INSTITUTET FÖR HÄLSO- OCH SJUKVÅRDSEKONOMI
THE SWEDISH INSTITUTE FOR HEALTH ECONOMICS

MT. HOOD 9

CHALLENGES AND OPPORTUNITIES ASSOCIATED WITH MODELING CARDIOPROTECTION IN ECONOMIC EVALUATION:

SOME INITIAL REFLECTIONS

Michael Willis, PhD
Christian Asseburg, PhD
Andreas Nilsson, MSc

October 6, 2018

Düsseldorf, Germany

IHE
Box 2127
SE-220 02 Lund, Sweden

Office address
Råbygatan 2
Lund, Sweden

Tel: +46-46 32 91 00
Fax: +46-46 12 16 04
www.ihe.se

Acknowledgements

- Michael Willis, Christian Asseburg, and Andreas Nilsson are employees of The Swedish Institute for Health Economics
- The Swedish Institute for Health Economics is majority owned by the non-profit *Bengt Jönsson Foundation for Health Economic Research* (along with small ownership stakes for a number of employees, which includes Michael Willis)
- The Swedish Institute for Health Economics is the creator and owner of ECHO-T2DM
- The Swedish Institute for Health Economics provides consulting services for a broad range of health care stakeholders, including national authorities, healthcare providers, branch organizations, and manufacturers.
- No remuneration was received for any part of our participation in the Mt. Hood Challenge

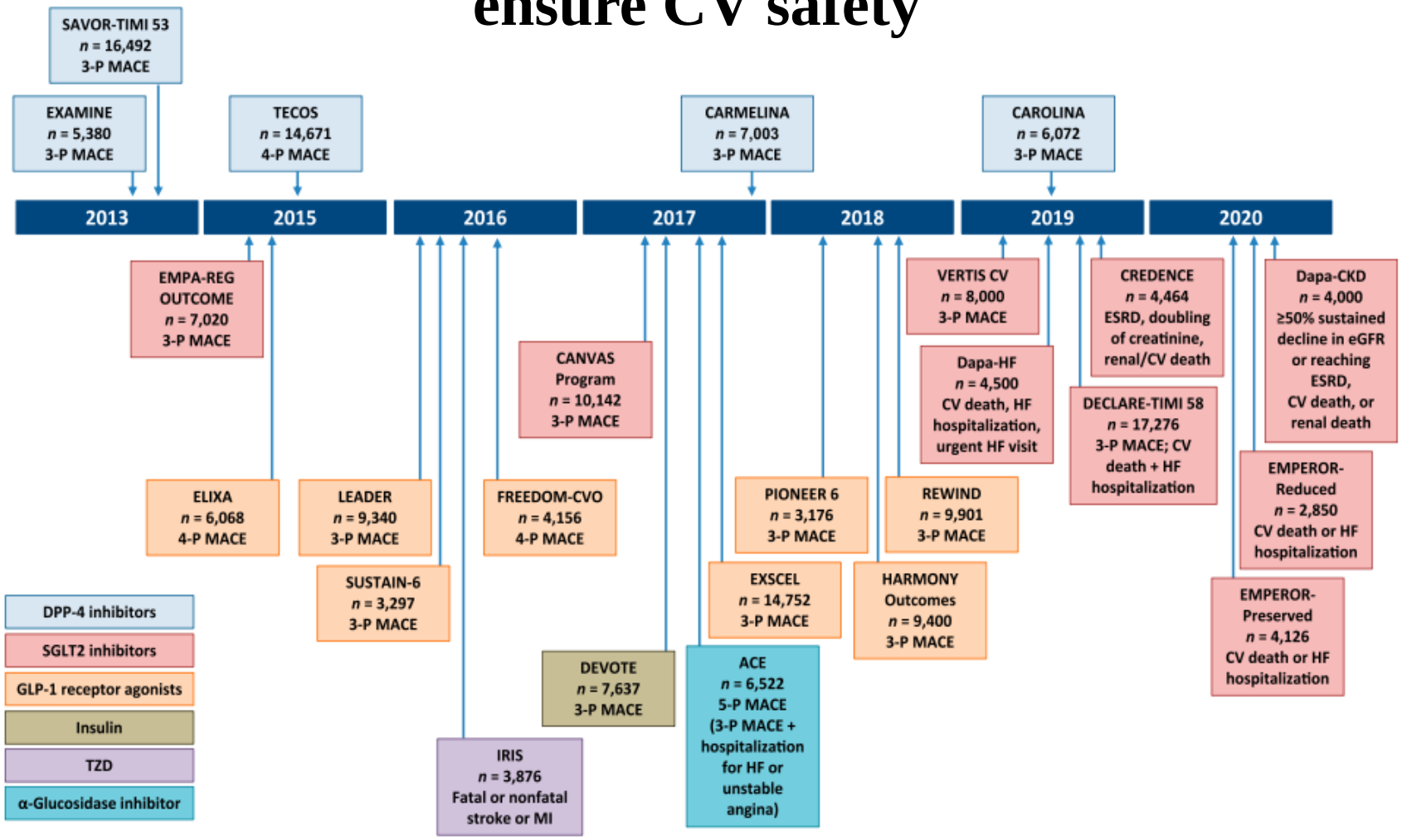
In December 2008, FDA issued new guidance to ensure CV safety

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Source: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

In December 2008, FDA issued new guidance to ensure CV safety



Source: Cefalu WT, et al. Diabetes care. 2018 Jan;41(1):14-31.

Evidence of CV protection that cannot be explained by improvements in known biomarkers has emerged for SGLTs and GLP1s

"Many CV experts appear to have revised their previous skepticism about the potential for CV benefits from diabetes-specific therapies. Diabetes researchers are exploring mechanisms that may explain the clinical effects first noted in these trials"

Cefalu et al. (2018):

Source: Cefalu WT, et al. Diabetes care. 2018 Jan;41(1):14-31.

EMPA-REG Mediation Analysis

Table 3—Univariable mediation analysis of risk of CV death with empagliflozin versus placebo: time-dependent covariate analysis adjusting for the updated mean of each variable

	HR for CV death with empagliflozin vs. placebo (95% CI)	Percentage mediation
Unadjusted	0.615 (0.491, 0.770)	
Adjusted for		
HbA_{1c}	0.687 (0.543, 0.868)	22.8
FPG	0.709 (0.559, 0.898)	29.3
SBP	0.610 (0.485, 0.766)	−1.7
DBP	0.618 (0.493, 0.774)	1.0
Heart rate	0.623 (0.497, 0.782)	2.7
LDL-C	0.591 (0.471, 0.741)	−8.2
HDL-C	0.629 (0.500, 0.789)	4.6
logTG	0.603 (0.481, 0.757)	−4.1
FFAs	0.587 (0.463, 0.743)	−9.6
logUACR	0.672 (0.536, 0.844)	18.2
eGFR (MDRD)	0.601 (0.480, 0.752)	−4.7
eGFR (CKD-EPI)	0.597 (0.477, 0.748)	−6.1
Weight	0.588 (0.466, 0.741)	−9.2
BMI	0.588 (0.466, 0.742)	−9.2
WC	0.602 (0.480, 0.755)	−4.4
Hematocrit	0.791 (0.620, 1.009)	51.8
Hemoglobin	0.768 (0.604, 0.978)	45.7
Albumin	0.717 (0.571, 0.900)	31.6
Uric acid	0.673 (0.536, 0.845)	18.5

Cox proportional hazards regression analysis in patients treated with one or more doses of study drug. FFA, free fatty acid; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglyceride; WC, waist circumference.

Inzucchi SE, et al. *Diabetes Care*. 2018;41(2):356-363.

To the extent that these benefits are not captured entirely by established biomarkers (like HbA1c, BP) included in risk prediction equations, …

They pose a challenge to economic evaluation that involves SGLT2s and GLP1s

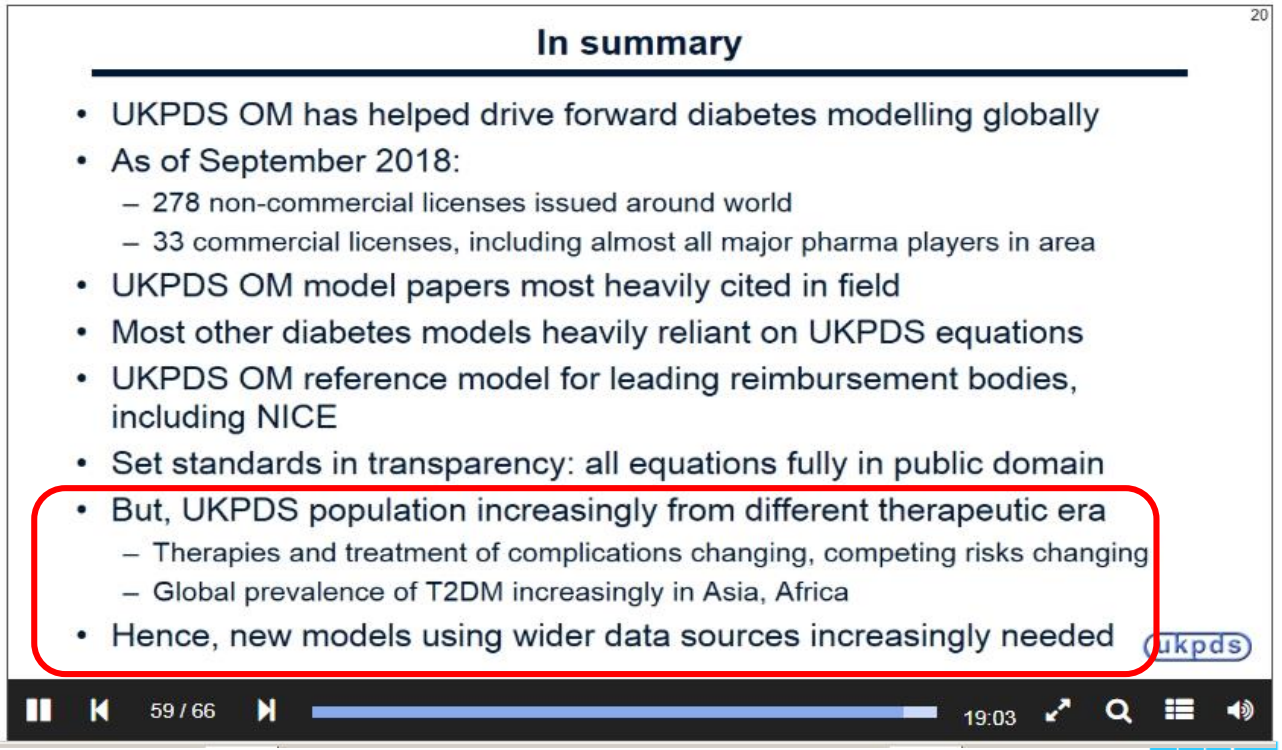
Thus, while clinicians investigate the source of these benefits, Economic modelers must use new methods and create new tools to support economic analysis

Insights from the UKPDS outcomes model

Oral Presentation # S15.3

Session: UKPDS

Berlin 2018 | Langerhans Hall | 3. October 2018 12:30 - 12:50 | 151 viewers



Source: Alastair Gray, "Insights from the UKPDS Outcomes Model, EASD 2018 website.

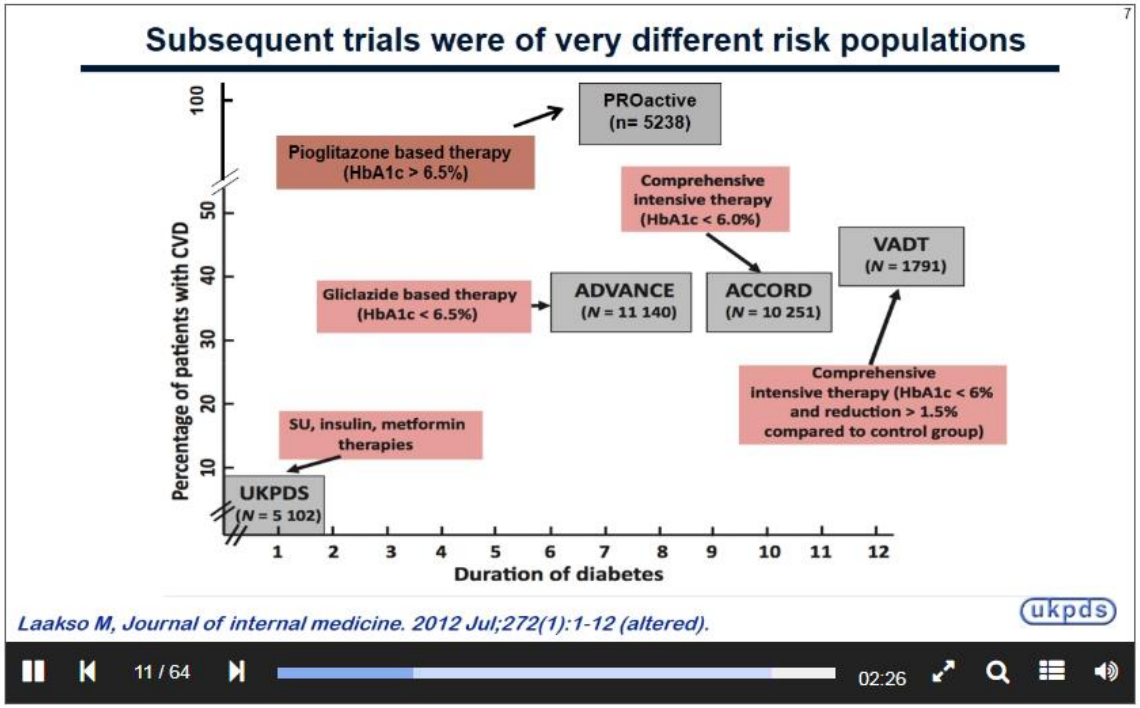
Indeed, the UKPDS (and the OM2) may be ”out of sample” for CV-rich populations with long disease durations: The patient population we are here to simulate

Putting the UKPDS into perspective

Oral Presentation # S15.4

Session: UKPDS

Berlin 2018 | Langerhans Hall | 3. October 2018 12:50 - 13:00 | 166 viewers



Source: David Matthews, ”Putting the UKPDS into perspective", EASD 2018 website.

At least 3 teams have found that cardioprotective benefits cannot entirely be accounted for by risk factors in economic modeling

- Willis et al., “The Importance of Considering the Evolving Evidence Base on Cardiovascular Effects of Anti-Hyperglycemic Agents on Estimates of ‘Value for Money’”, ADA, 2017.
- Kuo et al., “Are the favorable cardiovascular outcomes of empagliflozin treatment explained by its effects on multiple cardiometabolic risk factors? A simulation of the results of the EMPA-REG OUTCOME trial”. Diabetes research and clinical practice. 2018 Jul;141:181-9.
- Evans et al., ” Incorporating cardioprotective effects of once-weekly semaglutide in estimates of health benefits for patients with type 2 diabetes”, ADA, 2018.

For Example, Kuo et al (2018) found that most of the observed benefit in EMPA-REG was not captured via risk factor improvement with the MMD

Table 2. Observed and simulated primary and secondary cardiovascular outcomes

Outcome	Placebo (N=2,333)		Pooled Empagliflozin (N=4,687)		Hazard Ratio		Observed relative risk change	Simulated relative risk change	Proportion of relative risk change attributable by MMD simulation
	Observed rate/1000 patient-yr	Simulated rate/1000 patient-yr, mean (SD)	Observed rate/1000 patient-yr	Simulated rate/1000 patient-yr, mean (SD)	Observed Estimate (95% CI)	Simulated Mean (SD)			
Primary composite cardiovascular outcome*	43.9	41.84 (2.09)	37.4	39.44 (1.50)	0.86 (0.74-0.99)	0.94 (0.06)	-14%	-6%	43%
Fatal or nonfatal MI	19.3	16.90 (1.17)	16.8	15.52 (0.89)	0.87 (0.70-1.09)	0.92 (0.08)	-13%	-8%	62%
Nonfatal MI	18.5	11.60 (1.23)	16.0	10.70 (0.82)	0.87 (0.70-1.09)	0.88 (0.16)	-13%	-12%	92%
Coronary revascularization procedure	29.1	40.27 (2.00)	25.1	37.33 (1.33)	0.86 (0.72-1.04)	0.93 (0.06)	-14%	-7%	50%
Fatal or nonfatal stroke	10.5	6.97 (0.89)	12.3	6.01 (0.59)	1.18 (0.89-1.56)	0.88 (0.15)	+18%	-12%	0%
Nonfatal stroke	9.1	5.42 (0.78)	11.2	4.48 (0.48)	1.24 (0.92-1.67)	0.89 (0.35)	+24%	-11%	0%
Hospitalization for heart failure	14.5	10.53 (1.05)	9.4	9.11 (0.64)	0.65 (0.50-0.85)	0.87 (0.11)	-35%	-13%	37%
Death from cardiovascular causes	20.2	27.11 (1.65)	12.4	25.90 (1.25)	0.62 (0.49-0.77)	0.96 (0.08)	-38%	-4%	11%
Death from any cause	28.6	34.53 (1.74)	19.4	33.28 (1.45)	0.68 (0.57-0.82)	0.97 (0.07)	-32%	-3%	9%

Abbreviations: yr, year; SD, standard deviation; CI, confidence interval; MMD, Michigan Model for diabetes; MI, myocardial infarction.

*Primary composite cardiovascular outcome included death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Kuo S, et al. "Are the favorable cardiovascular outcomes of empagliflozin treatment explained by its effects on multiple cardiometabolic risk factors? A simulation of the results of the EMPA-REG OUTCOME trial". Diabetes research and clinical practice. 2018 Jul;141:181-9.

HTA Reviewers Also Calling for New Tools

- NICE (UK):
  - "UKPDS OM1 may be poorly suited to predicting CV outcomes and all-cause mortality in populations with high CV risk, and that the relative outcomes associated with SGLT-2 inhibitors might not be accurately captured" (NICE 2018, p. 265)
- CADTH (Canada):
  - "CDEC also noted that, in future reviews, as more cardiovascular outcome data become available for more drugs, CADTH should explore modification to this model or alternative model that might more effectively incorporate these data" (CADTH 2017, p.9)

CADTH 2017, New Drugs for Type 2 Diabetes: Second-Line Therapy Recommendations Report

NICE. Type 2 diabetes in adults: Management - Evidence reviews for SGLT-2 inhibitors and GLP-1 mimetics (NG28). 2018

Objective

Review potential approaches to modeling cardioprotection and discuss possible strengths and weaknesses

We are aware of 4 published studies, to date

Author	Comparison	Method
Iannazzo et al. 2017	EMPA vs. SoC	CV protection modelled by risk prediction equations based on EMPA-REG
Nguyen et al. 2018	EMPA vs. SoC	CV protection modelled by risk prediction equations derived by fitting parametric distribution to patient level data in EMPA-REG
Gourzoulidis et al. 2018	EMPA vs. SoC	CV protection modelled by risk prediction equations derived by fitting parametric distribution to patient level data in EMPA-REG
Arbel et al. 2018	EMPA vs. LIRA	CV protection modeled directly with event rates sourced from EMPA-REG and LEADER

- There are more analyses in conference proceedings (about 15 we are aware of), but it is much harder to understand methodologies used

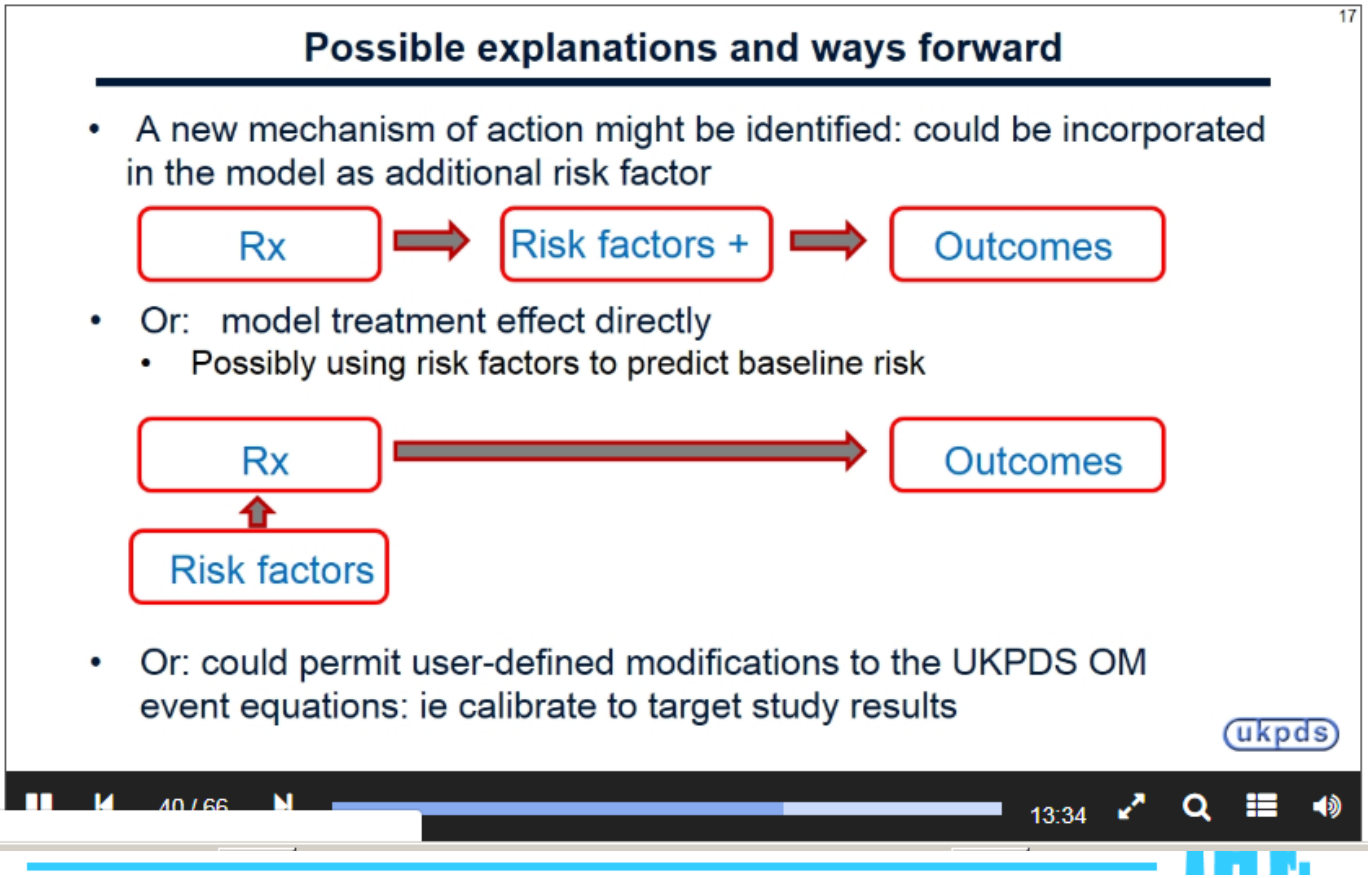
UKPDS Suggested a Couple of Paths Forwards at EASD 2018

Insights from the UKPDS outcomes model

Oral Presentation # S15.3

Session: UKPDS

Berlin 2018 Langerhans Hall 3. October 2018 12:30 - 12:50 151 viewers



Source: Alastair Gray, "Insights from the UKPDS Outcomes Model, EASD 2018 website.

We see a couple of more options as well

1. Ignore cardioprotection
2. Leverage the relative long study durations and model trials directly
3. Use conventional risk equations and HRs from CVOTs
4. Estimate (or update existing) risk prediction equations capable of capturing cardioprotection directly via covariates

1. Ignore Cardioprotection

- Simplest approach, long history
- Can argue that this misspecification leads *non-randomly* to an overestimate of ICER for cardioprotective agents vs. non-cardioprotective agents and the ICER may be considered *conservative* from a payer's vantage
- For most potential study questions, an unbiased point estimate more useful than a lower bound or hand-waving

2. Model CVOT Results Directly

- Relatively long durations, can estimate the cost-effectiveness directly (with or without modeling post-trial)
  - UKPDS 41 (2000) performed this (with post-trial modeling) in *pre-CVOT* history
  - Wilson et al (2017) estimated avoided events and cost-offsets for EMPA-REG (projected to 5 years)
- Plus Side:
  - These relationships are not confounded by *uncertain relationships* between surrogate biomarkers and outcomes
  - High internal validity, as outcomes do not need extrapolation using external risk equations
- Potential Limitations:
  - CVOTs are not as long as UKPDS (20 years, including PTM)
  - Requires indirect comparison for HRs to move beyond PBO/SoC comparisons--complicated
  - Limited to outcomes reported in trial
  - "Glycemic equipoise paradox", wrong study design to answer question directly

Putting the UKPDS into perspective

Oral Presentation # S15.4

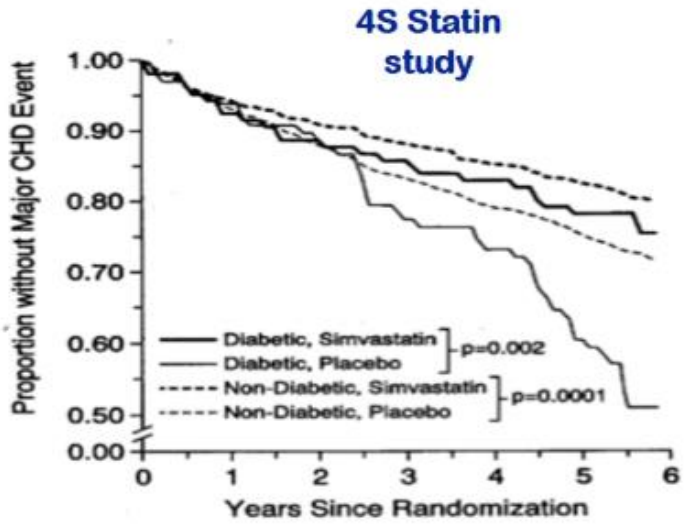
Session: UKPDS

Berlin 2018 | Langerhans Hall | 3. October 2018 12:50 - 13:00 | 166 viewers

23

Glycaemic equipoise – the paradox

- BUT if we do not allow the drug to have the differential effect for which it was designed, then we don't get the information we need.
- This would be like running a statin trial and pre-specifying that the control arm and the active arm needed to have the same cholesterol levels



ukpds

45 / 64

06:57

Source: David Matthews, "Putting the UKPDS into perspective", EASD 2018 website.

3. Use conventional risk equations and HRs from CVOTs

- Easily recognizable from Challenge #1 this morning
- Can apply biomarker effects as well, though this can create double-counting of benefit (Willis et al, 2017; Kuo et al, 2018; Evans et al, 2018)
- Plus Side:
  - Easy to implement, allows complications not reported from CVOTs, and easy to interpret
  - Can recalibrate risk equations to better match current praxis
  - Captures differences in baseline risk
- Potential Limitations:
  - If biomarker changes are not considered, it is difficult to model treatment sequences correctly (durability). If they are considered, double-counting is a real possibility (adjustment using patient-level data suggested).
  - What to assume following the study duration?
  - Again, interesting analyses are dependent on indirect comparison

4. Estimate (or update existing) risk prediction equations capable of capturing cardioprotection directly

- Ability to incorporate new science and new risk factors, with the potential to explain the ”unexplained” part of cardiprotection
- Ianazzo et al, 2017 estimated risk equations from EMPA-REG
  - Treatment assignment covariate, however, limits use in modeling non-EMPA-REG scenarios
  - Didn’t really explain anything new
- Plus Side:
  - Improved generalizability, can be applied to new settings and new agents
  - Potentially better reflect this “different therapeutic era”
- Potential Limitations:
  - Data access and data limitations (incomplete set of meaningful outcomes, glycemic equipoise, sufficient number of events, ...)
  - Complete set of equations not possible from a single CVOT (especially microvascular)
  - Requires indirect comparisons of treatment effects on biomarkers
  - Risk of misspecification (inclusion of biomarkers that are correlated, but not causal)

Iannazzo S, et al. 2017. 2017 2017-10-05;18(1).

Summary

- CVOTs provide interesting new data collected over relatively long time horizons
- CVOT data are problematic
  - Time horizons not "UKPDS long"
  - Glycemic equipoise, background therapy differs by treatment arm
  - Outcomes and disease definitions differ across trials
  - How to inform non-PBO comparisons? Need for indirect comparison for hard outcomes (small pool of CVOTs with substantial heterogeneity)?
- Different methods are available and have been used
  - Better understanding of pros and cons of different methods
- And if you think this is complicated, what until CREDENCE, DAPA-CKD, and other renal outcomes trials release results!!
  - But many of the same principles will apply

Thank You!!

References

- Arbel R, Hammerman A, Azuri J. Usefulness of Empagliflozin Versus Liraglutide for Prevention of Cardiovascular Mortality. The American journal of cardiology. 2018 Sep 15;122(6):981-4.
- CADTH. Therapeutic Review New Drugs for Type 2 Diabetes: Second-Line Therapy Recommendations Report 2017.
- Cefalu WT, Kaul S, Gerstein HC, Holman RR, Zinman B, Skyler JS, et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum. Diabetes care. 2018 Jan;41(1):14-31.
- FDA. Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes 2008; Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf
- Fitchett D, Butler J, van de Borne P, Zinman B, Lachin JM, Wanner C, et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial European heart journal. 2017; Epub ahead of print.
- Gourzoulidis G, Tzanetakos C, Ioannidis I, Tsapas A, Kourlaba G, Papageorgiou G, et al. Cost-Effectiveness of Empagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus at Increased Cardiovascular Risk in Greece. Clinical drug investigation. 2018 May;38(5):417-26.
- Gray A, Raikou M, McGuire A, Fenn P, Stevens R, Cull C, et al. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). United Kingdom Prospective Diabetes Study Group. BMJ (Clinical research ed). 2000 May 20;320(7246):1373-8.
- Gray A. Insights from the UKPDS outcomes model. Presentation at the 54th EASD; 2018 1-5 October; Berlin, Germany.
- Iannazzo S, Mannucci E, Reifsnider O, Maggioni AP. Cost-effectiveness analysis of empagliflozin in the treatment of patients with type 2 diabetes and established cardiovascular disease in Italy, based on the results of the EMPA-REG OUTCOME study. Farmeconomia Health economics and therapeutic pathways. 2017 2017-10-05;18(1).
- Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, et al. How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. Diabetes care. 2018;41(2):356.

References

- Kansal A, Odette R, Lee J, Fahrbach K, Gandhi P, Pfarr E, et al. Cost-Effectiveness Analysis of Empagliflozin Compared to Canagliflozin or Standard of Care (SoC) in Patients with T2DM and Established Cardiovascular (CV) Disease. ADA. Orlando, FL, USA2018.
- Kuo S, Ye W, Duong J, Herman WH. Are the favorable cardiovascular outcomes of empagliflozin treatment explained by its effects on multiple cardiometabolic risk factors? A simulation of the results of the EMPA-REG OUTCOME trial. Diabetes research and clinical practice. 2018 Jul;141:181-9.
- Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. The New England journal of medicine. 2016 Nov 10;375(19):1834-44.
- Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. The New England journal of medicine. 2016 Jul 28;375(4):311-22.
- Matthews D. Putting the UKPDS into perspective. Presentation at the 54th EASD; 2018 1-5 October; Berlin, Germany.
- Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England journal of medicine. 2017 Aug 17;377(7):644-57.
- Nguyen E, Coleman CI, Nair S, Weeda ER. Cost-utility of empagliflozin in patients with type 2 diabetes at high cardiovascular risk. Journal of diabetes and its complications. 2018 Feb;32(2):210-5.
- NICE. Type 2 diabetes in adults: Management - Evidence reviews for SGLT-2 inhibitors and GLP-1 mimetics (NG28). 2018; Available from: https://www.nice.org.uk/guidance/ng28/evidence/march-2018-evidence-reviews-for-sglt2-inhibitors-and-glp1-mimetics-pdf-4783687597
- Radholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation. 2018 Mar 11.
- Willis M, Neslusan C, Johansen P, Nilsson A. The Importance of Considering the Evolving Evidence Base on Cardiovascular Effects of Anti-Hyperglycemic Agents on Estimates of 'Value for Money'. poster presentation at 77th ADA San Diego, USA2017.
- Wilson M, Sander S, Kuti E, Lucas A. Cost Offsets Predicted With Empagliflozin in Patients with Type 2 Diabetes and Established Cardiovascular Disease. ISPOR. Denver,United States 2017.
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine. 2015 Nov 26;373(22):2117-28.

Only Indirect Comparison in the public domain we are aware of is Kansal et al. (2018) which supported a comparison of empagliflozin vs. canagliflozin

Table 2. Hazard Ratios of Event Rates

Clinical Events.	Rate per 1,000 PY	Mean Hazard Ratio (95% CI)	
	SoC	Empagliflozin + SoC vs. SoC	Canagliflozin + SoC vs. Empagliflozin + SoC
CV death	20.2	0.62 (0.49–0.77)	1.40 (1.05–1.88)
Non-fatal MI	18.5	0.87 (0.70–1.09)	0.98 (0.72–1.33)
Non-fatal stroke	9.1	1.24 (0.92–1.67)	0.73 (0.49–1.07)
Hospitalization for HF	14.5	0.65 (0.50–0.85)	1.03 (0.71–1.50)
Albuminuria progression	236	0.83 (0.76–0.90)	0.88 (0.79–0.99)
Composite renal outcome	14.0	0.55 (0.41–0.73)	1.09 (0.75–1.59)
Hospitalization for UA	10.0	0.99 (0.74–1.34)	NA
Transient ischemic attack	3.5	0.85 (0.51–1.42)	NA
Revascularization	29.1	0.86 (0.71–1.04)	NA
Genital mycotic infection	6.3	3.56 (NR–NR)	0.99 (0.70–1.40)
Acute kidney injury	5.5	0.50 (0.32–0.80)	1.45 (0.67–3.18)
Lower limb amputation	6.5	1.00 (0.70–1.44)	1.97 (1.20–3.23)
Bone fracture	13.7	0.95 (0.74–1.24)	1.36 (0.96–1.92)

Abbreviations: CI, confidence interval; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; NA, not applicable; PSA, Probabilistic Sensitivity Analysis; PY, patient-year; SoC, standard of care; UA, unstable angina

Kansal A, et al. Cost-Effectiveness Analysis of Empagliflozin Compared to Canagliflozin or Standard of Care (SoC) in Patients with T2DM and Established Cardiovascular (CV) Disease. ADA. Orlando, FL, USA 2018.