Clinical Perspectives from Recent CKD Trials

Failure of hard outcome renal CKD progression trials
New avenues?

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Disclosure:
Consultant to AbbVie, Astellas, AstraZeneca, Chemocentryx, Fresenius, Hemocue, Janssen, Novartis, Pfizer, Reata, Takeda;
honoraria paid to Institution

Recent failed trials in CKD protection

- Recently failed CKD progression trials:
  - ON-TARGET (dual RAAS)
  - SUN (sulodexide)
  - TREAT (EPO; darbepoetin)
  - ALTITUDE (dual RAAS; DRI)
  - VA-NEPHRON-D (dual RAAS)
  - BEACON (inflammation; bardoxolone)
  - ASCEND (endothelin antagonist; avosentan)

Reason for trial failure

- the new therapies are developed on the assumption that the intervention is providing additive renal (CV) protection
- Indeed, many of the failed trials conclude that the investigational drug was failing because of the characteristics of the drug itself or because of the wrong target/surrogate

I submit the hypothesis that it is not the wrong drug but the wrong trial design that might explain the trial failures

Trial failure; design issues?

- Recently failed CKD progression trials:
  - ON-TARGET (dual RAAS)
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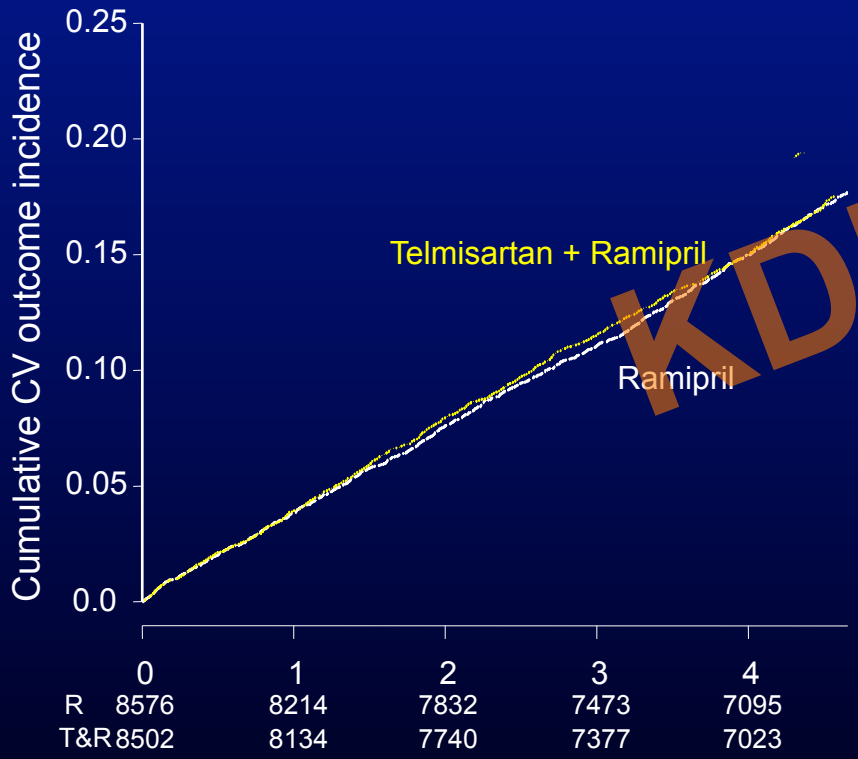
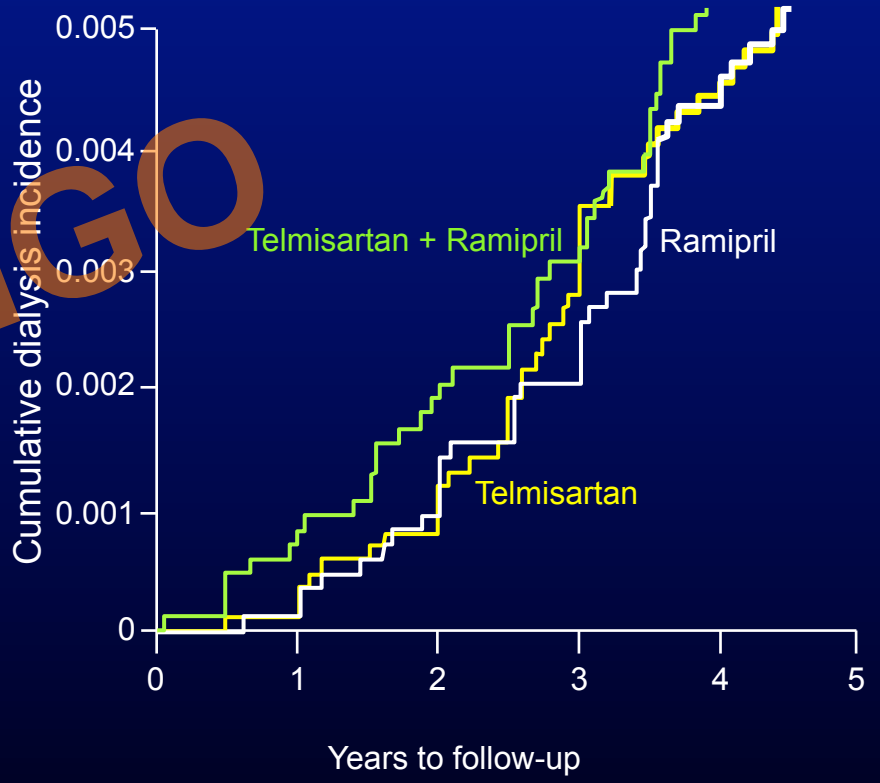
- Design issues:
  - Too low-risk population
  - No effect on surrogate
  - Too high dose
  - Wrong endpoints
  - Too many side effects

ONTARGET: CV and renal outcome during ACEi (ramipril) vs ACEi (ramipril) + AIIA (telmisartan) in high-risk patients





Yusuf S, et al. N Engl J Med 2008;358:1547–9
Mann J, et al. Lancet 2008;372:547–53

ONTARGET; Baseline albuminuria

- Microalbuminuria was present in 13.1% of all participants
  - 29.7% of those with diabetes
  - 9.2% of those without known diabetes

- Macroalbuminuria was seen in 4.0% of all participants
  - 12.2% of those with diabetes
  - 1.4% of those without known diabetes.

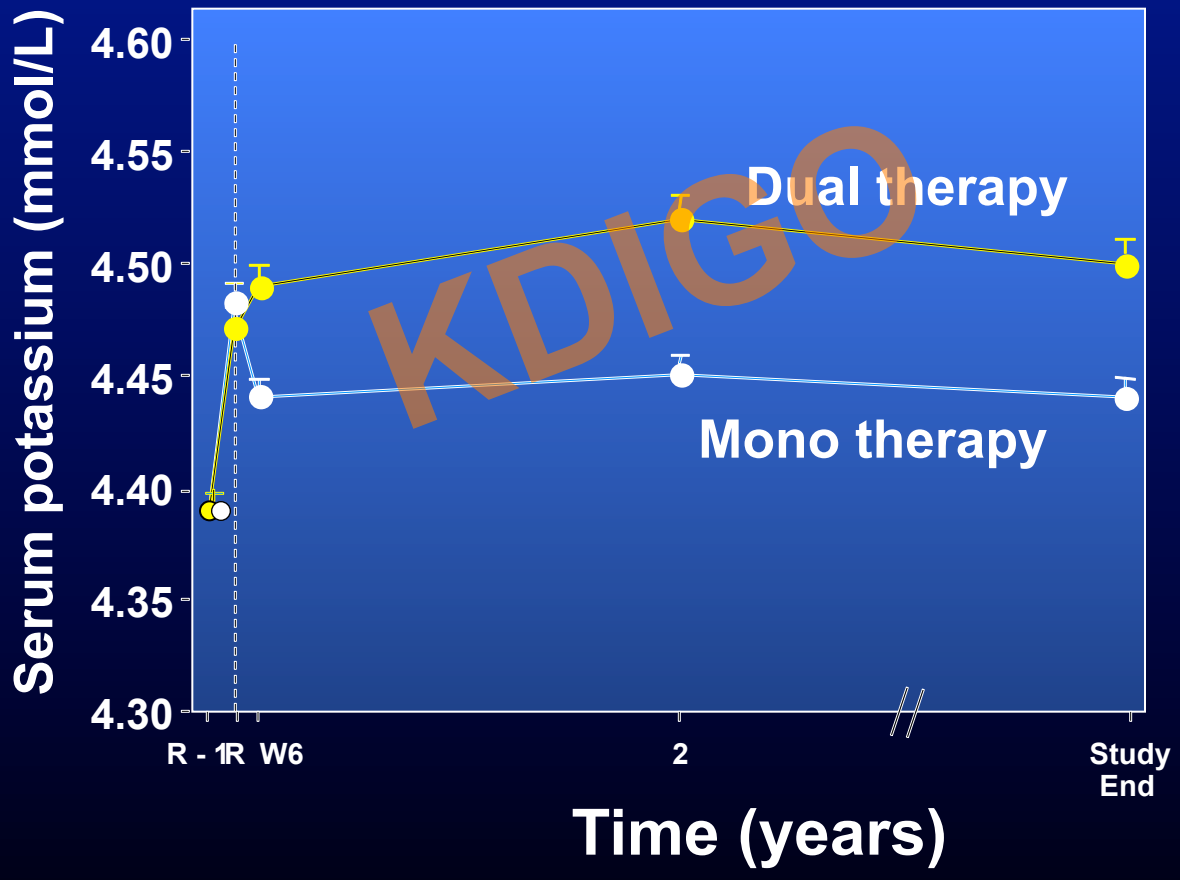
Mann JF et al; New Engl J Med 2008

ONTARGET: Incidence of primary and secondary renal outcomes and of its components

	Ramipril N	Telmisartan N	Ramipril + telmisartan N	Telmisartan *Vs* Ramipril HR	p	Ram +Telm *Vs* ramipril HR	p
All dialysis, doubling, death	1150	1147	1233	1·00	0·968	1·09	0·037
All dialysis and doubling	174	189	212	1·09	0·420	1·24	0·038
All dialysis	48	51	63	1·07	0·747	1·33	0·133
All death	1014	989	1065	0·98	0·641	1·07	0·144
Doubling	140	155	166	1·11	0·378	1·20	0·110
Acute dialysis	13	20	28	1·55	0·221	2·19	0·020
Chronic dialysis	33	31	34	0·94	0·817	1·05	0·854

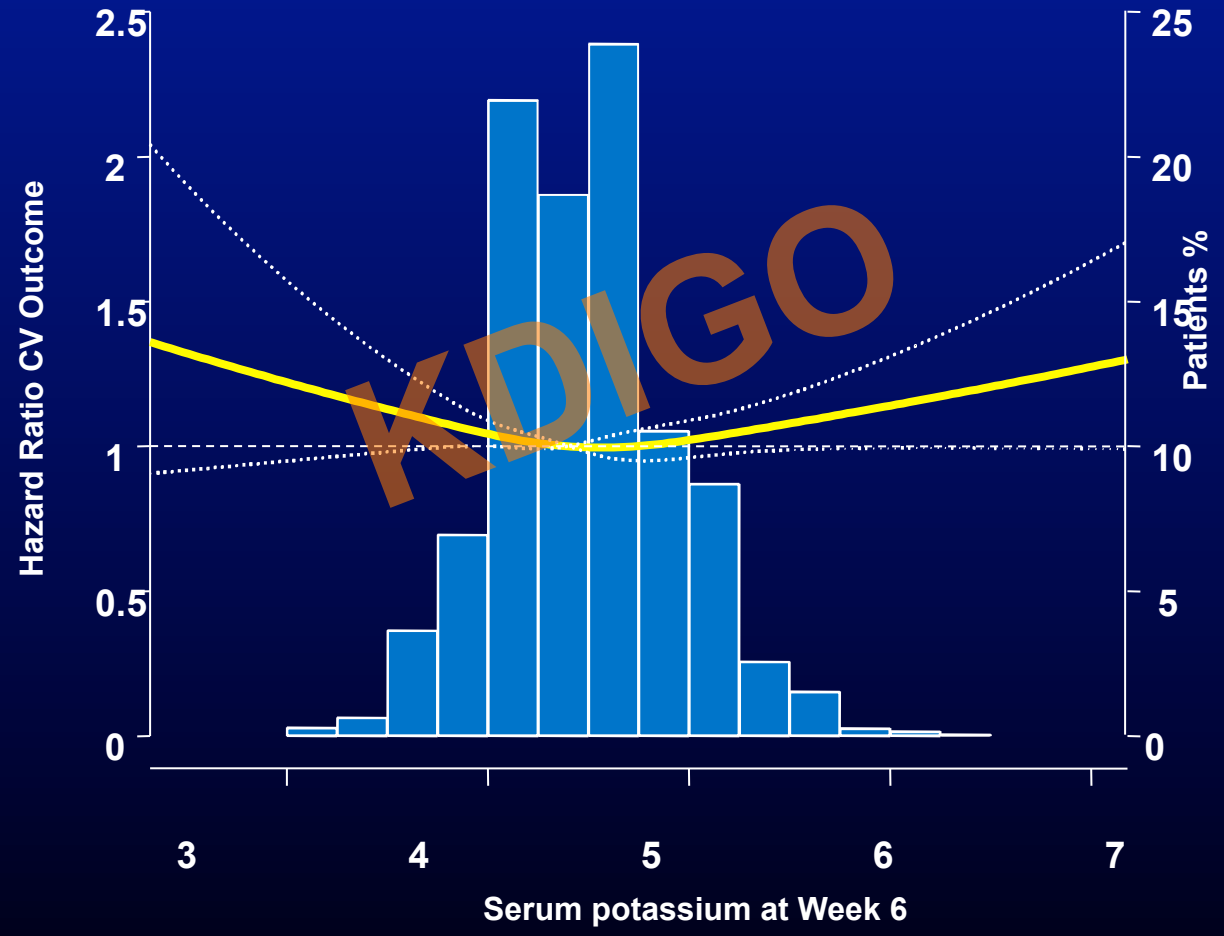
Mann JF et al; New Engl J Med 2008

ONTARGET: Effect of treatment on serum potassium



Lambers Heerspink et al; EJPC 2014

ONTARGET: Relationship on-treatment serum potassium and cardiovascular outcome



Adjusted risk: Age, gender, diabetes, eGFR, UACR, systolic blood pressure, diuretics

Lambers Heerspink et al; EJPC 2014

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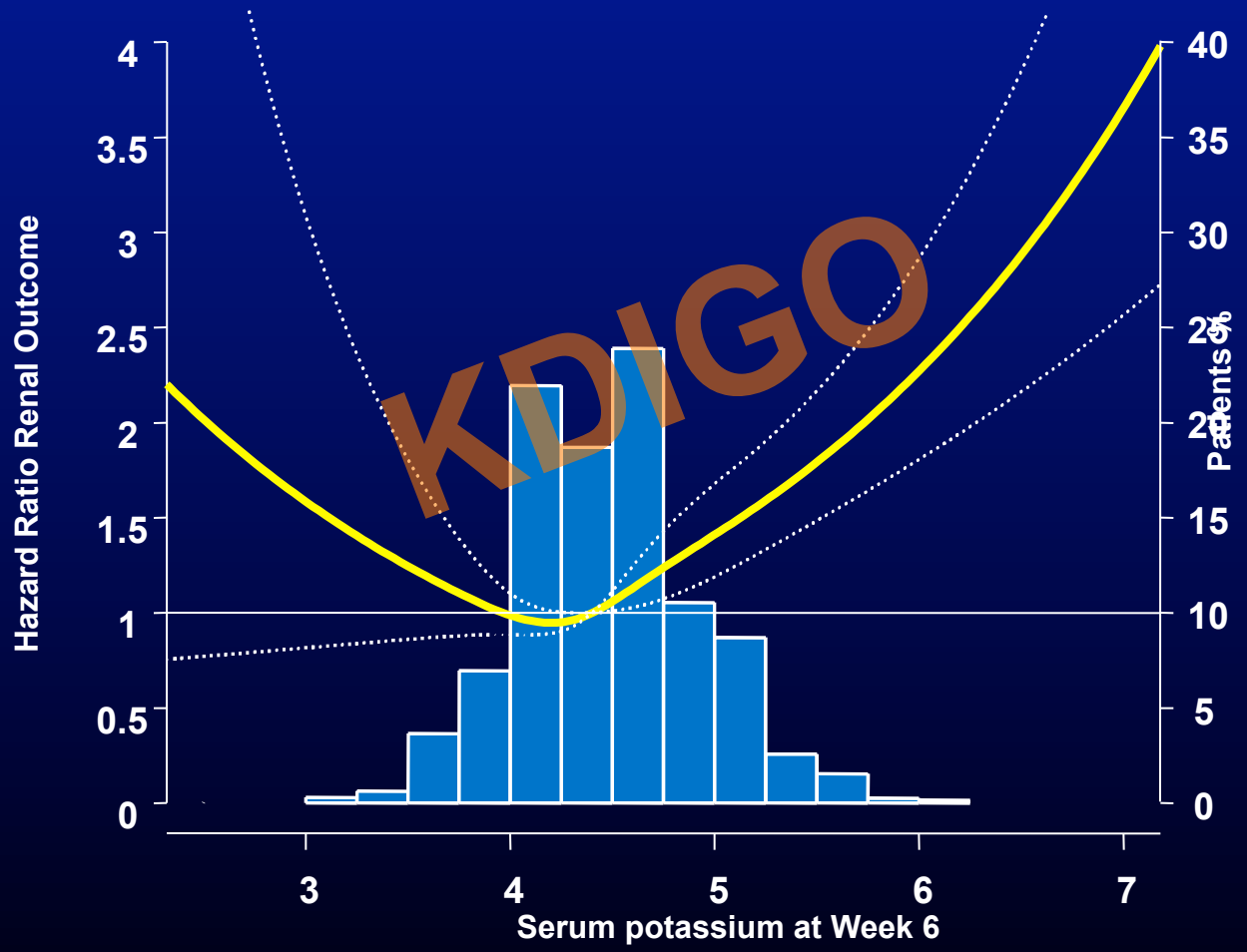
ONTARGET: Relation week-6 serum potassium and renal outcome



Adjusted risk: Age, gender, diabetes, eGFR, UACR, systolic blood pressure, diuretics

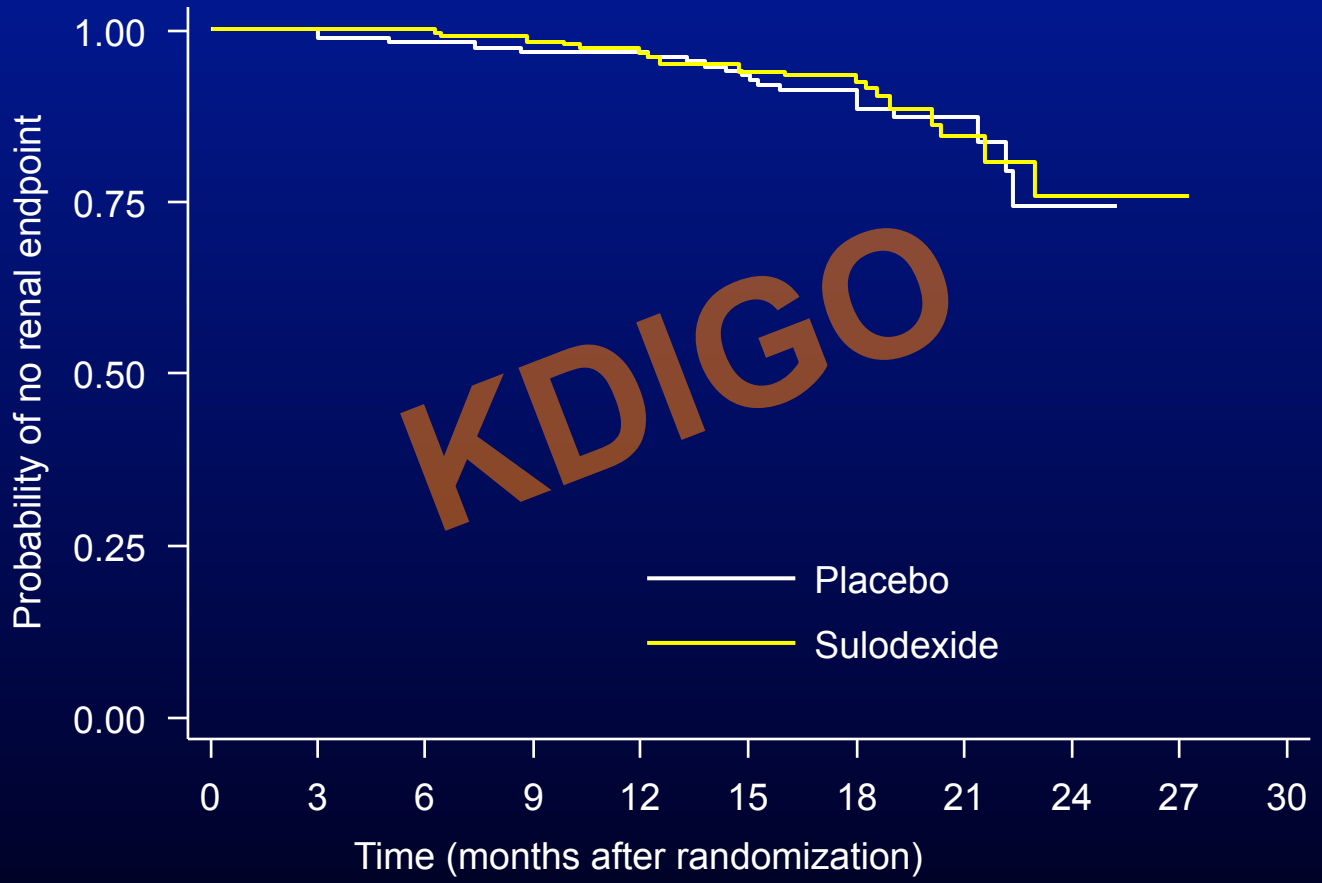
Lambers Heerspink et al; EJPC 2014

Trial failure; design issues?

- Recently failed CKD progression trials:
  - ON-TARGET (dual RAAS)
  - SUN (sulodexide)
  - TREAT (EPO; darbepoetin)
  - ALTITUDE (dual RAAS; DRI)
  - VA-NEPHRON-D (dual RAAS)
  - BEACON (inflammation; bardoxolone)
  - ASCEND (endothelin antagonist; avosentan)

- Design issues:
  - Too low-risk population — YES; eGFR >70; Macroalb 4%
  - No effect on surrogate
  - Too high dose
  - Wrong endpoints — YES; Acute dialysis
  - Too many side effects — YES; Potassium increase

SUN-Overt; effect of Sulodexide on renal outcome in type 2 diabetes with nephropathy

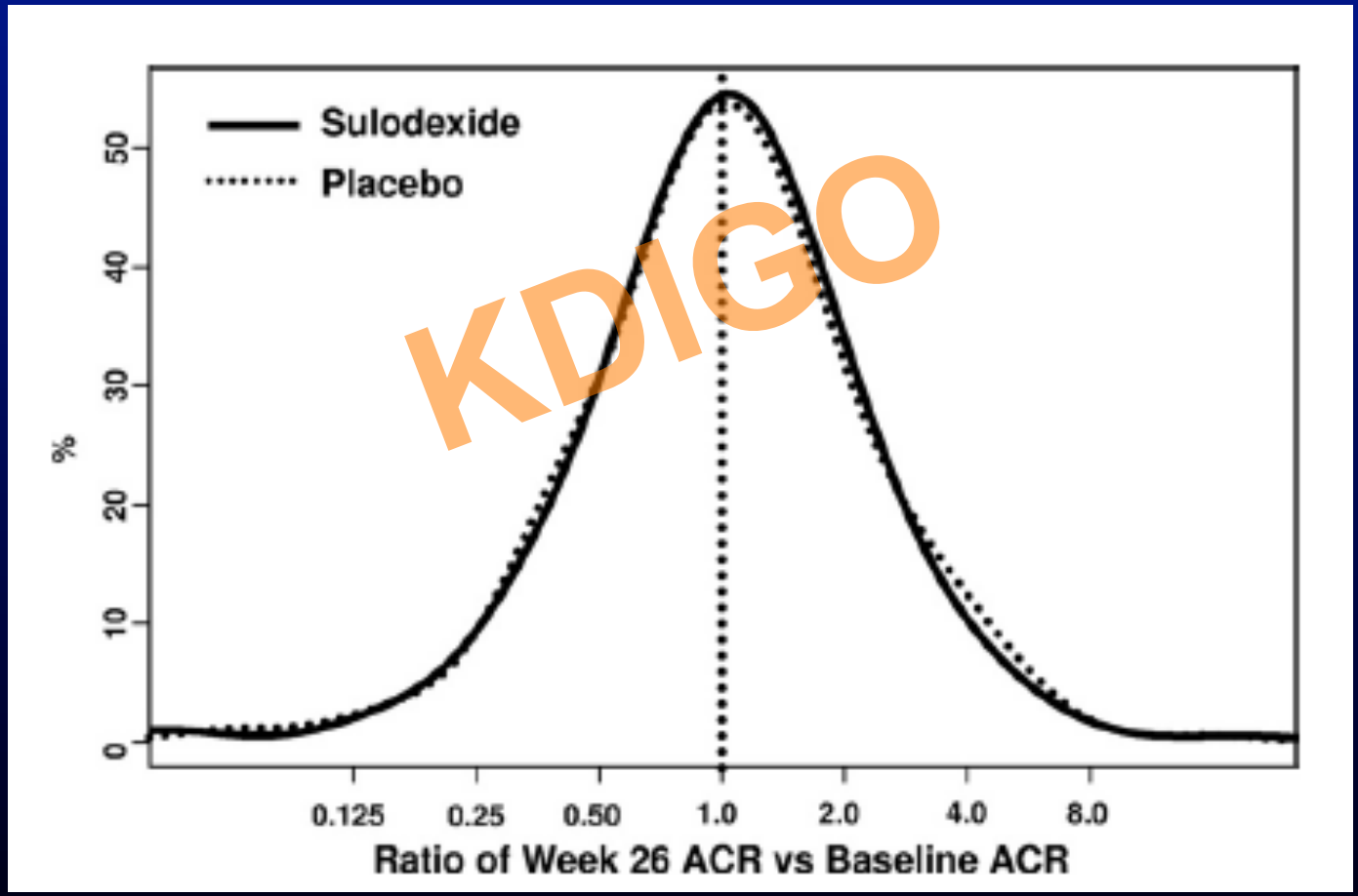


Number of participants still at risk (number of endpoints)

Placebo	580	(8)	396	(5)	243	(10)	101	(7)	6
Sulodexide	549	(0)	403	(9)	242	(9)	105	(8)	6

Packham D, et al. J Am Soc Nephrol 2012;23:123–30

SUN-Micro; effect of Sulodexide on albuminuria in type 2 diabetes with microalbuminuria



Lewis et al AJKD 2011

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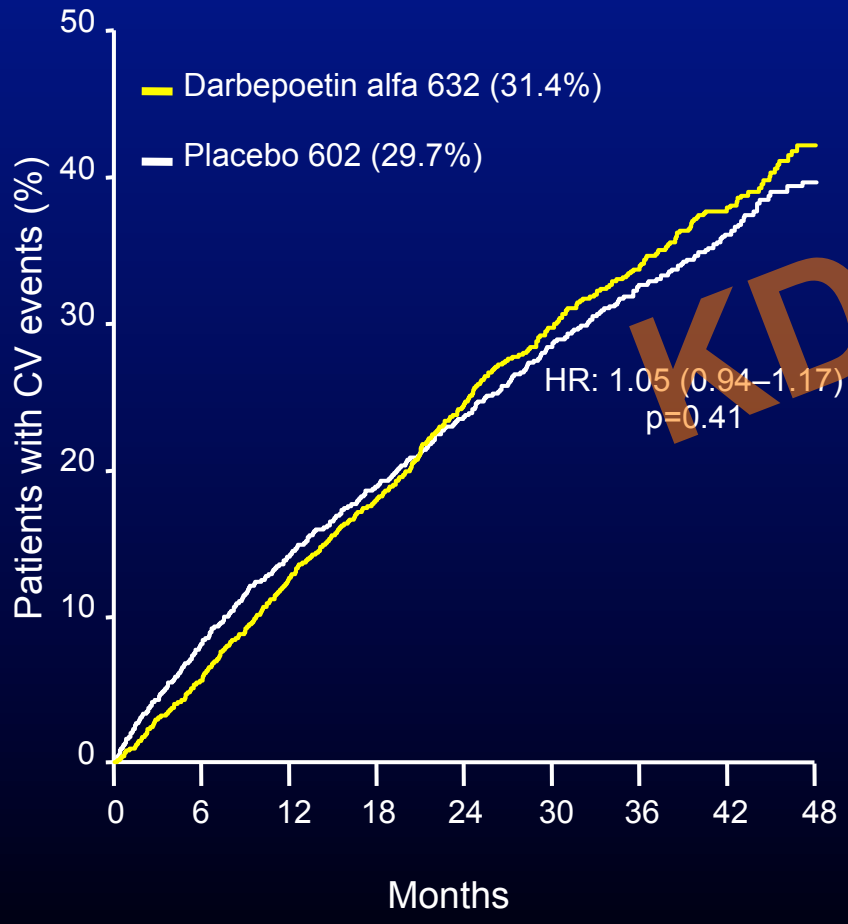
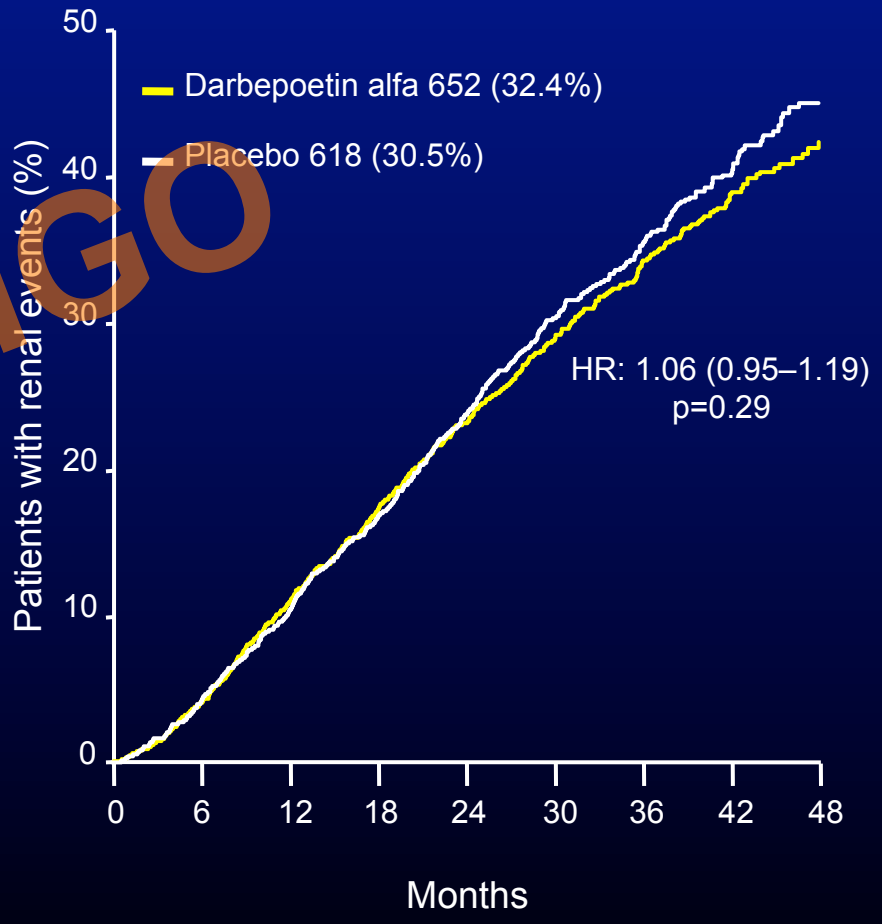
- Design issues:
  - Too low-risk population
  - No effect on surrogate YES
  - Too high dose
  - Wrong endpoints
  - Too many side effects

TREAT; CV (Death, MI, Myocardial Ischemia, HF, Stroke) and Renal (Death or ESRD) Composite





Pfeffer M, et al. N Engl J Med 2009;361:2019–32

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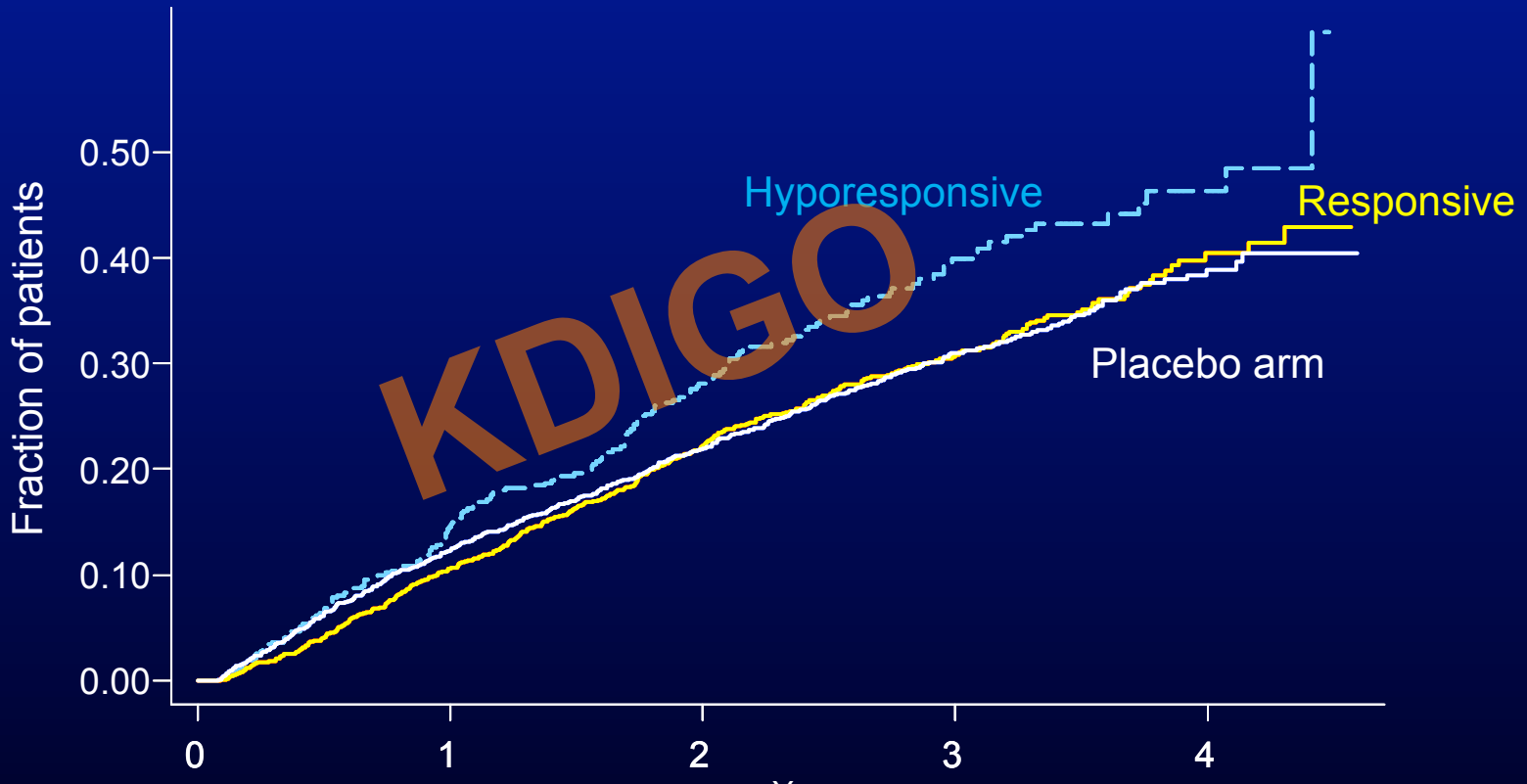
TREAT; post-hoc analysis; difference in CV outcome (Death, MI, Stroke, HF) for Hb non-responders vs responders



Number at risk					
Hyporesponsive	471	394	272	125	30
Responsive	1401	1234	854	408	94
Placebo	1889	1611	1138	514	117

Solomon S, et al. N Engl J Med 2010;363:1146–55

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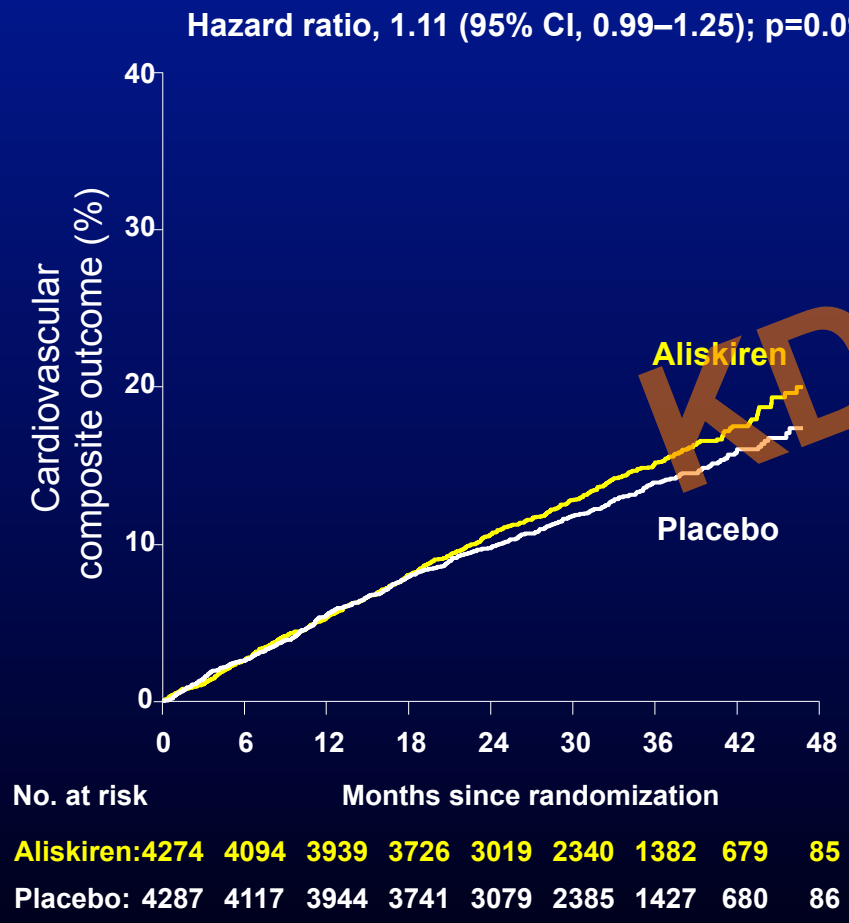
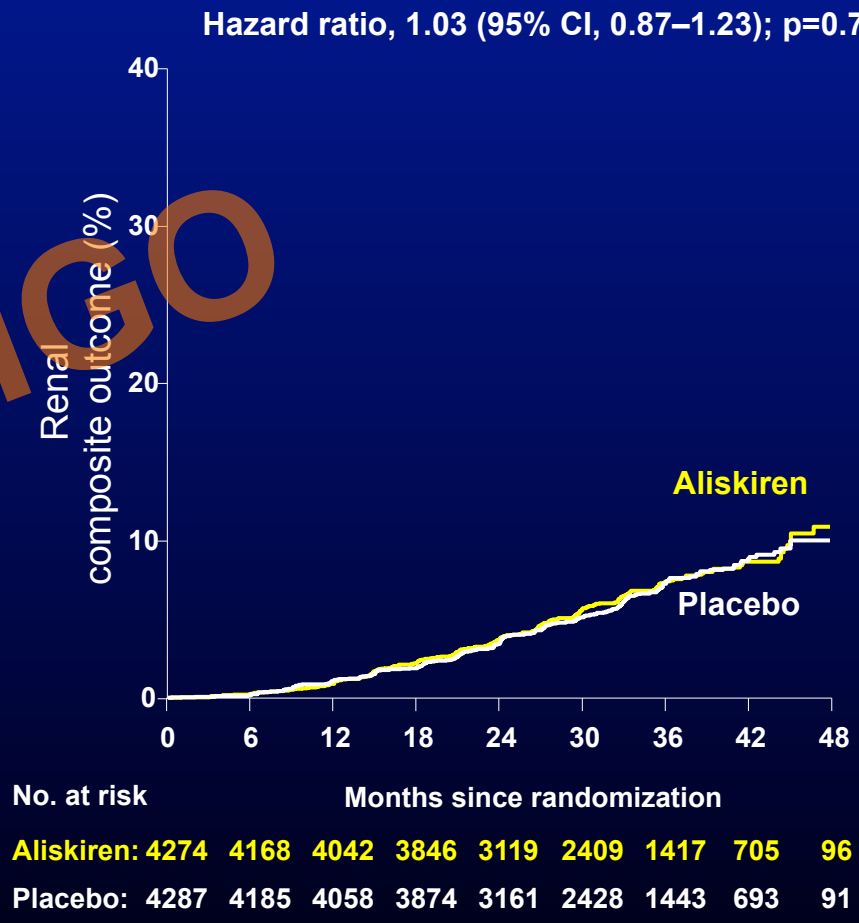
- Design issues:
  - Too low-risk population
  - No effect on surrogate — YES (with high dosing)
  - Too high dose — YES
  - Wrong endpoints
  - Too many side effects — ?

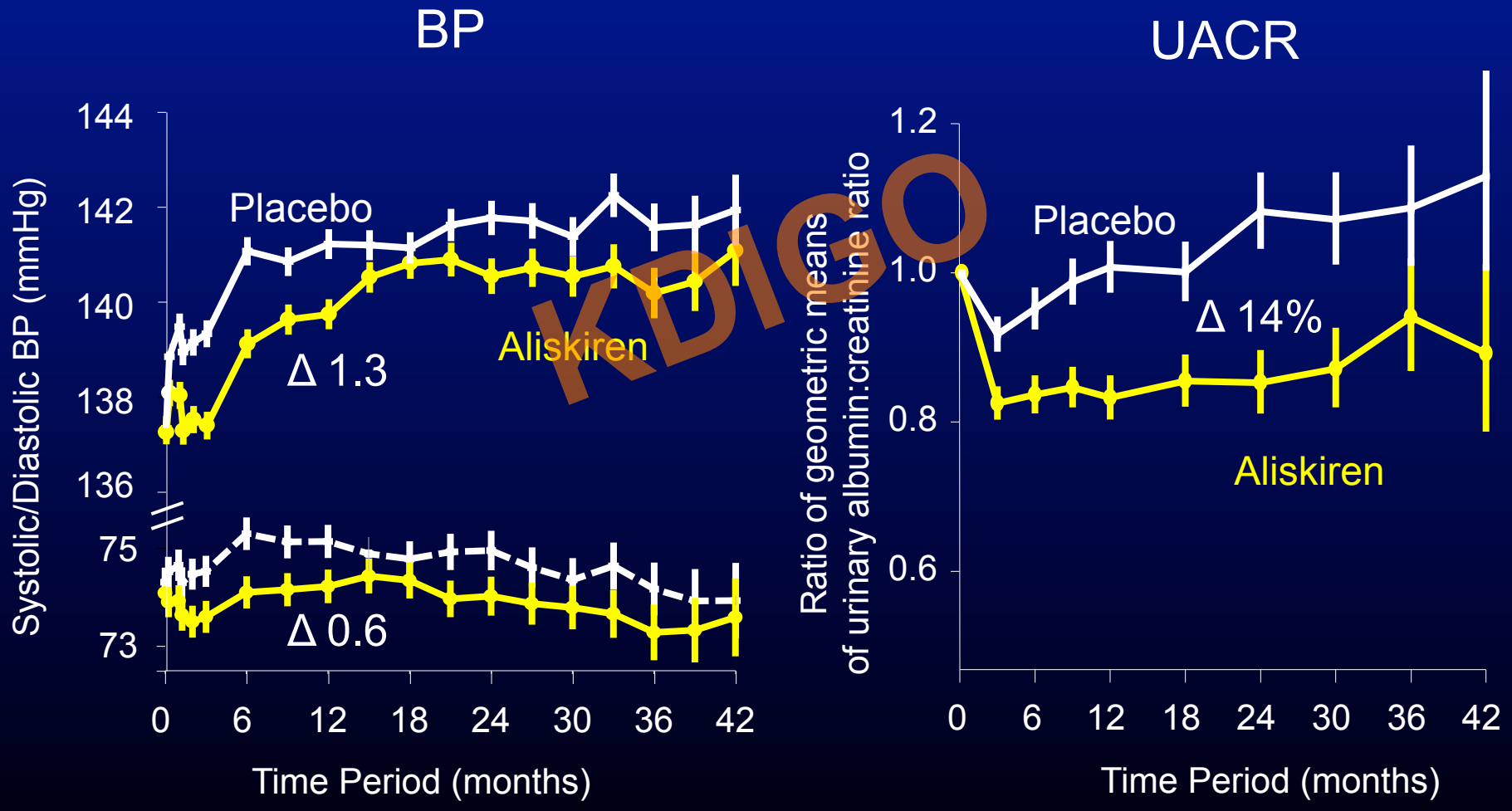
ALTITUDE:
CV and renal secondary composite endpoint





Parving H, et al. N Engl J Med 2012;367:2204–13

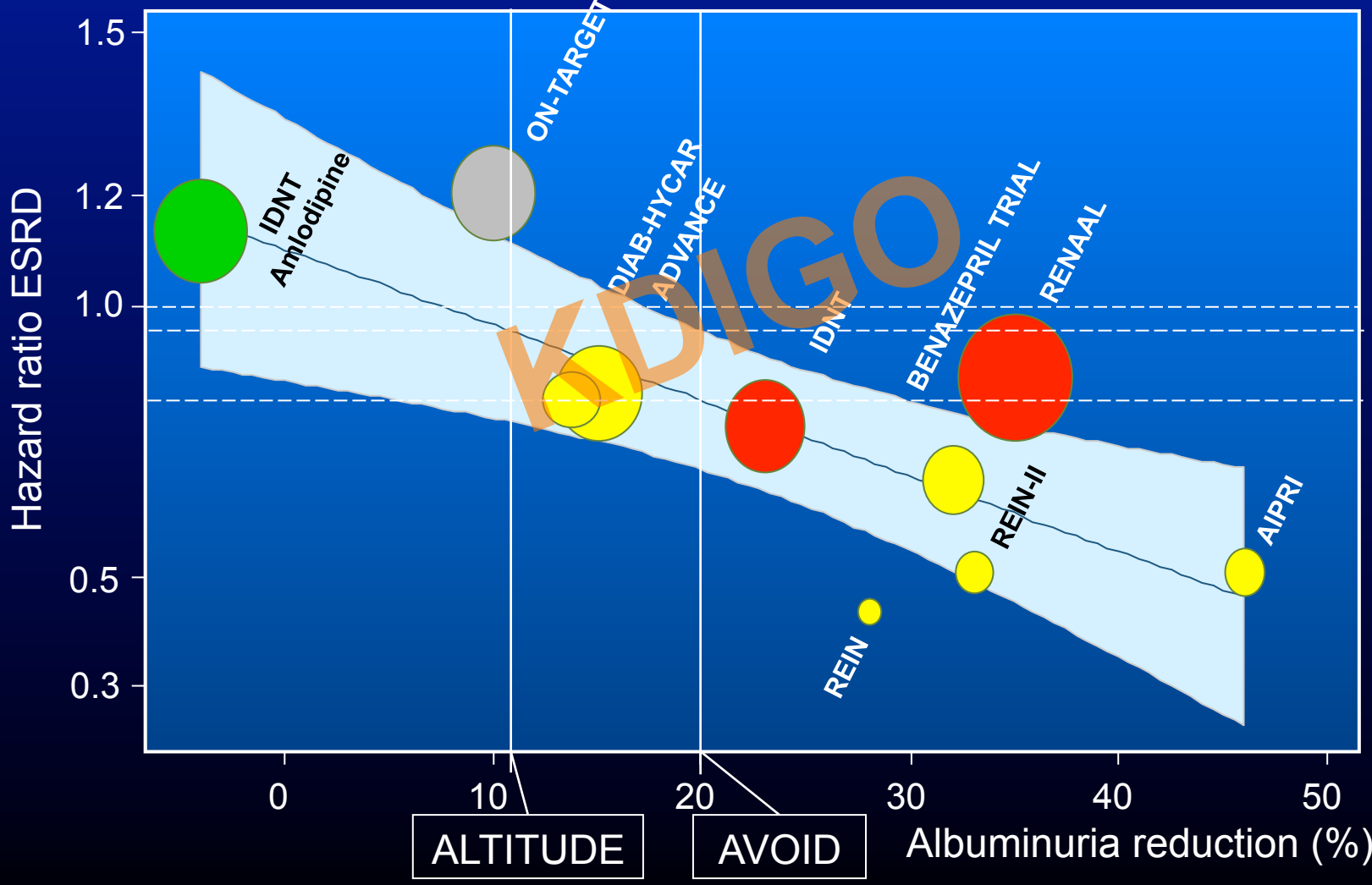
ALTITUDE; more blood pressure and albuminuria lowering during Aliskiren



Parving et al; NEJM 2012

Relationship between short-term decrease in albuminuria and long-term renal risk reduction:

different randomized clinical trials in different populations



Lambers Heerspink H, De Zeeuw D. Nephron Clin Pract 2010;116:c137–42

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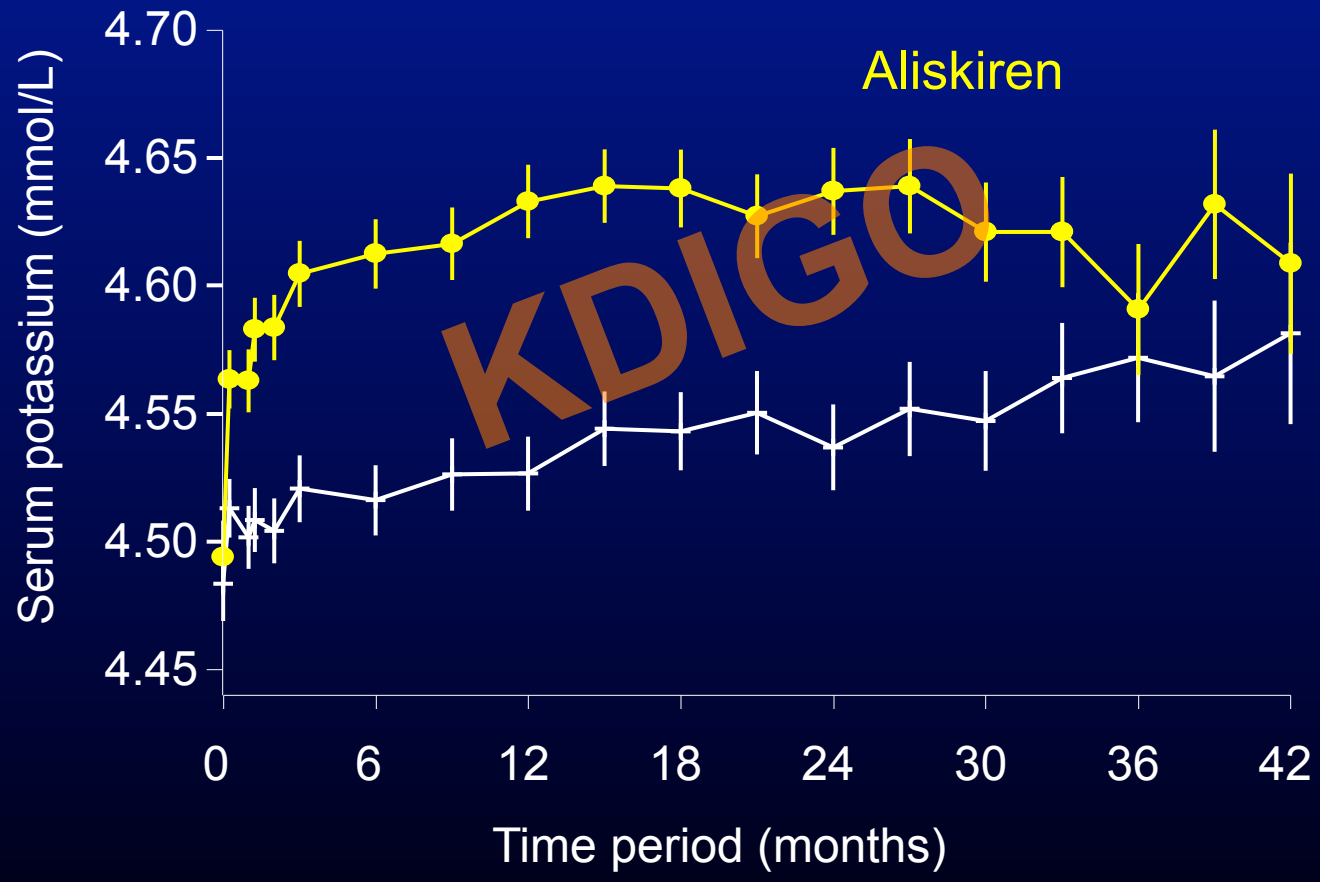
ALTITUDE; effect of Aliskiren on serum potassium course



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Trial failure; design issues?

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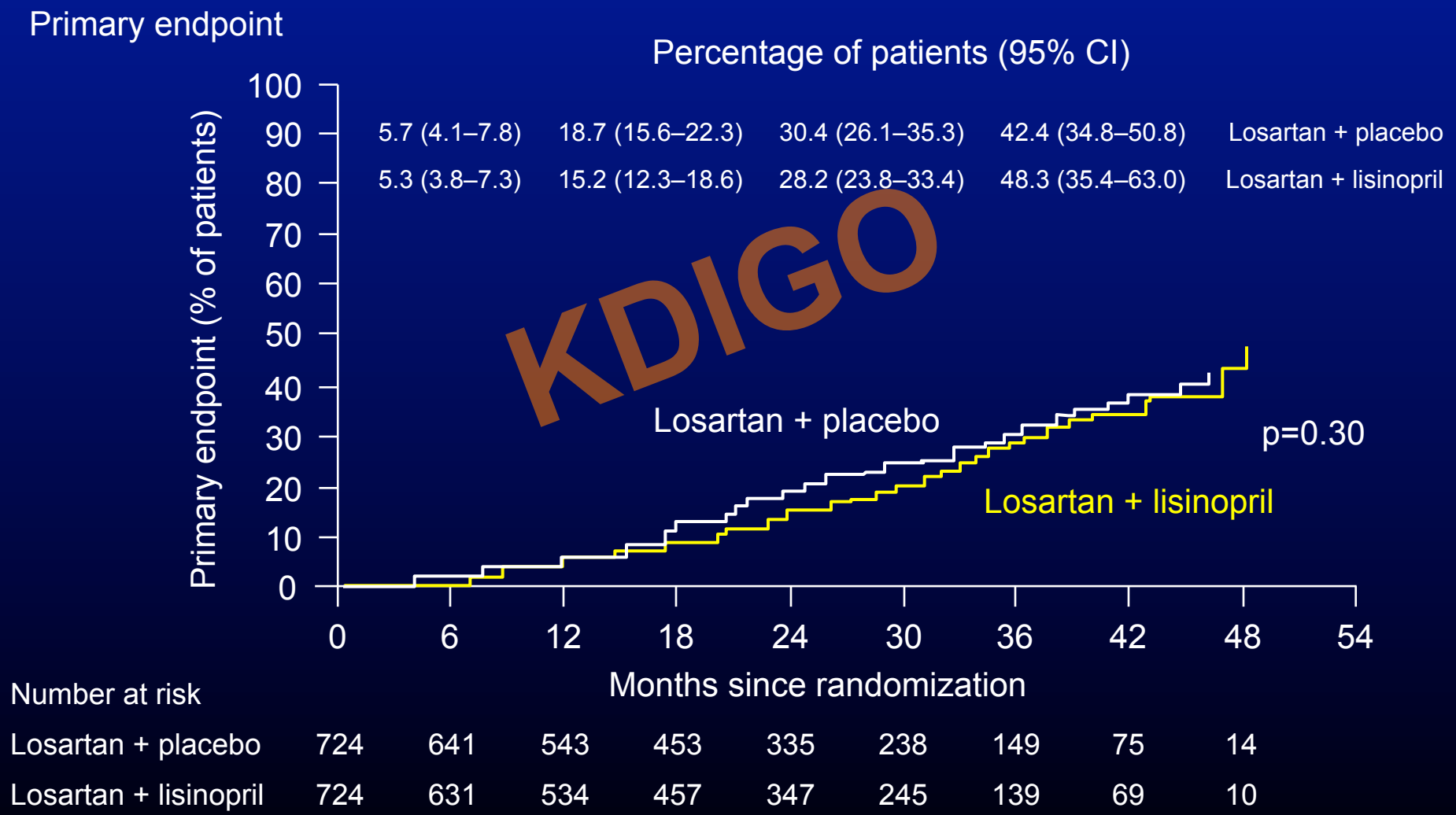
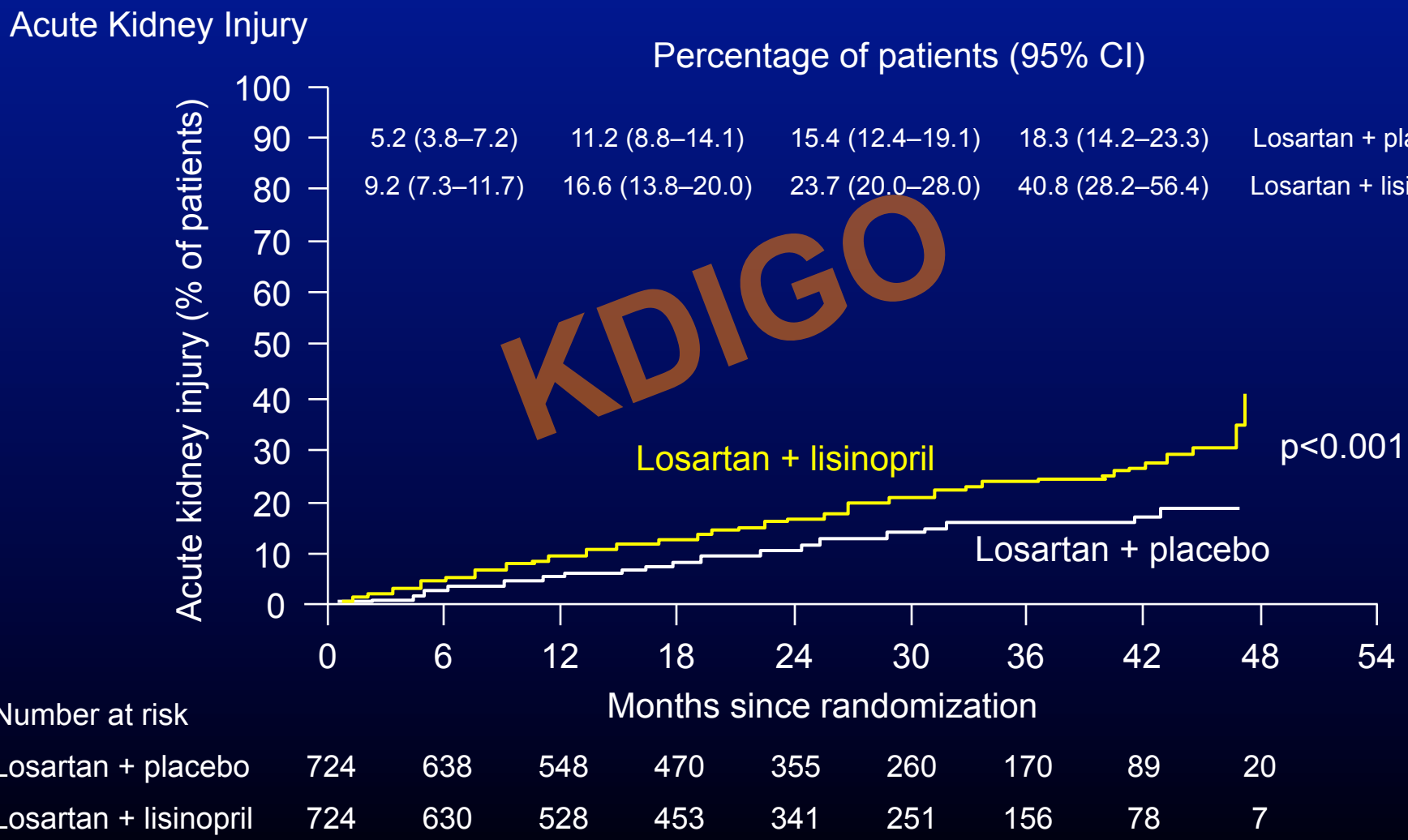
- Design issues:
  - Too low-risk population
  - No effect on surrogate YES
  - Too high dose
  - Wrong endpoints
  - Too many side effects YES

VA-NEPHRON-D: ACEi + ARB no renal protection in diabetes with nephropathy (n=1148)



Fried L, et al. N Engl J Med 2013;369:1892–903

VA-NEPHRON-D: Acute Kidney Injury



Fried L, et al. N Engl J Med 2013;369:1892–903

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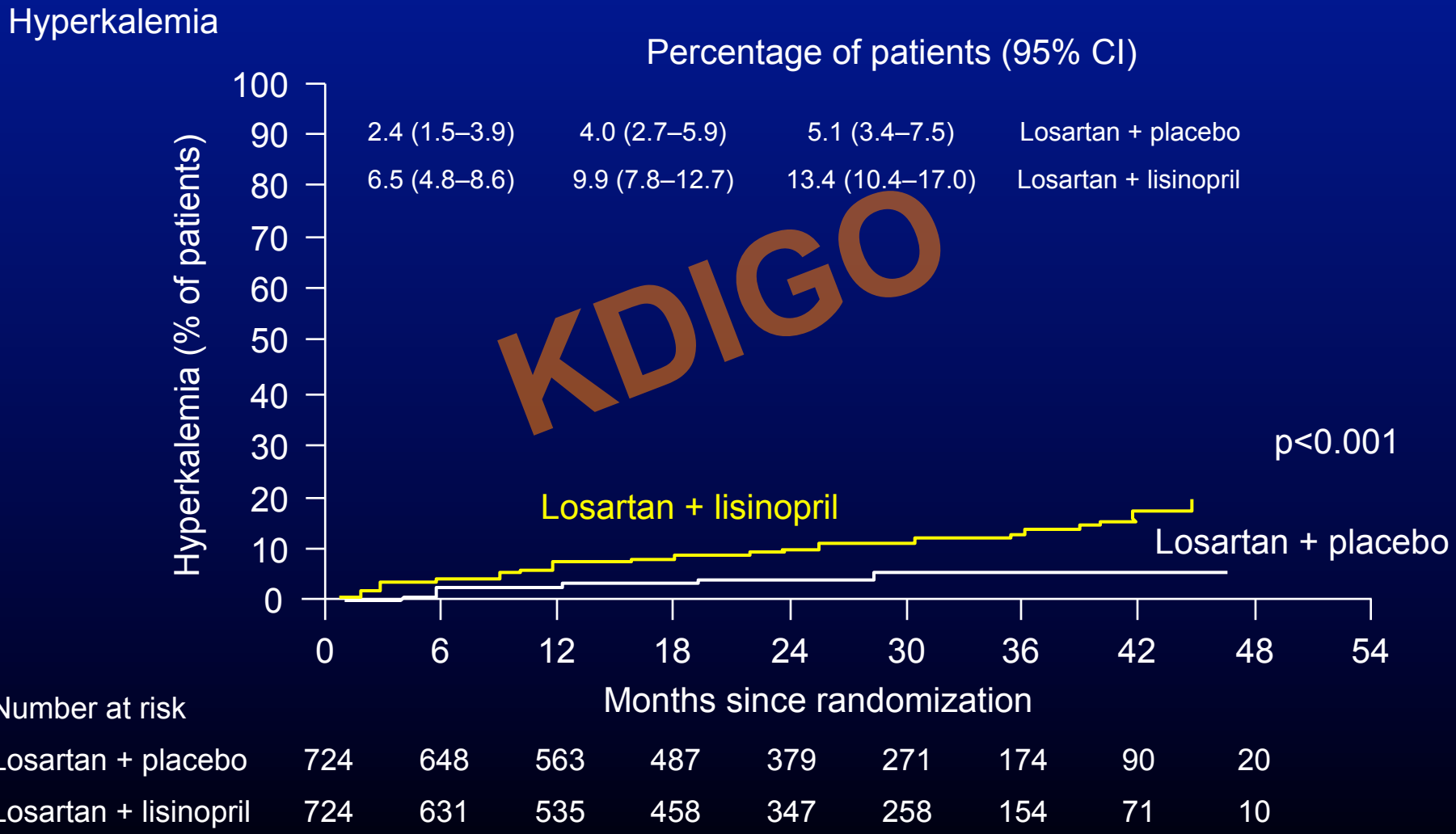
VA-NEPHRON-D: Hyperkalemia



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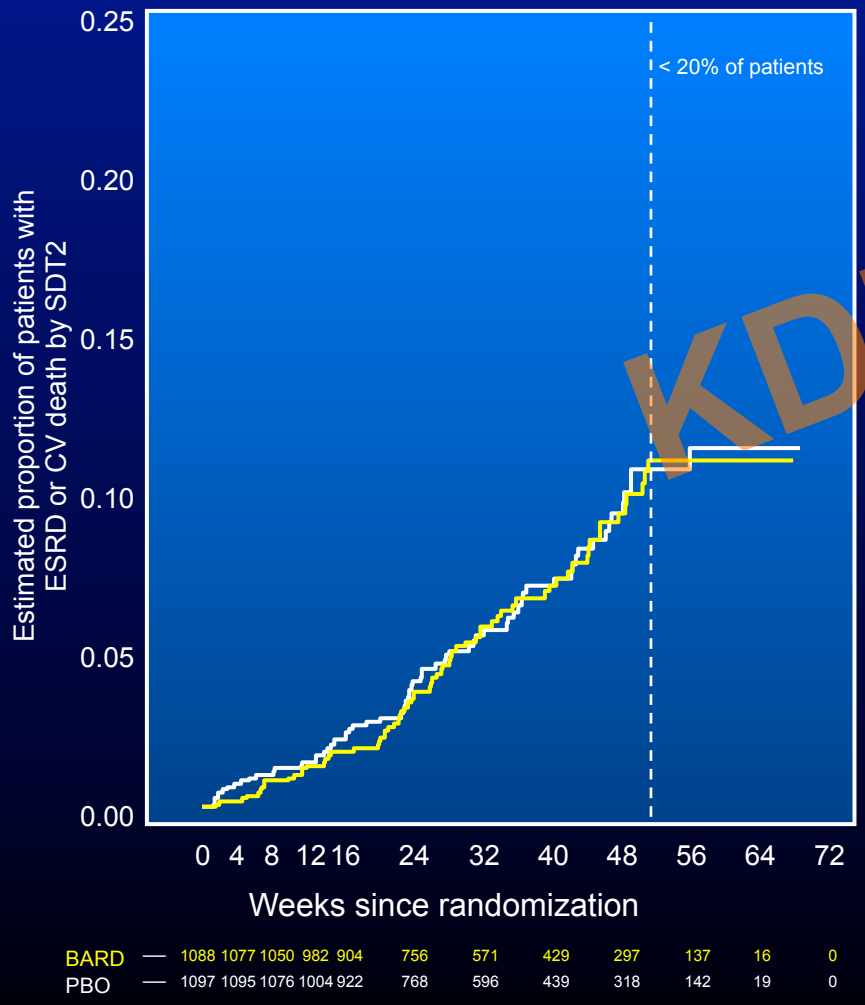
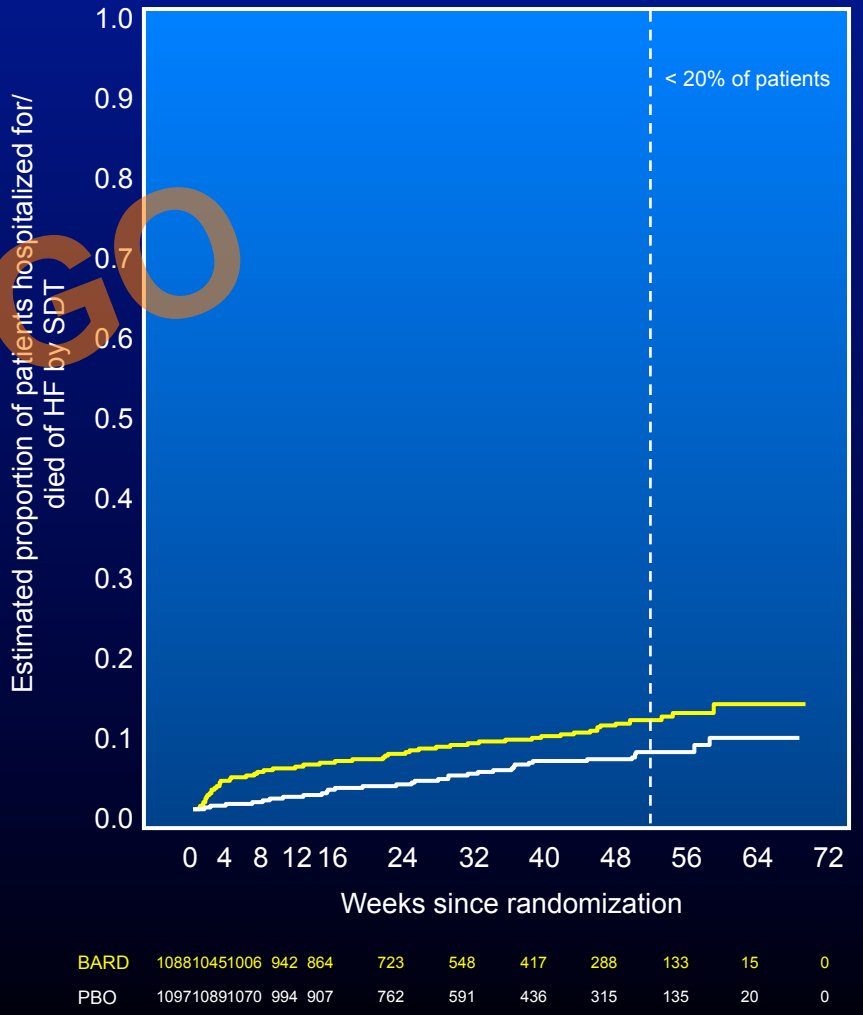
- Design issues:
  - Too low-risk population
  - No effect on surrogate
  - Too high dose
  - Wrong endpoints YES
  - Too many side effects YES

BEACON; Primary outcome (*ESRD or CV death*) and Secondary outcome (heart failure)





De Zeeuw et al; NEJM 2013

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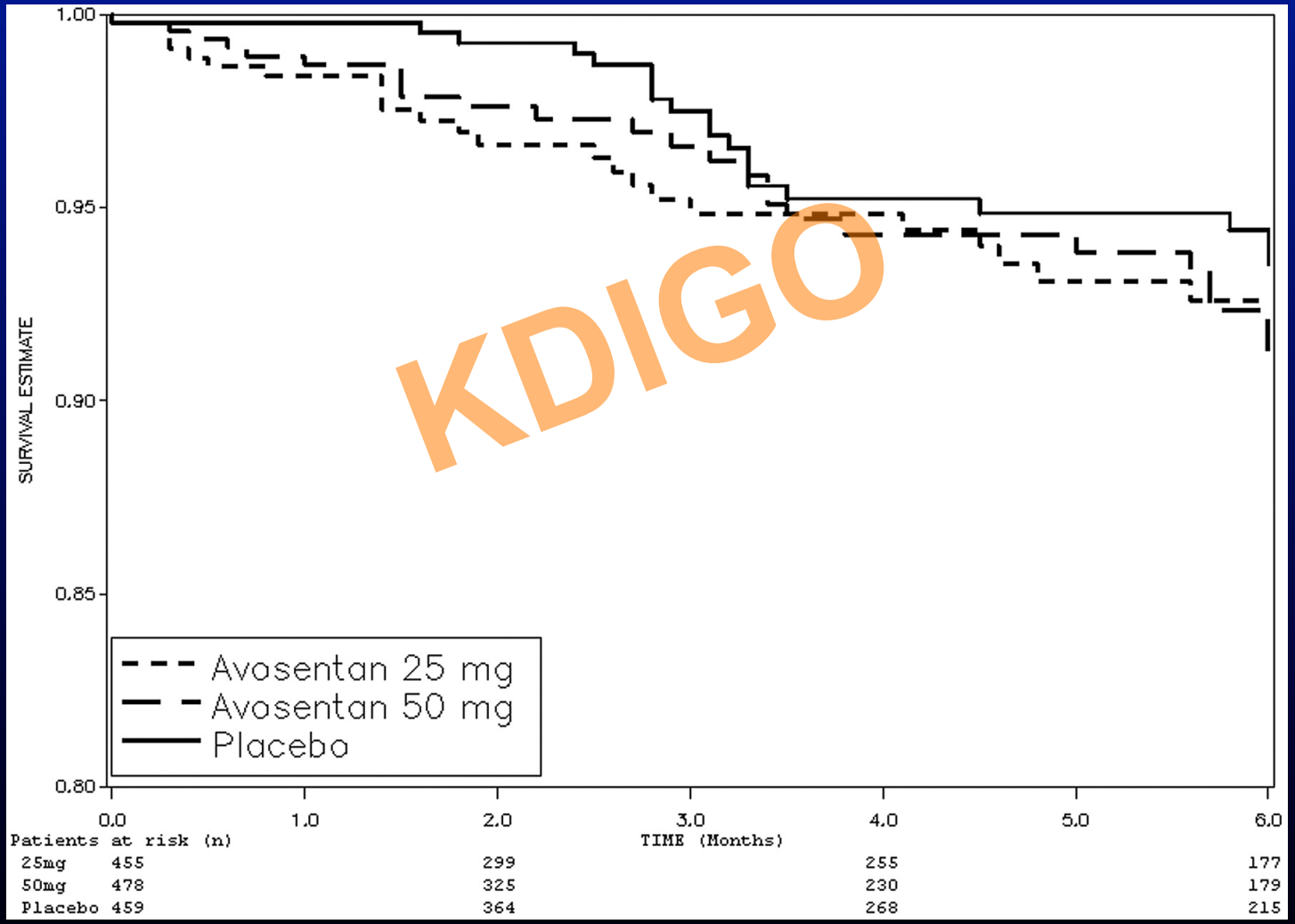
  - ASCEND (endothelin antagonist; avosentan)

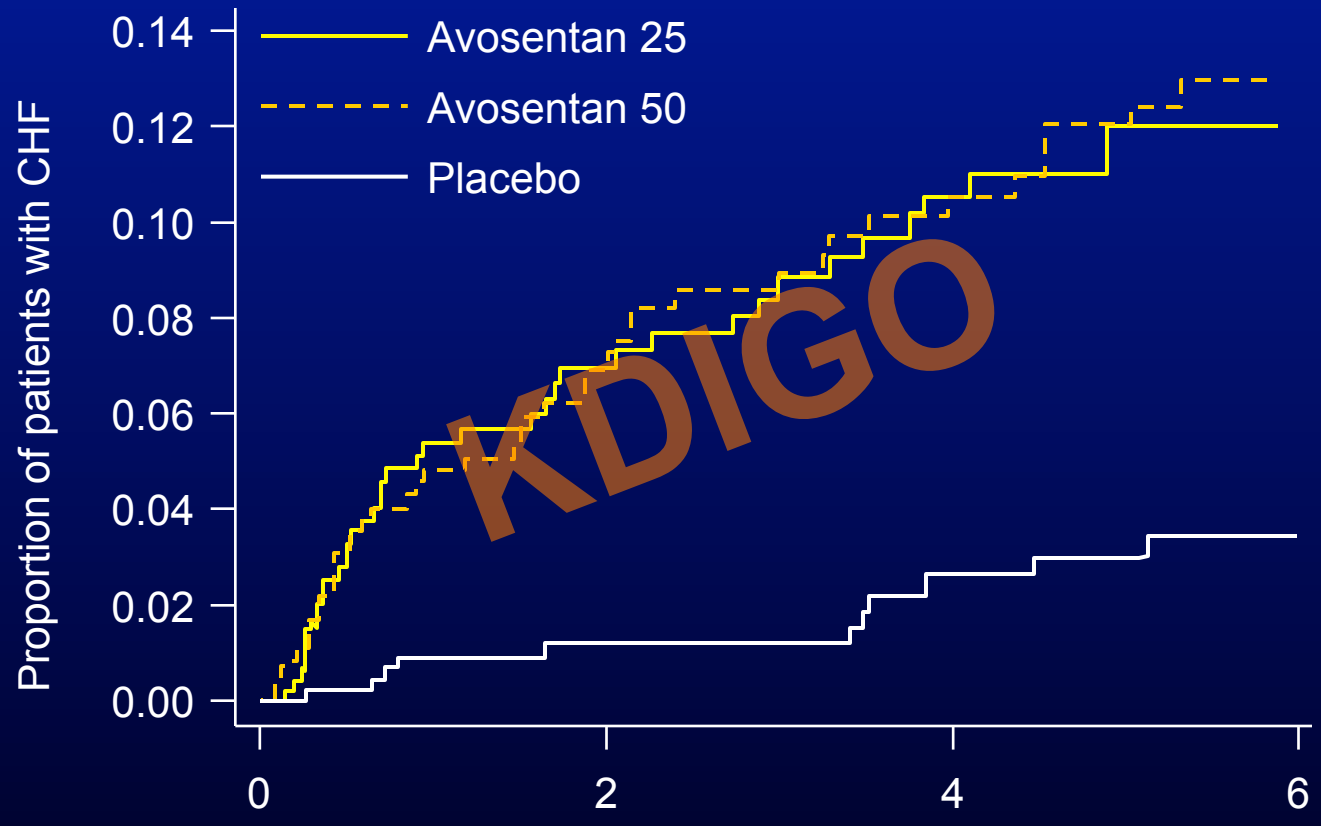
- Design issues:
  - Too low-risk population
  - No effect on surrogate
  - Too high dose ?
  - Wrong endpoints
  - Too many side effects YES

ASCEND; Effect of endothelin-antagonist Avosentan on primary renal outcome (doubling of serum creatinine, ESRD or death) in patients with type 2 diabetes and nephropathy (n = 1392)



Mann J, et al. J Am Soc Nephrol 2010;21:527–35

ASCEND; cumulative incidence of CHF by avosentan and placebo treatment arm



Number at risk				
Avosentan 25	455	274	201	162
Avosentan 50	478	289	207	159
Placebo	459	347	263	207

Hoekman et al; CJASN 2014; 9: 490-498

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Trial failure; design issues?

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- Design issues:
  - Too low-risk population
  - No effect on surrogate
  - Too high dose YES
  - Wrong endpoints
  - Too many side effects YES

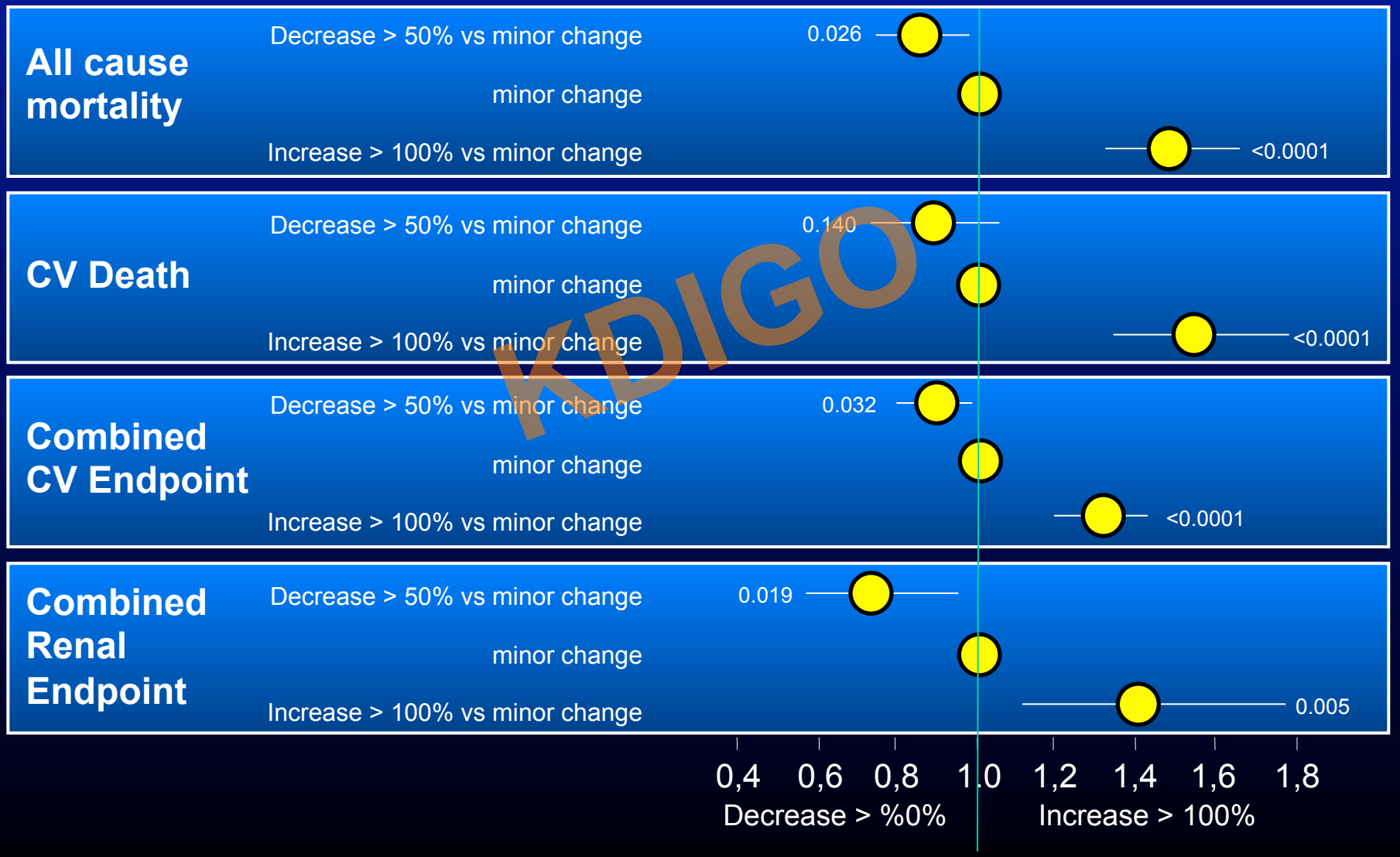
Trial failure; design issues?

- Design issues:
  - Too low risk population — Enrichment for risk
  - No effect on surrogate — Select responders
  - Too high dose — Dose to optimal effect
  - Wrong Endpoints — Correct endpoint definition
  - Too much side effects — Select “good” responders

What would have happened if previous trials would have looked at:

- The responders
- the good responders

ONTARGET/TRANSCEND; Post hoc; Changes in albuminuria predict outcome in vascular disease or high risk diabetes



Schmieder et al; JASN 2011

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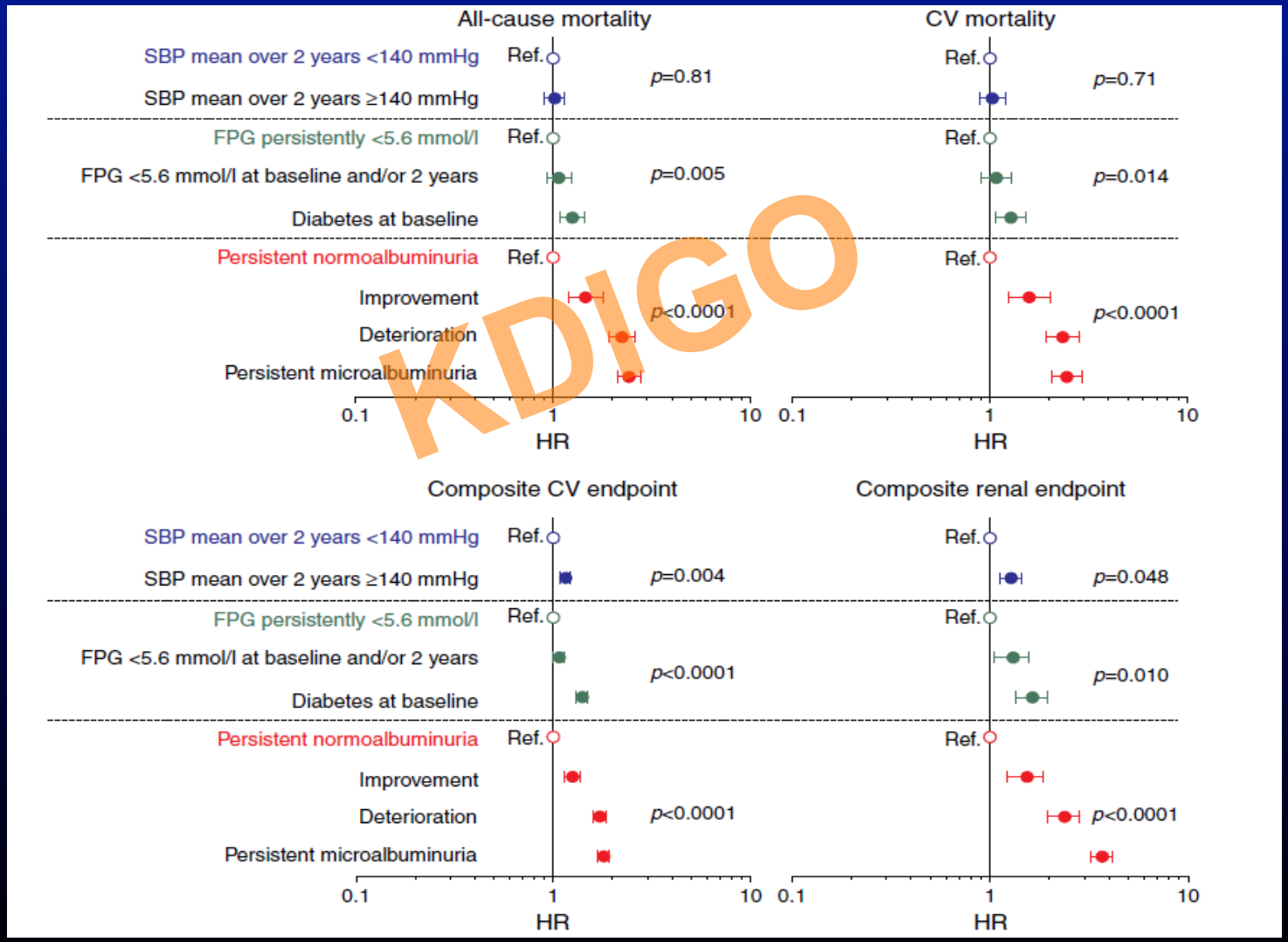
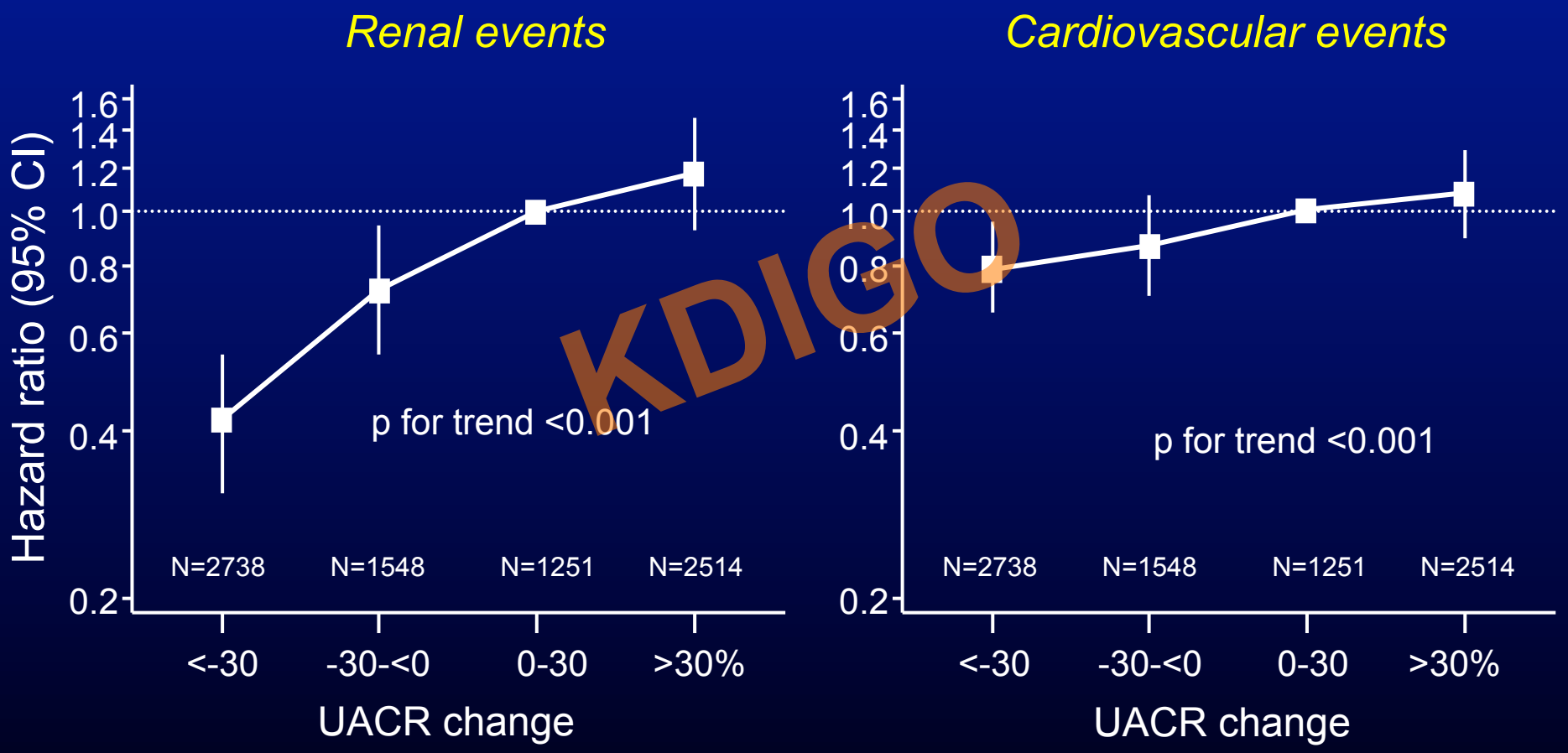
ONTARGET/TRANSCEND; Post hoc; Changes in albuminuria is best(?) predictor of outcome in patients with vascular disease or high risk diabetes



Schmieder et al; Diabetologia 2014

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



Adjusted for the baseline covariates including age, gender, log-transformed UACR, eGFR, systolic blood pressure, diastolic blood pressure, HemoglobinA1c, body mass index, HDL cholesterol, LDL-cholesterol, log-transformed triglycerides, hemoglobin, history of cardiovascular disease, serum potassium current smoking, current drinking and randomized active treatment, and the change of covariates for 6 months including eGFR, systolic blood pressure, diastolic blood pressure and serum potassium

Lambers Heerspink et al. ASN 2013

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BEACON; Post hoc analysis; Endpoints after excluding patients with BNP>200 pg/ml

	All Patients		BNP ≤ 200, No Prior HF Hospitalization	
Treatment	PBO (n = 1097)	BARD (n = 1088)	PBO (n = 544)	BARD (n = 503)
Event				
Primary Composite	69 (6)	69 (6)	**25 (5)**	**15 (3)**
ESRD	51 (5)	43 (4)	**20 (4)**	**8 (2)**
Any Cardiovascular Death	19 (2)	27 (2)	6 (1)	7 (1)
Secondary Composite	86 (8)	139 (13)	23 (4)	27 (5)
Heart Failure	55 (5)	96 (9)	**10 (2)**	**12 (2)**
Fatal or Non-fatal Myocardial Infarction	16 (1)	19 (2)	6 (1)	6 (1)
Fatal or Non-fatal Stroke	11 (1)	14 (1)	5 (1)	2 (<1)
All-Cause Death	31 (3)	44 (4)	8 (1)	11 (2)
Skin and subcutaneous tissue disorders	1 (<1)	4 (<1)	0 (<1)	3 (1)
Surgical and medical procedures	0	2 (<1)	0 (0)	1 (0)
Vascular disorders	18 (2)	20 (2)	10 (2)	8 (2)

Chin et al; submitted

From trial to practice

- We are carrying out hard end point trials for registration reasons:
  - The trials require to be representative of the patients to be treated with that indication in real life practice

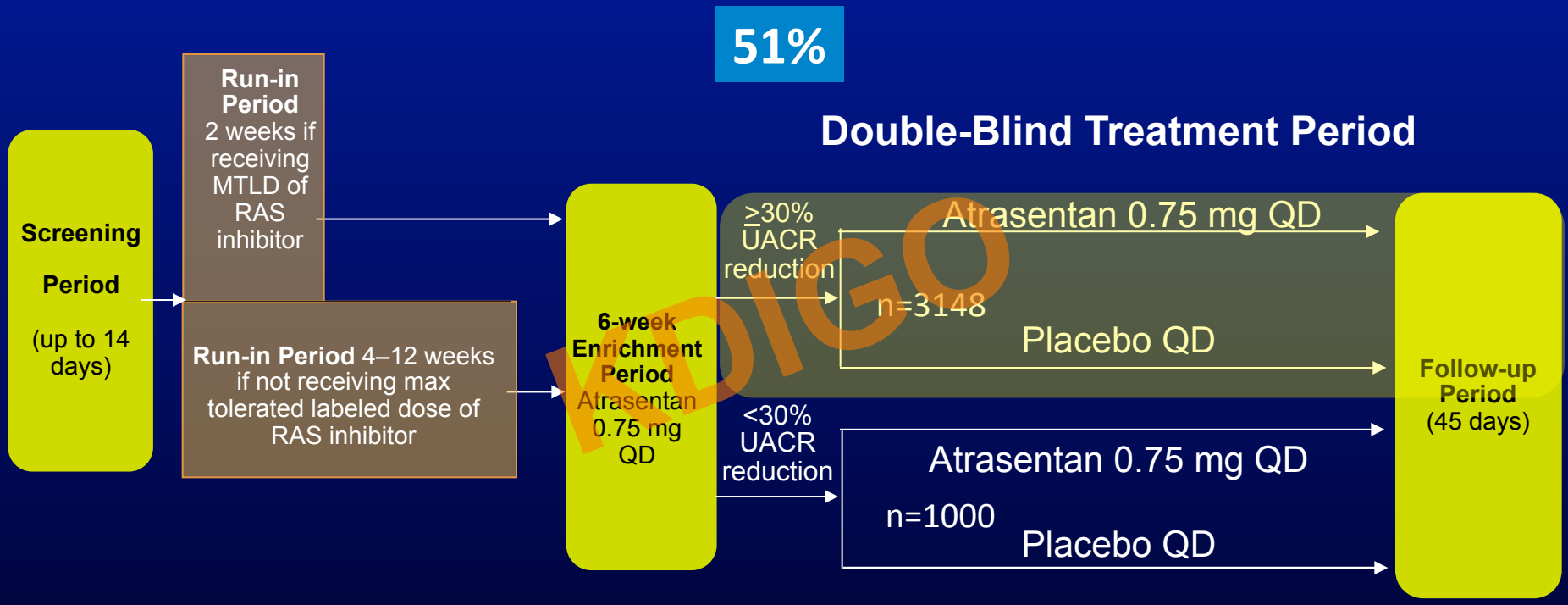
- In trial design:
  - Usually fixed dose
  - If no effect, drug is continued and patient stays in trial
  - Side effects are part of outcome of trial

- 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

Future

- Do a trial in which we:
  - Enrich for risk
  - Enrich for good response
  - Enrich to take out bad response

SONAR; 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

De Zeeuw D, et al. Manuscript in preparation; ClinicalTrials.gov NCT01858532

CONCLUSIONS

- Treatment of CKD progression (particularly in diabetes) leaves a large proportion of residual risk
- Recent efforts to slow progression with new medications on top of single RAASi have been unsuccessful
- These failures appear to be largely due to design failures