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

Mt. Hood 9

Diabetic Kidney Disease (DKD) and Renal Protection in T2DM: An Underappreciated Driver of C-E in Economic Evaluation?

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Diabetic Kidney Disease (DKD)

- Kidneys are responsible for filtering wastes and excess water from the blood and helping to control blood pressure
- Diabetes is one of the leading causes of kidney disease, in large part owing to chronic hyperglycemia and frequent hypertension
- DKD is chronic and progessive; end-stage kidney disease (ESKD) requires dialysis or kidney transplantation for continued survival
- NKF-KDOQI[1] (US) classify DKD two-dimensionally to capture risk prognosis
  - Kidney function as measured by eGFR (in intervals)
  - Kidney damage as measured by persistent albuminuria (normal to mildly increased, moderately increased, and severely increased)
- eGFR and albuminuria are independent and complementary predictors[2] of:
  - CKD progression
  - ESKD
  - Acute kidney injury
  - CV mortality
  - All-cause mortality

1. National Kidney Foundation. Am J Kidney Dis 2002;39(S2):S1-S266
2. Inker et al. Am J Kidney Dis. 2014;63(5):713-735

NKF Staging and Risk of Complications (Including CV Mortality)

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

1. Inker et al. Am J Kidney Dis. 2014;63(5):713-735

Some important consequences of DKD for economic modeling

- Associated with risk of CVD and mortality, increasing with severity of CKD
- Associated with risk of acute kidney injury
- Roughly 25% of US diabetes patients will eventually develop ESKD
  - Costly to treat (dialysis, transplantation)
  - Debilitating for patient (QoL poor)
  - Life expectancy shortened considerably
- Advanced CKD contraindicates some anti-diabetic medications

Inker et al. Am J Kidney Dis. 2014;63(5):713-735

Treatment of DKD

- Lifestyle changes (lowering sodium intake, avoiding high-protein diet)
- Multifactorial intervention, including as clinically indicated:
  - Improved glycemic control
  - Optimized blood pressure control
  - ACEi or ARB
  - Statins
  - Antiplatelet therapy
- Even differences in anti-diabetes therapies for patients with CKD (new ADA/EASD guidelines)

Inker et al. Am J Kidney Dis. 2014;63(5):713-735
ADA. Diabetes care. 2017;41(S1).

Some milestones of DKD in economic modeling

Seminal NIH model (Eastman et al. 1997) included kidney damage

- eGFR was not considered
- ESKD associated with increased mortality

Table 1—*Clinical definitions of the health states modeled*

Health state	Clinical definition
Retinopathy (R1)	No retinopathy
Retinopathy (R2)	Nonproliferative retinopathy (1)
Retinopathy (R3)	PDR (1)
Retinopathy (R4)	Significant ME (1)
Retinopathy (R5)	Visual acuity <20/100 in better eye (1)
Nephropathy (N1)	No nephropathy
Nephropathy (N2)	MA 0.03–0.3 g/l (14)
	American Indians 30–299 mg/g creatinine (16)
Nephropathy (N3)	Proteinuria ≥0.4 g/l (17)
Nephropathy (N4)	ESRD (18)
Neuropathy (Nu1)	No neuropathy
Neuropathy (Nu2)	Symptomatic neuropathy (20)
Neuropathy (Nu3)	First LEA (22)
CVD (C1)	No CVD
CVD (C2)	CVD morbidity and mortality (26)

Eastman RC, et al. Diabetes care. 1997 May;20(5):725-34.

UKPDS-OM1 (Clarke et al. 2004)

Table 3. Sample size, functional form, parameters and beta coefficients (SEs) for three equations to estimate the probability of mortality

	Eq. 8	Eq. 9	Eq. 10
Event	EVENT FATALITY[a]	DIABETES MORTALITY[a]	OTHER DEATH
No. of subjects	717	584	3642
Functional form	Logistic	Gompertz	Gompertz
Parameters	Estimate of coefficient (SE)		
λ	−3.251 (0.358)	−5.124 (0.363)	−6.373 (0.162)
ϕ		0.003 (0.038)	0.154 (0.016)
Ln (AGE_EVENT)	2.772 (0.716)	4.731 (1.066)	
AGE × (FEMALE)			0.081 (0.013)
AGE × (1-FEMALE)			0.104 (0.012)
SMOK			0.307 (0.141)
HBA1C	0.114 (0.053)		
TOTAL:HDL		0.109 (0.047)	
MI_EVENT	2.640 (0.336)	3.939 (0.275)	
MI_POST		1.119 (0.277)	
STROKE_EVENT	1.048 (0.376)	2.807 (0.408)	
RENAL		1.585 (0.315)	
AMP		1.032 (0.377)	

[a] Regression estimates based on the patients who experienced one or more of the following complications: MI, CHF, stroke, amputation, renal failure

Clarke PM, et al. Diabetologia. 2004 Oct;47(10):1747-59..

The Centers for Disease Control (CDC) and Research Triangle Institute (RTI) Raised the Bar (Hoerger et al, 2010)

- Model combined traditional aspect of *kidney damage* (albuminuria) with *kidney function* (eGFR) as well
  - Kidney damage (normal, microalbuminuria, macroalbuminuria), defined by UACR
  - Kidney function (eGFR modeled as continuous covariate), categorized into stages
  - ESKD as a final, chronic state (eGFR<15 ml/min/1.73m^2 for at least one year)
- Both for general population and for diabetes
- The trajectory of eGFR must be modeled explicitly

Hoerger TJ, et al. Am J Kidney Dis. 2010;55(3): 452-462.

More Detailed Analyses are Possible with Such A Model

- Motivating problem was CE of screening for CKD
- CE of treatment varies by dimension of kidney-related effect
  - Can evaluate therapies with different efficacy on eGFR and DKD progression

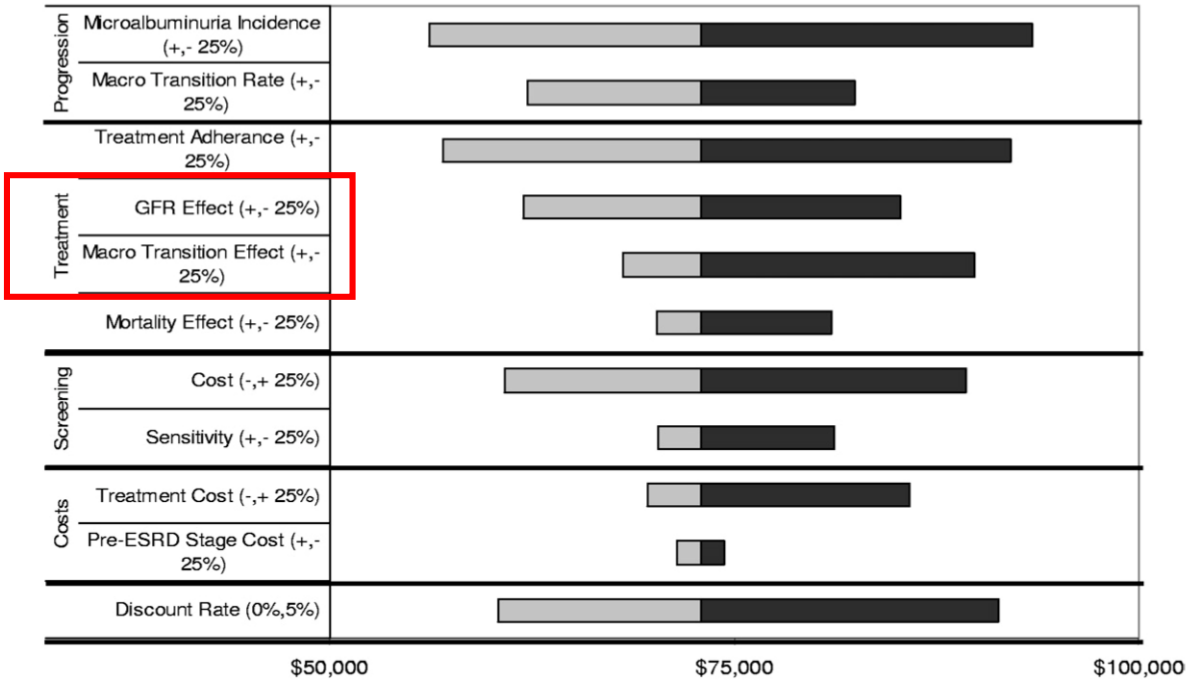


Figure 3. Sensitivity analysis, universal screening starting at age 50 years versus no screening. Abbreviations: ESRD, end-stage renal disease; GFR, glomerular filtration rate.

Hoerger TJ, et al. Am J Kidney Dis, 2010; 55: 463-473

The CDC Model of CKD leveraged Boulware et al (2003) to Simulate eGFR Decline Over Time

- Boulware et al. used literature review to inform a CE model of CKD screening

Annual Decline in eGFR (mL/min per 1.73m^2) by Diabetes and Proteinuria Status (Boulware et al.)

Diabetes			
No proteinuria			
≥90 to 15-89	1.1	Nelson et al,[64] 1996	II-2
		Nosadini et al,[68] 2000	II-2
		Rachmani et al,[69] 2000	II-2
15-89 to <15	2.8	Lebovitz et al,[65] 1994	I
Proteinuria			
≥90 to 15-89	4.1	Gaede et al,[66] 1999	I
		Gaede et al,[67] 2003	I
		Nosadini et al,[68] 2000	II-2
15-89 to <15	5.2	Lewis et al,[11] 2001	I
		Brenner et al,[12] 2001	I
		Ruggenenti et al,[56] 2000	I

Boulware et al. JAMA 2003;290(23):3101-3114

More recent data on the decline available from the Atherosclerosis Risk in Communities (ARIC) study (Warren et al.)

	Percentile and corresponding change in eGFR per year (mL/min/1.73m^2)									
	Unadjusted					Adjusted				
	10th	25th	50th	75th	90th	10th	25th	50th	75th	90th
No diabetes	-2.3	-1.9	-1.6	-1.3	-1.0	-1.9	-1.6	-1.4	-1.2	-1.0
Undiagnosed diabetes	-3.1	-2.5	-2.1	-1.7	-1.4	-2.4	-2.0	-1.8	-1.5	-1.3
Diagnosed diabetes	-4.1	-3.4	-2.9	-2.4	-2.0	-3.5	-2.7	-2.5	-2.2	-1.8

- Confirms that eGFR decline is faster at more advanced disease
- More recent than Boulware et al. review
- Not aware of an analysis that looks at eGFR decline by kidney function or damage, however

Figure 1 in Warren B, et al. Diabetes care. 2018 Aug;41(8):1646-53.

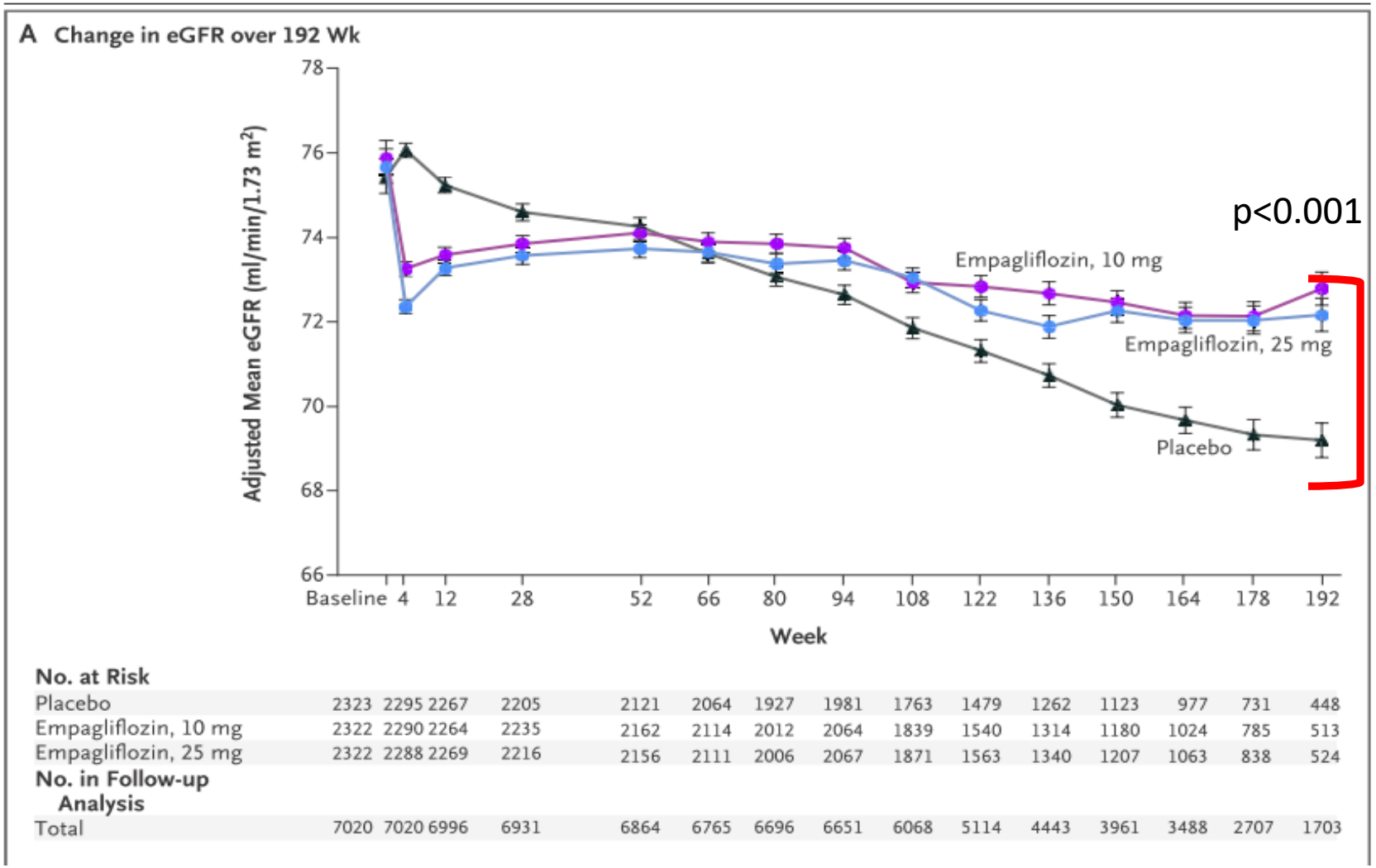
eGFR entered as an explanatory covariate in UKPDS-OM2 (Hayes et al. 2013), providing a direct link between time-varying eGFR and a number of complications

- Still only one outcome of "Renal failure"
- Predicts IHD, CHF, 1st stroke and renal failure
- Requires explicit projection of eGFR over time (UKPDS-OM1, but not UKPDS-OM2)

Hayes AJ, et al. Diabetologia. 2013 Sep;56(9):1925-33.

Renal outcomes in a number of CVOTs now suggest that some anti-diabetes drugs may slow or even pause eGFR decline over relatively long time horizons

For example, EMPA-REG



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

Wanner C, et al. The New England journal of medicine. 2016 Jul 28;375(4):323-34.

And the CANVAS Program

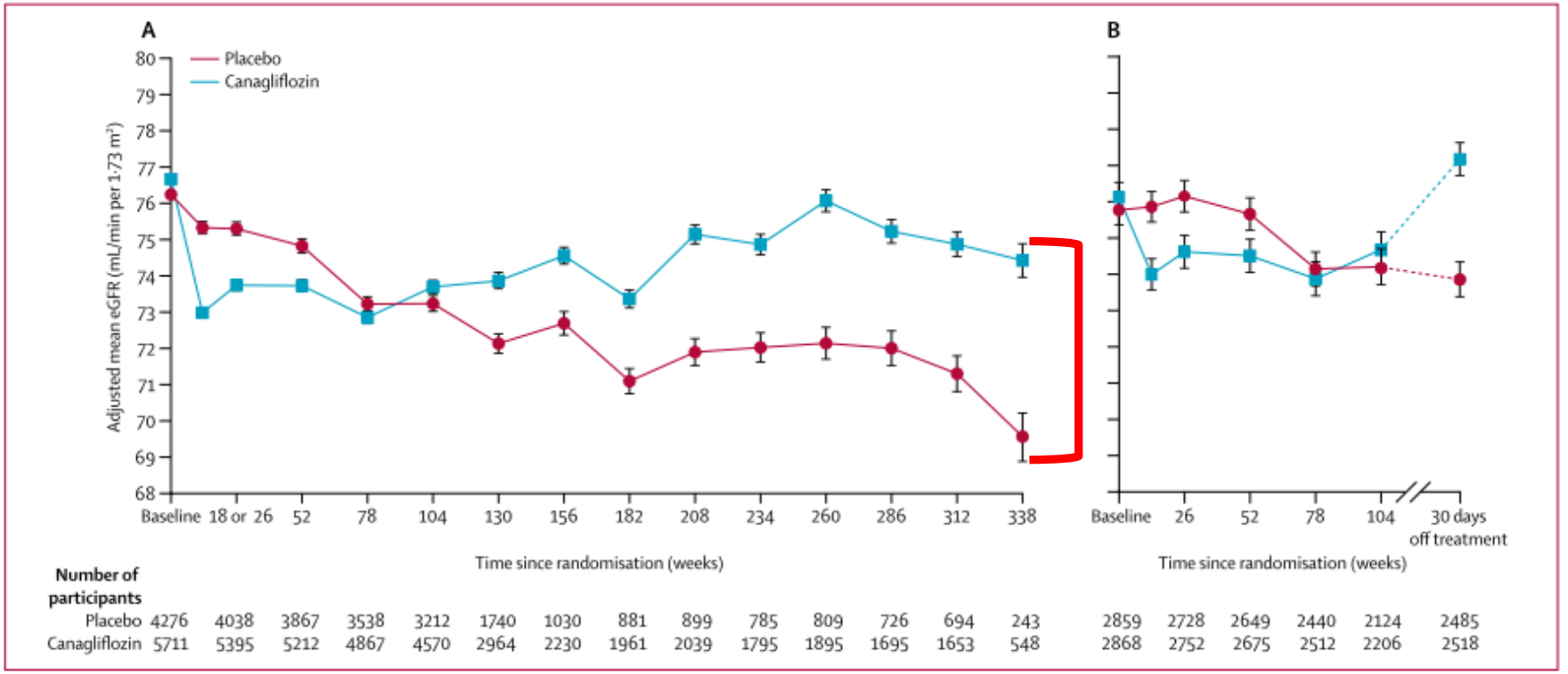


***Figure 4*: Effects of canagliflozin versus placebo on eGFR over time in the CANVAS Program (A) and eGFR over time and after a median of 30 days off-treatment in CANVAS-R (B)**
Error bars show SE. eGFR=estimated glomerular filtration rate.

Perkovic V, et al. The Lancet Diabetes & endocrinology. 2018 Sep;6(9):691-704..

The Canagliflozin and Renal Events in Diabetes with Established Neuropathy Clinical Evaluation (CREDENCE) Trial

News > Medscape Medical News

Canagliflozin Renal Outcomes Study Is Halted Early for Efficacy

Miriam E. Tucker

July 17, 2018

https://www.medscape.com/viewarticle/899424

DAPA-CKD will be completing in coming years as well

Implications for HE Modeling of DM

- Kidney disease (especially ESKD) associated with mortality, costs and disutility
- Important to model it in sufficient detail
  - An incomplete representation of disease can result in modeling bias
  - Modeling of multiple dimensions of DKD possible (CDC model of CKD, UKPDS-OM2 to some extent)
- Treatment effects on DKD vary by anti-diabetic treatment class and agent
  - May include direct and covariate-mediated effects (waiting for CREDENCE)
  - Ignoring these may underestimate treatment benefits

→ What are the economic consequences of misspecifying eGFR effects?

Objective

Leverage an economic simulation model that includes the CDC model of CKD to estimate the value of renal protection to patients in hypothetical scenarios over 30 years from the perspective of the Swedish health care system

Methods: Use ECHO-T2DM to investigate hypotheses

- Hypothetical patients (MET failure) defined to match Swedish National Diabetes Register data[1]
- Treatment with a generic agent with effects similar to an SGLT-2

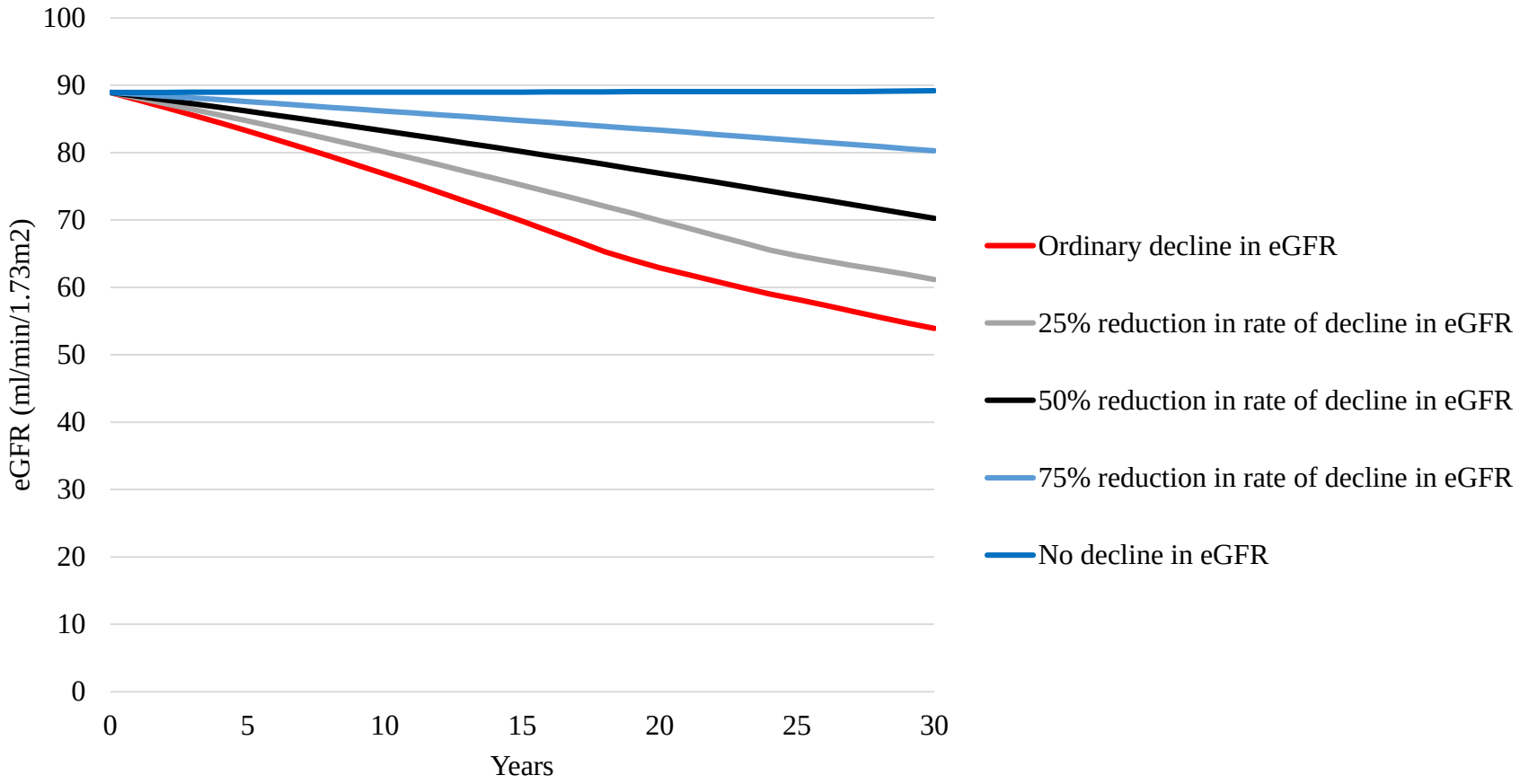
- Vary the simulated rate of eGFR decline:
  - Ordinary (as in the CDC-DKD model)
  - 25% reduction (= 75% of ordinary decline)
  - 50% reduction (= 50% of ordinary decline)
  - 75% reduction (= 25% of ordinary decline)
  - 100% reduction (= no decline)

- 30-year time horizon
  - Treatment costs were not considered
  - Discounting of costs and utilities at 3% p.a.

1. Ekstrom N, et al. Diabetes, obesity & metabolism. 2012 Aug;14(8):717-26.

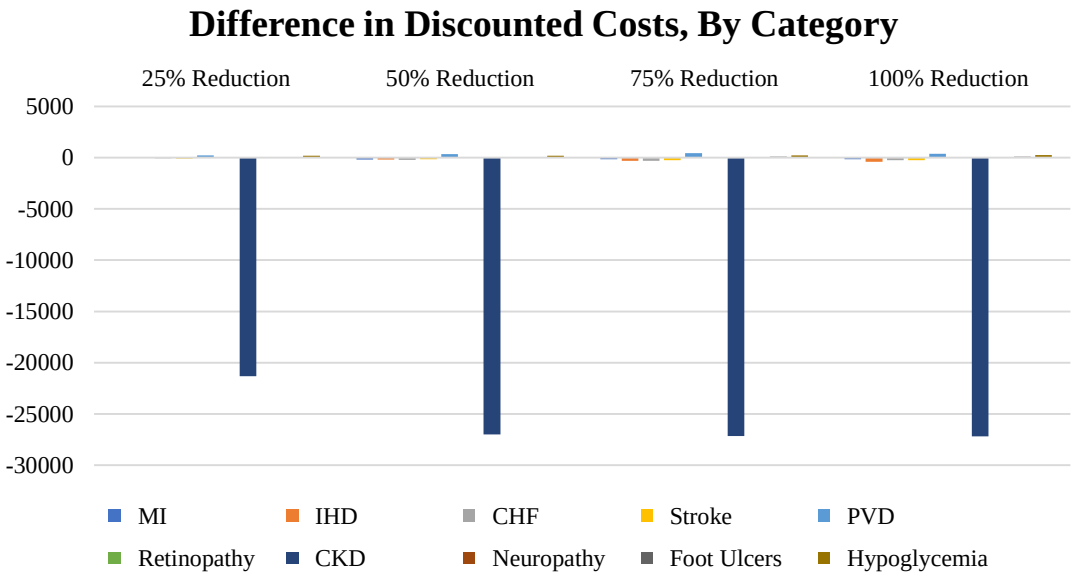
Results

Simulated Decline of Mean eGFR

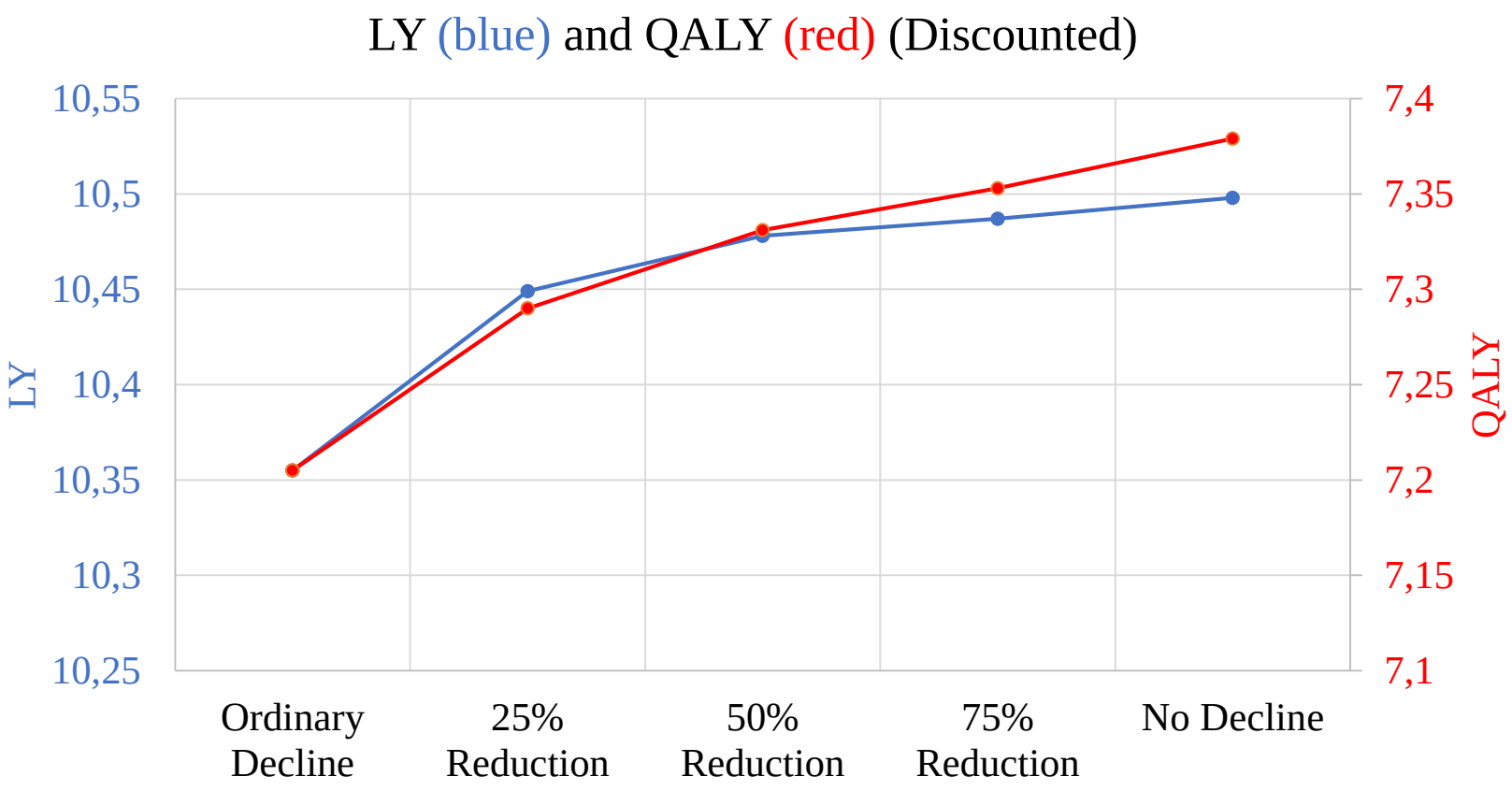


Lower decline in eGFR reduces total costs (SEK) mainly through costs of CKD

- Base-case “Ordinary eGFR Decline”:
  - Simulated total discounted costs of SEK 123,660 (30-year time horizon)
  - 23% of total costs were due to DKD
- Alternative eGFR treatment effects:
  - A 25% reduction in eGFR decline reduced costs by 17%, mainly through DKD
  - Larger reductions in eGFR decline reduced costs even more.



Lower decline in eGFR increases LY's and QALY's



Summary of Main Findings

- Including function (treatment effects on eGFR) in the model has important HE consequences:
  - Total discounted 30-year costs ranged from SEK 123,660 to 95,145, i.e., **23% cost savings**
  - Similarly, total discounted QALYs ranged from 7.205 to 7.379, i.e., an **increase by 2.4%**
- Modeling assumptions may lead to understatement of potential benefits.
  - Treatment effect limited to rate of eGFR decline
    - Whether direct improvements in UACR should be modeled will hopefully be answered soon.
  - Downstream treatment decisions related to kidney function not captured
  - Relatively healthy Swedish NDR population may not extrapolate to other settings
- Analysis was hypothetical in anticipation of more clarity with upcoming renal outcomes trials

Thank You!

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BACK UP

ECHO-T2DM

- Probabilistic (1st and 2nd order) micro-simulation with individual micro- and macrovascular Markov health states
- Internally and externally validated (Willis et al., 2017)
- Flexible treatment algorithm allowing treatment intensifications, and incorporating key AE´s
- Macrovascular risk are individualized to hypothetical patients using the UKPDS 82 risk equations (Hayes et al., 2013)
- Unit costs and QALY decrements applied based on patients health history, sourced from the literature

Hayes AJ, et al. Diabetologia. 2013 Sep;56(9):1925-33.
Willis M, et al. PharmacoEconomics. 2017 Mar;35(3):375-96.

Hypothetical Patient Cohort Matches Key Baseline Characteristics of Swedish Patients (Ekström et al. 2012)

Patient Population in the Swedish NDR	Metformin background	Met+SU background
Parameter	Mean/%	Mean/%
Demographics		
Age (years)	65.40 (11.20)	68.5 (10.9)
Males (%)	55.2%	58.0%
Disease duration (years)	5.50	10.3
Clinical indicators		
Smokers (%)	16.8%	15.2%
HbA1c (%)	6.8 (0.9)	7.2 (1.0)
SBP (mmHg)	136 (16.0)	138 (16.0)
BMI (kg/m2)	30.3 (5.2)	29.1 (4.8)
eGFR (ml/min/1.73m2)	**84.3 (22.7)**	**82 (24.4)**
Co-morbidities (Proportion)		
CKD		
Proportion Patients with Microalbuminuria	0.23	0.29
Proportion Patients with Macroalbuminuria	0.00	0.00
Proportion Patients with ESRD	0.00	0.00
Macrovascular		
Proportion with IHD	0.044	0.06
Proportion with MI	0.09	0.10
Proportion with CHF	0.04	0.04
Proportion with Stroke	0.09	0.10

Ekstrom N, et al. Diabetes, obesity & metabolism. 2012 Aug;14(8):717-26.

Unit costs and disutility weights obtained from the literature

DKD	First Year Costs*	Annual Follow-up Costs*	Utility Decrements**
No Nephropathy:			
eGFR > 90 mL/min/1.73 m^2	291	291	0.000
eGFR 60-89 mL/min/1.73 m^2	582	582	0.000
eGFR 30-59 mL/min/1.73 m^2	3,176	3,176	0.050
eGFR 15-29 mL/min/1.73 m^2	6,352	6,352	0.070
Microalbuminuria:			
eGFR > 90 mL/min/1.73 m^2	5,142	291	0.000
eGFR 60-89 mL/min/1.73 m^2	5,142	582	0.000
eGFR 30-59 mL/min/1.73 m^2	5,142	3,176	0.050
eGFR 15-29 mL/min/1.73 m^2	5,142	6,352	0.070
Macroalbuminuria:			
eGFR > 90 mL/min/1.73 m^2	7,639	291	0.048
eGFR 60-89 mL/min/1.73 m^2	7,639	582	0.048
eGFR 30-59 mL/min/1.73 m^2	7,639	3,176	0.098
eGFR 15-29 mL/min/1.73 m^2	7,639	6,352	0.138
ESRD, eGFR <15 mL/min/1.73 m^2	48,994	48,994	0.175

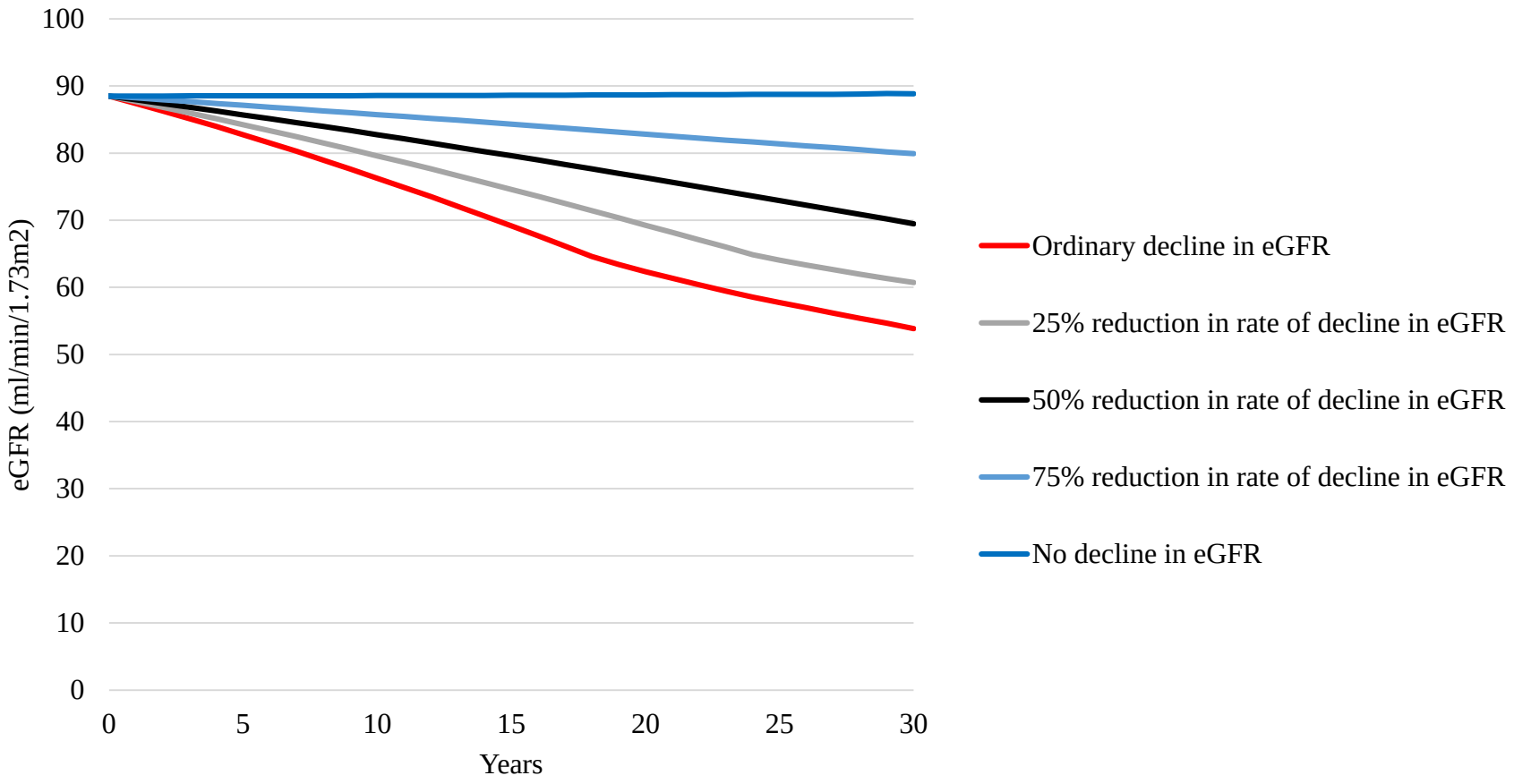
* Sourced from Persson et al. 2010 and Södra Regionvårdsnämnden 2018

** Sourced from Hoerger et al. 2010

Scenario uncontrolled with MET: Tabular results

	Ordinary decline in eGFR	25% reduction in rate of decline in eGFR	Difference	50% reduction in rate of decline in eGFR	Difference	75% reduction in rate of decline in eGFR	Difference	No decline in eGFR	Difference
Costs (Discounted)									
Macro- and Microvascular Complications									
MI	15,822	15,805	−17	15,642	−179	15,652	−169	15,666	−156
IHD	16,205	16,184	−21	16,023	−182	15,879	−326	15,782	−423
CHF	12,303	12,230	−73	12,096	−207	11,984	−320	12,047	−256
Stroke	17,863	17,767	−97	17,720	−143	17,614	−249	17,598	−265
PVD	14,354	14,561	207	14,686	331	14,799	445	14,731	376
Retinopathy	1,085	1,114	28	1,122	37	1,134	49	1,135	49
CKD	**27,957**	**6,640**	**−21,317**	**953**	**−27,004**	**804**	**−27,153**	**777**	**−27,179**
Neuropathy	291	293	2	292	1	296	5	293	2
Foot Ulcers	1,857	1,907	50	1,922	65	1,961	104	1,939	82
Adverse Events									
Hypoglycemia	15,923	16,099	176	16,104	181	16,152	230	16,178	256
Total Costs	**123,660**	**102,600**	**−21,060**	**96,560**	**−27,100**	**96,274**	**−27,386**	**96,145**	**−27,515**
Health Outcomes (Discounted)									
LY's	10.355	10.449	0.094	10.478	0.123	10.487	0.132	10.498	0.143
QALY's	**7.205**	**7.290**	**0.084**	**7.331**	**0.125**	**7.353**	**0.148**	**7.379**	**0.174**
Survival at End of Year 30	7.4%	8.7%	1.3%	9.5%	2.1%	9.7%	2.2%	9.7%	2.3%

Simulated decline of mean eGFR over time: add-on to MET+SU



Similar results were found for patients uncontrolled with MET+SU: Tabular Results

	Ordinary decline in eGFR	25% reduction in rate of decline in eGFR	Difference	50% reduction in rate of decline in eGFR	Difference	75% reduction in rate of decline in eGFR	Difference	No decline in eGFR	Difference
Costs (Discounted)									
Macro- and Microvascular Complications									
MI	14,217	14,132	−85	14,126	−90	14,045	−172	14,062	−154
IHD	15,240	15,237	−4	15,129	−111	15,036	−204	14,838	−402
CHF	10,644	10,582	−62	10,486	−157	10,405	−239	10,398	−246
Stroke	17,294	17,239	−56	17,053	−242	17,103	−191	17,096	−198
PVD	12,269	12,449	180	12,586	317	12,602	333	12,688	418
Retinopathy	1,024	1,047	23	1,056	32	1,061	37	1,063	39
CKD	22,863	5,591	−17,271	1,104	−21,758	879	−21,983	849	−22,013
Neuropathy	280	282	3	282	3	285	5	284	4
Foot Ulcers	1,520	1,564	44	1,580	60	1,601	81	1,605	85
Adverse Events									
Hypoglycemia	26,107	26,332	225	26,381	274	26,435	328	26,445	338
Total Costs	121,458	104,455	−17,003	99,784	−21,674	99,453	−22,005	99,329	−22,129
Health Outcomes (Discounted)									
LY's	9.296	9.367	0.071	9.395	0.100	9.413	0.117	9.425	0.130
QALY's	6.386	6.452	0.065	6.489	0.103	6.517	0.131	6.541	0.154
Survival at End of Year 30	4.9%	5.8%	0.9%	6.3%	1.5%	6.5%	1.6%	6.5%	1.6%