

# Potential items for the agenda of the Regulatory Science Network Netherlands

## *An Academic Viewpoint*

*The consequence of Personalized/Precision Medicine in treatment of chronic diseases like (type II) diabetes, obesitas and hypertension*

Dick de Zeeuw

Department of Clinical Pharmacy and Pharmacology

University Medical Center

Groningen

The Netherlands

*Disclosure:*

*Consultant/Speaker to/for AbbVie, Astellas, Bayer, Boehringer Ingelheim, Fresenius, Janssen, Mitsubishi-Tanake;*

*honoraria paid to Institution*

# Need for Personalized Medicine approach in the regulatory environment

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## ***Background:***

- Current drug registrations have a clear indication for a mostly “heterogeneous” group of patients
- Treatment guidelines are directed towards groups of patients
- Clinical practice is directed towards the individual patient

## ***Challenge:***

- Align drug registration with use in clinical practice
  - Adapt Trial design to personalized medicine
  - Use more real life cohorts/databases

# A typical example from my own research practice

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The search for new drugs in treating patients with type 2 diabetes with high renal and cardiovascular risk:

*Initial success*

Subsequent complete failure

*Reason*

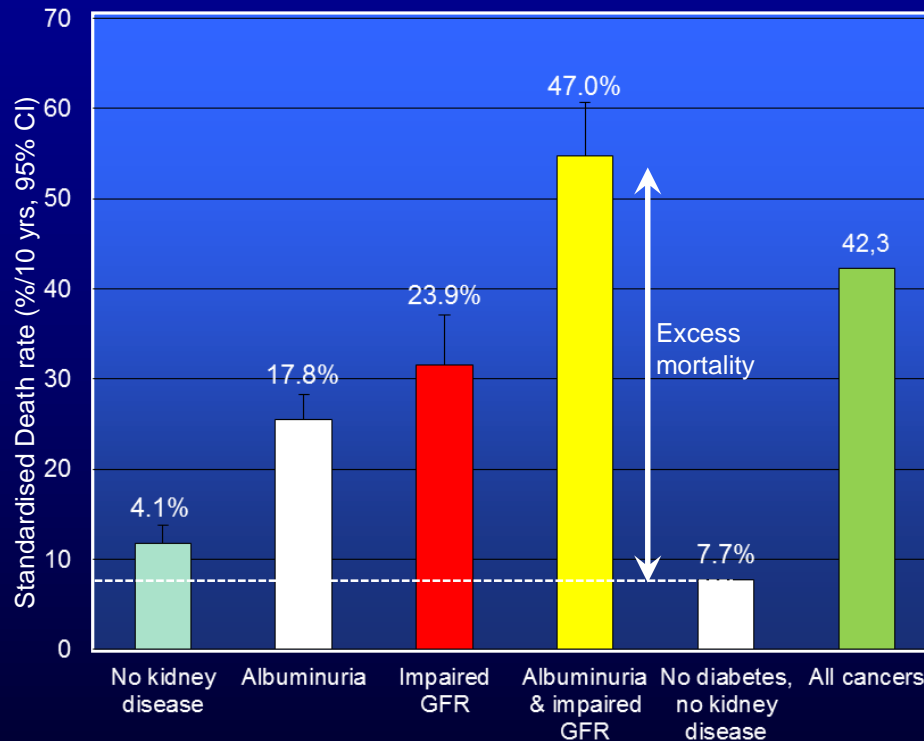
The group of patients approach?

*Solution*

The individual patient approach?

# Type 2 diabetes an urgent unmet need

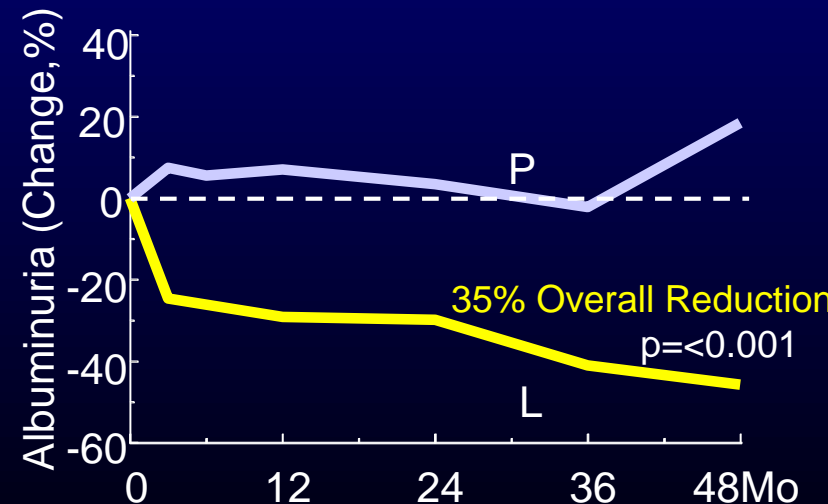
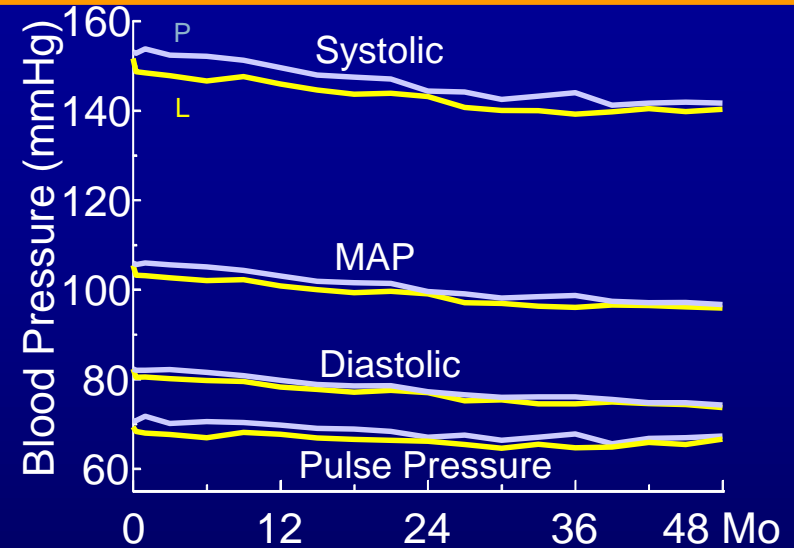
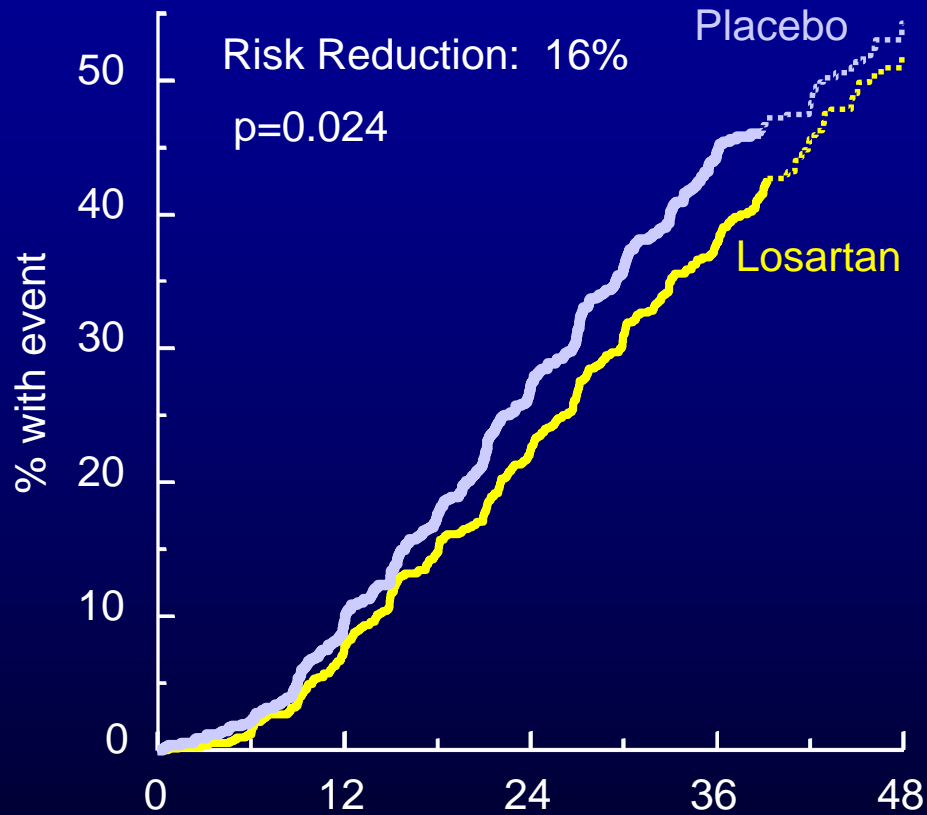
*Mortality is frequently present in type 2 diabetes and is higher than average mortality rates of all cancers (NHANES)*



# Drugs for slowing progression of renal function loss in patients with diabetes

- A new drug (losartan) is found that lowers renal risk factors, such as blood pressure and albuminuria, in patients with type 2 diabetes
- A registration trial is ultimately performed in a selected population (broad):
  - Type 2 diabetes
  - High risk for renal progression
  - Worldwide
  - Multi-ethnic
- Result shows significant renal risk reduction

# RENAAL; Renal protection with the Angiotensin Receptor Blocker (ARB) Losartan (+ conv tx) in type 2 diabetes

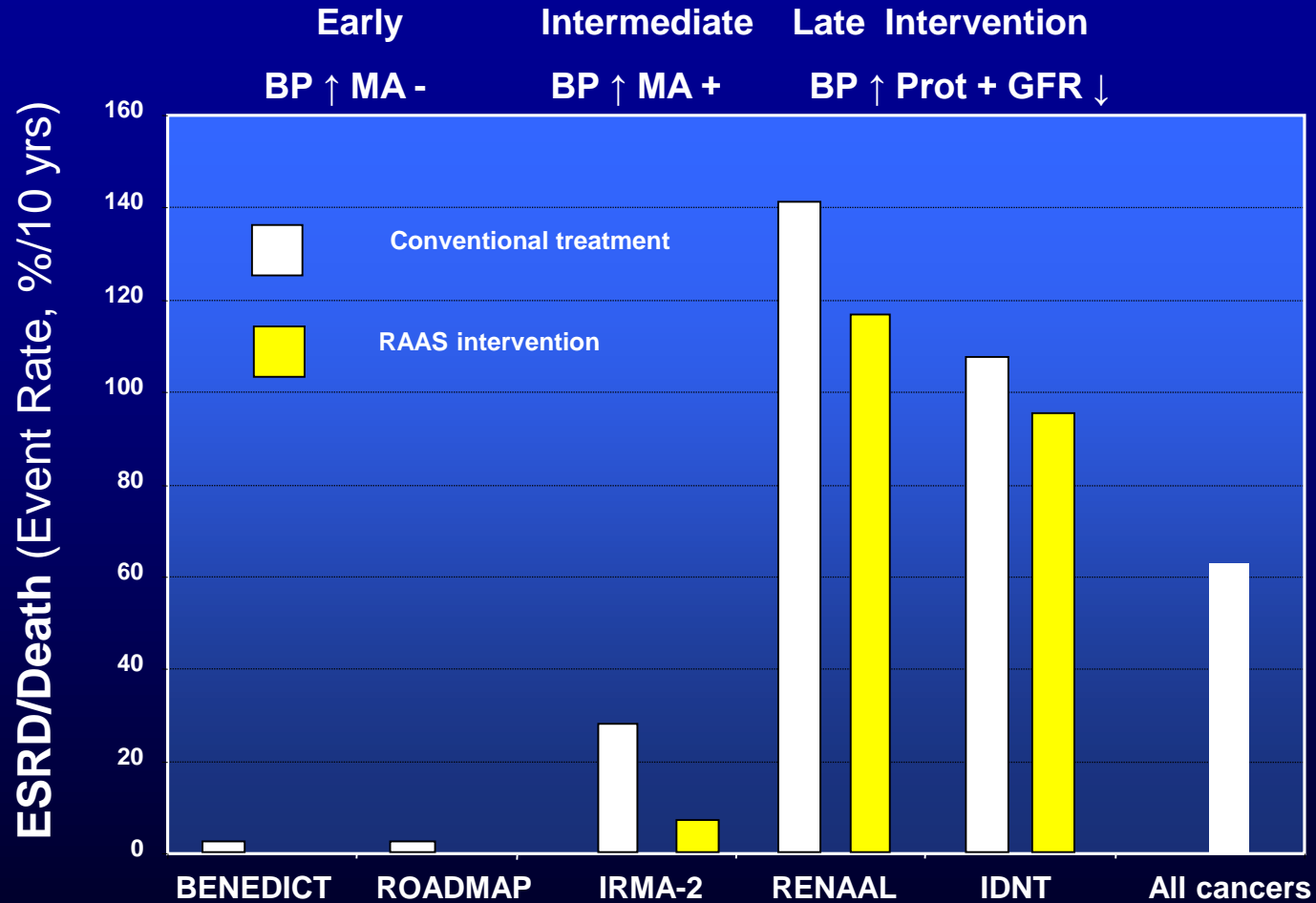


# Drugs for slowing progression of renal function loss in patients with diabetes

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- A new drug (losartan) is found that lowers renal risk factors, such as blood pressure and albuminuria, in patients with type 2 diabetes
- A registration trial is ultimately performed in a selected population (broad):
- Result shows significant renal risk reduction
- After confirmation in another trial (irbesartan) the drugs are registered for renal protection in patients with diabetes (and high renal risk)
- Drug is recommended in guideline for use in these patients

# HIGH RESIDUAL RISK: Even with guideline treatment residual risk of mortality is extremely high in type 2 diabetes

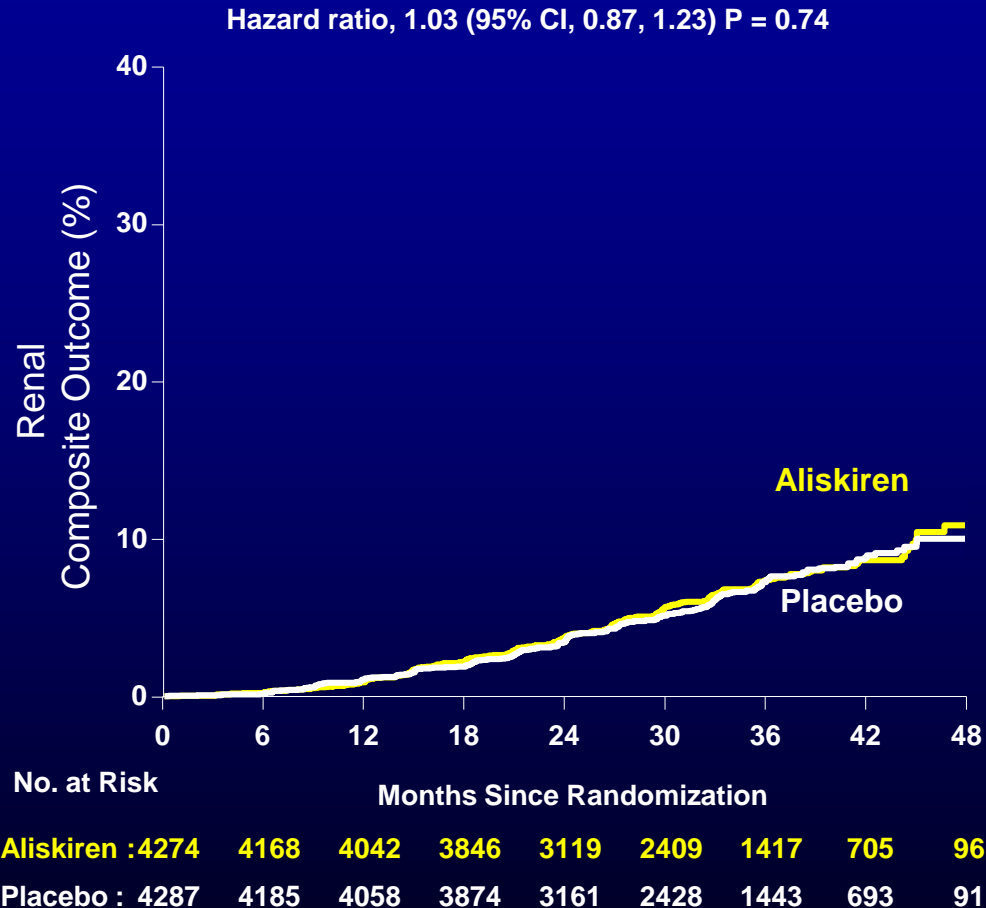




# Drugs for slowing progression of renal function loss in patients with diabetes

- We conclude that intervention in this pathway is successful but that we are clearly not inhibiting the pathway enough.
- We find a new drug that inhibits the pathway even more on top of previous medication and further lowers the renal risk factors like blood pressure and albuminuria
- A registration trial is ultimately performed in a selected population:
  - Type 2 diabetes using ACEi/ARB medication
  - High risk for renal progression
  - Worldwide
  - Multi-ethnic
- Result shows NO effect on renal risk

# ALTITUDE; Renin-inhibitor remikiren has no effect on renal composite end-point in patients with type 2 diabetes



# From trial to practice or from practice to trial?

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- We are carrying out (hard end point) trials for registration reasons:
  - We test for the ultimate efficacy and safety of the investigational drug
  - The trials require to be representative of the patients to be treated with that indication in real life practice
- The results of these trials (usually several) lead to consensus meetings and ultimately to GUIDELINES that define the optimal treatment (regimens) for our patients with a certain disease
- In practice doctors should follow guidelines (HOWEVER...)

# From trial to practice or from practice to trial

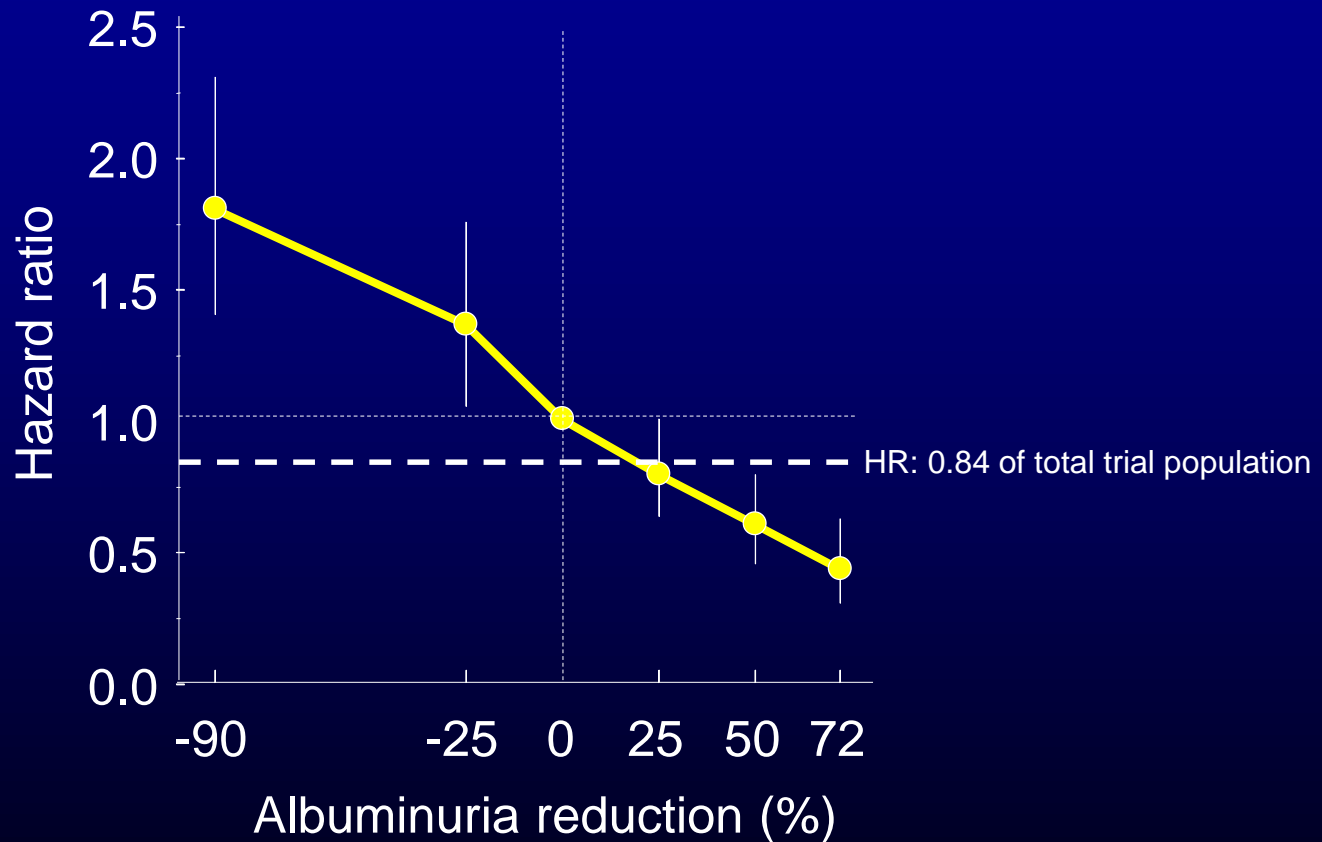
- In trial design:
  - Usually fixed dose
  - If no effect, drug is continued and patient stays in trial
  - If side effect, drug is continued and patient stays in trial
- In real life drug treatment:
  - Dose is titrated to a target
  - If no effect, drug is stopped
  - If side effect:
    - Side effect is managed
    - if side effect persists, drug is stopped

# Question

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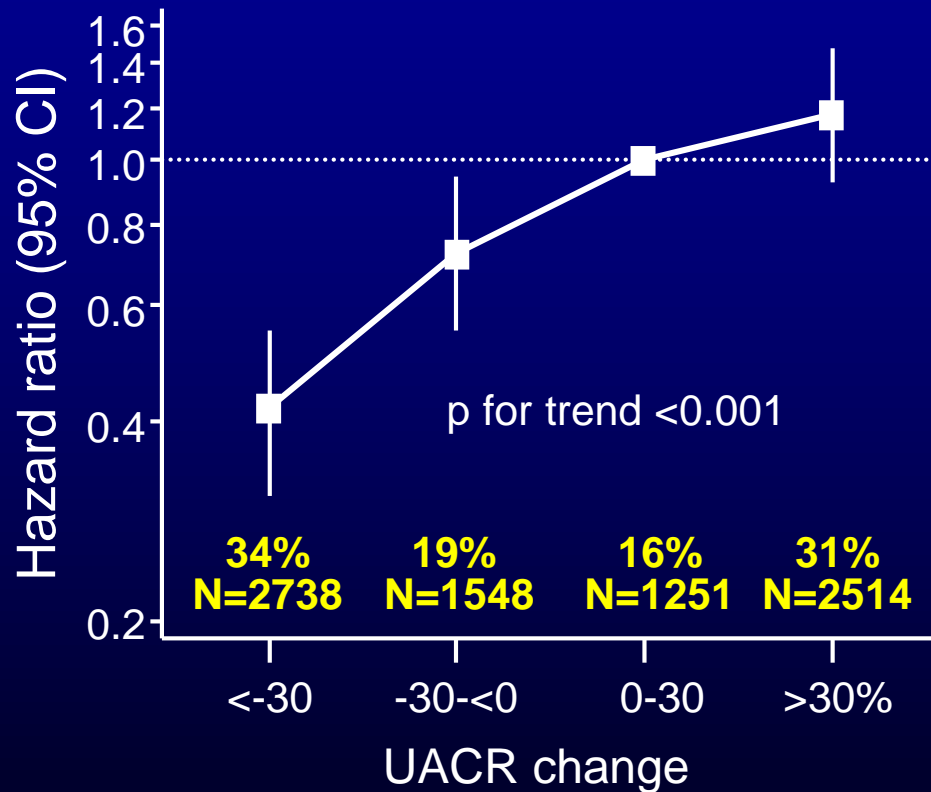
- How often does a patient respond to an investigational drug with a fall in the targetted risk marker?
- If no response in the risk marker is there no renal protection
- If no renal protection why do we enroll such patients in registration trials?

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

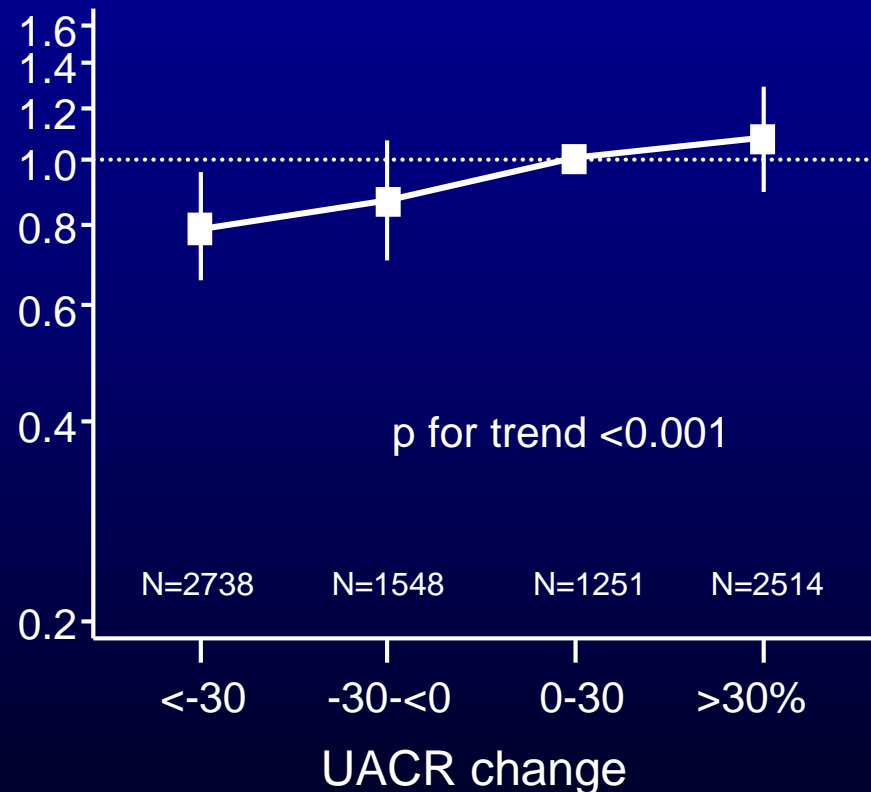


# ALTITUDE; Post hoc; Adjusted renal/CV hazard by 6 month albuminuria change (8561 type 2 diabetes with CKD and/or CV disease)

## Renal events

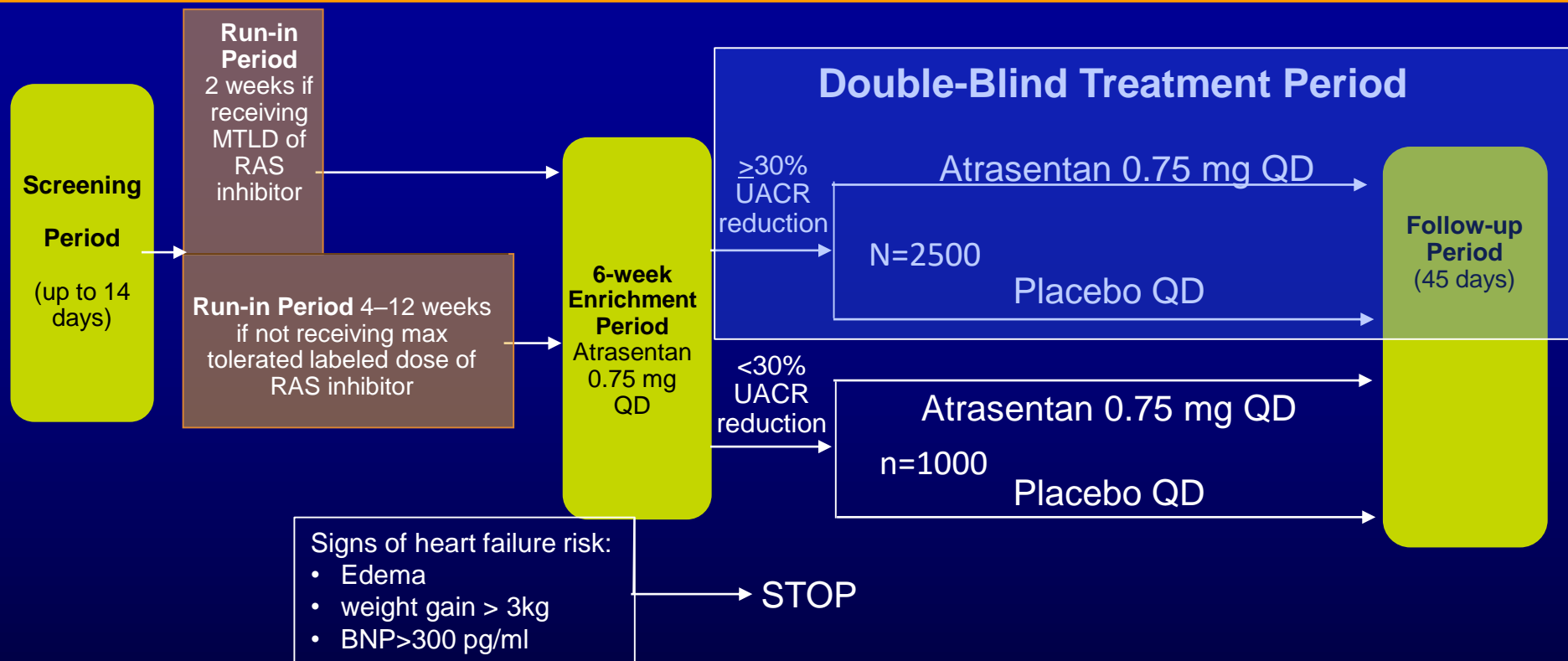


## Cardiovascular events



# SONAR (NCT01858532)

## Protocol scheme



### 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



# Possible items for the agenda of Regulatory Science Network Nederland

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Find new avenues to Personalized Medicine in the regulatory environment for chronic diseases with high societal impact like diabetes, obesitas, and hypertension

- Use of new biomarkers (or biomarker panels) to estimate risk and or to estimate reponse
- New trial design:
  - Facilitating testing the drug in the right patient (responder)
  - Facilitating finding solutions for non-responders
  - Facilitating mimicking more clinical practice

# Umbrella & platform trial designs

## *Potential use in large cohorts type 2 diabetes*

	Drug A	Drug B	Drug C	Drug D	Drug E
Patiënt type 1	Response				
Patiënt type 2	No Response →	Response			
Patiënt type 3	No Response →	No Response →	Response		
Patiënt type 4	No Response →	No Response →	No Response →	Response	
Patiënt type 5	No Response →	No Response →	No Response →	No Response →	Response

# Does the potential topic carry enough of the current expertise in the Netherlands

- **CBG:**
  - CBG and people within CBG have expertise and interest in trial design and in databases of “practice” cohorts and are already doing such research
- **Dutch Academia:**
  - Several European projects are running (including Marie Curie and IMI projects) that are supporting this approach
  - Several different academic centres have expertise and interest in this topic
- **Dutch Society:**
  - The Nationale WetenschapsAgenda (NWA) has Personalized Medicine as a front running topic

# Conclusion

- Chronic diseases like diabetes, obesity and hypertension are growing exponentially worldwide with a high cardiovascular and renal morbidity and mortality
- Current therapies leave a high unmet need
- A more personalized approach (aiming at individual response of risk markers) shows much better results.
- This approach will lower the attrition rate of new drugs and will reduce morbidity and mortality in these chronic diseases
- This will require a new and innovative approach and new regulations in the registration process of new drugs
- The currently available Dutch Network of Pharma, Regulatory and Academia is unique and well equipped to tackle this and find the required new approaches