



What is it that policy makers should know about statins?

A Bayesian approach to the question of the (in)equivalence of statins.

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The policy problem

- Statins (lipid-lowering drugs) differ substantially in costs, but do they also differ in clinical effectiveness?
- If so, does the associated health gain outweigh the extra costs?



Not a trivial issue

- High incidence & prevalence of hypercholesterolaemia: high volume



Policy measures

- Reimbursement limited to costs of cheapest statin
- Pre-utilization approval
- Guidelines



What are the risks of these policies?

		Reality:	
		inequivalence	equivalence
Policy based on:	inequivalence	✓	Type I error
	equivalence	Type II error	✓

Type I error: waste of communal resources, health losses elsewhere (= opportunity costs of allocating resources to statins!)

Type II error: avoidable cardiovascular disease (= the opportunity cost of allocating resources to other services)



Policy risks cannot be readily estimated on the basis of current analyses

Result of experiment (e.g., RCT): the absolute difference in the proportion of patients achieving target plasma lipid levels, six months after start of treatment with statin A or statin B, was 20%.

Question addressed in the statistical analysis:

What is the probability of finding such a difference when, in reality, the two statins do not differ in their lipid-lowering potential?

If this probability < 0.05 , what, then, is the probability of policy type I and II error?



The relevant question is:

What is the probability that the two statins are actually equivalent, given the observed difference in proportions of patients achieving target plasma lipid levels?



Bayesian approach

Prior estimate: how likely do you consider the proposition “The two statins are clinically equivalent” to be true?

Prior estimate may be informed by pathophysiological knowledge, by clinical experience, by scepticism towards validity of results of industry-supported trials, etc.



Prior estimate is combined with evidence

Likelihood ratio: how much more likely is it to obtain an experimental result like this, when the two statins are, indeed, clinically inequivalent, as compared to the situation where they are, in fact, equivalent?

How should our prior estimates be revised in the light of this new evidence?



Elicitation of empirical priors

- Analysis restricted to patients with familial hypercholesterolaemia
- Comparison: simvastatin vs. atorvastatin
- Participants: internists (40), cardiologists (34) and GPs (35)



Web-based application

“An adult patient with newly diagnosed familial hypercholesterolemia, without co-morbidity or medication history, and a baseline plasma LDL-cholesterol level of 7.0 mmol/L”

Reduction in LDL-cholesterol THERAPy 1: simvastatine (max. 80 mg/d) <i>Duration of therapy: 6 months</i>	
Reduction in LDL-C (%)	Probability (in %)
0 tot 10 % reduction
10 tot 20 % “	
20 tot 30 % “	
30 tot 40 % “	
40 tot 50 % “	
50 tot 60 % “	
60 tot 70 % “	
70 tot 80 % “	
80 tot 90 % “	
90 tot 100 % “	
Total:	100 %



- Forms pre-tested
- Instructions given during a general meeting
- Two reminders



Likelihood ratios: meta-analysis

- Sources: Ovid Medline (1966 to October 2008), EMBASE (1980 to October 2008), PubMed and the Cochrane Library (from inception to October 2008).
- Search terms: hydroxymethylglutaryl-CoA reductase inhibitors, statins, “simvastatin”; “atorvastatin”, (heterozygous) familial hypercholesterolemia, effectiveness, efficacy, potency, lipid lowering, randomized controlled trials, clinical trials, case-control studies and cohort studies.
- Supplemented with manual search of abstracts from major cardiology conferences in North America and Europe and references from retrieved publications.
- Selection criteria: 1) randomized controlled trials, clinical studies, cohort studies and case-control studies; 2) inclusion of HeFH patients or stratified results specifically for HeFH patients; 3) patients using simvastatin or atorvastatin; 4) patients were newly diagnosed or had a drug free history of at least 1 month; 5) documented plasma LDL-C baseline levels and follow up levels; and 6) at least 3 months of follow-up

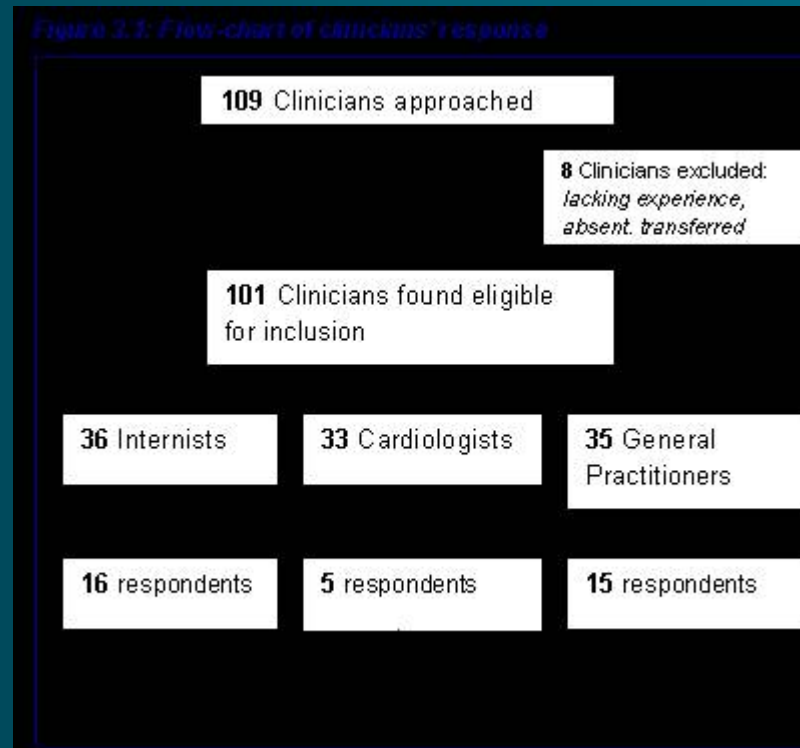


End-points:

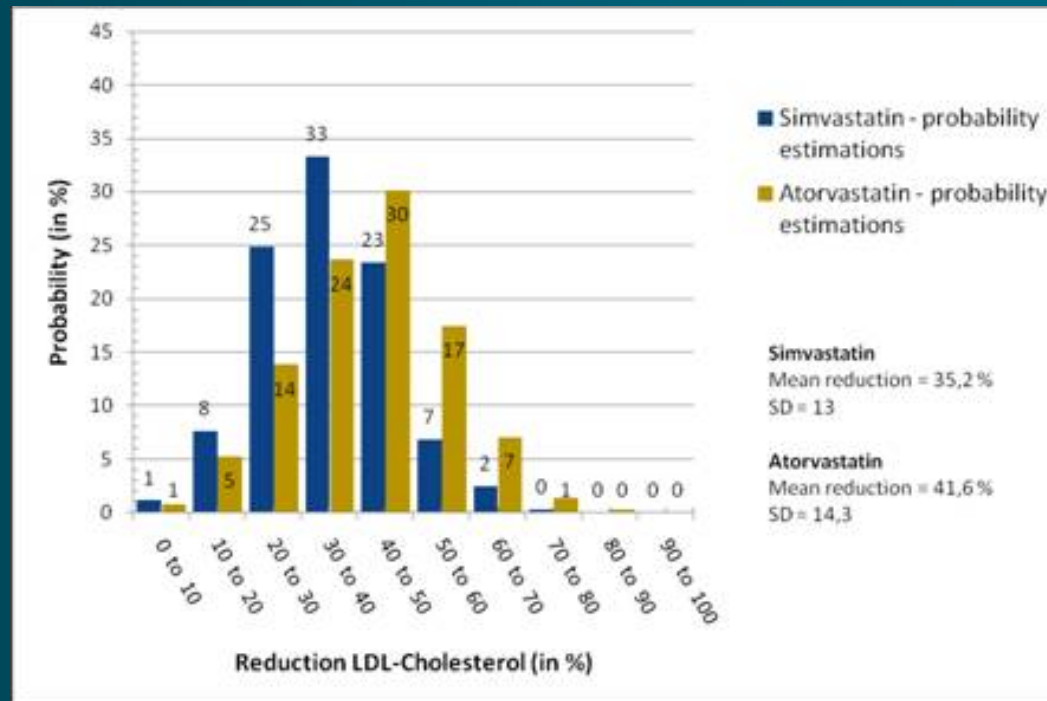
- Probability of the reduction in plasma LDLc being ..%
- Probability of the proportion of patients achieving target LDLc level (2.5) being ..%
- Probability of the excess risk of long term cardiovascular events associated with poor lipid control being ..%



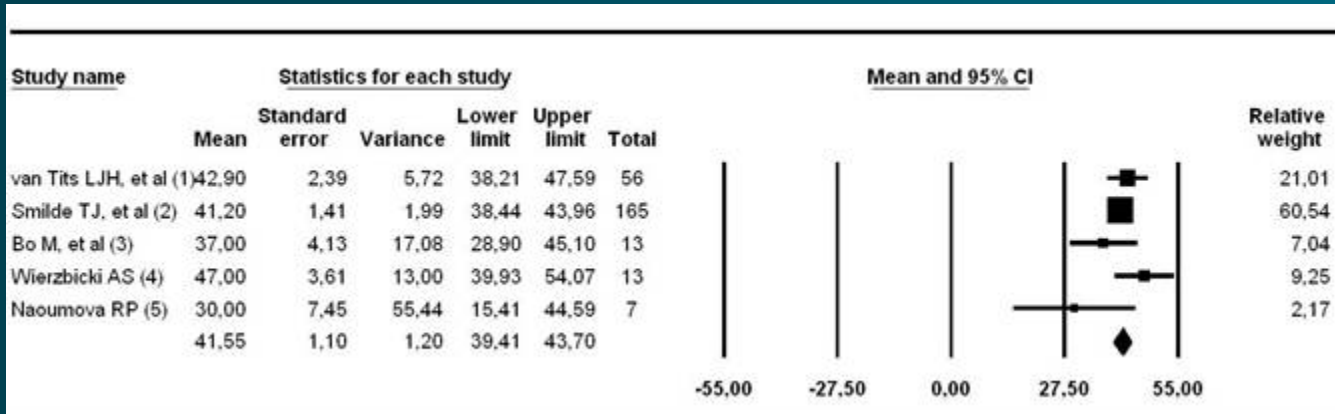
Overall response rate: 36%



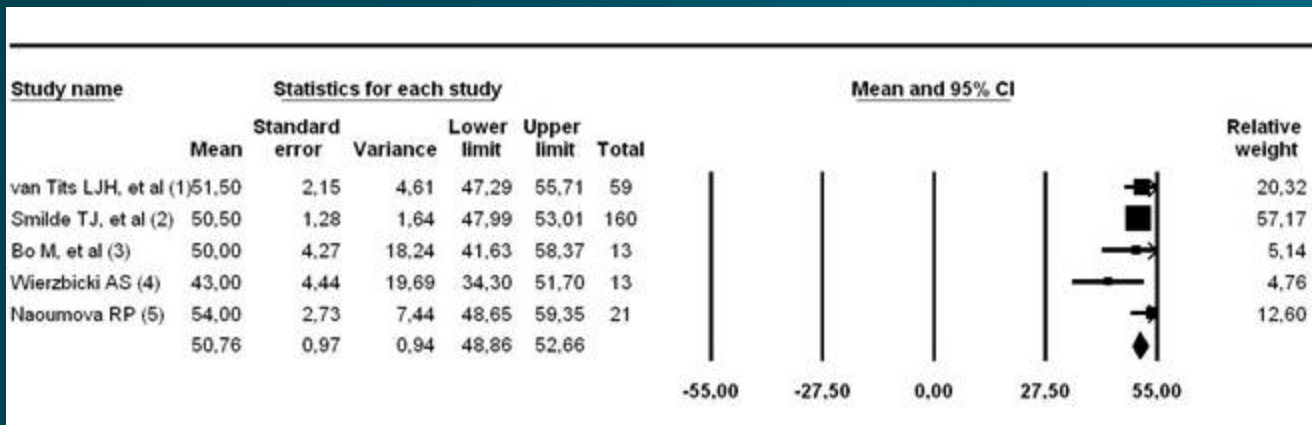
Empirical prior probability distribution



Meta-analysis, % reduction in plasma LDLc

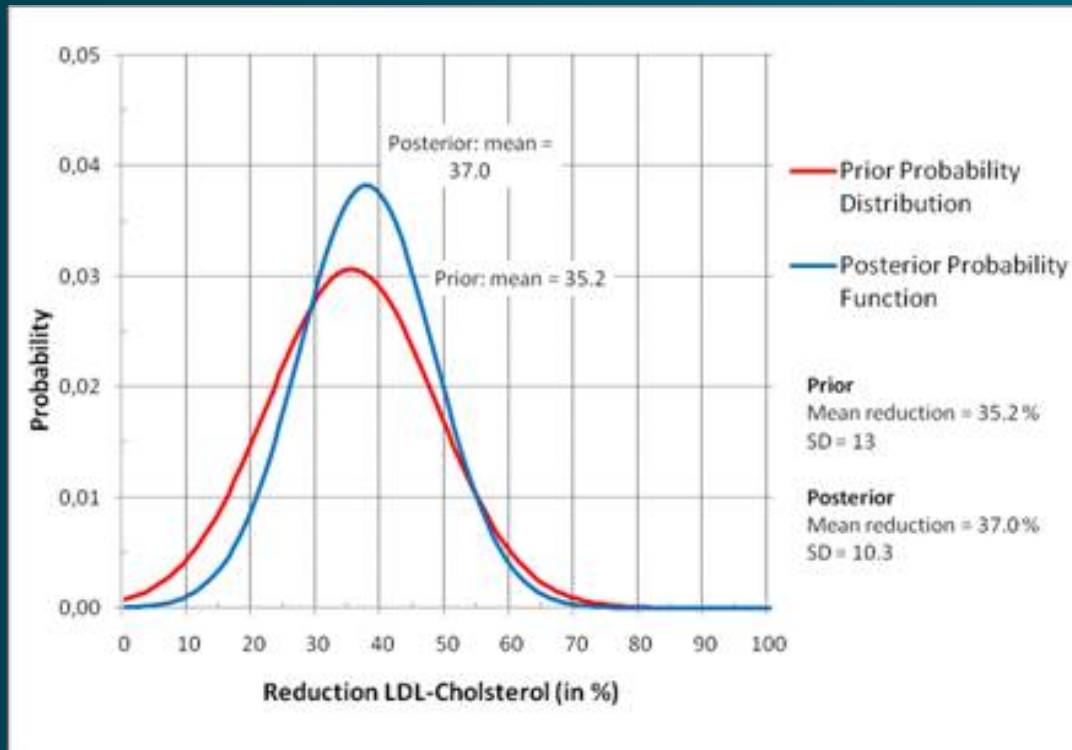


Simvastatin



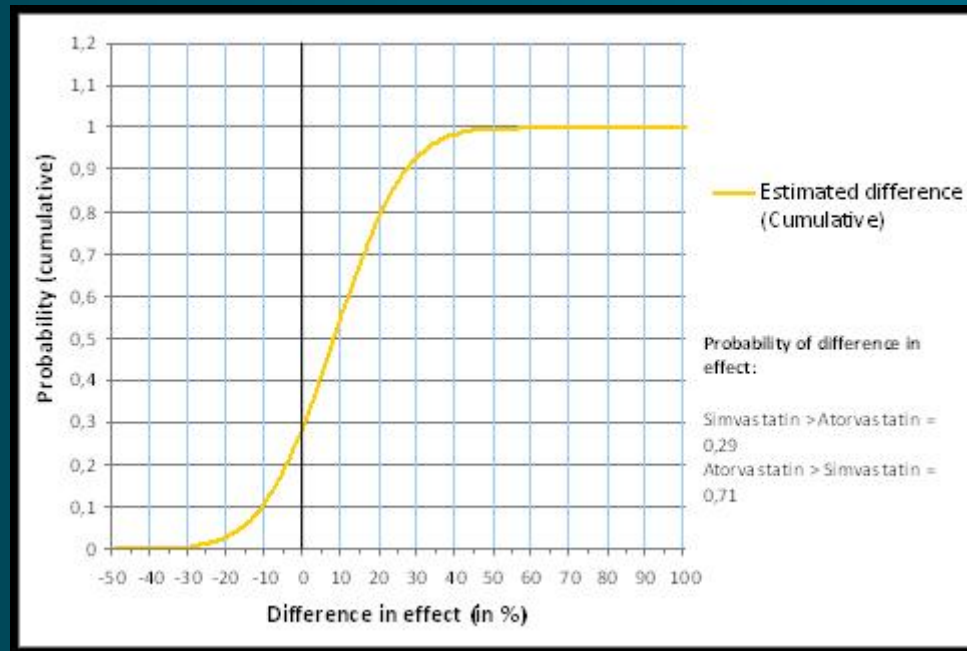
Atorvastatin

Combine prior & LR to define posterior

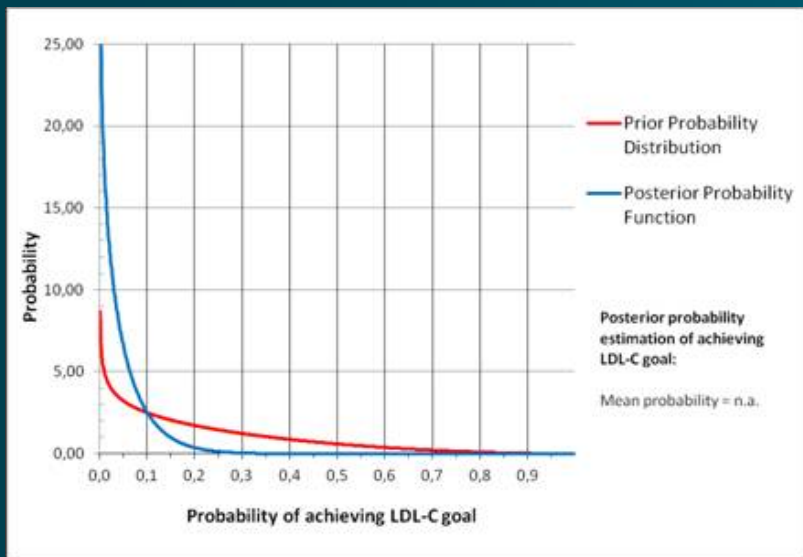


Simvastatin

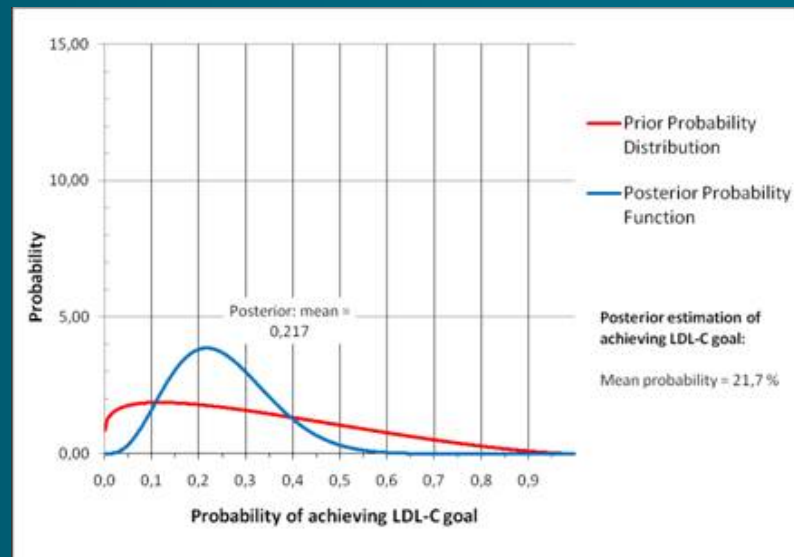
Cumulative probability



End-point: % patients achieving target

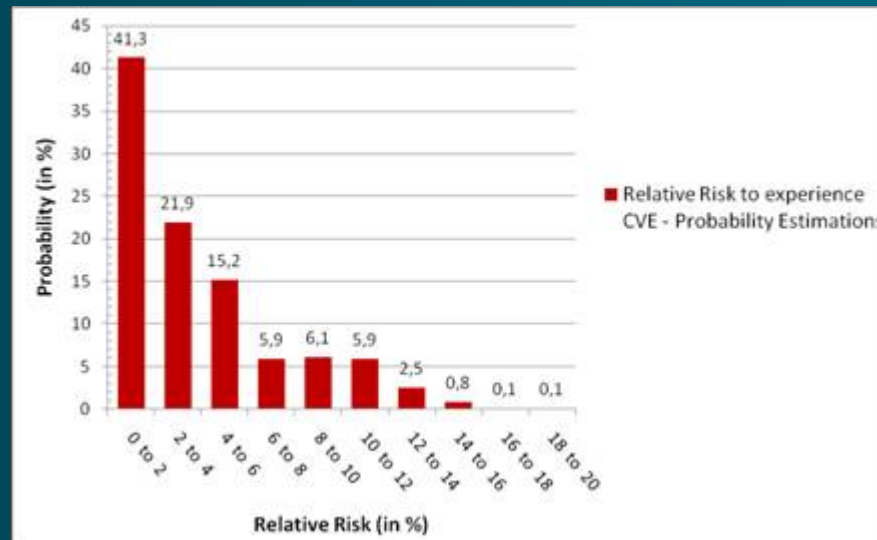


Simvastatin



Atorvastatin

Prior probability distribution: excess risk of CVE associated with poor lipid control





Conclusions

- Can we now estimate the probability of type I and type II policy error?
- What are the consequences of both types of policy error?





Thank you!

