Mario

Surrogacy and economic modelling

Disclaimer

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- I have no real or apparent relevant financial relationships to disclose.
- I am employed by Astrazeneca BioPharmaceutical Medicine Sweden and have nothing to disclose.
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Selection of a diabetes economic model relating the change in HbA1c to the change in late outcomes

Suppose we need to select a diabetes model out of the literature

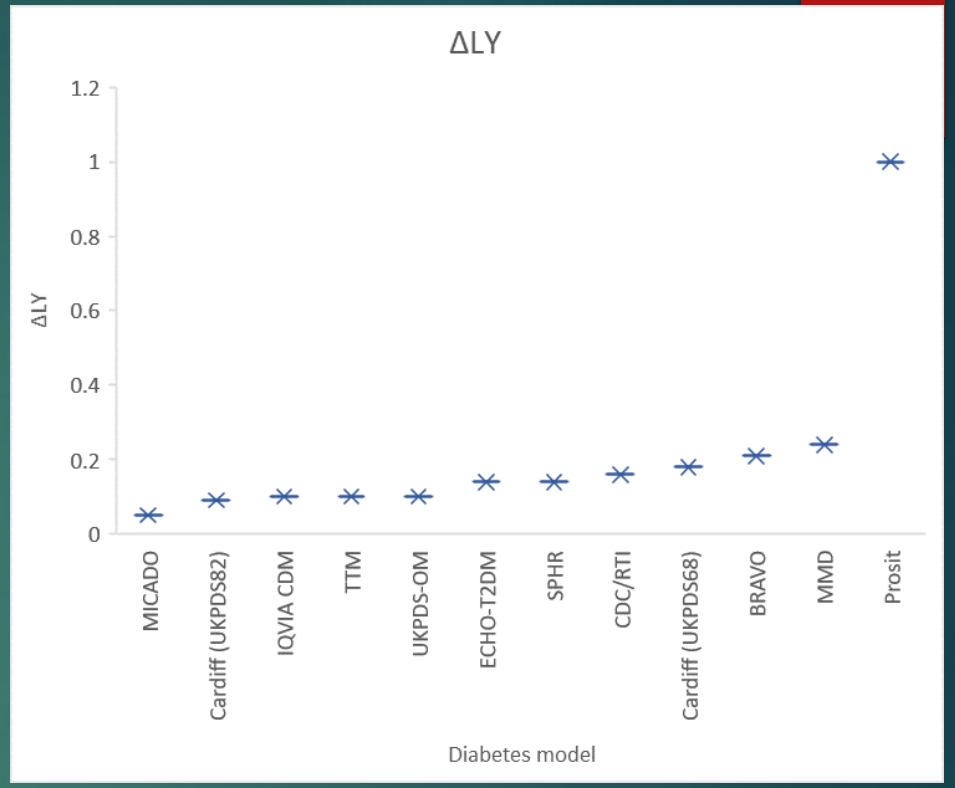
Let's limit to the 12 diabetes models evaluated at the 9th Mount Hood challenge: MICADO, Cardiff (UKPDS82), IQVIA CDM, TTM, UKPDS-OM, ECHO-T2DM, SPHR, CDC/RTI, Cardiff (UKPDS68), BRAVO, MMD, Prosit

The 9th Mount Hood challenge concerned the testing of the 12 Diabetes models for modelling the impact on QALY and LY in terms of changes in HbA1c, among others.

The information from 9th Mount Hood will be used in the next slides to discuss the selection of a diabetes model

In all models, a decrease of 0.5% in HbA1c positively impacts LY

	LY	ΔLYs
MICADO	13.2	0.05
Cardiff (UKPDS82)	16.5	0.09
IQVIA CDM	13.7	0.10
TTM	16.0	0.10
UKPDS-OM	15.9	0.10
ECHO-T2DM	14.3	0.14
SPHR	19.1	0.14
CDC/RTI	11.9	0.16
Cardiff (UKPDS68)	13.4	0.18
BRAVO	17.1	0.21
MMD	19.9	0.24
Prosit	13.5	1.00

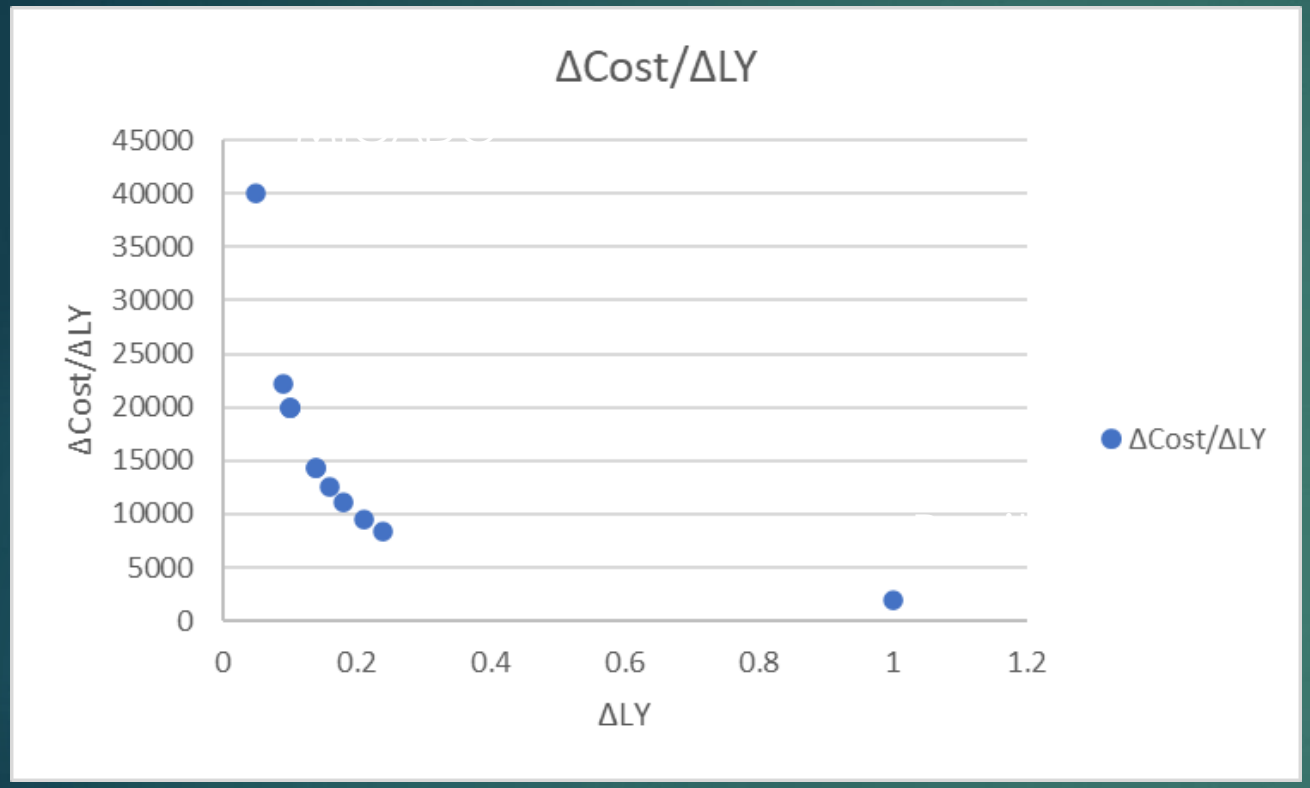


Which model to choose:

1. All models are acceptable from LY perspective
2. Would not use Prosit (ΔLY = 1 on 13 LY)
3. None of them should be used as they result in a decrease in mortality as a function of HbA1c
4. Other

Which one would be your base case?

Ratio: Small differences in ΔLY may lead to large differences in incremental costs per incremental LY



	LY	ΔLY	ΔCost	ΔCost/ΔLY
MICADO	13.2	0.05	2000	40000
Cardiff (UKPDS82)	16.5	0.09	2000	22222
IQVIA CDM	13.7	0.1	2000	20000
TTM	16	0.1	2000	20000
UKPDS-OM	15.9	0.1	2000	20000
ECHO-T2DM	14.3	0.14	2000	14286
SPHR	19.1	0.14	2000	14286
CDC/RTI	11.9	0.16	2000	12500
Cardiff (UKPDS68)	13.4	0.18	2000	11111
BRAVO	17.1	0.21	2000	9524
MMD	19.9	0.24	2000	8333
Prosit	13.5	1	2000	2000

Which model to choose:

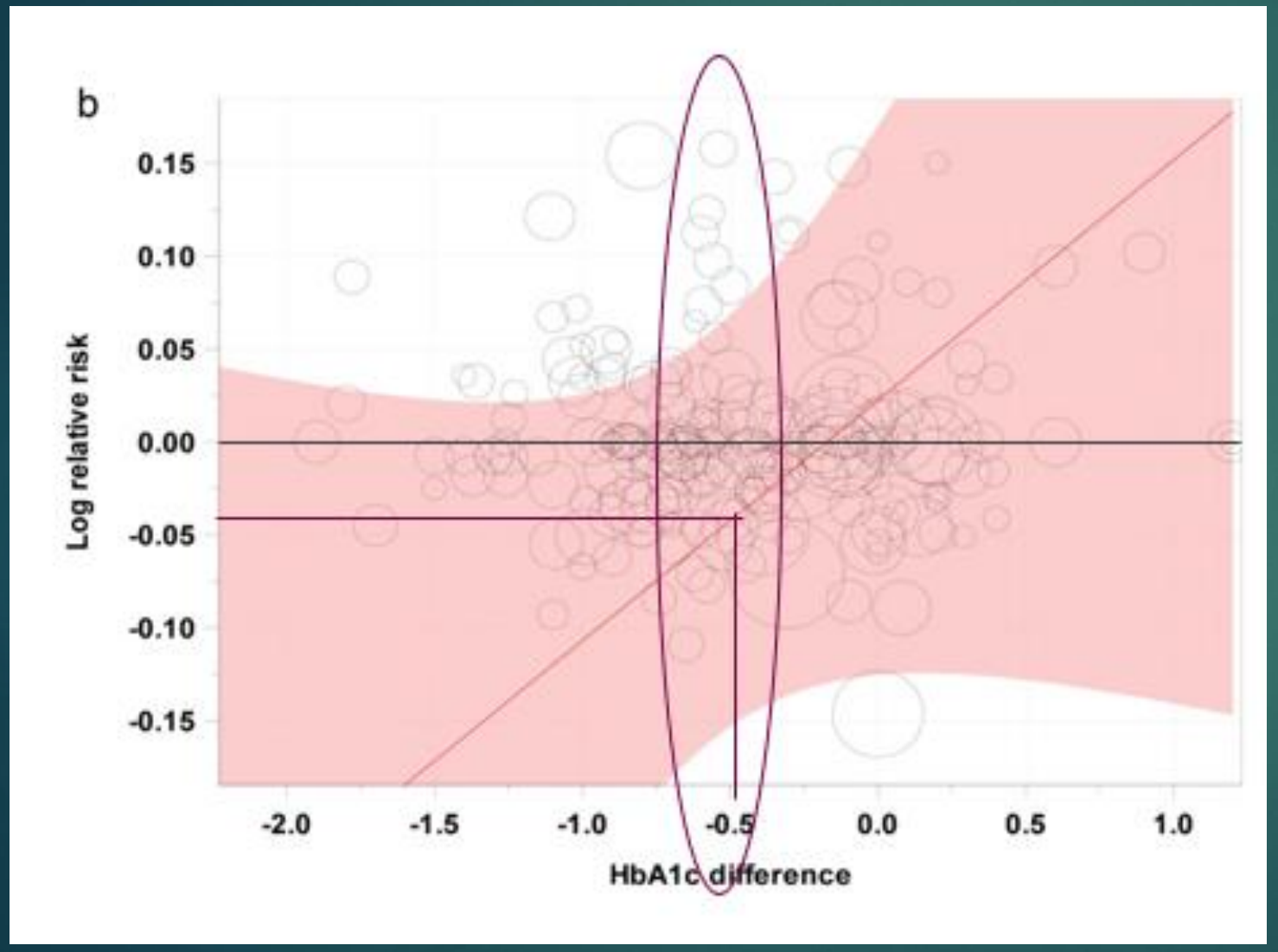
1. All models are acceptable from LY perspective
2. Would not use Prosit
3. None of them should be used as they result in a decrease in mortality as a function of HbA1c
4. Other opinion

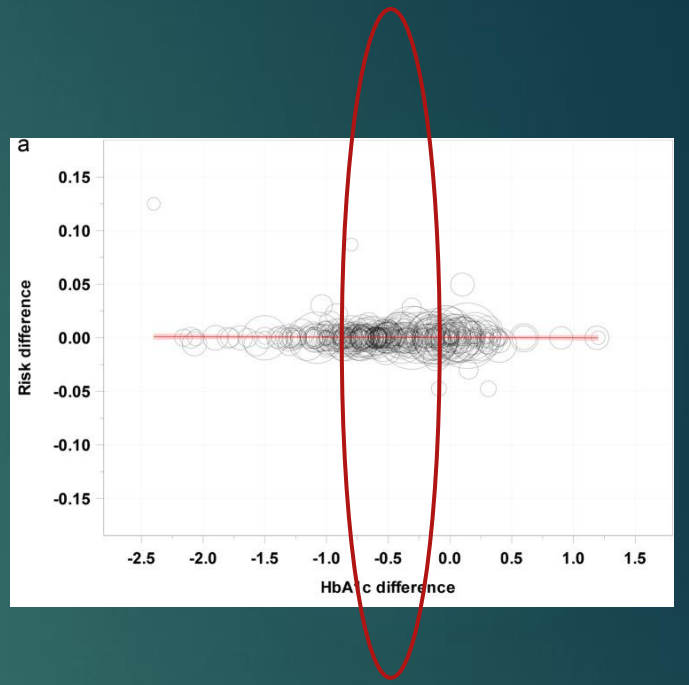
Positive impact on LY is not in line with surrogacy evaluations

HbA1c IS NOT A VALID SURROGATE MARKER for all-cause mortality in people with type 2 diabetes. (Baechle, Acta diabetologica Oct 2022 based on 205 RCTs)

HbA1c's RELIABILITY AS A PREDICTOR of hard outcomes is UNCERTAIN, mainly for macrovascular complications (Daly, Front Pharmacol May 2022)

Baechle (2022): About no relation tx effect HbA1c and tx effect mortality





Large uncertainty in relationship and whether a relationship exists

Do we want to select a different diabetes model?

	LY	ΔLYs
MICADO	13.2	0.05
Cardiff (UKPDS82)	16.5	0.09
IQVIA CDM	13.7	0.10
TTM	16.0	0.10
UKPDS-OM	15.9	0.10
ECHO-T2DM	14.3	0.14
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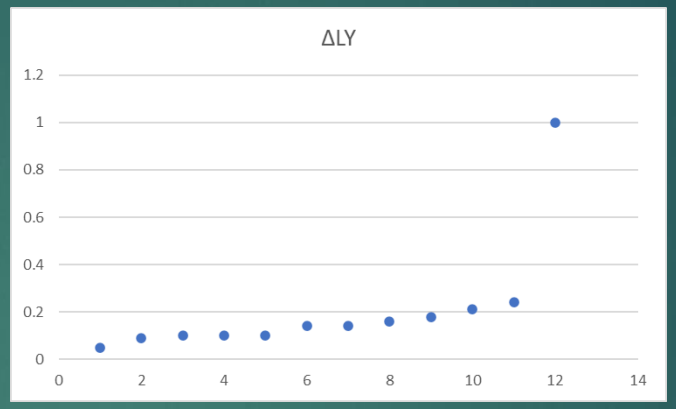
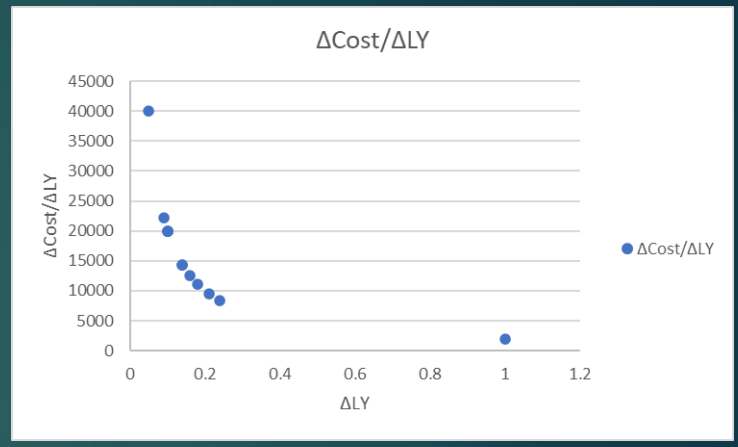




"HbA1c is not a surrogate"

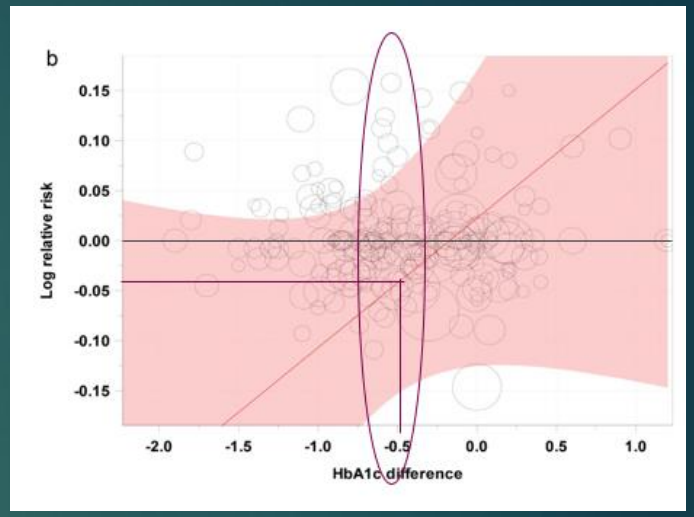
Which model to choose:

1. All models are acceptable from LY perspective
2. Would not use Prosit (ΔLY = 1 on 13 LY)
3. None of them should be used as they result in a decrease in mortality as a function of HbA1c
4. Other

Which one would be your base case?

Baechle point estimate log relative risk indicates high impact on LY.

	LY	ΔLYs	ΔLYs no relation	line Baechle
MICADO	13.2	0.05	0	0.55
Cardiff (UKPDS82)	16.5	0.09	0	0.69
IQVIA CDM	13.7	0.10	0	0.57
TTM	16.0	0.10	0	0.67
UKPDS-OM	15.9	0.10	0	0.66
ECHO-T2DM	14.3	0.14	0	0.60
SPHR	19.1	0.14	0	0.80
CDC/RTI	11.9	0.16	0	0.49
Cardiff (UKPDS68)	13.4	0.18	0	0.56
BRAVO	17.1	0.21	0	0.71
MMD	19.9	0.24	0	0.83
Prosit	13.5	1.00	0	0.56



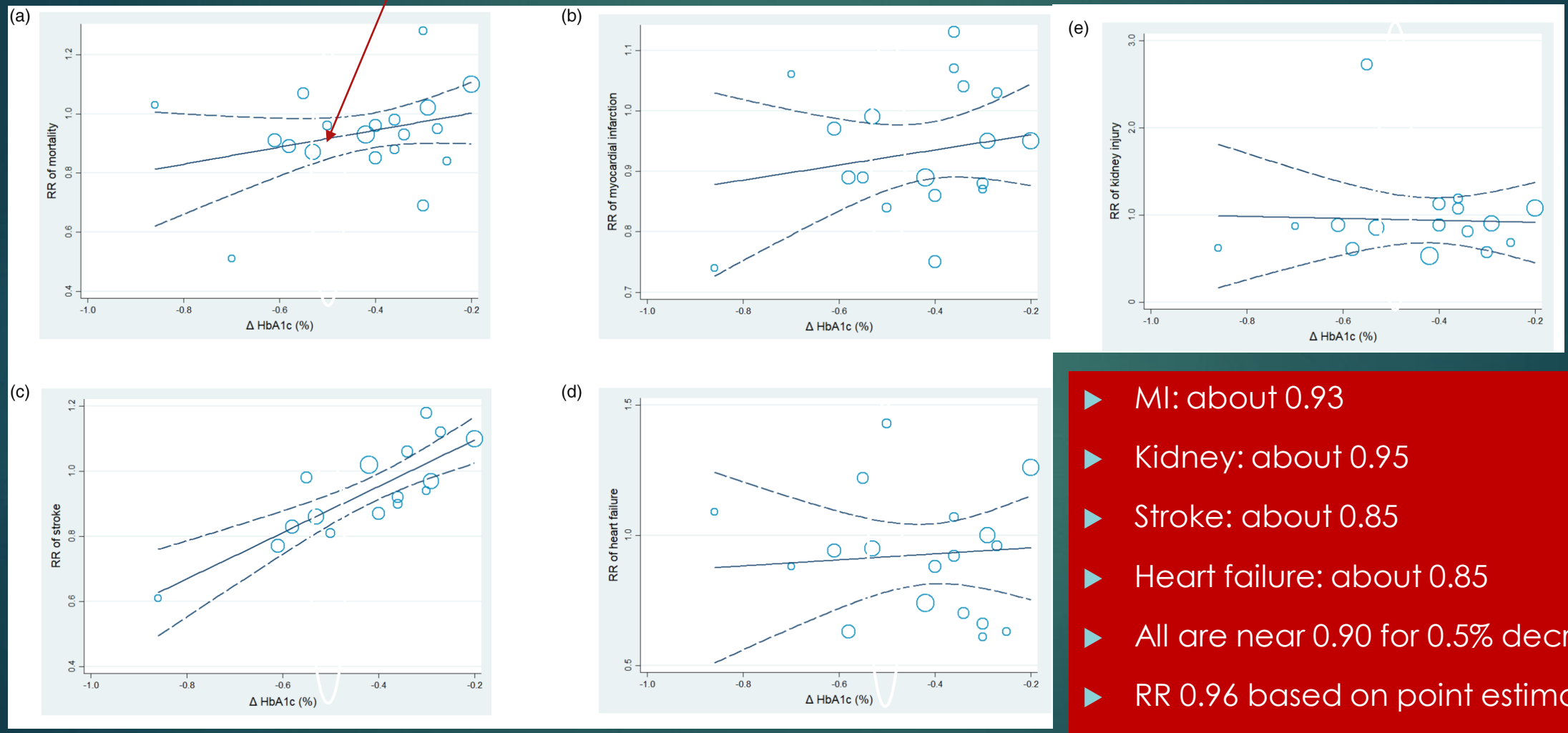
Which model to choose:

1. All models are acceptable from LY perspective
2. Would not use Prosit
3. None of them should be used as they assume that a decrease in HbA1C impacts mortality
4. Other

Which one would be your base case?

Rivera (2022) shows relations of HbA1c with late outcomes occurring before death
Only studies with at least 1000 subj, 20 events and 52 weeks follow-up included

About 0.9



- MI: about 0.93
- Kidney: about 0.95
- Stroke: about 0.85
- Heart failure: about 0.85
- All are near 0.90 for 0.5% decrease HbA1c
- RR 0.96 based on point estimate Beachle

Mount Hood vs Baechle vs Rivera

	LY	ΔLYs	ΔLYs no relation	ΔLYs Baechle	ΔLYs Rivera
MICADO	13.2	0.05	0	0.55	1.47
Cardiff (UKPDS82)	16.5	0.09	0	0.69	1.83
IQVIA CDM	13.7	0.10	0	0.57	1.52
TTM	16.0	0.10	0	0.67	1.78
UKPDS-OM	15.9	0.10	0	0.66	1.77
ECHO-T2DM	14.3	0.14	0	0.6	1.59
SPHR	19.1	0.14	0	0.8	2.12
CDC/RTI	11.9	0.16	0	0.49	1.32
Cardiff (UKPDS68)	13.4	0.18	0	0.56	1.49
BRAVO	17.1	0.21	0	0.71	1.90
MMD	19.9	0.24	0	0.83	2.21
Prosit	13.5	1.00	0	0.56	1.50

Which model to choose:

1. All models are acceptable from LY perspective
2. Would not use Prosit
3. None of them should be used as they assume that a decrease in HbA1C impacts mortality
4. Other

Which one would be your base case?

Mount Hood vs Baechle vs Rivera: Has your opinion changed throughout the presentation?

	LY	ΔLYs	ΔLYs no relation	ΔLYs Baechle	ΔLYs Rivera
MICADO	13.2	0.05	0	0.55	1.47
Cardiff (UKPDS82)	16.5	0.09	0	0.69	1.83
IQVIA CDM	13.7	0.10	0	0.57	1.52
TTM	16.0	0.10	0	0.67	1.78
UKPDS-OM	15.9	0.10	0	0.66	1.77
ECHO-T2DM	14.3	0.14	0	0.6	1.59
SPHR	19.1	0.14	0	0.8	2.12
CDC/RTI	11.9	0.16	0	0.49	1.32
Cardiff (UKPDS68)	13.4	0.18	0	0.56	1.49
BRAVO	17.1	0.21	0	0.71	1.90
MMD	19.9	0.24	0	0.83	2.21
Prosit	13.5	1.00	0	0.56	1.50

Which model to choose:

1. All models are acceptable from LY perspective
2. Would not use Prosit
3. None of them should be used as they assume that a decrease in HbA1C impacts mortality
4. Other

Which one would be your base case?

Has your opinion changed throughout the presentation?

Would other sources of information potentially influence your opinion?

Would the following sources of information influence your choice?

1. HbA1c shown to be related to mortality benefit in **other related indication**
2. HbA1c shown to be related to mortality benefit in **later lines**
3. **Ad board** of clinicians indicates that HbA1c is a surrogate for mortality benefit
4. **Real world evidence**

Multiple early outcomes (If there is time left)

- Mount Hood evaluates 4 outcomes:
  - HbA1c
  - LDL-C
  - BMI
  - SBP
- Surrogacy evaluates whether one outcome is a surrogate for one other outcome
- Audience interaction: What is your opinion about
  - Changing surrogacy analyses into answering the question:
    What set of early outcomes can be measured that is related to the late outcomes of interest
  - Expecting that HbA1c is a surrogate of the late outcome, while treatment can have an independent effect on LDL-C, BMI and SBP as well, seems naive

Additional examples

Three ICERS in three situations (If there is time left)

Scenario 1:
Oncology: ICER 19.000.
PSA CI [17.000, 22.000]
80% of patients have died at first pricing and reimbursement negotiations.
HR mortality 0.80 [0.75, 0.85]

Scenario 2:
CKD: ICER 12.000.
PSA CI [5.000, 22.000].
40% has died at first pricing and reimbursement negotiations.
Mature mortality data are expected within the next 4 years (before the therapy is off-patent or superseded).
HR death 0.70 [0.40, 0.90]

Scenario 3:
Diabetes: ICER 2.000.
PSA CI [dominant, 50.000]
No mortality data are available at first pricing and reimbursement decisions, limited mortality data will be available during the therapy life cycle.
No HR death.

- How should we compare the three situations?
- What information would you at least want to have to be convinced?