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University of Medical Sciences  
International Campus

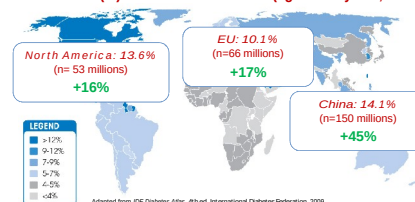
## Diabetic Nephropathy

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## Diabetes, a growing global epidemic likely to affect ~500 million people by 2030<sup>1a</sup>

Prevalence (%) estimates of diabetes\* (age 20-79 years, 2030)<sup>1a</sup>



>90% of diabetic patients have type 2 diabetes<sup>1</sup>

\*All cases of diabetes, including type 1 and type 2 diabetes, and impaired glucose tolerance (IGT), in patients aged 20-79 years.  
Absolute number of cases and national prevalence.  
International Diabetes Federation, IDF Diabetes Atlas, 4th ed. Brussels, Belgium: International Diabetes Federation, 2009. <http://www.idf.org/diabetesatlas>, accessed July 6th 2011.

## Mortality and morbidity in type 2 diabetes in relation to the normal population

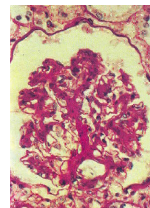
- Cardiovascular diseases → 2-3 times higher <sup>1)</sup>
- Stroke → 2-3 times higher <sup>2)</sup>
- Fatal myocardial infarction → 50 % <sup>2)</sup>
- Foot amputation → 40 times higher <sup>2)</sup>
- Blindness  
(» Severe retinopathy «) → 5 times higher <sup>3)</sup>
- Nephropathy  
(endstage renal disease) → 17 times higher <sup>3)</sup>
- Hypertension → 2-3 times higher <sup>2)</sup>
- Dyslipidemia → 3 times higher <sup>1)</sup>

<sup>1)</sup> Panzram, G.: Diabetologia 30 (1987): 123-131; <sup>2)</sup> MMWR 40 (1991): 737-773;

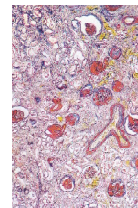
<sup>3)</sup> Leese, B.: The costs of diabetes and its complications, Soc. Sci. Med. 35 (1992): 1303-1310

## Diabetic Nephropathy Histopathological renal disorders

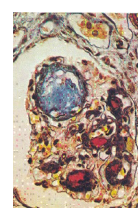
Alteration of  
mesangial space



Hyaline deposition  
in renal vessels



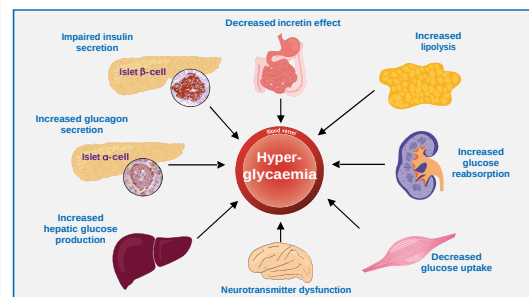
Glomerulosclerosis  
(Kimmelstiel-Wilson)



G. Williams et al.

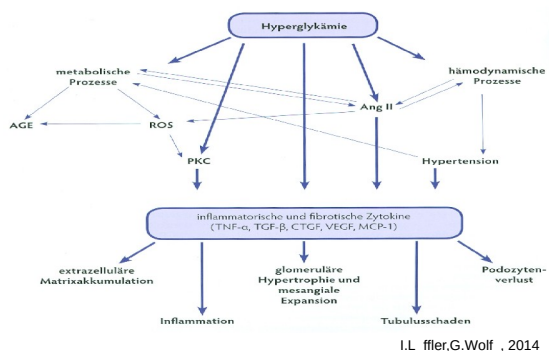
## Pathophysiological alterations

## Multiple pathophysiological failures contribute to hyperglycaemia

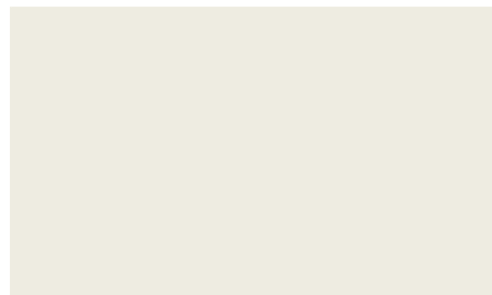


Adapted from: DeFronzo RA. Diabetes 2009;58:773-95. ©Wolters Kluwer Health

### Pathophysiological reactions determine renal damages

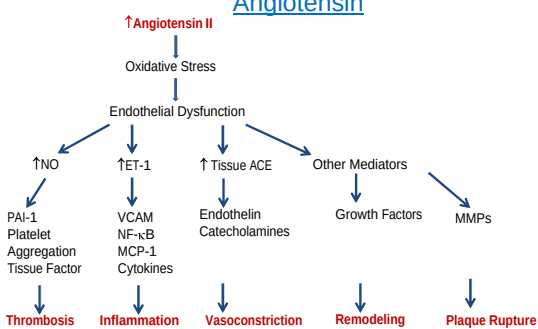


### Insulin-/aldosterone signaling in the aldosterone sensitive part of the nephron

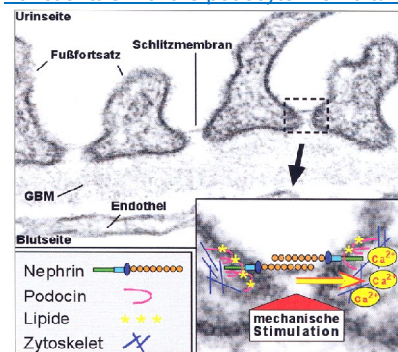


Friedrich B.: Diab. und Stoffw. 2010; 6:24-32

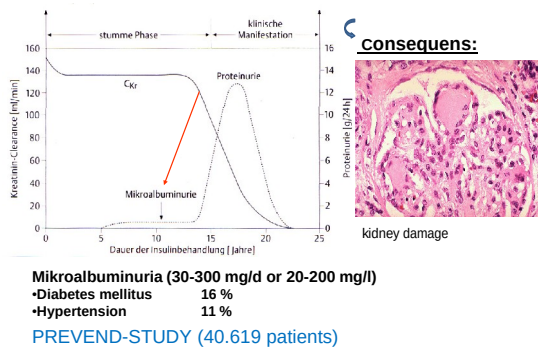
### Multiple effects of increased tissue production of Angiotensin



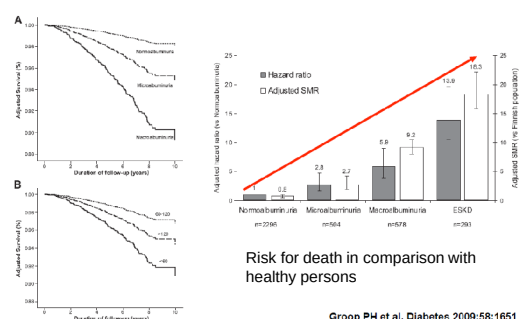
### Functionalism of the podocyte membrane



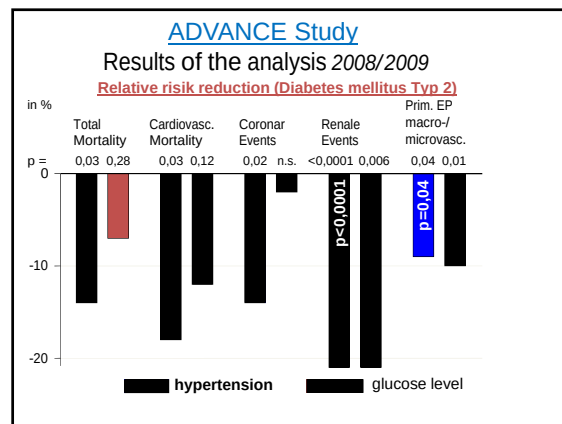
### Mikroalbuminuria and creatinine level in the phase of onset of Diabetic Nephropathy



### Diabetic Nephropathy and mortality



What can we do ?

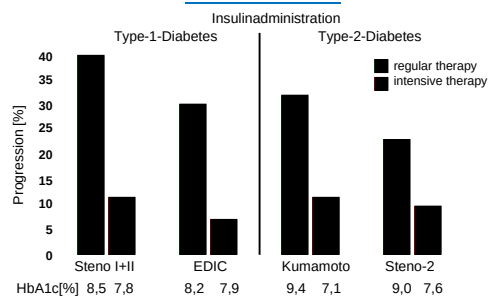


Most current therapies for type 2 diabetes have an insulin-dependent mechanism of action



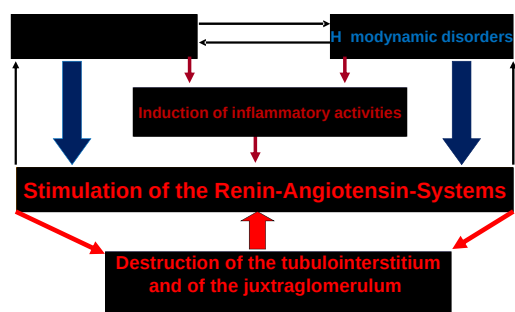
DPP4 = Dipeptidyl peptidase 4; FFA = free fatty acids; Adapted from Tahrani AA, et al. Lancet 2011;378182-97.

Optimal metabolic regulation depends on deterioration of renal function



C. Hasslacher  
Arzneimitteltherapie. 6, 199 – 205, 2009

Regulation of hemodynamic disorders



Nephroprotection is means early use of ACE-inhibitors

### **BENEDICT**

(Bergamo Nephrologic Diabetes Complication Trial, N.Engl. J. Med. 351, 2004, 1941 - 45)

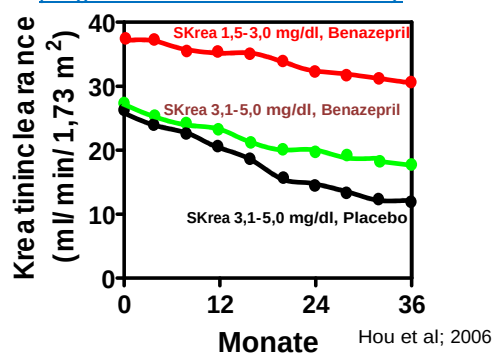
► 1204 hypertensive diabetic patients (Diab. mel. T 2) :

► Primary endpoint: manifestation of microalbuminuria



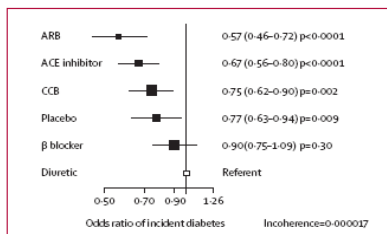
The manifestation of a microalbuminuria can be prolonged over a period of 3.6 years by early administration of ACE-inhibitors (Trandolapril)

### ACE-inhibitors are usefull to reduce process of progression of renal insufficiency



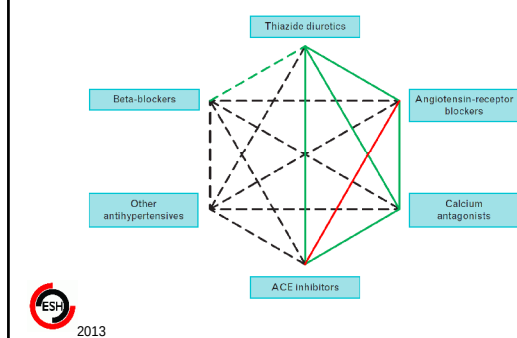
### Relative risk to initiate metabolic disorders by antihypertensive drugs

Results of a metaanalysis in 143.153 hypertensive patients including in 22 clinical studies

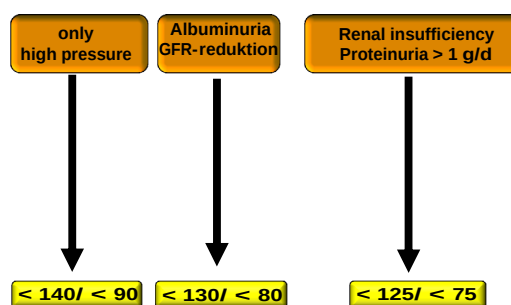


Elliott, WJ. et al., Lancet. 2007;369:201-207

### Recommendations for antihypertensive treatment

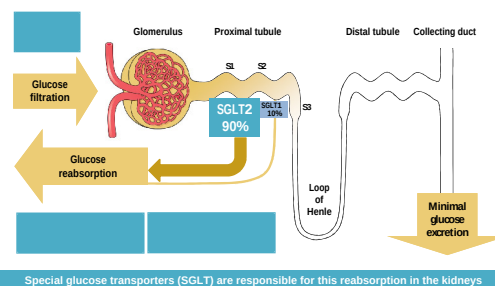


### Optimal blood-pressure in patients with Diabetic Nephropathy



### New therapeutical option for optimizing the metabolic situation

### Kidneys filter and reabsorb 180 g of glucose per day in the nephrons by active transport



Wright EM. Am J Physiol Renal Physiol 2001;280:F10-8; Lee YJ, et al. Kidney Int Suppl 2007;106:S27-35; Brown GK. J Inherit Metab Dis 2000;23:237-246.

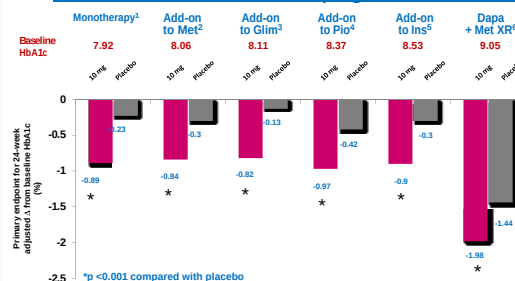
### Gliflozines are potent and selective SGLT2 inhibitors in vitro and in vivo

- 1 Good oral bioavailability independent of food intake<sup>1</sup>
- 2 Half-life consistent with once-daily dosing<sup>1</sup>
- 3 Low risk of drug-drug interactions<sup>1-5</sup>
- 4 1200-fold selectivity for SGLT2 vs. SGLT1<sup>6</sup>

<sup>1</sup>Komoroski BJ, et al. Clin Pharmacol Ther 2009;85:520-526. <sup>2</sup>Obermeier M, et al. Drug Metab Dispos 2010;38:405-414. <sup>3</sup>Kasichayanula S, et al. Diabetes Obes Metab 2011;13:47-54. <sup>4</sup>Kasichayanula S, et al. AAPS 2010, Diabetes Obes Metab 2011;13:770-773. <sup>5</sup>Wilcox, et al. ASN 2010, Denver, CO [Poster 4509]. <sup>6</sup>Han S, et al. Diabetes 2008;57:1723-1729

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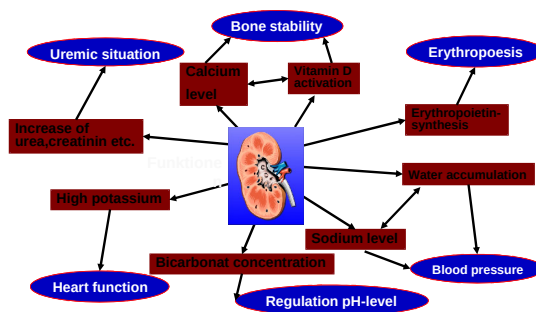
### Consistent decreases in HbA1c from baseline at week 24 across all dapagliflozin studies



<sup>1</sup>Ferrannini E, et al. Diabetes Care 2010;33:2217-24. <sup>2</sup>Bailey CJ, et al. Lancet 2010;375:2223-33. <sup>3</sup>Stojek K, et al. Diabetes Obes Metab 2011;13:928-38. <sup>4</sup>Rosenstock J, et al. 71<sup>st</sup> ADA Scientific Sessions, San Diego, 24-28 June, 2011 Abstract 0986-P. <sup>5</sup>Wilding J, et al. Diabetes. 2010;59 (Suppl 1):A21-A22. Abstract 0078-0P. <sup>6</sup>Henry R, et al. 71<sup>st</sup> ADA Scientific Sessions, San Diego, 24-28 June, 2011 Abstract 307-0P.

### General recommendations

### Consequences of the deterioration of renal function



R.Fünfstück, 2014

### Concepts of therapy in Diabetic Nephropathy (important supplementary strategies)

- Renal anemie : supplementation of erythropoietin- and compensation of the ferrum-deficit (Hb-level <11-12g/dl)
- Protein intake should be restricted (ca.0.8g/kg/Tag)
- Compensation of the metabolic acidosis
- Ban of nicotin
- Cave: administration of nephrotoxic substances (antibiotics, contrast media.....)
- Influence of renal osteodystrophia/osteopathia (supplementation of Vitamin D, prevention of the secondary HPT)

### Effect of a multifactorial intervention on mortality in type 2 Diabetes complications



