Banting & Best Diabetes Centre
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Renal Implications of Diabetes Treatment

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Presenter Disclosure

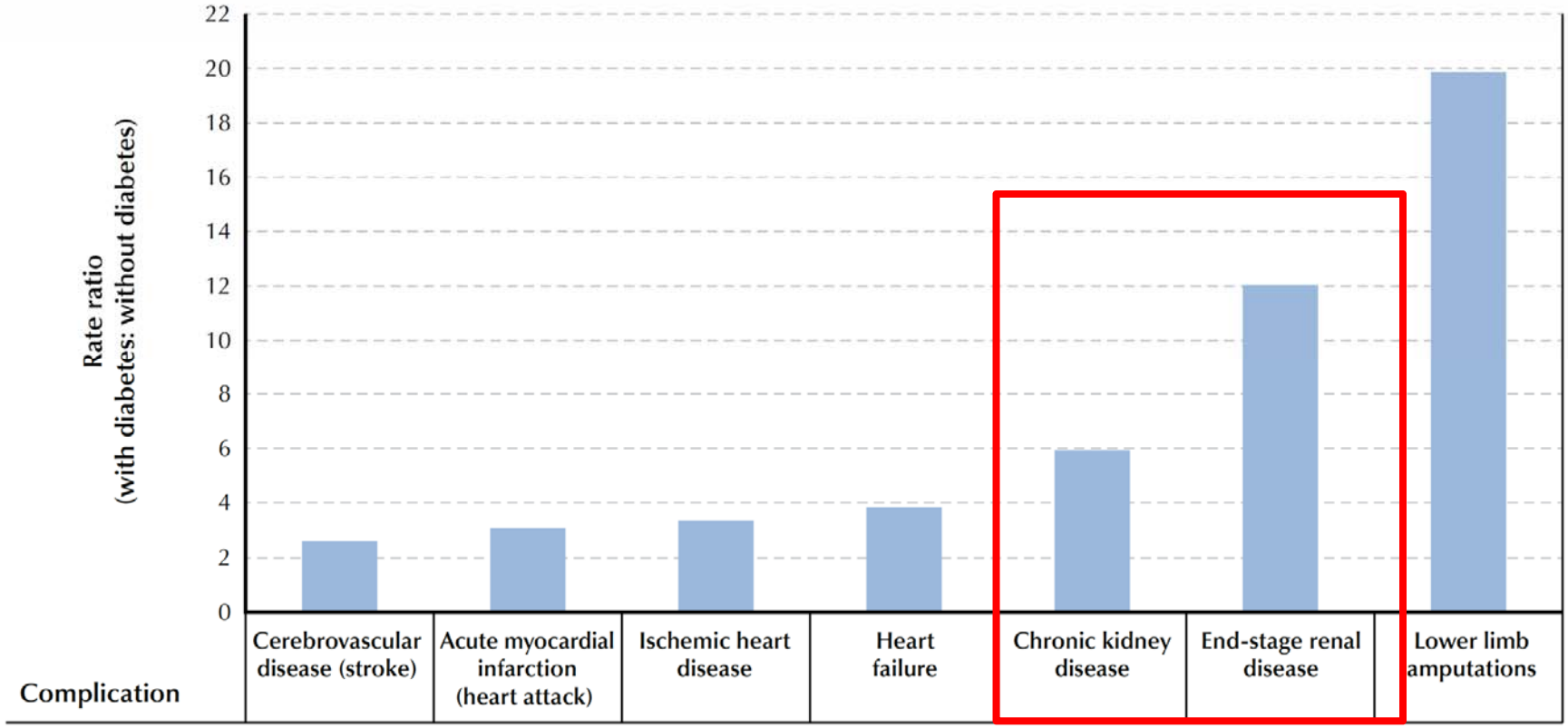
- **Grants/Research Support:** AstraZeneca, Boehringer Ingelheim, Merck, Servier
- **Speakers Bureau/Honoraria:** None
- **Consulting Fees:** AstraZeneca, Boehringer Ingelheim, Janssen, Merck, Servier
- **Other:** None

Objectives

- to discuss the incidence of ESRD in patients with diabetes and various therapuetic options
- Sodium glucose cotransport-2 inhibitors (SGLT2i): mode of action
- Renal effects:
  - Renal protective pathways
    - Hemodynamic (hyperfiltration)
  - Effects in patients with chronic kidney disease
- EMPA-REG Outcome
  - Mechanisms responsible for renal protection

Patients with DM 6-12X more likely to be hospitalized for CKD or End-stage renal disease

Figure 2-2. Prevalence rate ratios† of complications among hospitalized individuals‡ aged 20 years and older, by diabetes status, Canada, 2008/09



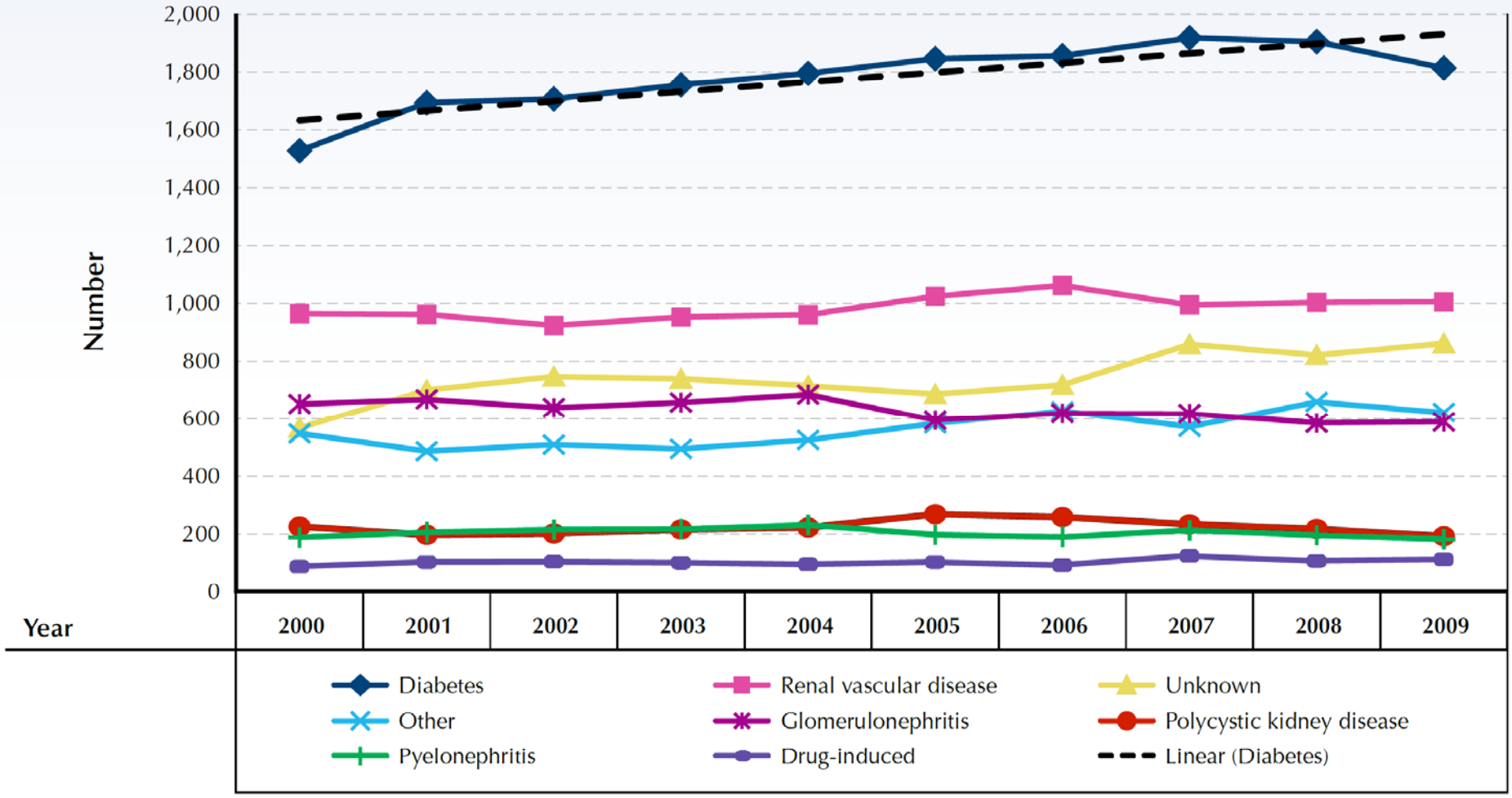
† Rate ratios based on rates age-standardized to the 1991 Canadian population.

‡ A person with diabetes hospitalized with more than one complication was counted once in each category, except for cases of acute myocardial infarction, where regardless of multiple counts in the acute myocardial infarction category, the individual was counted only once under the broader ischemic heart disease category.

Public Health Agency of Canada (August 2011); using 2008/09 data from the Canadian Chronic Disease Surveillance System (Public Health Agency of Canada).

Diabetes is #1 Cause of New Cases of ESRD

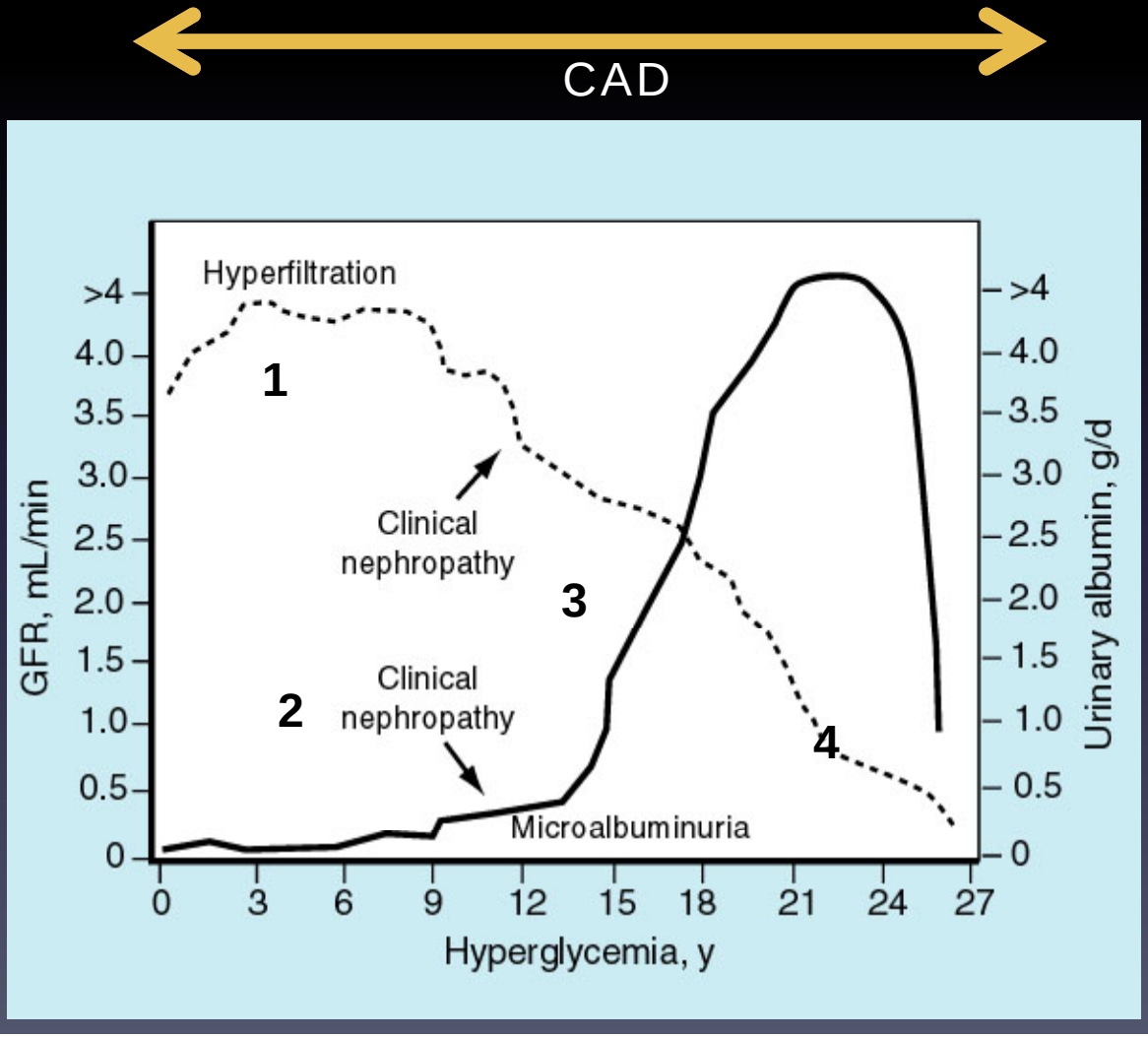
Figure 2-3. Number of incident cases of end-stage renal disease, by primary diagnosis, Canada, 2000 to 2009



Source: Public Health Agency of Canada (2011); adapted from Canadian Institute for Health Information. Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2000 to 2009. 2011. Ottawa.

Public Health Agency of Canada (August 2011); using 2008/09 data from the Canadian Chronic Disease Surveillance System (Public Health Agency of Canada).

Natural history of diabetic nephropathy Development of proteinuria and decline in GFR



1. Silent clinical phase
   Hyperfiltration
   Increased GFR

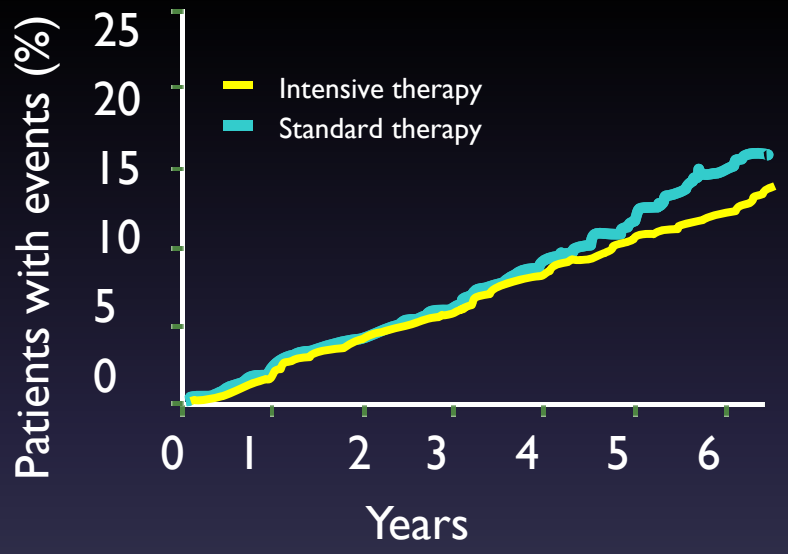
2. Microalbuminuria
   [20 - 200ug/d]

3. Clinical nephropathy
   [proteinuria > 0.5g/d]

4. Endstage renal failure

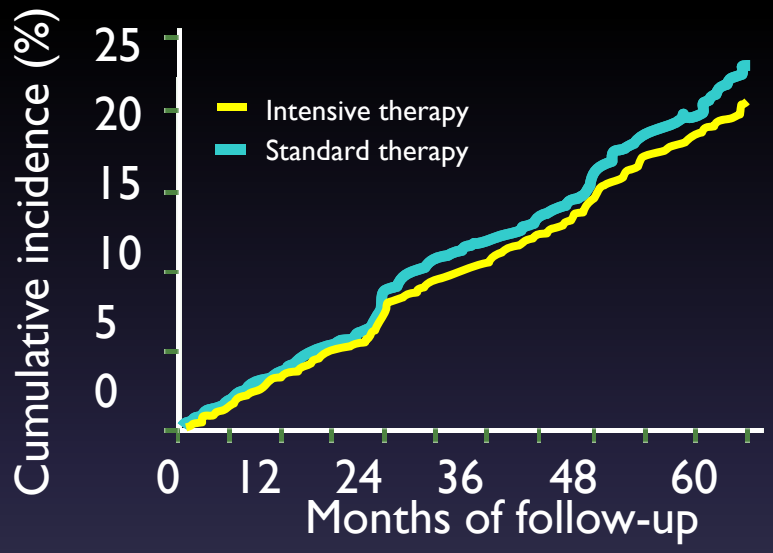
Trials Show No Reduction in CV Events with More Intensive Glycemic Control

ACCORD: Primary Outcome



Number at Risk							
Intensive	5128	4843	4390	2839	1337	475	448
Standard	5123	4827	4262	2702	1186	440	395

ADVANCE: Primary Outcome

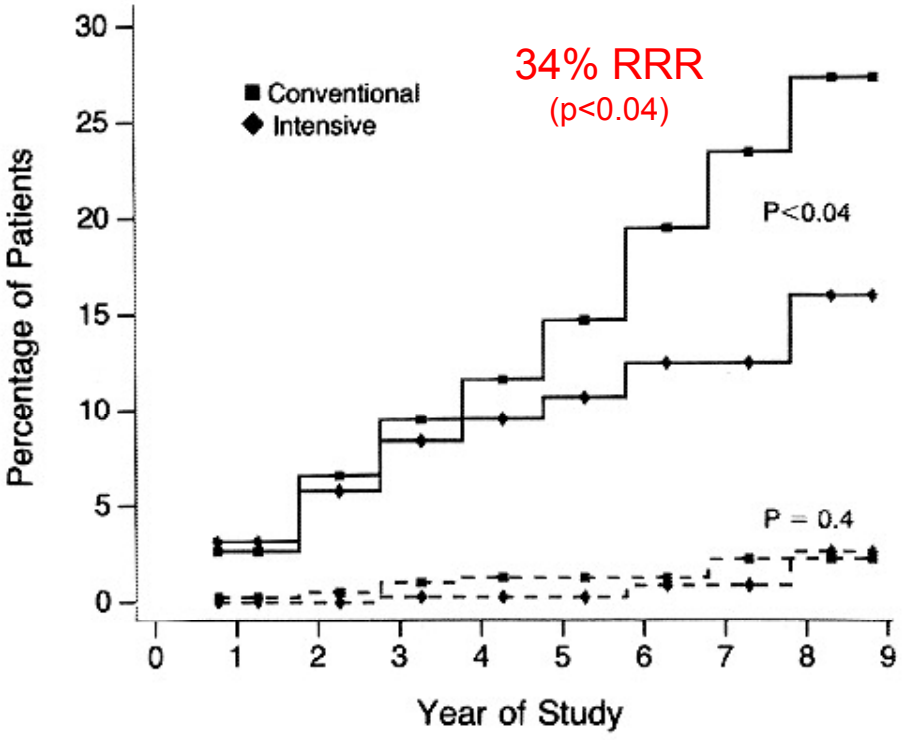


Number at Risk						
Intensive	5570	5369	5100	4867	4599	1883
Standard	5569	5342	5065	4808	4545	1921

[1]ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559.
[2]ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572.

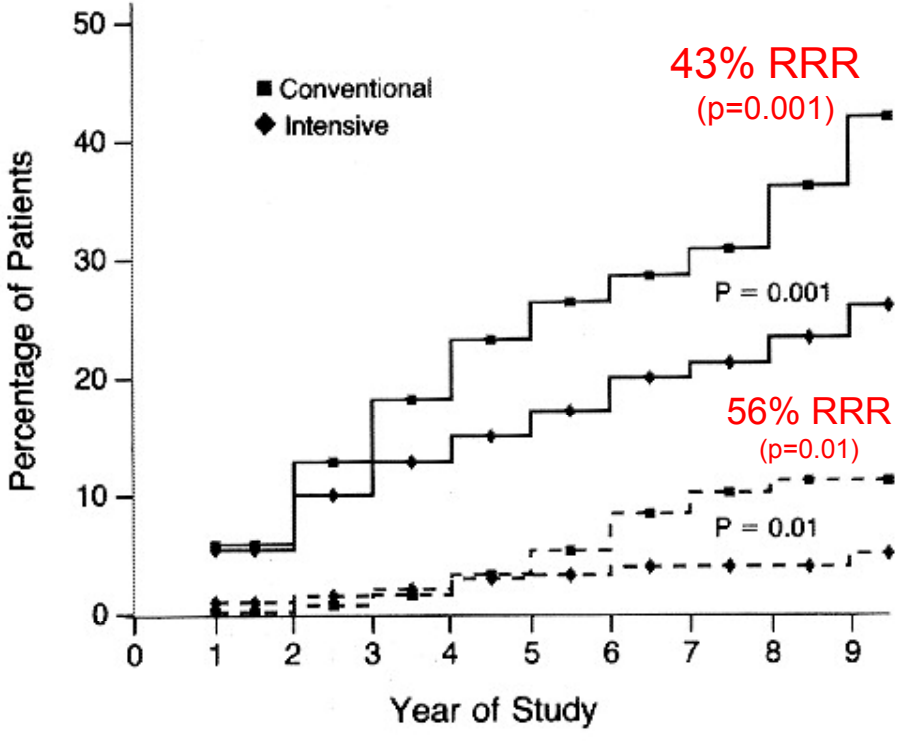
DCCT: Reduction in Albuminuria in T1DM

Primary Prevention



A

Secondary Intervention



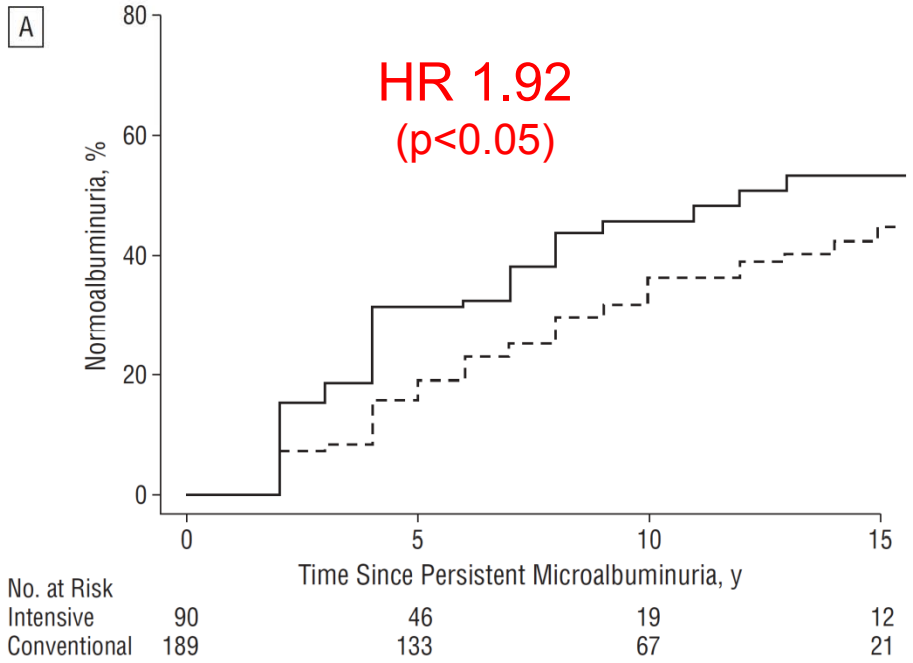
Solid line = risk of developing microalbuminuria
Dashed line = risk of developing macroalbuminuria

RRR = relative risk reduction
CI = confidence interval

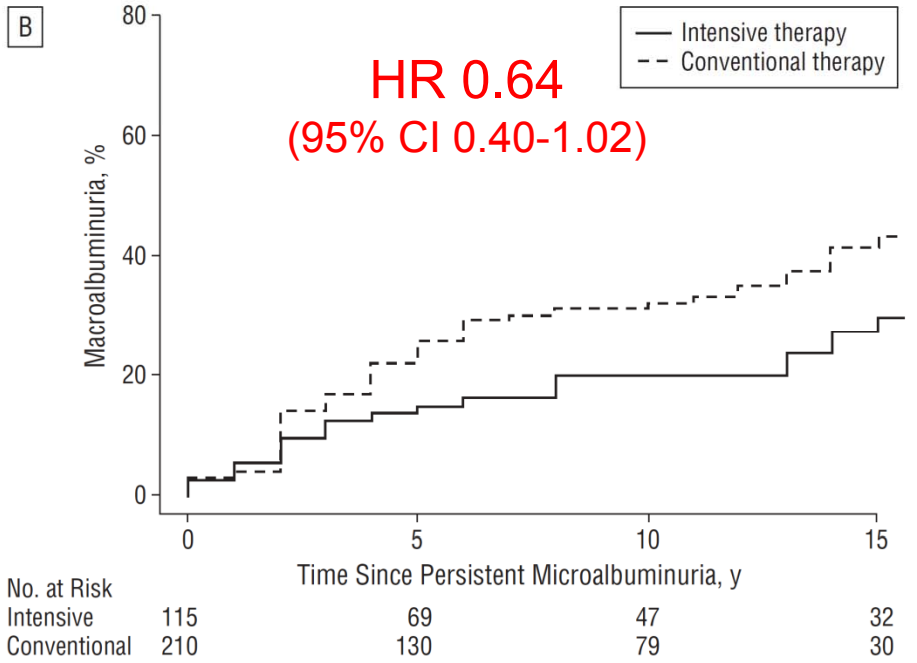
The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977-986.

EDIC: Continued Reduction in Albuminuria in T1DM

Return to normoalbuminuria



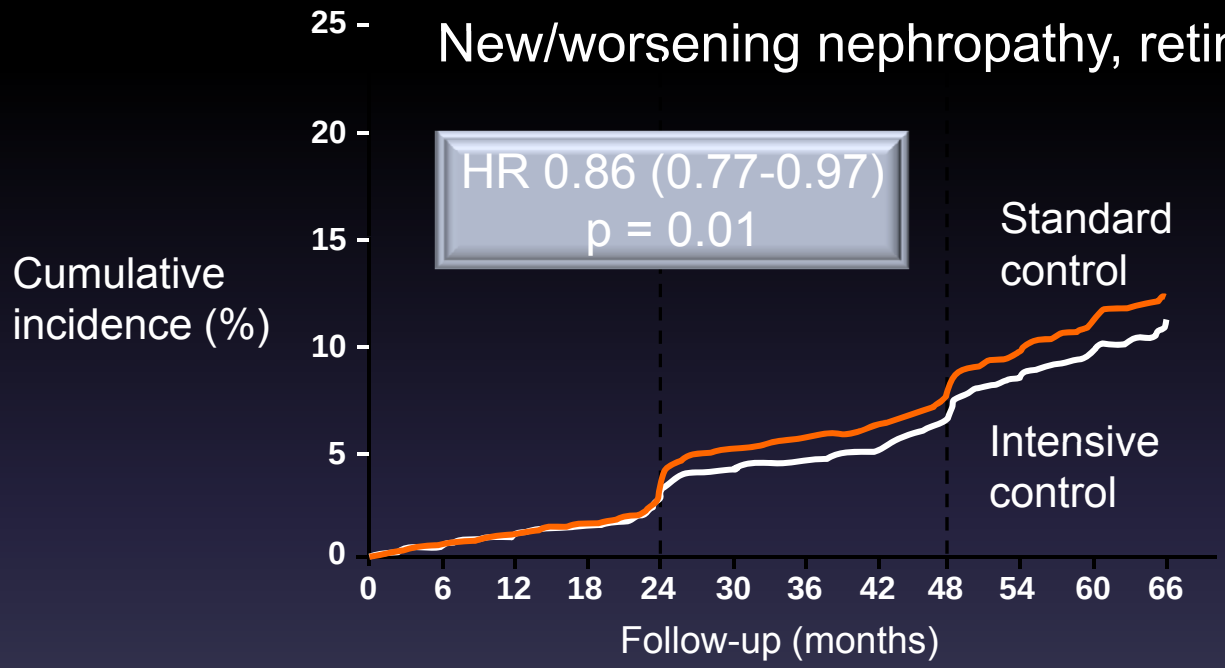
Macroalbuminuria



HR = hazard ratio
CI = confidence interval

deBoer IH et al. Arch Intern Med 2011;171(5):412-420.

ADVANCE: Primary Microvascular Outcomes

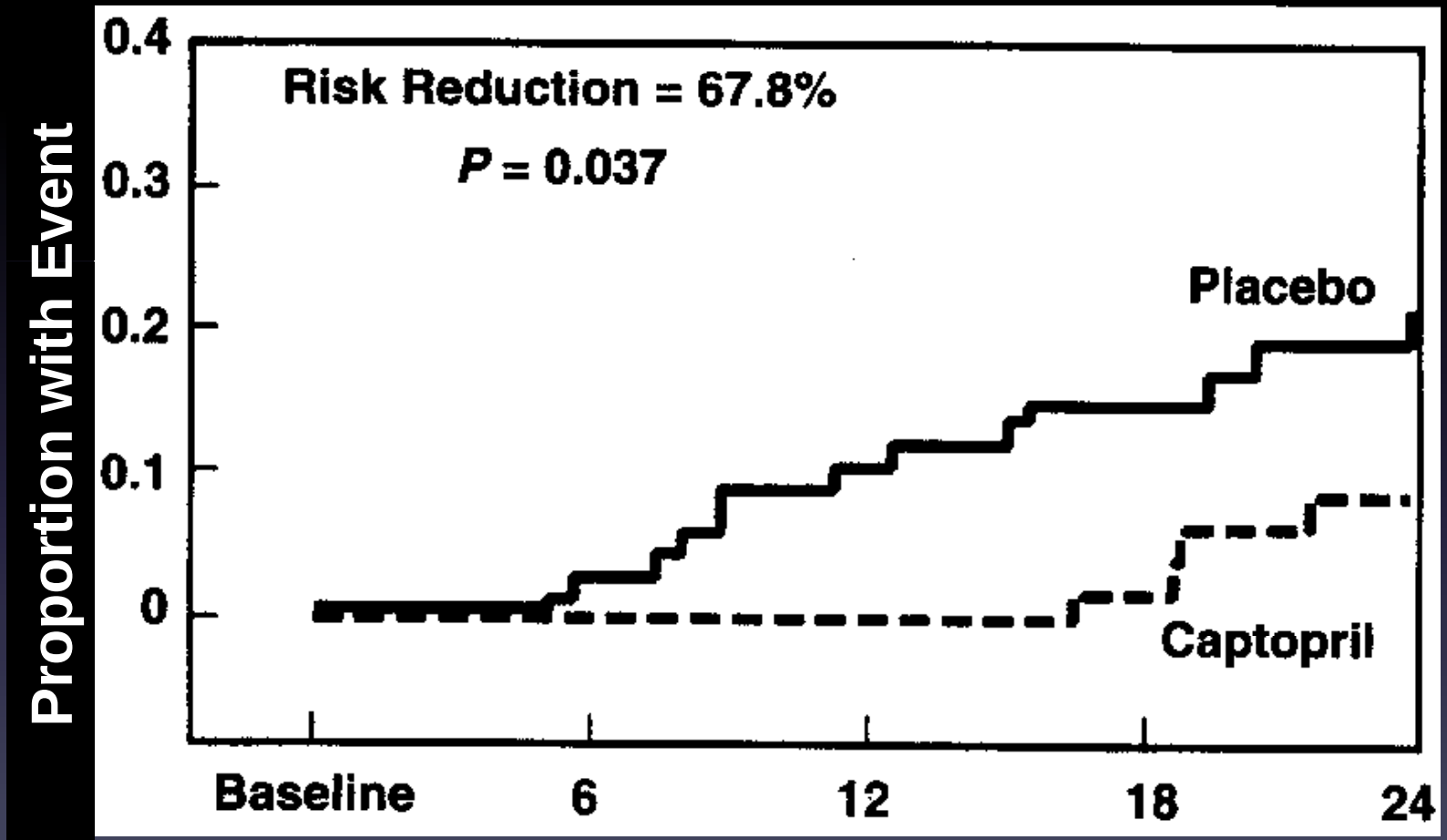


	Intensive	Standard	HR	p
Nephropathy/retinopathy (%)	9.4	10.9	0.86	0.01
Nephropathy (%)	4.1	5.2	0.79	0.006
Retinopathy (%)	6.0	6.3	0.95	NS

Adapted from:
ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560-72.

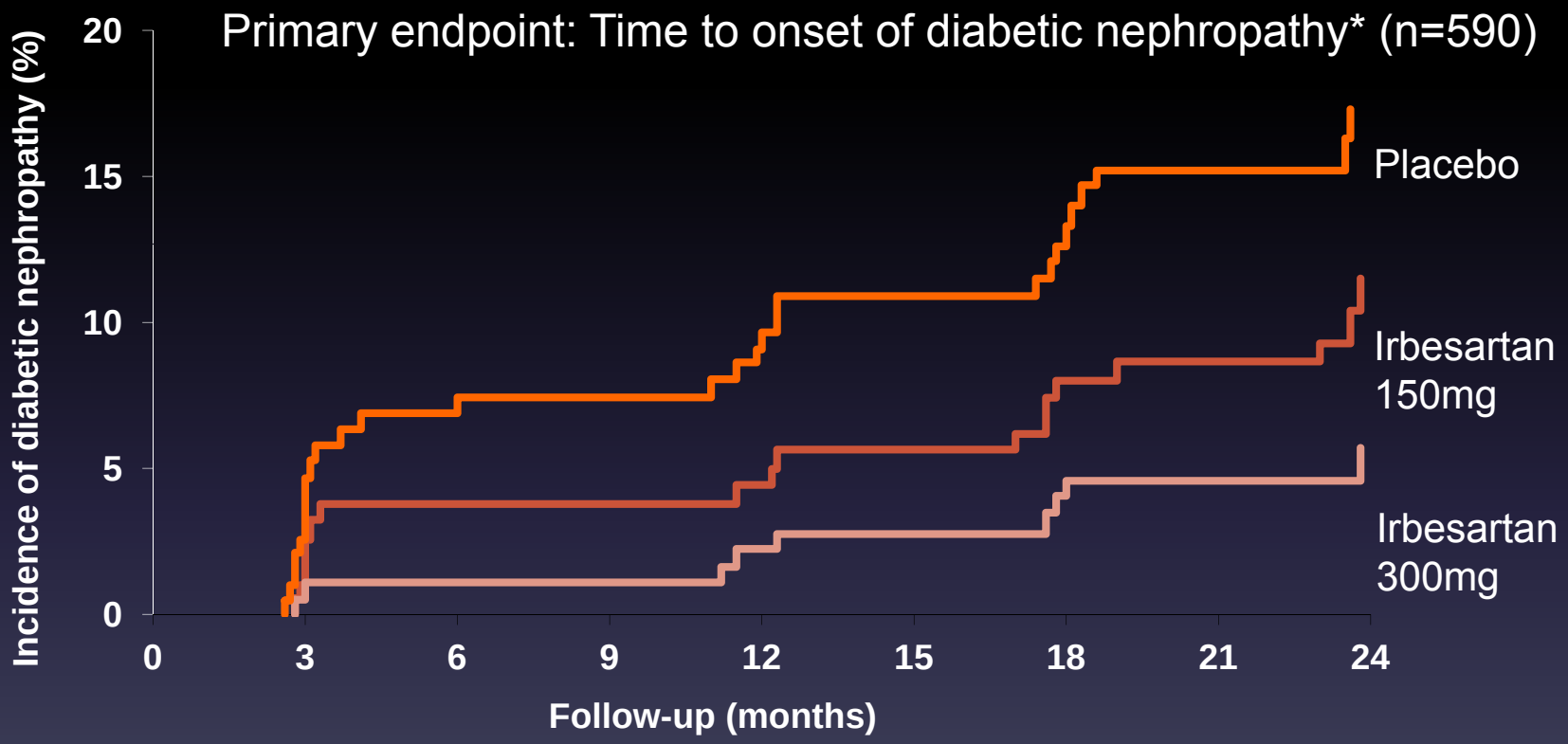
ADVANCE Collaborative Group. N Engl J Med 2008;358:24.

ACE-inhibitor in T1DM with MAU Reduces Progression to Clinical Proteinuria



Laffel LM et al. Am J Med 1995;99(5):497-504.

ARB in T2DM with MAU reduces progression

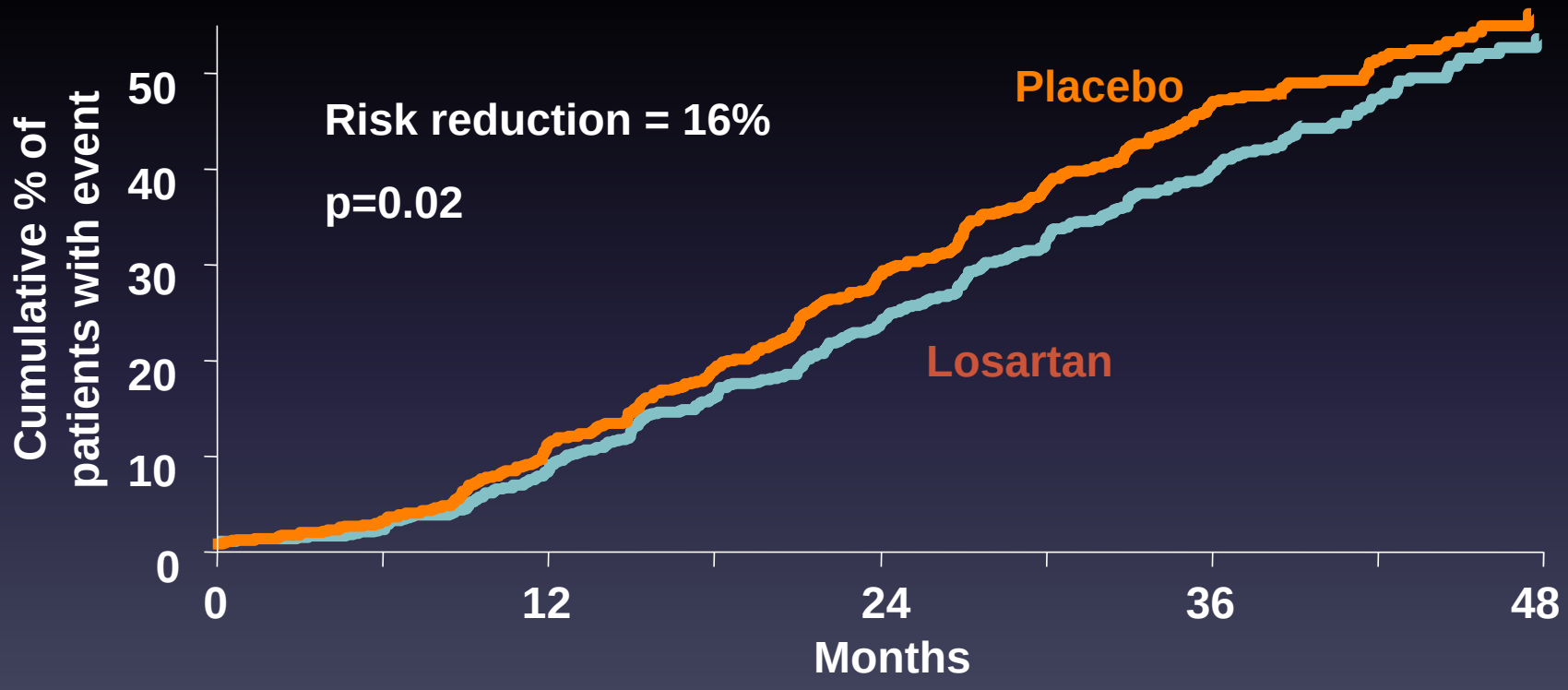


*defined by persistent albuminuria in overnight specimens,
with urinary albumin excretion rate <200 µg/min and ≥30% higher than baseline level

Parving et al. *N Engl J Med* 2001;345:870-8

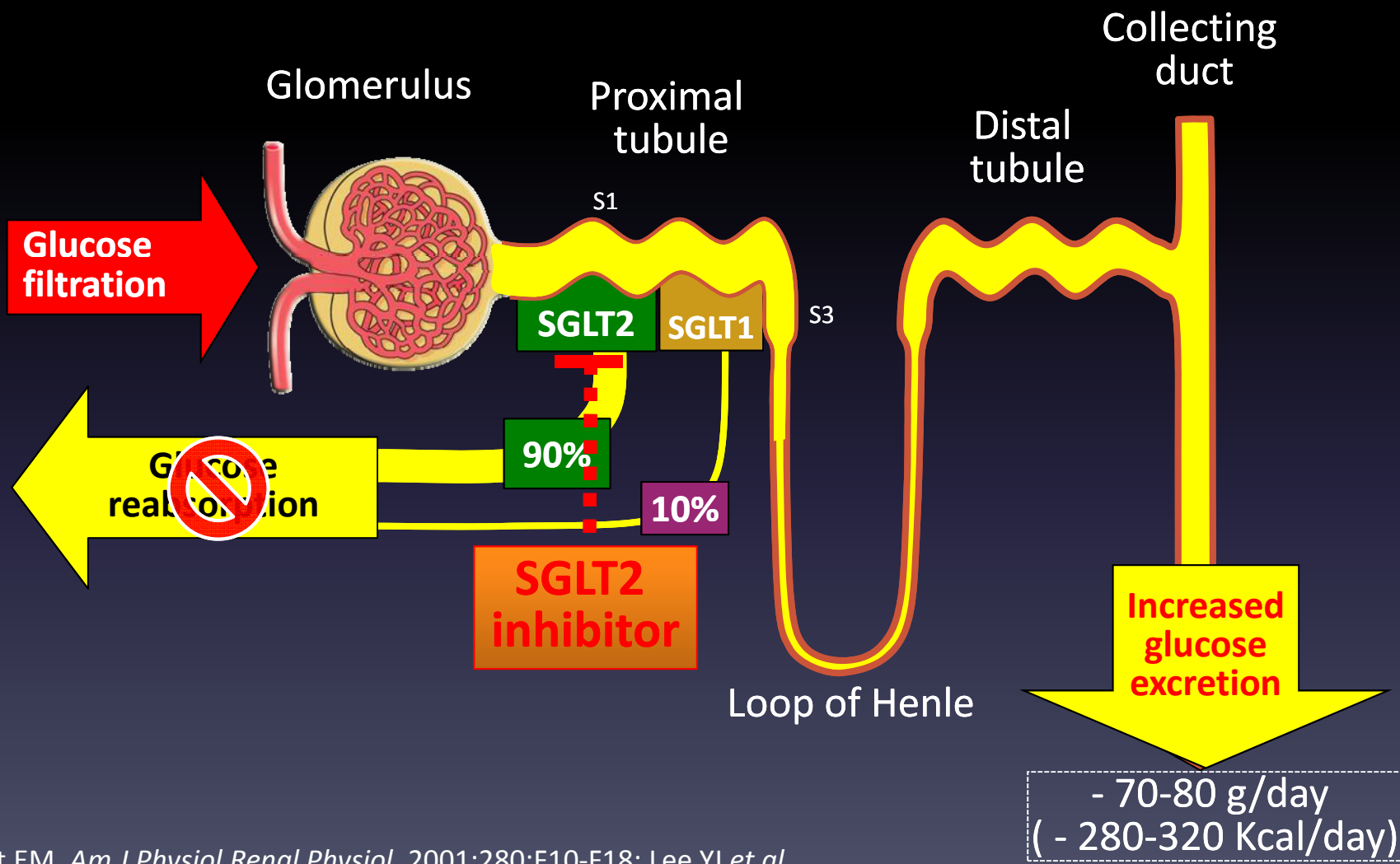
ARB in T2DM with Macroalbuminuria Reduces Renal Outcomes

Primary endpoint: Time to doubling of serum creatinine, ESRD, or death (n=1513)



Brenner et al. *N Engl J Med* 2001;345:861-9

SGLT2 Inhibition Reduces Renal Glucose Reabsorption



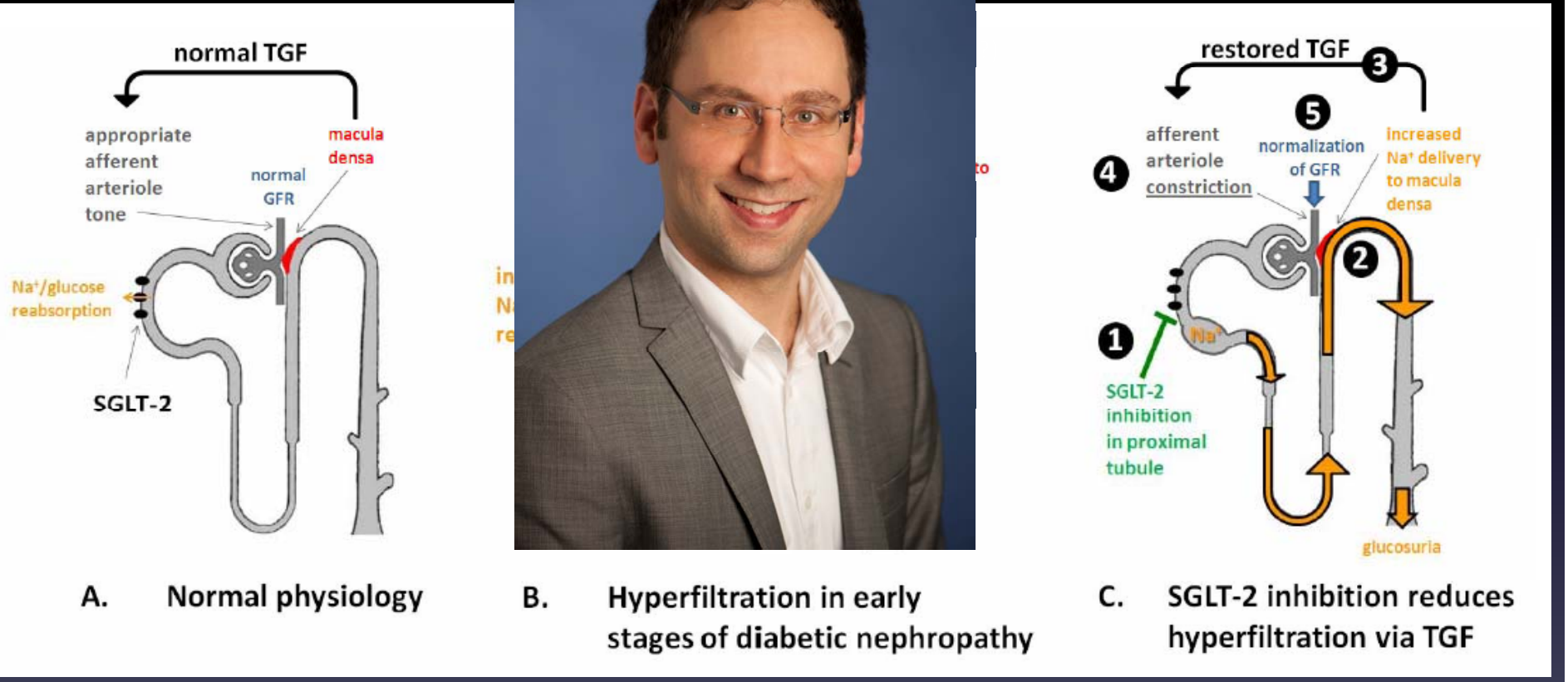
Wright EM. *Am J Physiol Renal Physiol.* 2001;280:F10-F18; Lee YJ *et al. Kidney Int Suppl.* 2007;106:S27-S35; Han S. *Diabetes.* 2008;57:1723-1729.

Renal Protection with SGLT2 Inhibition

Indirect effects	Direct effects
Improved glycemic control	Prevent hyperfiltration -↓intraglomerular pressure -↓proteinuria
↓Insulin levels	Prevent tubular hypertrophy, glomerular and TI injury
Improved insulin sensitivity	↓tubular toxicity of glucose -↓inflammation, ROS
↓Weight	
↓Blood pressure	
↓Uric acid levels	

Thomas et al. Ther Adv Endo Metab 2014;5:53-61
Skrtic//Cherney. Curr Op Nephrol Hypertens 2015;24:96-103
Lytvyn//Cherney. Am J Physiol-Renal Physiol 2015;308:F77-83

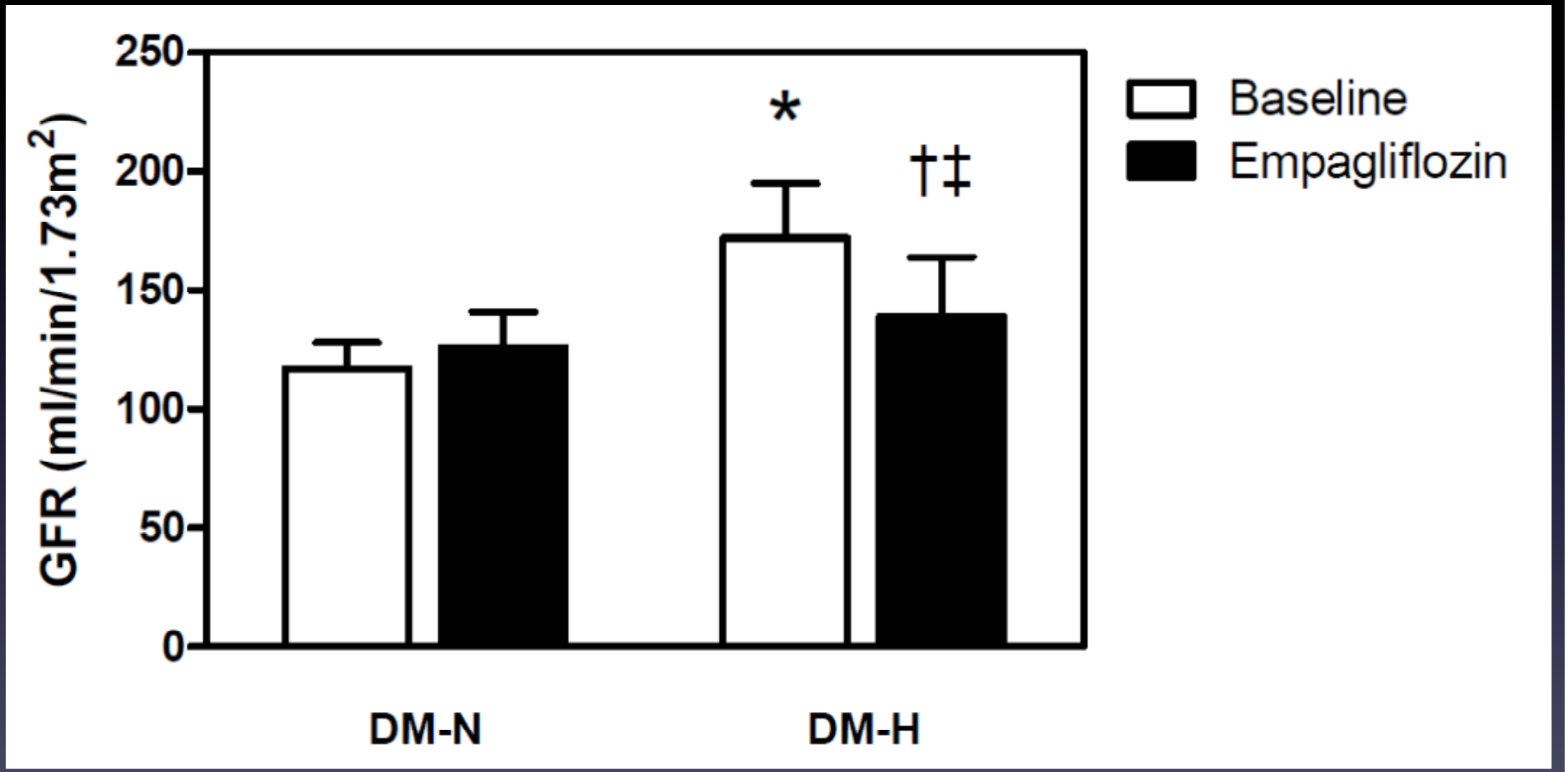
The "Tubular Hypothesis": Normal Physio iabetes



- SGLT2i ↓hyperfiltration in animals T1D, T2D

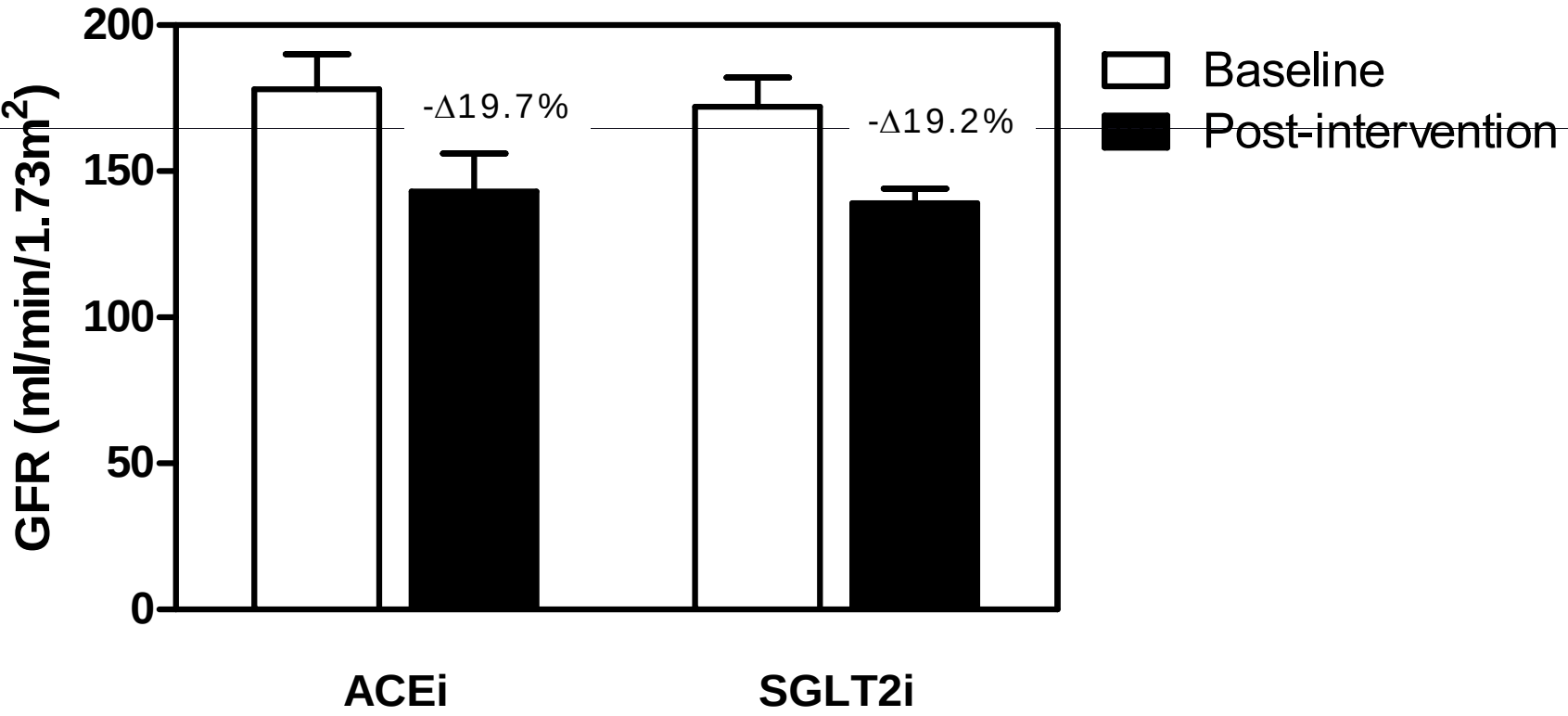
Cherney et al. Circulation 2014;129:587
Vallon et al. Nephron Physiol 2009;111:30-38

Primary endpoint: GFR at baseline, after 8 weeks - clamped euglycemia in T1DM



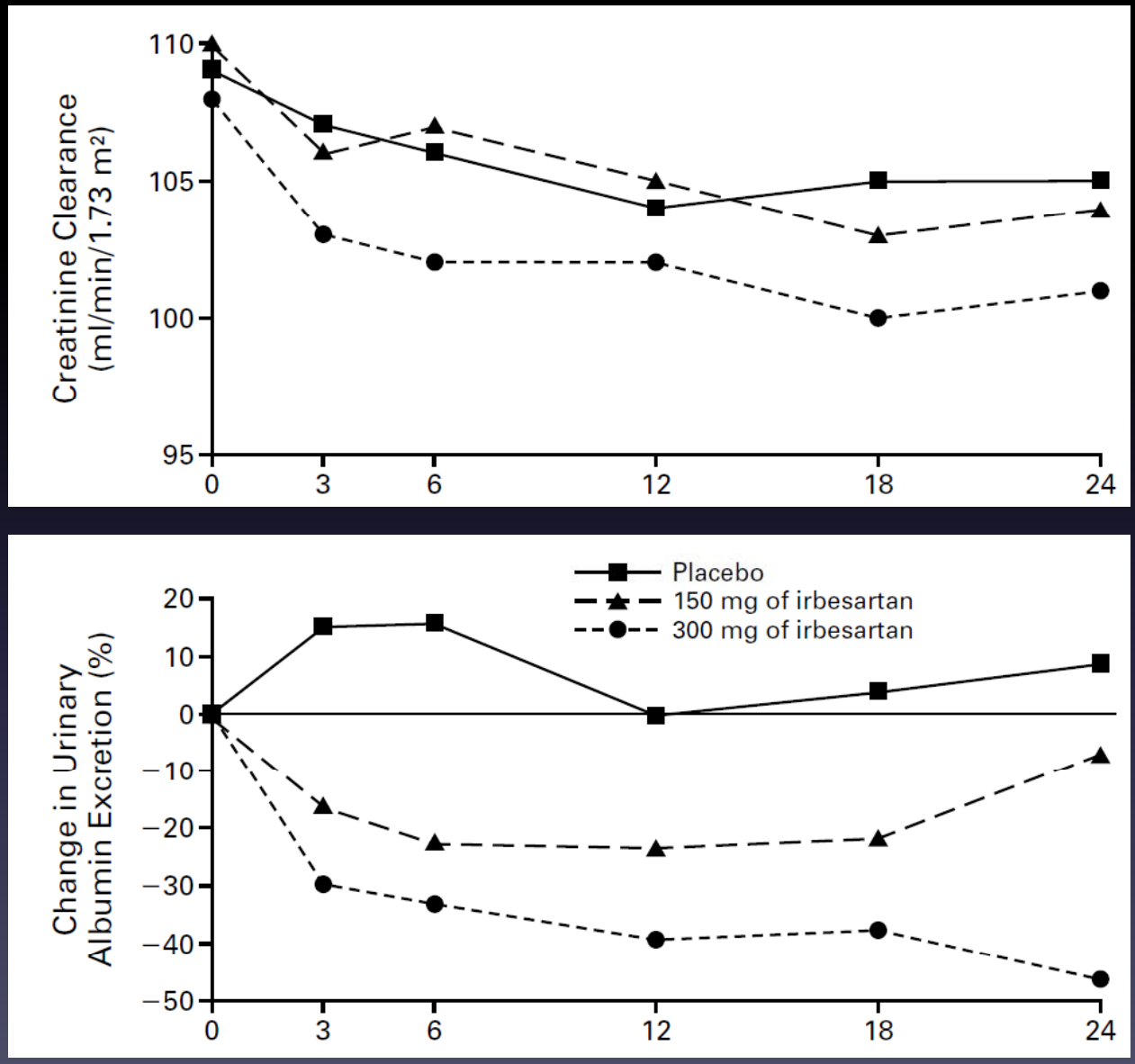
Cherney et al. Circulation 2014;129:587

How does this compare to existing renal protective therapies?



Sochett, Cherney, Miller et al. JASN, 2006
Cherney, Perkins et al. Circulation 2014;129:587

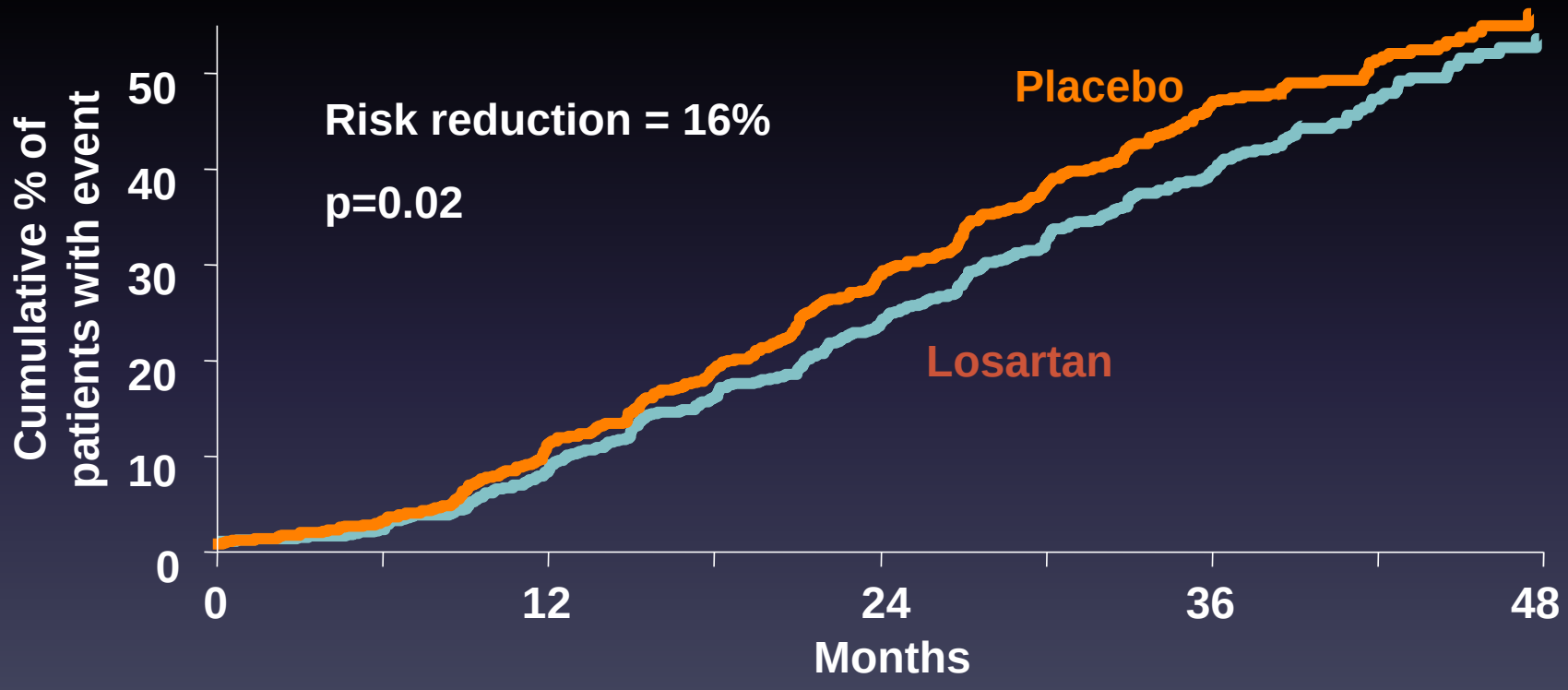
The effect of RAAS inhibition on eGFR



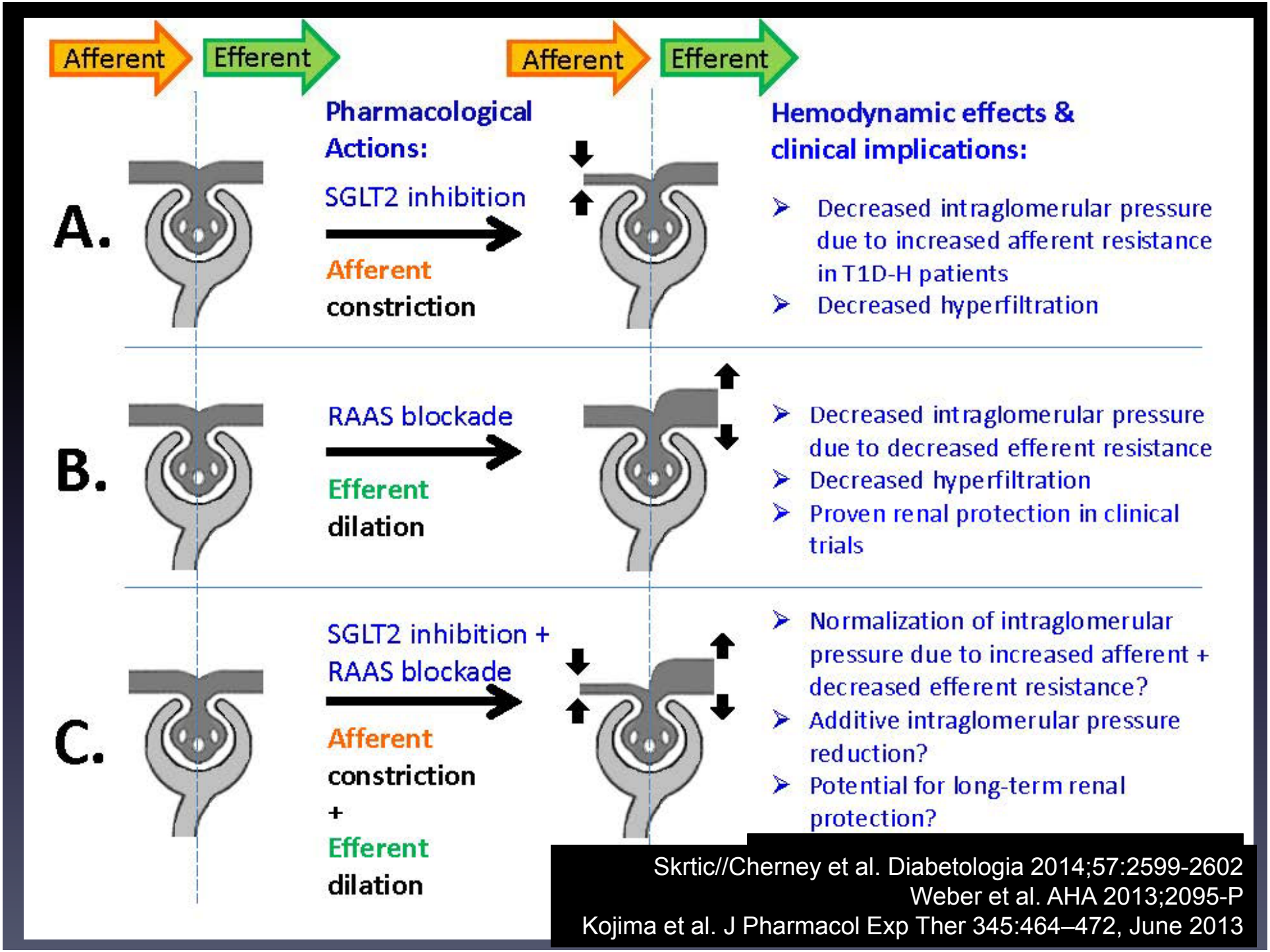
Parving et al (Irbesartan-Microalbuminuria). NEJM 2001;345:870

ARB in T2DM with Macroalbuminuria Reduces Renal Outcomes

Primary endpoint: Time to doubling of serum creatinine, ESRD, or death (n=1513)



Brenner et al. *N Engl J Med* 2001;345:861-9



Skrtic//Cherney et al. Diabetologia 2014;57:2599-2602
Weber et al. AHA 2013;2095-P
Kojima et al. J Pharmacol Exp Ther 345:464–472, June 2013

Canagliflozin vs. SU (104 weeks) – Normal Renal Function

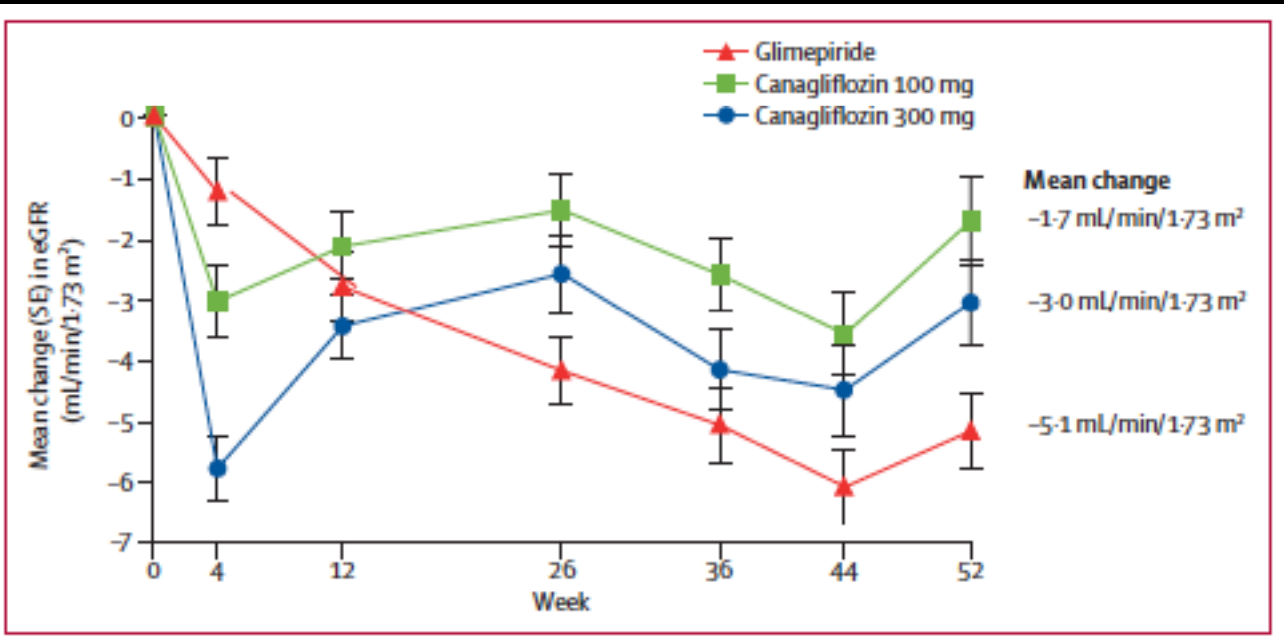


***Figure 6*: Change in eGFR over time**
Statistical comparison for canaqliflozin 100 mq and 300 mq versus qlimepiride not undertaken (not prespecified). eGFR=estimated glomerular filtration rate.

- ↓30-50% proteinuria (similar to RAAS blockade)

Cefalu et al. ADA 2013, LB 65
Parving et al (IRB-MicroAlb). NEJM 2001;345:870

Empagliflozin: EMPA REG Outcome (Renal)

New onset or worsening nephropathy

- New onset macroalbuminuria
- Doubling of creatinine and GFR<45
- Initiation of renal replacement therapy
- Death due to renal disease
- *HR 0.61 (95% CI 0.53-0.70, p<0.0001)*

- Composite of doubling of creatinine and GFR<45, initiation of renal replacement therapy, death due to renal disease
  - *HR 0.54 (95% CI 0.40-0.75, p=0.0002)*

Wanner et al. ASN High Impact Trials Session, 2015

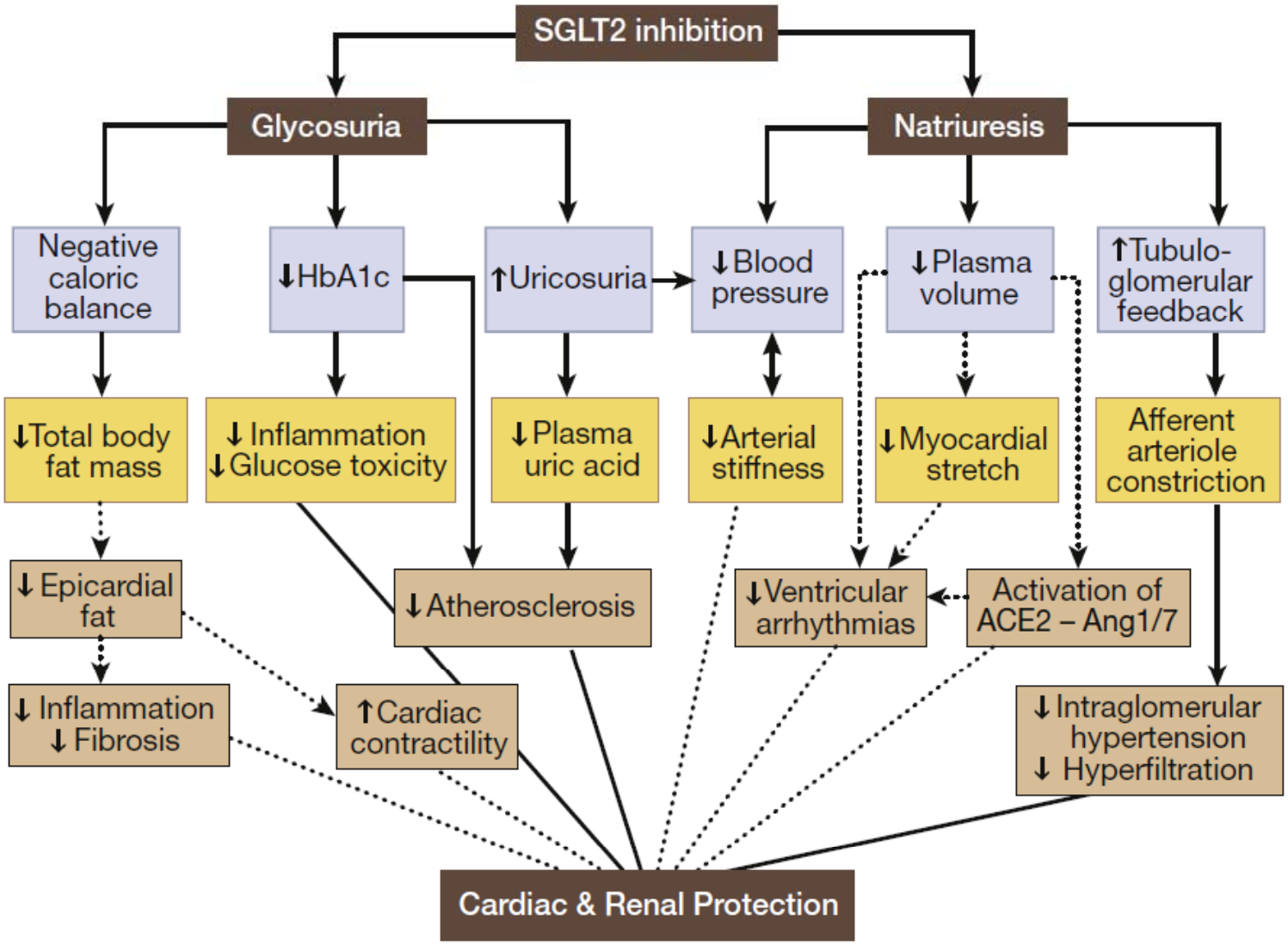


Figure 1 | Possible mechanisms responsible for cardiovascular and renal protection with sodium–glucose cotransporter 2 (SGLT2) inhibition. Solid lines represent pathways supported by existing data; dashed lines represent possible areas for future research. ACE2, angiotensin-converting enzyme-2; Ang1/7, angiotensin 1/7; HbA1c, hemoglobin A1c.

Rajasekeran/Lytvyn/Cherney. Kidney Int 2016;89:524-526

Conclusions:

- SGLT2 inhibition ↓intraglomerular hypertension
  - Effect appears to occur in CKD 3a, 3b
  - Renal protection in EMPA-REG Outcome
- ↓CV mortality may be due to ↓ heart failure
  - ↓volume overload
  - Role of renal protection on overall CV benefit