Nephro Update Europe 2018

5-6 October, Budapest

Diabetic Nephropathy

Hiddo Lambers Heerspink, Netherlands

Conflicts of Interest

Research Support:	Boehringer Ingelheim AstraZeneca Abbvie Janssen
Lecturing:	Abbvie AstraZeneca
Consulting activities:	Abbvie Astellas AstraZeneca Boehringer Ingelheim Gilead Fresenius Janssen Merck

Diabetic Kidney Disease

- *Epidemiology*
- *Pathophysiology*
- *Pharmacotherapy*

Question to the audience

- In your experience, which microvascular complication is the most common in T2D?

A. Neuropathy

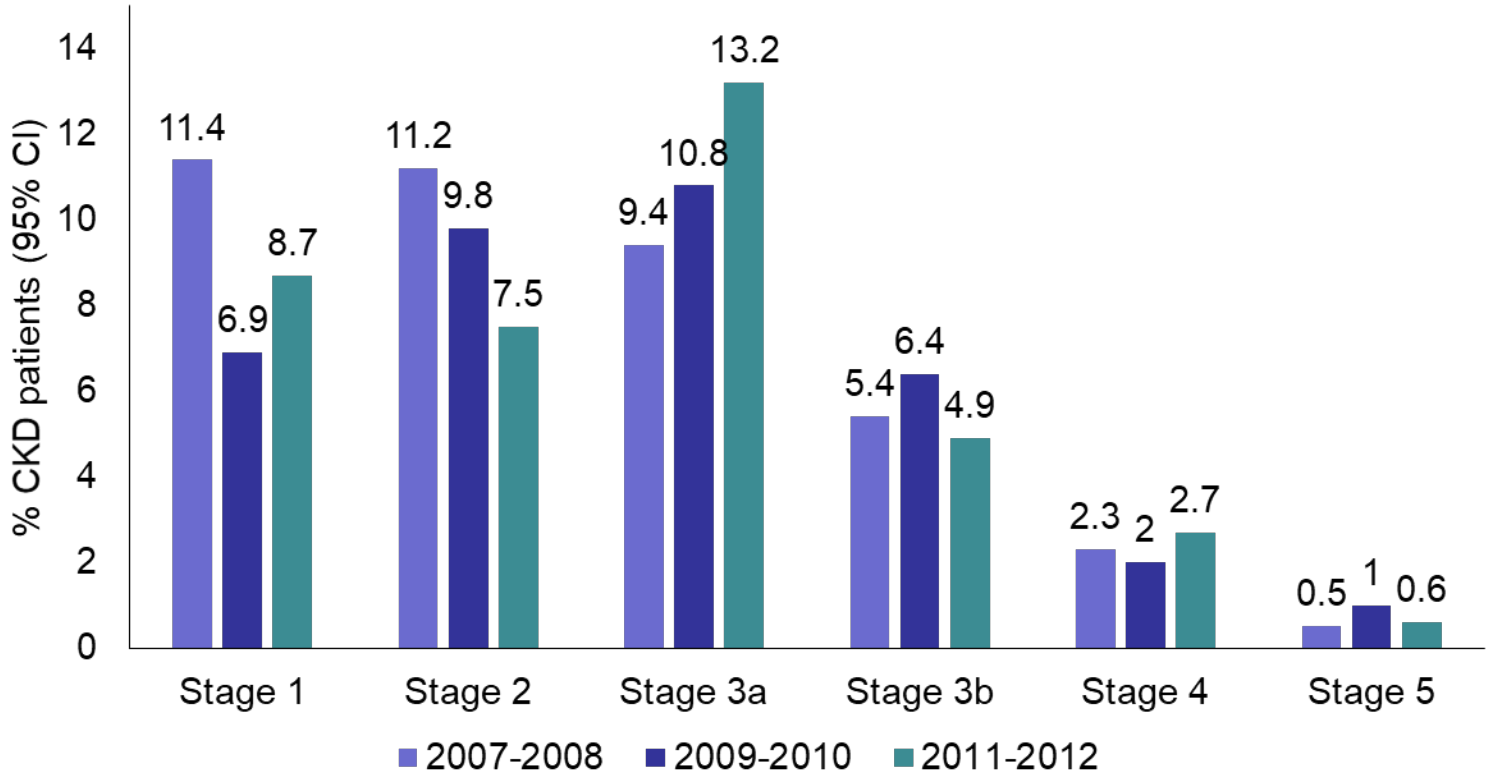
B. Nephropathy

C. Retinopathy

D. All are common

T2D, Type 2 diabetes

NHANES: Prevalence of CKD in diabetes constant over time

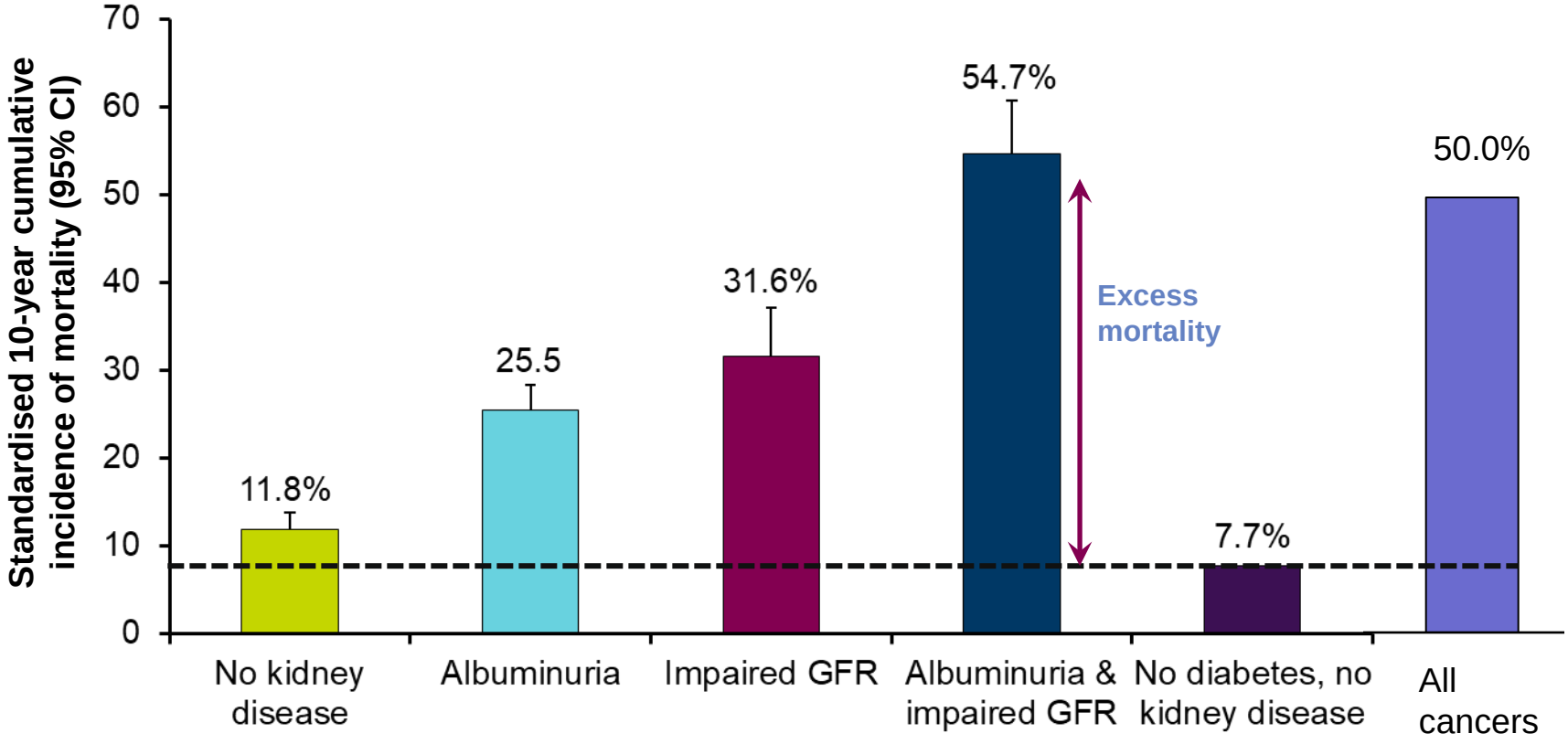


Age-adjusted prevalence of CKD in T2DM: NHANES 2007-2012

2006 patients with type 2 diabetes of whom 884 had diabetes and CKD (44%)

Wu Bell BMJ open diabetes research & care. 2016;4(1):e000154

Mortality rates in DKD equal average cancer mortality rates



Afkarian M et al. J Am Soc Nephrol 2013;24:302
Lancet 2014 pii: S0140-6736(14)61396-9

Causes of death in diabetes

(Gregg et.al. Lancet. 2018 Jun 16;391(10138):2430-2440)

- The prevalence of kidney disease in patients with diabetes remains high
- Cardiovascular disease historically accounts for the majority of deaths
- More recent studies suggest that the character of diabetes related complications could be changing
- Mortality rates due to CV deaths declined in the US potentially increasing the relative importance of other causes of death including renal disease.
- Aim of the study was to assess the mortality burden associated with diabetes and determine of causes of death change over time

Study Design

- *Design:*

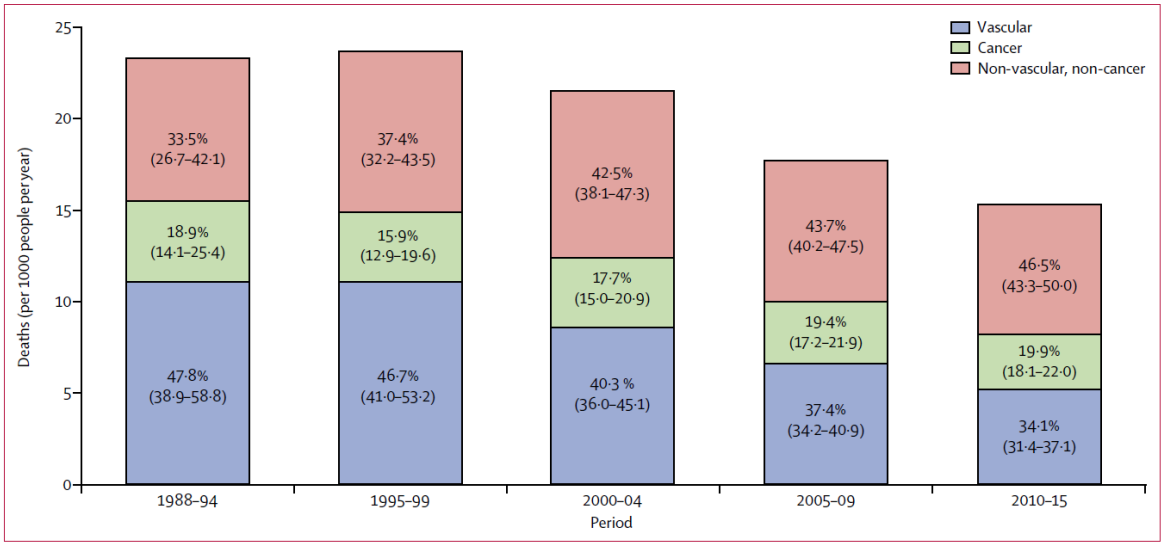
  Observational study in the NHANES cohort: annual cross sectional survey of health status among 35000 randomly selected households.
- *Diabetes Status:*
  - Diabetes status assessed by interviewers
  - 677060 individuals included among which 50200 diabetics
- *Outcomes*
  - Mortality (through national death files) from 1990 to 2015 using ICD-9 coding
- *Comparisons*
  - To examine association with specific causes of death
  - To examine trends in cause specific mortality from 1990 to 2018

(Gregg et.al. Lancet. 2018 Jun 16;391(10138):2430-2440)

Trends in Cause Specific Mortality in adults with Diabetes

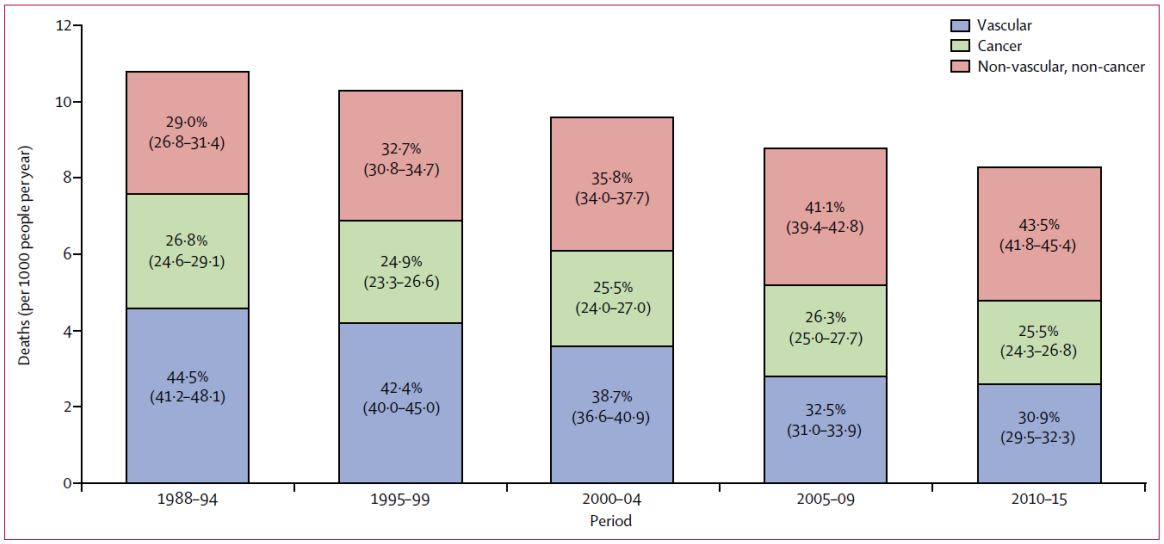
(Gregg et.al. Lancet. 2018 Jun 16;391(10138):2430-2440)

Diabetes (Deaths per 1000 pt per yr)



2-fold difference

Non-diabetes (Deaths per 1000 pt per yr)



Cause specific mortality by diabetes status and time-period

	1988–94	1995–99	2000–04	2005–09	2010–15	Average 10-year difference	10-year percentage change	p value for linear trend
Diseases of the heart								
Diabetes	9·1 (7·7 to 10·6)	9·0 (7·9 to 10·6)	7·1 (6·3 to 7·8)	5·1 (4·6 to 5·5)	4·1 (3·8 to 4·5)	−2·6 (−3·2 to −2·1)	−33·2 (−37·7 to −28·3)	<0·0001
No diabetes	4·1 (3·8 to 4·4)	3·7 (3·5 to 3·9)	3·1 (2·9 to 3·2)	2·4 (2·3 to 2·5)	2·2 (2·1 to 2·3)	−0·9 (−1·0 to −0·8)	−26·6 (−29·4 to −23·8)	<0·0001
Relative risk (95% CI)	2·2 (1·9 to 2·6)	2·4 (2·1 to 2·8)	2·3 (2·0 to 2·6)	2·1 (1·9 to 2·3)	1·9 (1·7 to 2·1)	..	..	..
Malignant neoplasms								
Diabetes	4·4 (3·2 to 5·5)	3·7 (3·0 to 4·5)	3·8 (3·2 to 4·4)	3·4 (3·0 to 3·8)	3·0 (2·8 to 3·3)	−0·6 (−1·1 to −0·2)	−15·7 (−25·7 to −5·7)	0·0199
No diabetes	3·2 (2·9 to 3·4)	2·8 (2·7 to 3·0)	2·8 (2·6 to 2·9)	2·6 (2·5 to 2·7)	2·4 (2·3 to 2·5)	−0·3 (−0·4 to −0·2)	−11·8 (−15·0 to −8·5)	<0·0001
Relative risk (95% CI)	1·4 (1·1 to 1·8)	1·3 (1·1 to 1·6)	1·4 (1·2 to 1·6)	1·3 (1·2 to 1·5)	1·3 (1·2 to 1·4)	..	..	..
Chronic lower respiratory disease								
Diabetes	0·4 (0·1 to 0·6)	0·7 (0·4 to 1·1)	0·7 (0·5 to 0·9)	0·9 (0·7 to 1·1)	0·8 (0·7 to 0·9)	0·2 (0·0 to 0·3)	25·2 (4·5 to 50·1)	0·0023
No diabetes	0·5 (0·5 to 0·6)	0·6 (0·5 to 0·7)	0·6 (0·6 to 0·7)	0·7 (0·6 to 0·7)	0·6 (0·6 to 0·7)	0·0 (−0·0 to 0·1)	5·3 (−1·7 to 12·9)	0·1798
Relative risk (95% CI)	0·7 (0·3 to 1·3)	1·2 (0·7 to 1·9)	1·1 (0·8 to 1·5)	1·4 (1·1 to 1·7)	1·3 (1·1 to 1·6)	..	..	..
Accidents								
Diabetes	0·2 (0·0 to 0·4)	0·3 (0·1 to 0·5)	0·5 (0·3 to 0·8)	0·6 (0·4 to 0·7)	0·6 (0·4 to 0·7)	0·1 (0·0 to 0·2)	38·2 (6·8 to 78·9)	0·0001
No diabetes	0·3 (0·3 to 0·4)	0·4 (0·3 to 0·4)	0·4 (0·3 to 0·4)	0·4 (0·4 to 0·5)	0·4 (0·4 to 0·5)	0·1 (0·0 to 0·1)	18·9 (9·1 to 29·6)	0·0007
Relative risk (95% CI)	0·7 (0·2 to 1·9)	0·8 (0·4 to 1·6)	1·4 (0·8 to 2·2)	1·4 (1·0 to 1·8)	1·2 (0·9 to 1·7)	..	..	..
Essential hypertension or renal								
Diabetes	0·1 (0·0 to 0·1)	0·1 (0·0 to 0·1)	0·1 (0·0 to 0·2)	0·2 (0·1 to 0·3)	0·2 (0·1 to 0·2)	0·1 (0·0 to 0·1)	66·8 (13·4 to 145·3)	0·0010
No diabetes	0·1 (0·0 to 0·1)	0·1 (0·0 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·0 (0·0 to 0·0)	36·3 (8·7 to 70·9)	0·0011
Relative risk (95% CI)	1·0 (0·2 to 4·5)	0·9 (0·3 to 3·0)	0·9 (0·4 to 2·0)	2·4 (1·5 to 3·7)	1·3 (0·9 to 2·0)	..	..	..

(Gregg et.al. Lancet. 2018 Jun 16;391(10138):2430-2440)

Limitations and Conclusions

Limitations

- Causes of death subject to medical opinion and subjective judgment
- Diabetes was self-reported

Conclusions – What is new

- Excess mortality among diabetics across multiple and diverse organ systems
- The diversification of causes of death has important implications for health policies, prioritization of health budgets and development of therapies.

Effect of diabetes on 14-yrs cause-specific mortality in Mexican adults

Herrington et.al. Lancet Diabetes & Endocrinology 2018:6;455-463

- Prevalence and complications of diabetes are expected to increase in particularly in low and middle income countries
- Effect of diabetes on mortality predominantly derived from high-income countries
- Mexico example of a large upper/middle income country with large prevalence of diabetes
- Diabetes diagnosis in Mexico associated with 4-fold increase in mortality risk
- Aim of the study was to assess the cause-specific mortality burden associated with diabetes

Study Design

- *Design:*

  Long-term follow-up study of the Mexico City Prospective Study

  (Recruitment of 159755 inhabitants occurred between 1998 and 2014;
- *Diabetes Status:*
  - Diabetes status assessed by interviewers
  - 133662 individuals included among which 16940 (13%) diagnosed diabetics and 6541 (5%) had undiagnosed diabetes
- *Outcomes*
  - Mortality (through national death files) from 1998 to 2016 using ICD-9 coding
- *Comparison*
  - Association of diabetes vs non-diabetes with death due to vascular disease, CKD or infections.

  (Herrington et.al. Lancet Diabetes & Endocrinology 2018:6;455-463)

Attributable risk of diabetes for kidney death

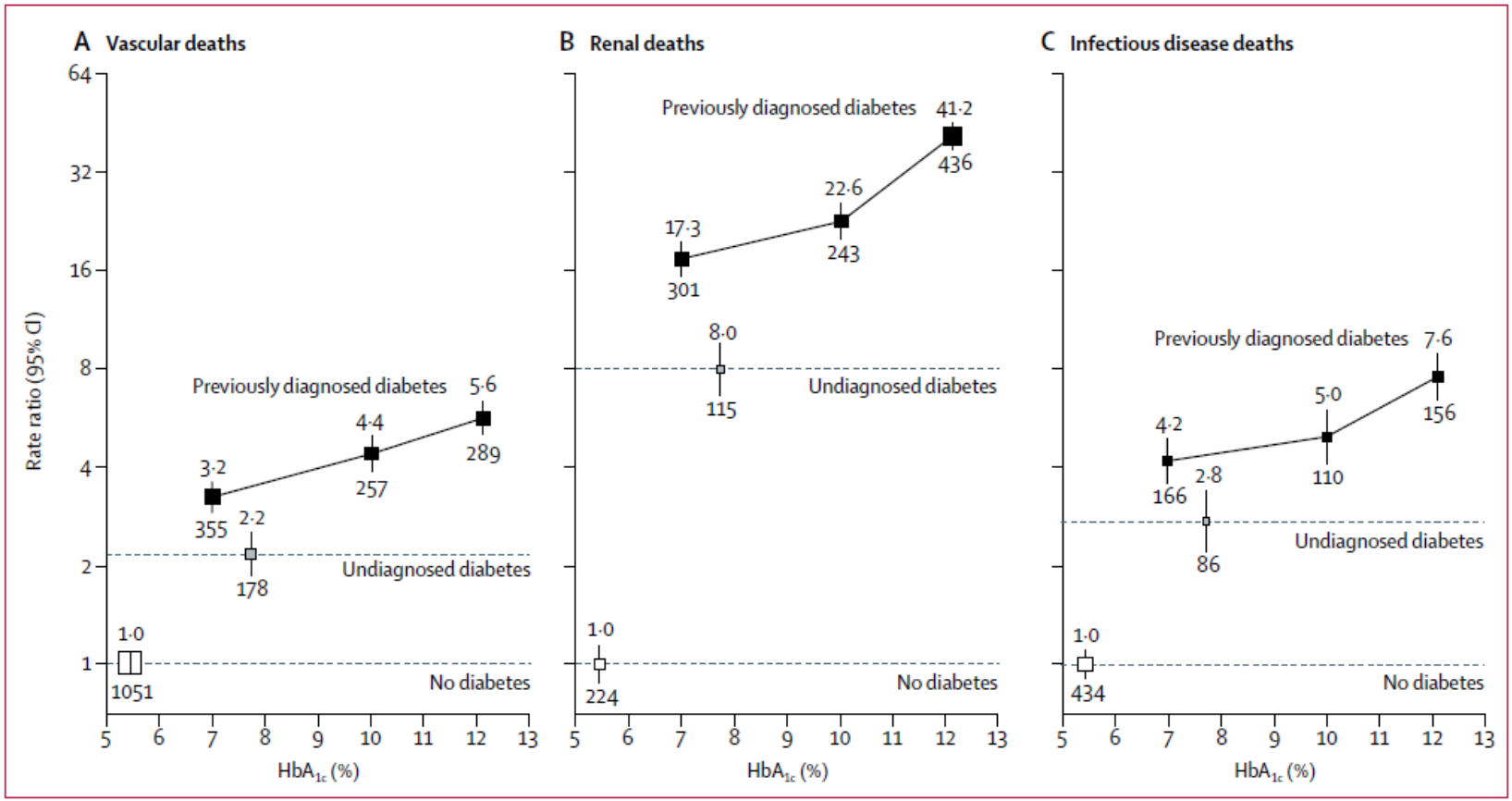
	Number of deaths				Death RR (95% CI) vs no diabetes*				Attributable mortality†
	No diabetes (n=110 181)	Undiagnosed diabetes (n=6541)	Previously diagnosed diabetes		No diabetes	Undiagnosed diabetes	Previously diagnosed diabetes		
			HbA_{1c} <9% (n=8475)	HbA_{1c} ≥9% (n=8465)			HbA_{1c} <9%	HbA_{1c} ≥9%	
All-cause mortality	3944	595	1184	1960	1·0	2·1 (1·9–2·2)	3·0 (2·8–3·3)	5·2 (4·9–5·5)	35%
Any vascular, renal, or infectious	1709	379	822	1491	1·0	3·0 (2·7–3·4)	4·9 (4·5–5·3)	9·1 (8·5–9·8)	51%
Renal	224	115	301	679	1·0	8·0 (6·4–10·1)	15·8 (13·2–18·9)	33·6 (28·8–39·3)	79%
Cardiac	697	127	244	362	1·0	2·4 (2·0–2·9)	3·3 (2·8–3·8)	5·3 (4·7–6·0)	37%
Infectious	434	86	166	266	1·0	2·8 (2·2–3·5)	4·0 (3·3–4·8)	6·6 (5·6–7·7)	43%
Cerebrovascular	268	37	79	132	1·0	1·7 (1·2–2·4)	2·6 (2·0–3·3)	4·7 (3·8–5·8)	32%
Other vascular	86	14	32	52	1·0	2·1 (1·2–3·8)	3·5 (2·3–5·3)	6·3 (4·4–9·0)	40%
Acute diabetic crises‡	48	28	86	156	..	..	..	..	100%
Neoplastic	1051	85	102	121	1·0	1·1 (0·9–1·4)	1·0 (0·8–1·2)	1·2 (1·0–1·5)	2%
Cirrhotic	436	42	58	55	1·0	1·2 (0·9–1·7)	1·4 (1·0–1·8)	1·3 (1·0–1·8)	6%
Chronic obstructive pulmonary disease	136	12	27	20	1·0	0·9 (0·5–1·7)	1·5 (1·0–2·3)	1·2 (0·8–2·0)	6%
Ill-defined, other, or external	564	49	89	117	1·0	1·2 (0·9–1·7)	1·7 (1·4–2·2)	2·3 (1·9–2·8)	14%

RR=rate ratio. *Death RR estimates for those with versus without diabetes at recruitment were adjusted for age, sex, district, educational level, smoking status, and anthropometric measures. †For each of previously diagnosed diabetes with HbA_{1c} ≥9%, previously diagnosed diabetes with HbA_{1c} <9%, and undiagnosed diabetes, the number of deaths attributable to the excess risk associated with that level of diabetes was calculated as number of deaths × (RR–1)/RR, where RR is the cause-specific death RR for that group relative to those without diabetes. These three numbers were then summed and presented as a percentage of all such deaths. For example, for renal death, the calculation was 100 × ([679 × 32·6/33·6] + [301 × 14·8/15·8] + [115 × 7·0/8·0])/1319=79%. ‡Death RR estimates are not shown for deaths attributed to acute diabetic crises as all such deaths were due to diabetes, irrespective of whether diabetes was diagnosed before recruitment.

Table 2: **Excess cause-specific mortality at ages 35–74 years associated with previously diagnosed or undiagnosed diabetes at recruitment**

(Herrington et.al. Lancet Diabetes & Endocrinology 2018:6;455-463)

Relevance of previously diagnosed and undiagnosed diabetes for vascular / renal and infectious disease deaths



(Herrington et.al. Lancet Diabetes & Endocrinology 2018:6;455-463)

Limitations and conclusions

Limitations

- No data on non-fatal cardiovascular outcomes
- Data collection occurred between 1998 and 2004; unclear if results are relevant for contemporary diabetes care
- **Conclusions – What is new?**
- Uncontrolled glycemic control strongest contributor to renal death
- Vascular, renal and infections death rates increase steeply with both duration of diabetes and worsened glycemic control.
- Strategies to delay diabetes are needed to improve outcomes in population with high prevalence of diabetes

(Herrington et.al. Lancet Diabetes & Endocrinology 2018:6;455-463)

End-stage renal disease in Type 1 diabetes

- End-stage renal disease is one of the most severe complications of type 1 diabetes
- Long-term follow-up studies allow adequate assessment of incidence of ESRD and trends over time
- Three recent studies, two in Europe and another in the US, assessed long-term incidence of ESRD in patients with type 1 diabetes

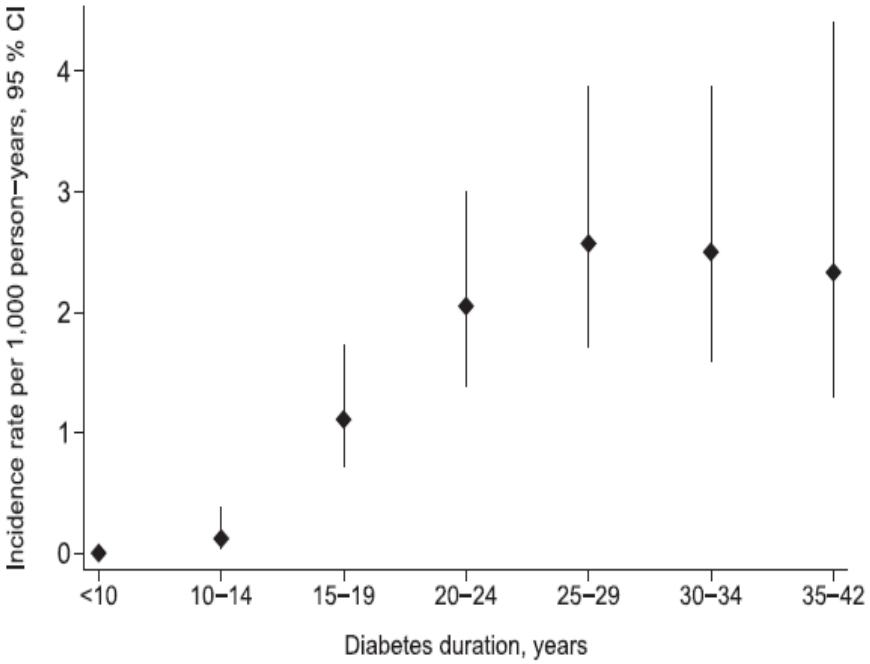
Study characteristics

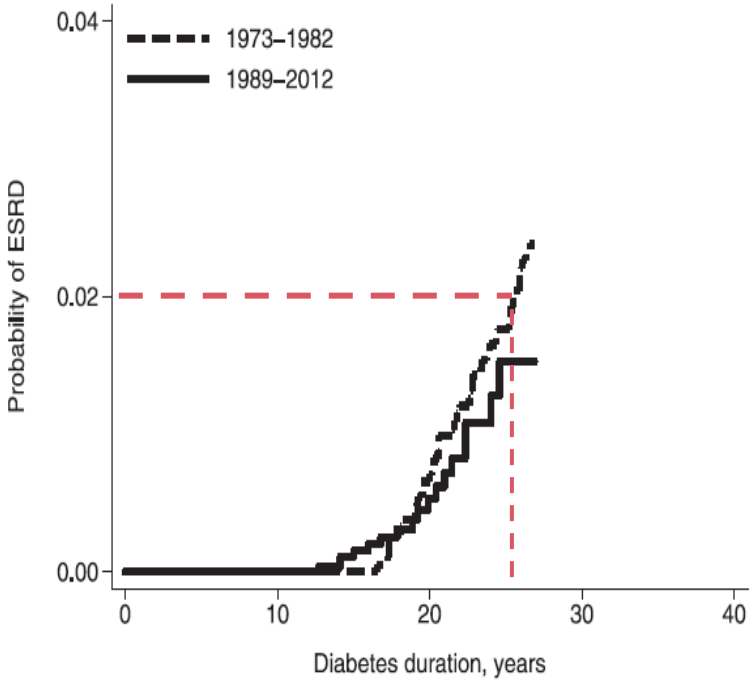
- Studies:
  - *Norwegian Childhood Diabetes Registry*
    - Nationwide registry including all new-onset cases of childhood diabetes (<15 yrs)
    - Data collection since 1973; N=7871 participants
    - Follow-up 42 year.
  - *FinnDiane study: Type 1*
    - Observational study in Finnland
    - Data collection since 1965
    - All patients who started insulin therapy before age of 30 (N=29,906)
  - *Pittsburgh Epidemiology of Diabetes Complication Study*
    - Observational study in Pittsburgh region
    - Data collection since 1950;
      - 390 participants started between 1950 – 1964
      - 542 participants started between 1965 - 1980
    - Follow-up 50 year

(*Gagnum et. al. Diabetes Care 2018;41:420-25; Castacou et.al Diabetes Care 2018;41:426-33; Helve et.al. Diabetes Care 2018;41:434–439*)

Low incidence ESRD in Norwegian Childhood Registry

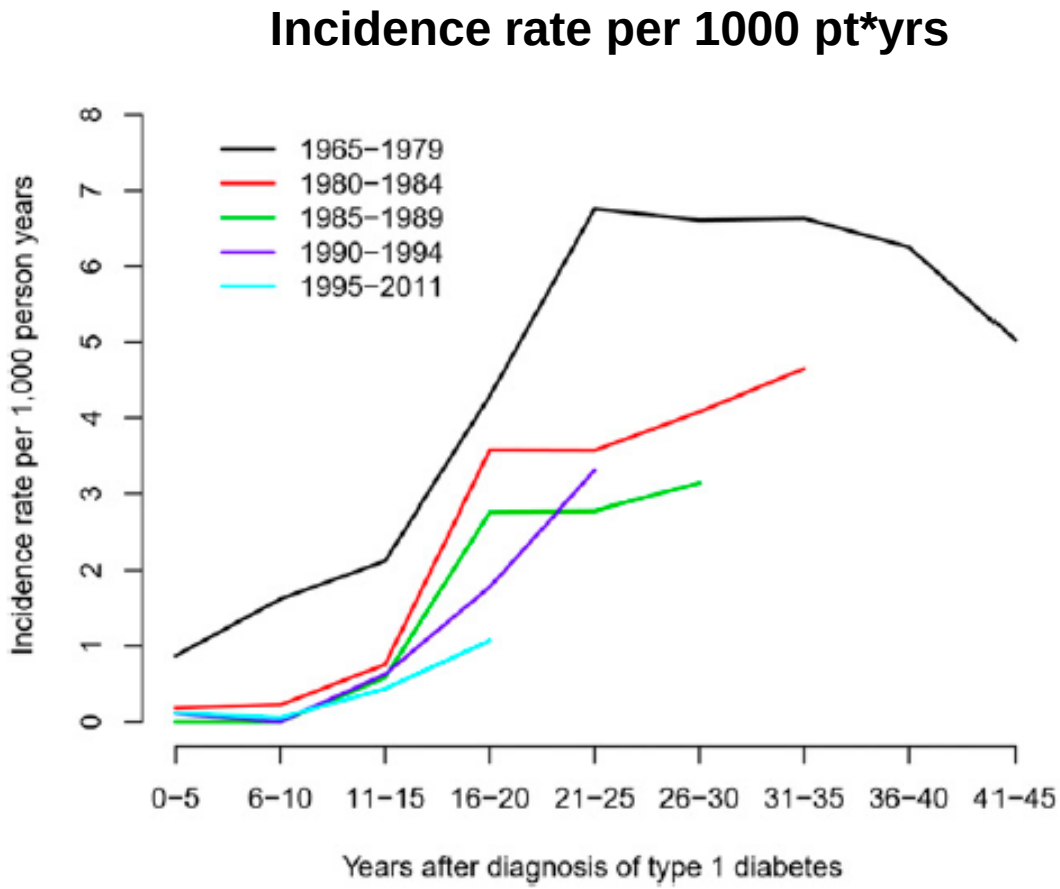
Incidence rate per 1000 pt*yrs





Gagnum et. al. Diabetes Care 2018;41:420-25

Risk of ESRD has decreased considerably over time in Finnland



Helve et.al. Diabetes Care 2018;41:434–439

High incidence ESRD in Pittsburgh

Table 2—The 25-year cumulative incidence of microalbuminuria, macroalbuminuria, and ESRD by diagnosis cohort and duration of T1D

	Microalbuminuria		Macroalbuminuria		ESRD		ESRD/mortality	
	1950–64	1965–80	1950–64	1965–80	1950–64	1965–80	1950–64	1965–80
Duration of T1D								
20 years	—	54.7 (215/393)	—	27.1 (105/388)	14.5 (53/366)	5.5 (27/491)	24.1 (94/296)	7.9 (40/505)
					$P < 0.0001$		$P < 0.0001$	
30 years	65.2 (122/187)	70.0 (254/363)	43.3 (87/201)	39.9 (127/318)	34.6 (111/321)	14.5 (63/435)	46.9 (182/388)	21.9 (104/474)
	$P = 0.26$		$P = 0.45$		$P < 0.0001$		$P < 0.0001$	
40 years	79.0 (169/214)	81.7 (188/230)	57.1 (113/198)	57.3 (102/178)	48.5 (145/299)	26.5 (62/234)	59.9 (232/387)	39.1 (108/276)
	$P = 0.46$		$P = 0.96$		$P < 0.0001$		$P < 0.0001$	
50 years	88.0 (176/200)	—	71.8 (117/163)	—	61.3 (165/269)	—	75.1 (277/369)	—

Data are % (*n* cases/total *n*).

Big difference between Norwegian and Pittsburgh study explained by:

- Younger population in Norway (8.7 years vs 27.4 years Pittsburgh)
- Shorter follow-up in Norway; Vast majority of patients could only contribute to 20 years incidence estimate rates – much longer in Pittsburgh

Costacou et.al. Diabetes Care. 2018 Mar;41(3):426-433

What‘s new?

- Studies suggest that the incidence of ESRD decreases over time since the 1980s
- This reduced ESRD rate is likely a result of improvements of blood pressure and glycemic control as well as institution of RAAS blockers in advanced CKD
- Thus clinicians need to continue to monitor GFR and albuminuria and start guideline recommended treatment when necessary

Diabetic Kidney Disease

- *Epidemiology*
- *Pathophysiology*
- *Pharmacotherapy*

Heterogeneity in type 2 diabetes

- Diabetes stratified in type 1 and type 2 diabetes
- Type 2 diabetes is particularly heterogeneous
- Study aim was to reclassify type 2 diabetes

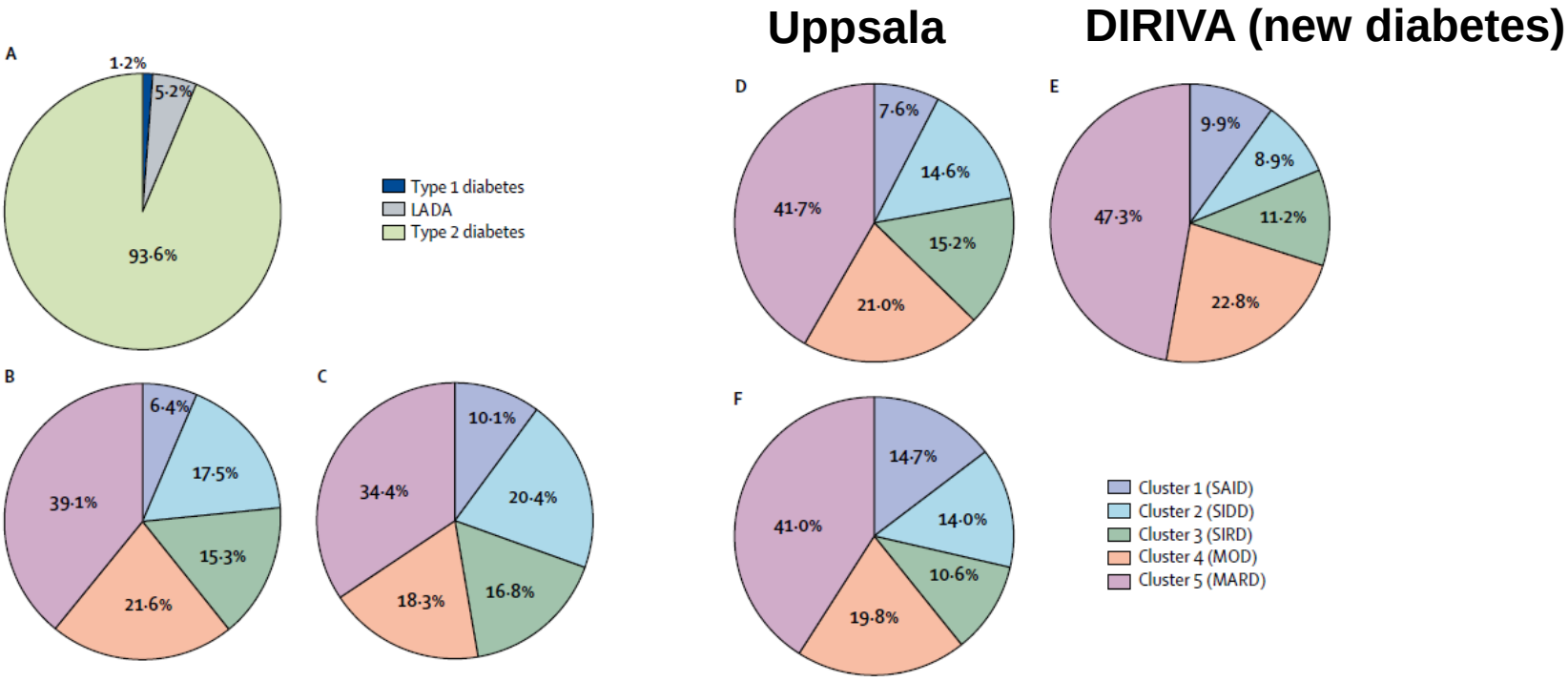
Ahlqvist et.al. Lancet D&E 2018;6:361-369

Methods

- Data-driven cluster analysis in newly diagnosed diabetes in Sweden (N=8980)
- Clusters were based on GABA-antibodies, BMI, age, Hba1c and HOMA-indices for β-cell function and insulin resistance
- Replication done in three independent cohorts

Ahlqvist et.al. Lancet D&E 2018;6:361-369

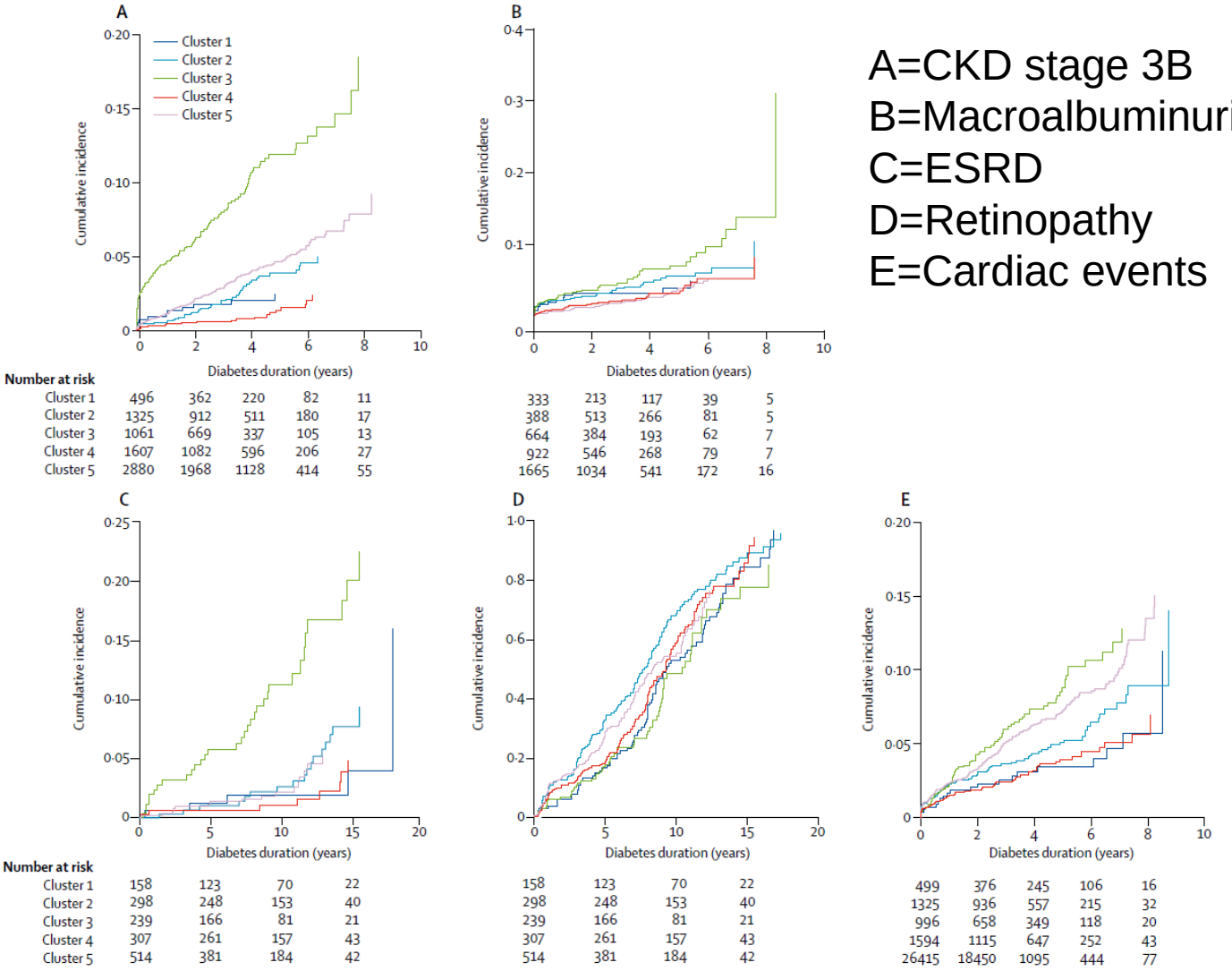
5-clusters of diabetes



Cluster 1 Severe autoimmune diabetes
Cluster 2 Severe insulin-deficient diabetes
Cluster 3 Severe insulin resistant diabetes
Cluster 4 Mild-obesity-related diabetes
Cluster 5 mild- age related diabetes

Ahlqvist et.al. Lancet D&E 2018;6:361-369

Cluster 3 (Severe insulin resistant diabetes) associated with progression of kidney disease



A=CKD stage 3B
B=Macroalbuminuria
C=ESRD
D=Retinopathy
E=Cardiac events

Ahlqvist et.al. Lancet D&E 2018;6:361-369

Limitations – What is new?

Limitations

- Only cohorts in Northern Europe limiting generalizability

What is new?

- New classification of diabetes suggested
- Readily available clinical parameters used
- Study suggests different options for treatment according to subtype (targeting insulin secretion vs. insulin resistance)

Genetic predisposition for development kidney disease?

- Considerable variation in progression of DKD among individuals
- Some evidence support a genetic contribution in the progression of DKD as:
  - DKD in type 2 diabetes aggregates in families
  - Prevalence of DKD varies among ethnic groups
- Identification of genetic variants may shed light in biological basis of DKD

Van Zuydam et.al. Diabetes 2018 Jul;67(7):1414-1427

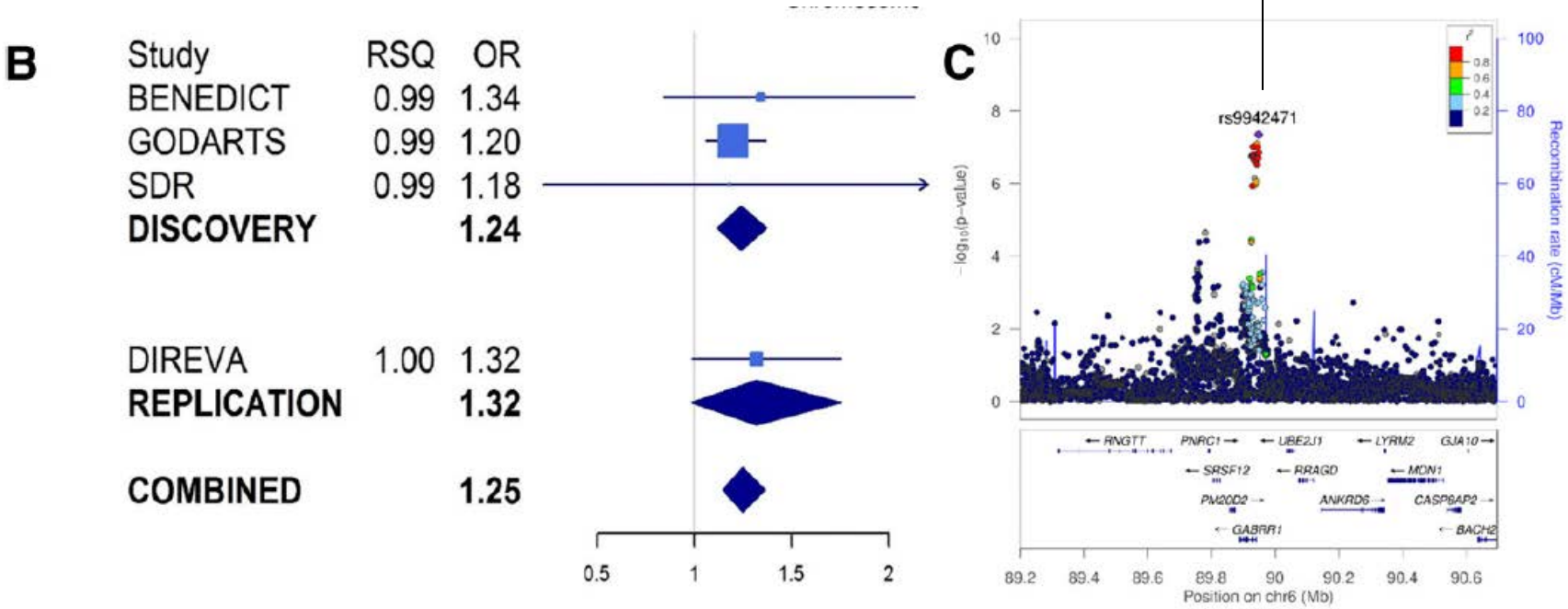
Methods

- Largest genetic study of diabetic kidney disease to date
- ***Cohorts:***
  - **Discovery**: Scania Diabetes Registry ; GoDARTS Scotland; Steno Diabetes Center; BENEDICT Study (N=5717)
  - **Replication:** DECODE, DIREVA, DOLCE, ADDITION, RIKEN, SDCS, HKDR, SMART2D (N=26827)
- ***Genetic analyses:*** Affymetrix Illumina express GWAS array for discovery cohorts
- ***Study power:*** 80% power to detect an odds ratio of 1.4 at α $5*10^{-8}$

Van Zuydam et.al. Diabetes 2018 Jul;67(7):1414-1427

SNP rs9942471 consistently associated with microalbuminuric phenotype

1 SNP associated with microalbuminuric phenotype



Van Zuydam et.al. Diabetes 2018 Jul;67(7):1414-1427

What's new?

- Largest study to date on the genetic basis of DKD in type 2 diabetes
- Only one novel locus for microalbuminuria was discovered *(GABRR1; Gamma-aminobutyric acid type A receptor)*
- GABRR1 expression is upregulated in renal biopsies BUT
- GABRR1 could not be replicated in type 1 diabetes of European ancestry or type 2 diabetes of Asian ancestry
- Further validation is thus required
- The research questions the genetic basis of DKD, illustrates the difficulties of genetic association studies and need for solid phenotype assessment

Diabetic Kidney Disease

- *Epidemiology*
- *Pathophysiology*
- *Pharmacotherapy*

Established and novel agents for slowing progression of diabetic kidney disease

Antihyperglycemic Agents

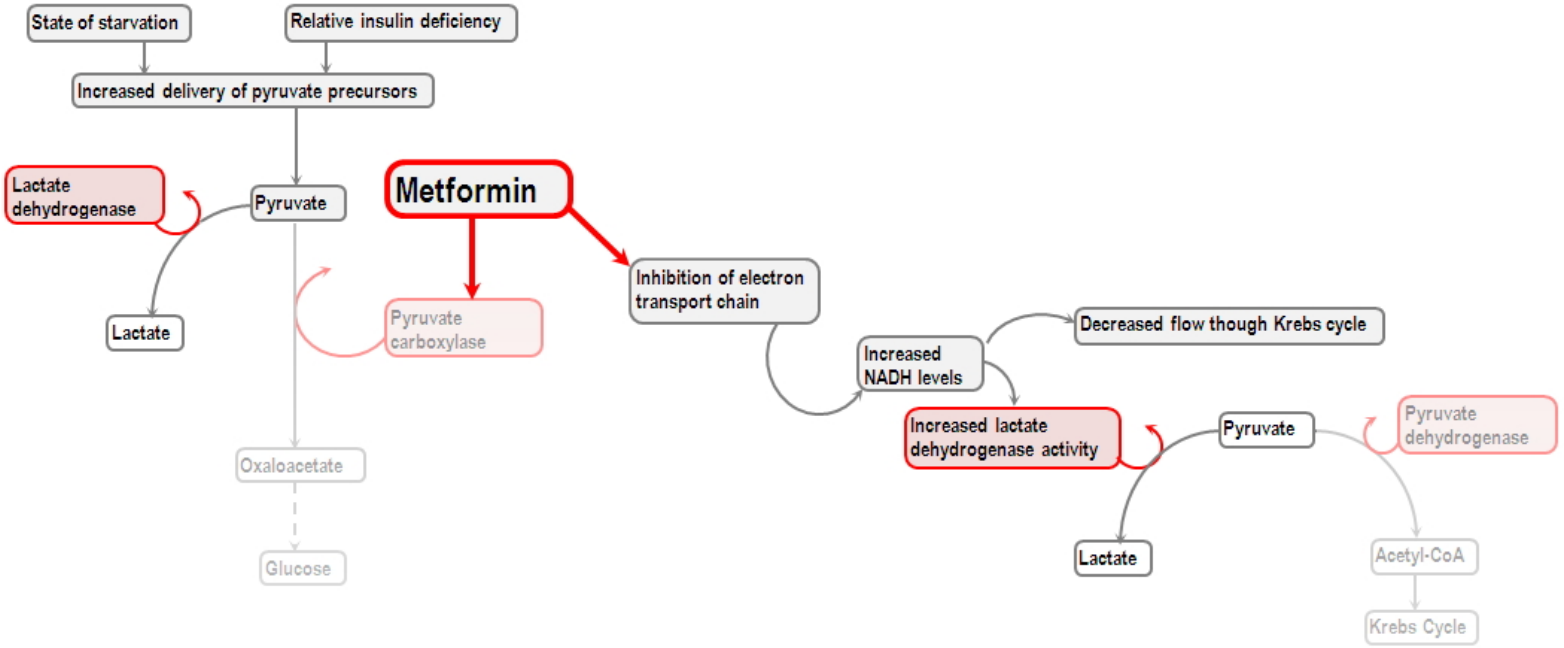
- Metformin
- Sodium Glucose Co-Transporter 2 inhibition
- GLP1-Receptor Agonists

Beyond Glycemic control:

- Endothelin Receptor Antagonist

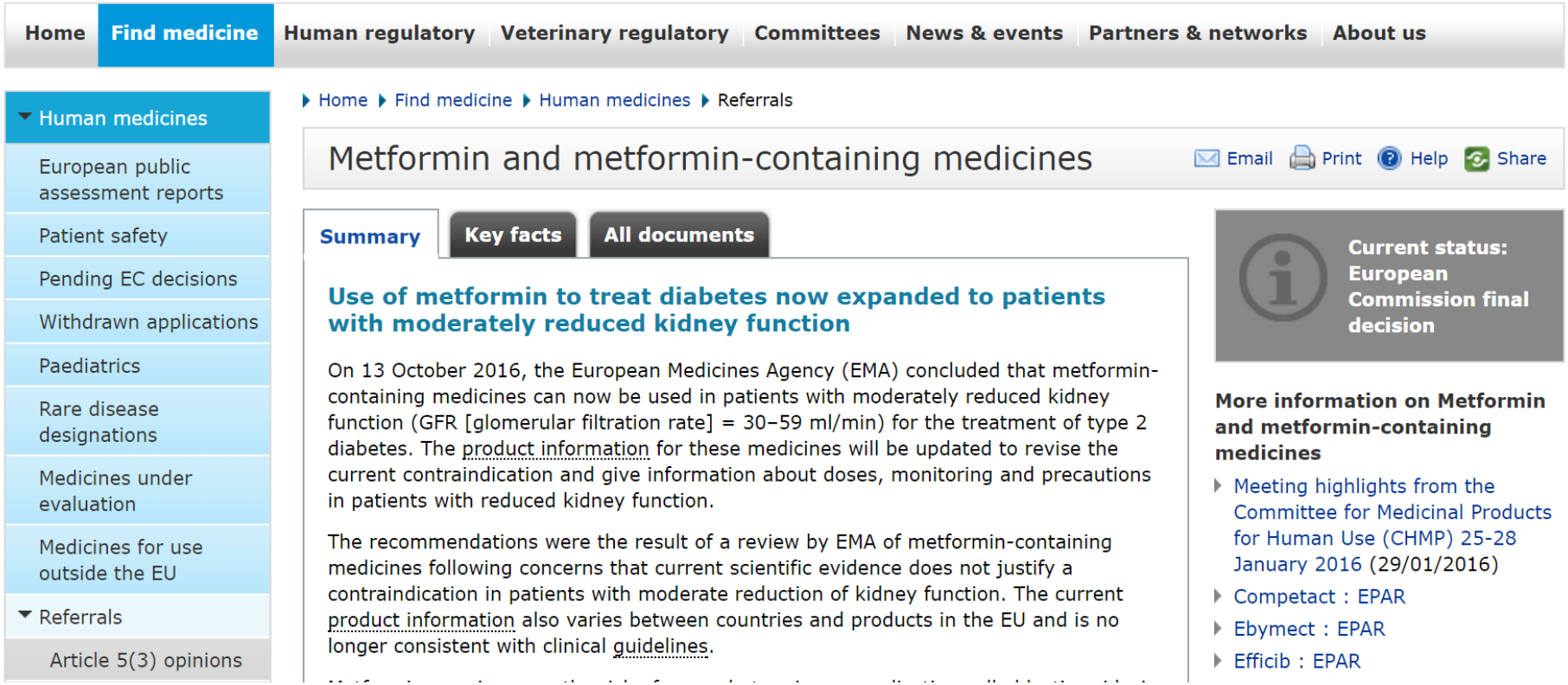
Metformin in patients with diabetic kidney disease

- Metformin is traditionally contra-indicated in patients with diabetic kidney disease because of risk of lactate acidosis
- Metformin inhibits conversion of lactate conversion via gluconeogenesis



Dembo et.al. Diabetes 1975 Vol 24; 28-35

Metformin in CKD – still contraindicated?



http://www.ema.europa.eu/ema/

Metformin in diabetic kidney disease

- Guidelines discourage metformin in patients with moderate-to-severe chronic kidney disease (CKD) because of the fear of lactic acidosis attributed to metformin accumulation
- EMA guideline changed in absence of prospective studies

- Lalou et.al performed three complimentary study to assess efficacy/safety of metformin in CKD
  - Dose finding study
  - Chronic metformin study
  - PK/PD study

Lalou et.al. Diabetes Care. 2018 Mar;41(3):547-553

Study Design

- *Design study 1:*

  Dose titration (1 week treatment) of metformin 1000 mg QD; 500 mg BID; 1000 mg BID in patients with type 2 diabetes CKD stage 1-5 (N=78)

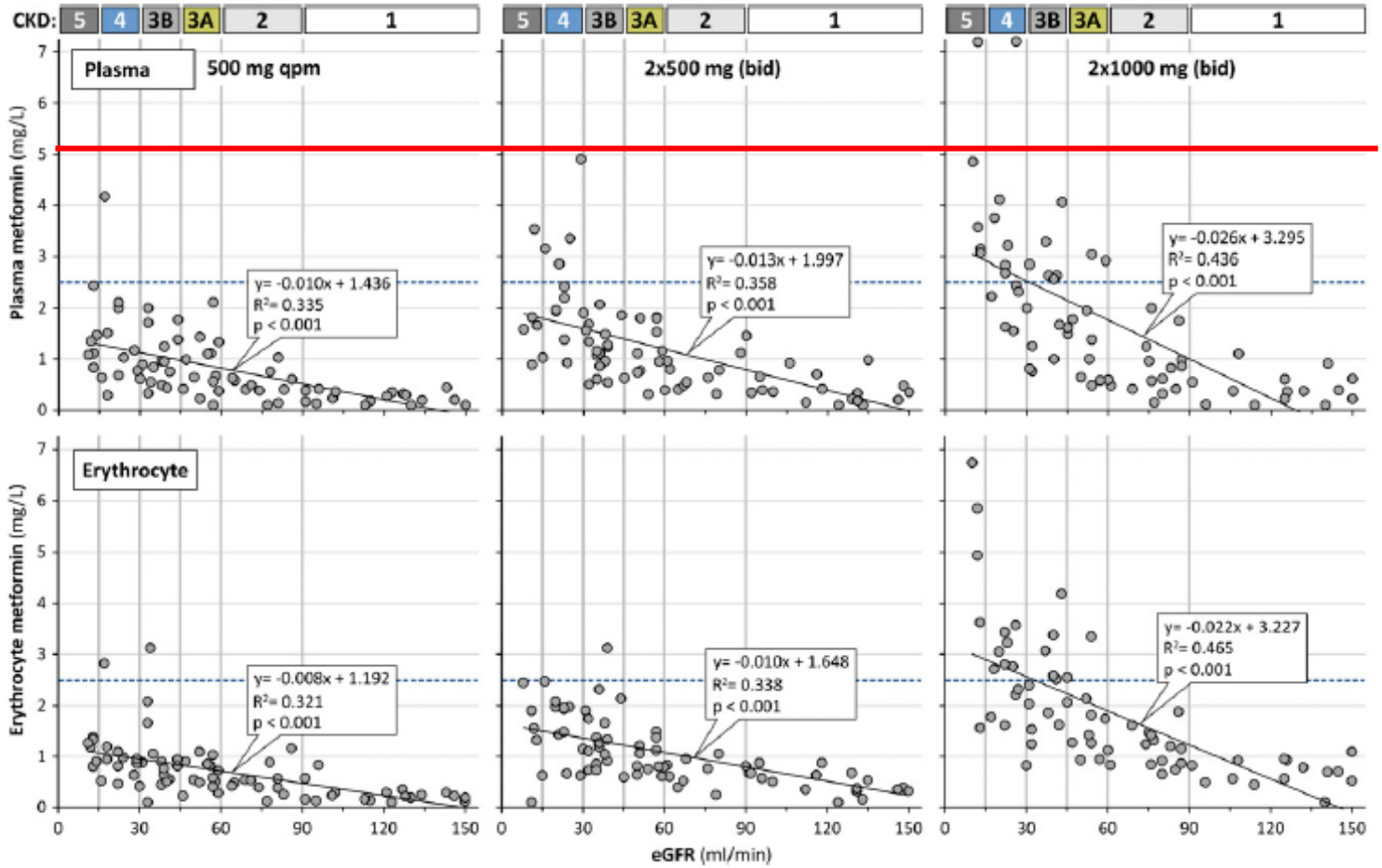
- *Design study 2*

  Four month chronic study of metformin 1500 mg/d in patients with type 2 diabetes CKD stage 3 or 4 (N=46). Hba1c and lactate were monitored

- *Design study 3*
  - PK/PD study of metformin in CKD stage 3A, 3B, or 4 (n=5 per group). Metformin dosed 500 mg in the morning and an evening dose depending on CKD stage. Blood samples taken after the morning dose at 0,0.5,1,2,4,6,8,12 and 24hrs.

Lalou et.al. Diabetes Care. 2018 Mar;41(3):547-553

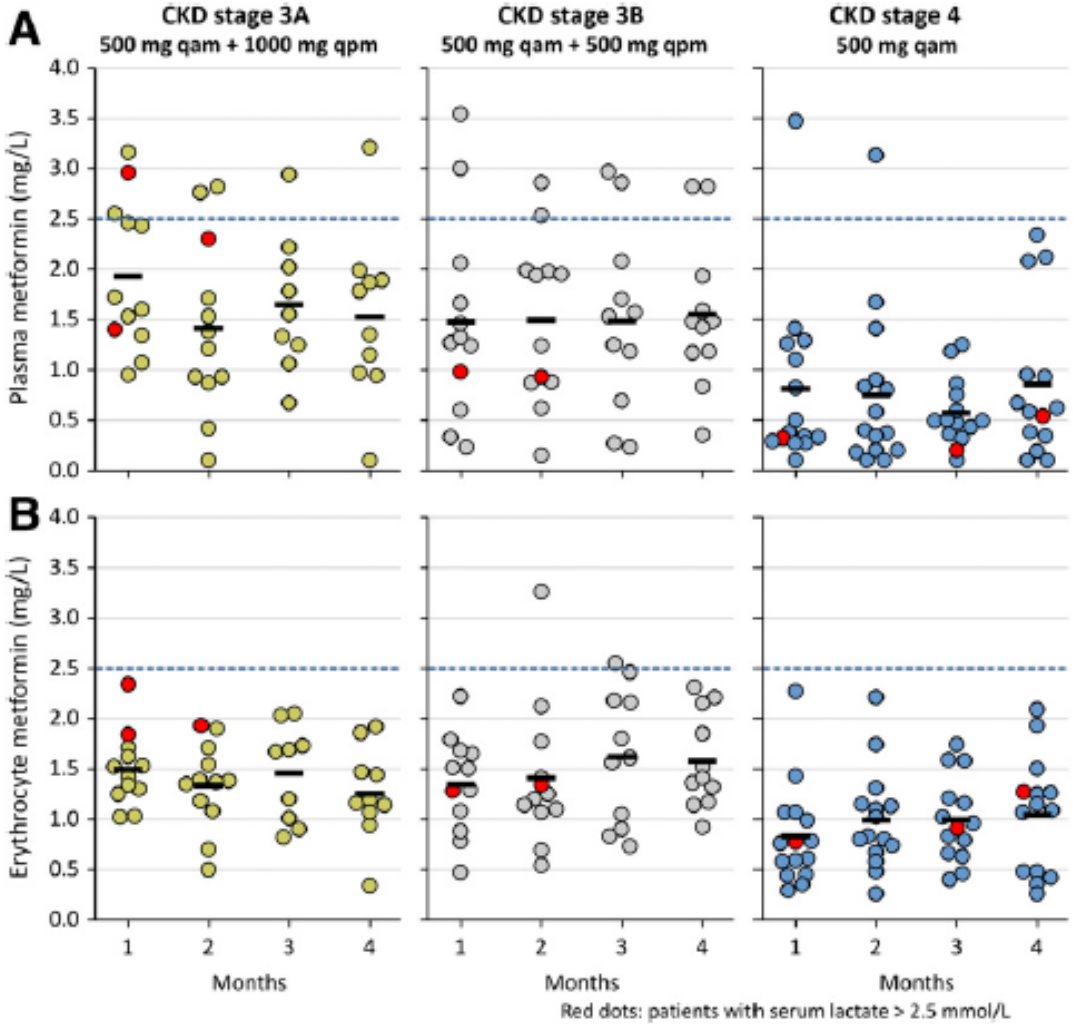
Results study 1



Hyperlactemia (>5mmol/L) not observed in the study. One patient CKD stage 3A had two consecutive lactate contrations >2.5 mmol/L but no metformin accumulation.

Lalou et.al. Diabetes Care. 2018 Mar;41(3):547-553

Results study 2



6 patients with elevated lactate (>2.5mmol/L)
No correlation between lactate and metformin concentration

Lalou et.al. Diabetes Care. 2018 Mar;41(3):547-553

No difference in PK parameters across CKD stages

Table 1—Data from the PK study

Parameters	Compartment	CKD stage 3A	CKD stage 3B	CKD stage 4	*P* value (comparison of the CKD stages)
AUC, h · mg/L	Plasma	26.01 ± 8.89 (14.64–35.94)	38.54 ± 11.00 (27.78–53.19)	31.35 ± 11.06 (16.03–44.39)	0.31
	Erythrocyte	25.85 ± 6.19 (32.99–61.55)	46.40 ± 12.50 (14.64–35.94)	23.07 ± 15.00 (5.27–41.93)	0.11
T_{max}, h	Plasma	3.40 ± 1.95 (1.0–6.0)	4.20 ± 2.49 (1.0–8.0)	4.00 ± 00.00 (4.0–4.0)	0.88
$t_{1/2}$, h	Plasma	6.88 ± 2.8 (3.23–10.05)	7.69 ± 1.15 (6.22–8.7)	11.10 ± 5.87 (5.85–19.85)	0.28
C_{max}, mg/L	Plasma	2.13 ± 0.57 (1.33–2.74)	3.38 ± 1.60 (2.13–5.94)	2.30 ± 0.83 (1.32–3.28)	0.43
C_{avss}, mg/L	Plasma	1.57 ± 0.54* (1.00–2.17)	2.31 ± 0.78* (1.77–3.51)	1.31 ± 0.46† (0.67–1.85)	0.22
	Erythrocyte	1.17 ± 0.20* (1.07–1.54)	1.96 ± 0.55* (1.27–2.66)	0.96 ± 0.62† (0.22–1.75)	0.11

Data are shown as the mean ± SD (range). $t_{1/2}$, terminal half-life; T_{max}, time to C_{max}. *C_{avss} at 12 h. †C_{avss} at 24 h.

Lalou et.al. Diabetes Care. 2018 Mar;41(3):547-553

Metformin use in real world setting

- *Design:*

  Community-based cohort of 75 413 patients with diabetes in Geisinger Health System from 2004 - 2007. Replication in 67 578 new metformin users from 2010 – 2015
- *Exposure:*
  - Metformin use
- *Outcomes*
  - Hospitalization with acidosis (International Classification of Diseases, Ninth Revision, Clinical Modification code of 276.2)*Comparison*
- *Statistics*
  - Cox model with time varying metformin and eGFR use adjusted for graphic characteristics, eGFR, serum bicarbonate level, smoking status, BMI, cardiovascular disease, heart failure.

Lazarus JAMA Intern Med. 2018 Jul 1;178(7):903-910

No association between metformin use and lactate acidosis if eGFR>30

Table 3. Association of Time-Dependent Metformin Use With Acidosis Hospitalization by Time-Dependent Estimated Glomerular Filtration Rate (eGFR) Category in Geisinger Health System

	HR[a] (95% CI) for Acidosis Associated With Metformin Use by Time-Dependent eGFR Category, mL/min/1.73 m^2					
Parameter	Overall[b]	≥90	60-89	45-59	30-44	<30
Person-time (on metformin/off metformin)	188 578/281 536	80 653/98 905	79 788/102 110	21 232/40 861	6358/29 834	548/9827
Acidosis events (on metformin/off metformin)	737/1598	206/323	288/446	157/286	64/314	22/229
Unadjusted (n = 75 413)	0.89 (0.81-0.97)	0.77 (0.65-0.92)	0.82 (0.71-0.95)	1.05 (0.87-1.28)	0.95 (0.73-1.25)	1.71 (1.10-2.64)
Demographic adjusted[c] (n = 75 413)	0.89 (0.81-0.97)	0.75 (0.63-0.90)	0.82 (0.71-0.96)	1.07 (0.88-1.30)	0.98 (0.75-1.28)	1.76 (1.14-2.73)
Fully adjusted[d] (n = 72 232)	0.98 (0.89-1.08)	0.88 (0.73-1.05)	0.87 (0.75-1.02)	1.16 (0.95-1.41)	1.09 (0.83-1.44)	2.07 (1.33-3.22)
Fully adjusted with time-dependent medication use[e] (n = 72 232)	0.94 (0.83-1.05)	0.80 (0.66-0.97)	0.81 (0.68-0.95)	1.14 (0.93-1.40)	1.13 (0.85-1.49)	2.21 (1.42-3.44)
Sensitivity analyses						
Fully adjusted[d] excluding baseline insulin users (n = 60 112)	1.02 (0.91-1.13)	0.88 (0.71-1.09)	0.89 (0.75-1.06)	1.21 (0.97-1.50)	1.16 (0.87-1.57)	2.22 (1.41-3.51)
Fully adjusted[d] including adjustment for baseline hemoglobin A_{1c} (n = 58 093)	1.01 (0.90-1.14)	0.84 (0.67-1.04)	0.93 (0.78-1.12)	1.23 (0.98-1.55)	1.07 (0.78-1.46)	2.22 (1.37-3.59)
Fully adjusted[d] in incident diabetes mellitus cohort (n = 49 839)	0.91 (0.79-1.04)	0.85 (0.68-1.06)	0.82 (0.66-1.01)	1.15 (0.86-1.53)	0.88 (0.55-1.39)	2.37 (1.20-4.71)
Fully adjusted[d] with early censoring of metformin (n = 72 232)	1.04 (0.95-1.15)	0.93 (0.78-1.12)	0.93 (0.80-1.09)	1.23 (1.01-1.50)	1.17 (0.89-1.54)	2.26 (1.45-3.51)

Lazarus JAMA Intern Med. 2018 Jul 1;178(7):903-910

What's new?

- Both studies support recent guidelines to consider metformin in moderate to severe CKD providing that the metformin dose is adjusted
- Suggested daily doses and guidance:
  - CKD stage 3A: 1500 mg (500mg morning / 1000 mg evening
  - CKD stage 3B: 1000 mg (500 mg morning / evening)
  - Assess eGFR at least every 6 months
  - Withold metformin in case of reduced circulating volume (fluid loss) or in patients likely to experience AKI

Can SGLT2 inhibitors be used in DKD?

Dapagliflozin

Use in patients with renal impairment

The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2). In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension,

Canagliflozin

Renal impairment

For patients with an eGFR 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2 or CrCl 60 mL/min to < 90 mL/min, no dose adjustment is needed.

Canagliflozin should not be initiated in patients with an eGFR < 60 mL/min/1.73 m^2 or CrCl < 60 mL/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m^2 or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m^2 or CrCl persistently below 45 mL/min (see sections 4.4, 4.8, 5.1, and 5.2).

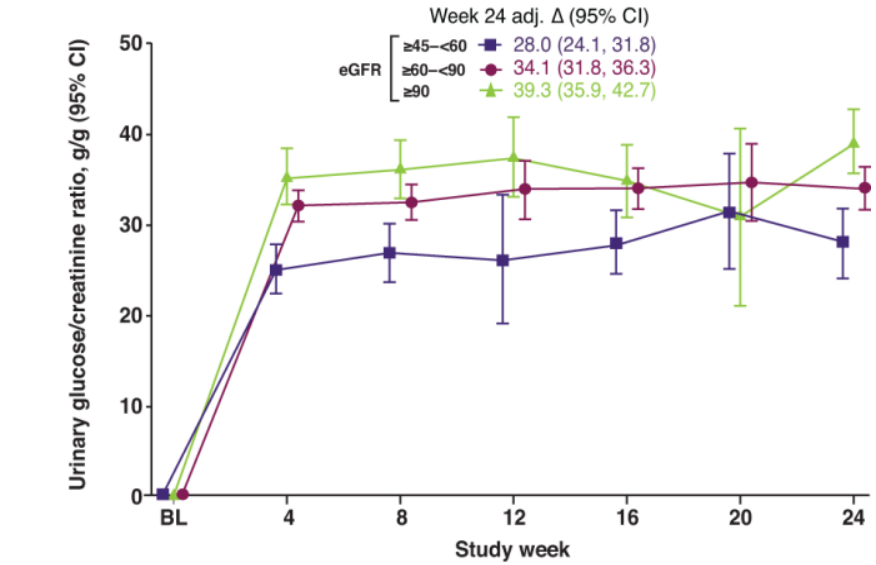
Empagliflozin

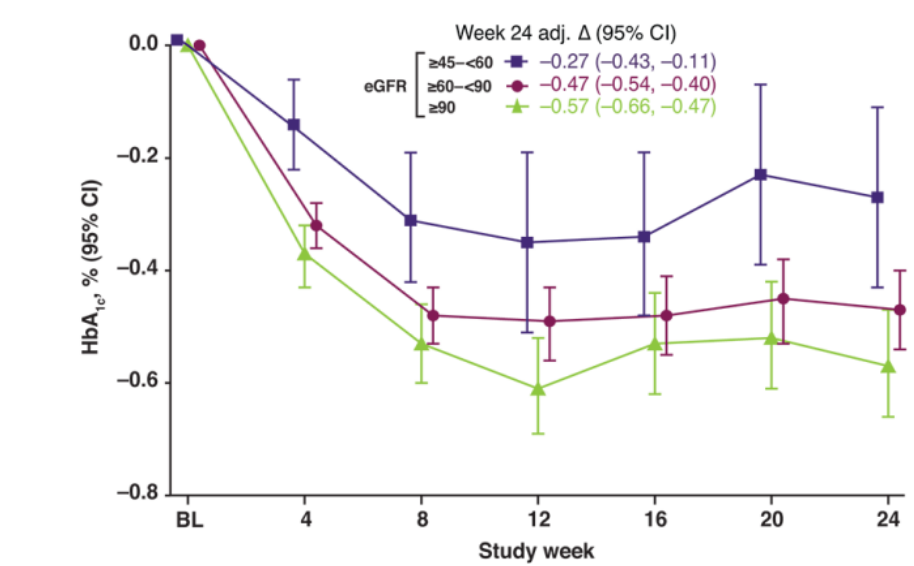
Jardiance should not be initiated in patients with an eGFR below 60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR is persistently below 60 ml/min/1.73 m^2 or CrCl <60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below

SUMMARY OF PRODUCT CHARACTERISTICS www.ema.europa.eu

Glycemic effects of SGLT2i are blunted in DKD

Placebo-adjusted change from baseline over time with dapagliflozin in HbA1c in the overall population

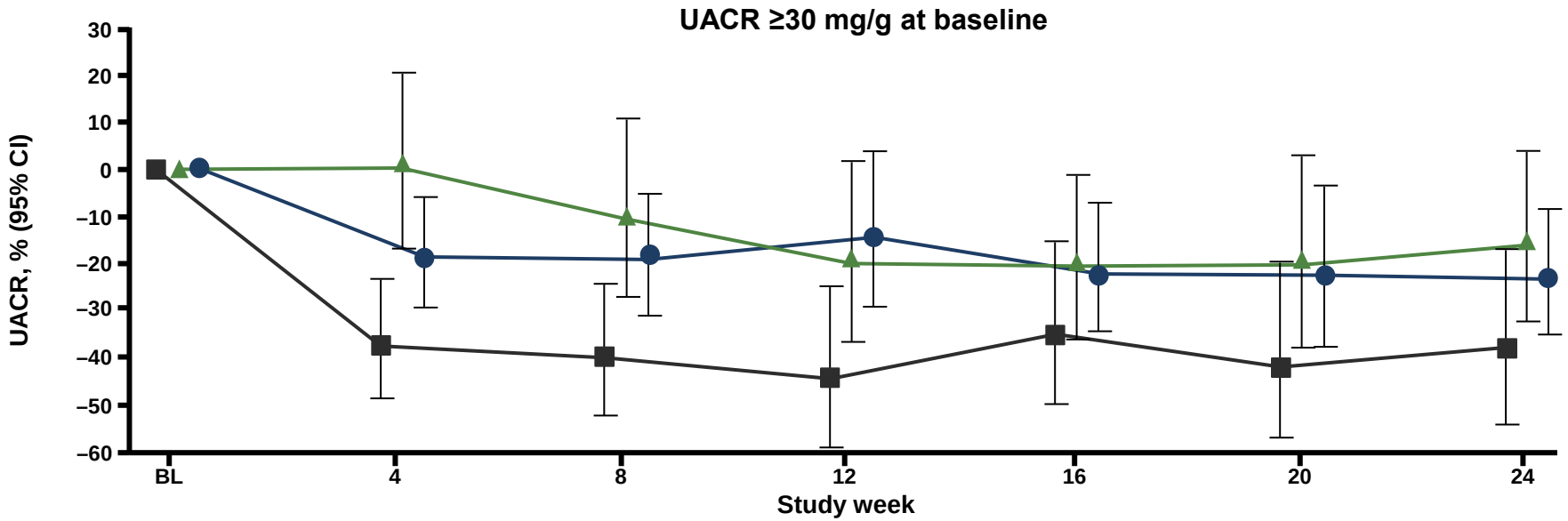




Excludes data after rescue. Adj., adjusted; BL, baseline; CI, confidence interval.

Petrykiv et.al. CJASN 2017: 8:751-759

Non-glycemic effects of SGLT2i persist in DKD



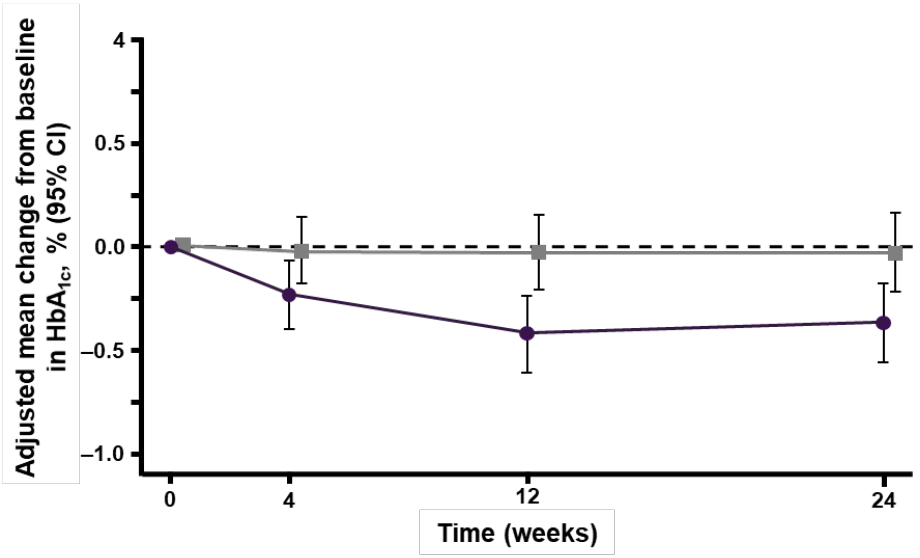
eGFR							
≥45–<60, n	90	88	82	40	74	36	71
≥60–<90, n	310	306	293	126	269	105	261
≥90, n	175	173	168	94	145	77	150

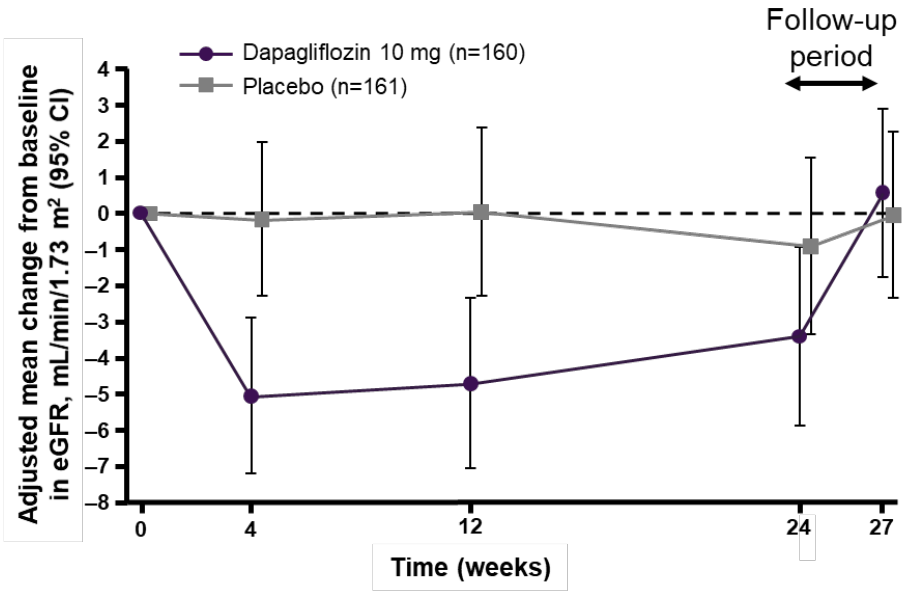
eGFR subgroup (mL/min/1.73 m²)	Mean UACR		
	Baseline (SD)	Week 24 adjusted Δ (%)	95% CI
≥45–<60	211 (370)	–38.3	–54.4, –16.6
≥60–<90	206 (350	–23.3	–35.5, –8.7
≥90	170 (248)	–16.1	–32.3, 3.8

Petrykiv et.al. CJASN 2017: 8:751-759

DERIVE: Dapagliflozin reduces HbA_{1c} in patients with CKD stage 3A

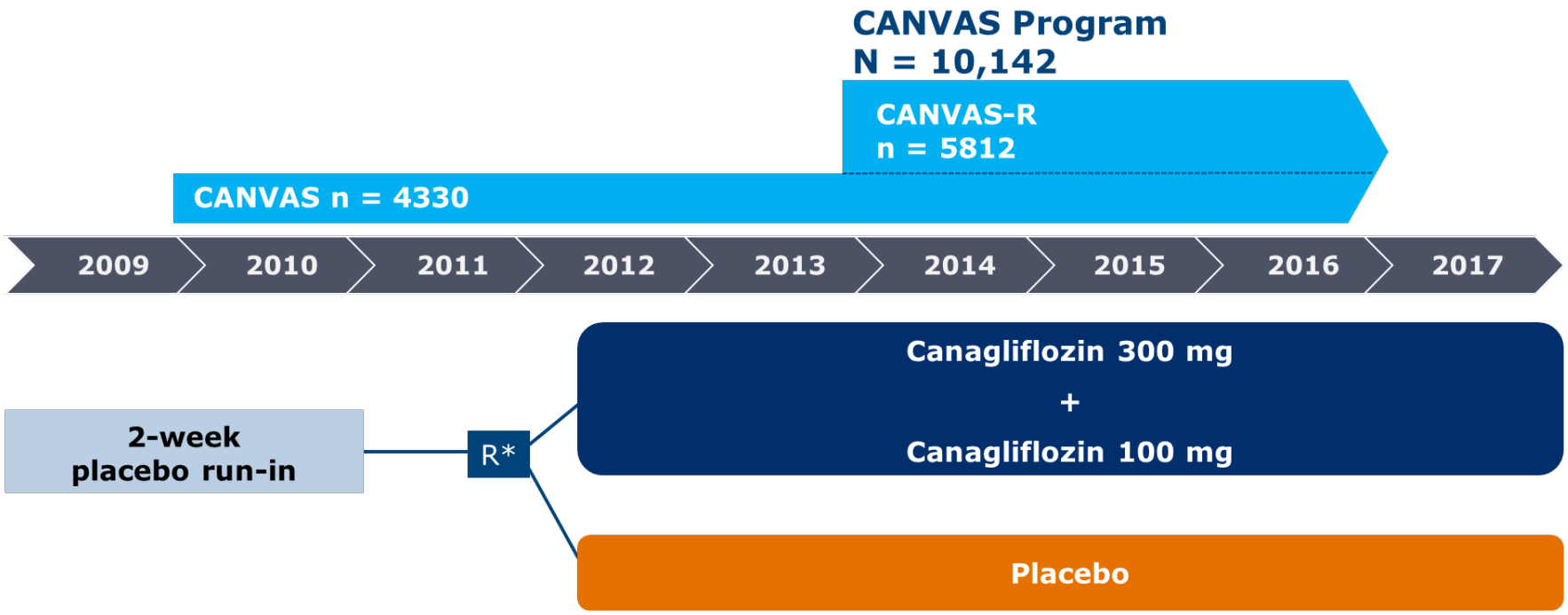
- Treatment with dapagliflozin over 24 weeks significantly improved glycemic control, body weight, and systolic blood pressure in patients with T2DM and 3A CKD stage,[a] with no reduction in eGFR





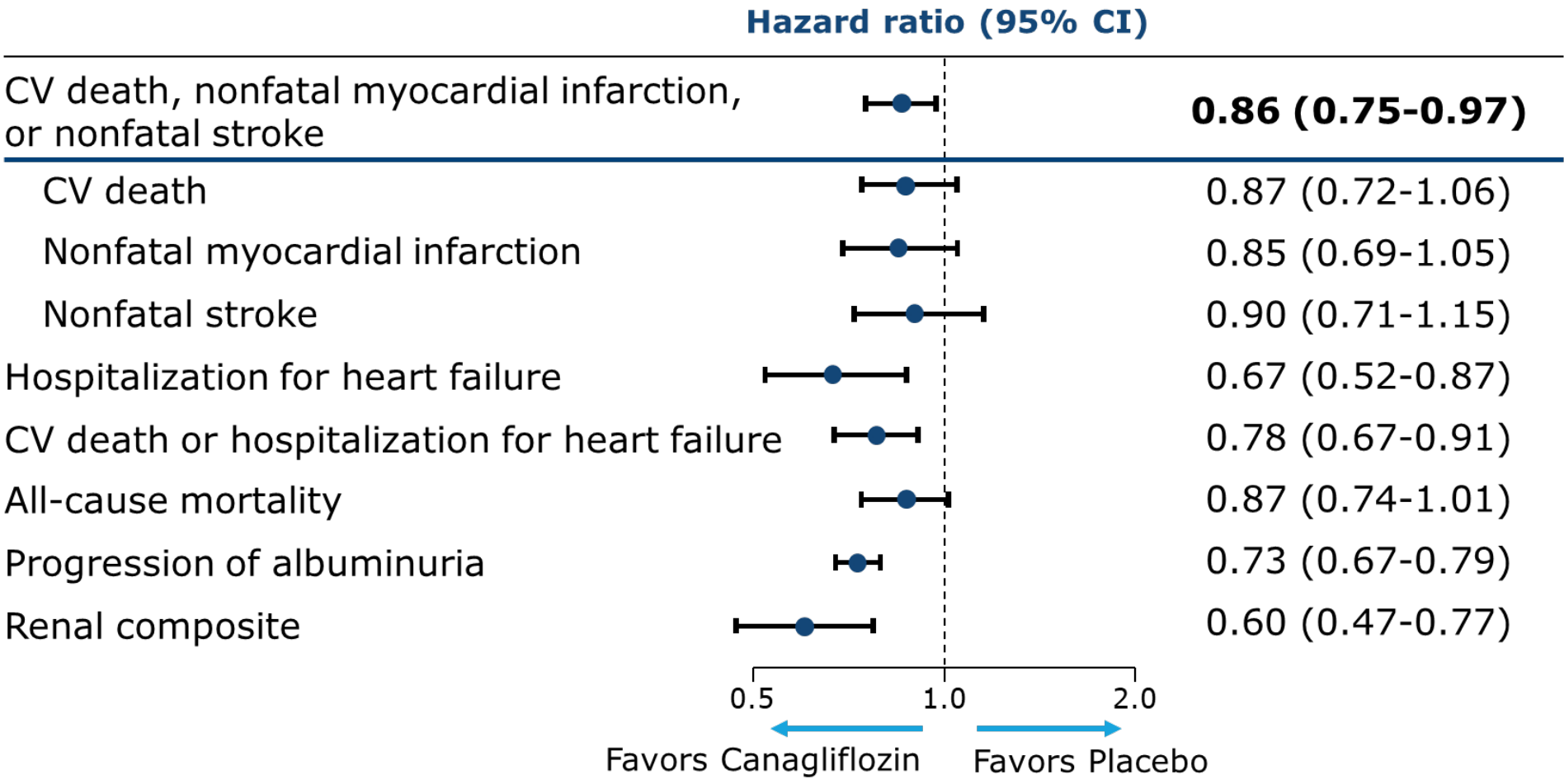
Fioretto et.al. Diabetes Obesity and Metabolism 2018 Jun 11

CANVAS Program: Design



Neal et al. *N Engl J Med*. 2017;377(7):644-657.

CANVAS: Summary of CV and mortality outcomes



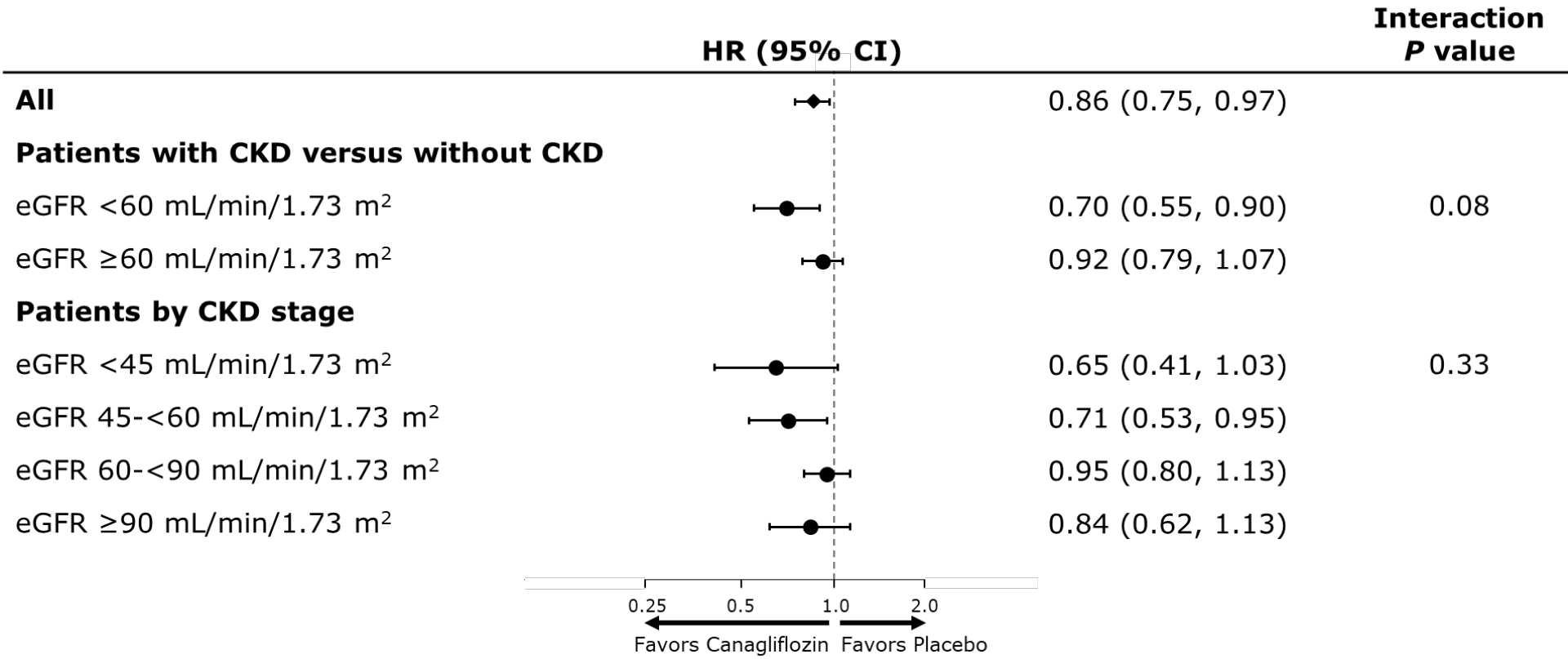
Neal et al. *N Engl J Med*. 2017;377(7):644-657.

CANVAS baseline characteristics by eGFR

	eGFR <45 mL/min/1.73 m^2 (N = 554)	eGFR 45-<60 mL/min/1.73 m^2 (N = 1485)	eGFR 60-<90 mL/min/1.73 m^2 (N = 5625)	eGFR ≥90 mL/min/1.73 m^2 (N = 2476)
Mean age, y	69	67	64	59
Female, %	44	41	35	33
Mean duration of diabetes, y	17	16	13	12
Mean HbA1c, %	8.3	8.2	8.2	8.3
Hypertension, %	95	95	90	85
CV disease history, %	73	71	65	62
Atherosclerotic vascular disease history, %				
Coronary	63	62	58	49
Cerebrovascular	24	22	19	18
Peripheral	26	24	19	21
eGFR, mL/min/1.73 m^2	38	53	75	103
Median UACR, mg/g	43	17	11	12
Albuminuria, %				
Normoalbuminuria	44	60	73	75
Micro- or macroalbuminuria	56	40	27	25

Neuen B et.al. Circulation. 2018 Jun 25. pii: CIRCULATIONAHA.118.035901.

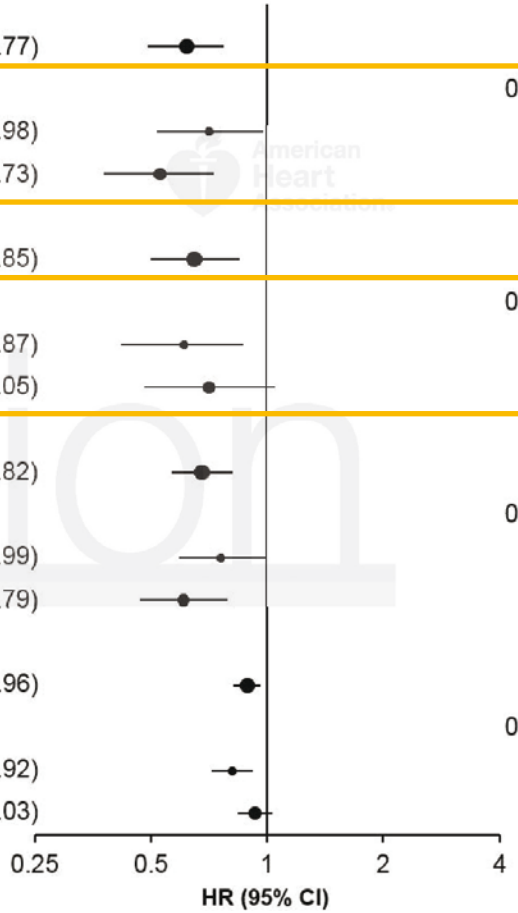
CANVAS by baseline eGFR



Neuen B et.al. Circulation. 2018 Jun 25. pii: CIRCULATIONAHA.118.035901.

EMPAREG by baseline eGFR

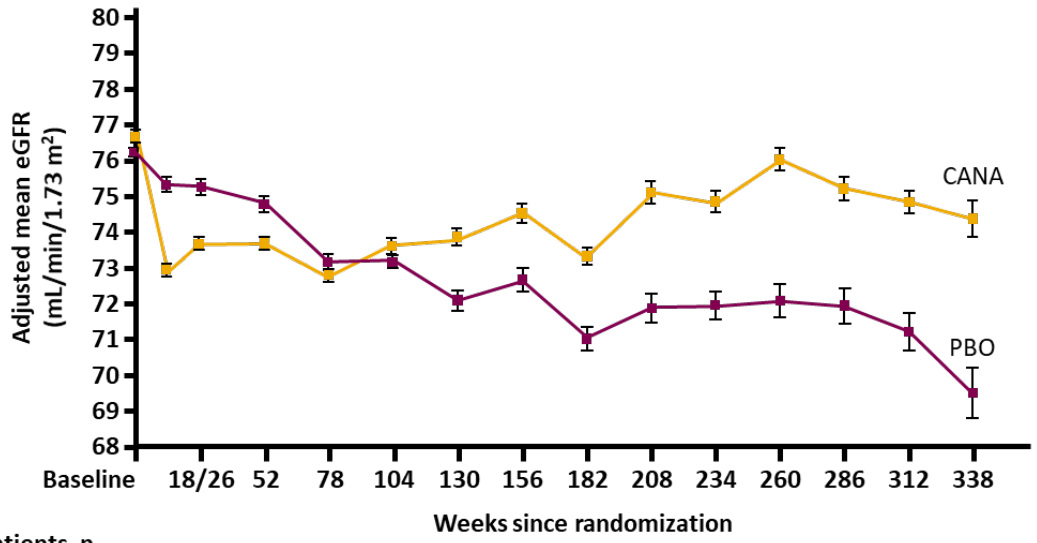
	Empagliflozin		Placebo			Interaction p-value
	n with event/N (%)	Rate/ 1000 pt-yr	n with event/N (%)	Rate/ 1000 pt-yr	HR (95% CI)	
Cardiovascular death						
All patients	172/4687 (3.7)	12.4	137/2333 (5.9)	20.2	0.62 (0.49, 0.77)	
Prevalent kidney disease*						0.1926
Yes	94/1498 (6.3)	21.4	65/752 (8.6)	30.1	0.71 (0.52, 0.98)	
No	77/3149 (2.4)	8.3	72/1569 (4.6)	15.7	0.53 (0.38, 0.73)	
Hospitalization for heart failure						
All patients	126/4687 (2.7)	9.4	95/2333 (4.1)	14.5	0.65 (0.50, 0.85)	
Prevalent kidney disease*						0.5780
Yes	66/1498 (4.4)	15.5	53/752 (7.0)	25.9	0.61 (0.42, 0.87)	
No	60/3149 (1.9)	6.6	42/1569 (2.7)	9.4	0.71 (0.48, 1.05)	
All-cause mortality						
All patients	269/4687 (5.7)	19.4	194/2333 (8.3)	28.6	0.68 (0.57, 0.82)	
Prevalent kidney disease*						0.2242
Yes	143/1498 (9.5)	32.5	92/752 (12.2)	42.5	0.76 (0.59, 0.99)	
No	125/3149 (4.0)	13.4	102/1569 (6.5)	22.2	0.61 (0.47, 0.79)	
All-cause hospitalization						
All patients	1725/4687 (36.8)	161.9	925/2333 (39.6)	183.3	0.89 (0.82, 0.96)	
Prevalent kidney disease*						0.1234
Yes	663/1498 (44.3)	208.4	375/752 (49.9)	258.9	0.81 (0.72, 0.92)	
No	1046/3149 (33.2)	141.8	549/1569 (35.0)	154.1	0.93 (0.84, 1.03)	



Wanner C. et.al. Circulation. 2018 Jan 9;137(2):119-12

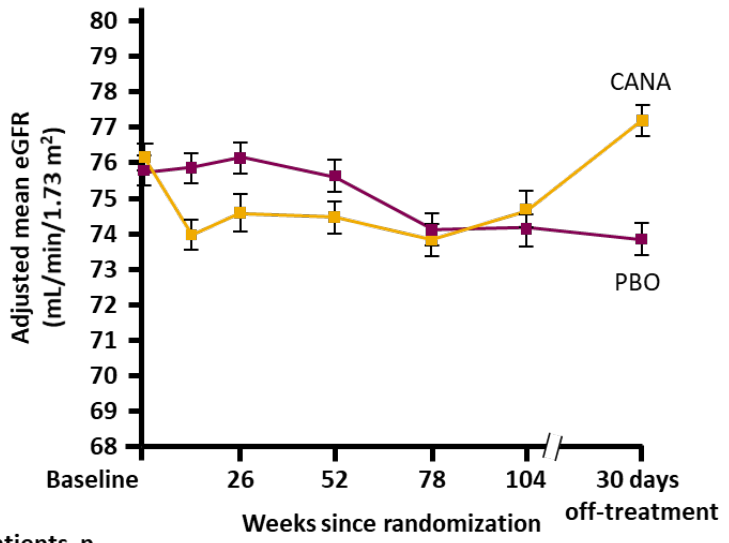
CANVAS: eGFR decline over time

CANVAS



Patients, n														
PBO	4276	4038	3967	3538	3212	1740	1030	881	899	785	809	726	694	243
CANA	5711	5355	5212	4867	4570	2964	2230	1961	2039	1795	1895	1695	1653	548

CANVAS-R

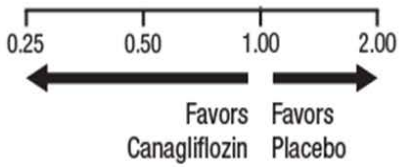


Patients, n						
PBO	2859	2728	2649	2440	2124	2485
CANA	2868	2752	2675	2512	2206	2518

Perkovic et.al. Lancet Diabetes Endocrinol. 2018 Sep;6(9):691-704

CANVAS RENAL RESULTS

	Number of patients	Canaglifozin patients per 1000 patient-years	Placebo patients per 1000 patient-years	Hazard ratio (95% CI)
New onset microalbuminuria	1935	96.7	127.3	0.80 (0.73–0.87)
New onset macroalbuminuria	636	15.1	27.6	0.58 (0.50–0.68)
dScr,[a] ESKD,[b] or renal death[c]	73	1.5	2.8	0.53 (0.33–0.84)
dSCr,[a] ESKD,[b] renal death,[c] or new onset macroalbuminuria	698	15.1	27.4	0.58 (0.50–0.67)
dSCr,[a] ESKD,[b] or renal or CV death[c]	518	13.2	15.8	0.82 (0.68–0.97)
40% reduction in eGFR,[a] ESKD, or renal death[c]	249	5.5	9.0	0.60 (0.47–0.77)
40% reduction in eGFR,[a] ESKD,[b] renal death,[c] or new onset macroalbuminuria	847	18.6	33.3	0.57 (0.50–0.66)
40% reduction in eGFR,[a] ESKD,[b] or renal or CV death[c]	679	16.9	21.6	0.77 (0.66–0.89)
40% eGFR reduction	239	5.3	8.7	0.60 (0.47–0.78)
dSCr	60	1.2	2.4	0.50 (0.30–0.84)
ESKD	18	0.4	0.6	0.77 (0.30–1.97)
ESKD or renal death[b]	21	0.4	0.8	0.56 (0.23–1.32)



Perkovic et.al. Lancet Diabetes Endocrinol. 2018 Sep;6(9):691-704

CREDENCE stopped early for efficacy

Phase 3 CREDENCE Renal Outcomes Trial of INVOKANA® (canagliflozin) is Being Stopped Early for Positive Efficacy Findings

Jul 16, 2018
United States

- INVOKANA® has the potential to be the first new therapy in more than 15 years for slowing the progression of chronic kidney disease in patients with type 2 diabetes

- Worldwide, 160 million patients with type 2 diabetes are at risk for developing chronic kidney disease[i]

- CREDENCE assessed INVOKANA® for renal protection by evaluating the risk reduction of the composite endpoint of time to dialysis or kidney transplantation, doubling of serum creatinine, and renal or cardiovascular death, when used in addition to standard of care

RARITAN, N.J., July 16, 2018 -- The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that the Phase 3 CREDENCE (**C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation) clinical trial, evaluating the efficacy and safety of INVOKANA® (canagliflozin) versus placebo when used in addition to standard of care for patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), is being stopped early based on the achievement of pre-specified efficacy criteria.

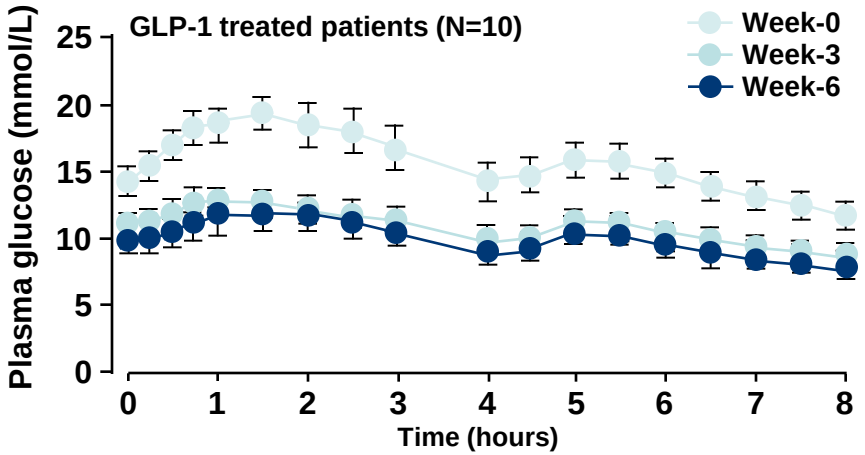
The decision is based on a recommendation from the study's Independent Data Monitoring Committee (IDMC) that met to review the data during a planned interim analysis. This recommendation was based on demonstration of efficacy, as the trial had achieved pre-specified criteria for the primary composite endpoint of end-stage kidney disease (time to dialysis or kidney transplantation), doubling of serum creatinine, and renal or cardiovascular (CV) death, when used in addition to standard of care.

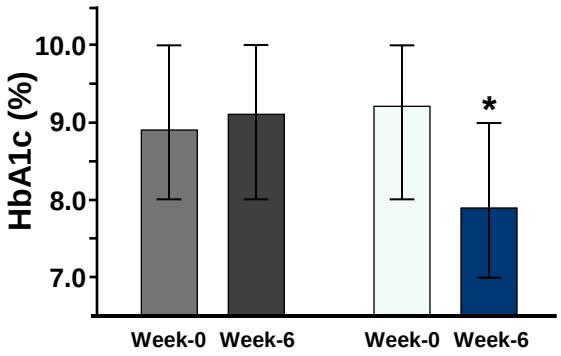
Janssen, Johnson & Johnson Press Release Jul. 16, 2018

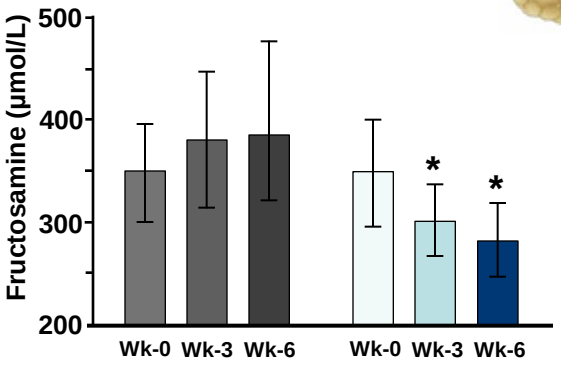
What's new?

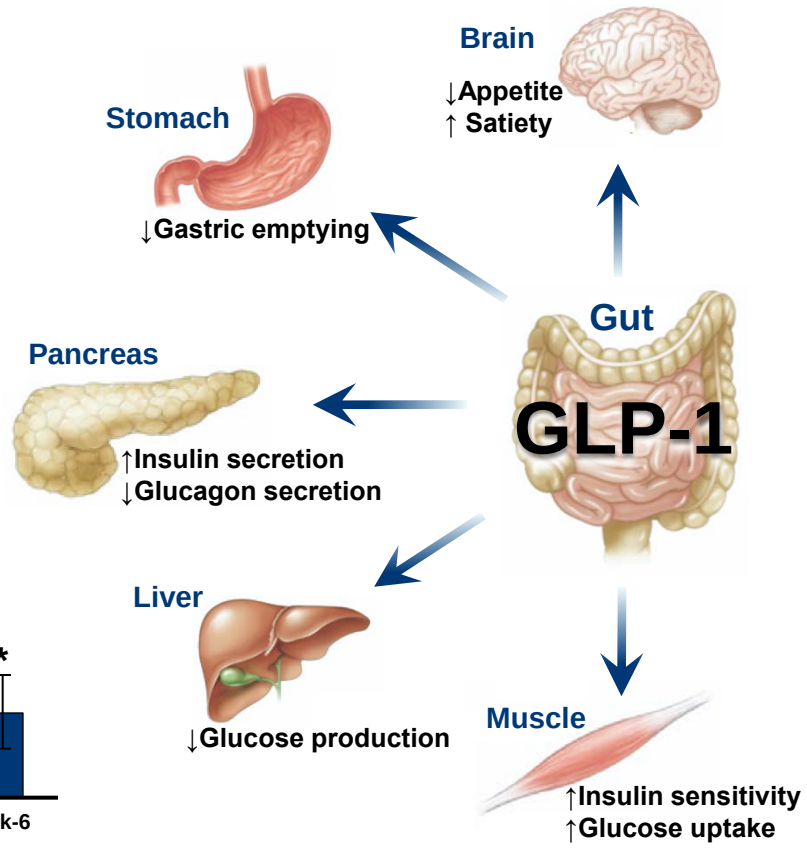
- SGLT2 inhibitors are promising agents to slow progression of DKD and to reduce the risks of cardiovascular events
- Hba1c lowering effect attenuated in people with DKD
- Cardio-renal benefits are independent of renal function
- CREDENCE trial will likely be the first trial in 15 years to deliver a new drug for patients with DKD
- Ongoing trials, like DAPA-CKD, test the effects of SGLT2 inhibitors in diabetic *as well as* non-diabetic CKD

Native GLP-1 infusion in type 2 diabetes patients improves glycemic control through various mechanisms



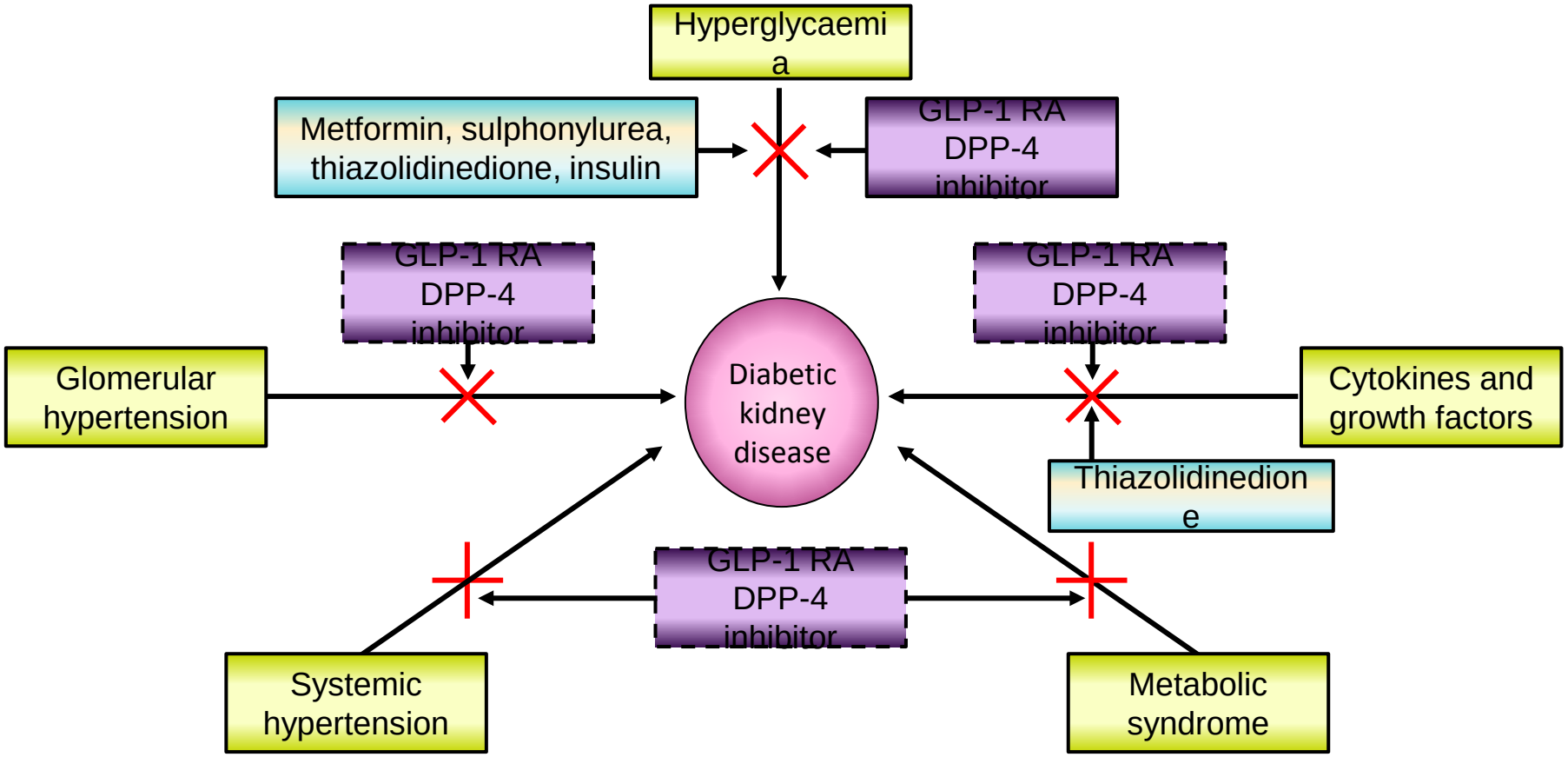






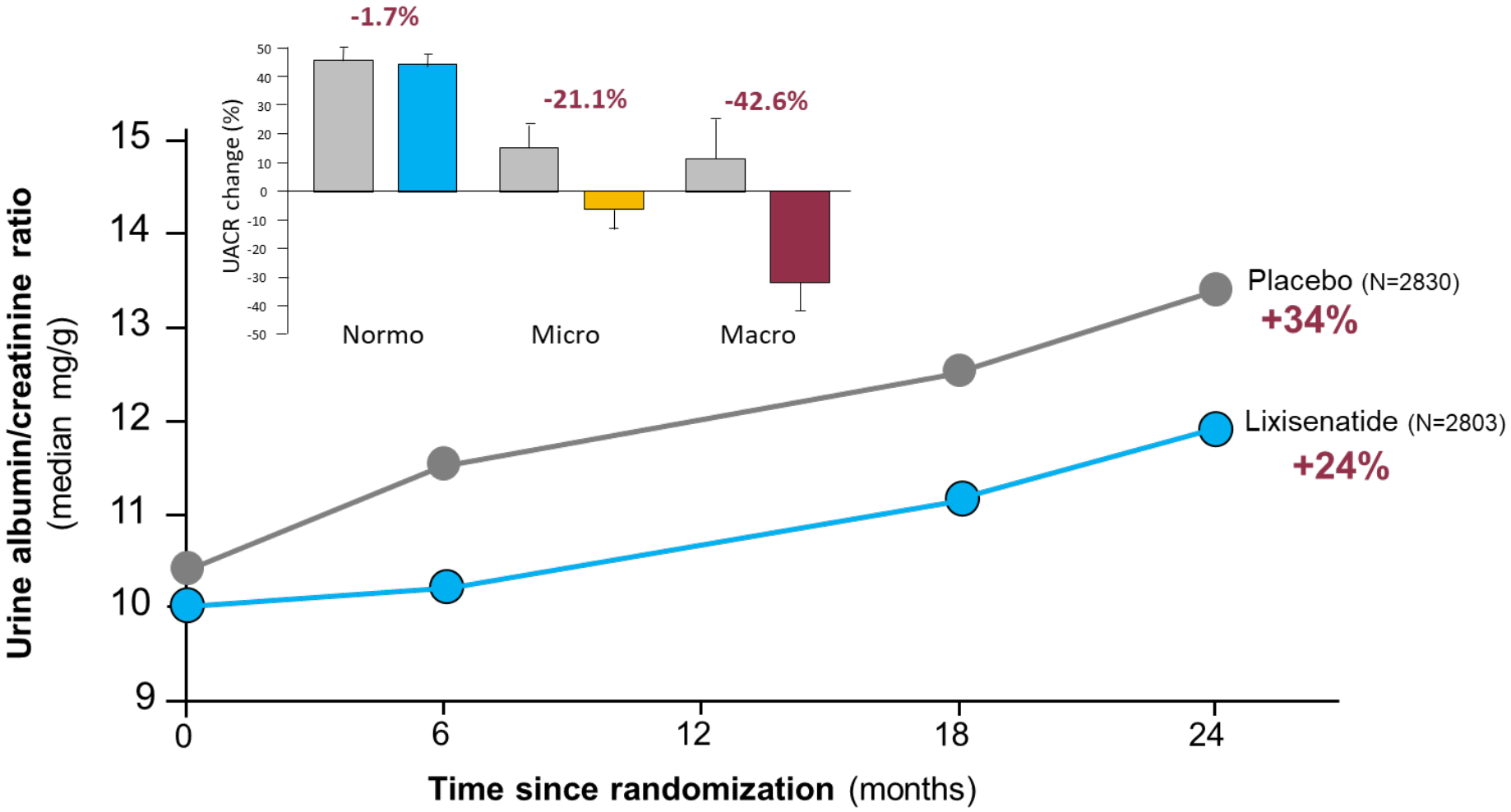
Zander M. Lancet 2002;359(9309):824-30.

Incretins may protect the kidney via multiple pathways



Muskiet et.al. Nature Reviews Nephrology 2017; 13(10):605-628

ELIXA: Effect of lixisenatide on albuminuria



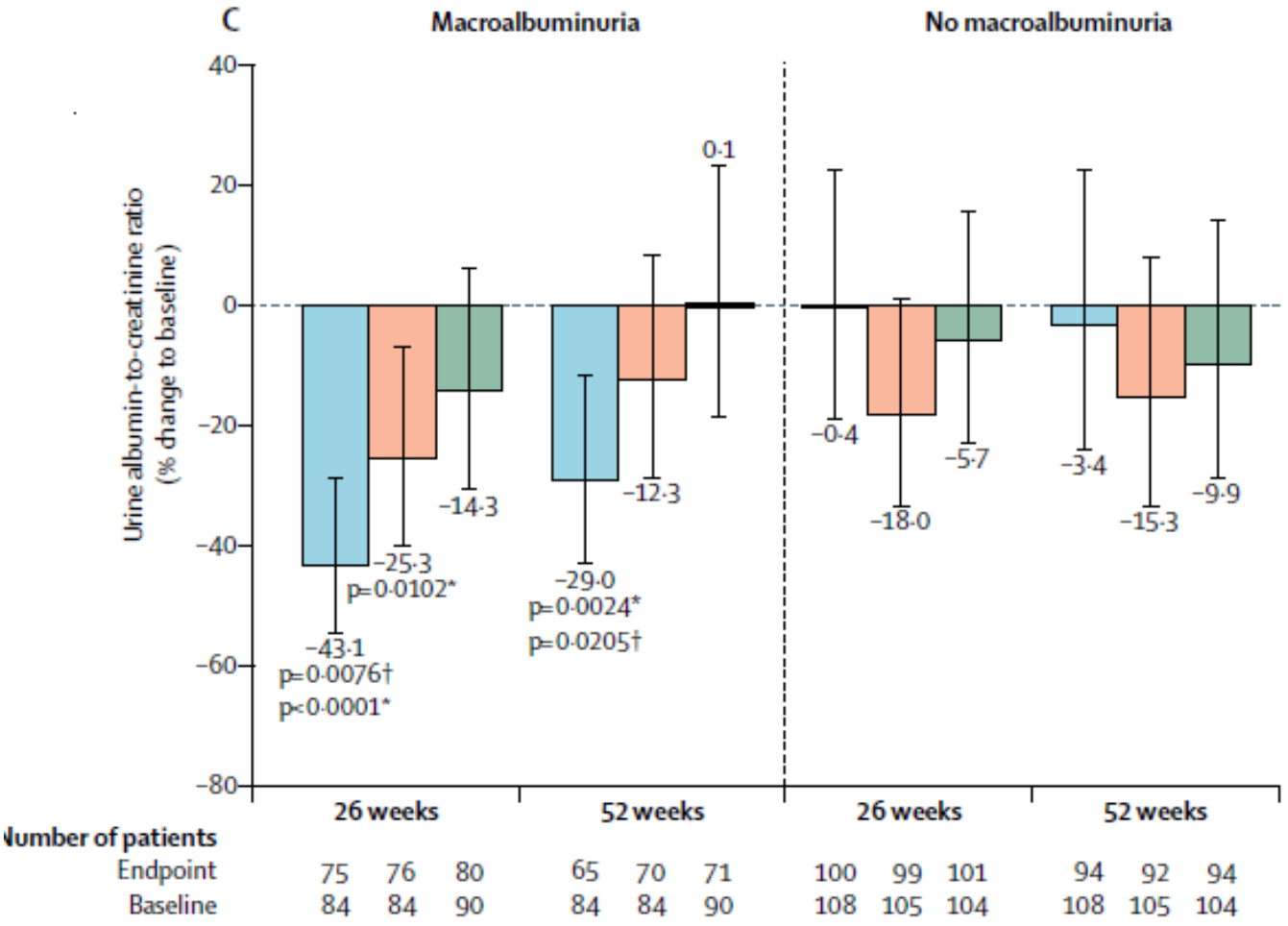
Muskiet M et.al. Lancet Diabetes Endocrinol. 2018 Sep;6(9):674-676

AWARD-7: Effects of dulaglutide in patients with diabetic kidney disease

	DU 1.5 mg (N=192)	DU 0.75 mg (N=190)	Glargine (N=194)
Duration of CKD stage ≥3, years	4.2 ± 5.6	4.0 ± 4.9	3.5 ± 4.0
eGFR, mL/min/1.73m^2	38.0 ± 13.3	38.4 ± 12.3	38.5 ± 13.0
60 ≤ Baseline eGFR <90	9 (4.7)	7 (3.7)	14 (7.2)
45 ≤ Baseline eGFR <60	53 (27.6)	53 (27.9)	51 (26.3)
30 ≤ Baseline eGFR <45	73 (38.0)	75 (39.5)	67 (34.5)
15 ≤ Baseline eGFR <30	55 (28.6)	55 (28.9)	61 (31.4)
Baseline eGFR <15	2 (1.0)	0 (0.0)	1 (0.5)
UACR, mg/g, mean (median)	779 (214)	842 (234)	920 (196)
Normal albuminuria	34 (17.7)	44 (23.3)	48 (24.7)
Microalbuminuria	74 (38.5)	61 (32.3)	56 (28.9)
Macroalbuminuria	84 (43.8)	84 (44.4)	90 (46.4)

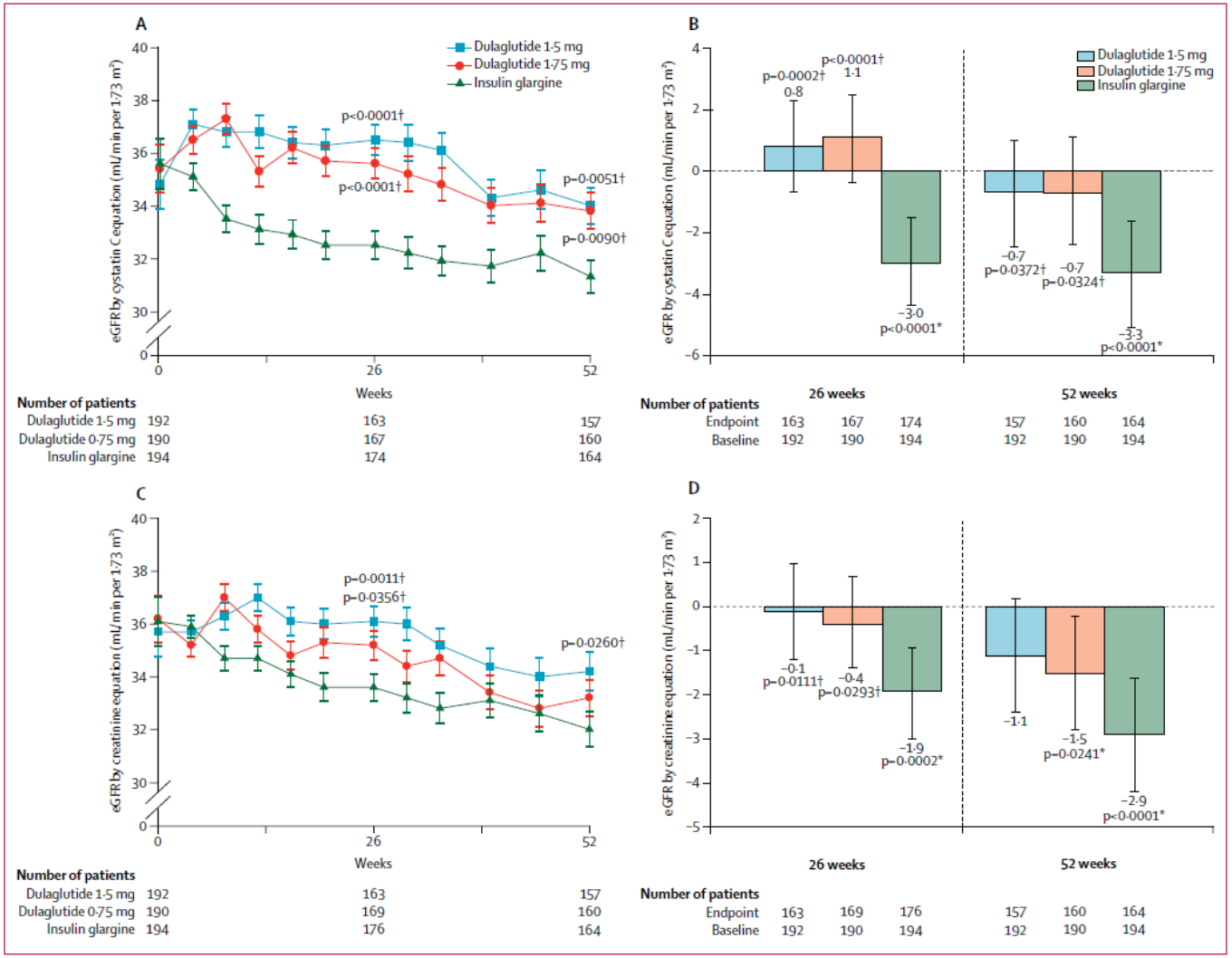
Tuttle et.al. Lancet Diabetes Endocrinol. 2018 Aug;6(8):605-617

AWARD-7: Effects of Dulaglutide on albuminuria



Tuttle et.al. Lancet Diabetes Endocrinol. 2018 Aug;6(8):605-617

AWARD-7: Effects of dulaglutide on eGFR in patients with diabetic kidney disease



Tuttle et.al. Lancet Diabetes Endocrinol. 2018 Aug;6(8):605-617

Question for the audience

- In view of the evidence, dependent on baseline eGFR and albuminuria status, which second-line therapy (after metformin) may be considered for a patient with T2D and albuminuria?

A. Insulin

B. SGLT2 inhibitor

C. GLP-1 receptor agonist

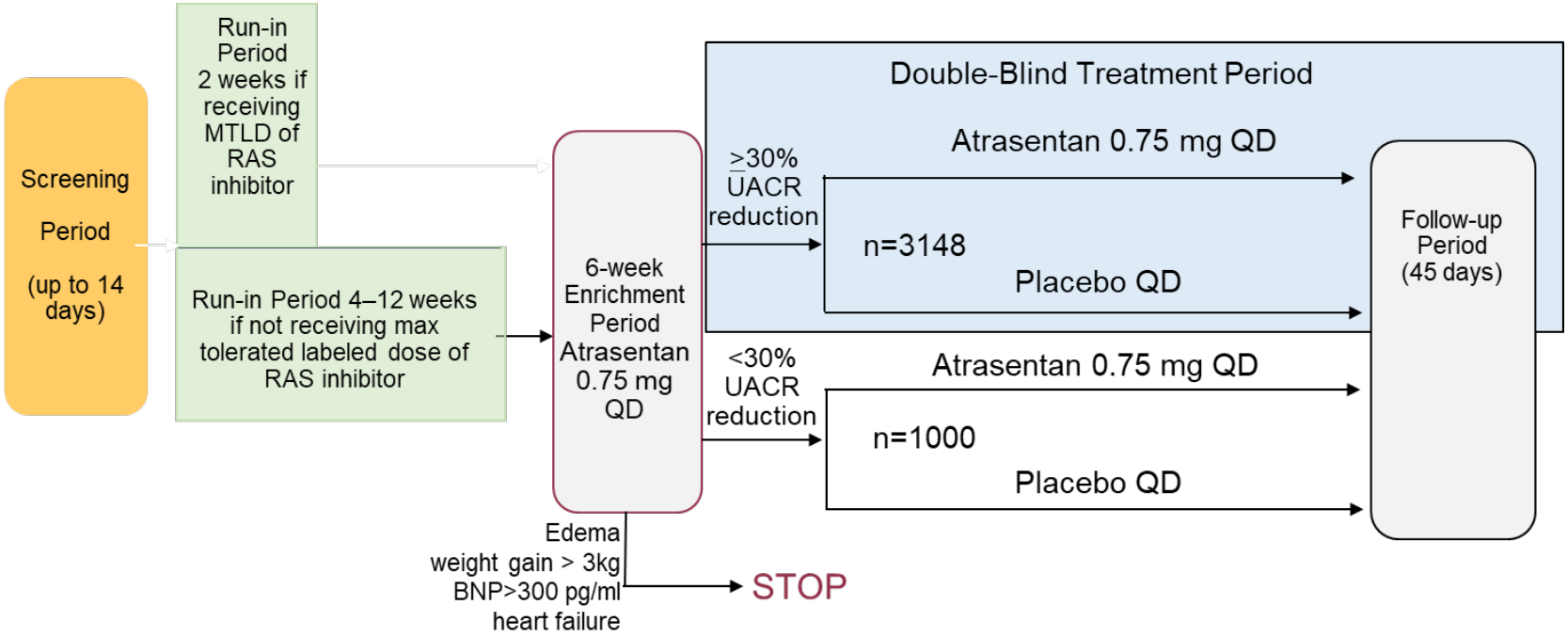
D. DPP-4 inhibitor

E. Sulfonylurea

What's new?

- GLP-1 analogues decrease albuminuria independent of HbA1c lowering effects
- GLP-1 analogues may slow progression of GFR decline
- Large outcome studies are lacking and therefore no definitive proof about efficacy and safety of these agents

SONAR: First response enrichment trial



- Primary endpoint
  Time to first occurrence of composite renal endpoint: doubling of serum creatinine or onset of ESRD (needing chronic dialysis or renal transplantation or renal death)
- Study completion
  425 distinct primary renal events have occurred (adjudicated) in the responder population

Lambers Heerspink et.al. Diabetes Obes Metab. 2018 Aug;20(8):1829-1835

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