Precision Medicine in Diabetes

How to protect the kidney and cardioavascular system

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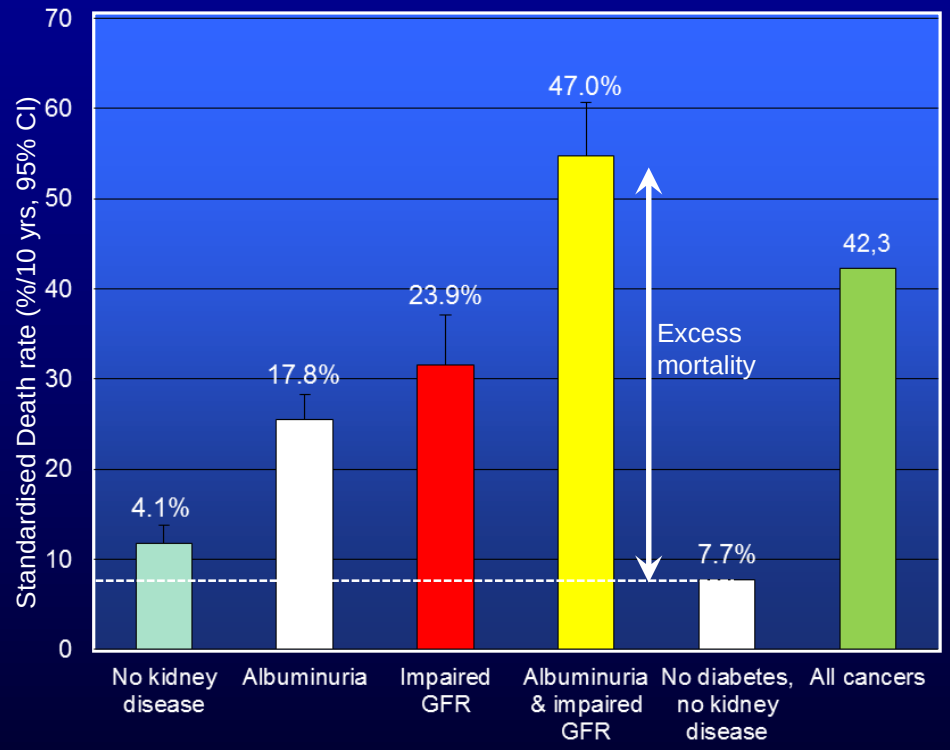
Disclosure:
Consultant/Speaker to/for:
Abbvie, Astellas, Bayer, Boehringer Ingelheim, Fresenius, Janssen, Mitsubishi-Tanake
honoraria paid to Institution

Type 2 diabetes an urgent unmet need

Mortality is frequently present in type 2 diabetes and is higher than average mortality rates of all cancers (NHANES)



Afkarian M et al. J Am Soc Nephrol 2013;24:302; Lancet 2014

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Common early risk markers and targets for cardiovascular and renal disease progression

- High Mortality in Diabetes caused by primarily cardiovascular and renal morbidity
- Risk factors for this morbidity:
  - Age
  - Gender
  - Body Weight
  - Smoking
  - Blood pressure
  - Blood Glucose
  - Blood Hemoglobin
  - Blood Cholesterol
  - Blood Potassium
  - Urine Protein

Structure of presentation

- Type 2 diabetes is a fast growing disease with high morbidity and mortality
- Cardiovascular and renal disease are leading cause
- Current therapeutic strategy:
  - Find drug to lower a risk factor (e.g. blood pressure)
  - Test in clinical trial (hard outcome)
  - Register as antihypertensive drug
  - Include drug in diabetes guideline
  - Use in all diabetics with increased blood pressure

Need for Personalized/Precision Medicine
Diabetes leading to Renal/Cardiovascular Disease

In case of diabetes and renal/cardiovascular disease we are still at:

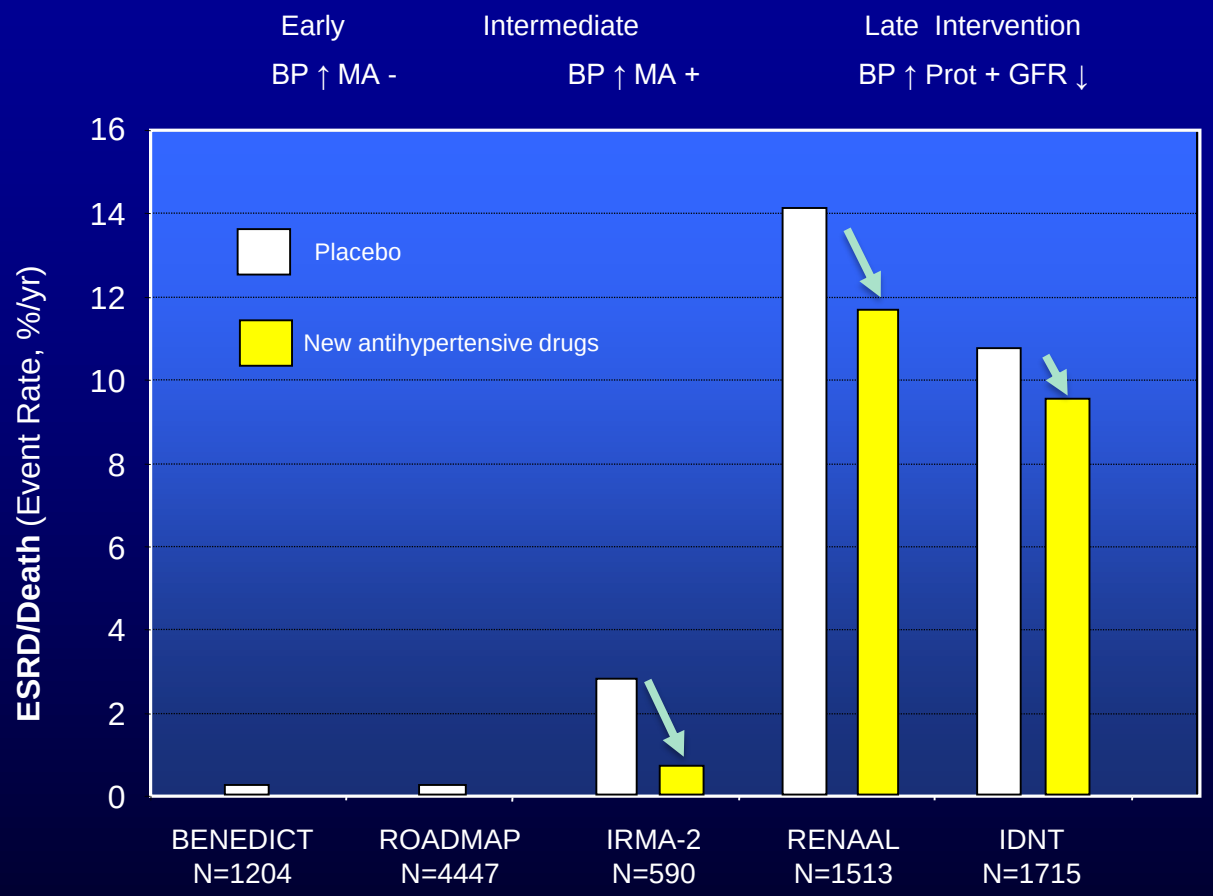
One size fits all

The guideline for treatment of diabetes gives us a recipe that should be applied to each patient!

Is this correct?

Randomized Controlled Clinical Trials for drug registration are carried out in large groups and expressed as group effects

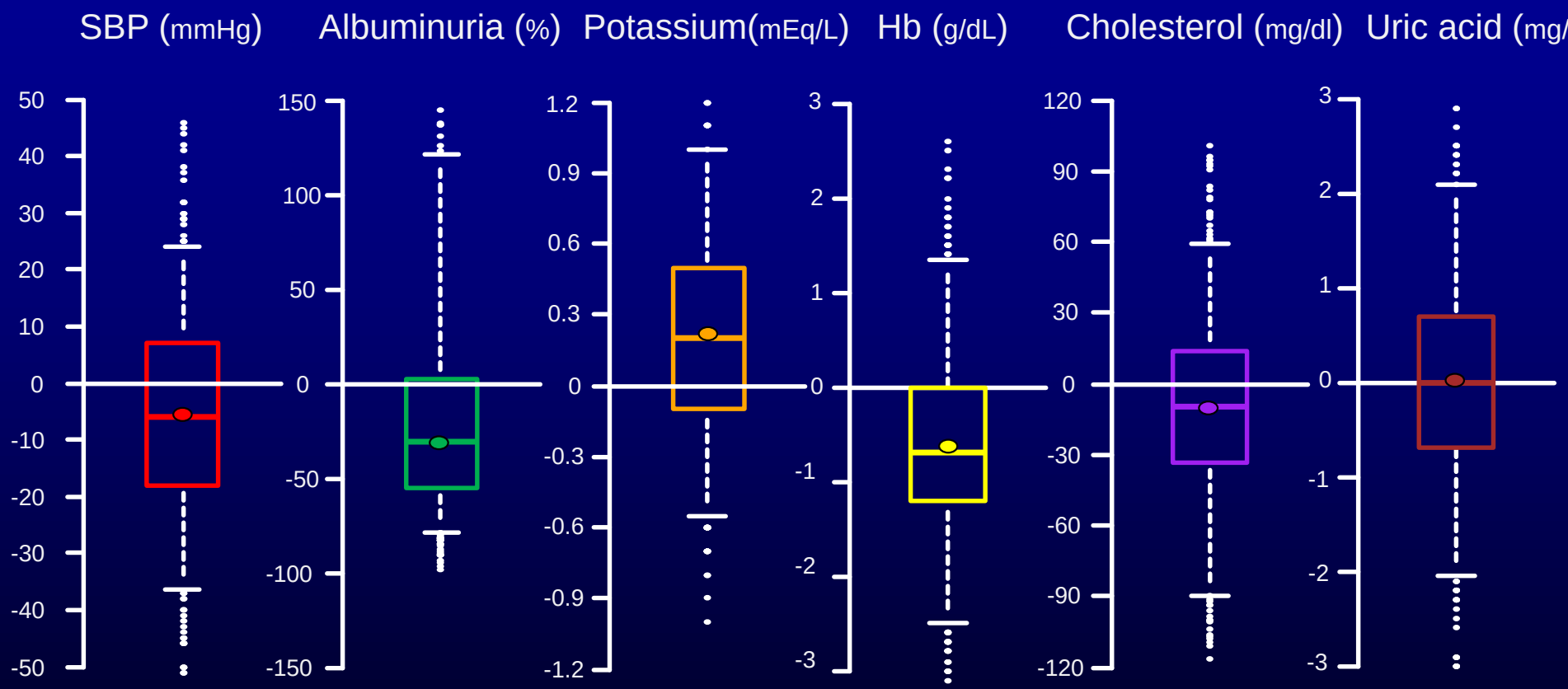
Renal protection by new antihypertensive drugs with marked residual risk



What are the reason(s) for a poor “group” protection

1. All drugs have effects on other risk factors than the target risk factor
2. The effect on the target risk factor as well as on the off-target risk factors may vary between patients and within patients

RENAAL: between patient variability in response to losartan; on-target (blood pressure) and off-target parameters



Schievink et al; BJCP 2015

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Effect of response variation on patient outcome in randomized control registration trials

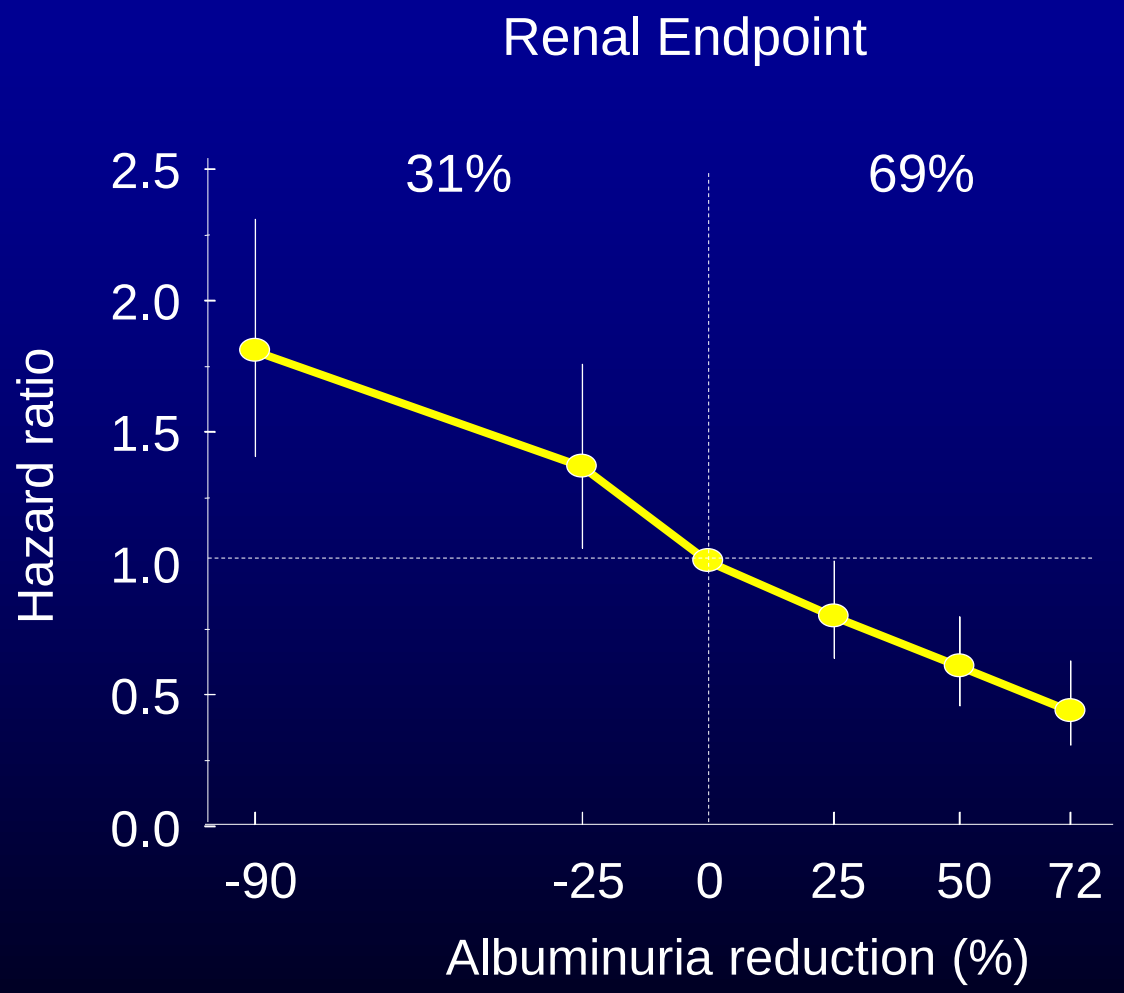
1. In the target parameter
2. In target and off-target parameter

RENAAL; Response variability to losartan for albuminuria (715 type 2 diabetes with nephropathy)

Increased albuminuria	>+30%	17.8%	**31**
	0 to +30%	13.3%	
Decreased Albuminuria	-30 to 0%	22.5%	**69**
	>-30%	46.6%	

Eijkelkamp et al; JASN 2007

RENAAL; Degree of initial albuminuria reduction (6 mo) predicts the long term renal risk in type 2 diabetes



De Zeeuw et al; Kidney Int 2004

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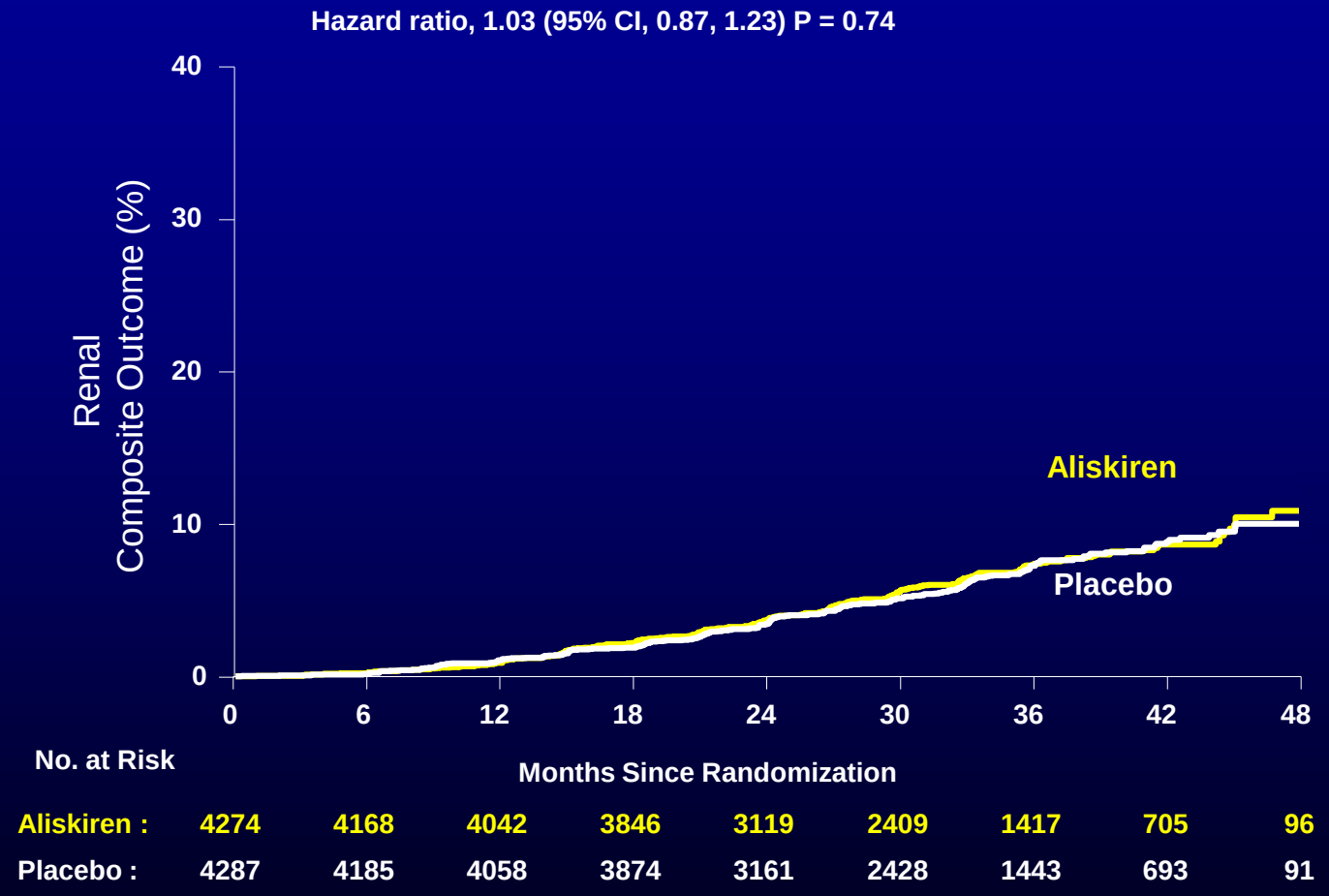
ALTITUDE; No group effect on renal/CV outcome

Due to variable good effect on albuminuria



Parving et al; NEJM 2012

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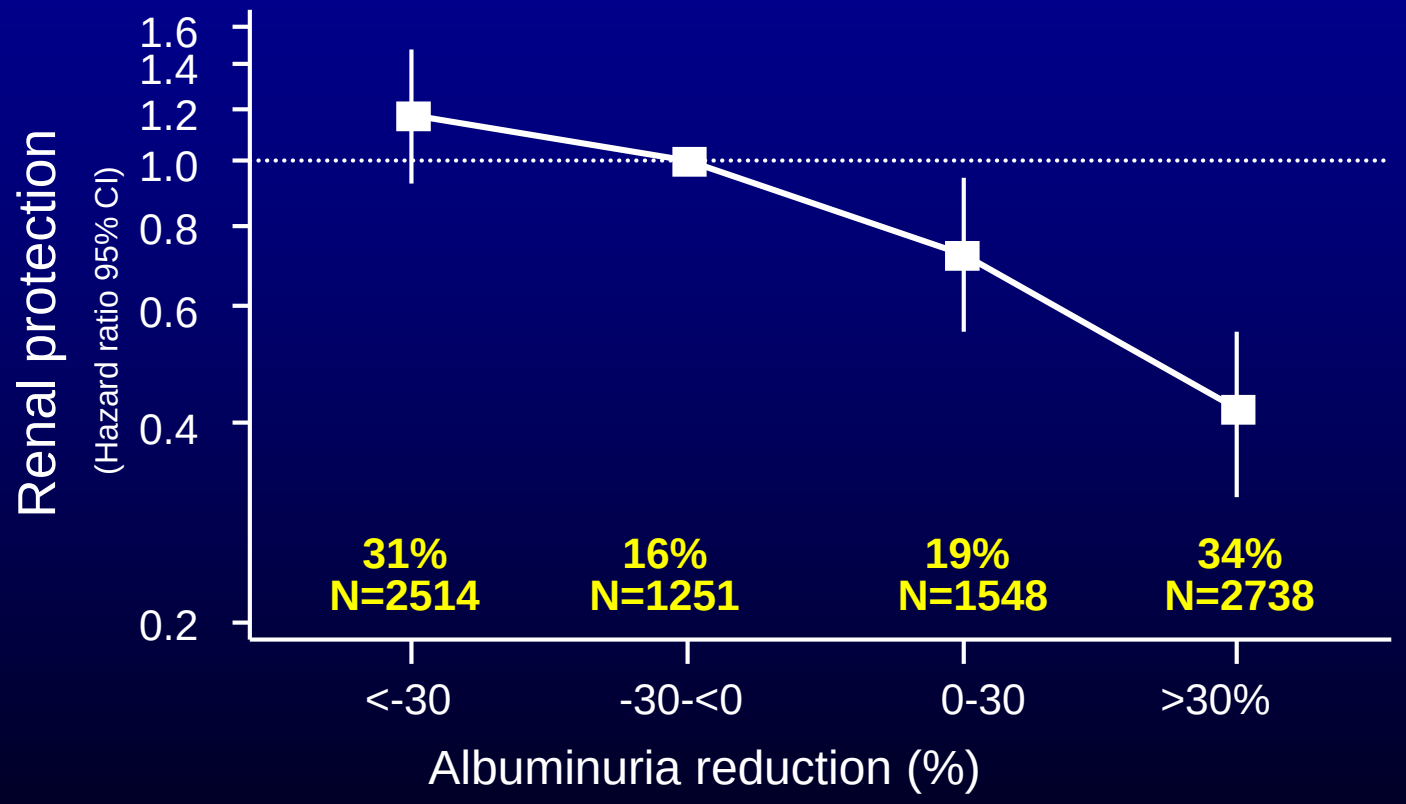
ALTITUDE; Patients that show an albuminuria lowering have big renal protection



Lambers Heerspink et al. Diabetes Obes Metab 2016

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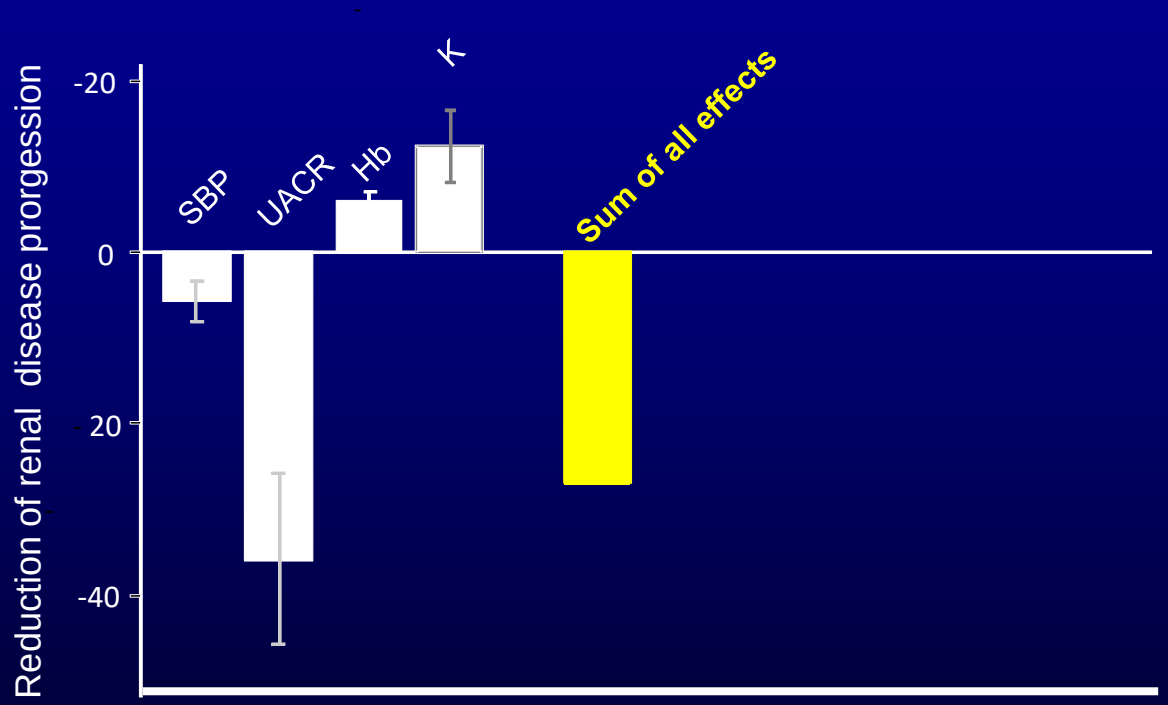
Effect of response variation on patient outcome in randomized control registration trials

1. In the target parameter
2. In target and off-target parameter

Changes of the individual risk factors by a blood pressure lowering agent (losartan) have their own and a group effect on renal risk



Smink et al; Clin Pharm & Ther 2014

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"'Possible Solutions" to improve trial outcomes and individual patient practice: Precision medicine for renal/CV protection

Change the practice of:

1. Drug trial methodology from group to the "individual good responders''
2. Doctor in prescribing/protecting the individual patient

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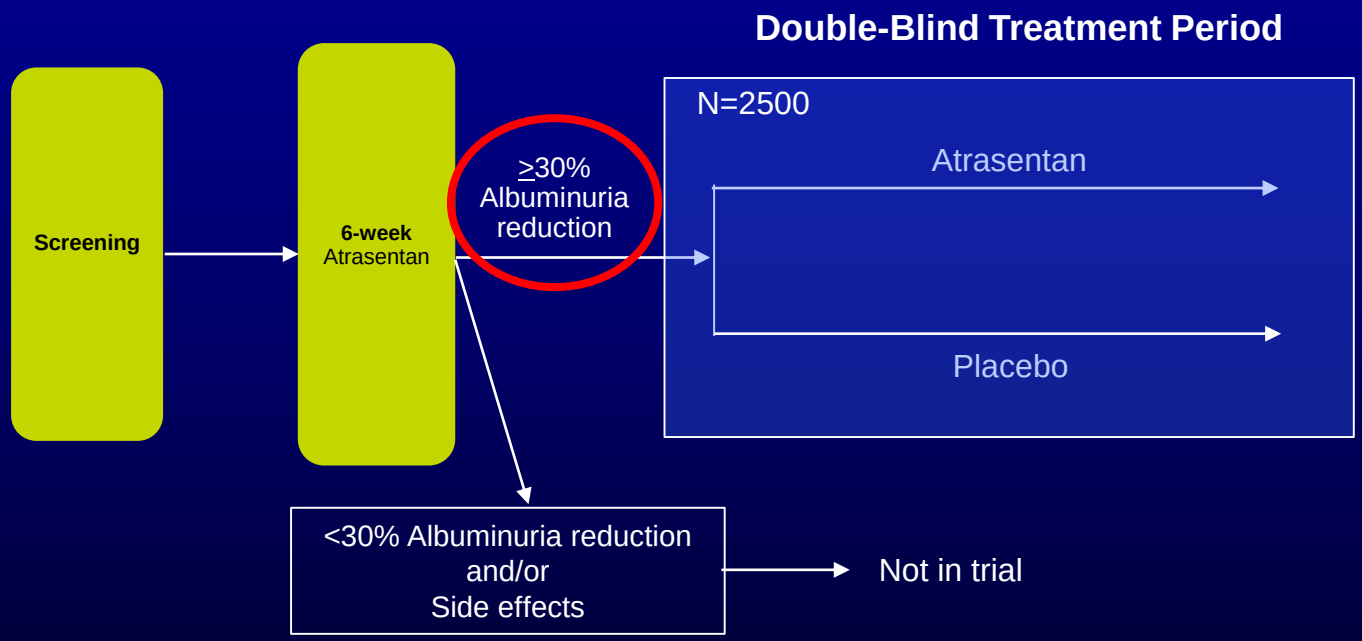
Personalized Medicine approach works in a large trial with a new albuminuria lowering drug (atrasentan) in diabetes: SONAR



Heerspink et al; DOM 2018

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Future guideline of therapy for renal/CV protection in (diabetes) renal disease

To improve the current care of a (diabetic) patient:

- We should not treat each individual patient to one guideline therapy approach, which is based on trial results of a large group response

- We should treat each patient according to his/her individual response of all risk factors, including positive responses and negative responses of the risk markers

Example of integrated approach for cardiovascular and renal protection in the individula diabetes patients (PRE-score algorithm)

https://mulderst.shinyapps.io/prescore_demo/

What are the estimated PRO's/CON's

PRO:

- Improved patient adherence to therapy
- Improved and more selective drug use
- Improved risk factor control
- Improved renal/CV outcomes
- Improved pharmaco-economic performance

CON:

- ?