Safety assessment

José Sánchez 2020-02-19

Safety and efficacy

What is the most important?

You can't have one without the other!

Equally important but with very different characteristics

Safety and efficacy

Hypotheses for efficacy are (should be) well-defined

Clinical trials are most often dimensioned for the primary efficacy variable

Hypotheses concerning safety assessments are less well-defined

Dimensioning for safety would require very large studies, since also very rare events could be of outmost importance

Safety assessments in clinical trials

We don’t know what we are looking for,
just that we will not like it when we find it!

- Extent of exposure
- Adverse events and laboratory test data
- Serious adverse events and other significant adverse events

Extent of exposure

How many?

- Number of patients exposed to drug

How long?

- Duration of exposure

How much?

- Dose

$$\text{Toxicity} = f(\text{exposure})$$

Extent of exposure: Examples

Number of subjects	Number of doses	Doses received
8	2	60 mg + 480 mg
8	2	120 mg + 600 mg
8	1	240 mg

		Treatment A (n = 1698)	Treatment B (n = 1699)
Duration (patient years)	Total	2255.4	2336.1
Duration (days)	Total	823222	852670
	Mean	485	502
	SD	170	145
	Range	2-743	1-730

Terminology for adverse events

Adverse drug reaction

Toxicities

Side effect

Severe adverse event

Risk

Significant adverse event

Adverse experience

Adverse event

Serious adverse event

Adverse event

Definition (ICH): An adverse event is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product.

Serious adverse event

Definition (ICH): A serious adverse event or reaction is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalisation
- Results in persistent of significant disability/incapacity
- Is a congenital anomaly/birth defect

Adverse Reaction (AR)

Adverse Reaction (AR)

- Any unintended responses to an investigational medicinal product **related** to any dose administered
- *Comment:* All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction

Unexpected Adverse Reaction (UAR)

- An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)
- *Comment:* When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Definition of Seriousness

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any AE, AR or UAR that at any dose:

- results in death
- is life-threatening*
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect

Coding of adverse events

Dictionaries needed in order to group similar events

Many different dictionaries available:

- Coding Symbols for a Theaurus of a Adverse Reaction Term (COSTART)
- World Health Orginasation Adverse Reaction Terminology (WHOART)
- Medical Dictionary for Regulatory Activities (MedDRA)

MedDRA coding

MedDRA Structure Hierarchy	Example
System Organ Class (SOC)	Infections and infestations
High Level Group Term (HLGT)	Infections – pathogen unspecified
High Level Term (HLT)	Upper respiratory tract infections
Preferred Term (PT)	Nasopharyngitis
Lowest Level Term (LLT)	Common cold

Types of adverse events

Different types of events:

Absorbing events (e.g. death)

- Probability of occurrence

Recurrent events with negligible duration (e.g.)

- Number of events

Recurrent events with nonnegligible duration (e.g. headache)

- Proportion of time affected

Different measures and analysis are relevant!

Analysis of adverse events

- Descriptive statistics often the primary approach
  - Number and proportion of AEs
  - Number and proportion of patients with AEs
- Rates of occurrence of (rare) adverse events
  - Number of events per patient years
- Relative risks of (common) adverse events
  - Treatment comparison
  - Hazard rate
  - Stratified Mantel-Haenszel estimate of relative risk

Example

Number (%) of patients with at least one AE and total number of AEs

	Treatment A N = 87	Treatment B N = 83
Number (%) of patients with AE		
Any AE	57 (65.5%)	64 (77.1%)
SAE with outcome death	0 (0%)	1 (1.2%)
SAE	5 (5.7%)	4 (4.8%)
AE leading to discontinuation of study drug	4 (4.6%)	11 (13.3%)
AE leading to discontinuation of study	0 (0%)	0 (0%)
Total number of AEs		
Any AE	133	184
SAE	6	5

Example continued

Number (%) of patients with SAEs by preferred term

	Treatment A N = 87	Treatment B N = 83
Patients with any SAE	5 (5.7%)	4 (4.8%)
Preferred term		
Back pain	1 (1.1%)	1 (1.2%)
Cerebrovascular accident	1 (1.1%)	
Hypotension	2 (2.3%)	1 (1.2%)
Lower limb fracture		1 (1.2%)
Major depression	1 (1.1%)	
Pneumonia	1 (1.1%)	2 (2.4%)

Estimating relative risk

Assume k trials, each with two treatments (A and B). The relative risk of a certain (absorbing!) event is assumed to be the same in each trial and the number of events are assumed to follow a Poisson distribution.

- $i = 1,\ldots,k$ (trials); $j = A,B$ (treatments)
- E_{ij} = number of events in trial i on treatment j (random variable)
- e_{ij} = observed number of events in trial i on treatment j
- t_{ij} = total exposure time in trial i on treatment j
- $E_{ij} \in Po(\lambda_{ij} t_{ij})$
- $Var[E_{ij}] = \lambda_{ij} t_{ij}$
- $\lambda_{ij} = e_{ij} / t_{ij}$

The Mantel-Haenszel estimate

Mantel-Haenszel estimate (stratified by trial) of the common relative risk, RR_{MH}:

$$\lambda_j = \Sigma_i \, w_i \cdot \lambda_{ij} \; / \; \Sigma_i \, w_i$$

$$w_i = 2 \; / \; (1/t_{iA} + 1/t_{iB})$$

$$RR_{MH} = \lambda_A \; / \; \lambda_B$$

$$\log RR_{MH} = \log \lambda_A - \log \lambda_B$$

Variance

Variance of the Mantel-Haenszel estimate :

$$\mathrm{Var}\,[\lambda_j] = (\Sigma_i\, w_i^2 \cdot e_{ij} / t_{ij}^2) \;/\; (\Sigma_i\, w_i)^2$$

$$\mathrm{Var}\,[\log \lambda_j] = 1/\lambda_j^2 \cdot \mathrm{Var}\,[\lambda_j] = (\Sigma_i\, w_i^2 \cdot e_{ij} / t_{ij}^2) \;/\; (\Sigma_i\, w_i \cdot e_{ij} / t_{ij})^2$$

Confidence intervals

Confidence intervals:

$$CI_{\lambda_j} = \lambda_j \pm 1.96 \cdot (\mathrm{Var}\,[\lambda_j])^{1/2}$$

$$CI_{\lambda_A - \lambda_B} = \lambda_A - \lambda_B \pm 1.96 \cdot (\mathrm{Var}\,[\lambda_A] + \mathrm{Var}\,[\lambda_B])^{1/2}$$

$$CI_{\log RR_{MH}} = \log \lambda_A - \log \lambda_B \pm 1.96 \cdot (\mathrm{Var}\,[\log \lambda_A] + \mathrm{Var}\,[\log \lambda_B])^{1/2}$$

$$CI_{RR_{MH}} = \lambda_A / \lambda_B \cdot \exp \{ \pm 1.96 \cdot (\mathrm{Var}\,[\log \lambda_A] + \mathrm{Var}\,[\log \lambda_B])^{1/2} \}$$

Example

Summary of exposure and number of patients with renal impairment

	Treatment A				Treatment B			
	N	Events	Exposure (pt yrs)	Event rate (per pt yr)	N	Events	Exposure (pt yrs)	Event rate (per pt yr)
Trial 1	325	11	101.7	0.108	85	1	35.7	0.028
Trial 2	86	0	12.2	0.000	49	1	6.9	0.145
Trial 3	307	10	411.5	0.024	252	7	340.1	0.021
Trial 4	153	3	32.3	0.093	74	1	17.9	0.056

Example

Mantel-Haenszel estimates of the event rate (per pt yr) for renal impairment

	Estimate	95% confidence interval
Treatment A	0.037	[0.025, 0.056]
Treatment B	0.026	[0.014, 0.048]

Mantel-Haenszel estimates of the risk for renal impairment for treatment A compared to treatment B

	Estimate	95% confidence interval
Risk difference (A-B)	0.011	[-0.0107, 0.0335]
Relative risk (A versus B)	1.44	[0.68, 3.05]

Analysis of laboratory data

Lab Variable = Variable indicating biological function observed from biological sample (analysed in a lab)

Clinical chemistry

aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin (total), creatinine, thyroid stimulating hormone, thyroxin (free), urate, albumin, C-reactive protein

glucose, sodium, potassium, calcium (albumin corrected), creatine kinase

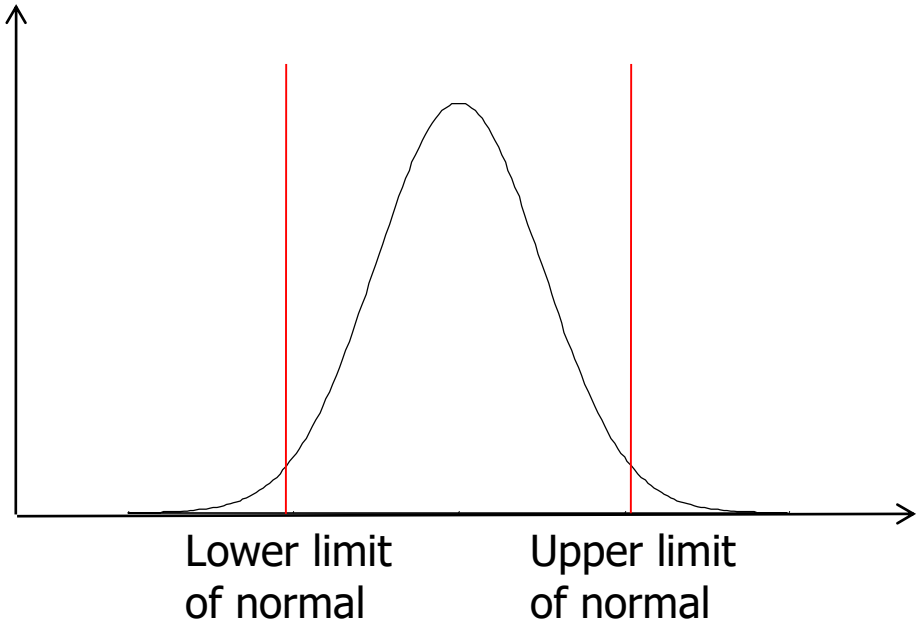
Haematology

haemoglobin, haptoglobin, leukocyte count, thrombocyte count, reticulocyte count, leukocyte differential count, mean corpuscular volume, mean corpuscular haemoglobin concentration

Urinalysis

protein, glucose, haemoglobin

Reference limits



Created from a population data set, often specific to each lab leading to different labs having different reference limits

Used to indicate abnormal values.

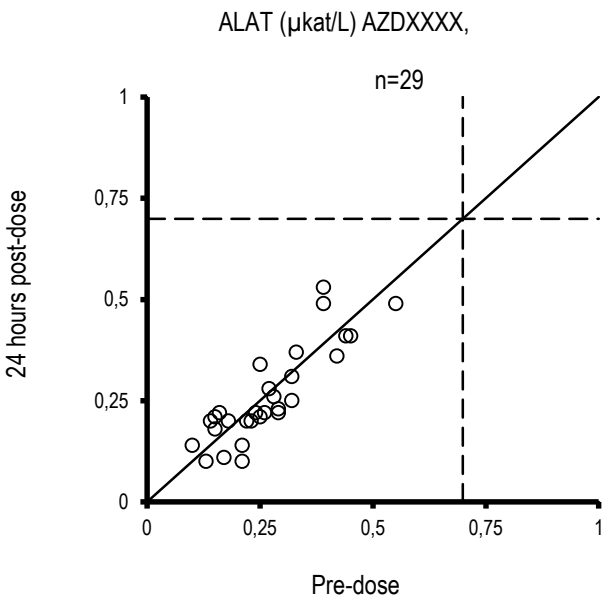
May differ between males, females, age groups

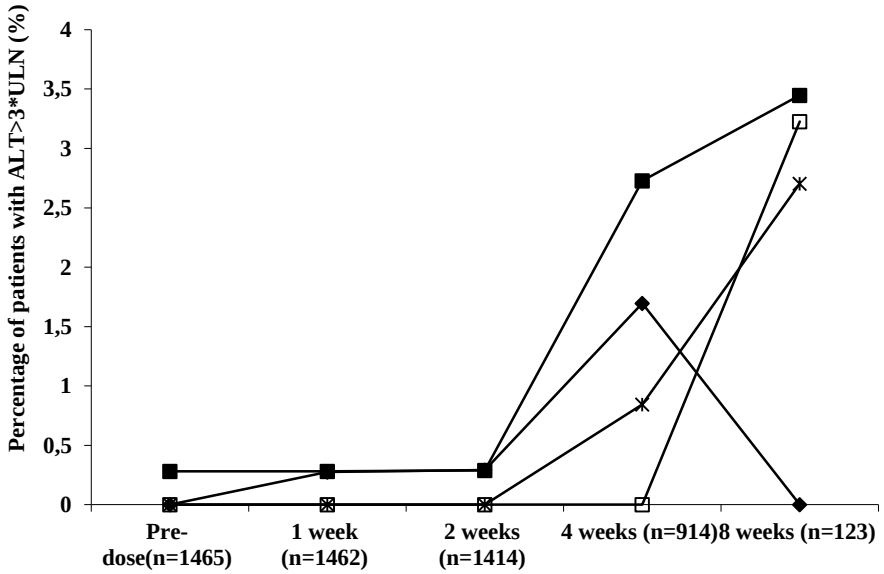
What are we looking for?

- Long term gradual effects
- Acute toxic reactions

- Shift in population average
- Reactions in few sensitive patients

Example

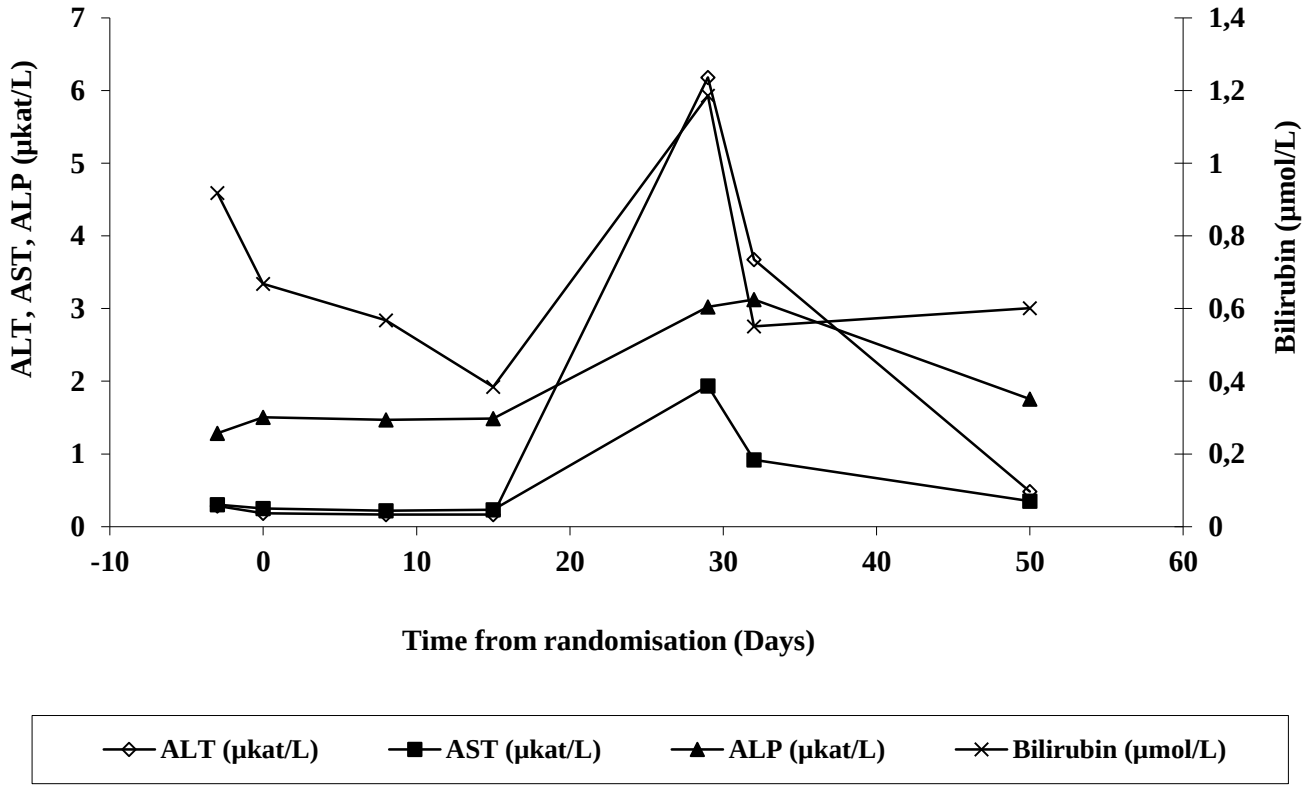




No indication of acute effect of a single dose on the liver.

An increase in the percentage of patients with ALT>3*ULN indicates potential liver issues developing over time.

Example

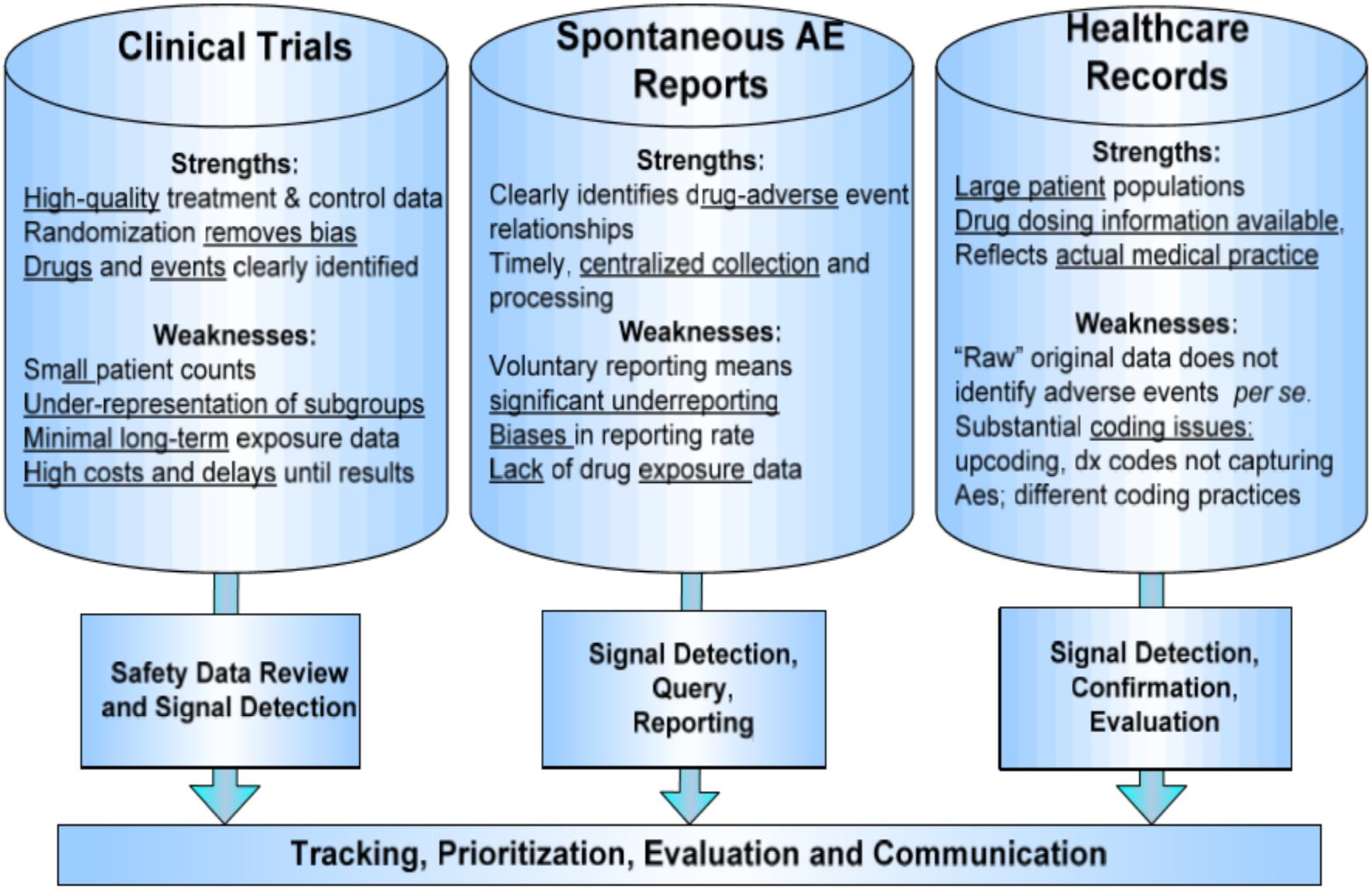


Liver values for a single patient

Table 1 Pre-dose and last visit observations of clinical chemistry variables, Safety Population

Lab variable (unit)	Treatment	Pre-dose Mean (SD)	Last visit[a] Mean (SD)	Change[b] Mean (SD)
ALT (µkat/L)	AZDXXXX5 25 mg	0.51 (0.30)	0.52 (0.30)	0.01 (0.22)
	AZDXXXX5 50 mg	0.50 (0.27)	0.54 (0.30)	0.05 (0.21)
	AZDXXXX5 75 mg	0.51 (0.29)	0.53 (0.34)	0.02 (0.22)
AST (µkat/L)	AZDXXXX5 25 mg	0.41 (0.20)	0.41 (0.15)	0.00 (0.17)
	AZDXXXX5 50 mg	0.39 (0.14)	0.42 (0.18)	0.03 (0.13)
	AZDXXXX5 75 mg	0.40 (0.15)	0.41 (0.16)	0.01 (0.14)
ALP (µkat/L)	AZDXXXX5 25 mg	1.37 (0.40)	1.34 (0.39)	-0.03 (0.18)
	AZDXXXX5 50 mg	1.35 (0.40)	1.34 (0.39)	-0.01 (0.17)
	AZDXXXX5 75 mg	1.36 (0.39)	1.33 (0.37)	-0.02 (0.19)
CK (µkat/L)	AZDXXXX5 25 mg	2.84 (14.54)	2.18 (1.57)	-0.66 (14.36)
	AZDXXXX5 50 mg	2.20 (1.55)	2.17 (1.77)	-0.03 (1.81)
	AZDXXXX5 75 mg	2.13 (1.44)	2.14 (1.37)	0.01 (1.37)
Creatinine (µmol/L)	AZDXXXX5 25 mg	78.80 (17.45)	77.42 (16.71)	-1.38 (11.00)
	AZDXXXX5 50 mg	80.52 (18.03)	78.12 (16.06)	-2.40 (13.78)
	AZDXXXX5 75 mg	80.31 (17.59)	78.38 (16.48)	-1.92 (10.54)
Bilirubin, tot (µmol/L)	AZDXXXX5 25 mg	9.66 (4.53)	9.56 (4.81)	-0.10 (3.57)
	AZDXXXX5 50 mg	10.29 (5.36)	9.33 (4.45)	-0.97 (3.82)
	AZDXXXX5 75 mg	9.69 (4.80)	8.90 (4.00)	-0.79 (3.55)
Sodium (mmol/L)	AZDXXXX5 25 mg	142.02 (2.51)	142.42 (2.75)	0.41 (2.90)
	AZDXXXX5 50 mg	142.11 (2.49)	142.25 (2.71)	0.14 (2.70)
	AZDXXXX5 75 mg	142.10 (2.38)	142.52 (2.57)	0.42 (2.75)

Primary Sources of Safety Evidence



Regulatory Considerations

- Patient safety is the paramount concern
- Ensuring validity of statistical inferences and minimizing bias
- Maintaining study integrity (preplanning endpoints and analyses and maintaining blind)
- Data Safety Review Committees to have access to blinded data is accepted practice
- No official regulatory opinion on validity of using prior distributions and surrogate placebo populations as comparators

Further issues in Drug Safety

- Data Monitoring Committees
- stopping for harm/futility
- quality reporting of harms
- absolute risk matters
- balancing efficacy and harm
- scare stories $\Rightarrow$ good evidence
- posting-licencing safety trials
- meta-analyses (good and bad)
- observational data (tricky)

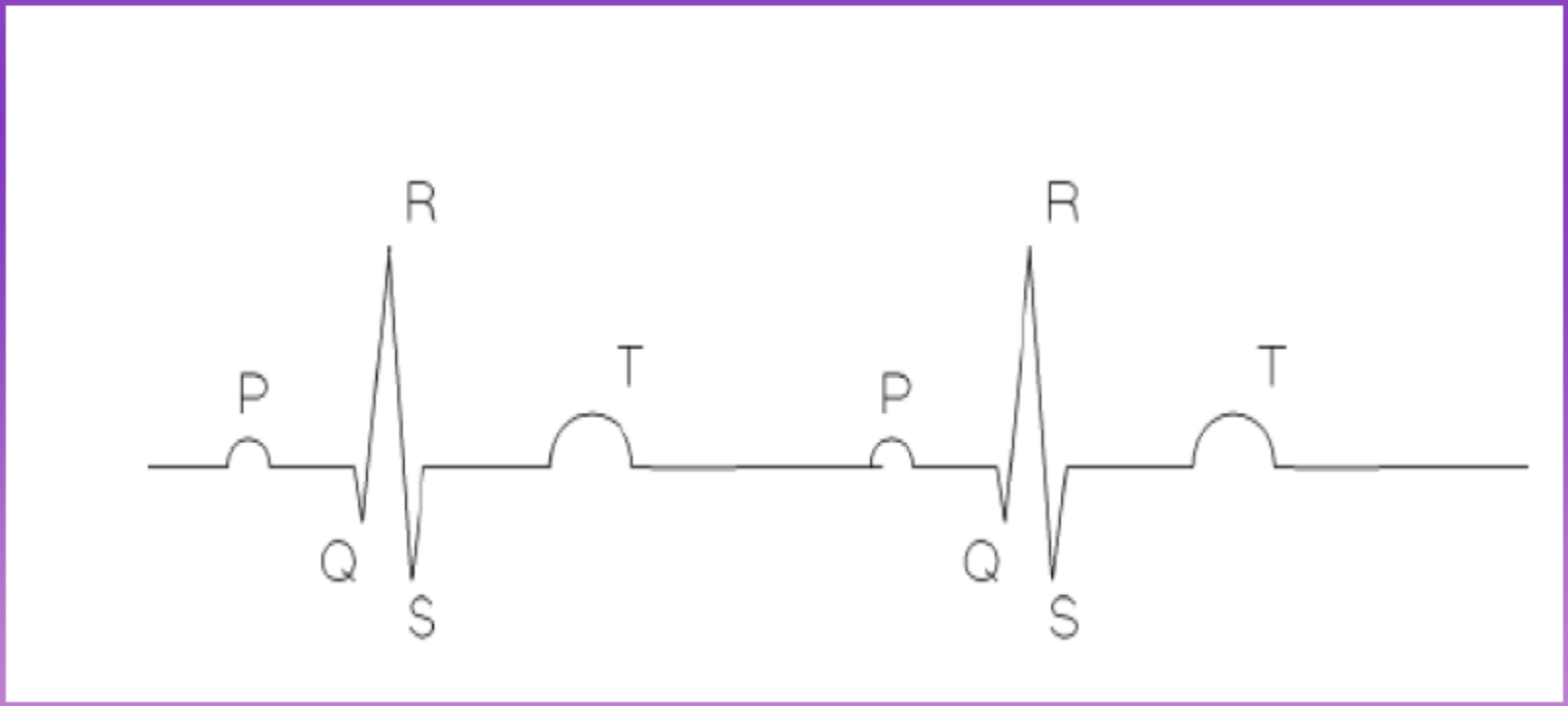
Heart Arrhythmias - Background

Arrhythmias: QT/QTc Interval Prolongation

- In the past decade, the single most common cause of the withdrawal or restriction of the use of marketed drugs
- A significant prolongation of the QT interval is a biomarker of pro-arrhythmic risk including a potentially fatal condition: torsade de pointes

QT Interval - Definition

- QT Interval – ECG tracings:



QT interval

- Distance between the begining of the Q wave and the end of the T wave.
- QTc interval is the QT interval corrected by heart rate.
- QT/QTc interval prolongation is related to increased risk of cardiotoxicity, such as life-threatening cardiac arrhythmias.

QT Interval Prolongation

- QT interval prolongation induced by the usage of a given drug is detected from ECG tracings as shown in the 2004 NEJM article by Roden

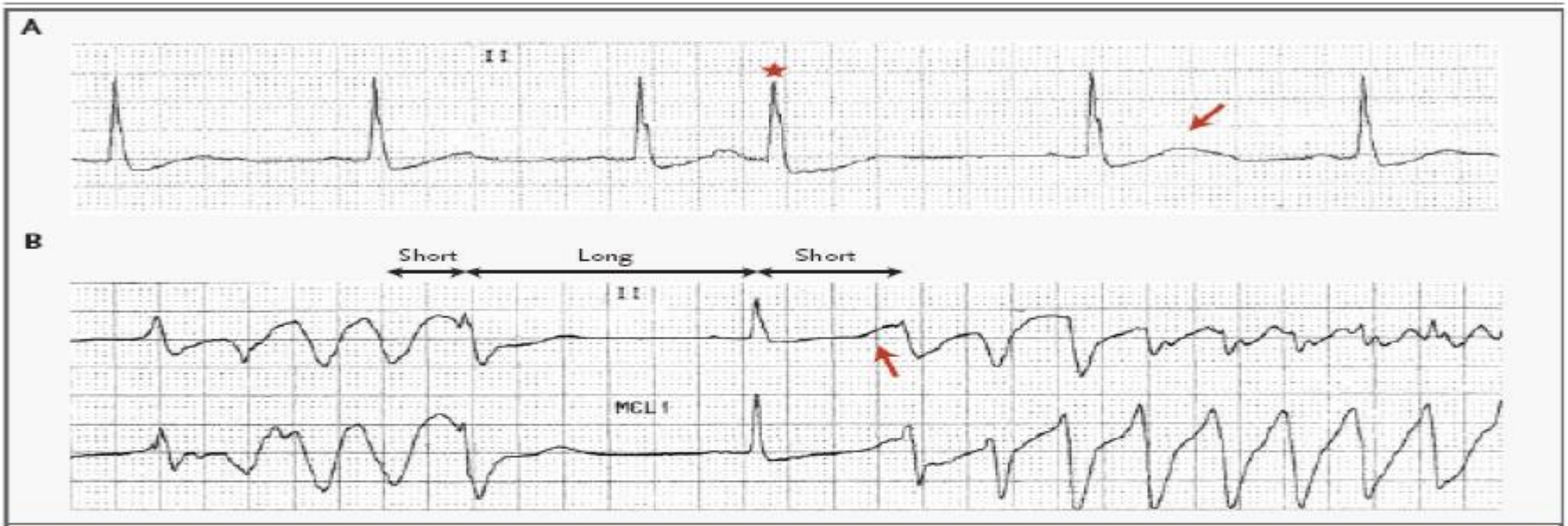


Figure 1. Rhythm Recordings from a 76-Year-Old Woman with Renal Dysfunction Who Was Treated with Sotalol for Atrial Fibrillation.

Panel A was recorded after spontaneous conversion to sinus rhythm. There is a premature atrial beat (star) followed by a pause, and the subsequent sinus beat shows marked QT prolongation and deformity (arrow). Panel B was recorded several minutes later and shows a typical episode of torsade de pointes: there is a four-beat run of polymorphic ventricular tachycardia, a pause, and a sinus beat with a long and deformed QT interval (arrow), interrupted by another episode of polymorphic ventricular tachycardia (torsade de pointes). This pattern of onset — a short cycle followed by a long one followed by a short one — is typical of drug-associated torsade de pointes. Risk factors in this case included female sex, the administration of sotalol in a patient with renal failure (causing increased drug levels), and recent conversion from atrial fibrillation.

QT safety

- Drugs that have been withdrawn from the market because they cause *torsade de pointes*
- It is not clear whether arrhythmia development is more closely related to an increase in the absolute QT interval or QTc.
- ICH - E14 – October 2005: Clinical Evaluation of QT/QTc Interval Prolongation and Pro-arrhythmic Potential for Non-Anti-arrhythmic Drugs

Guidance

- Thorough investigation of potential for QT/QTc prolongation is recommended for
  - All systemically bio-available new drugs
  - Excludes topically active medications and antiarrhythmic medications
  - Includes approved drugs investigated for new routes of administration or higher dosages, new patient populations/indications
  - Especially important for drugs within a “suspect drug class”

Case studies

Data Monitoring for Safety

- **Apparent harm with a new treatment**
  ILLUMINATE trial **Torcetrapib vs. placebo**
- In 15067 patients at high risk of CVD
- Primary endpoint: CHD death, MI, stroke + unstable angina
- Accrual Aug 2004 to Dec 2005
- Torcetrapib raises HDL cholesterol
- (but also raises BP)

the agonizing negative trend

- emerging evidence of excess deaths on torcetrapib
- monthly safety report 30 Nov 2006
- 82 vs 51 deaths P=0.007
- statistical stopping guideline for safety: P<0.01
- DSMB teleconference 1 Dec 2006, recommendation to stop
- Sponsor stopped torcetrapib trials on 2 Dec 2006.

Stopping for futility

HEART2D Trial: insulin lispro vs standard insulin

planned 1355 patients with type 2 diabetes and acute MI
primary endpoint: major CV events over mean 3 years

stopping guideline for futility in 4th interim analyses:

stop if conditional power < 40%, assuming
true effect corresponds to observed hazard ratio

"The DMC has the authority to overrule the stated guidelines"

4th interim analysis	**lispro**	vs	**control**
primary endpoints	170/558		173/557

hazard ratio 0.98 (95%CI 0.79, 1.21) conditional power < 1%

DMC recommended stopping, sponsor agreed

Stopping for efficacy: need overwhelming evidence

ASCOT trial in hypertension [Lancet 2005 366 p 895-]

amlodipine-based vs atenolol-based regimes in 19257 patients

DSMB recommended stopping in Nov 2003

	amlodipine	atenolol	
coronary events (primary)	313	354	P = .14
strokes	230	339	P = .00004

- Trial Executive informed

- much debate, collective decision to continue

- tricky to stop on basis of secondary endpoint,
- even if in hindsight primary endpoint debatable

- DSMB again recommends stopping, October 2004:
- mortality difference significant
- other differences unchanged

ASCOT final results (N=19257, median 5.5 years)

	amlodipine	atenolol	hazard ratio	
non-fatal MI & fatal CHD	429	474	0.90	P=.11
stroke	327	422	0.77	P=.0003
CV deaths	263	342	0.76	P=.001
all deaths	738	820	0.89	P=.02
new diabetes	567	799	0.70	P<.0001

Improving the Reporting of Harms (Safety)

CONSORT extension

[Ann Intern Med 2004; 141 p 781-]

essentials: collect quality data on harms
include harms in any trial report
quantify them appropriately

START trial

budesonide vs placebo in recent-onset asthma
7241 patients, including 1974 aged 10 or less

initial manuscript
"Early intervention with budesonide in mild persistent asthma: a worldwide effectiveness study"

no mention of reduced growth in children

published paper [Lancet 2003: 361 p 1071-]

"Early intervention with budesonide in mild persistent asthma: a randomised double blind trial"

"3 year growth was reduced in budesonide group by 1.34cm"

44% reduction in hazard of severe asthma exacerbation

Prasugrel vs Clopidogrel in acute coronary syndromes

[NEJM 2007; 357 p 2001-]

more bleeding events on prasugrel

sensational approach:

four-fold increase in fatal bleeds on prasugrel

switching from clopidogrel to prasugrel would cause thousands more major bleeds per year worldwide

The data as published

TRITON – TIMI 38 trial, 15 months follow-up

	prasugrel	**clopidogrel**	hazard ratio(95%CI)
N	6741	6716	
fatal bleed	21(0.4%)	5(0.1%)	4.19(1.58-11.11)
major bleed (non CABG related)	**146(2.4%)**	**111(1.8%)**	**1.32(1.03-1.68)**
bleeding requiring transfusion	244(4.0%)	182(3.0%)	1.34(1.11-163)
all bleeds	303(5.5%)	231(3.8%)	1.31(1.11-1.56)

Absolute risk is key

major bleeds increased by 0.6% (35 events)

[95% CI 0.1% to 1.1%]

no. needed to harm is around 170, with wide CI

Balancing efficacy and harm

	prasugrel	clopidogrel	
N	**6813**	**6795**	**hazard ratio (95%CI)**
CV death	**133**	**150**	
non fatal MI	**475(7.3%)**	**620(9.5%)**	**0.76 (0.67-0.85)**
non-fatal stroke	**61**	**60**	
composite	**673**	**781**	**0.81 (0.73-0.90)**
stent thrombosis	**68**	**142**	

major bleeds increased by 0.6% (35 events)

[95% CI 0.1% to 1.1%]

no. needed to harm is around 170, with wide CI

myocardial infarction reduced by 2.2% (145 events)

[95% CI 1.2% to 3.2%]

no. needed to treat (NNT) is around 45

overall, **benefit outweighs risk of harm**

but need to assess **individual risk**

who's at high risk of bleed? Eg women

Scare stories, politics and the media

1)Avandia (Rosiglitazone)

2) Drug-eluting stents

how can we avoid over-reaction

what's the real evidence

what's the appropriate consequences

Safety issues in the real world

activists ⟷ **defensive companies**

⇑

objective

unbiassed

evidence

clinical trials, meta-analyses, observational data, media distortions

decisions by: regulatory authorities

treating physicians

patients

Rosiglitazone (rosi) and cardiovascular risk

Meta-analysis of 42 trials [NEJM 14 June 2007]

Rosi vs Control	**odds ratio**	(95% CI)
Myocardial infarction	**1.43**	(1.03 to 1.98)
CV death	**1.64**	(0.98 to 2.74)

limited evidence, mostly small trials, unvalidated events

high profile, Congress involved, FDA under attack

"I was truly frightened on behalf of our patients"

The Times (business section)

"Alarmist headlines and confident declarations help nobody"

The Lancet

"Meta-analysis seems a rushed and incomplete examination"

Nature

RECORD Trial Interim Analysis

[NEJM 5 July 2007]

Rosi + M or S vs Metformin + Sulfonylurea

4458 diabetic patients, mean 3.75 years follow-up

	Rosi	**Control**	
CV death	29	35	P=.46
Myocardial infarction	49	40	P=.34
Heart failure	**47**	**22**	**P=.003**
Any CV hosp/death	217	202	P=.43

no excess of CV deaths

inconclusive evidence re myocardial infarction

the real problem is heart failure

other trials and meta-analyses:
applies to rosi and pioglitazone

avoid their use in high-risk patients

"A thunderstorm from scarce and fragile data" Ann Int Med

"Thiazolidinediones, deadly sins, surrogates and elephants"
Lancet

Rosiglitazone (rosi) increases risk of fractures?

ADOPT trial *[NEJM 2006; 355 p 2427-]*

4360 diabetic patients, mean 4.0 years follow-up

	incidence of fractures		
	rosi	**metformin**	**glyburide**
men	32 (4.0%)	29 (3.4%)	28 (3.4%)
women	60 (9.3%)	30 (5.1%)	21 (3.5%)

a problem in women only? doubtful

also happens with pioglitazone? probably

Fracture risks of rosi and pioglitazone

lack of trial data $\Rightarrow$ try observational registries

Case-Control Study using GPRD

[Archives Int Med 2008; 168 p 820-]

1020 fracture cases and 3728 matched controls (all diabetic)

Rosi or Pio prescriptions	**cases**	**controls**	**adjusted odds ratio (95% CI) versus no use**
< 8	13	54	**0.90** (0.46-1.74)
8-14	13	27	**1.85** (0.86-3.98)
≥15	22	38	**2.86** (1.57-5.22)

search for consistency with alternative analyses

self-controlled case series approach [unpublished]
also using GPRD
1819 diabetic patients with fracture
before or after start of rosi or pioglitazone

compare pre-and post-exposure periods in same patient
conditional Poisson regression, age adjusted

	rate ratio	(95% CI)
females	**1.42**	(1.20, 1.69)
males	**1.44**	(1.18, 1.77)

Increasing risk by duration of exposure

safety concerns re drug-eluting stents

scare story ⇒ sensible risk-benefit assessment

drug-eluting stent (DES) vs bare-metal stent (BMS) in PCI

ACC presentation March 2006
BASKET LATE trial (N=743)
cardiac death and MI 4.9% vs 1.3% P=.01

ESC presentations Sept 2006
two poor quality meta-analyses and large
Swedish registry all showing mortality risks of DES

major outcry, reduced use of DES

- **Drug-Eluting Stent (DES) vs Bare Metal Stent (BMS)**

- a **meta-analysis** update re **mortality risk**
- by Ajay Kirtane, Gregg Stone et al (2008)

- **21 RCTs:** 8867 patients, mean f/u 2.9 years

- **31 Registries:** 169,595 patients, mean f/u 2.5years

Hazard Ratios for Mortality

21 RCTs

Fixed Effect **0.97** **95% CI** **0.81, 1.15** **P=.72**

31 Registries

Fixed Effect **0.81** **95% CI** **0.78, 0.85** **P<.001**

Random Effects 0.78 95% CI 0.71, 0.86

Heart. Org Sept 2008 the latest registry [JACC 2008; 52 p1041-]
"DES in real-world setting $\Rightarrow$ lower mortality"
Cleveland Clinic: 6053 DES, 1983 BMS, mean f/u 4.5 years

hazard ratio **0.54** **95% CI** **0.45, 0.66**
with propensity matching

too good to be true?

Why such discrepancies between RCTs and Registries?

RCTs not representative of real-world use

Registries prone to selection bias,
not captured by adjustment for confounders,
which vary enormously across registries

mortality risk depends on so many factors
not related to specific PCI

any true effect (DES vs BMS) should be small?

Interpretation of Surprises, especially re Safety

Excess of Cancers in the SEAS trial [NEJM Sept 2008]

	simvastatin + ezetimibe	**placebo**	
N	944	929 with aortic stenosis median 1 year follow-up	
primary CV outcome	333	355	P=.59
incident cancer	**105**	**70**	**P=.01**
cancer death	**39**	**23**	**P=.05**

when faced with a surprise (benefit or harm) collect more data

and expect "regression to the truth"

- **interim results from SHARP and IMPROVE-IT**
- [NEJM Sept 2008]

	ezetimibe	**placebo**	
N	10319	10298	
incident cancer	**313**	**329**	**P=.61**
cancer death	**97**	**72**	**P=.07**

- illogical pattern, no specific cancers
- "the available results do not provide credible evidence
- of any adverse effect of ezetimibe on rates of cancer"?

New trends

- There is a clear renewed emphasis on drug safety in today on drug safety in today's regulatory s regulatory environment with impact on study design and environment with impact on st udy design and statistical analyses: statistical analyses: – – Specialized studies designed to test hypotheses Specialized stu dies designed to test hypotheses about safety about safety – – New requirements for additional analyses New requirements for additional analyses involving inferential statistical methods app lied to involving inferential statistical methods applied to indivi dual studies and safety databases for entire individual studies and safety databases for entire development programs