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Challenges with Economic Models Driven by a Validated Surrogate Outcome

An Example

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Disclosures

- Incoming senior leader at the Institute for Clinical and Economic Review, which has conducted an assessment of therapies described in this case study.
- The Center for the Evaluation of Value and Risk in Health receives financial support from drug and device manufacturers, governments, and academic institutions to develop and maintain a number of research datasets.

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The Challenges with Surrogates

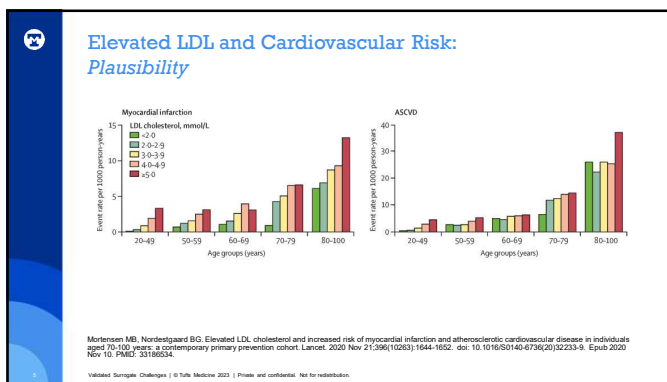
- Plausibility of link to meaningful outcomes
- Precision of surrogate measurement
- Level of correlation between surrogate and outcome of interest

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What if the Surrogate Has Been Validated?
Elevated LDL and Cardiovascular Risk

- Plausibility of link to meaningful outcomes ✓
- Precision of surrogate measurement ✓
- Level of correlation between surrogate and outcome of interest ✓

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Elevated LDL and Cardiovascular Risk:
Precision

LDL Calculated

Total Cholesterol: 248

HDL Cholesterol: 48

Triglycerides: 160

LDL Calculated: 156.0 mmol/L

<https://www.mdcalc.com/calc/70/ldl-calculated>

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Why Careful Scrutiny of LDL Hypothesis Matters

- Later modeling based on CV event rates from later RCTs:
 - E.g., Repatha

Outcome	Expected Effect of PCSK9 Inhibitor Therapy based on 60mg/6L reduction in LDL-C ^a HR	Expected Effect of PCSK9 Inhibitor Therapy based on MA of earlier trials ^b HR	Observed Effect of PCSK9 Inhibitor Therapy in the EVOLUCA Trial ^c HR
All-cause death	0.69 (0.3-0.87)	0.48 (0.27-0.87)	1.04 (0.7-1.57)
CVD death	0.81 (0.75-0.86)	0.49 (0.23-1.07)	1.05 (0.68-1.75)
MI	0.58 (0.52-0.66)	0.49 (0.28-0.93)	0.73 (0.65-0.82)
Stroke	0.75 (0.67-0.83)	NR ^d	0.79 (0.66-0.95)
Unstable Angina	NR	0.51 (0.05-4.86)	0.59 (0.62-1.10)
Revascularization	0.61 (0.57-0.66)	NR	0.78 (0.71-0.86)

^a Based on LDL-C reduction of 60 mg/dL or 1.55 mmol/L, and the relative risks for clinical events per 1 mmol/L reduction estimated by the Cholesterol Treatment Trialists' Collaborators¹

^b Meta-analysis combining events from all doses of both alirocumab and evolocumab²

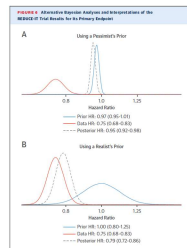
^c CVD: cardiovascular disease, LDL-C: low-density lipoprotein cholesterol, MA: meta-analysis, MI: myocardial infarction, NR: not reported, HR: relative risk

Institute for Clinical and Economic Review, Evolocumab for Treatment of High Cholesterol: Effectiveness and Value. New Evidence Update https://icer.org/wp-content/uploads/2020/10/ICER_PC-SK9_NEU_091117.pdf

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A Bayesian View on Surrogate Performance

- Many failed prior trials of fish oil supplements for lowering CV risk
- New trial of icosapent ethyl (Vascepa®) shows 25% risk reduction
- Bayesian analysis can consider prior experience in evaluating findings



Proctor SJ, Collier TJ. Statistical Appraisal of 6 Recent Clinical Trials in Cardiology: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Jun 4;73(21):2740-2750. doi: 10.1016/j.jacc.2019.03.044. Epub 2019 May 3. Erratum in: J Am Coll Cardiol. 2019 Jul 30;74(4):595-597. PMID: 31060767.

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Summary

- Some surrogate outcomes have been tested and well-validated over many years and in many individuals
- "Watch your cholesterol!"
- In certain situations, even validated surrogates:
 - May under- or over-predict outcomes
 - May not predict outcomes at all!
- Guidance:
 - Use caution (and maybe Bayesian techniques?)
 - Make every attempt to express and test uncertainty in estimates using surrogates, even if validated
 - Compare early estimates with results from confirmatory studies whenever possible

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Thank You!

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