Using multiple biomarkers to predict renal and cardiovascular drug efficacy:

*Implications for drug development and registration*

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• Chronic disease growing, hypertension/diabetes
• Despite treatment high Residual Risk
• Current strategy is to target a single drug to a single risk factor

• However, ultimate outcomes involve multiple risk factors
• Drugs have multiple effects

• Should we include multiple effects on multiple risk factors in the efficacy of the drug on CV/renal outcome? And if so, how to include in the registration and use of drugs
High residual risk for renal death in type 2 diabetes under optimal \textit{(antihypertensive)} treatment in RCT's

De Zeeuw \textit{et al}, European Nephrol 2009
High residual risk warrants new approaches

• We need new drugs or new approaches

• Current strategy is to target a single drug to a single risk factor e.g. to blood pressure

• This is not a target per se, since by lowering the blood pressure, the intention is to lower renal and CV risk on the long run

• This may lead to the false assumption that we are treating that risk factor: if we have lowered it it should be good
RENAAL; Differential effect of antihypertensive treatment on proteinuria and BP has differential effect on ESRD

*Eijkelkamp et al; JASN 2007*
Multiparameter short term response determines long term effect

• Thus, not only the on-target (blood pressure) effect of the Angiotensin Receptor Blocker determines the long term outcome, but also its off-target effect on albuminuria

• Is such a multiple (off-target) effect of a single drug common?
Multiple effects of RAAS-intervention

• Several RAAS-inhibitors are on the market including classes like ACEi, ARB and DRI

• These are all registered as antihypertensives

• They all have additional renal and CV protective properties beyond blood pressure lowering

• Which additional effects?

• How do they relate to the renal outcome?
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RENAAL/IDNT; Change in biomarkers at month 6 in ARB and placebo groups in type 2 diabetes

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RENAAL; Effect of losartan vs placebo on albuminuria in type 2 diabetes

Albuminuria (Change, %)

35% Overall Reduction

p = <0.001

Placebo

Losartan

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

Hazard ratio ESRD

De Zeeuw et al; Kidney Int 2004
RENAAL; Effect of treatment on serum potassium in type 2 diabetes

Miao Y et al; Diabetologia 2011
RENAAL; Serum Potassium during treatment effect renal outcome (doubling Scr/ESRD) in type 2 diabetes

Miao Y et al; Diabetologia 2011
Conclusion and Question

- Antihypertensive drugs that intervene in the RAAS have many more short-term (off-target) effects than the on-target effect of blood pressure lowering.

- These off-target effects include changes that contribute either in a positive or negative way on final CV/renal outcome.

- Combining the off-target short-term effects into a multiple Parameter risk Response Efficacy (PRE) score might give better prediction of final long-term renal and cardiovascular outcome?
Principle of the PRE score

- Blood pressure is related to renal/cv outcome: the higher the blood pressure the more risk. There is thus a algorithmic relation between BP and CV/renal risk

- Assume a drug lowers the blood pressure. One can calculate from the above algorythmic relation how much renal/CV risk reduction could be anticipated.

- In RENAAL study losartan lowered blood pressure more than placebo. If the drug only had an effect on BP, this can thus be translated to an expected outcome of RENAAL.
RENAAL; Predicting long term RENAL outcome in type 2 diabetes using the **SBP** effect at 6 mo of ARB tx

Predicted long-term renal risk change (%)

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**Smink et.al.; Clin Pharm & Ther 2013 In Press**
Principle of the PRE score

- The higher albuminuria the more renal/CV risk.

- Losartan lowered albuminuria more than placebo. Assuming losartan would only lower albuminuria, one can again predict how renal/CV risk reduction would occur.
RENAAL; Predicting long term RENAL outcome in type 2 diabetes using the *albuminuria* effect at 6 mo of ARB tx

**Predicted long-term renal risk change (%)**

**Albuminuria (%)**

[Graph showing predicted long-term renal risk change and albuminuria levels for Placebo and Losartan groups.]

*Smink et al.; Clin Pharm & Ther 2013 In Press*
Principle of the PRE score

- The higher the serum potassium the more renal/CV risk.

- Losartan increased serum potassium more than placebo. Assuming losartan would only increase serum potassium, one can again predict how renal/CV risk increase would occur.
RENAAL; Predicting long term RENAL outcome in type 2 diabetes using the Potassium effect at 6 mo of ARB tx

Smink et al.; Clin Pharm & Ther 2013 In Press
RENAAL; Predicting long term RENAL outcome in type 2 diabetes using the PRE score at 6 mo of ARB tx

Observed renal risk reduction -22% (-35 to -6)

Smink et.al.; Clin Pharm & Ther 2013 In Press
Validation of the PRE score (a multiple risk response score): score developed in RENAAL and applied to IDNT

Renal outcome

Relative renal risk change (%)

-40 -30 -20 -10 0 10

predicted ARB effect observed ARB effect

Smink et al.; Clin Pharm & Ther 2013 In Press
Use of the PRE score

- The PRE score can thus be used in estimating renal protection for RAASi antihypertensive medications in diabetes

- Can it be used for CV protection?
RENAAL; Predicting long term CV outcome in type 2 diabetes using the PRE score at 6 mo of ARB tx

Observed cardiovascular risk reduction -9%(-24 to +8)

Smink et al.; Clin Pharm & Ther 2013 In Press
Validation of the PRE score (a multiple risk response score): score developed in RENAAL and applied to IDNT.

Smink et al.; Clin Pharm & Ther 2013 In Press
CONCLUSIONS

• Cardiovascular/Renal risk is determined by multiple different risk factors such as age, high blood pressure, cholesterol etc.

• Multiple risk scores (like Framingham/ UKPDS score) determine the CV/renal risk of subjects. The risk scores are based on the combination of single parameters that each affect CV/renal outcome.

• Targeting and lowering the modifiable individual risk parameters with different single drugs is the current treatment guideline, and should lead to CV/renal protection.

• Drug registration is based on the effect of a single drug on such a risk factor (hypertension, cholesterol etc) and will usually require a post registration validation on hard outcomes (of which many fail!)
However, single drugs affect usually not only the one target parameter, but may have off-target effects.

Such off-target effects may affect the CV/renal outcome as much or more than the on-target effect.

This off-target effect can be positive or negative on CV/renal outcome.

Thus, the composite effect on “all identifiable” risk factors determines the ultimate CV/renal outcome.

The registration of drugs should reflect these multiple effects.
Advantages of the PRE score
Optimize Hard Outcome Trial Design

- Phase IIb/Phase III (hard outcome trials):
  - Better prediction of the potential results of drugs on CV/renal
  - Cost effectiveness Pharma (prevent starting or early stopping of potential negative trials)
  - Less patient exposure/burden