Dyslipidemia and chronic kidney disease (CKD)

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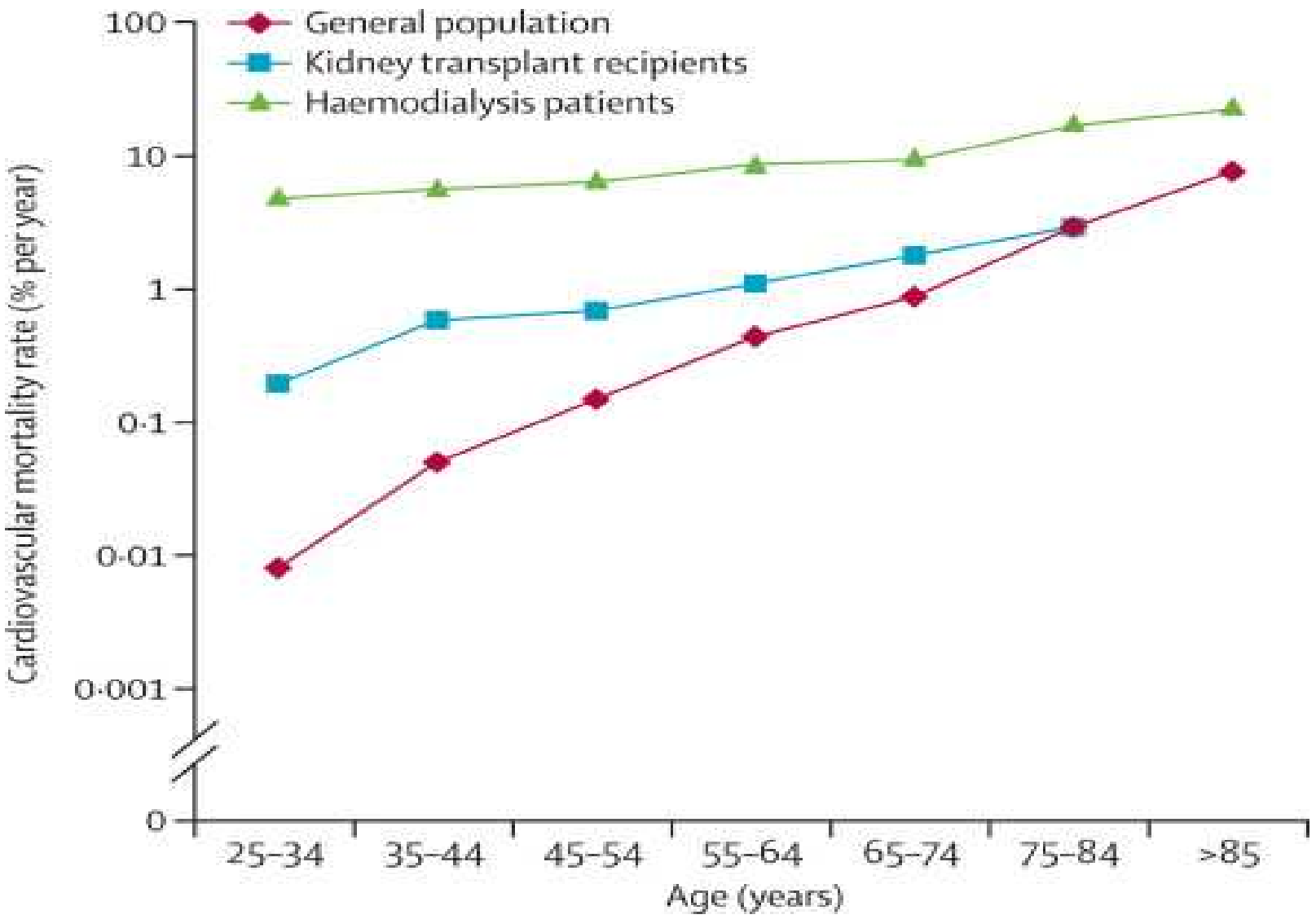
Plan

- CKD : a major cardiovascular disease (CVD) risk factor
- Lipid parameters in CKD
- Role of lipids in the atherosclerotic lesions in CKD
- Epidemiological data
- Large Randomized Clinical Trials with statin in CKD
  - special focus on SHARP
- Conclusions

CKD : a major cardiovascular disease (CVD) risk factor [CKD stage 5]



CKD : a major cardiovascular disease (CVD) risk factor [before CKD stage 5]

Lancet 2010; 375: 2073–81

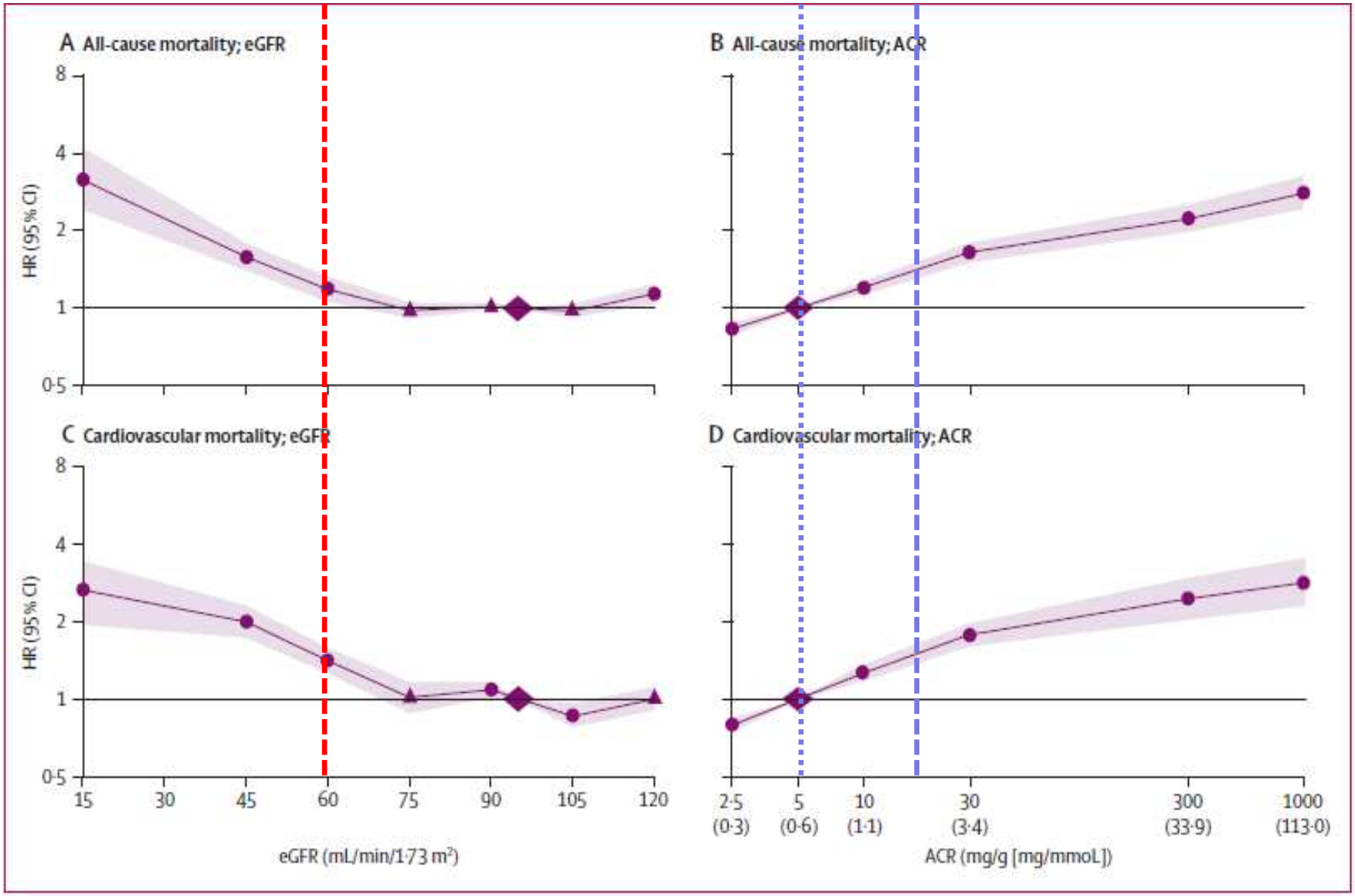
Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis

*Chronic Kidney Disease Prognosis Consortium**

	Region	Number of participants	Age, mean (years)	Male (%)	Black (%)	Current smoker (%)	Cardio-vascular disease (%)	Hyper-cholestero-laemia (%)	Hyper-tension (%)	Diabetes (%)	eGFR, mean (mL/min/ 1·73 m²)	ACR, median (mg/mmol; mg/g)	Follow-up, mean (years)	Number of deaths (all-cause)	Number of deaths from cardio-vascular disease
Studies with ACR measurements															
ARIC[20]	USA	11 408	63	44%	22%	15%	9%	35%	48%	17%	83	0·42; 3·7	8·0	1235	443
AusDiab*[21]	Australia	11 244	52	45%	0	16%	8%	71%	33%	8%	79	0·55; 4·9	7·9	667	166
Beijing[22]	China	1563	60	50%	0	24%	18%	29%	47%	28%	85	0·32; 2·8	3·9	59	NA
CHS[23]	USA	3230	78	40%	16%	8%	29%	31%	50%	15%	79	0·99; 8·8	7·6	1487	562
COBRA[24]	Pakistan	2872	52	48%	0	39%	9%	35%	44%	21%	110	0·59; 5·2	4·1	212	95
Framingham[25]	USA	2956	59	47%	0	15%	6%	24%	40%	10%	87	0·72; 6·4	10·5	301	93
Gubbio[26]	Italy	1684	55	45%	0	31%	5%	47%	39%	5%	78	0·97; 8·6	10·7	119	NA
HUNT[3]	Norway	9525	62	45%	0	20%	23%	61%	83%	18%	84	0·85; 7·5	9·3	1916	981
MESA[27]	USA	6705	62	47%	28%	13%	0	9%	45%	13%	81	0·60; 5·3	4·7	222	NA
NHANES III[15]	USA	15 853	47	47%	27%	25%	11%	62%	40%	7%	103	0·70; 6·2	8·5	2119	910
PREVEND[28]	Netherlands	8370	49	50%	1%	38%	5%	36%	33%	3%	81	0·79; 7·0	7·2	438	132
Rancho Bernardo[29]	USA	1759	71	39%	0	7%	11%	29%	56%	12%	77	1·31; 11·6	10·4	587	233
REGARDS[30]	USA	27 583	65	45%	42%	15%	23%	59%	60%	22%	85	0·85; 7·5	4·0	1380	NA
ULSAM[31]	Sweden	1120	71	100%	0	20%	42%	56%	75%	11%	75	0·86; 7·6	11·6	467	208
Studies with dipstick measurements															
AKDN[16]	Canada	690 680	47	45%	NA	NA	2%	NA	20%	6%	81	NA	2·3	14 628	NA
Beaver Dam[32]	USA	4926	62	44%	0	20%	15%	54%	51%	10%	76	NA	11·6	1576	709
ESTHER[33]	Germany	9350	62	45%	0	16%	17%	46%	60%	11%	88	NA	2·1	171	NA
MRC Older People[34]	UK	12 158	81	39%	0	11%	17%	NA	73%	8%	59	NA	6·4	6927	2936
Ohasama[35]	Japan	1466	63	34%	0	14%	3%	18%	37%	10%	80	NA	10·5	201	61
Severance[36]	South Korea	42 637	46	51%	0	31%	5%	12%	25%	6%	84	NA	8·8	1291	239
Taiwan[3]	Taiwan	367 093	42	50%	0	24%	3%	14%	18%	5%	84	NA	7·1	9581	1869

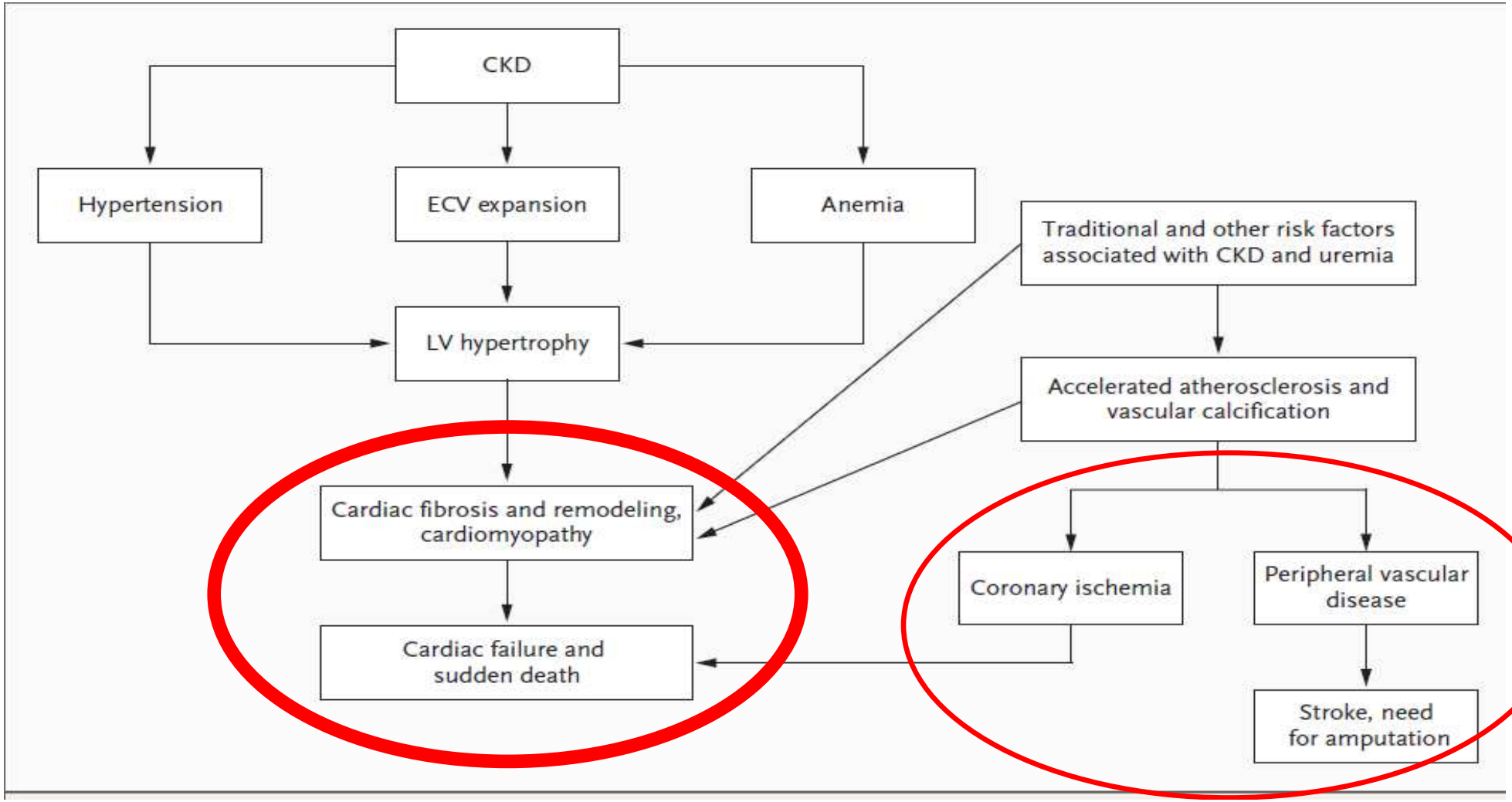
ACR=urine albumin-to-creatinine ratio. NA=not applicable. Study acronyms and abbreviations are listed in webappendix p 23. *Also included in dipstick analyses.

Table 1: **Characteristics of included studies**


A All-cause mortality; eGFR
B All-cause mortality; ACR
C Cardiovascular mortality; eGFR
D Cardiovascular mortality; ACR
HR (95% CI)
8
4
2
1
0·5
15
30
45
60
75
90
105
120
eGFR (mL/min/1·73 m²)
2·5 (0·3)
5 (0·6)
10 (1·1)
30 (3·4)
300 (33·9)
1000 (113·0)
ACR (mg/g [mg/mmoL])

Risk factors for CVD in CKD patients

Classical risk factors	CKD specific risk factors
Age (male > 50 years, female > 60 years)	Micro-albuminuria, protéinuria
Family history	Anemia
Tobacco use	Hyper-homocysteinemia
HTA	Uremic toxins (oxydative stress, endothelial dysfonction)
Diabete Mellitus	High serum phosphate level and high Ph x Ca^{++} product
LDL > 1,6 g/L	Sleep apnea syndome
HDL < 0,4 g/L	Infections and chronic inflammation
Physical inactivity	



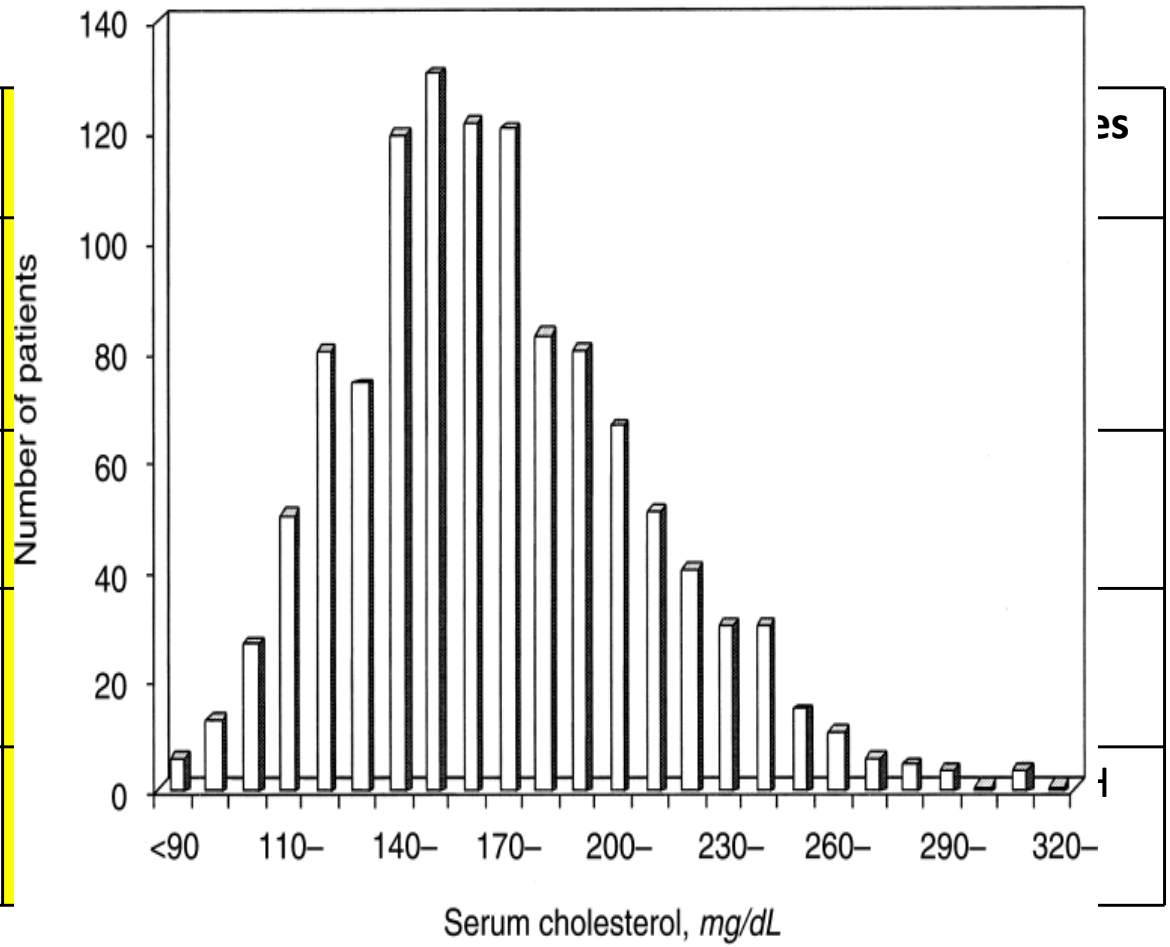
Sudden cardiac death :

No CKD	1.8 person-years
CKD stage 1/2	3.8/1000 patient-years
CKD stage 3/4	7.3/1000 patient-years
CKD stage 5	12.6/1000 patient-years
CKD stage 5D	24.2/1000 patient-years

Kidney Int 2009, 67: 652-658

Lipid parameters in Chonic Kidney Disease

	Total Cholesterol
Chronic Kidney Disease stage 1 to 5	Normal
Hemodialysis	Normal
Peritoneal Dialysis	Elevé (rarely normal)
Kidney Transplantation	VERY HIGH



Is dyslipidemia involved in uremic atherosclerosis?

- We do not known… partly because :
  - numerous risk factors that are intricated
  - uremic atherosclerosis looks different from ‘usual’ atherosclerosis. Uremic lesions are :
    - more fibrotic
    - more calcified
    - with less cholesterol cystals
- No direct link between CHO and arterial lesions

Is dyslipidemia involved in uremic atherosclerosis?

- Retrospective study in 19.440 patients with moderate CKD and coronary ischemic disease
- N = 542 sudden cardiac death during 12 years
- Multivariate analysis

	HR (95% CI)	p
GFR (HR per 10ml/min decrease)	1.11 (1.06-1.17)	< 0.001
Coronary intervention (CABG, PCI)	0.41 (0.31-0.56)	< 0.001
History of diabetes	1.49 (1.19-1.87)	< 0.001
Smoking history	1.30 (1.06-1.60)	0.012
History of peripheral vascular disease	1.31 (1.02-1.66)	0.032
History of dyslipidemia	0.80 (0.67-0.97)	0.019

Kidney Int 2009, 67: 652-658

Is dyslipidemia involved in uremic atherosclerosis?

- Prospective study in 226 CKD stage 5D patients followed by supra-aortic echoDoppler for 5 years (in Japan)
- 73 patients died (> 30% CVD mortality)

Multivariate analysis	RR (95% CI)	p
Serum Albumin (10g/L)	0.31 (0.13-0.75)	0.009
History of diabetes	2.03 (1.24-3.31)	0.005
Plaque number	1.11 (1.02-1.21)	0.023
Age	1.04 (1.02-1.07)	0.001
Ca^{++} x Ph product $(1mg/dL)^2$	1.02 (1.01-1.03)	0.05

- Lipid parameters non independent risk factor

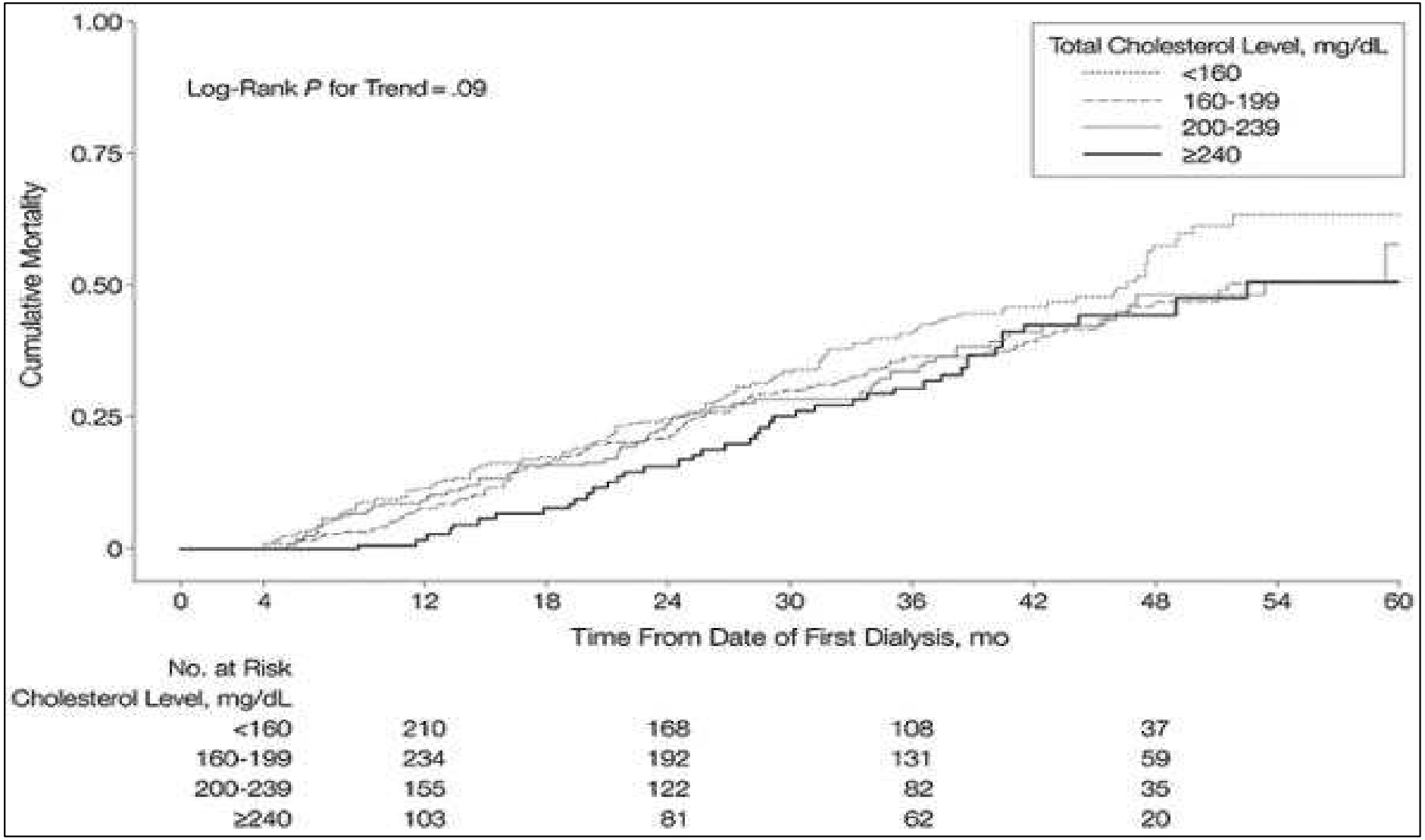
Atherosclerosis 2009; 204: 549-555

Epidemiological Data (search for correlation between CHO and all-cause mortality and CVD mortality) [stage 5D]

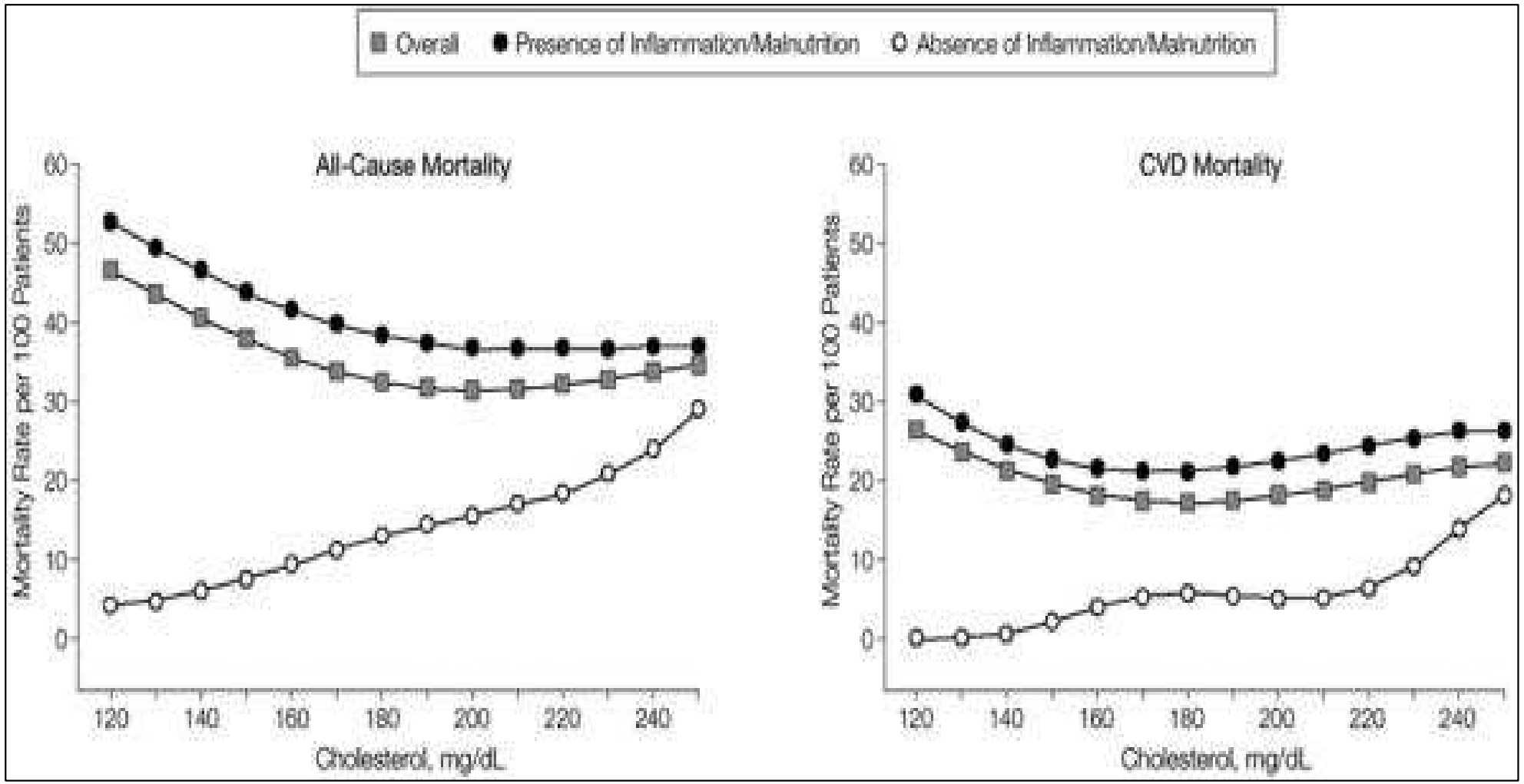
CHOICE study (**C**hoices for **H**ealthy **O**utcomes **I**n **C**aring for **E**SRD)

- 823 incident hemodialyzed patients :
  - 189 (23%) without inflammation/malnutrition
  - 634 (77%) with inflammation/malnutrition
    - CRP ≥ 10 mg/L and/or
    - albuminemia < 36 g/L and/or
    - IL6 ≥ 3.09 pg/mL (447 patients!!, 70%)
- Median follow up 2.5 years (1875 person-years)
- 324 deaths (50% CVD)

JAMA 2004; 291: 451-459



Unadjusted Cumulative All-Cause Mortality by Cholesterol Level



Estimated 3-Year All-Cause and Cardiovascular Disease (CVD) Mortality by Cholesterol Level Serum cholesterol is modeled as a fifth-order polynomial, and all values are predicted from Cox models adjusted to age, sex, race, modality, and smoking status of the entire study group at each cholesterol level

Epidemiological Data
[CKD stages 3 and 4]

- Ancillary study from the MDRD study
- Correlation between serum cholesterol with all-cause mortality and CVD mortality
- N = 840 patients

N = 275	CHO < 1.93g/L	1st tertile
N = 284	1.93g/L< CHO < 2.32g/L	2nd tertile
N = 281	CHO > 2.32g/L	3rd tertile

- Follow up 10 years
- 128 CVD deaths

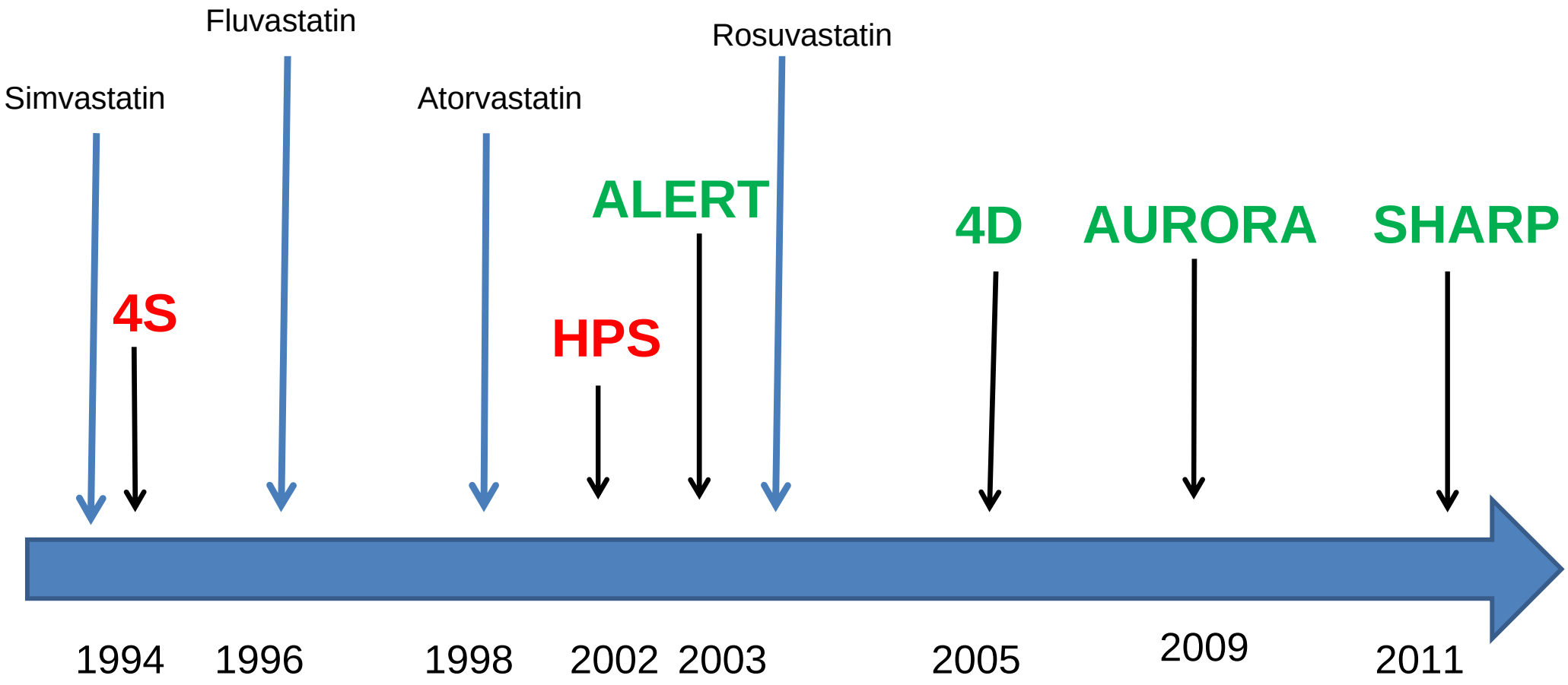
Parameter	All-cause mortality	CVD mortality
Total CHO		
Tertile 1	1.0	1.0
Tertile 2	1.13 (0.8-1.6)	0.86 (0.6-1.4)
Tertile 3	1.05 (0.7-1.5)	0.81 (0.5-1.3)
LDL CHO		
Tertile 1	1.0	1.0
Tertile 2	1.16 (0.8-1.7)	0.98 (0.6-1.5)
Tertile 3	1.12 (0.8-1.6)	0.82 (0.5-1.3)
TG		
Tertile 1	1.0	1.0
Tertile 2	0.91 (0.6-1.3)	1.27 (0.8-2.0)
Tertile 3	0.94 (0.7-1.3)	0.96 (0.6-1.5)
HDL CHO		
Tertile 1	1.17 (0.8-1.7)	1.04 (0.6-1.7)
Tertile 2	1.34 (0.9-1.9)	0.98 (0.6-1.6)
Tertile 3	1.0	1.0

Same study with lipids as continuous variables Cox models

Parameter	All-cause mortality	CVD mortality
Total CHO	1.02 (0.98-1.05)	1.0 (0.96-1.04)
LDL CHO	1.01 (0.98-1.05)	1.02 (0.95-1.03)
TG	1.02 (0.79-1.31)	0.97 (0.70-1.32)
HDL CHO	1.02 (0.91-1.14)	1.09 (0.95-1.26)

The CHOICE and the MDRD studies were done in USA.
What about CKD patients from other countries???

Large Randomized Clinical Trials with statin in CKD



4D - AURORA

- Aim : to reduce CVD death and morbidity by decreasing LDL CHO with powerful statin among stage 5D CKD (either diabetic or not)
- Key outcome (KO) : CVD death + non fatal MI + non fatal stroke

	4D	AURORA
Statin	Atorvastatin 20mg/d	Rosuvatatin 10mg/d
Number of patients	1.200	2.776
% of diabetes mellitus	100%	24%
Prevention primary/secondary	60%/40%	60%/40%
Follow -up	4 years	3.2 years
Baseline LDL CHO	1.2 g/L	1g/L
% of CHO reduction	-40%	-43%
Sponsor	Pfizer	Astra-Zeneca

4D

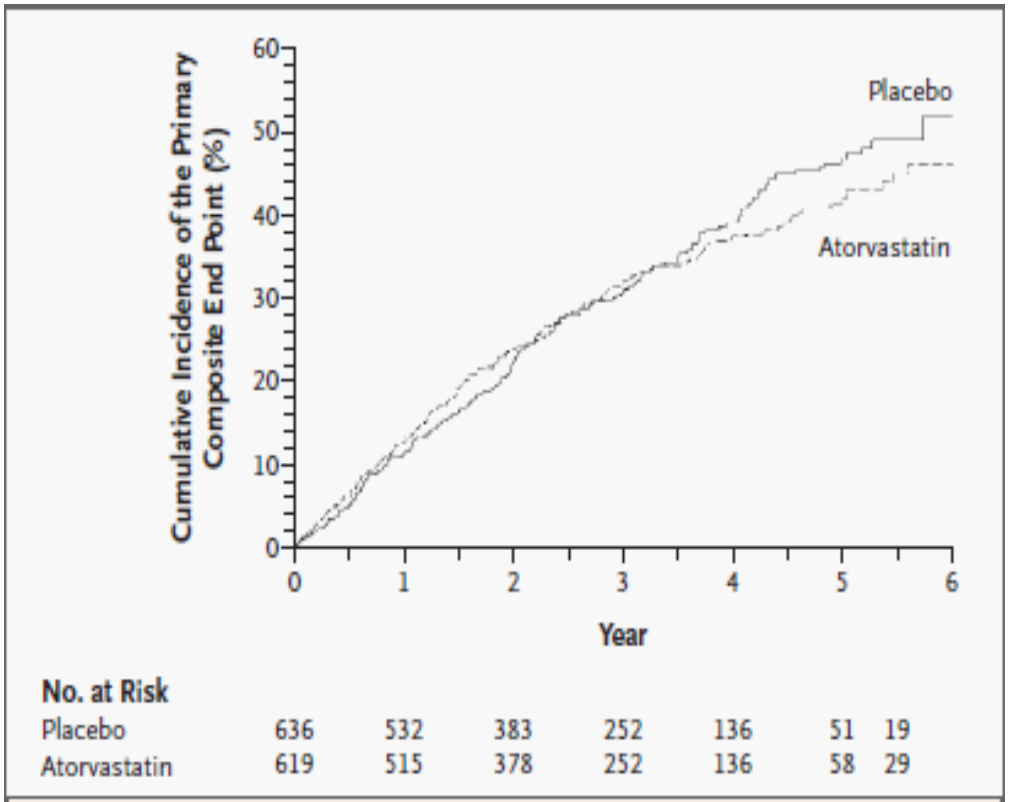


Figure 3. Estimated Cumulative Incidence of the Composite Primary End Point.

AURORA

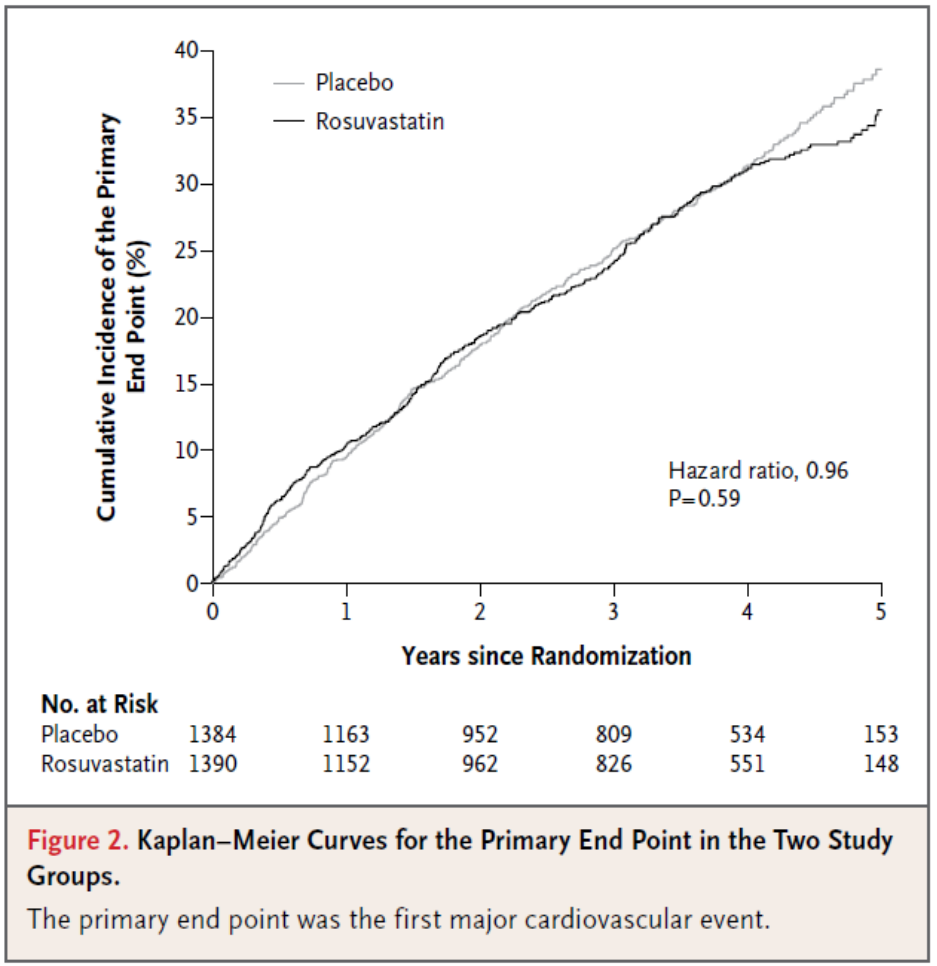


Figure 2. Kaplan–Meier Curves for the Primary End Point in the Two Study Groups.

The primary end point was the first major cardiovascular event.

4D N Engl J Med 2005; 353: 238-248

AURORA N Engl J Med 2009; 360: 1395-1407

4D - AURORA Interpretation

- No effect!!!!! «it was too late» …expected results
- Deleterious effect : increase risk of stroke in diabetic patients in both studies
- Poor compliance because of numerous adverse effects. Drug discontinuation :
  - 4D 20%
  - AURORA >30%
- Very reliable studies +++
  - No methodological caveats
  - Pfizer and Astra Zeneca (sponsors) had obvious commercial interests but…

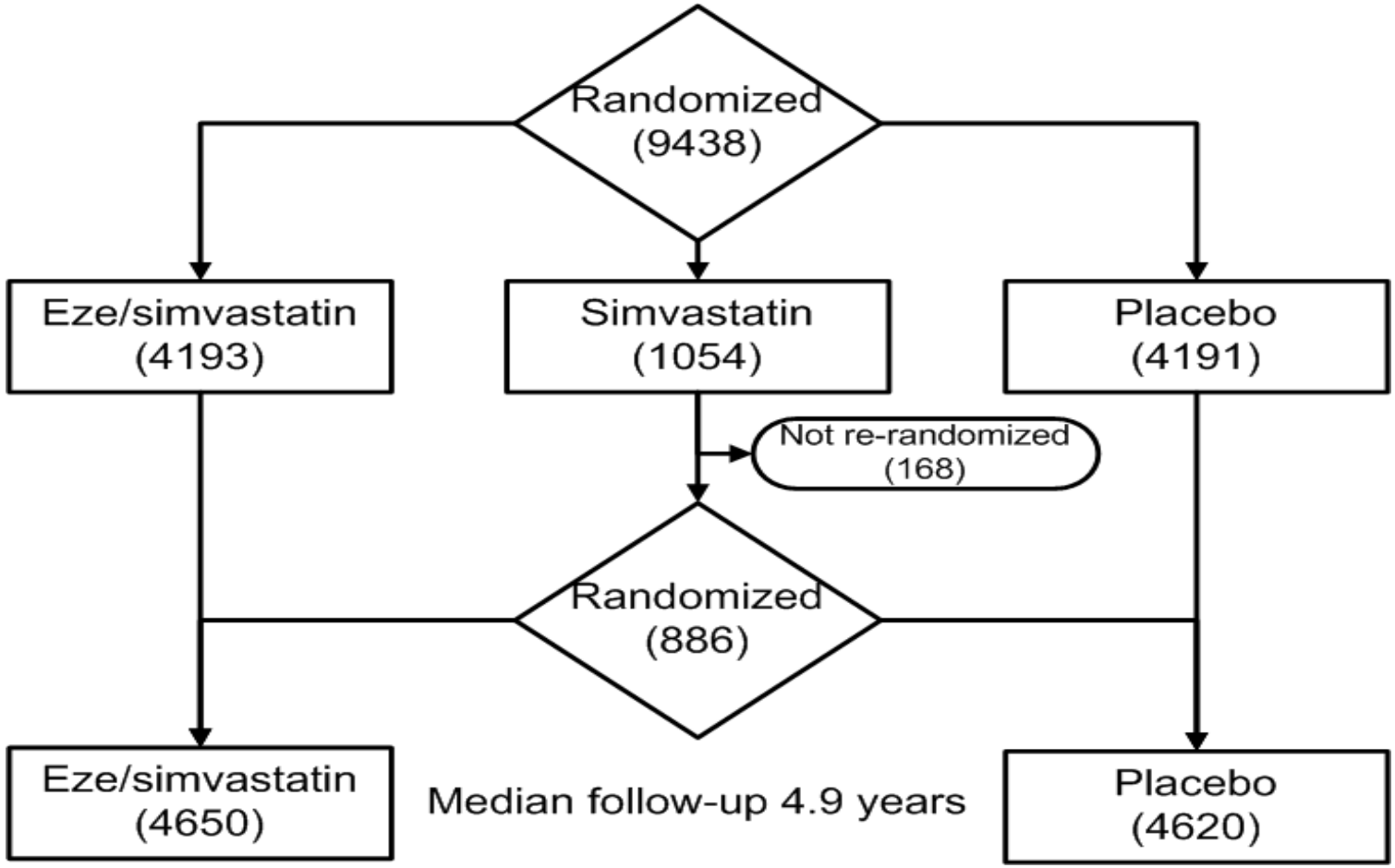
Study Heart And Renal Protection

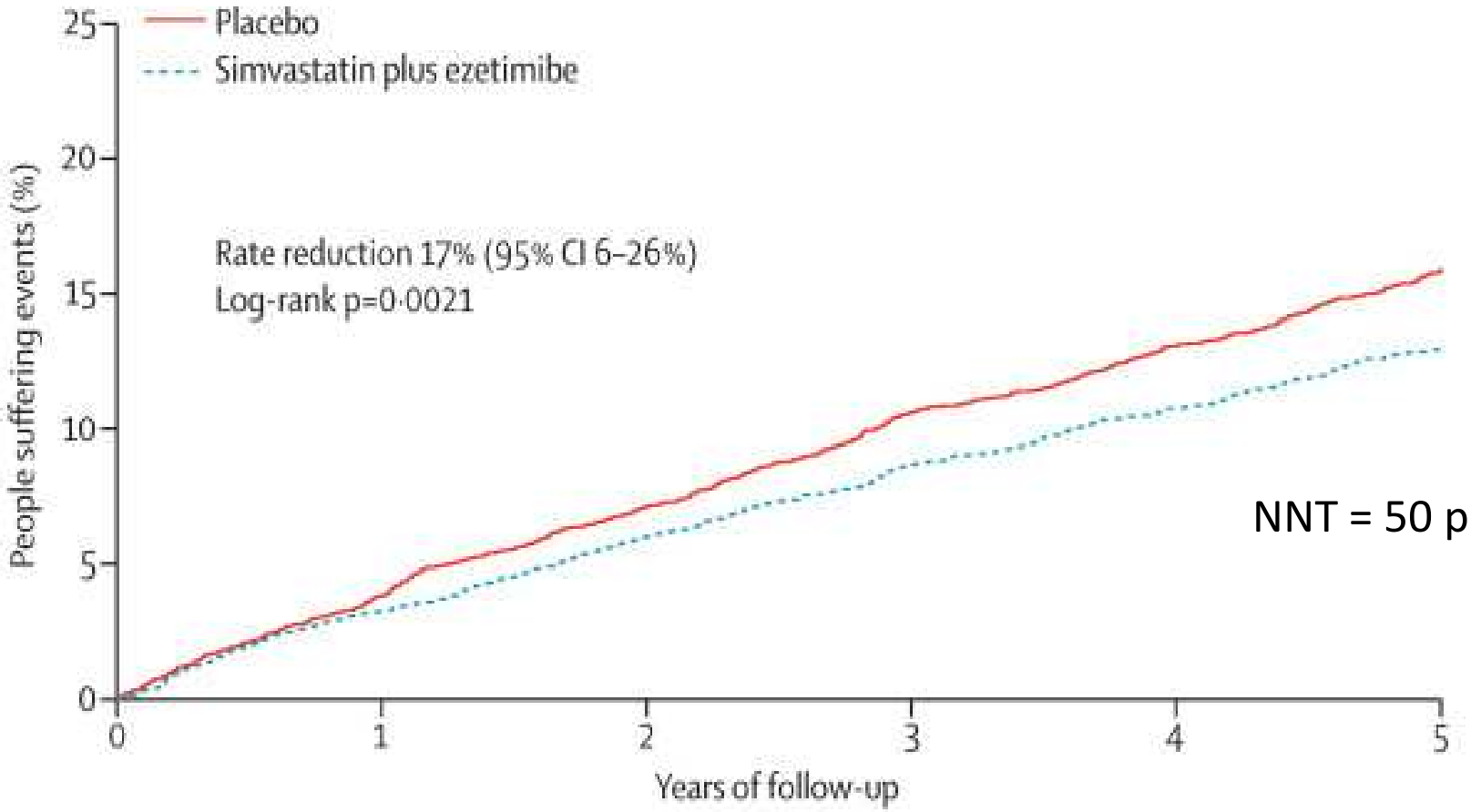
- Aim : same as 4D and AURORA

Statin	Simvastatin 20mg/d + ezetimibe 10mg/d
Number of patients	9.270
CKD 5D/not on dialysis	33%/67%
Mean eGFR (MDRD)	26 ml/min
% of diabetes mellitus	23%
Prevention primary/secondary	85%/15%
Follow -up	4.9 years
Baseline LDL CHO	1.1 g/L
% of LDL CHO reduction	-31% (1.1 g/L to 0.76 g/L)
Sponsor	Merck/Schering Plough

SHARP : key outcomes and flow chart

- Major atherosclerotic events !!!!!!!! (coronary death, MI, non-haemorrhagic stroke, or any revascularization)
- End stage renal disease (dialysis or transplant)





NNT = 50 pdt 5 ans

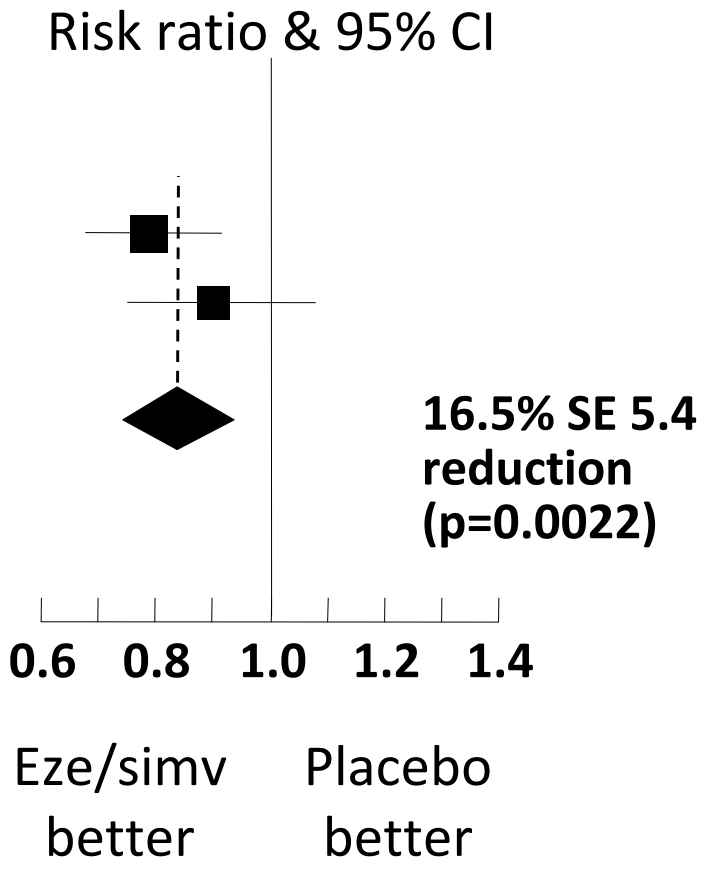
Number at risk						
Placebo	4620	4204	3849	3469	2566	1269
Simvastatin plus ezetimibe	4650	4271	3939	3546	2655	1265

Primary outcome	**HR 0.83 (0.74-0.94)**	**p=0.0021**
All cause Mortality	**HR 1.02 (0.94-1.11)**	**p=0.63**
CVD mortality	**HR 0.93 (0.80-1.07)**	**p=0.3**
ESRD or baseline creatinine doubling	**HR 0.94 (0.86- 1.01)**	**p=0.55**

SHARP: Major Atherosclerotic Events by renal status at randomization

	Eze/simv (n=4650)	Placebo (n=4620)
Non-dialysis (n=6247)	296 (9.5%)	373 (11.9%)
Dialysis (n=3023)	230 (15.0%)	246 (16.5%)
Major atherosclerotic event	**526 (11.3%)**	**619 (13.4%)**

No significant heterogeneity between non-dialysis and dialysis patients (p=0.25)



Lancet 2011; 377: 2181-2192

SHARP: Safety

	Sim/Eze (N=4650)	Placebo (N=4620)
Myopathy		
CK >10 x but ≤40 x ULN	17 (0.4%)	16 (0.3%)
CK >40 x ULN	4 (0.1%)	5 (0.1%)
Persistently ALT/AST >3x ULN	30 (0.6%)	26 (0.6%)
Cancer incidence	438 (9.4%)	439 (9.5%)
Cancer mortality	132 (2.8%)	114 (2.5%)

No explanations for the discrepancy between these data and the low compliance (drug discontinuation 32%)

SHARP – a critical reappraisal
Methodological flaws

1. In the CVD field, the only reliable outcome is mortality (either CVD mortality or all-cause mortality) because it is, by far, the most frequent event

   Case fatality rate (= taux de décès) in the first 3 to 4 weeks after MI or stroke is 50%

   - in all the countries (even in populations with low CVD risk as Japan)
   - WHO study : MONICA

   SHARP is «positive» but not on the main symptom of the disease

SHARP – a critical reappraisal
Methodological flaws

2. The primary outcome (CVD morbidity) was changed for atherosclerotic morbidity during the study (against MERCK advice !!!)

   Two consequences :

   The key outcome is less pertinent : all-cause mortality > CVD mortality > CVD morbidity > atherosclerotic morbidity

   The study basis (number of patients to be included) was obsolete

SHARP – a critical reappraisal
Methodological flaws

3. Group heterogeneity ++++
   - 4200 Sim/Eze –vs– 1054 Simastatin –vs– 4200 plac

   - There were 4 groups… (+++)
     - Sim/Eze
     - Sim then Sim/Eze
     - Sim then placebo
     - placebo
   - The justification for the checking of the tolerance of the Sim/Eze association is strange

SHARP – a critical reappraisal
Methodological flaws

4. Major conflict of interest
   - CTRU Oxford had financial ties with Merck/Schering Plough

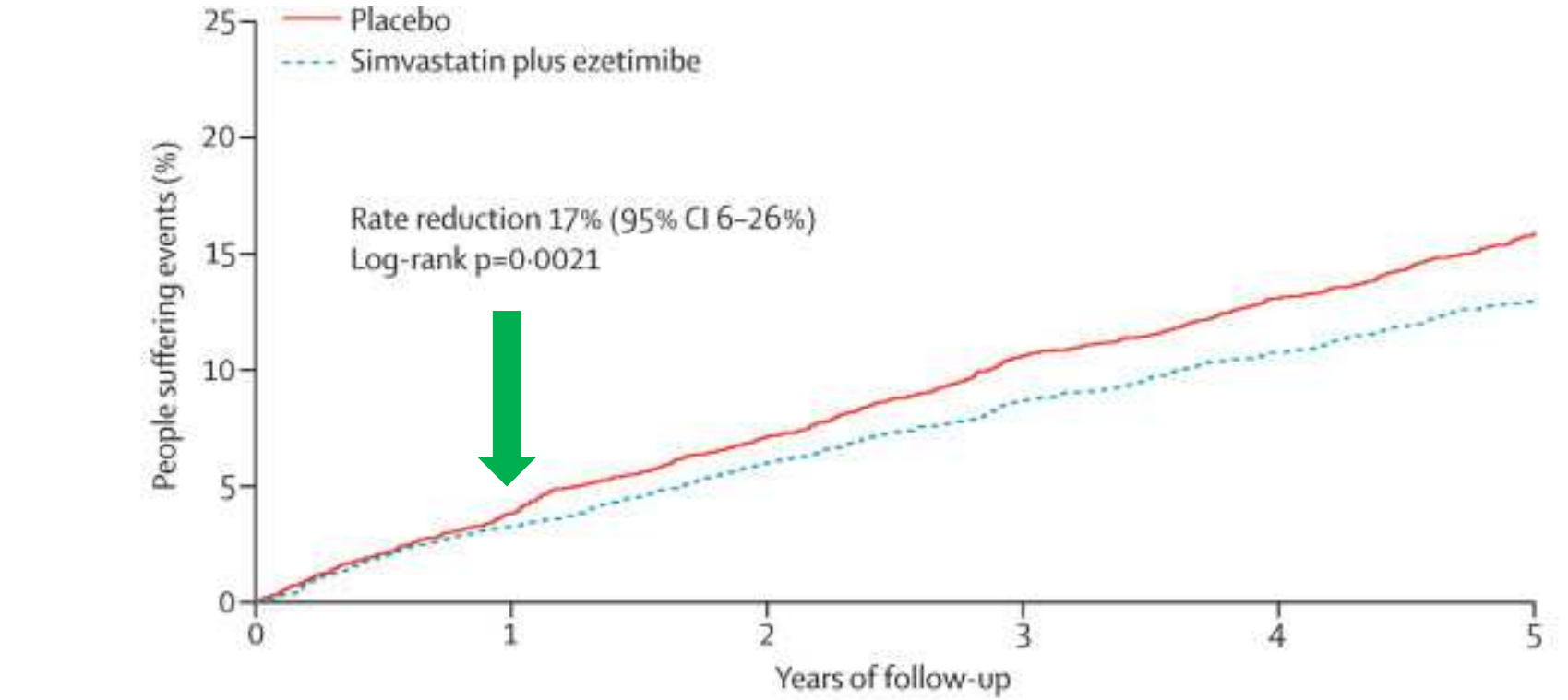
SHARP – a critical reappraisal Inconsistencies

	Sim/Eze	Placebo	p	Absolute difference
All-cause mortality	1142	1115	NS	-
CVD mortality	90	91	NS	-
Non fatal MI*	134	159	NS	-
Stroke*	171	210	p = 0.04 RR 0.81 (0.66-0.99)	4.5% - 3.7% = 0.8% NNT = 125 patients/5 years
Revascularisation (bypass , ACT, etc…)**	284	352	p = 0.0036 RR 0.79 (0.68-0.93)	7.6% - 6.1% = 1.5% NNT = 67 patients/5 ans

* In the Sim/Eze arm : less MI and stroke but same mortality (case fatality rate is 50%!!!)

** -medical decision but not a clinical event (useless for the patient)
-blindness is over +++

SHARP – a critical reappraisal
Other problems



Number at risk

Placebo	4620	4204	3849	3469	2566	1269
Simvastatin plus ezetimibe	4650	4271	3939	3546	2655	1265

- The two lines suddenly diverged at 1 year = time of the re-randomisation of the patients in the sim group ==> effet prothrombotic et pro-inflammatoiry effect of the sudden withdrawal of statin ➔ CVD events

ALERT (**A**ssesment of **LE**scol in **R**enal **T**ransplantation)

- Aim : to reduce CVD death and morbidity by decreasing LDL CHO with fluvastatin among stage 5T CKD
- KO : CVD death + non fatal MI + coronary procedures

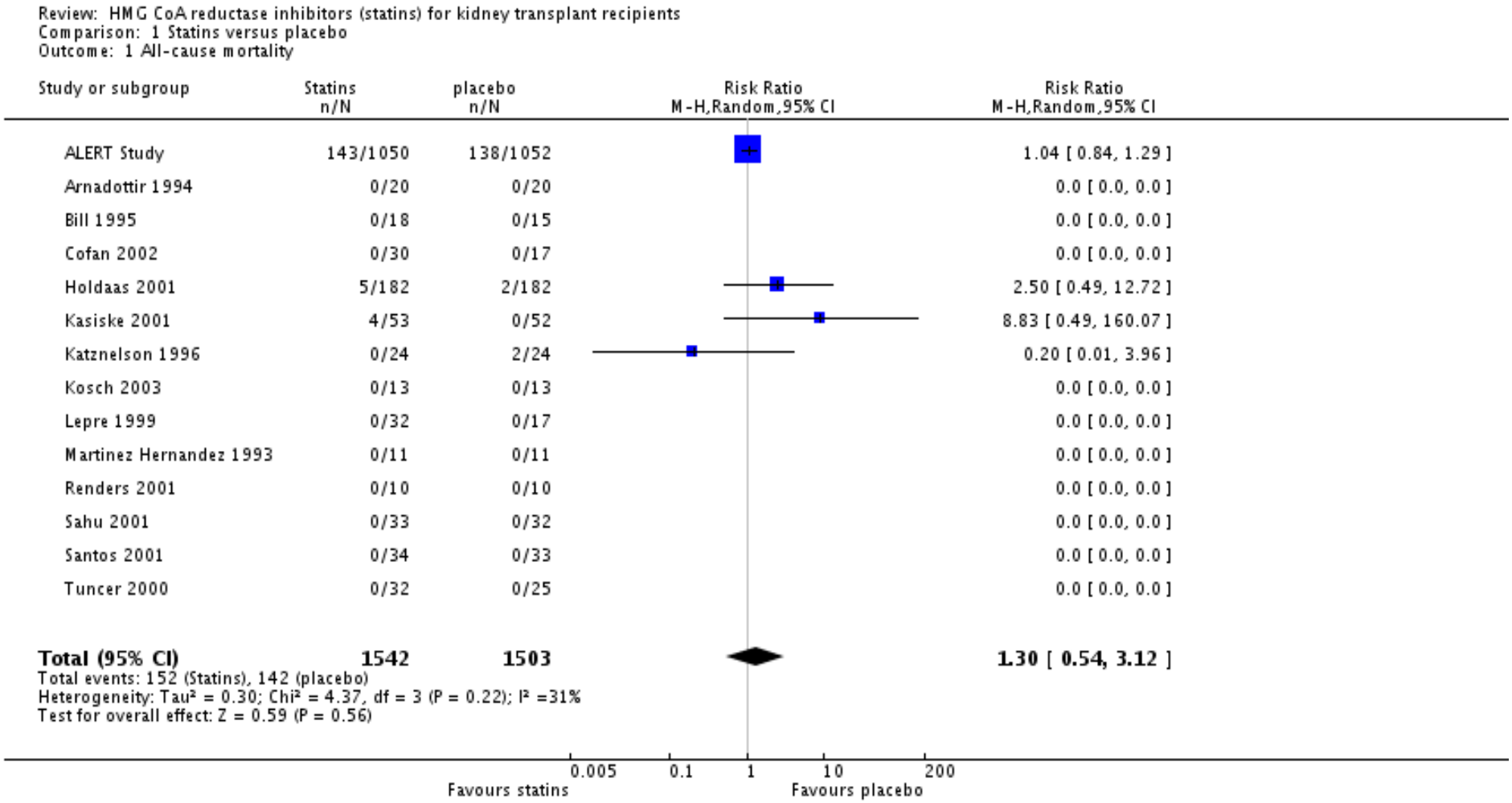
Statin	Fluvastatin 40mg/day
Number of patients	2.102
Transplantation vintage	7 years
Mean eGFR (MDRD)	52 ml/min
% of diabetes mellitus	20%
Prevention primary/secondary	90%/10%
Follow -up	5.5 years
Baseline LDL CHO	1.1 g/L
% of LDL CHO reduction	-32% (1.1 g/L to 0.76 g/L)
Sponsor	Novartis

ALERT - Results

- Key outcome : NS
- All cause death : NS
- Cardiac death : HR 0.62 (0.40 – 0.96) p<0.03
- MI : NS
- Stroke : NS
- No effect on renal function and on rejection
- Compliance : drug discontinuation 30%

Lancet 2003; 361: 2024-2031
Kidney Int 2004; 66: 1549-1555

Meta-analysis from the Cochrane group



Cochrane Database Syst Rev 2009; 15(2): CD 005019

Conclusions (1)

- Lipid parameters are usually normal in CKD patients
- There are no evidences that CHO is implicated in atherosclerotic lesions in CKD
- No correlation between lipid parameters and CVD death or morbidity (+++)
  - CKD stage 3 to 5
  - CKD 5D

Conclusions (2)

- 3 randomized controlled studies are negative among
  - hemodialysis patients (CKD 5D)
  - kidney transplant recipients
- The only positive study (SHARP) in CKD stage 3 to 5 is flawed by :
  - conflicts of interest
  - methodological problems
  - inconstitencies

In 2013, there are no evidences that statins are useful in CKD patients either they are in primary or secondary prevention.

Conversely, in this population, statins are associated with :

-adverse effects (➔ poor compliance)

-a higher risk of stroke among diabetic patients???