Pharmacovigilance in Clinical Trials

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The traditional drug safety model

- Passive surveillance of real-world usage
- Phase IIIb and IV trials
- Spontaneous adverse-events reports

- Spontaneous adverse-events reports
- Minimal clinical trials
- Infrequent aggregate safety reporting

- Fewer clinical trials than in early stage 2
- Frequent aggregate safety reporting

Phase III Clinical Trials

- The exposure of a limited number (generally between 500–3000) of patients during clinical development and for a limited time.
- The randomized controlled trials may control for disease variability, but generally not for variability in individual response rates or adverse events that are difficult to anticipate.
- Many serious ADRs are infrequent or rare (<1 in 1000 in most cases and occasionally <1 in 10,000) and may not be detected against a background rate in the population receiving a placebo or active control.
- To identify an ADR that occurs in one in 10,000 patients, at least 30,000 patients would need to be enrolled in the randomized clinical trial program to have any chance of detecting it.

The challenges of identifying rare adverse drug reactions in clinical trials

Most clinical trials are designed and powered to detect differences in primary efficacy end points

- e.g. for medications for chronic, non-life-threatening conditions, ICH Technical Requirements recommends sample sizes that might not have adequate power to detect adverse drug reactions (ADRs) occurring in as many as 1 in 100 patients.

- Although extremely rare ADRs can be practically detected only in a post-marketing setting, using larger pre-marketing safety databases can be beneficial and cost-effective
Avoidable and unavoidable adverse drug reactions

Avoidable and Unavoidable ADRs

- Off-target binding of the drug could lead to ADRs and may not be related to the same level of exposure that is responsible for on-target efficacy.

- Unavoidable ADRs are the idiosyncratic reactions for which the underlying mechanisms are not understood - these have been reported to contribute to 10% of ADRs.

- Unavoidable ADRs may become avoidable after gaining insight into the mechanisms underlying the ADRs, e.g. carbamazepine-induced SJS/TEN and HLA-B*1502, or considered acceptable based upon benefit–risk considerations.

Toxicities leading to drug withdrawal from the US market


<table>
<thead>
<tr>
<th>Withdrawn</th>
<th>Approval</th>
<th>Drug name</th>
<th>Use</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>1997</td>
<td>Mibefradil</td>
<td>High blood pressure/ Chronic stable angina</td>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>1998</td>
<td>1997</td>
<td>Bromfenac</td>
<td>NSAID</td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>1998</td>
<td>1985</td>
<td>Terfenadine</td>
<td>Antihistamine</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td>1999</td>
<td>1988</td>
<td>Astemizole</td>
<td>Antihistamine</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td>1999</td>
<td>1997</td>
<td>Grepafloxacin</td>
<td>Antibiotics</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>2000</td>
<td>2000</td>
<td>Alosetron*</td>
<td>Irritable bowel syndrome in women</td>
<td>Ischemic colitis; complications of constipation</td>
</tr>
<tr>
<td>2000</td>
<td>1993</td>
<td>Cisapride</td>
<td>Heartburn</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td>2000</td>
<td>1997</td>
<td>Troglitazone</td>
<td>Diabetes</td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>2001</td>
<td>1997</td>
<td>Cerivastatin</td>
<td>Cholesterol lowering</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td>2001</td>
<td>1999</td>
<td>Rapacuronium</td>
<td>Anesthesia</td>
<td>Bronchospasm</td>
</tr>
</tbody>
</table>

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QT interval prolongation and torsades de pointes

Atrial fibrillation
QT interval 420 msec

QT interval prolongation and torsades de pointes

Atrial fibrillation
QT interval 420 msec

Sinus rhythm after a single dose of dofetilide
QT interval 560 msec

QT interval prolongation and torsades de pointes

A Thorough QT Study - TQT

- QTci - QTcorrected individual, exponential
- QTciL - QTcorrected, individual, linear
- QTcF - QTcorrected, Fridericia
- QTcB - QTcorrected, Bazett.

Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

Patient with long-QT syndrome type 1 with QTc of 410 ms

Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

Spontaneous generation of polymorphic ventricular tachycardia

Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

Treated with nadolol and implantable cardioverter-defibrillator but still had arrhythmic episodes

Drugs That May Cause Torsade de Pointes

Drugs commonly involved
- Disopyramide
- Dofetilide
- Ibutilide
- Procainamide
- Quinidine
- Sotalol
- Bepridil

Others:
- Amiodarone
- Arsenic trioxide
- Cisapride
- Calcium-channel blockers: lidoflazine (not marketed in the United States)
- Antiinfective agents: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin
- Antiemetic agents: domperidone, droperidol
- Antipsychotic agents: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- Methadone

## Associations between polymorphisms and drug-induced torsades de pointes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug category</th>
<th>Gene(s)</th>
<th>Cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibutramine</td>
<td>Serotonin and noradrenaline re-uptake inhibitor</td>
<td>KCNQ1</td>
<td>1</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>H₁-receptor antagonist</td>
<td>HERG</td>
<td>1</td>
</tr>
<tr>
<td>Multiple, including sotalol and quinidine</td>
<td>Anti-arrhythmics and non-anti-arrhythmics</td>
<td>KCNQ1 HERG SCN5A</td>
<td>92/67</td>
</tr>
<tr>
<td>Cisapride Bactrim</td>
<td>Parasympathomimetic para-aminobenzoic acid inhibitor</td>
<td>HERG SCN5A</td>
<td>32/32</td>
</tr>
<tr>
<td>Sotalol Amiodarone Contrast-media containing iodide</td>
<td>β-adrenergic antagonist Vaughan-Williams class III anti-arrhythmic Contrast agent</td>
<td>KCNH2</td>
<td>9/16</td>
</tr>
</tbody>
</table>

Drug-induced liver injury

Troglitazone (Rezulin) – thiazolidinedione
Developed by Daiichi Sankyo Co.
Introduced and manufactured by Parke-Davis
Associated with idiosyncratic hepatitis.
Withdrawn in the UK in December 1997
Withdrawn in the USA 21 March 2000
Withdrawn in Japan soon afterwards
Selected reports of genetic associations with drug-induced liver injury

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene(s)</th>
<th>Drug class</th>
<th>Form of toxicity</th>
<th>Cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ximelagatran</td>
<td>DRB1<em>07, DQA1</em>02</td>
<td>Oral thrombin inhibitor</td>
<td>Elevation in transaminase</td>
<td>74/130</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>UGT1A16</td>
<td>Catechol-O-methyltransferase inhibitor</td>
<td>Asymptomatic liver transaminase elevation</td>
<td>135/274</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>UGT2B7, CYP2C8, ABCC2</td>
<td>NSAID</td>
<td>Range from acute liver failure to non-specific symptoms with transaminase elevation</td>
<td>24/48</td>
</tr>
<tr>
<td>Tranils</td>
<td>UGT1A1</td>
<td>TGF-β antagonist</td>
<td>Unconjugated hyper-bilirubinaemia</td>
<td>127/909</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>CYP2E1, NAT2</td>
<td>Antibiotic</td>
<td>Elevation in serum transaminases</td>
<td>49/269</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>GSTM1, NAT2</td>
<td>Antibiotic</td>
<td>Icteric hepatitis (serum bilirubin &gt; 3.0 mg/dl)</td>
<td>37/33</td>
</tr>
<tr>
<td>Isoniazid Rifampin Ethambutol Pyrizinamide Streptomycin</td>
<td>DRB1<em>03, DAO1</em>0102, DOB1*0201</td>
<td>Antibiotic</td>
<td>Elevation in serum bilirubin or transaminases</td>
<td>22/134</td>
</tr>
<tr>
<td>Amoxicillin/ Clavulanic acid</td>
<td>DRB1<em>1501, DRB1</em>0102, O1*0202</td>
<td>Antibiotic/penicillin analogue</td>
<td>Jaundiced elevation in serum bilirubin</td>
<td>22/134</td>
</tr>
<tr>
<td>Tacrine</td>
<td>GST T1, GST M1</td>
<td>Parasympathomimetic</td>
<td>Elevation in serum transaminases</td>
<td>52/89</td>
</tr>
<tr>
<td>Teglitrazone</td>
<td>GST T1, GST M2</td>
<td>Thiazolidinedione</td>
<td>Elevation in serum transaminases</td>
<td>25/83</td>
</tr>
</tbody>
</table>

Statins

Statins have diverse chemical structures governing binding affinity and lipophilicity but share the common pharmacophore with resemblance to HMG

Simvastatin and lovastatin are given as lactones and have to be converted to the open acid moiety for enzyme binding

Clinical pharmacokinetics of cerivastatin

• Cerivastatin is exclusively cleared via metabolism. No unchanged drug is excreted. Cerivastatin is subject to 2 main oxidative biotransformation reactions: demethylation of the benzylic methyl ether moiety leading to the metabolite M-1 [catalysed by cytochrome P450 (CYP) 2C8 and CYP3A4] and stereoselective hydroxylation of one methyl group of the 6-isopropyl substituent leading to the metabolite M-23 (catalysed by CYP2C8). All 3 metabolites are active inhibitors of hydroxymethylglutaryl-coenzyme A reductase with a similar potency to the parent drug. Approximately 70% of the administered dose is excreted as metabolites in the faeces, and 30% in the urine. Metabolism by 2 distinct CYP isoforms renders cerivastatin relatively resistant to interactions arising from inhibition of CYP. If one of the pathways is blocked, cerivastatin can be effectively metabolised by the alternative route.

• In addition, on the basis of in vitro investigations, there is no evidence for either cerivastatin or its metabolites having any inducing or inhibitory activity on CYP. The apparent lack of any clinically relevant interactions with a variety of drugs commonly used by patients in the target population supports this favourable drug-drug interaction profile.

Cerivastatin

- >90% intestinal absorption
- Highly selective to liver
- Water-soluble
- Rapid hepatic clearance
- Metabolites
  - M-1 and M-23 (50% and 100% relative potency of cerivastatin)
  - excretion: 70% feces, 24% urine
- Linear pharmacokinetics
- $t_{1/2} = 2 - 4$ hours

Data from cerivastatin prescribing information
Cerivastatin - Clinical Pharmacokinetic Profile

- Cerivastatin is a non-complicated drug with respect to bioavailability and biopharmaceutics.

- Cerivastatin has dual metabolic pathways with the involvement of more than one cytochrome P450 isozyme (CYP 2C8, 3A4).

- Cerivastatin has very favourable interaction profile with many common drugs such as digoxin, warfarin, antacids, cimetidine, nifedipine, omeprazole, erythromycin, and itraconazole.
Cerivastatin
Contraindication

- Cerivastatin is contraindicated in patients with hypersensitivity to any component of this medication, in patients with active liver disease or unexplained persistent elevations of serum transaminases, in women during pregnancy, and in nursing mothers.

**The combined use of cerivastatin and gemfibrozil is contraindicated due to a risk for rhabdomyolysis**

In December 1999 Bayer proactively placed the contraindication in the Baycol PI. This was reinforced at the same time by a letter to Health Care Professionals informing them of this contraindication in the PI. To date, a majority of the cases of rhabdomyolysis reported with cerivastatin have occurred when used in combination with gemfibrozil.

Data from cerivastatin prescribing information 1999
Interaction of statins with gemfibrozil

- Rhabdomyolysis due to combination therapy with cerivastatin and gemfibrozil.
  Patient on gemfibrozil and pravastatin 20 mg daily switched to cerivastatin 0.6 mg daily developed rhabdomyolysis

- Predictable since this dose of cerivastatin is equivalent to 4 times that dose of pravastatin and lipophilicity is many times greater (octanol/water ratio 29.5 for cerivastatin, 0.6 for pravastatin)
Cerivastatin and Rhabdomyolysis

**US-FDA:** “... has received reports of 31 U.S. deaths due to severe rhabdomyolysis associated with use of Baycol®, 12 of which involved concomitant gemfibrozil use...”

**EU-EMEA:** “...480 reports of a sometimes fatal muscle reaction called rhabdomyolysis had been received globally from patients taking Baycol®.”

http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01095.html
*European Medicines Evaluation Agency, Reuters News, August 8-2001*
Baycol (cerivastatin sodium tablets) Aug 2001
Audience: Health Professionals and Consumers
Bayer announced the withdrawal of all dosages of its cholesterol-lowering drug with the brand names Baycol/Lipobay (active ingredient: cerivastatin), due to increasing reports of side effects involving muscular weakness (rhabdomyolysis). Fatal rhabdomyolysis associated with Baycol have been reported most frequently when used at higher doses, when used in elderly patients, and particularly, when used in combination with gemfibrozil (LOPID and generics), another lipid lowering drug. [August 08, 2001 - Letter - Bayer]
Cerivastatin withdrawal

- The problem with cerivastatin was identified by pharmacovigilance by US, European and other agencies
- Better awareness/communication of the data may have identified it earlier
- More detailed Phase I studies might have prevented the problem – older female patients were at greater risk
CPK Elevations with Cerivastatin 0.8 mg

Incidence of CPK >10 X ULN in Patients Taking Cerivastatin 0.8 mg

* Of Patients with Elevated CPK: 70% were symptomatic and 80 % discontinued drug

Gemfibrozil greatly increases cerivastatin plasma concentrations

Cerivastatin metabolism pathways

Statin distribution, metabolism and elimination

Cerivastatin and gemfibrozil

Genetic variation associated with statin-induced myotoxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene(s)</th>
<th>Form of toxicity</th>
<th>Cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerivastatin</td>
<td>CYP2C8, OATP2, OATP1B1, (SLCO1B1)</td>
<td>Rhabdomyolysis</td>
<td>1</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>OATPC, OATP1B3, (SLCO1B3)</td>
<td>Myopathy</td>
<td>1</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>ABCB1, (MDR1)</td>
<td>Myalgia</td>
<td>15/99</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>CYP3A5</td>
<td>Myalgia</td>
<td>69/68</td>
</tr>
<tr>
<td>Multiple statins, including cerivastatin</td>
<td>CPT 2, AMPD, PYGM</td>
<td>Myopathy</td>
<td>136/116</td>
</tr>
<tr>
<td>Multiple statins, including rosuvastatin and atorvastatin</td>
<td>COQ2</td>
<td>Myopathy</td>
<td>133/158</td>
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</table>

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group

ABSTRACT

BACKGROUND
Lowering low-density lipoprotein cholesterol with statin therapy results in substantial reductions in cardiovascular events, and larger reductions in cholesterol may produce larger benefits. In rare cases, myopathy occurs in association with statin therapy, especially when the statins are administered at higher doses and with certain other medications.

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FDA News

Simvastatin Used With Amiodarone

Audience: Cardiologic healthcare professionals, pharmacists, other healthcare professionals

[Posted 08/08/2008] FDA notified healthcare professionals of the risk of muscle injury, rhabdomyolysis, which can lead to kidney failure or death, when simvastatin is used with amiodarone. This risk is dose-related and increases when a dose of simvastatin greater than 20 mg per day is given with amiodarone. Although a revision of the simvastatin labeling in 2002 described an increased risk of rhabdomyolysis when amiodarone is taken with simvastatin doses greater than 20 mg daily, FDA continues to receive reports of rhabdomyolysis in patients treated concurrently with amiodarone and simvastatin. Prescribers should be aware of the increased risk of rhabdomyolysis when simvastatin is prescribed with amiodarone, and they should avoid doses of simvastatin greater than 20 mg per day in patients taking amiodarone.

[August 08, 2008 - Drug Information Page - FDA]
[August 08, 2008 - Information for Healthcare Professionals - FDA]
Simvastatin-amiodarone interaction

Simvastatin 80 mg /day
Amiodarone 200 mg /day

Figure 1. Changes in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), and creatinine (Cr) before and during rhabdomyolysis. ALT = ◆; AST = ▲; CK = ◆; Cr = ■.

Simvastatin-amiodarone interaction

Simvastatin acid AUC(0-24) ↑ by 73% with amiodarone 400mg/day for 3 days

SLCO1B1 Variants and Statin-Induced Myopathy - a Genomewide Study

Nearly complete LD with rs4149056 (521 T>C) in SLCO1B1

Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genomewide Association Study.

P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association (P<5x10^-7).

SLCO1B1 Variants and Statin-Induced Myopathy - a Genomewide Study

Estimated cumulative risk of myopathy associated with taking 80 mg of simvastatin daily, according to SLCO1B1 rs4149056 (*5, 521T>C) genotype.

60% of myopathy cases could be attributed to the C variant.

**SLCO1B1 521 T>C polymorphism markedly affects the pharmacokinetics of simvastatin acid**

Open squares --- c.521TT genotype (n=16);
solid squares --- c.521TC genotype (n=11);
solid triangles --- c.521CC genotype (n=4).

Simvastatin acid AUC\((0-\infty)\) ↑ 3.2x in CC vs. TT

FDA issues rosuvastatin advisory highlighting revised label

March 2, 2005
Wilkinson, DE - The Food and Drug Administration (FDA) issued a public-health advisory on rosuvastatin (Crestor®) today that highlights a revised package insert for the cholesterol-lowering medication.

Also, based on a pharmacokinetic study that found elevated drug levels in a population of Asian patients, the "Dosage and Administration" section of the label now advises that the 5-mg dose of rosuvastatin be considered the starting dose in this population.
Associations of \(ABCG2\) 421C>A Polymorphism and Pharmacokinetics of Rosuvastatin

**Chinese subjects**

![Rosuvastatin 20 mg](image)


**Finnish subjects**

![Rosuvastatin 20 mg](image)

ABCG2 polymorphism increases rosuvastatin plasma levels and efficacy

ABCG2 Polymorphism Is Associated With the Low-Density Lipoprotein Cholesterol Response to Rosuvastatin

B Tomlinson¹, M Hu¹, VWY Lee², SSH Lui¹, TTTW Chu¹, EF Poon³, GTC Ko³, I Baum², LS Tam¹ and EK Li³

The ATP-binding cassette G2 (ABCG2) c.421C>A (rs2231142) polymorphism influences the pharmacokinetics of rosuvastatin. We examined whether this polymorphism influences the low-density lipoprotein cholesterol (LDL-C)-lowering efficacy of the drug. In 305 Chinese patients with hypercholesterolemia who were treated with rosuvastatin at a dosage of 10 mg daily, the c.421A variant was found to be significantly associated with greater reduction in LDL-C level, in a gene-dose-dependent manner. In comparison to subjects with the c.421CC genotype, those with the c.421AA genotype showed a 6.9% greater reduction in LDL-C level, which would be equivalent to the effect obtained by doubling the dose of rosuvastatin.

in drug metabolizing enzymes, given that rosuvastatin undergoes relatively little enzymic modification and is a substrate for a number of drug transporters that influence its disposition.⁶⁷ The efflux transporter ATP-binding cassette G2 (ABCG2) plays a significant role in the disposition of rosuvastatin in vitro.⁷ The c.421C>A (rs2231142, Gln141Lys) single-nucleotide polymorphism of ABCG2 influences the pharmacokinetics of rosuvastatin in Chinese and Caucasian subjects.⁶⁸ We examined whether this ABCG2 single-nucleotide polymorphism influences the reduction of LDL-C levels when rosuvastatin is administered to Chinese patients with hypercholesterolemia, including some with familial hypercholesterolemia (FH).

Hepatic Uptake and Efflux Transporters Which Influence Statin Pharmacokinetics

Rosuvastatin – are there interactions with ABCG2 inhibitors?
Metabolism of HDL-C and its role in reverse cholesterol transport

Cholesteryl ester transfer protein inhibitors


<table>
<thead>
<tr>
<th>Compound</th>
<th>CE transfer IC₅₀ (nM)</th>
<th>CETP binding</th>
<th>Complex between CETP and HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalcetrapib</td>
<td>1178 ± 443</td>
<td>Covalent</td>
<td>Yes</td>
</tr>
<tr>
<td>Torcetrapib</td>
<td>13 ± 2.7</td>
<td>Reversible</td>
<td>Yes</td>
</tr>
<tr>
<td>Anacetrapib</td>
<td>17 ± 4.8</td>
<td>Reversible</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ILLUMINATE: Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events

- Torcetrapib $\rightarrow$ 72.1% increase in HDL-C, 24.9% decrease in LDL-C
- Increased risk of CV events (HR, 1.25; 95% CI, 1.09 to 1.44; $P = 0.001$)
- Increased risk death from any cause (HR, 1.58; 95% CI, 1.14 to 2.19; $P = 0.006$)
- Increase in SBP (5.4 mm Hg), serum Na+, HCO$_3^-$, and aldosterone; decrease in K$^+$
- Post hoc analyses: increased risk of death with ↓ in K$^+$ or ↑ in HCO$_3^-$ > the median

Putative site of action of torcetrapib on the angiotensin II /aldosterone pathway involving L-type calcium channels

Learning lessons from Pfizer’s $800 million failure

The catastrophic failure of Pfizer’s torcetrapib looked like it might doom an entire class of cholesterol modulators, but next month Merck will move its anacartapib into one of the largest cardiovascular trials ever. Asher Mullard investigates how drug developers have reignited hope for the CETP inhibitors.
Cardiovascular outcome studies for diabetes drugs


  - TECOS - sitagliptin
  - SAVOR-TIMI – saxagliptin
  - LEADER – liraglutide
  - EXSCEL – exenatide once weekly
Conclusions

• Pre-marketing drug safety data is gradually improving
• Better understanding of mechanisms of toxicity and genetic predisposition can facilitate identification of problems at an early stage:
  – QT prolongation
  – Drug interactions through enzymes and transporters
• Thorough assessment of the clinical pharmacology of new drugs is essential
• Liver toxicity and off-target effects remain a problem
• Anecdotal evidence should not be ignored
If it were not for the great variability among individuals, medicine might as well be a science and not an art.

Sir William Osler (1892)