Decision Models Based on Individual Patient and Summary Data

Mark Sculpher
Neil Hawkins

Centre for Health Economics, University of York

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Why decision models? A re-iteration

- The primacy of decisions
- The need to extrapolate
- The need to compare all relevant options
- The need to assess heterogeneity
- The need to include all relevant evidence

..a move away from trial-based economic evaluation

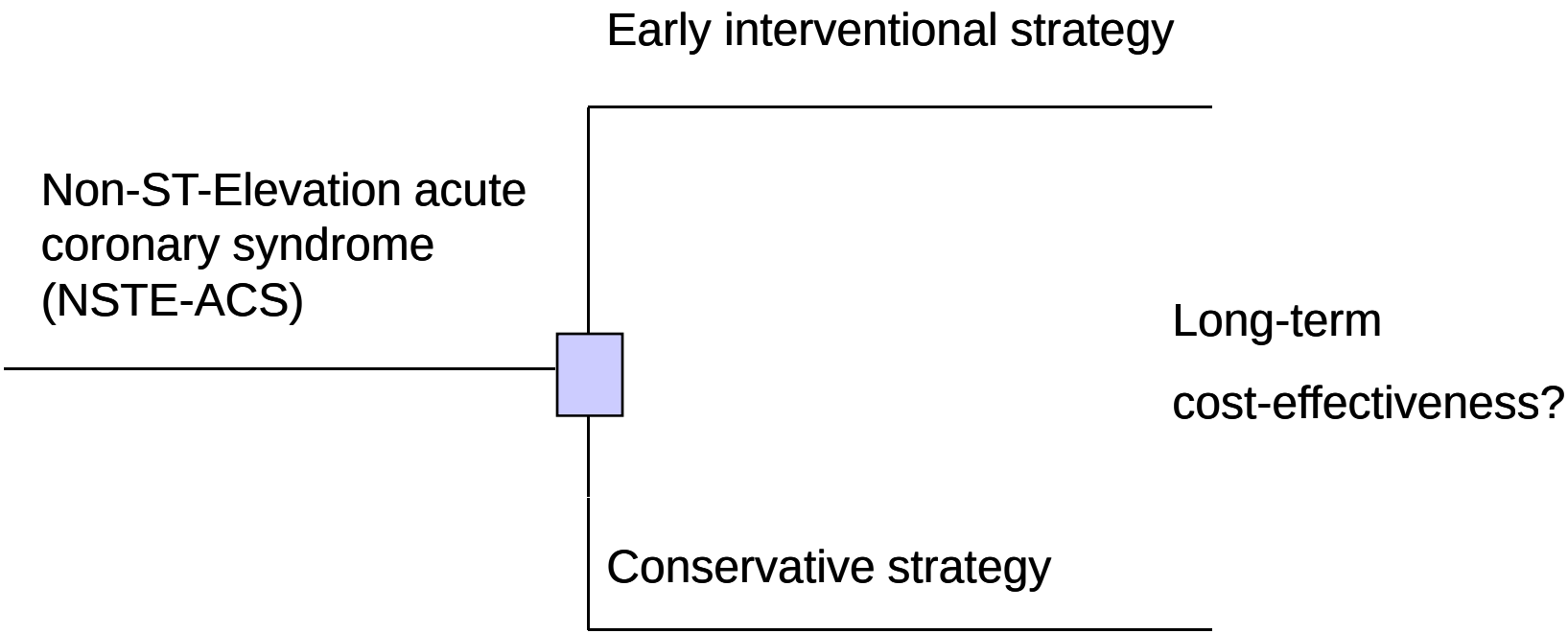
- Clear value of IPD over summary data
- But arguments to move away from averaging costs and effects of a sample
- Towards use of IPD to estimate parameters (with uncertainty and covariance) in decision models
- But also a need to incorporate other evidence, in particular trials which will usually be summary data

Two cardiac examples

- Example 1 (early intervention in acute coronary syndrome)
  - IPD from one trial
  - Collected cost and utility data in that trial
  - But other clinical evidence available (meta-analysis)
- Example 2 (drug eluting stents)
  - Series of trials
  - IPS for some, summary data for others

Example 2: The Cost-Effectiveness of an Early Interventional Strategy in Non-ST-Elevation Acute Coronary Syndrome

Example 1: Decision problem



Henriksson et al. The Cost-Effectiveness of an Early Interventional Strategy in Non-ST-Elevation Acute Coronary Syndrome Based on the RITA 3 Trial. *In submission.*

The RITA 3 trial

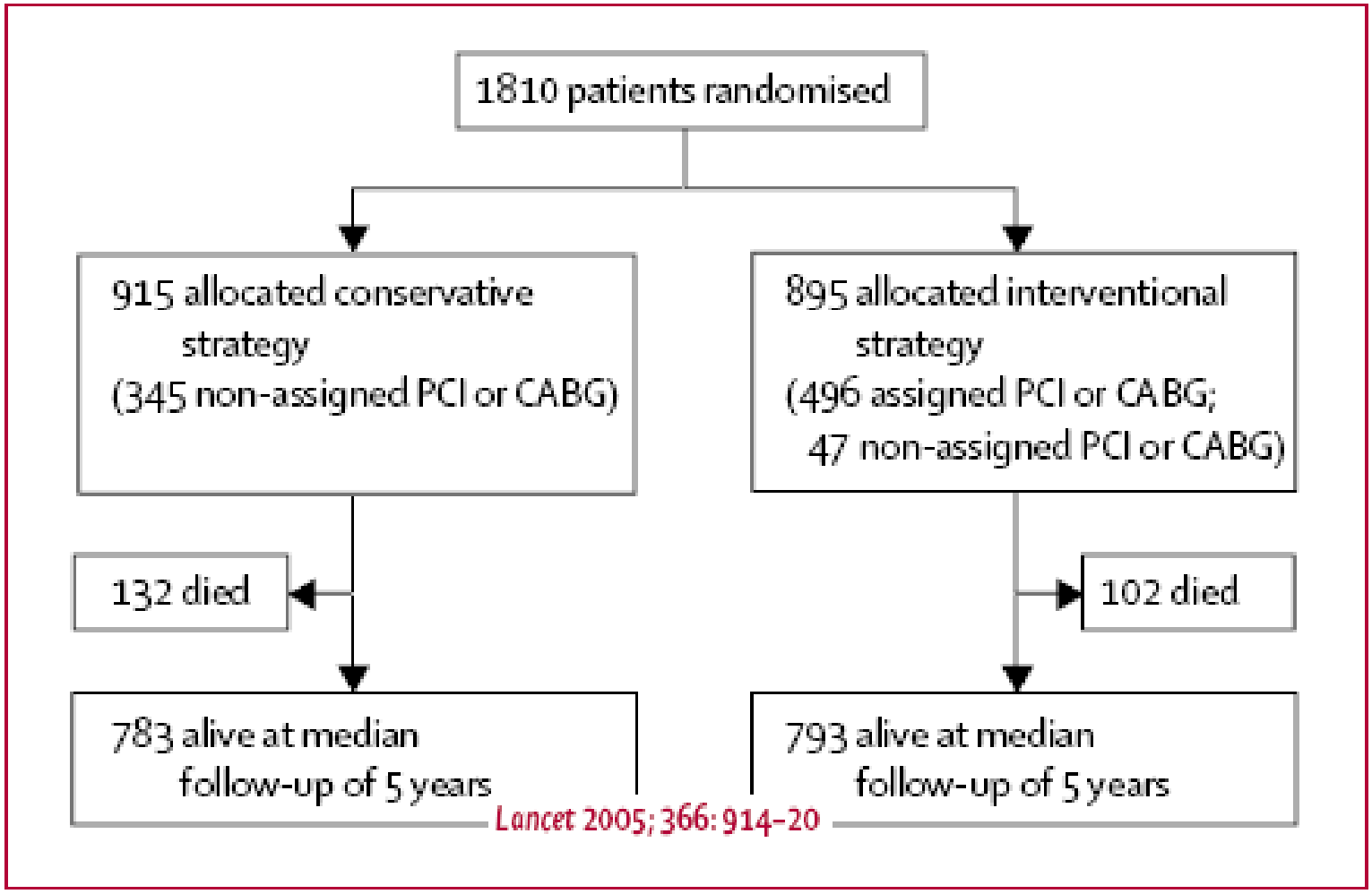


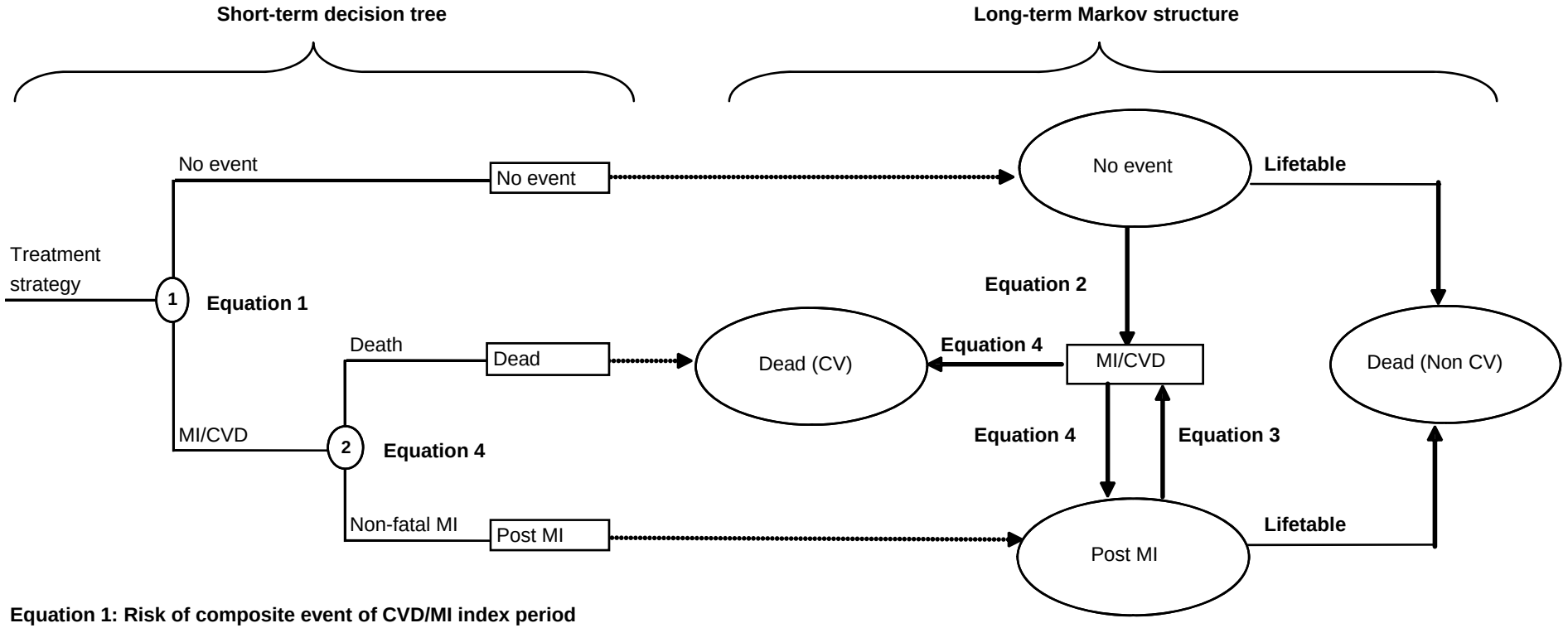
Figure 1: Trial profile

IPD on costs and health-related quality of life (utilities) collected within the trial

Methods

- Two-part model structure
- Baseline event rates, costs and QALYs
  - Statistical modeling
  - RITA 3 data
- Treatment effect
  - RITA 3
  - Pooled from eight trials in this patient population
  - Interaction model (baseline risk and treatment effect)

Model structure and statistical equations

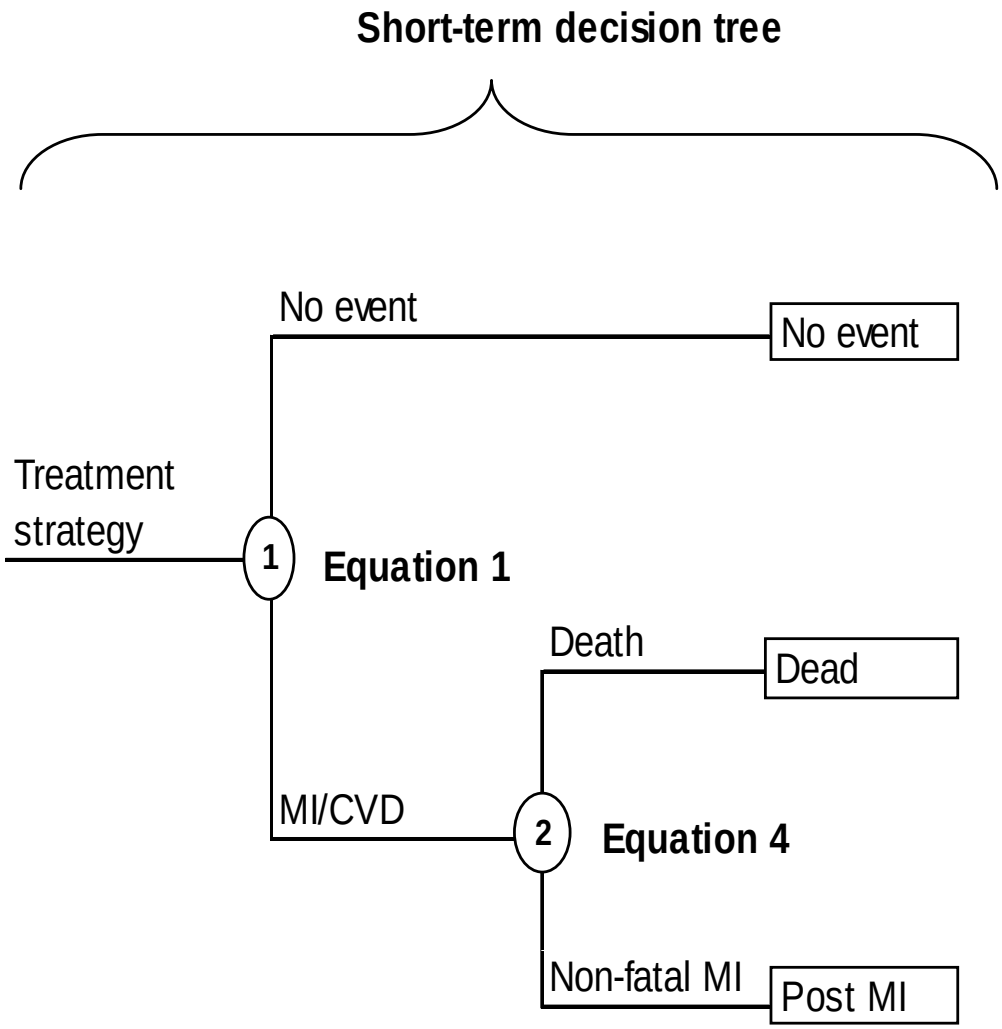


Equation 1: Risk of composite event of CVD/MI index period
Equation 2: Risk of composite event of CVD/MI follow-up
Equation 3: Risk of a further composite event of CVD/MI follow-up
Equation 4: Probability composite event is non-fatal

Cost equation for the short-term tree

Cost and QALY equations for the long-term Markov structure

Short-term model



Odds ratio of composite endpoint (CVD/MI)

	Coefficient	95% CI	
Intervention	1.520	0.864	2.675
Age	1.731	1.262	2.374
Angina	1.893	1.086	3.299

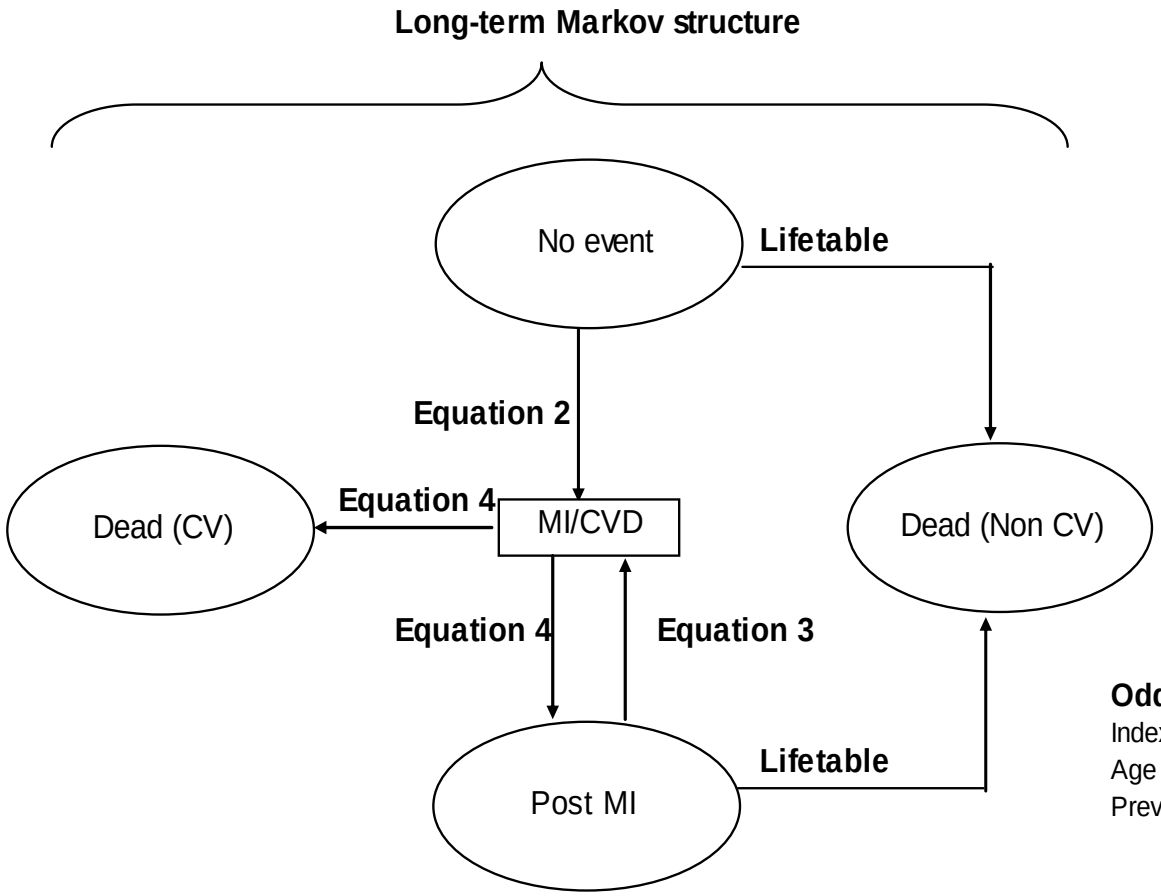
Odds ratio of composite endpoint being non-fatal

Index period	3.040	1.614	5.726
Age	0.699	0.520	0.941
Previous MI	0.492	0.286	0.847

Regression on costs - index admission

Variable	Coefficient	95% CI	
MI during index	6221	4315	8128
Die during index	7947	5536	10359
Intervention	5654	5151	6157
Male	1035	516	1554
Age	878	579	1178
ST depression	1224	699	1750
Constant	1778	1199	2358

Long-term model



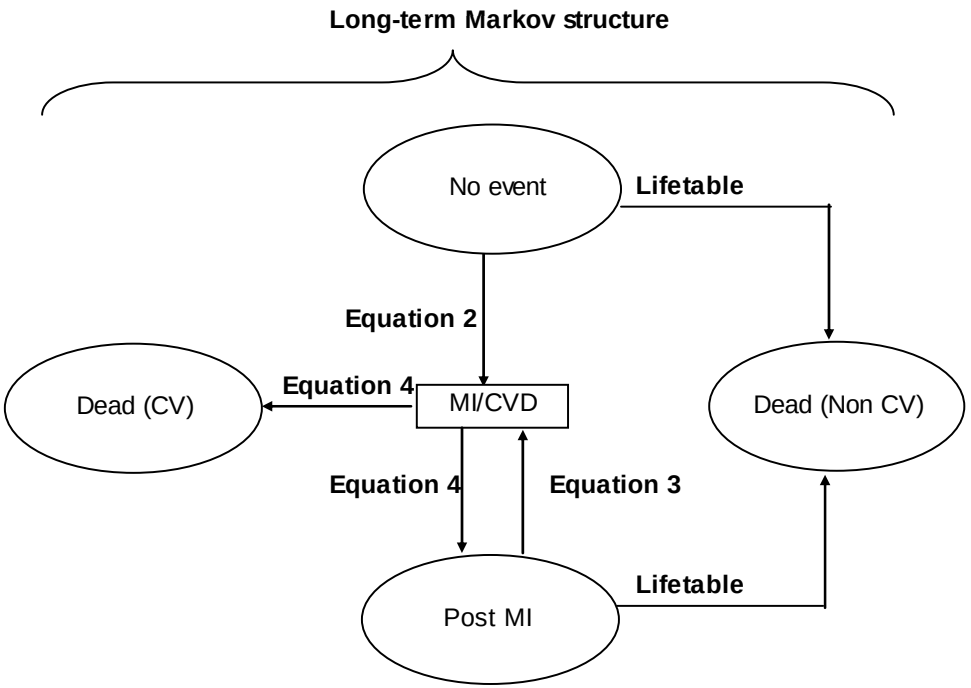
Hazard ratio of composite endpoint (CVD/MI)

	Coefficient	95% CI	
Intervention	0.621	0.464	0.830
Angina	1.323	0.988	1.771
Age	1.777	1.499	2.108
Diabetes	1.905	1.359	2.672
Previous MI	1.471	1.087	1.990
Smoker	1.651	1.207	2.258
Pulse	1.062	1.012	1.114
ST-depression	1.429	1.067	1.913
Male	1.372	1.007	1.869
Left BBB	1.977	1.169	3.344
Gamma	0.579	0.505	0.664

Odds ratio of composite endpoint being non-fatal

Index period	3.040	1.614	5.726
Age	0.699	0.520	0.941
Previous MI	0.492	0.286	0.847

Long-term model



Regression on costs - follow-up

Variable	Coefficient	95% CI	
MI during year	5467	3890	7044
Intervention	-1106	-1562	-650
Male	586	111	1061
Angina	1034	550	1518
Previous MI	724	210	1239
Constant	2735	2249	3220

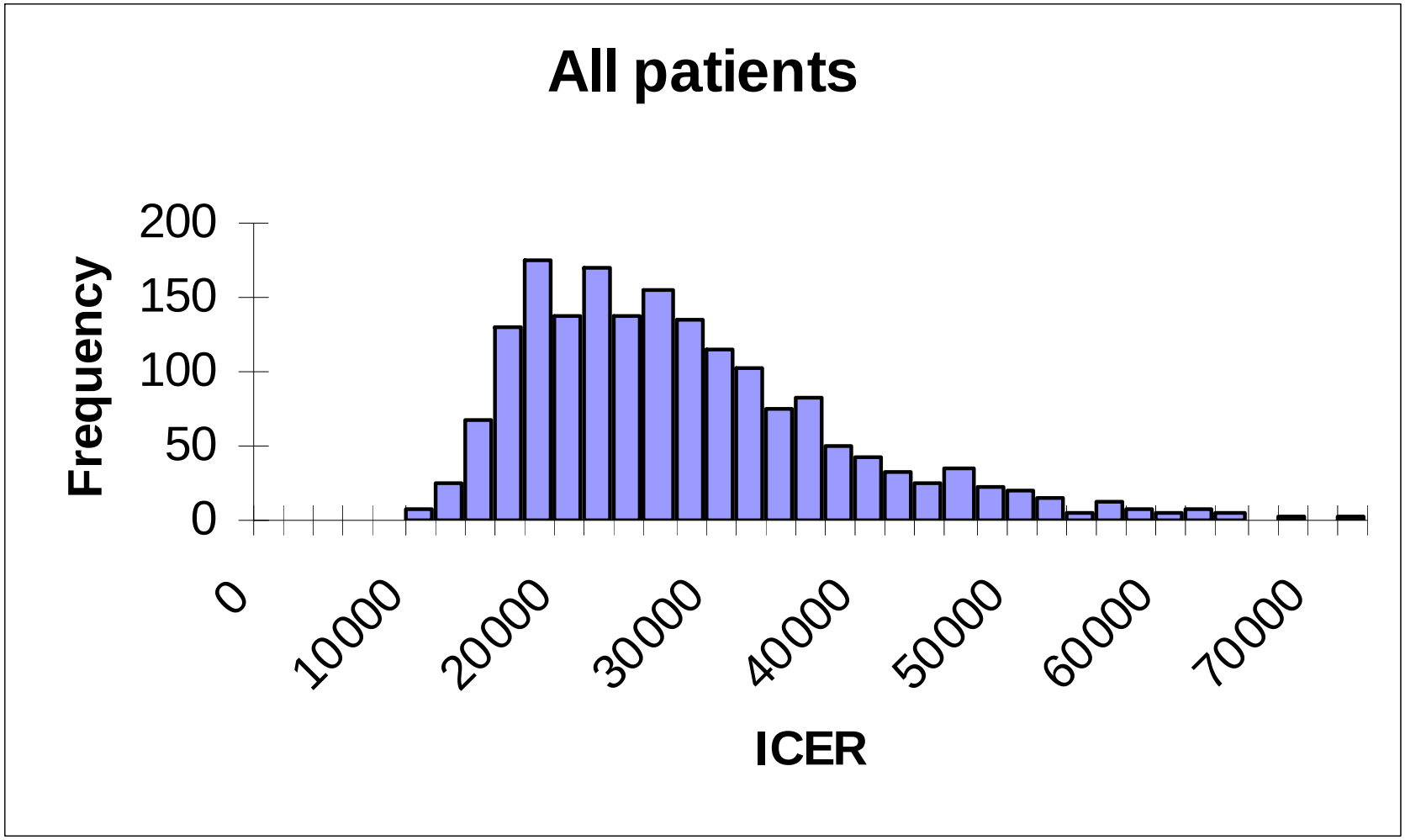
QALY model - baseline

Variable	Coefficient	95% CI	
Diabetes	-0.051	-0.092	-0.010
Previous MI	-0.044	-0.076	-0.012
ST-depression	-0.066	-0.095	-0.037
Angina	-0.074	-0.103	-0.044
Male	0.073	0.044	0.102
Constant	0.692	0.664	0.721

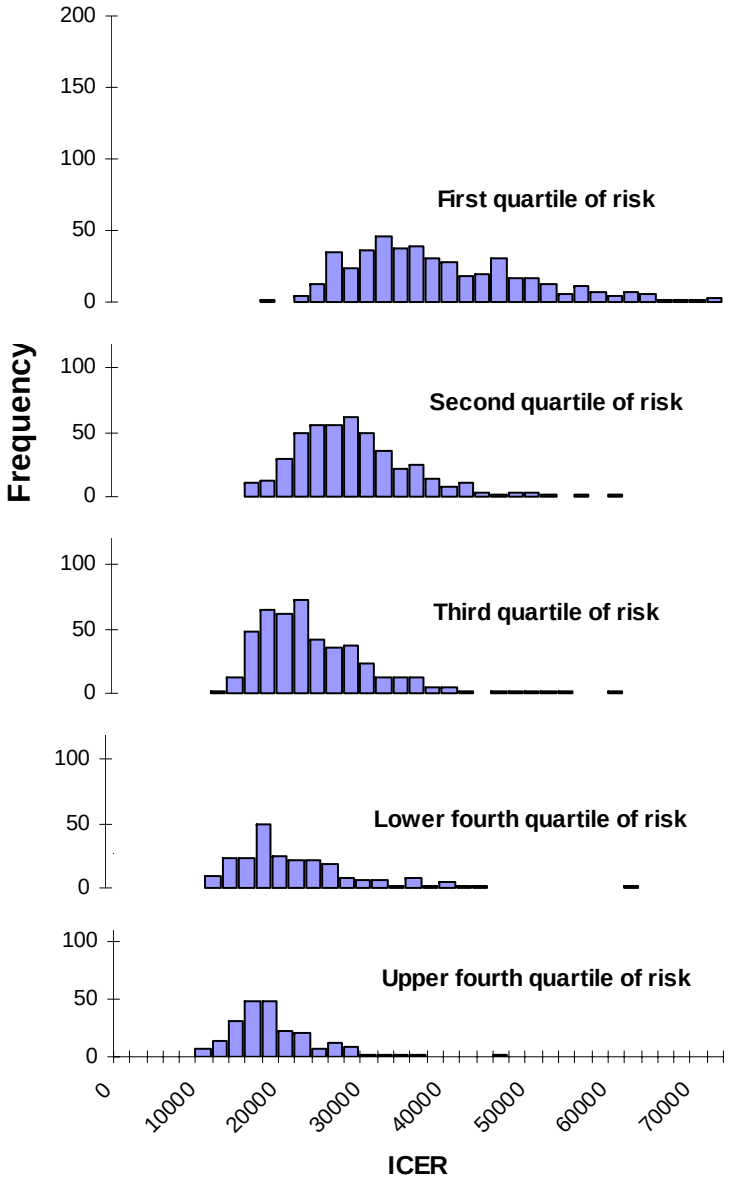
QALY model - changes

Variable	Coefficient	95% CI	
Intervention 4m	0.038	0.005	0.071
Conservative 12m	0.038	0.023	0.053
Intervention 12m	0.018	-0.013	0.048
Previous MI	-0.010	-0.040	0.021
MI during year	-0.035	-0.078	0.008
Constant	0.044	0.020	0.069

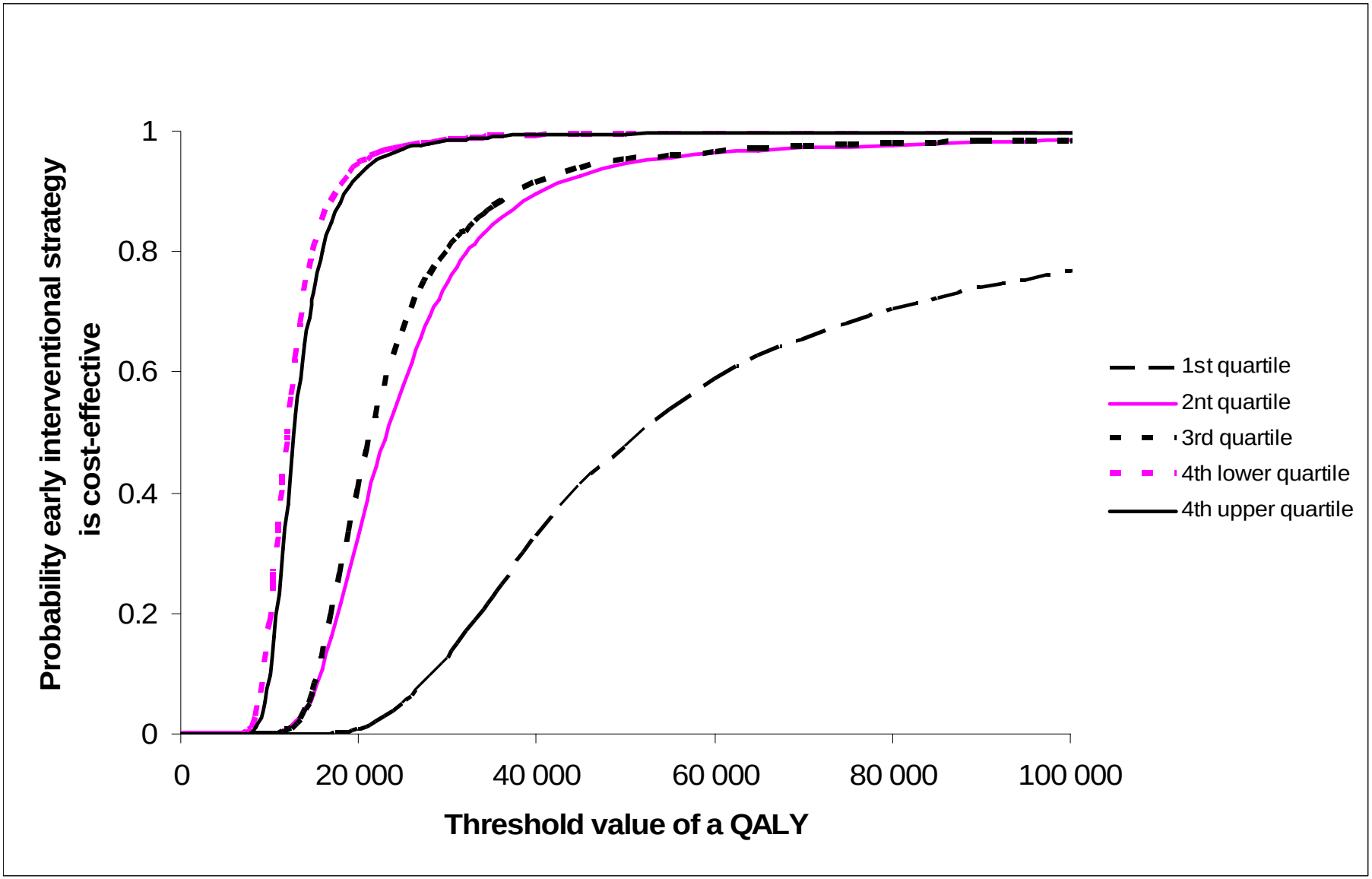
Cost-effectiveness results



Cost-effectiveness by clinical risk groups

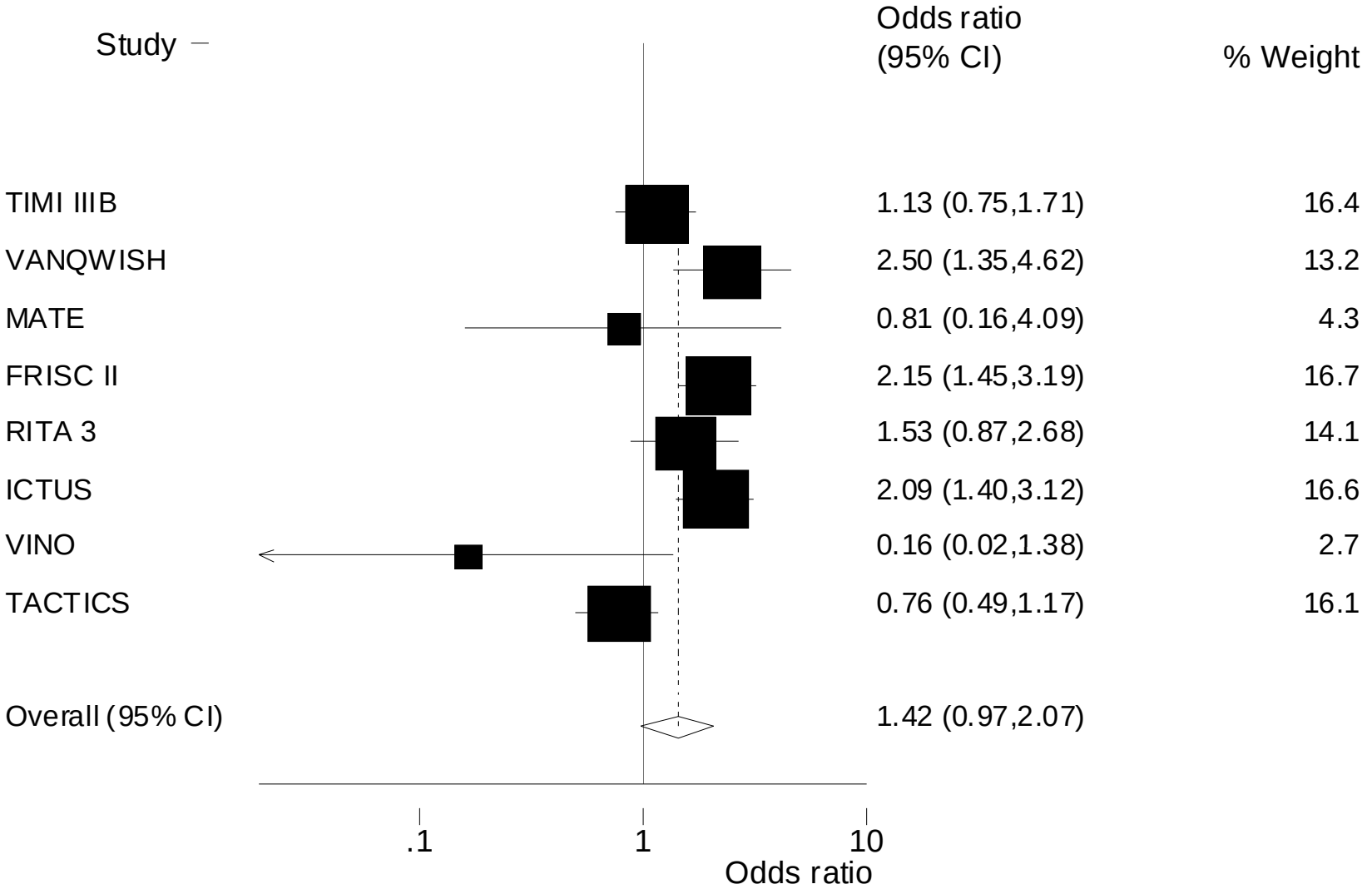


Cost-effectiveness acceptability curves



Results of meta analysis

Odds of CVD/MI in the index period



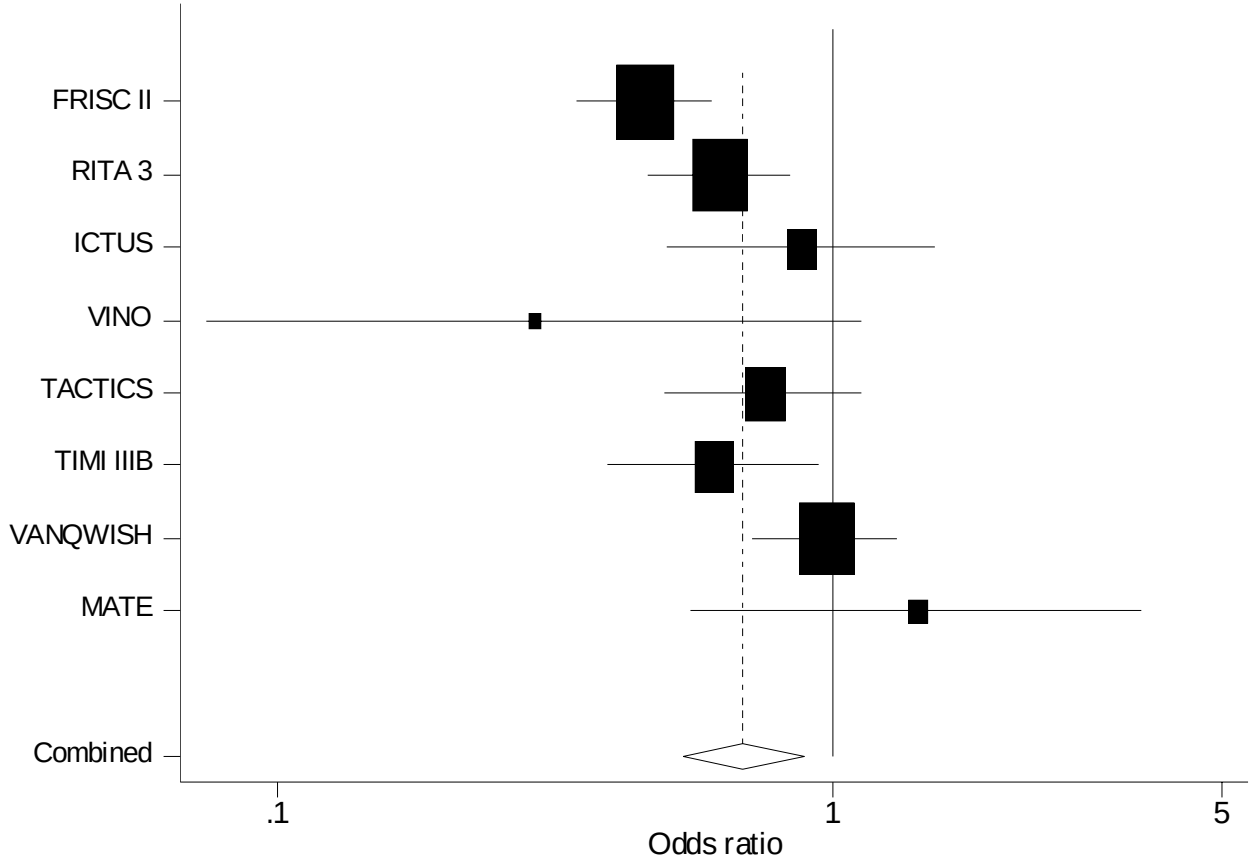
Incorporating the meta analysis results

Odds of CVD/MI in the index period

Risk factor	Odds ratio	SE
Treat	1.520	0.438
Age	1.731	0.279
Angina	1.893	0.537
Constant	0.010	0.004
Pooled treatment effect	1.420	0.290

Results of meta analysis

Pooled treatment effect – long-term



	Odds ratio (95 % CI)	% Weight
FRISC II	0.46 (0.34,0.60)	0.179
RITA 3	0.62 (0.46,0.83)	0.176
ICTUS	0.87 (0.50,1.52)	0.108
VINO	0.29 (0.07,1.12)	0.029
TACTICS	0.74 (0.50,1.12)	0.143
TIMI IIIB	0.60 (0.39,0.93)	0.135
VANQWISH	0.96 (0.71,1.30)	0.174
MATE	1.40 (0.55,3.55)	0.055
Combined	0.69 (0.54,0.88)	

Updating the long-term equation

Risk factor	Hazard ratio	SE
Age	1.777	0.154
Diabetes	1.905	0.329
Previous MI	1.471	0.227
Smoker	1.651	0.264
Pulse	1.062	0.026
ST depression	1.423	0.213
Angina	1.323	0.197
Male	1.372	0.216
Left BBB	1.977	0.530
Treat	0.621	0.092
Constant	0.008	0.003
Gamma parameter	0.579	0.040
Pooled treatment effect	0.688	0.137

Results using a pooled treatment effect from 8 trials

	Risk group 1	Risk group 2	Risk group 3	Risk group 4a	Risk group 4b
Odds ratio index hospitalisation with early intervention	1.42	1.42	1.42	1.42	1.42
Hazard ratio in follow-up period with early intervention	0.69	0.69	0.69	0.69	0.69
Incremental cost (£)	4,819	4,852	5,788	6,163	6,129
Incremental QALY	0.0824	0.1847	0.2397	0.4517	0.4178
ICER (£)	58,490	26,265	24,143	13,646	14,673

Example 2: The cost-effectiveness of drug eluting stents in patient subgroups

Decision Problem

- Narrowed coronary arteries may be treated by inflating of a balloon within the artery to crush the plaque into the walls of the artery (Percutaneous coronary intervention or PCI)
- Introduction of stents have resulted in an increasing use of PCI
- However, restenosis remains high – 15%-40% after 6 months based on angiography
- Clinical Trials indicate that drug-eluting stents (DES) reduce restenosis rates
- The acquisition costs of DES are, however, appreciably higher than bare metal stents (BMS)

- Should DES be used?
- In which patients should DES be used ?

Original NICE recommendation

"The use of either a Cypher (sirolimus-eluting) or Taxus (paclitaxel-eluting) stent is recommended in PCI for patients with symptomatic coronary artery disease (CAD), in whom the target artery is less than 3 mm in calibre (internal diameter) or the lesion is longer than 15 mm."

Reference: Final Appraisal Determination: Coronary artery stents 8 September 2003

Decision model

- Clinical effect represented by rate of restenosis from synthesis of multiple trials.
  - Assumed restenosis requires intervention, CABG or repeat PCI
  - Assumed no differential effects on mortality, myocardial infarction or cerebrovascular events

- Impact on Quality Adjusted Life from reduction in utility during waiting period for further revascularisation following restenosis
  - Mean waiting time of 196 days[3]
  - Utility symptoms of restenosis 0.69 compared to 0.84 without[4] based on EQ5D responses

- Costs includes acquisition costs of stents and costs of further revascularisations for restenosis - stents, angiography (£372), PCI (£2,609) , CABG (£7,066)

Systematic review of trial data

- 15 RCTs identified
  - CYPHER vs BMS (4) [IPD available]
  - CYPHER vs TAXUS (5)
  - TAXUS vs BMS (5)
  - TAXUS vs CYPHER vs BMS (1) [IPD available]
- As far as possible, restenosis rates extracted from each trial were clinically determined (i.e. based on symptoms) rather than angiographically driven

Evidence Synthesis
Bayesian Hierarchical Model

IPD: $p = \text{logit}^{-1}(\alpha_{study} + \beta_{Cypher} + \beta_{Taxus} + \beta_{Small} + \beta_{Diabetes\ es} + \beta_{Long})$

$r \sim Bern(p)$

Aggregate data: $p = \text{logit}^{-1}(\alpha_{study} + \beta_{Cypher} + \beta_{Taxus})$

$r \sim Bin(p,n)$

- Covariates influence 'baseline' risk of restenosis
- Effect of stent choice on the risk of restonosis assumed to independent of covariates (on the log-odds scale). Required to include aggregate data?
- IPD data allows the assumption of independence to be tested
- Trade-off between model complexity and data utilisation

Results of the evidence synthesis. Probability of restenosis in year 1

Risk Factors	**Type of Stent**		
	BMS	*Cypher*	*Taxus*
None	0.13	0.04	0.05
Narrow Vessels	0.19	0.07	0.08
Long Lesions	0.16	0.05	0.07
Diabetes	0.19	0.06	0.08

Cost-effectiveness results for different sub-groups

No Risk factors

	QALYs	Costs	
	Mean	**Mean**	**ICER**
BMS	-0.01187	1760	-
Taxus	-0.0047	2025	Extended
Cypher	-0.00353	2044	34041

Small Vessel Disease

	QALYs	Costs	
	Mean	**Mean**	**ICER**
BMS	-0.0176	2079	-
Taxus	-0.00753	2199	Extended
Cypher	-0.00606	2214	11744

long Vessel Disease

	QALYs	Costs	
	Mean	**Mean**	**ICER**
BMS	-0.01467	1915	-
Taxus	-0.00607	2109	Extended
Cypher	-0.00475	2126	21208

Discrimination between sub-groups

Populaton	Prop.	Prob.	DES ICER	Net Benefit*		Optimum
		Restenosis		BMS	DES	Stent
Diabetic	0.25	0.26	2443	6131	**6247**	DES
Non-diabetic	0.75	0.18	18115	**6434**	6345	BMS
Whole Population	1	0.2	13147	**6358**	6321	BMS

*Net Benefit = QALYs x £10,000 per QALY – COST

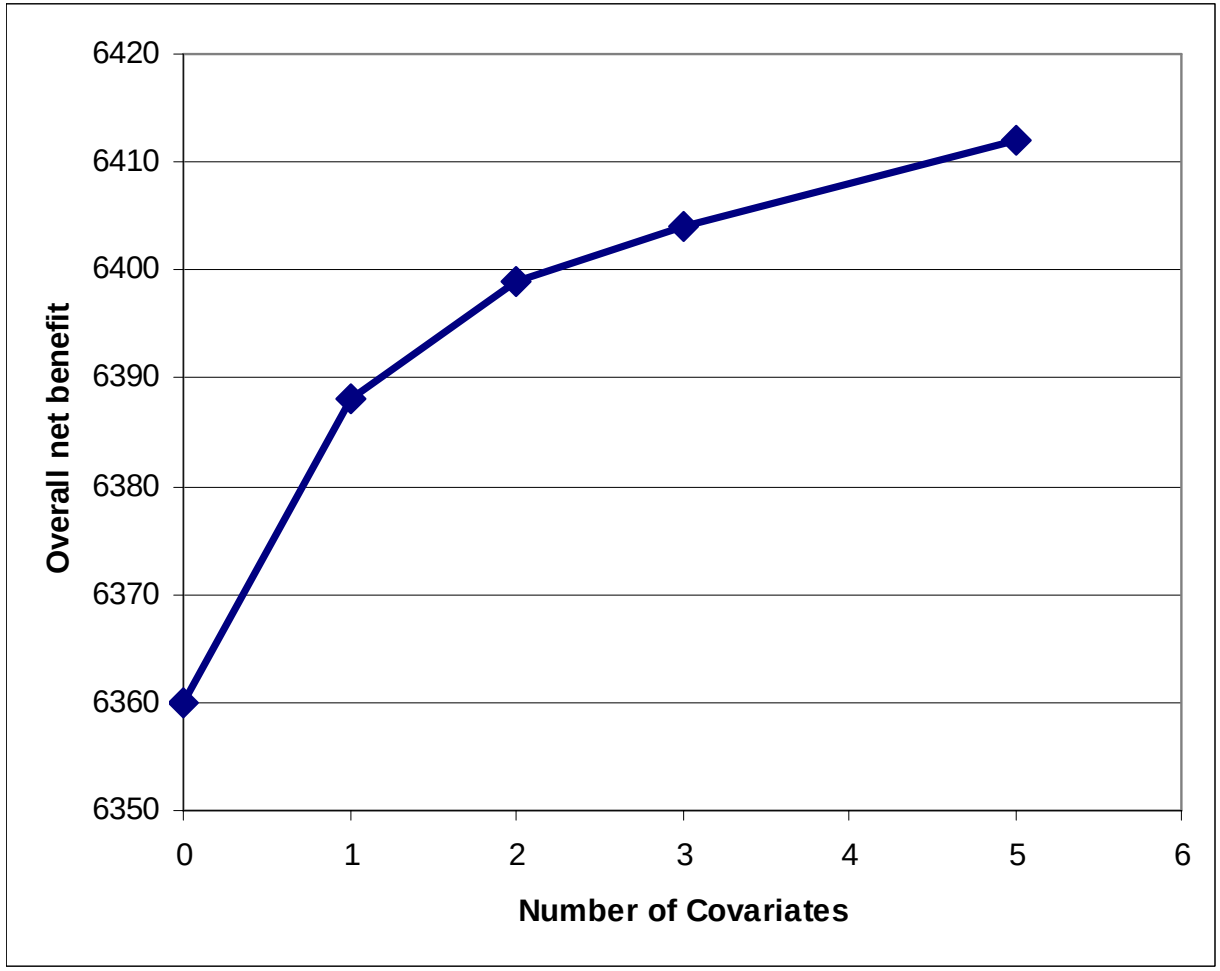
Overall Net Benefit if we discriminate = 6387

Overall Net Benefit if we do not discriminate = 6358

Selection of Subgroups: Discrimination and model fit

N	Covariates	Overall Net Benefit	DIC
0	None	6360	1234
1	**diabetes**	**6388**	**1227**
1	narrow	6377	1227
1	long	6366	1235
2	narrow long	6392	1227
2	**narrow diabetes**	**6399**	**1222**
2	long diabetes	6394	1228
3	**narrow long diabetes**	**6404**	**1221**
…	…	…	…
5	narrow long diabetes XX XX	6412	1223

Complexity vs. Efficiency Trade-off



Selection of Subgroups: Practicality

Population	Probability of Reste	
	BMS	DES
No risk factors	0.12	0.03
long	0.15	0.04
diabetes	0.18	0.04
narrow	0.19	0.05
long diabetes	0.22	0.06
narrow long	0.23	0.06
narrow diabetes	0.26	0.07
narrow long diabetes	0.32	0.09

Conclusions

- Individual patient level data facilitates evaluation of cost-effectiveness in subgroups

- Selection of relevant patient variables:
  - Discrimination vs. model fit
  - Discrimination vs. practicility
  - Continuous vs. dichotomous variables
  - modelling vs. subgrouping
  - Discrimination depends on population distribution