Therapeutics/Pharmacology

Prevention of cardiovascular morbidity in HD patients: the role of therapeutics versus dialysis technique

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KDIGO Controversies Conference
Novel techniques and innovation in blood purification: How can we improve clinical outcomes in hemodialysis?
Paris, France, 14-15 October, 2011,

HD Patients: Randomised Trials with Endpoint Cardiovascular Disease

Intervention	Year	N	Event	P-value
EPO-Hematocrit [1]	1998	1233	372	P>0.05
Vitamin E [2]	2000	196	48	P=0.01
Acetylcysteine [3]	2003	134	51	P=0.03
Carvedilol [4]	2003	130	71	P<0.01
Dialysis Dosê x Flux [5]	2004	1800	735	P>0.05
Atorvastatin [6]	2005	1255	469	P>0.05
ACE-Inhibitor [7]	2006	450	130	P>0.05
Folic acid [8]	2007	2056	884	P>0.05
Rosuvastatin	2009	2776	804	P>0.05

[1] Besarab et al, *N Engl J Med* 1998;339:584
[2] Boaz et al, *Lancet* 2000;356:1231
[3] Tepel et al, *Circ* 2003;107:992
[4] Cice et al, *JACC* 2003;41:1438
[5] Cheung et al, *Kidney Int* 2004;65:2380
[6] Wanner et al, *N Engl J Med* 2005;353:238
[7] Zannad et al, *Kidney Int* 2006;70:1318
[8] Jamison et al, *JAMA* 2007;15:420

Why are we not successful identifying therapeutic options / pharmacologic interventions for cardio-vascular (cardiac & vascular) protection in renal failure patients ?

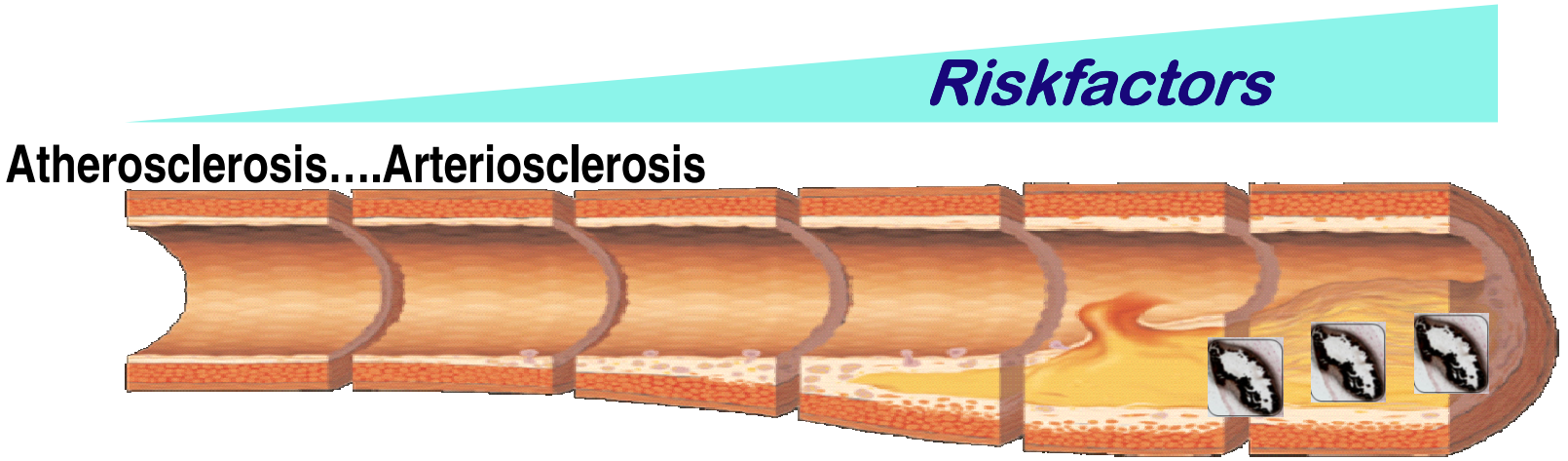
Did we do something wrong ?

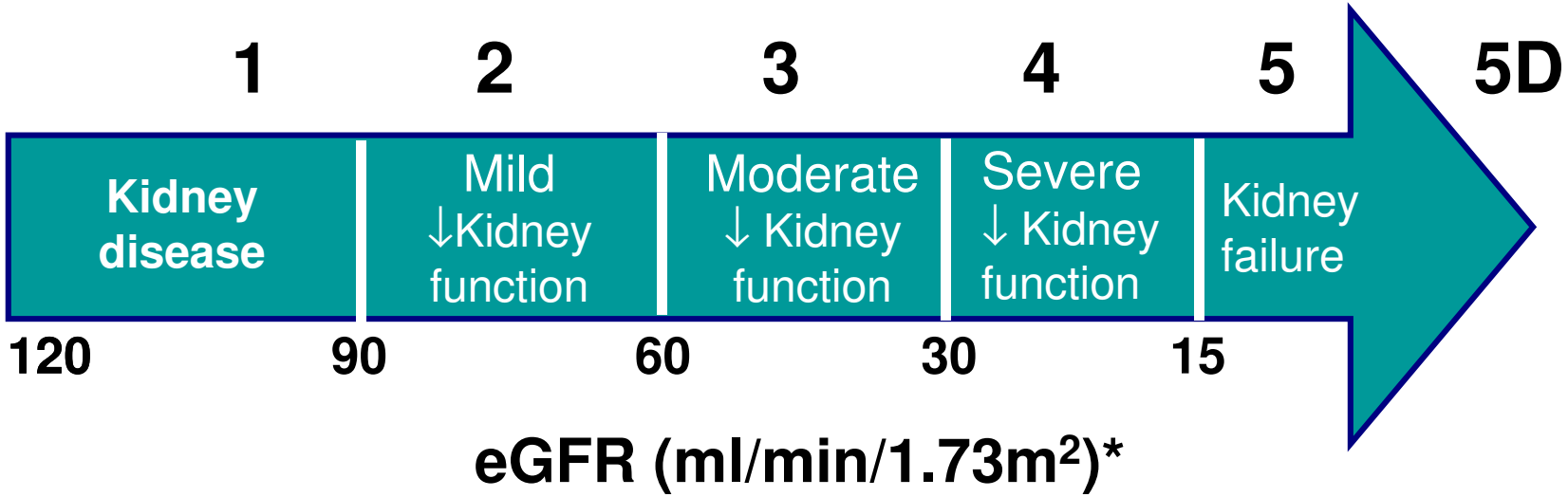
How to approach the problem ?

Heterogeneity: there are many potent risk factors (non-traditional) but also many outcomes (different from the general population)

The risk factors and outcomes vary in its expression between stages of CKD

Vascular status in stages of CKD





Statin trials serve as role models: Examples

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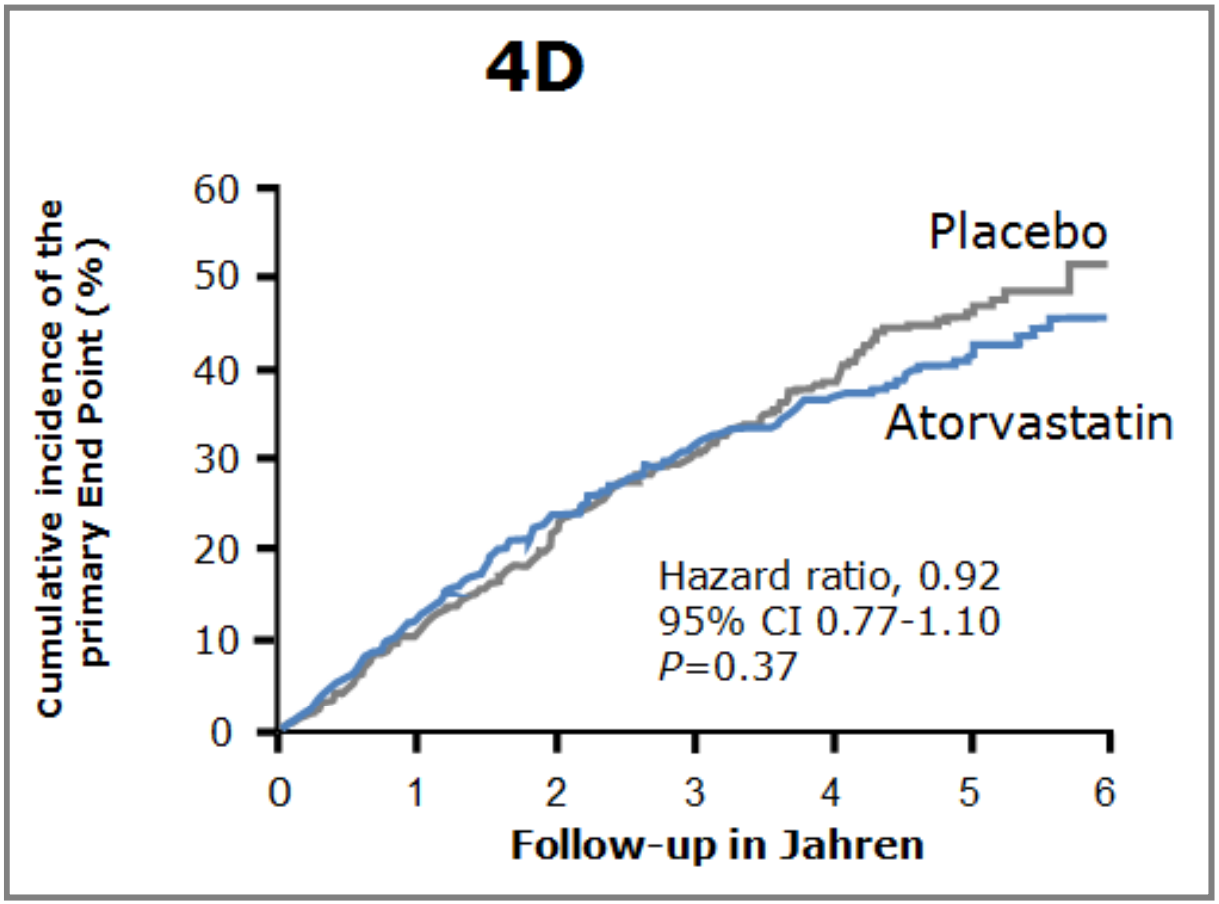
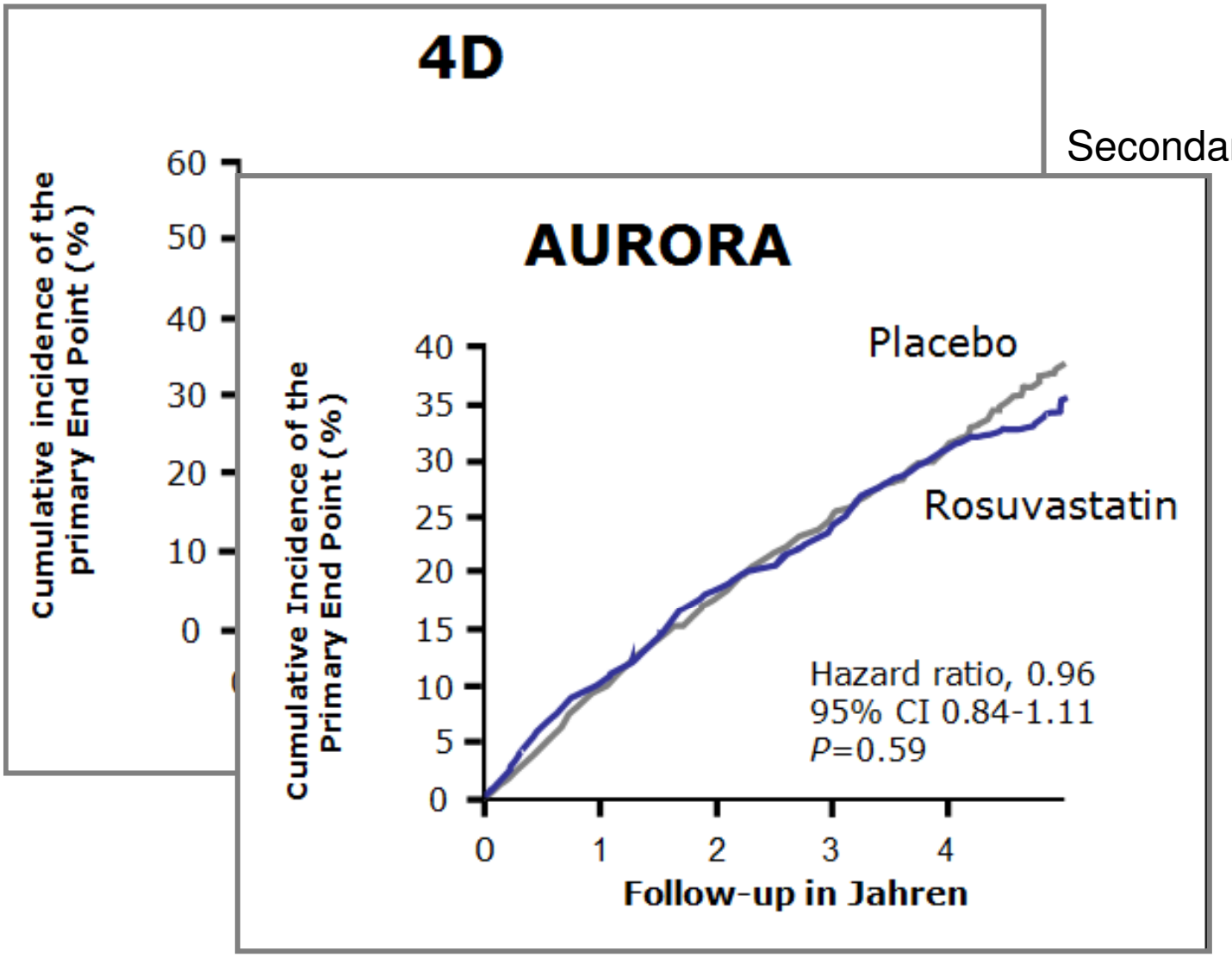
could not detect a benefit !

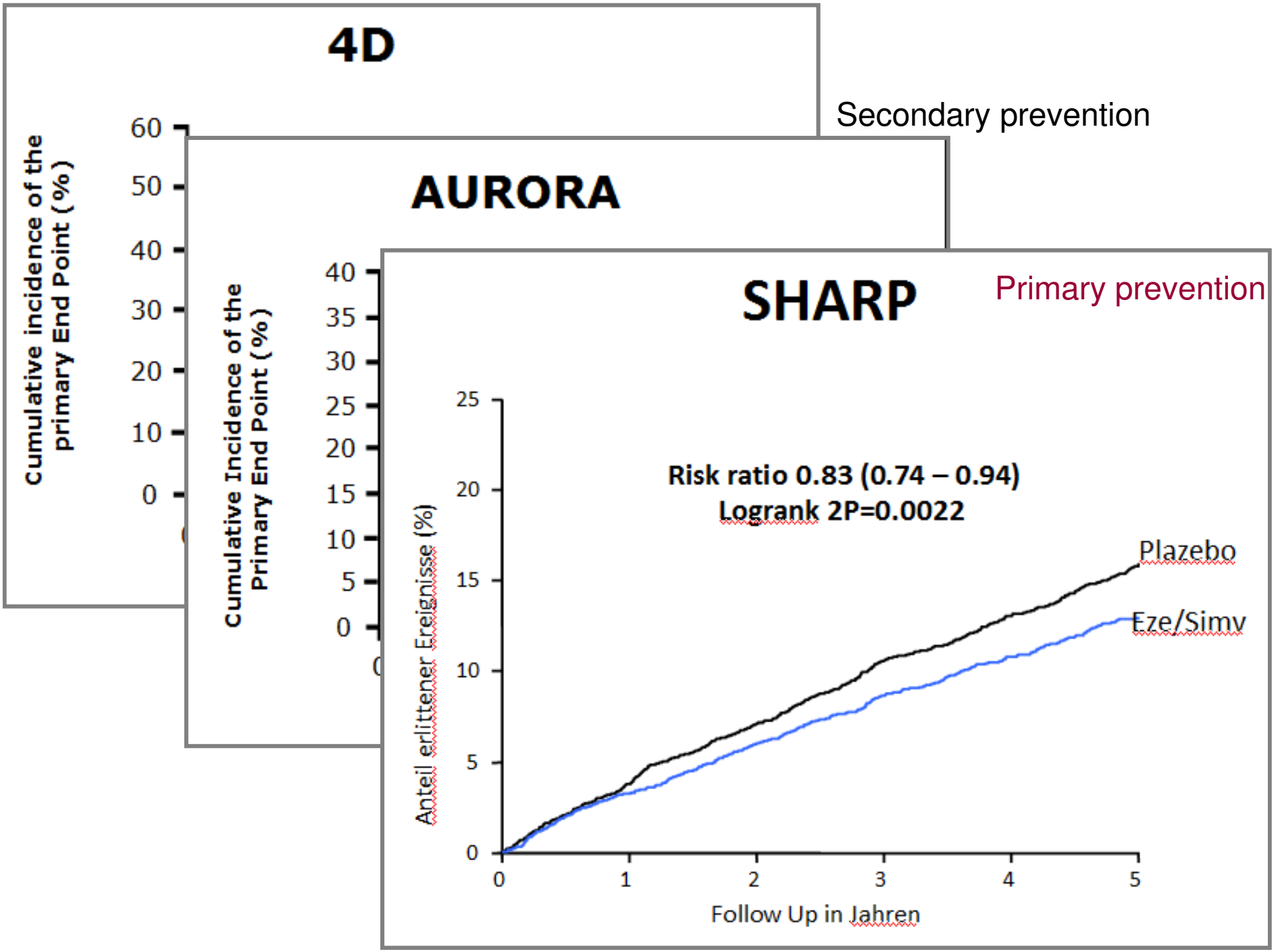
was successful !



Secondary prevention

Secondary prevention





Secondary prevention

n=1255

T2DM

20 mg Atorvastatin

66 years, 46% F,
8,5 mo on dialysis

n=2776

10 mg Rosuvastatin

64 years, 38% F, 28% D
3,5 y on dialysis

n=9479

HD	2540
PD	490
CKD	6408
CKD3	2086
CKD4	2552
CKD5	1236

20 mg Simvastatin /
10 mg Ezetimibe

62 years, 37% F, 23% D
eGFR 27 ml/min/1.73m^2

About primary endpoints

4D & *AURORA* - cardiovascular:

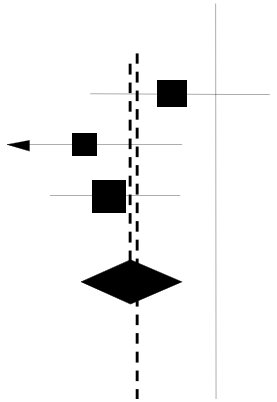
death from cardiac (*cardiovascular*) causes,
nonfatal myocardial infarction
stroke

SHARP - atherosclerotic:

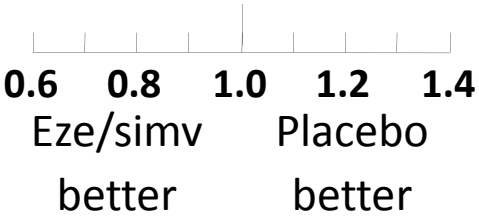
major coronary event
non-haemorrhagic stroke
any revascularization

SHARP: Major Atherosclerotic Events

Event	Eze/simv (n=4650)		Placebo (n=4620)	
Major coronary event	213	(4.6%)	230	(5.0%)
Non-haemorrhagic stroke	131	(2.8%)	174	(3.8%)
Any revascularization	284	(6.1%)	352	(7.6%)
Major atherosclerotic event	**526**	**(11.3%)**	**619**	**(13.4%)**



16.5% SE 5.4 reduction (p=0.0022)



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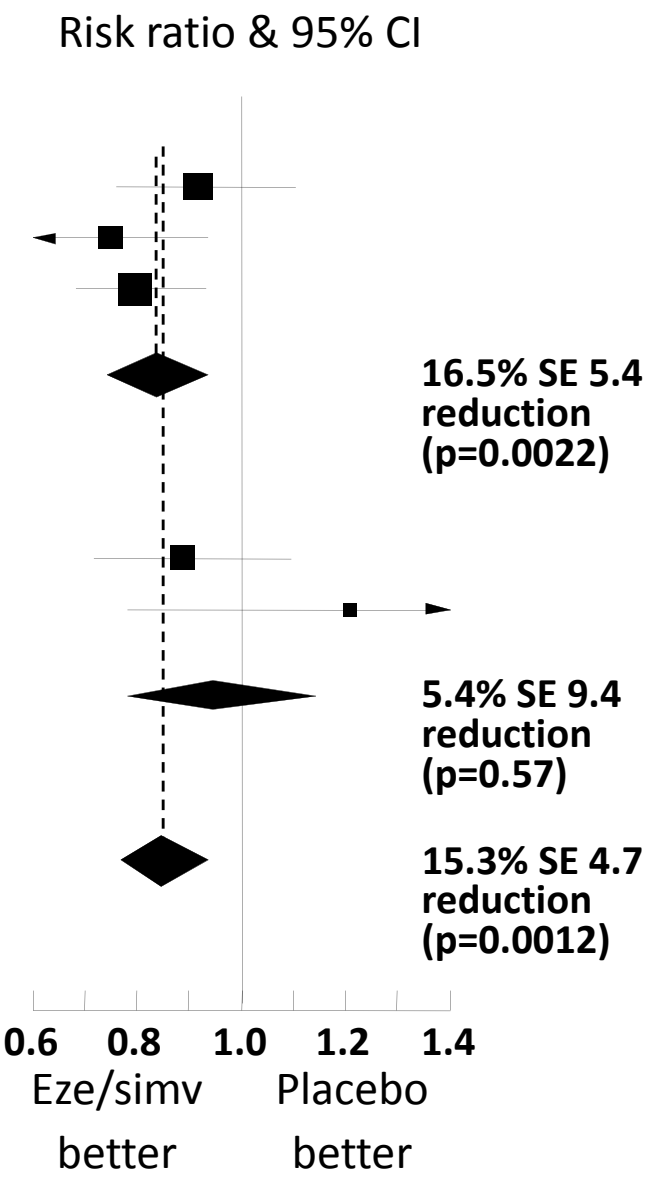
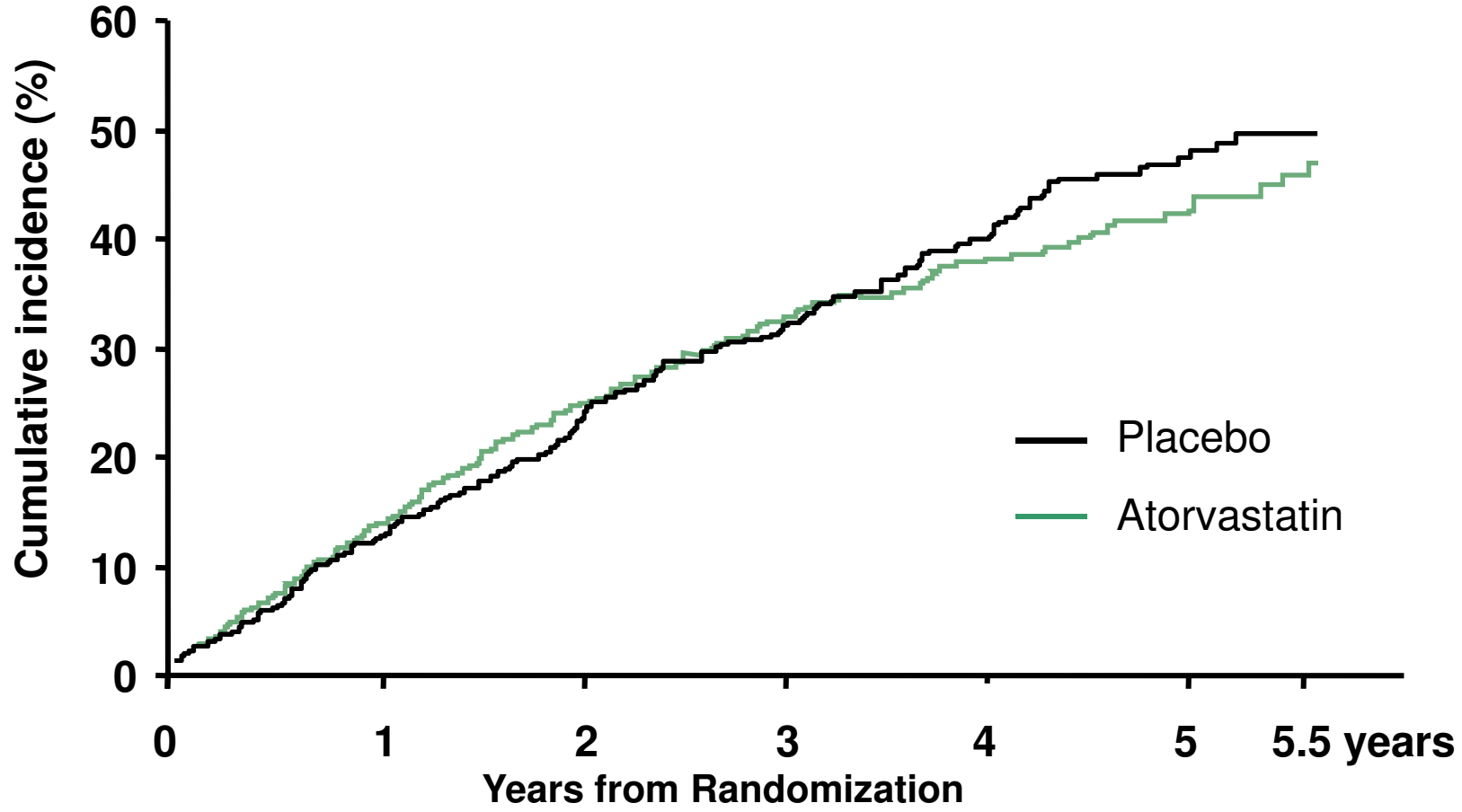
Major atherosclerotic event	**526**	**(11.3%)**	**619**	**(13.4%)**
Other cardiac death	162	(3.5%)	182	(3.9%)
Haemorrhaghic stroke	45	(1.0%)	37	(0.8%)
Other major vascular events	**207**	**(4.5%)**	**218**	**(4.7%)**
Major vascular event	**701**	**(15.1%)**	**814**	**(17.6%)**



Primary composite end point

Relative Risk Reduction 8 % (95 % CI: 0.77-1.10, P=0.37)

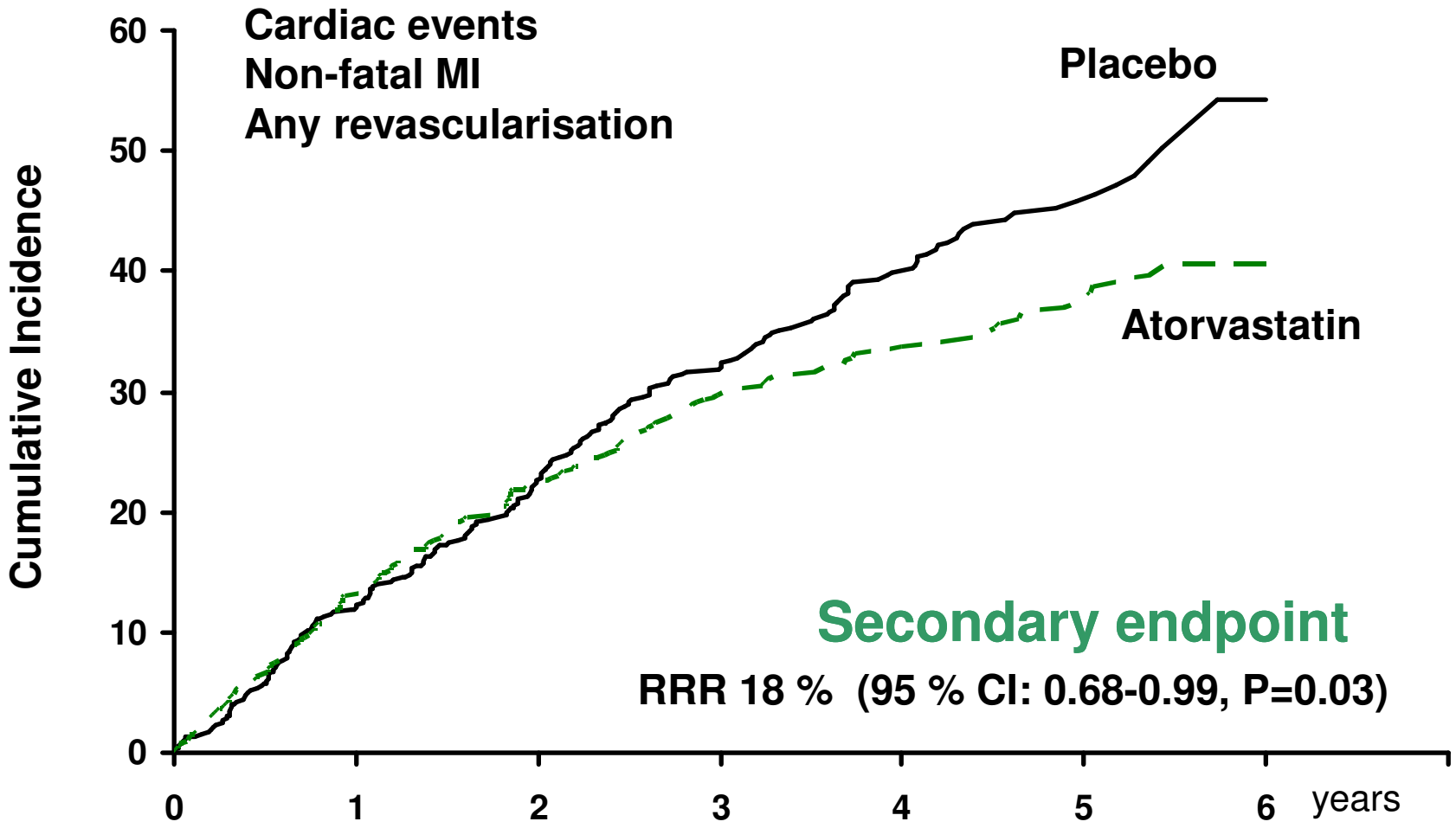


Placebo	636	532	383	252	136	51	29
Atorvastatin	619	515	378	252	136	58	19

Median follow-up time of 4 years

Major Atherosclerotic Events

- All cardiovascular events combined -



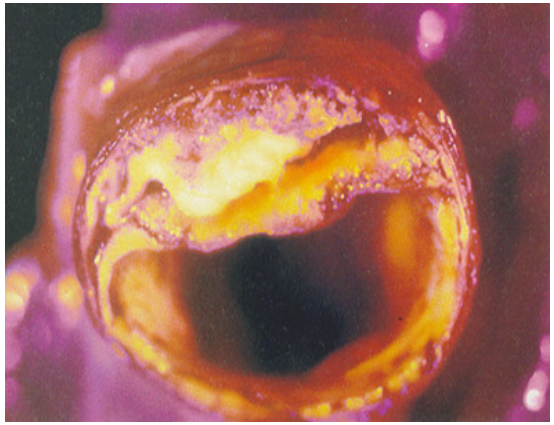
Secondary endpoint

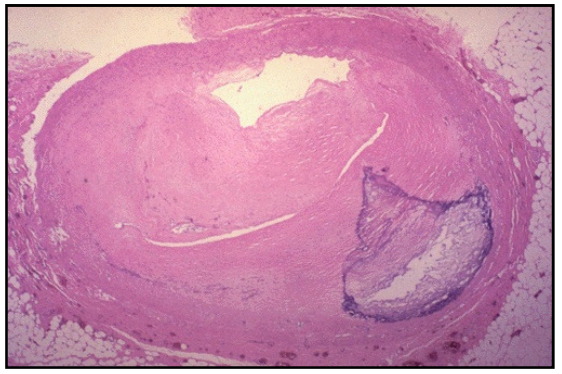
RRR 18 % (95 % CI: 0.68-0.99, P=0.03)

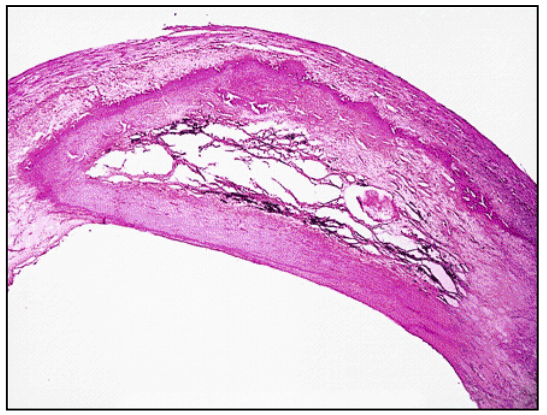
Placebo	636	532	383	252	136	51	19
Atorvastatin	619	515	378	252	136	58	29

Vascular active treatments:

- Lipids (statins)
- Phosphate (binders)
- Oxidative stress – acute phase response
- Deficiencies, multiple
- Cinacalcet (EVOLVE Study)

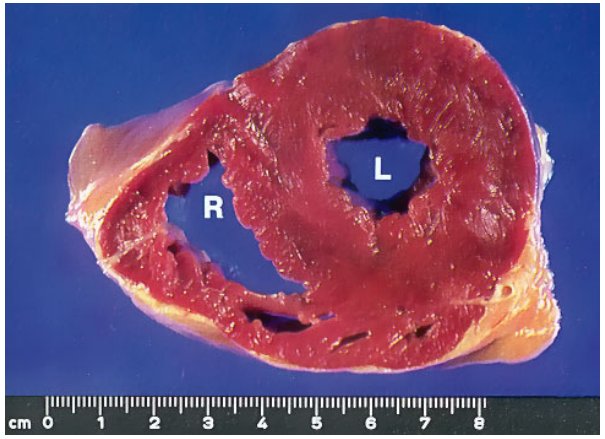


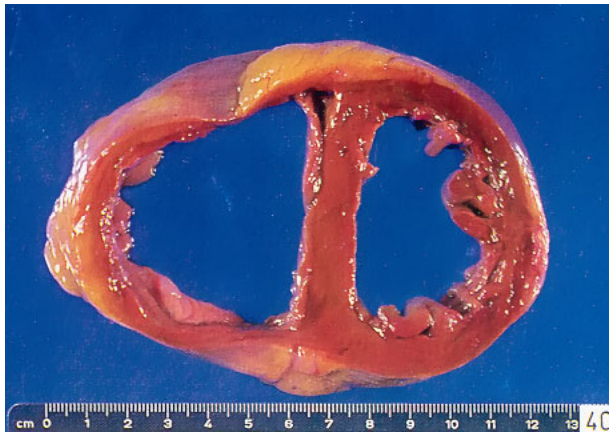


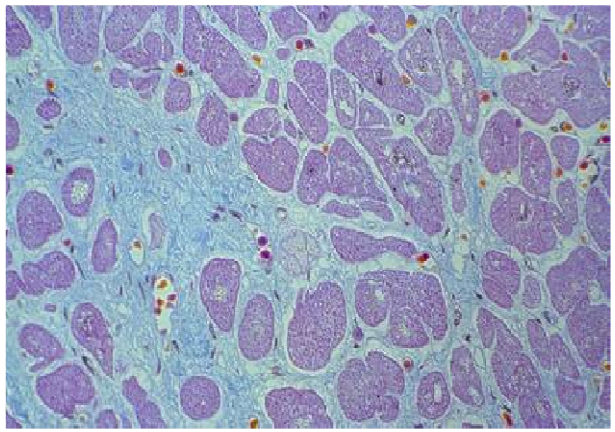


„Antifibrotic“ treatments:

- Aldosterone blockade (spironolactone)
- VDRA (paricalcitol)
- Volume control (diuretics, ultrafiltration)
- - ß-Blockade (carvedilol)
- - Glycation
- - „Anemia“







„Antifibrotic“ treatments:

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- V
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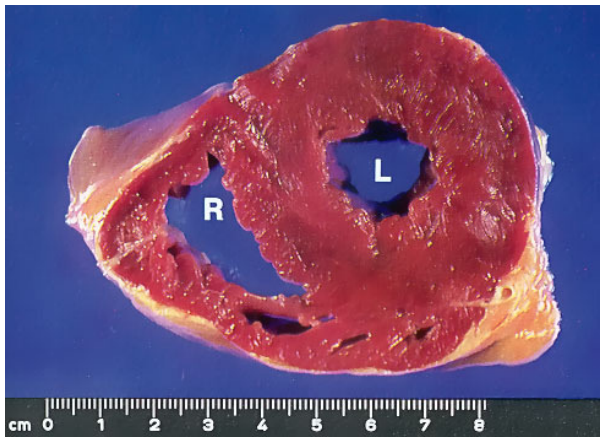
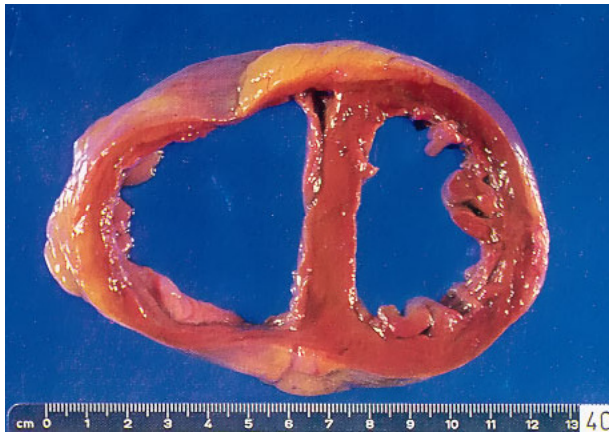
- -
- - Glycation
- - „Anemia“

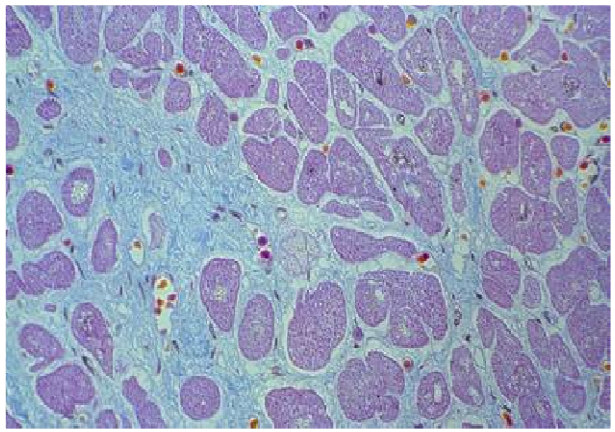
MiREnDa - Mineralocorticoid Receptor antagonists in End stage renal DiseAse

PRIMO - Paricalcitol benefits in Renal failure Induced cardiac MOrbidity

BOND – Beta Blocker Outcomes in Nephrological Diseases







How to solve the problem ?

Identify the underlying pathogenesis of the disease and assign potential treatments (athero- vs arteriosclerosis).

Causal relationship of an intervention can only be established by randomization.

Many more trials should be done, all sufficient in size. We have global networks in place !

To be realistic ….

We cannot established effectiveness for all kinds of treatments with outcome trials (feasiblity and finances).

We may see more surrogate endpoint marker studies (imaging, histology, biomarker). Do we accept these studies ?

How many different treatments / treatment strategies can we establish in a given patient in a specific stage of disease?

Can we bring the magnitude of effect into an order to prioritize the most potent treatments ?

Thank you for your attention !