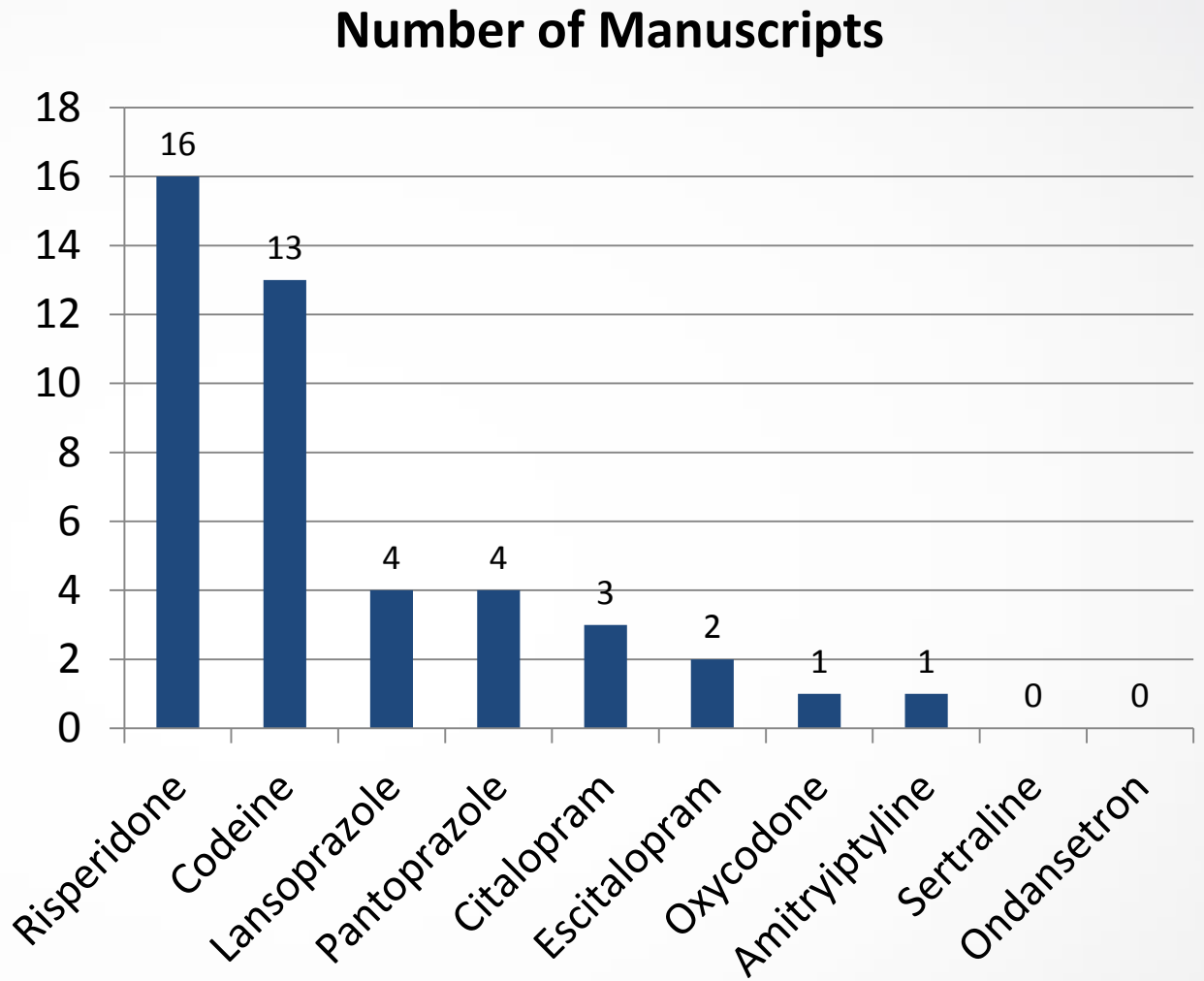
Van Driest et al, *Br J Clin Pharm.* 2016

Background: Few pediatric patients undergo PGx testing



Background: Lack of evidence for pediatric PGx



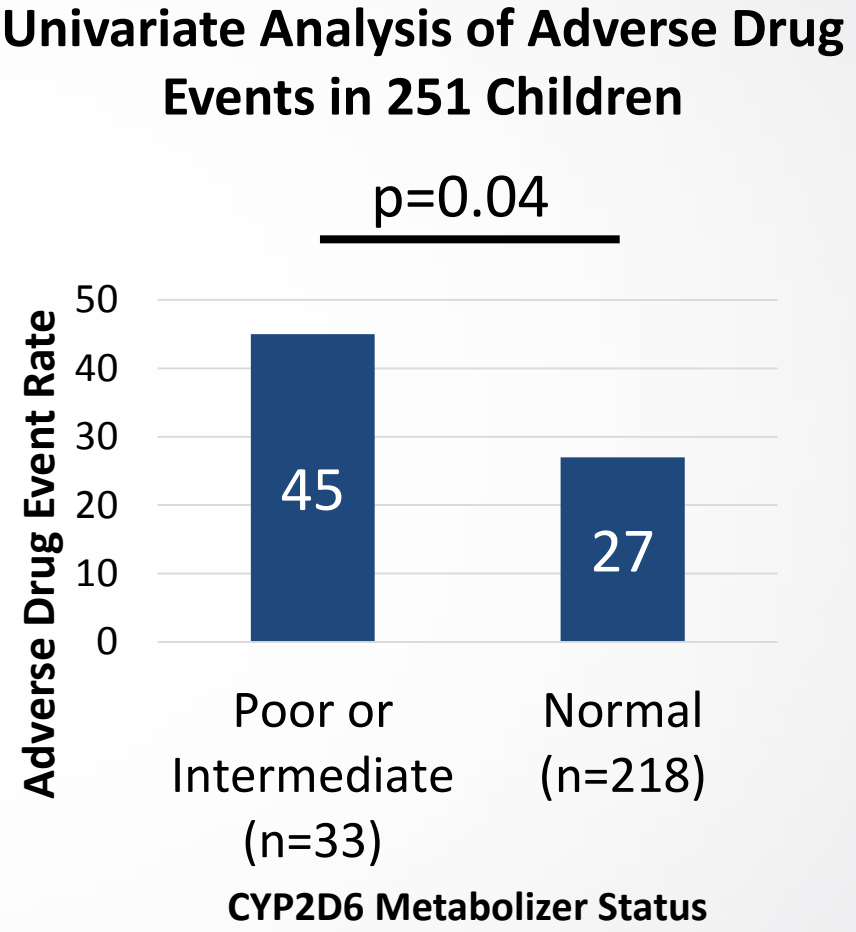


Aka, et al. *J Personalized Med* 2017

Results from BioVU Cohort

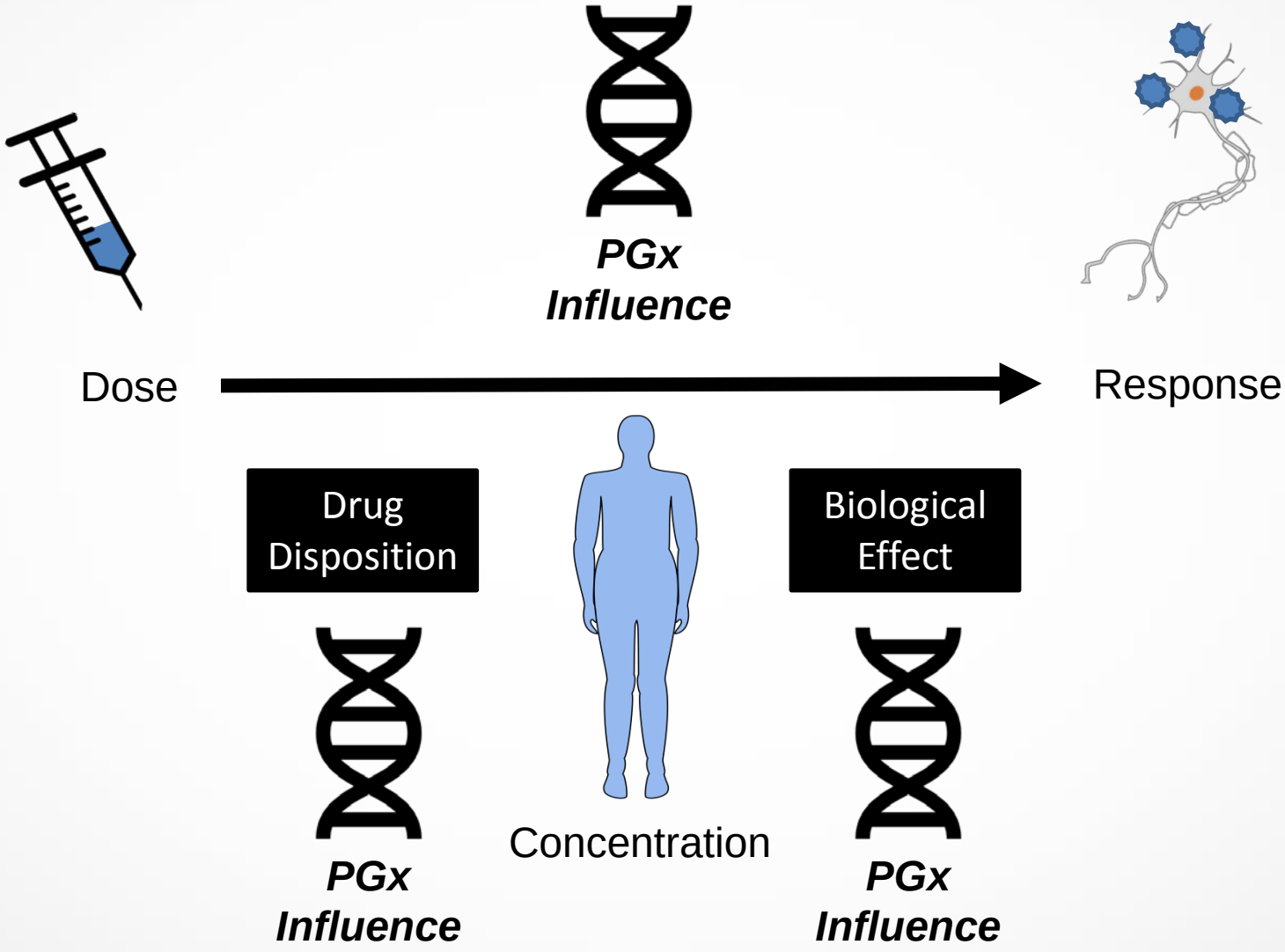
Cohort Summary Characteristics	
Variable	**N=257**
Age (Years)	8.3 (6.3-10.5)
Male Sex	188 (73%)
Adverse Events	76 (30%)
Metabolizer Status	
Ultrarapid	6 (2%)
Normal	218 (85%)
Intermediate	18 (7%)
Poor	15 (6%)

Number (%) or Median (Interquartile Range)



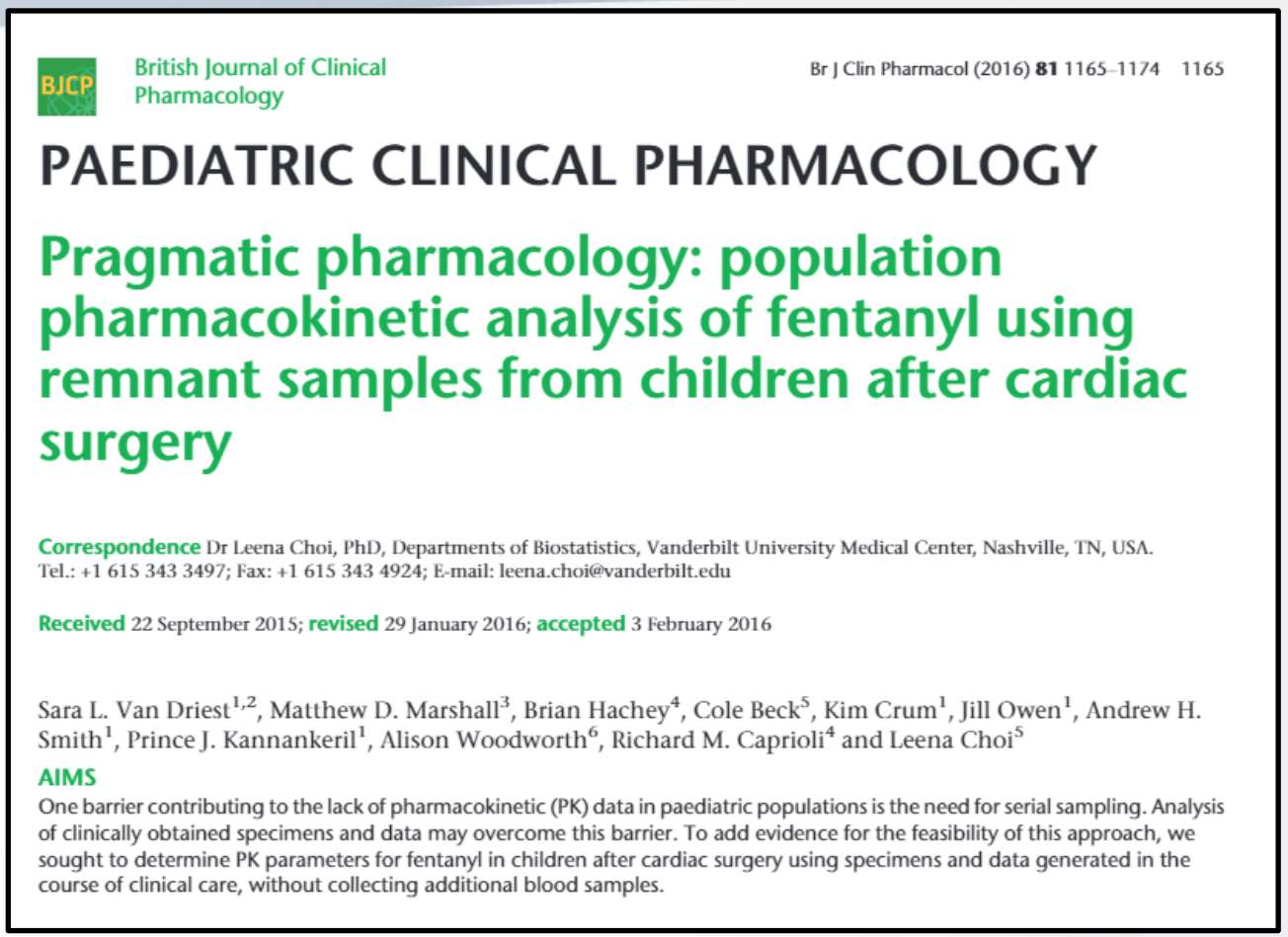
Oshikoya et al. *Pediatric Res* 2019

Common Theme in Pharmacogenetics



Clinical Sources for Pop PK Dataset

- Pediatric cardiac surgery patients
- Fentanyl doses from EHR
- All covariates from EHR
- All remnant plasma from chemistry lab scavenged for fentanyl concentration measurement



British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **81** 1165–1174 1165

PAEDIATRIC CLINICAL PHARMACOLOGY

Pragmatic pharmacology: population pharmacokinetic analysis of fentanyl using remnant samples from children after cardiac surgery

Correspondence Dr Leena Choi, PhD, Departments of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA. Tel.: +1 615 343 3497; Fax: +1 615 343 4924; E-mail: leena.choi@vanderbilt.edu

Received 22 September 2015; **revised** 29 January 2016; **accepted** 3 February 2016

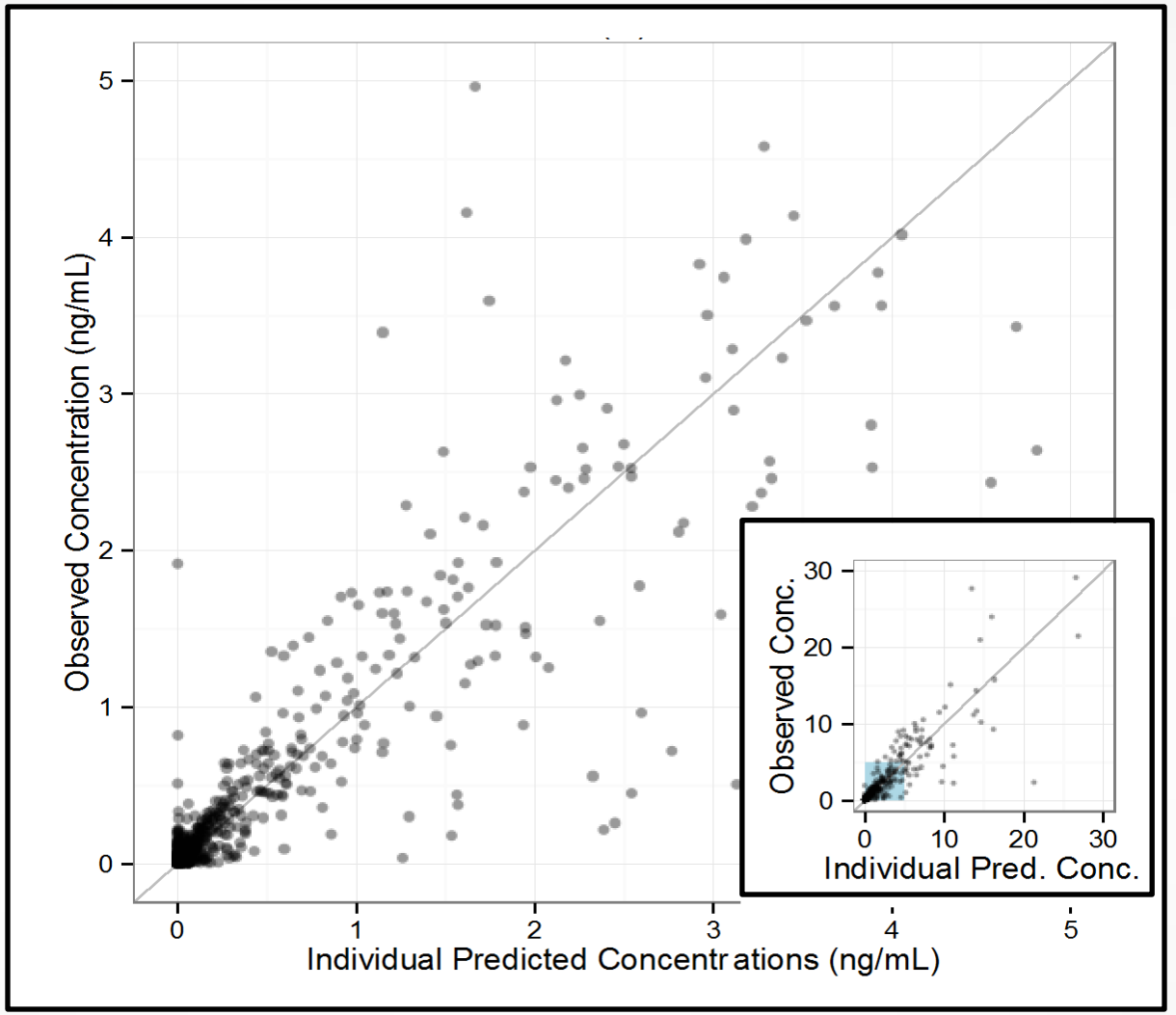
Sara L. Van Driest[1,2], Matthew D. Marshall[3], Brian Hachey[4], Cole Beck[5], Kim Crum[1], Jill Owen[1], Andrew H. Smith[1], Prince J. Kannankeril[1], Alison Woodworth[6], Richard M. Caprioli[4] and Leena Choi[5]

AIMS

One barrier contributing to the lack of pharmacokinetic (PK) data in paediatric populations is the need for serial sampling. Analysis of clinically obtained specimens and data may overcome this barrier. To add evidence for the feasibility of this approach, we sought to determine PK parameters for fentanyl in children after cardiac surgery using specimens and data generated in the course of clinical care, without collecting additional blood samples.

Van Driest et al, *Br J Clin Pharm.* 2016

PopPK Model – Pharmacogenetic analyses in progress!



Van Driest et al, *Br J Clin Pharm.* 2016

Final Summary

- EHR data can be used to define a wide variety of drug related traits
- Variability inherent to “routine” clinical care creates natural experiments
- Inherent limitations to retrospective data collection and “real world” data

Acknowledgements

Pharmacogenomics
- Kazeem Oshikoya
- Tiana Bernal
- Ida Aka
- Katelyn Neely
- Dan Roden

Population PK
- Leena Choi
- Cole Beck
- Prince Kannankeril
- Kim Crum
- Darlene Fountain
- Carla Hissam
- Brian Hachey

Statin Daptomycin
- Ryan Dare
- Chad Tewell
- Bryan Harris
- Patty Wright
- Eric Farber-Eger
- George Nelson
- Thomas Talbot

AKI and TZP
- Katie Cook
- Jessica Gillon
- Alison Grisso
- Ritu Banerjee
- Natalia Jimenez-Truque
- Elizabeth J. Phillips

Statin Dose Response
- Wei-Qi Wei
- Quiping Feng
- Lan Jiang
- Otito Iwuchukwu
- Dan Roden
- Collaborators at Univ of Texas, Children's Hospital Oakland, Los Angeles BioMedical Research Institute, University of Washington, Kaiser Permanente Georgia, Marshfield Clinic, Essentia Institute of Rural Health, Sanford Healthcare

Funding

NIH National Institute of General Medical Sciences

Doris Duke Charitable Foundation

PhRMA Foundation

Burroughs Wellcome Fund