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Clinical Measurement of Drug Action

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The $1,000,000 Questions

- Is this drug effective?
  - is it better than a competitor/alternative?
- Is this drug safe?
  - or at least is it reasonably well-tolerated?

What has to be measured to answer these questions?

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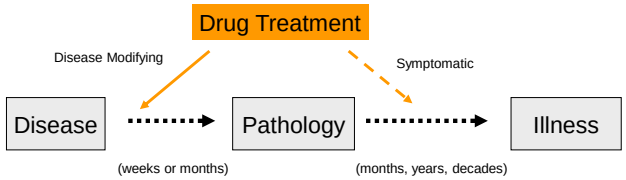
Phases of Drug Development

- Phase 0
  - » Predictions for Humans
- Phase 1
  - » Tolerability
- Phase 2
  - » Effectiveness
- Phase 3
  - » Safety
- Phase 4
  - » Post Marketing

Slide 4

Drug Treatment
Biomarkers and Outcome



Biomarker
e.g. tumour size

Outcome
e.g. death

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Terminology: definitions

- Biomarker
  - » Readily measurable marker of response
  - e.g. Drop in blood pressure, lowering of plasma glucose conc
- Surrogate endpoint
  - » Biomarker used for Regulatory Approval
  - e.g. Reduction in viral load, CD4+ cell count, plasma cholesterol concentration
- Outcome
  - » What the patient feels/functions/survives
  - e.g. pain/hospital admission/surgery/death

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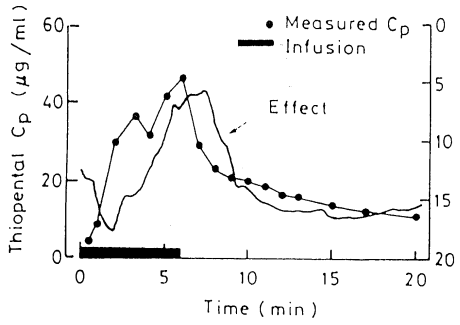
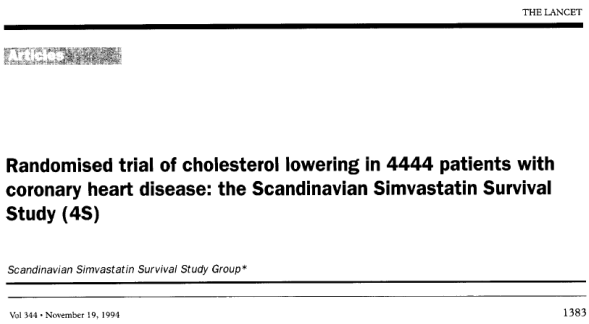
Biomarker

EEG Slowing



Slide 7	**Surrogate Endpoint** **HIV viral load and CD4 count** Enfuvirtide, an HIV-1 Fusion Inhibitor, for Drug-Resistant HIV Infection in North and South America "At 24 weeks, the … change from base line in the viral load (intention-to-treat, last observation carried forward) was a decrease of 1.696 … in the enfuvirtide group, and a decrease of 0.764 log 10 copies per milliliter in the control group (P<0.001). The mean increases in CD4+ cell count were 76 cells per cubic millimeter and 32 cells per cubic millimeter, respectively (P<0.001)." Lalezari et al. NEJM 2003 	Lalezari JP, Henry K, O'Hearn M, Montaner JS, Piliero PJ, Trottier B, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med. 2003;348(22):2175-85.
Slide 8	**Clinical Outcome** **Decreased Risk of Death**  THE LANCET **Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)** *Scandinavian Simvastatin Survival Study Group** Vol 344 • November 19, 1994 1383 	Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383-89.
Slide 9	**Biomarkers vs. surrogate endpoints** ● Biomarkers *reflect an important feature* of a disease, so reliably reflect biological response to drug » this is not the same as therapeutic response in terms of improved patients outcomes ● Surrogate endpoints are *supposed to be* readily measurable biomarkers that closely reflect eventual clinical outcomes » a laboratory substitute for a clinically meaningful result, causally linking disease with outcome 	

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Examples of biomarkers, surrogate endpoints and clinical outcomes

Therapeutic class	Biomarker/surrogate	Clinical endpoint
Physiologic markers		
Antihypertensive drugs	↓Blood pressure	↓Stroke
Drugs for glaucoma	↓Intraocular pressure	Preservation of vision
Drugs for osteoporosis	↑Bone density	↓Fracture rate
Antiarrhythmic drugs	↓Arrhythmias	↑Survival
Laboratory markers		
Antibiotics	Negative culture	Clinical cure
Antiretroviral drugs	↑CD4 count, ↓viral RNA	↑Survival
Antidiabetic drugs	↓Blood glucose	↓Morbidity
Lipid-lowering drugs	↓Cholesterol	↓Coronary artery disease
Drugs for prostate cancer	↓Prostate-specific antigen	Tumor response

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Important characteristics & distinctions

- Biomarkers
  - » Repeated measurements possible
  - » Usually cheap
  - » Often high content information
  - » Often give rapid indication of response
  - » Can be of prognostic or diagnostic value
- Clinical Outcome
  - » Subjective (e.g. pain)
  - » Often only happens once (e.g. death)
  - » Can take many years for differences to be evident

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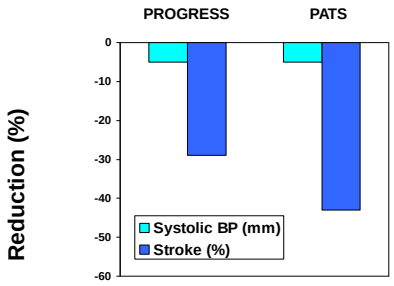
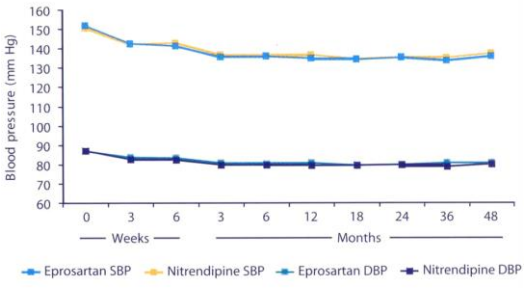
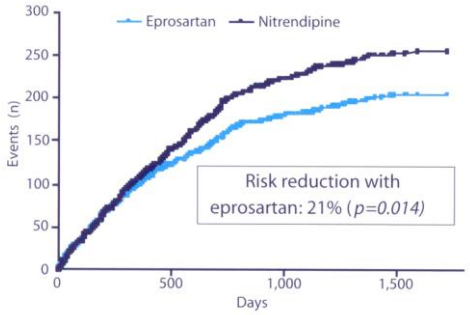
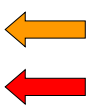
Information Content

- Biomarker e.g. Blood Pressure
  - » 40-300 mm/hg
  - » 2-3 decimal digits
  - » High information
- Clinical Outcome e.g. Death
  - » Dead or alive
  - » Only 1 binary digit
  - » Low information

Slide 13	**The Problem of Biomarkers** **The Responder Paradox** ● Blood Pressure lowering is predictable » Blood pressure is lowered in nearly all patients who are treated ● Blood pressure rarely predicts individual beneficial Clinical Outcome » Only a small percentage of patients will have death or disability prevented » A larger percentage will have adverse effects 	
Slide 14	**Biomarkers and outcomes** **Independent, linked, causative….?**  Two trials show the beneficial effects of lowering blood pressure and reducing stroke 	Scheen AJ. [Clinical study of the month. Secondary prevention of cerebrovascular accident with perindopril: the PROGRESS study]. Rev Med Liege. 2001;56(11):792-5. PATS Collaborating Group. Post-stroke antihypertensive treatment study. A preliminary result. Chin Med J (Engl). 1995;108(9):710-7.
Slide 15	**Biomarkers – blood pressure** ***Secondary prevention trial for stroke***  ***Eprosartan is an angiotensin-II receptor antagonist. Nitrendipine is a calcium channel blocker*** 	Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). Stroke. 2005;36(6):1218-26.

Slide 16	**Outcomes – clinical events**  The combined primary endpoints of mortality plus the total number of cardiovascular events and cerebrovascular events was reduced by eprosartan compared to nitrendipine. The difference emerges after 1 year and becomes more pronounced with follow-up. 	
Slide 17	**Blood Pressure is Not a Good Surrogate Endpoint** ● Biomarker (BP) data would predict equal effectiveness of treatments ● Outcome assessment reveals marked differences between treatments! ● Disease processes are complex and outcomes are subject to many variables that are not always reflected adequately by measuring a simple biomarker 	
Slide 18	**Surrogates are Cost Effective** ● Surrogate Endpoint » High information » Low Cost » "Accepted" to be strongly correlated with outcome ● Using Surrogate Endpoint instead of Outcome » cheaper and shorter clinical trials 	

Slide 19	**New formulations and generics** ● Drug concentration is the most widely used surrogate endpoint ● Formulations with equivalent rate and extent of absorption are considered inter-changeable ● No clinical outcome required ● Generic drugs are a BIG industry 	
Slide 20	**Is the Drug Safe?** **(toxicity and adverse events)** ● Adverse Events are hard to detect ● Some are predictable from pharmacological mechanism » e.g. BP lowering leads to fainting ● Many are idiosyncratic ('individual mix') and difficult to predict in the individual » e.g. dry cough associated with ACE inhibitors 	
Slide 21	**Phases of Drug Development** **Safety and monitoring** ● Phase 0 » Predictions for Humans ● Phase 1 » Tolerability ● Phase 2 » Effectiveness ● Phase 3 » Safety ● Phase 4 » Post Marketing  Adverse event assessment & monitoring 	

Slide 22	**Adverse Event Detection** ● Clinical outcomes can be hard to observe and connect to drug exposure » Phase 3 – Systematic from trained monitor » Phase 4 – Spontaneous reports from clinicians » Causality, timing, plausibility, dose-response? NZ Pharmacovigilance Centre In Dunedin at University of Otago https://nzphvc-01.otago.ac.nz/carm-adr/ Centre for Adverse Reactions Monitoring (CARM) Intensive Medicines Monitoring Programme (IMMP) iPhone App available for making reports 	http://itunes.apple.com/us/app/adr-online/id403478954?ls=1&mt=8#
Slide 23	**Adverse Event Detection** **Toxicity monitoring** ● Biomarker/Surrogate Endpoints » Liver: ALT (alanine aminotransferase) » Kidney: Serum creatinine » Heart: QT Interval 	
Slide 24	**Conclusions** ● **Biomarkers** are essential for learning and understanding clinical pharmacology ● **Surrogate Endpoints** are optional (but commercially important) for regulatory decisions ● **Clinical Outcome** is essential before new drugs are licensed for patients 	