The future of DKD management; clinical studies

Precision Medicine in Diabetes

How to protect the kidney and cardiovascular system

CHANGE OF DAILY CLINICAL CARE?

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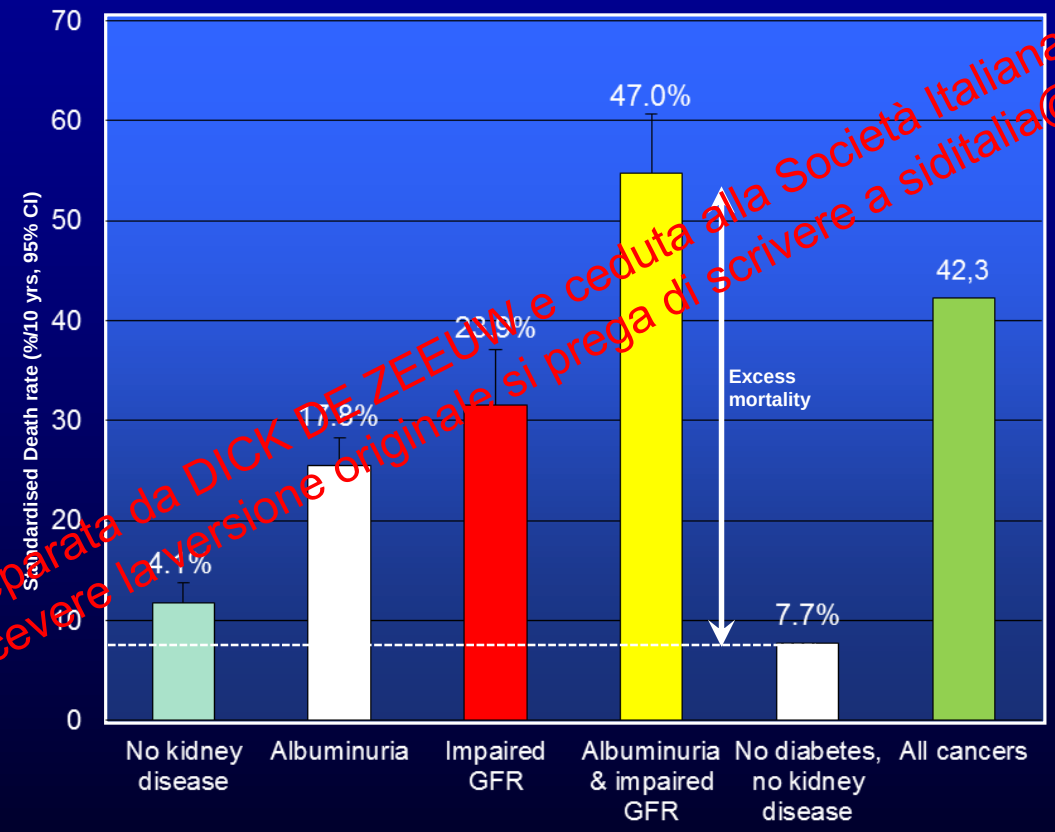
Disclosure:
Consultant/Speaker to/for:
Abbvie, Bayer, Boehringer Ingelheim, Fresenius, Janssen, Mitsubishi-Tanabe, Mundipharma

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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Definition of Personalized/Precision Medicine

A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.

Need for Personalized/Precision Medicine

Bacterial infection and cancer

In case of bacterial infection and cancer we have found that we need a specific drug for a specific patient with a specific disease.

Thus, we moved from:

One size fits all

to

A fit for each size

Need for Personalized/Precision Medicine

Diabetes leading to Renal/Cardiovascular Disease

Next to infection and cancer, diabetes is a disease with a world wide growing prevalence, and with high renal and cardiovascular morbidity and mortality

What is the treatment status in diabetes to prevent this?

Need for Personalized/Precision Medicine

Diabetes leading to Renal/Cardiovascular Disease

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

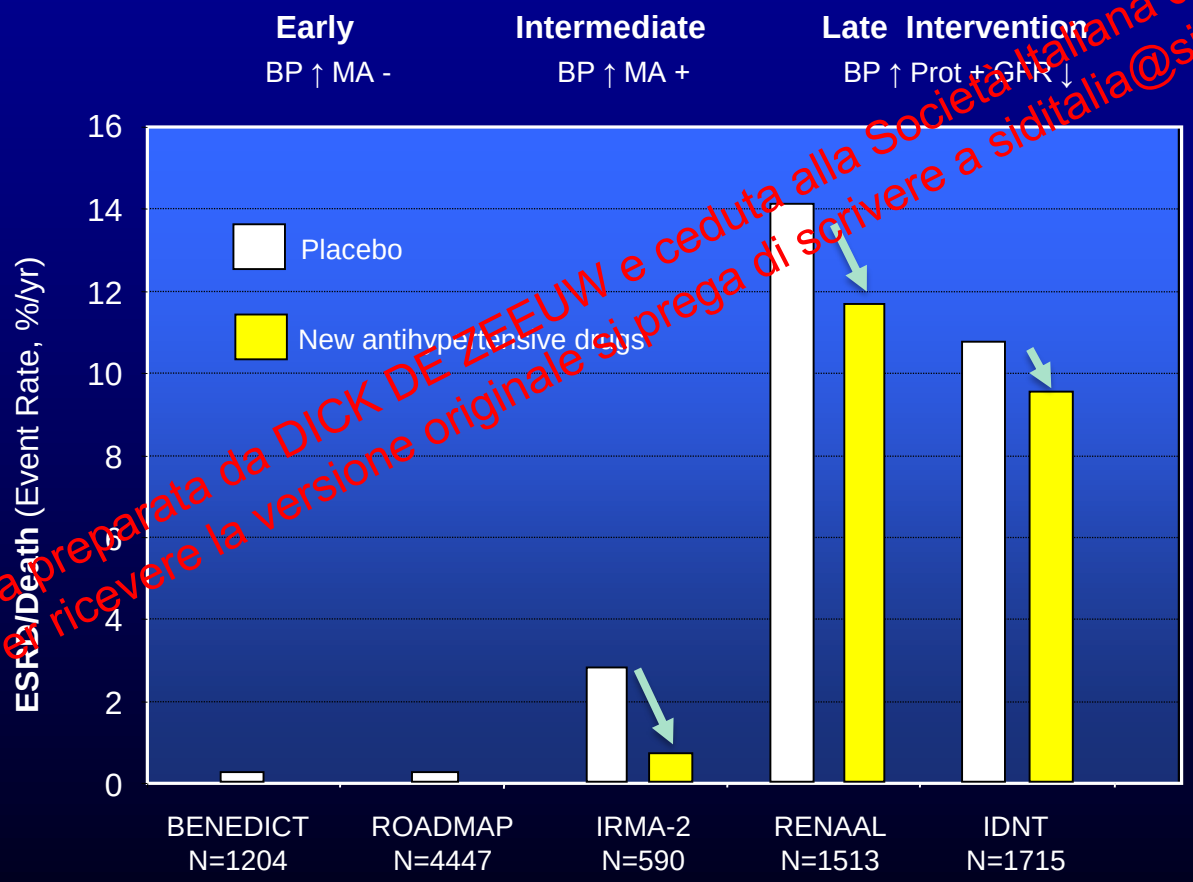
One size fits all

The guideline for treatment of renal/CV risk in diabetes gives us a recipe that should be applied to each patient!

Is this correct?

The last succesfull trials to reduce renal risk in type 2 diabetes with nephropathy: RENAAL and IDNT HIGH RESIDUAL RISK

Renal protection by new antihypertensive drugs with marked residual risk



Succes and Failure of hard outcome trials to stop Cardiovascular/Renal risk in type 2 diabetes

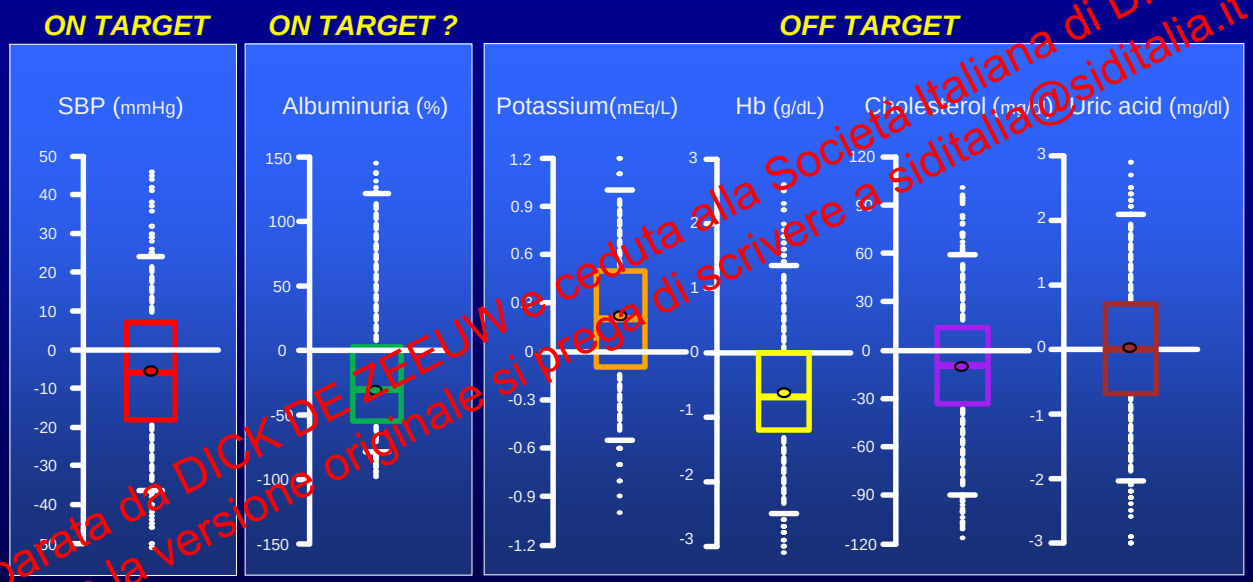
- ***Successful trials:***
  - *Control of blood pressure (and albuminuria)*
    - RENAAL
    - IDNT
    - IRMA-2
    - STENO-2

- ***Failed Trials***
  - *More control of blood pressure and albuminuria, hemoglobin, inflammation*
    - SUN (sulodexide)
    - TREAT (EPO; darbepoetin)
    - ALTITUDE (dual RAAS; DRI)
    - VA-NEPHRON-D (dual RAAS)
    - BEACON (inflammation; bardoxolone)
    - ASCEND (endothelin antagonist; avosentan)

Reason for failure of these trials
“Non-responders and Multiple drug effects”

1. Non-responders (no effect on target)
2. Drugs have more than one effect (off target effects)
   a) Good off target effects (more CV/renal protection)
   b) Bad off target effects (no CV/renal protection)

A single antihypertensive drug (losartan) changes at least six risk factors with different impact on renal outcome



Effect on										
Surrogate	**Fall**		**Fall**		**Rise**	**Fall**	**Fall**	**Fall**
Renal Outcome	**+**		**+**		**-**	**-**	**+**	**+**

Schievink et al; BJCP 2015

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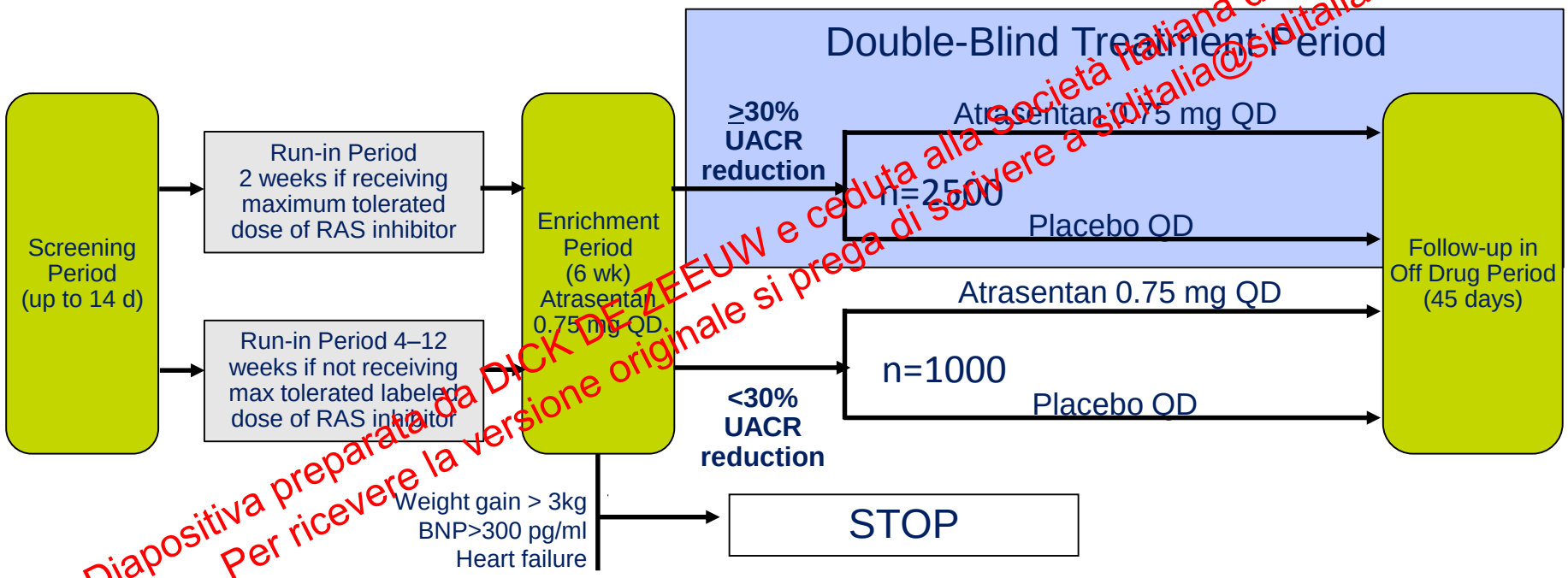
Future solution for new trials
“Personalized approach”

1. Do trial like SONAR:
   a) With multiple targets (good and bad)
   b) Including only responders for the good target
   c) Excluding patients with bad off-target effects

2. Do trial like CREDENCE with a drug:
   a) With multiple good target effects
   b) No off-target bad effects

Trial scheme (enrichment design)



Heerspink et al; Diabetes Obesity Metab 2018: 20(6):1369-1376

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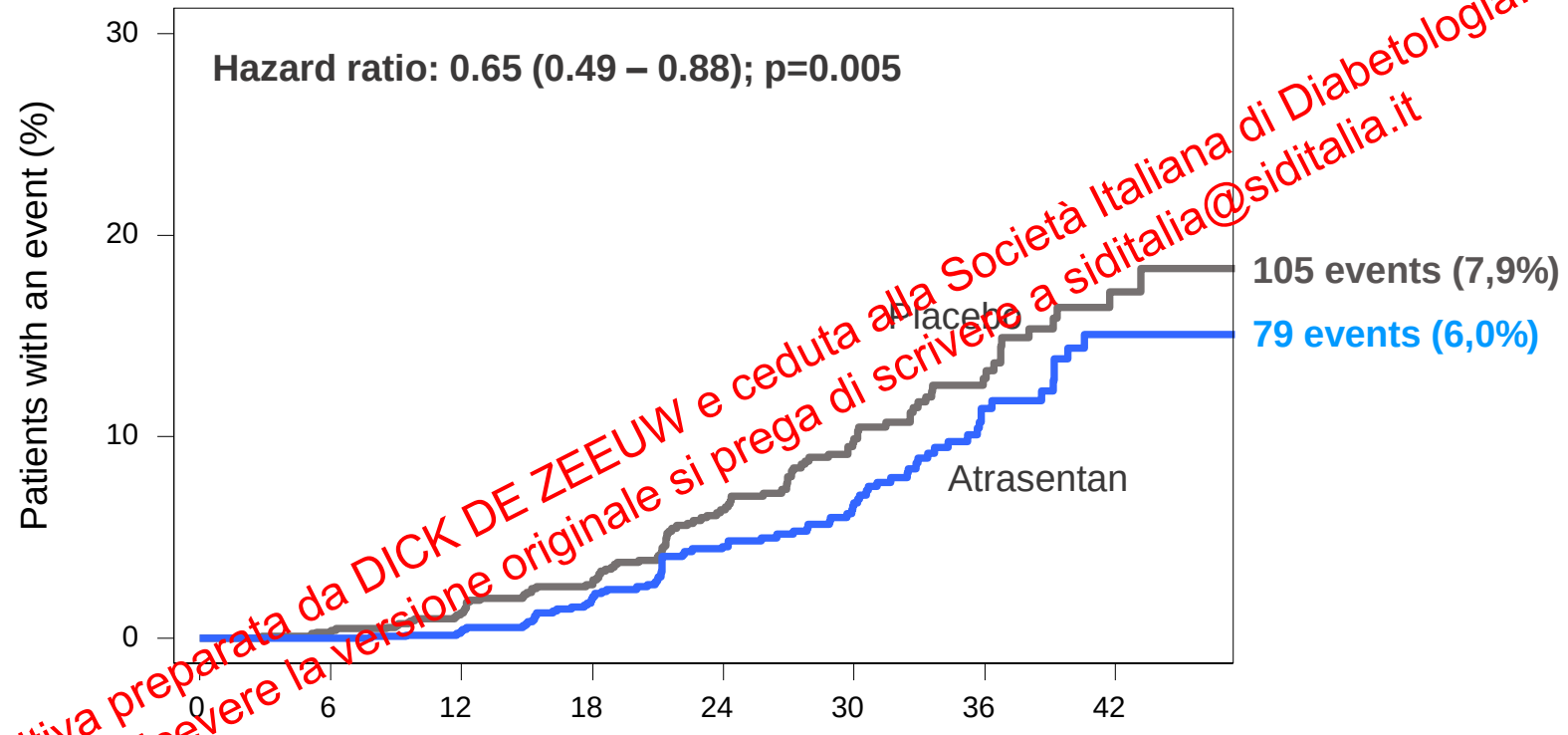
Results

Primary outcome (Doubling serum creatinine or ESRD)*

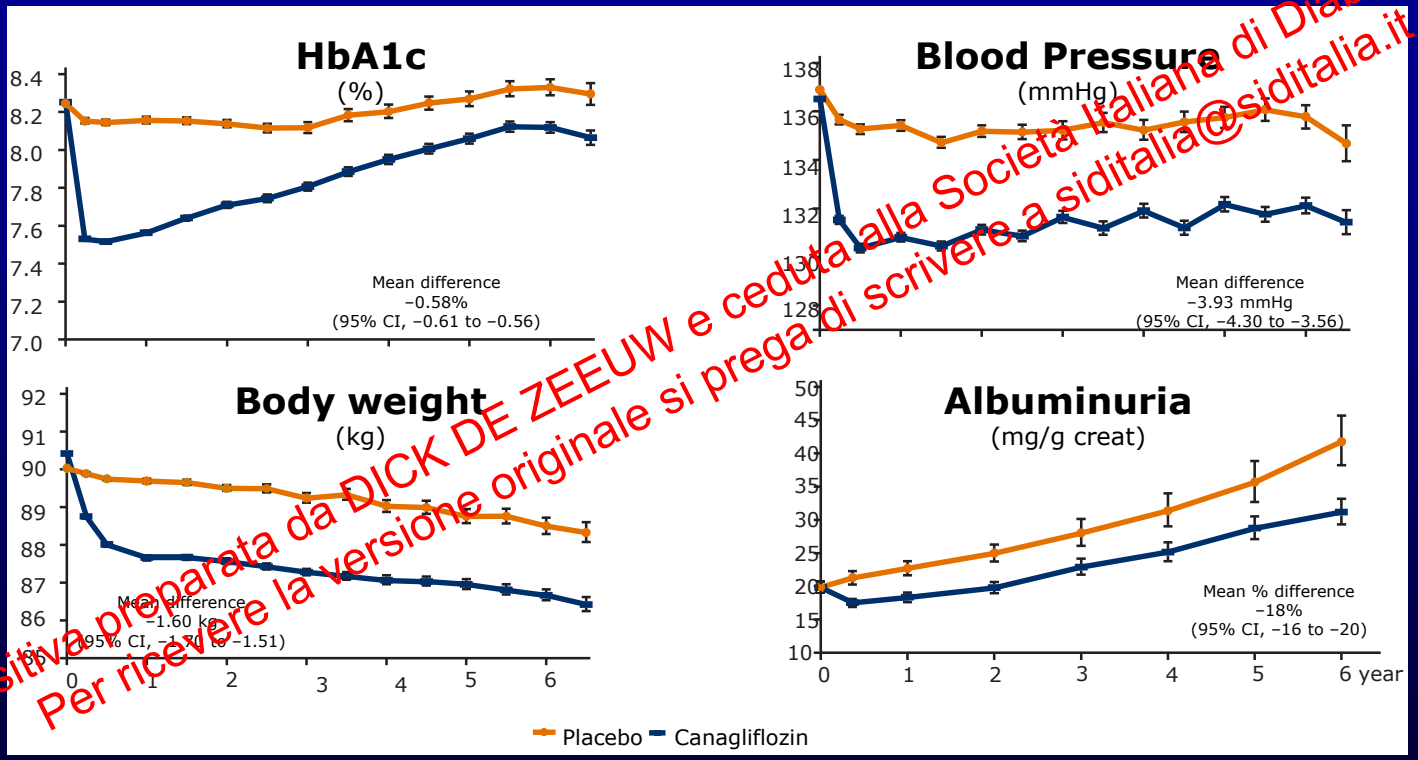


No. at risk								
Placebo	1323	1259	1091	914	685	466	234	103
Atrasentan	1325	1267	1096	888	690	496	248	108

** ESRD: defined as eGFR < 15 ml/min/1.73 m^2 confirmed at 90 days, receiving chronic dialysis, renal transplantation or renal death*

Heerspink et al; Lancet 2019

A single pill, the SGLT-2 inhibitor Canagliflozin, lowers 4 important CV and renal risk factors at the same time (A POLYPILL!)



Data from: Neal B et.al. N Engl J Med. 2017

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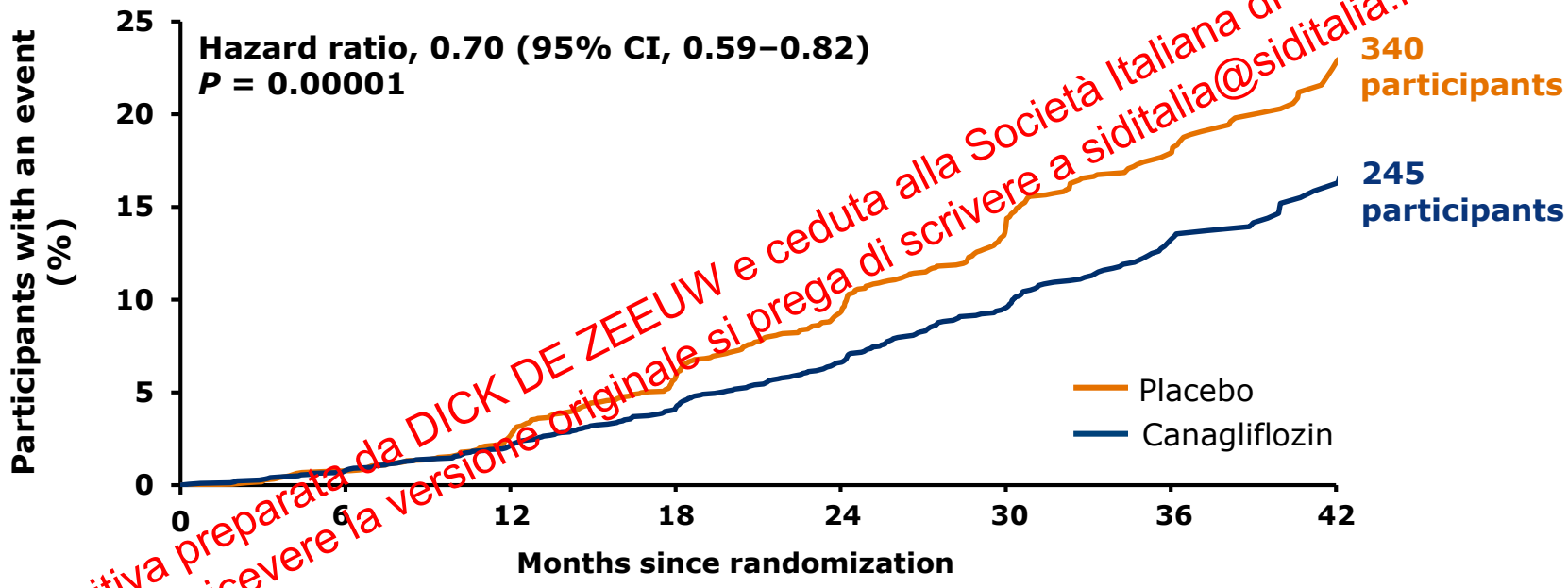
Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic et al, NEJM April 14, 2019; DOI: 10.1056/NEJMoa1811744

CREDENCE

Conclusion

In patients with type 2 diabetes and nephropathy, current guideline treatment with ACEi/ARB leaves a larger proportion of patients with high renal (and CV) risk

Many new drugs (on top of ACEi/ARB) have been tried to further reduce this risk, without succes, likely due to: little effect on target, and/or non-target effects that offset the target effect.

With enrichment design or with a multiple target drug, we, finally, after 20 years have two new drugs that have significant impact:

- Atrasentan in reducing renal risk
- Canagliflozin in reducing renal and cardiovascular risk

Future

- Although CREDENCE and SONAR delivers a new improved kidney and CV protection, there is still very high residual risk due to non-response

- Apparently we are still not having enough personalized approach.

Possible solutions should look at the individual approach:

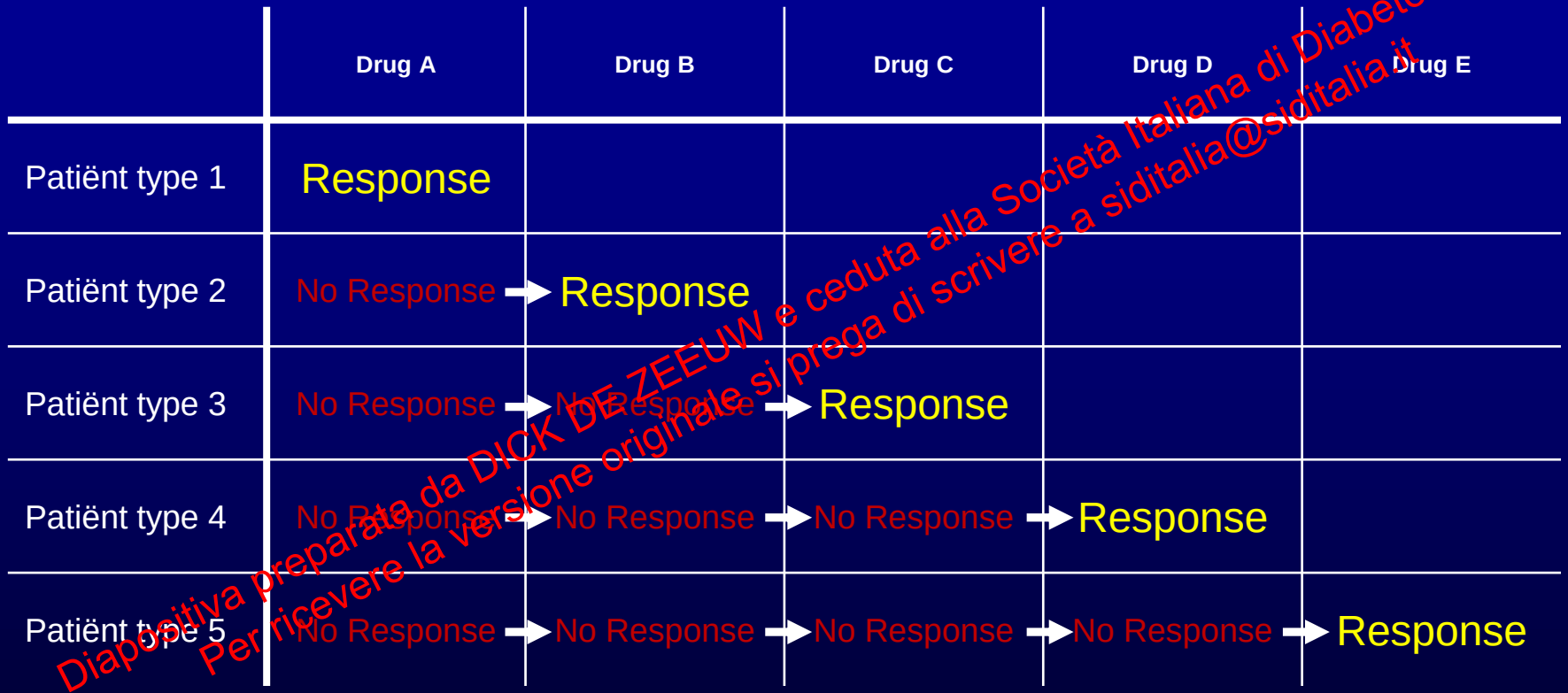
- Trial level: Platform/Umbrella trials
- Daily/regular care practice: Decision Support system using multiple parameter response scores for each individual patient

“Possible Solutions” to improve trial outcome and individual patient care
Precision medicine for renal/CV protection

Change the practice of:

1. Drug trial methodology from group to the ”individual good responders”
   - Do enrichment designs / do umbrella/platform designs
   - For response use : multiple parameter response scores
2. Doctor in prescribing/protecting the individual patient

Future for trials: Umbrella & platform trial designs



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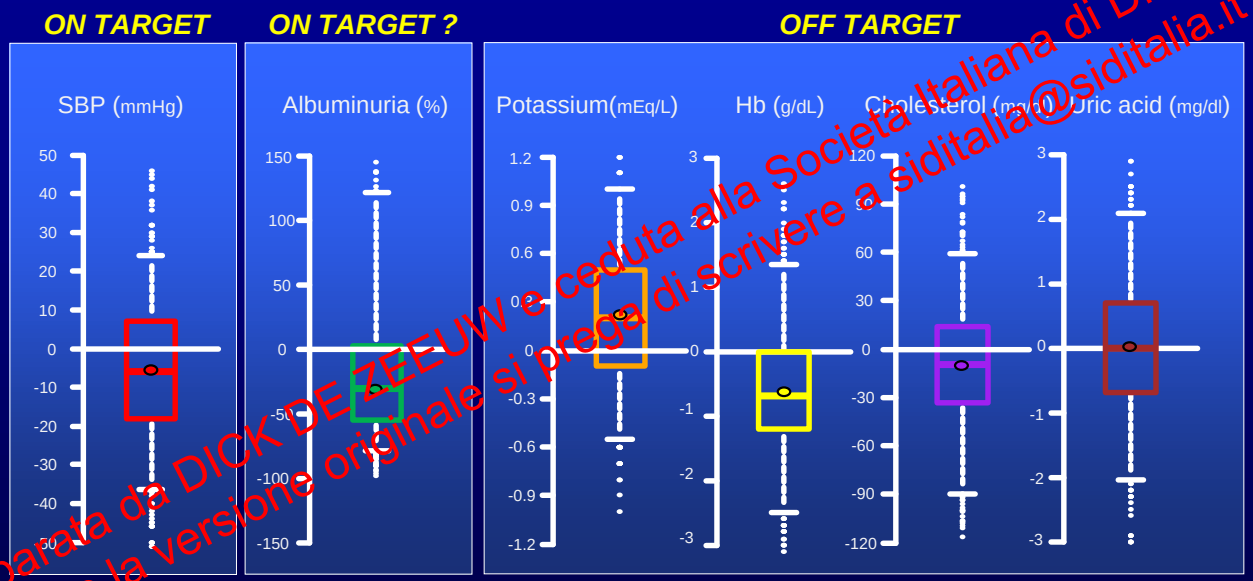

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Schievink et al; BJCP 2015

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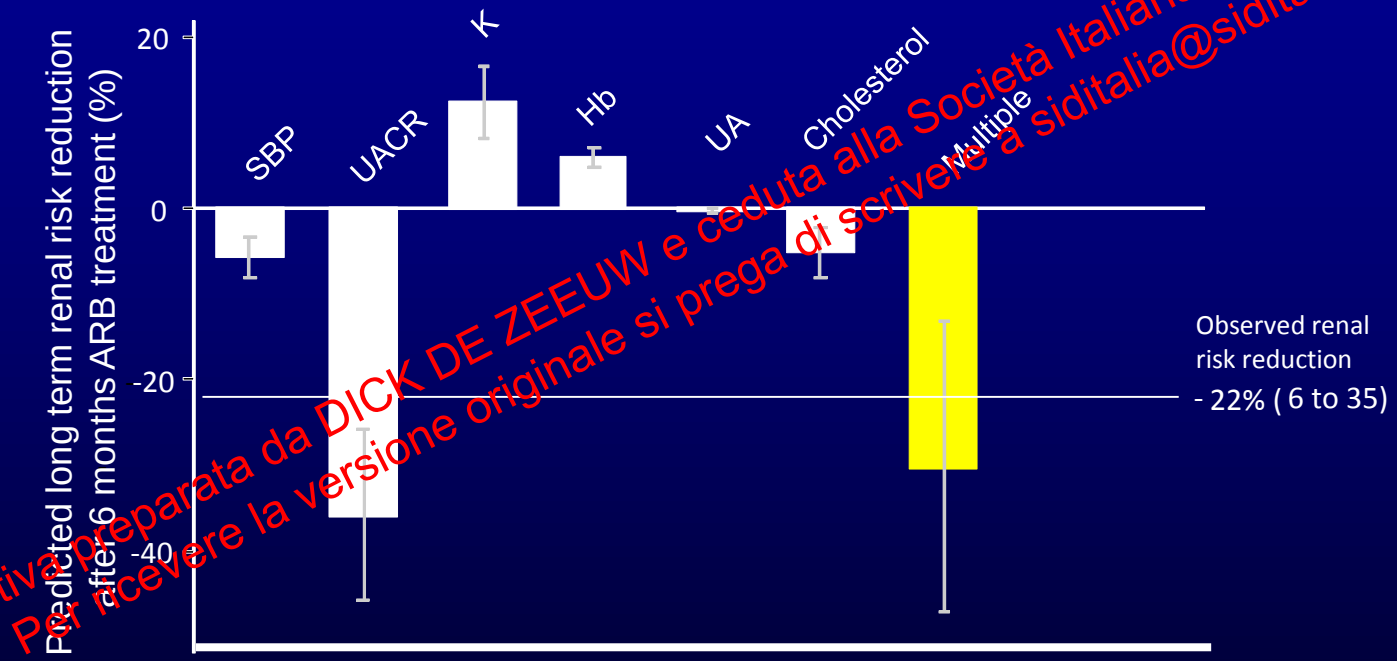
Changes of the individual risk factors by a blood pressure lowering agent (losartan) have their own and a group effect on renal outcome



Smink et.al.; Clin Pharm & Ther 2014

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ALTITUDE: Predicting Renal/CV outcome with PRE-Score on basis of 6 mo effects in AVOID

Smink et al; EJPC 2013

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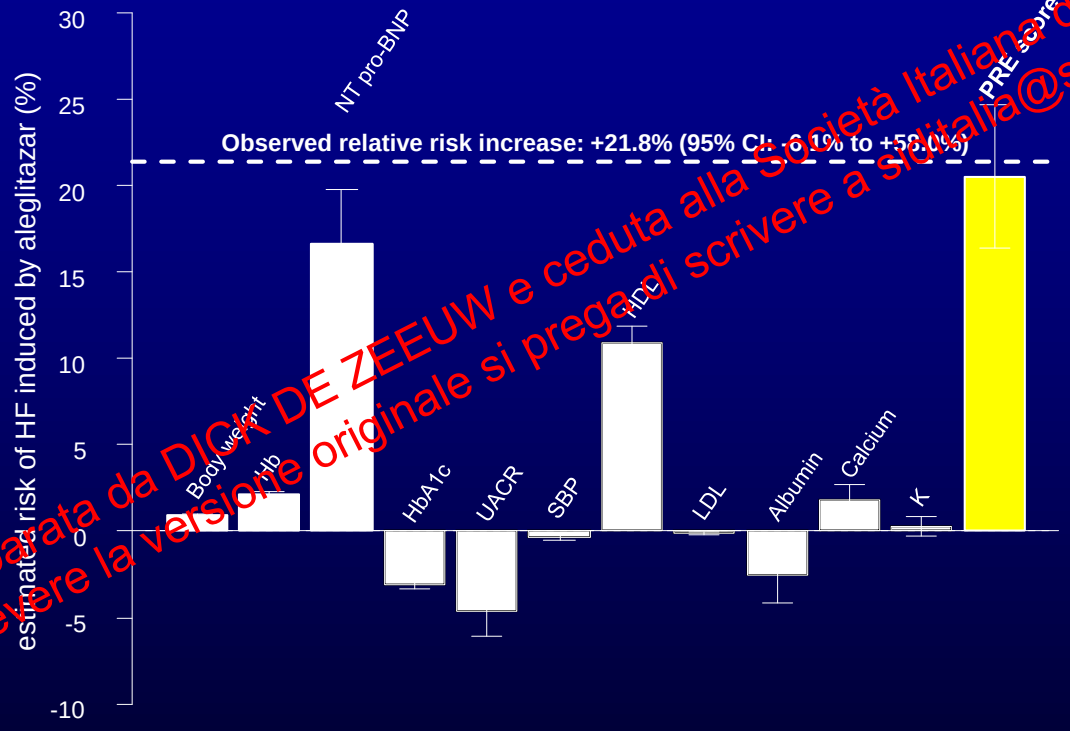
ALECARDIO: Predicting HF outcome in T2D with the PRE-Score after 6 months aleglitazar therapy



Schievink et al; Submitted

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“Possible Solutions” to improve trial outcome and individual patient care
Precision medicine for renal/CV protection

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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

Precision medicine for renal/CV protection to practice
Doctor's practice

- Use an algorithm that calculates the renal/CV risk for a patient on the basis of multiple available risk factors (e.g. blood pressure, cholesterol, glucose, potassium, albuminuria, etc).
- Start a therapy that changes these risk factors.
- Measure the change in all the risk factors, and use an algorithm to calculate the renal/CV risk reduction for that patient.
- Adjust the therapy (change dose, stop and start new therapy) to improve the changes in the risk factors and outcome
- Repeat this cycle untill renal/CV risk is acceptable to patient/doctor

Test whether this works better than regular care in a clinical setting

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:

- ?

Conclusion

In patients with type 2 diabetes and nephropathy, current guideline treatment leaves a larger proportion of patients with high renal (and CV) risk

Is this preventable?:

YES PRECISION MEDICINE

but

Conclusion
Is the progression of DKD preventable?

YES, But it is difficult:

1. We need to leave the road of general guideline treatment and dive into the individual mechanism and treatment of disease

2. We need to find better risk markers that define the mechanism of disease progression of that individual and we need to find a therapy for that individual mechanism

3. Finally, we need to not only start prevention when there is already progression of disease, but we need to start much earlier with true prevention of disease.