

Disclosures:

Alongside my day job at the University, I am Director & Principal at Occam Research Ltd, a consultancy with industry clients. This particular work is academic, unfunded by industry, and there are no relevant conflicts of interest. The original EUROPA model development was funded by Servier over twenty years ago.

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Modelling Heterogeneity Without Individual Simulation: Structural Choices And Sampling Strategies

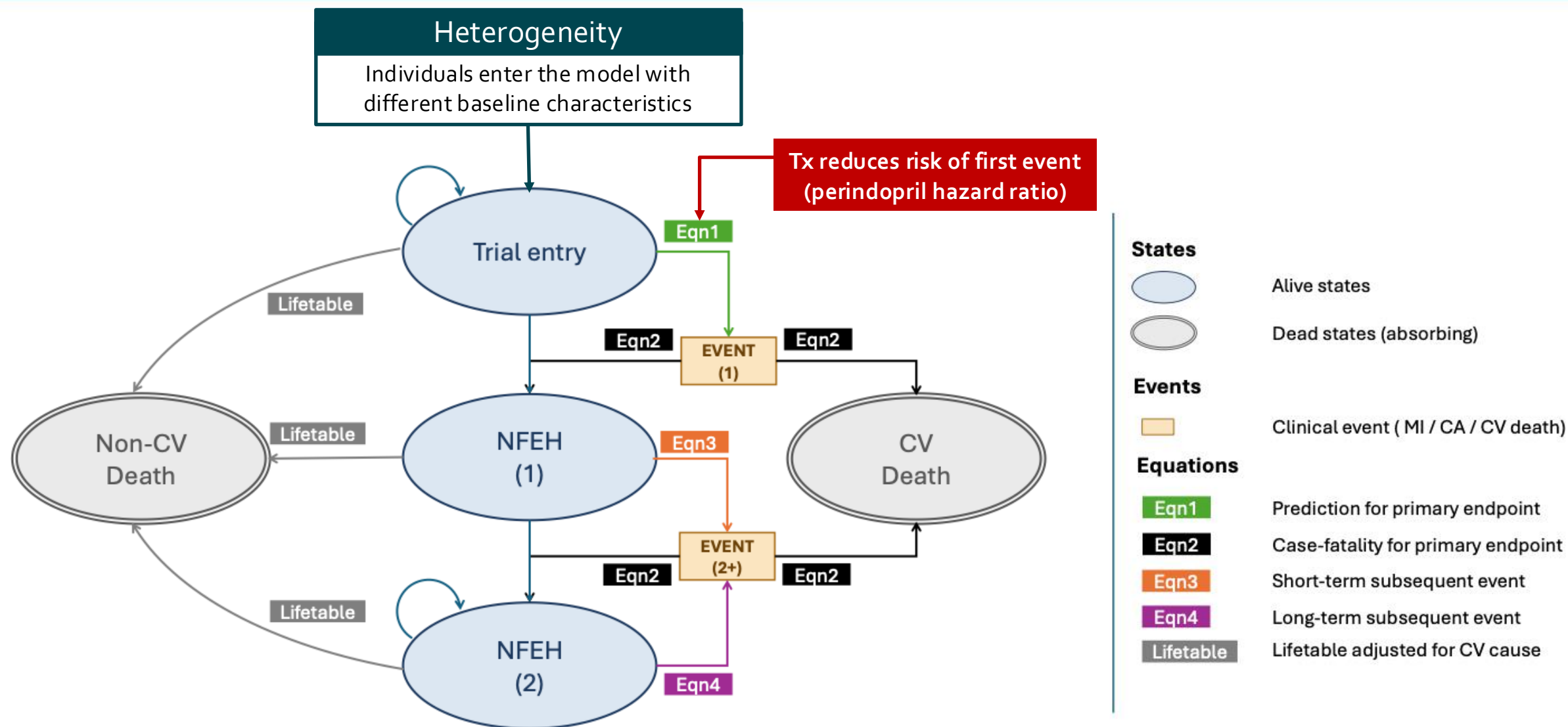
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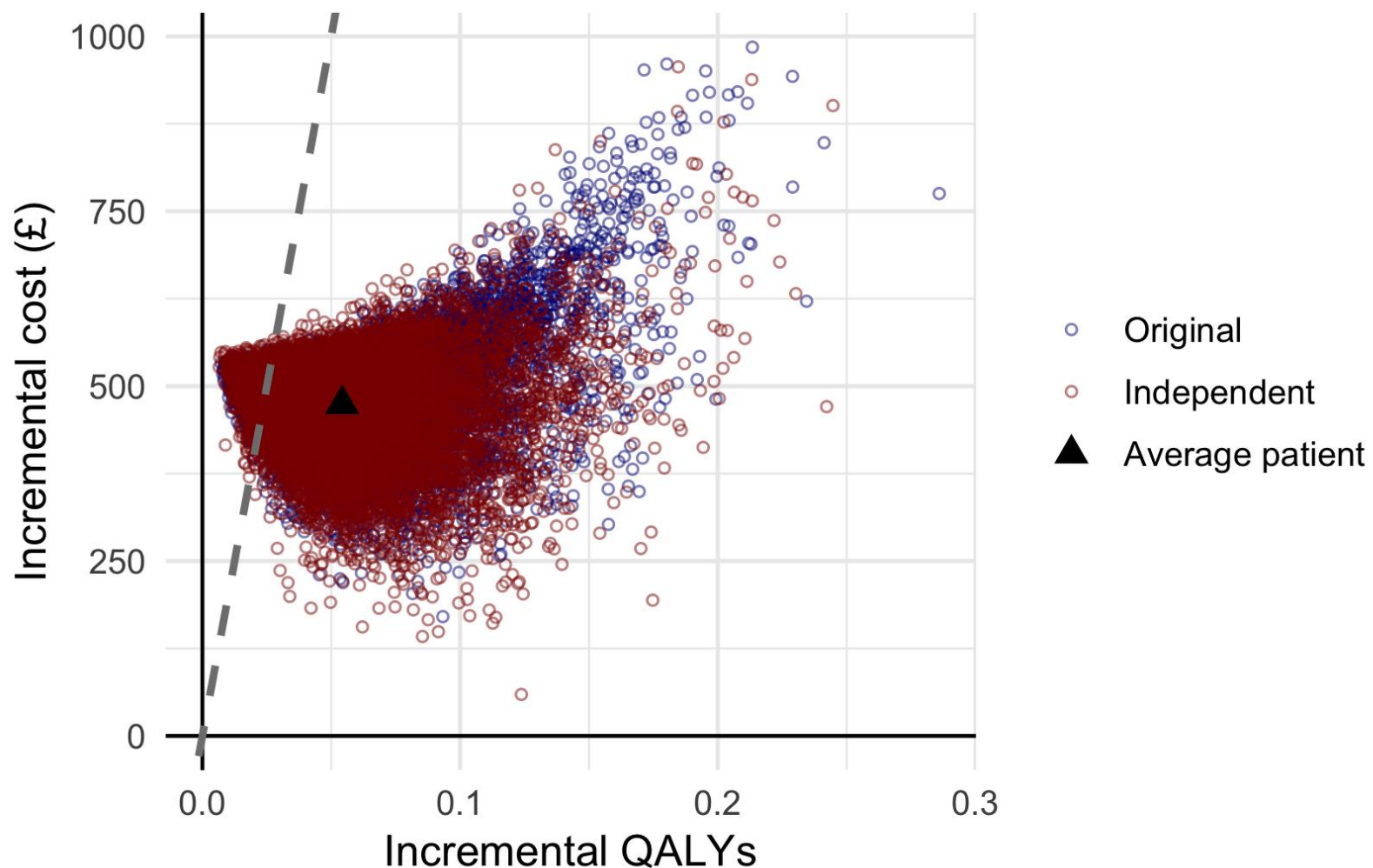


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EUROPA model



Three views of the same cohort



Heterogeneity summary

	Avg. patient	Original	Indep.-permuted
ΔC (£)	474	485	474
ΔQ	0.0543	0.0557	0.0550
ICER, ratio of means (£/QALY)	8,736	8,709	8,616
Median of patient ICERs (£/QALY)	—	9,723	9,694
NMB at $\lambda = £20,000$ (£)	611	629	626
SD of patient NMB (£)	—	623	601
% NMB > 0	—	87.4	89.1

Stratification – four approaches

1. Cox 1957 optimal grouping applied to NMB.

Cox showed that grouping a continuous variable to minimise within-group variance is solved exactly by one-dimensional dynamic programming. Applied to NMB directly, gives the theoretical upper bound on information recovery – no rule built on observable covariates can recover more NMB variance than a rule built on NMB.

2. Equal-sized groups by clinical risk.

The clinically familiar benchmark – using the validated EUROPA-derived risk score

3. Cox 1957 optimal grouping applied to risk score .

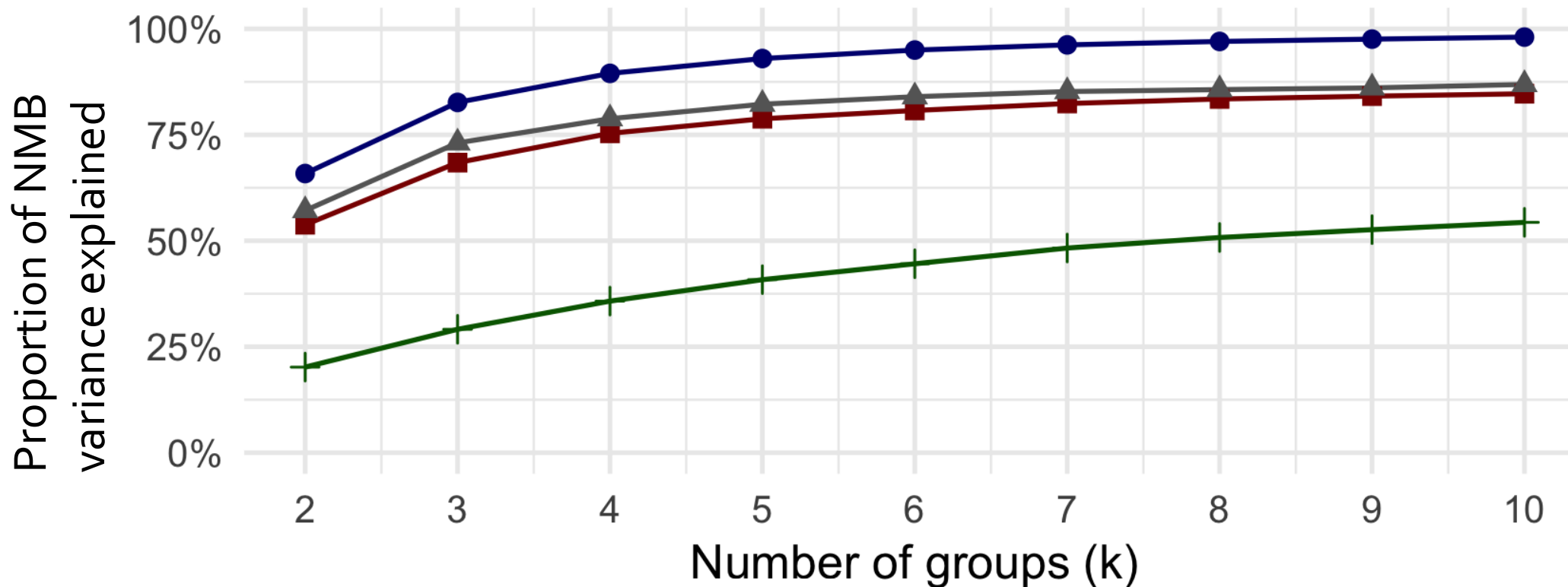
Asks what happens when you replace equal-sized cuts with optimised cuts on the same score.

4. CART regression trees.

CART is a binary recursive partitioning algorithm: at each step it finds the covariate and threshold that maximally reduce within-leaf NMB variance, then prunes back to a target number of leaves.

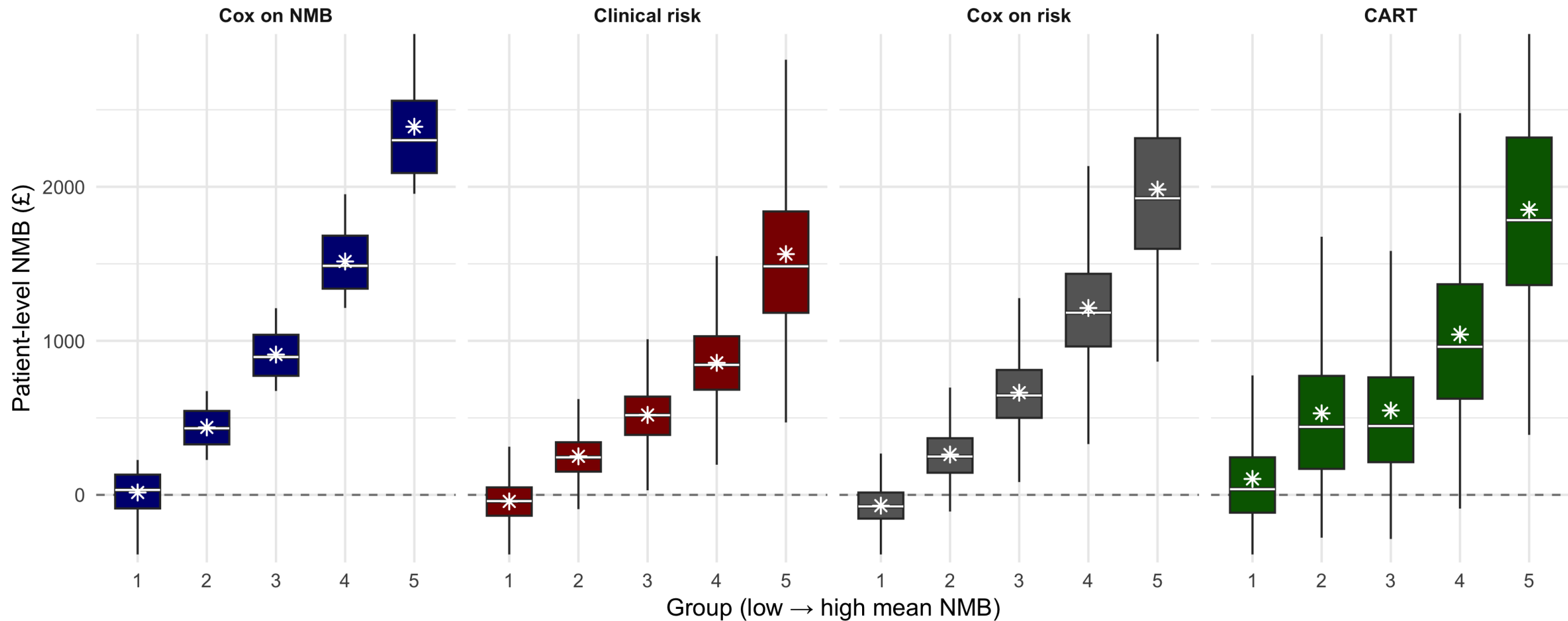
It uses the full covariate set rather than the composite score.

Information recovery curves



- Cox (1957) optimal grouping on NMB
- ▲ Cox (1957) optimal grouping on clinical risk
- Equal-sized groups by clinical risk
- + CART regression tree

Box plots for $k = 5$ quintiles



Future development and conclusions

- What is the right stopping rule for enough variance explained?
- EUROPA has validated clinical risk score driving it. How best to represent heterogeneity when direct link to clinical risk is not so apparent?
- Jensen's inequality did not seem hugely import for EUROPA, but not clear this is a generalizable finding? Need to apply to other examples.
- Choice of model architecture should be justified on structural grounds. Baseline heterogeneity is a feature of the population and cohort models can handle it.
- Preservation of correlated structure of risk factors should be preserved. For EUROPA the differences were not large, but were there.
- Heterogeneous results should be handled through principled stratification. Means of heterogenous cohorts obfuscate policy decisions.