

**Effect of statin therapy on CV outcome  
in dyslipidemia patients  
with Chronic Kidney Disease (CKD)**

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# **01. Cholesterol, CKD and CVD**



# Definition and Stage of CKD (NKF)

- **Definition of CKD**

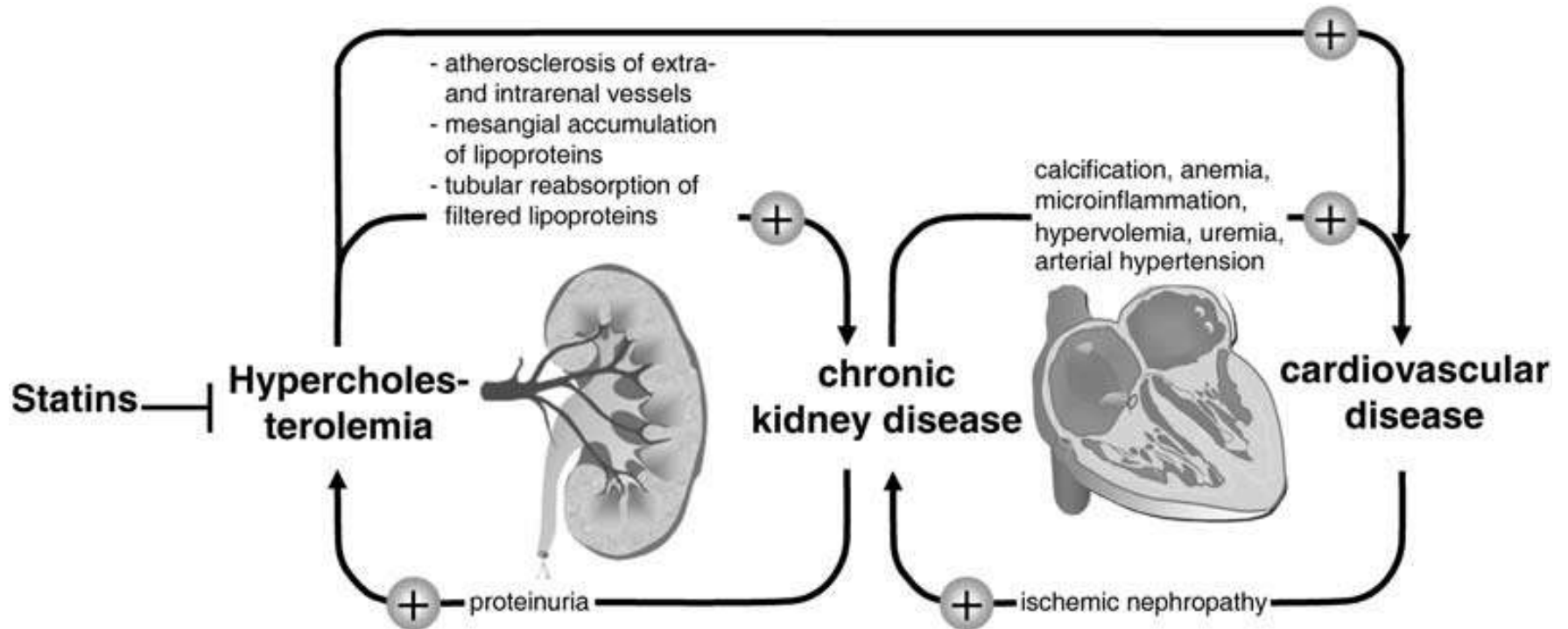
At least 3 months of either

- structural or functional abnormalities of the kidney that can lead to kidney failure
- GFR < 60 mL/min/1.73m<sup>2</sup>

Stage	Description	GFR (mL/min/1.73 m <sup>2</sup> )	Clinical Term
1	Kidney damage with normal or ↑ GFR	≥90	
2	Kidney damage with mild ↓ GFR	60-89	
3	Moderate ↓ GFR	30-59	CKD
4	Severe ↓ GFR	15-29	Advanced CKD
5	Kidney failure	<15 (or dialysis)	ESRD

# Cholesterol, CKD and CVD

## Central role of hypercholesterolemia in chronic kidney disease



# Cholesterol and the Risk of Renal Dysfunction

A prospective cohort study  
4,483 initially healthy men

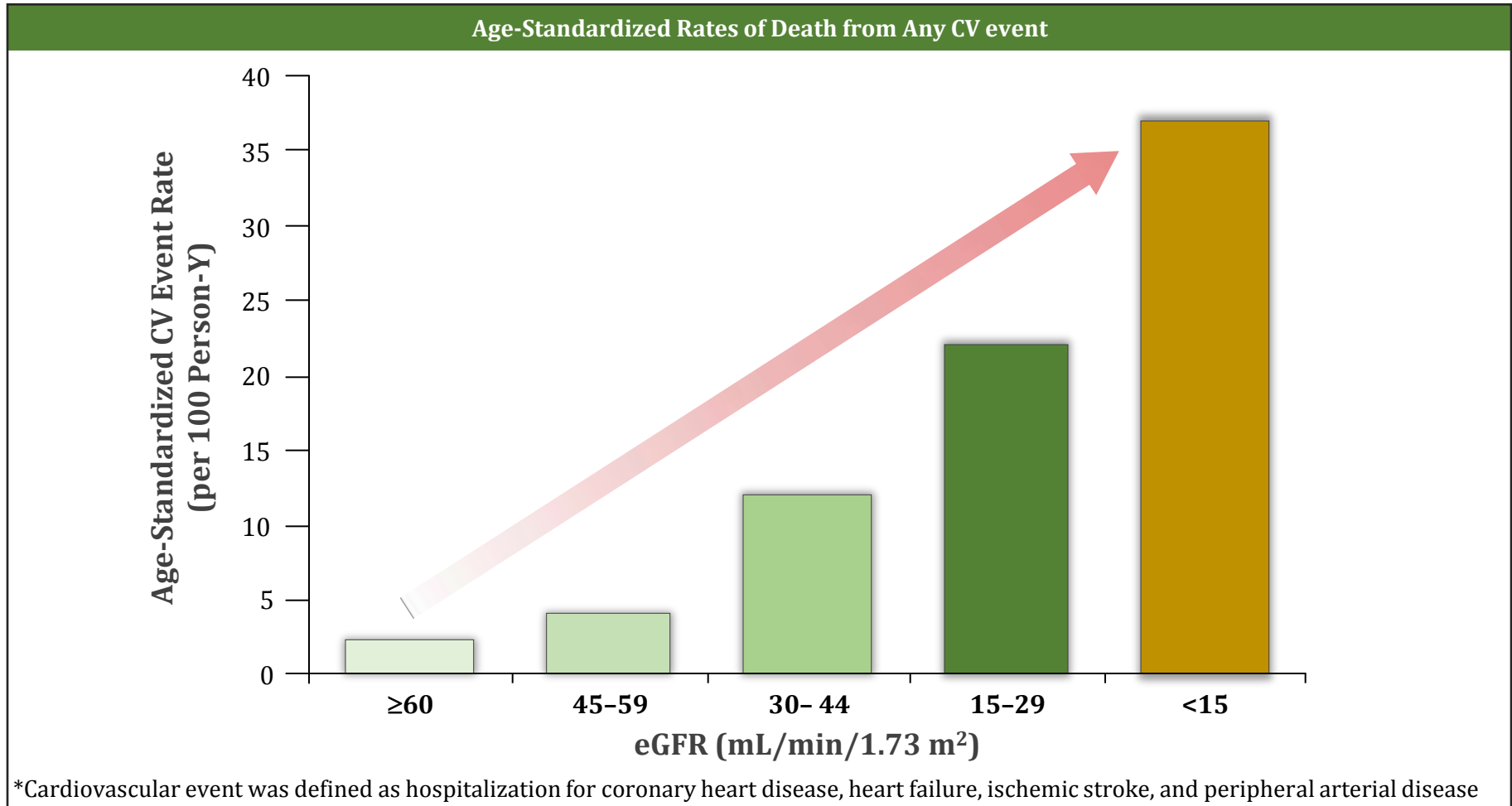
Age-adjusted and multivariable-adjusted RR and 95% CI of reduced GFR (<55 mL/min)

	Age-Adjusted RR (95% CI)	Model 1 <sup>b</sup> RR (95% CI)	Model 2 <sup>c</sup> RR (95% CI)
<b>Total cholesterol (mg/dl)</b>			
<200	1.00	1.00	1.00
200 to 239	1.12 (0.79 to 1.59)	1.09 (0.74 to 1.61)	1.07 (0.72 to 1.58)
≥240	1.38 (0.96 to 2.00)	1.38 (0.91 to 2.08)	1.33 (0.88 to 2.01)
<b>HDL (mg/dl)</b>			
≥40	1.00	1.00	1.00
<40	1.15 (0.86 to 1.53)	1.54 (1.09 to 2.17)	1.45 (1.03 to 2.05)
<b>Non-HDL cholesterol<sup>a</sup></b>			
<142.1	1.00	1.00	1.00
142.1 to 168.0	1.13 (0.72 to 1.79)	1.35 (0.81 to 2.26)	1.32 (0.79 to 2.22)
168.1 to 196.1	1.23 (0.78 to 1.93)	1.42 (0.85 to 2.38)	1.38 (0.82 to 2.32)
≥196.1	↓ 1.42 (0.92 to 2.20)	↓ 1.81 (1.10 to 2.97)	↓ 1.70 (1.03 to 2.82)
<b>Ratio of total cholesterol/HDL</b>			
<4.1	1.00	1.00	1.00
4.1 to 5.2	↓ 0.76 (0.49 to 1.18)	↓ 0.88 (0.54 to 1.44)	↓ 0.86 (0.53 to 1.41)
5.3 to 6.8	↓ 0.84 (0.55 to 1.28)	↓ 1.05 (0.65 to 1.70)	↓ 1.01 (0.62 to 1.64)
≥6.8	↓ 1.22 (0.83 to 1.82)	↓ 1.89 (1.19 to 3.01)	↓ 1.71 (1.07 to 2.74)

\***Model 1:** Adjusted for age, smoking, alcohol consumption, diabetes, BMI, exercise, history of hypertension, parental history of MI 60 years, history of past or current cholesterol treatment at baseline, and randomized treatment assignment. **Model 2:** Adjusted for all variables in model 1, plus additionally for the development of hypertension and CVD during follow-up period.

# Relationship between eGFR and CV event

1,120,195 adults, Mean follow-up : 2.84 years  
Cardiovascular Events\* = 139,011





# CVD risk of patients with ESRD

CV Risk According to Stages of CKD

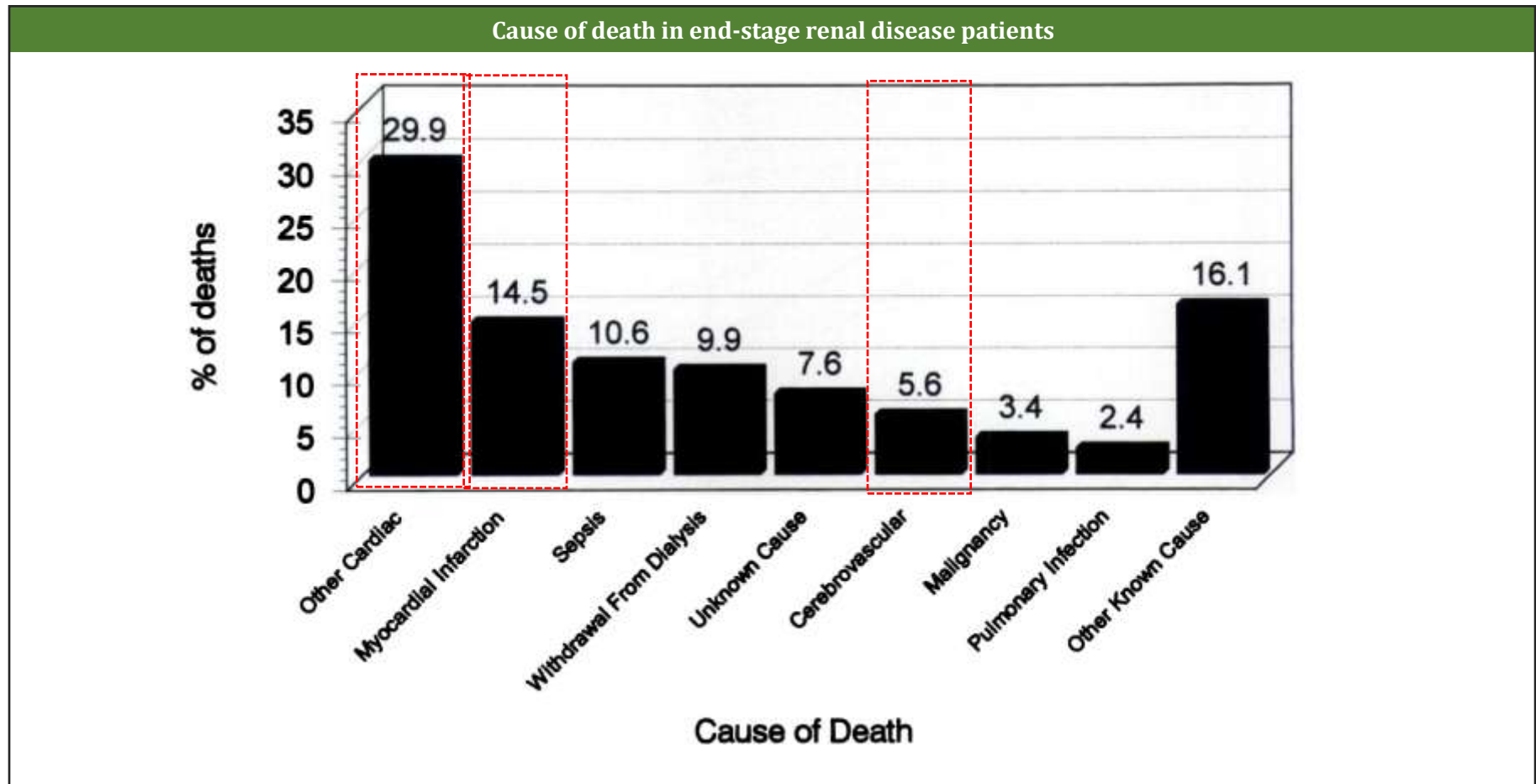
Stage	CV Risk (Odds Ratio, Univariate)
1	Depending on degree of proteinuria
2	1.5
3	2 to 4
4	4 to 10
5	10 to 50
ESRD	20 to 1000

The increase in risk in comparison with people free of CKD depends on the age of the population studied. The younger the person, the higher the relative risk.  
Microalbuminuria increases the CV risk 2- to 4-fold



# CV mortality in ESRD

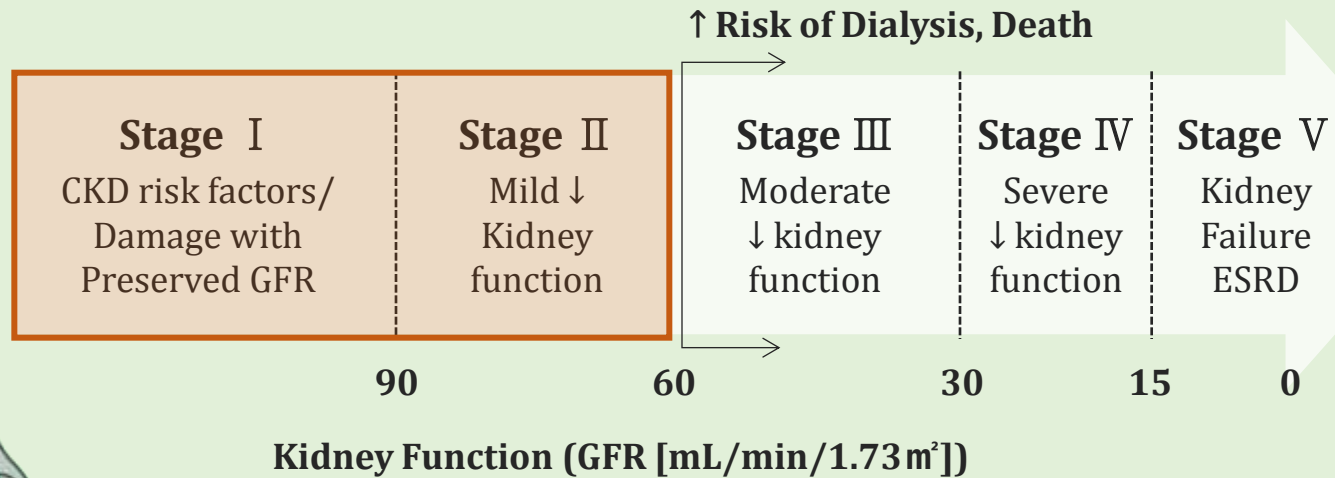
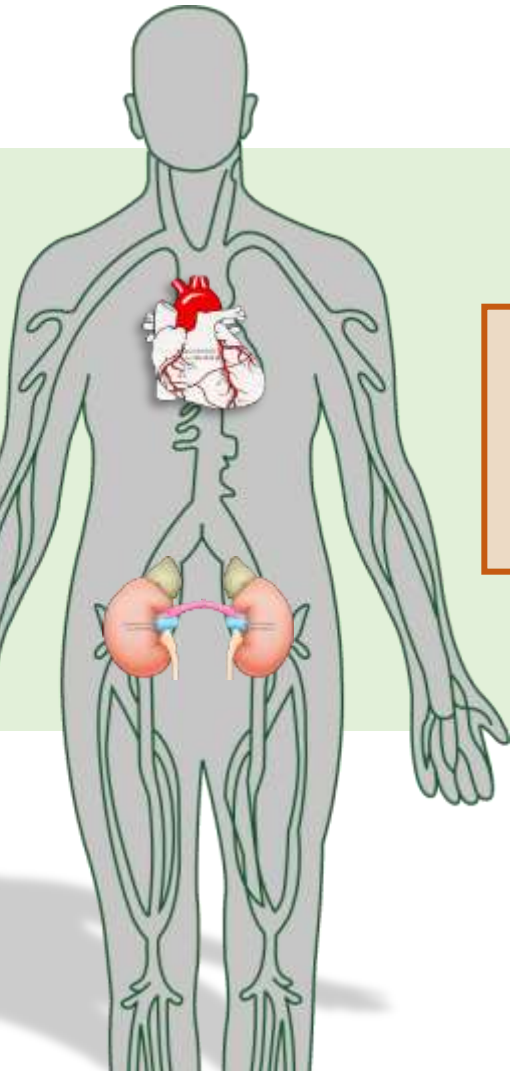
Cardiovascular disease accounts for almost half of the total mortality in patients with ESRD in **US (1989-1992)**





## **02. Statin Effects on each CKD Stage**

# Statin Effect on CKD stage I -II





# CARDS trial: Effects of Atorvastatin 10 mg on Kidney Outcomes in Patients with DM

2,838 patients with T2DM and no prior CVD

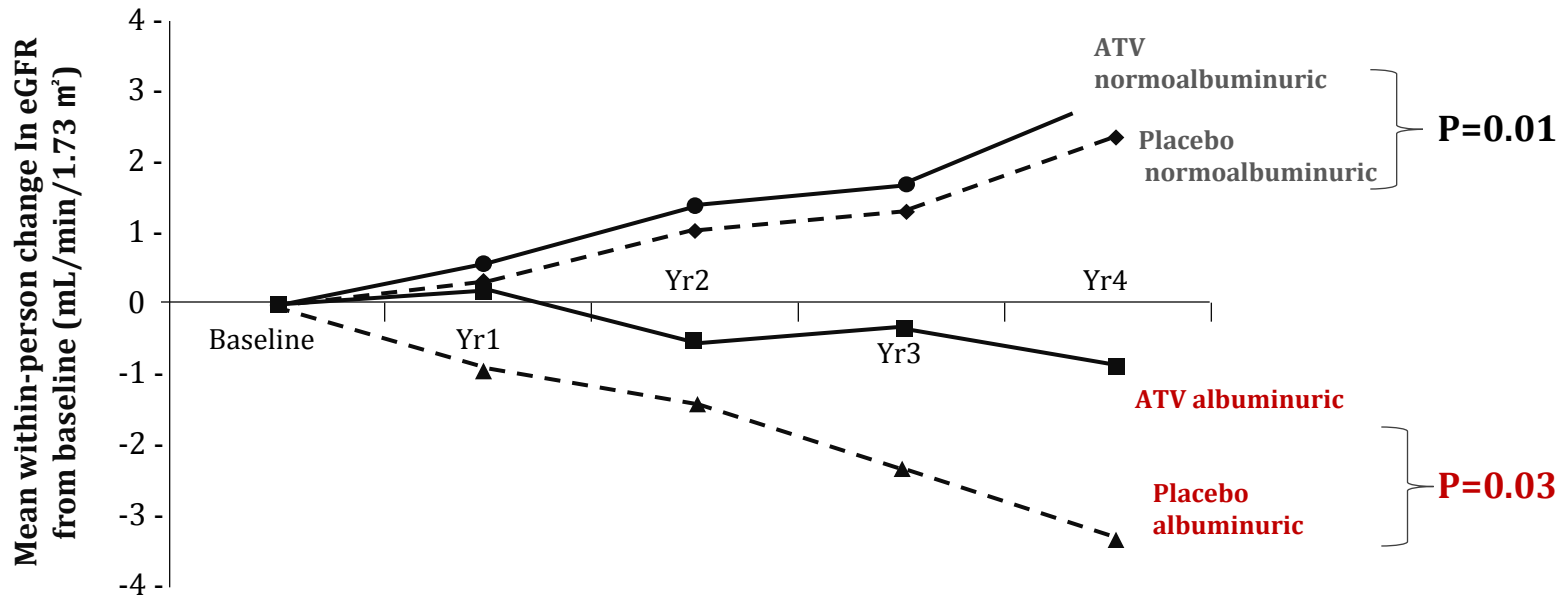
Placebo plus usual care

Atorvastatin 10 mg/day

- Primary endpoint : eGFR, albuminuria, CVD.
- Median follow-up = 3.9 years

\* Albuminuria :  $U_{ACR} \geq 22$  mg/g

Result : Yearly mean within-person change in eGFR by treatment group and baseline albuminuria.

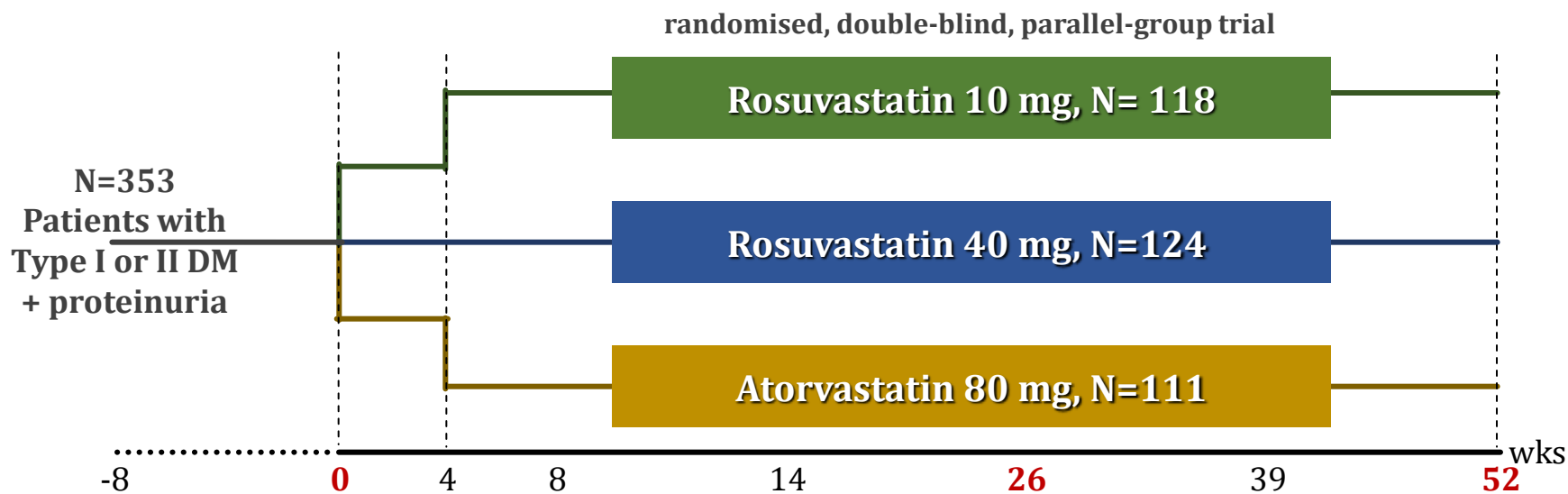


# CARDS – CKD : Effects of Atorvastatin 10 mg on CV Outcomes in Patients with DM

Treatment Effect on Efficacy End Points by Baseline eGFR Status

End Point	% With Event (n/N)		HR (95% CI) for Treatment Effect	P	Adjusted HR* (95% CI)	P
	Placebo	Atorvastatin				
<b>Major cardiovascular disease</b>						
eGFR ≥ 60 mL/min/1.73 m <sup>2</sup>	9.22% (85/922)	6.13% (58/946)	0.65 (0.46-0.90)	0.01	0.65 (0.47-0.91)	0.01
eGFR < 60 mL/min/1.73 m <sup>2</sup>	8.61% (42/488)	5.19% (25/482)	0.58 (0.36-0.96)	0.03	0.57 (0.35-0.94)	0.02
All	9.01% (127/1410)	5.81% (83/1,428)	0.63 (0.48-0.83)	<0.001	0.63 (0.48-0.83)	<0.001
Treatment-eGFR interaction coefficient, -0.14 (95% CI, -0.74 to 0.46); P = 0.6						
<b>Coronary heart disease</b>						
eGFR ≥ 60 mL/min/1.73 m <sup>2</sup>	5.42% (50/922)	3.49% (33/946)	0.63 (0.40-0.98)	0.04	0.64 (0.41-0.99)	0.04
eGFR < 60 mL/min/1.73 m <sup>2</sup>	5.53% (27/488)	3.73% (18/482)	0.66 (0.36-1.20)	0.2	0.65 (0.36-1.17)	0.2
All	5.46% (77/1,410)	3.57% (51/1,428)	0.64 (0.45-0.91)	0.01	0.64 (0.45-0.91)	0.01
Treatment-eGFR interaction coefficient, 0.02 (95% CI, -0.72 to 0.76); P = 0.9						
<b>Stroke</b>						
eGFR ≥ 60 mL/min/1.73 m <sup>2</sup>	2.60% (24/922)	1.59% (15/946)	0.60 (0.32-1.14)	0.1	0.62 (0.33-1.18)	0.3
eGFR < 60 mL/min/1.73 m <sup>2</sup>	3.07% (15/488)	1.24% (6/482)	0.39 (0.15-1.01)	0.04	0.38 (0.15-0.99)	0.04
All	2.77% (39/1,410)	1.47% (21/1,428)	0.52 (0.31-0.89)	0.01	0.53 (0.31-0.89)	0.02
Treatment-eGFR interaction coefficient, -0.48 (95% CI, -1.62 to 0.67); P = 0.4						
<b>Coronary revascularization</b>						
eGFR ≥ 60 mL/min/1.73 m <sup>2</sup>	2.39% (22/922)	2.01% (19/946)	0.83 (0.45-1.54)	0.6	0.84 (0.45-1.54)	0.6
eGFR < 60 mL/min/1.73 m <sup>2</sup>	2.46% (12/488)	1.04% (5/482)	0.41 (0.14-1.17)	0.08	0.40 (0.14-1.15)	0.07
All	2.41% (34/1,410)	1.68% (24/1,428)	0.69 (0.41-1.16)	0.2	0.68 (0.41-1.15)	0.2
Treatment-eGFR interaction coefficient, 0.73 (95% CI, -0.48 to 1.94); P = 0.2						
<b>Death from any cause</b>						
eGFR ≥ 60 mL/min/1.73 m <sup>2</sup>	5.64% (52/922)	3.59% (34/946)	0.63 (0.41-0.98)	0.04	0.65 (0.42-1.00)	0.05
eGFR < 60 mL/min/1.73 m <sup>2</sup>	6.15% (30/488)	5.60% (27/482)	0.89 (0.53-1.50)	0.7	0.86 (0.51-1.45)	0.6
All	5.82% (82/1,410)	4.27% (61/1,428)	0.73 (0.52-1.01)	0.06	0.73 (0.53-1.02)	0.06
Treatment-eGFR interaction coefficient, 0.29 (95% CI, -0.39 to 0.96); P = 0.4						

# PLANET I : Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease



## Population

- Age  $\geq$  18 yrs with diabetes
- Moderate proteinuria (urinary protein / creatinine ratio 500–5,000 mg/g)
- Hypercholesterolemia (fasting LDL-C  $\geq$ 90 mg/dL (2.33 mmol/L))
- ACE inhibitors or ARBs for  $\geq$ 3 months prior to screening

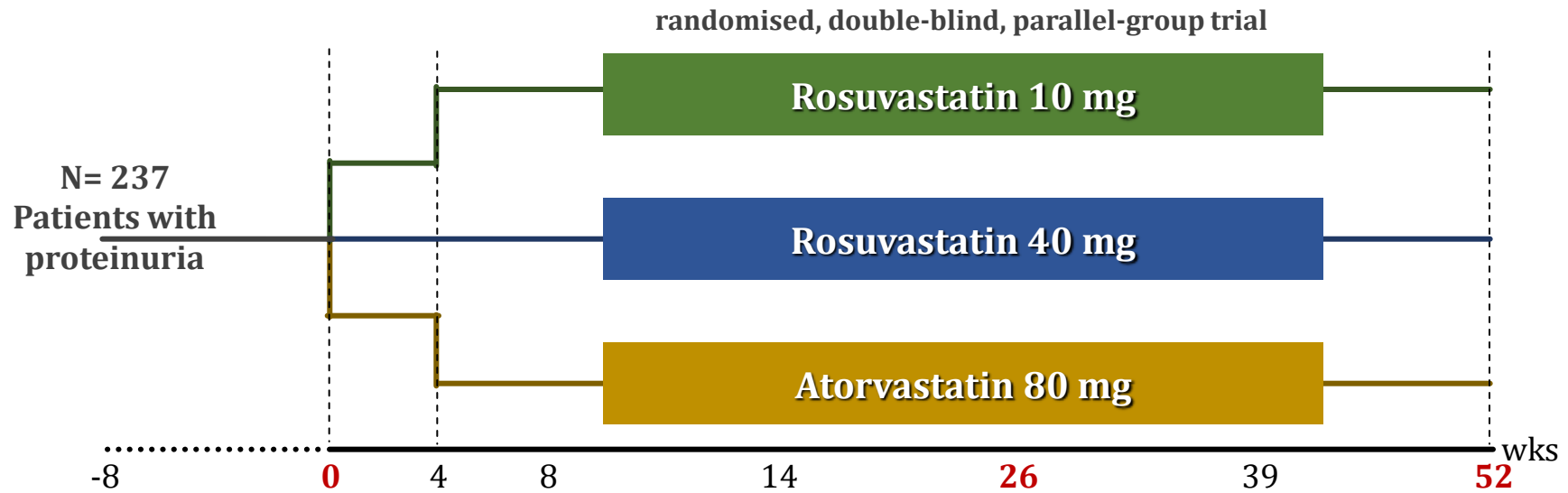
## Endpoint

- **Primary endpoint :**
  - Change in  $U_{PCR}$  from baseline to Week 52
- **Secondary endpoint :**
  - Change in  $U_{PCR}$  from baseline to Week 26
  - Change in eGFR from baseline to Week 26, 52
  - Change in  $U_{ACR}$  from baseline to Week 26, 52
  - Change in lipid level from baseline to Week 52

\*  $U_{PCR}$ , urine protein/creatinine ratio,  $U_{ACR}$ , urine albumin/creatinine ratio, eGFR estimated glomerular filtration rate



# PLANET II : Renal effects of atorvastatin and rosuvastatin in patients who have progressive renal disease



## Population

- Age  $\geq$  18 yrs
- Moderate proteinuria (urinary protein / creatinine ratio 500–5,000 mg/g)
- Hypercholesterolemia (fasting LDL-C  $\geq$ 90 mg/dL (2.33 mmol/L))
- ACE inhibitors or ARBs for  $\geq$ 3 months prior to screening

## Endpoint

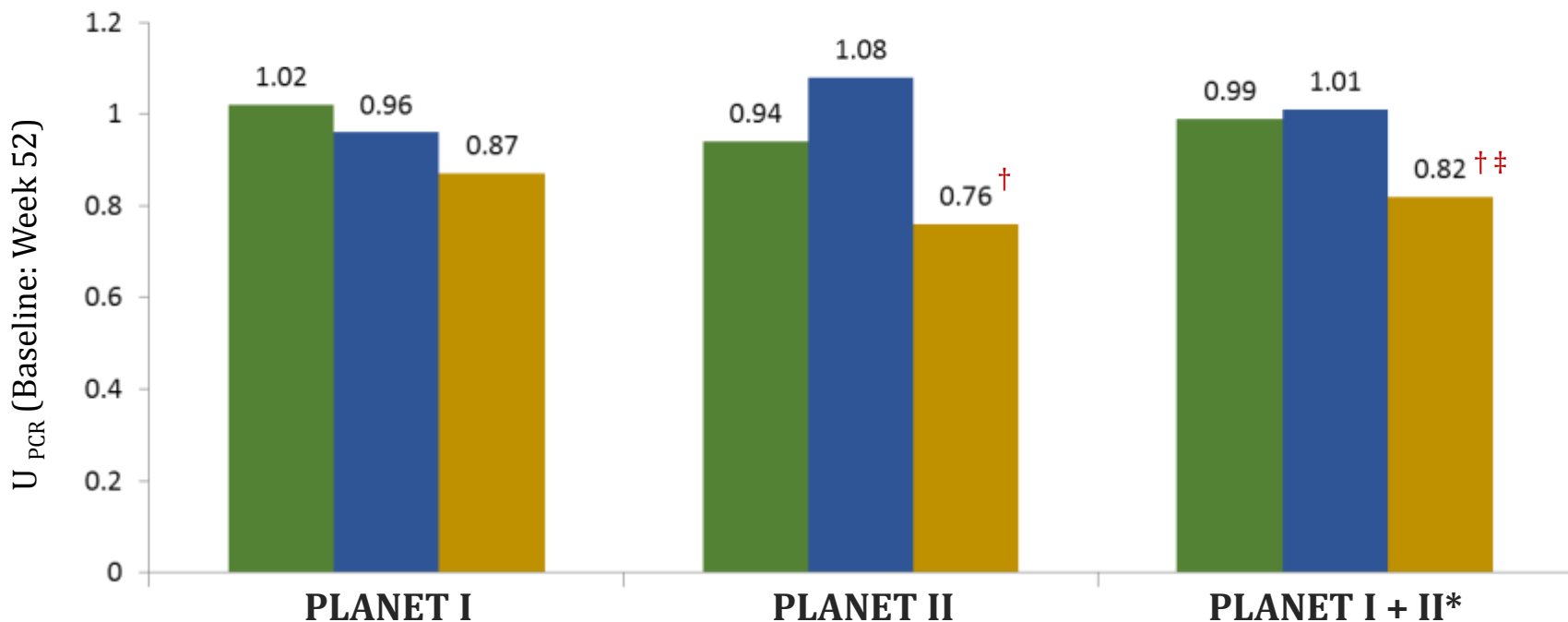
- **Primary endpoint :**
  - Change in  $U_{PCR}$  from baseline to Week 52
- **Secondary endpoint :**
  - Change in  $U_{PCR}$  from baseline to Week 26
  - Change in eGFR from baseline to Week 26, 52
  - Change in  $U_{ACR}$  from baseline to Week 26, 52
  - Change in lipid level from baseline to Week 52

\*  $U_{PCR}$ , urine protein/creatinine ratio,  $U_{ACR}$ , urine albumin/creatinine ratio, eGFR estimated glomerular filtration rate

# PLANET I and II : Primary endpoint

■ Rosuvastatin 10 mg (n=107)   ■ Rosuvastatin 40 mg (n=116)   ■ Atorvastatin 80 mg (n=102)

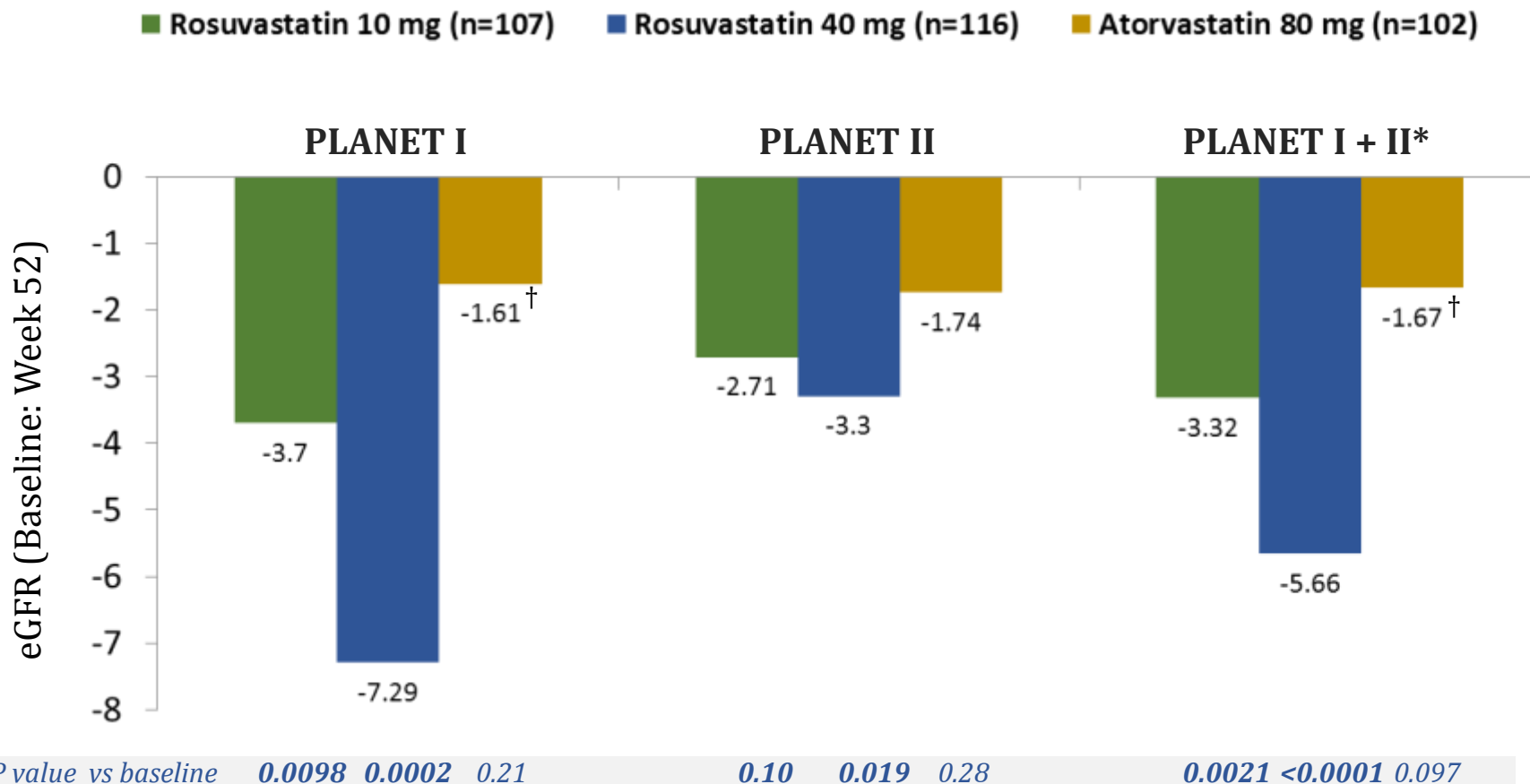
*P value vs baseline*   0.83   0.53   0.033                      0.62   0.31   0.003                      0.83   0.93   0.0003



\*Post-hoc analysis

<sup>†</sup> p<0.05 vs rosuvastatin 40 mg in exploratory analysis; <sup>‡</sup> p<0.05 vs rosuvastatin 10 mg in exploratory analysis

# PLANET I and II : Secondary endpoint



\*Post-hoc analysis

<sup>†</sup> p<0.05 vs rosuvastatin 40 mg in exploratory analysis



# PLANET 1 : Reported adverse events

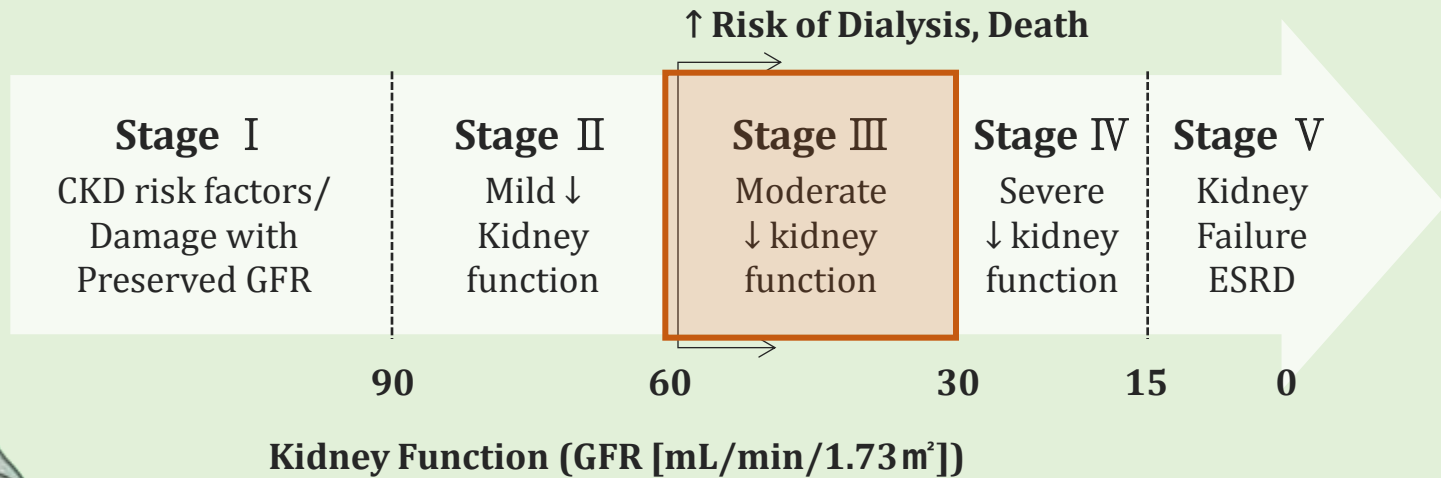
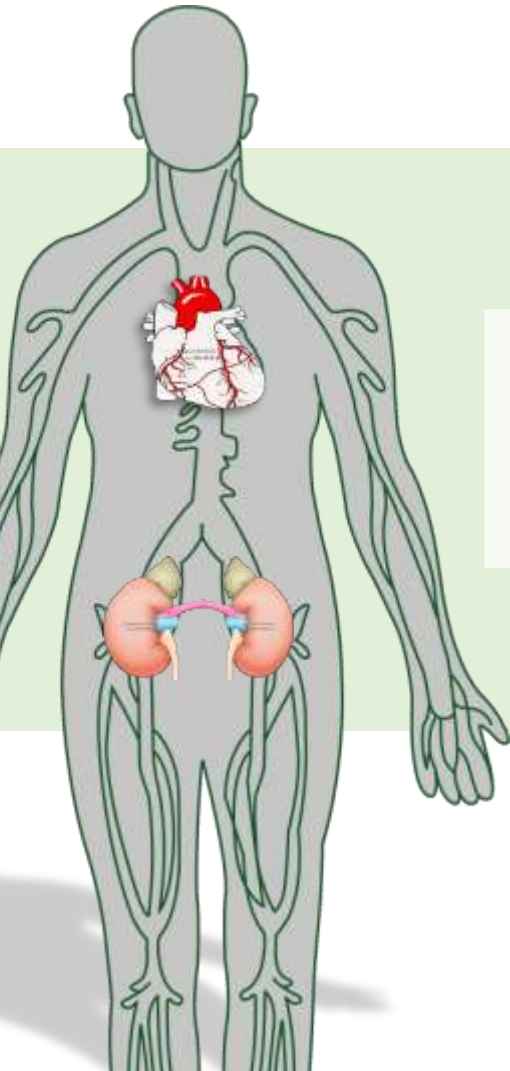
n (%)	Rosuvastatin 10 mg n = 116	Rosuvastatin 40 mg n = 123	Atorvastatin 80 mg n = 110
Any adverse event	69 (59.5)	79 (64.2)	63 (57.3)
Any serious adverse event	18 (15.5)	20 (16.3)	21 (19.1)
Any renal adverse event	9 (7.8)	<b>12 (9.8)</b>	5 (4.5)
Acute renal failure	0	<b>5 (4.1)</b>	1 (0.9)
Serum creatinine doubling	0	<b>6 (4.9)</b>	0
Doubling of serum creatinine or acute renal failure	0	<b>9 (7.3)</b>	1 (0.9)
Death	4 (3.4)	1 (0.8)	0

Statistical analysis of adverse events was not presented

One serious AE (2 episodes of cardiac failure in rosuvastatin 10 mg group) was considered related to study drug

No episodes of acute renal failure were considered related to study drug

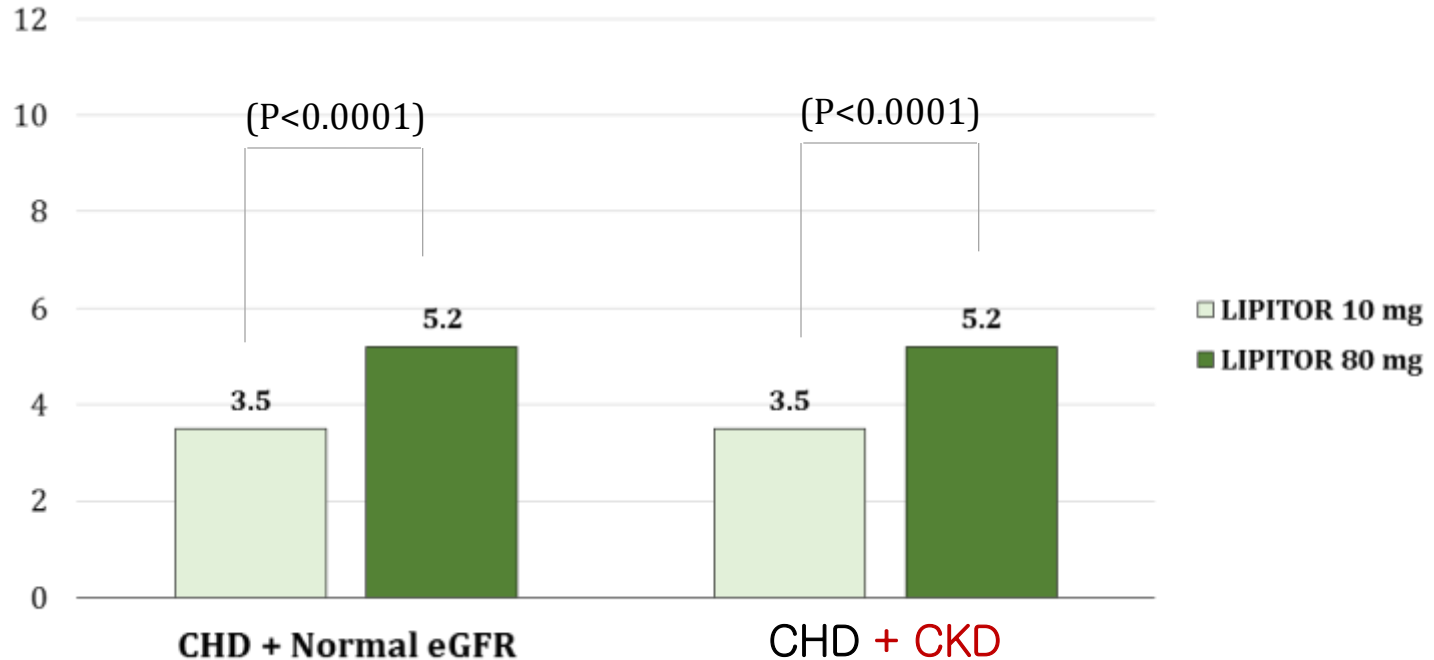
# Statin Effect on CKD stage III



# TNT – CKD : Effects of Atorvastatin 80 mg on Kidney Outcomes in Patients with CHD

[Effect of LIPITOR 10 mg on eGFR (annual rate of eGFR change) (mL/min/1.73 m2 per year)]

Mean change from baseline to last visit  
in eGFR (mL/min/1.73 m2)





# TNT- CKD subgroup: Effects of Atorvastatin 80 mg on CV Outcomes in Patients with CHD & CKD

10,001 Patients aged 35 to 75 years with stable CHD

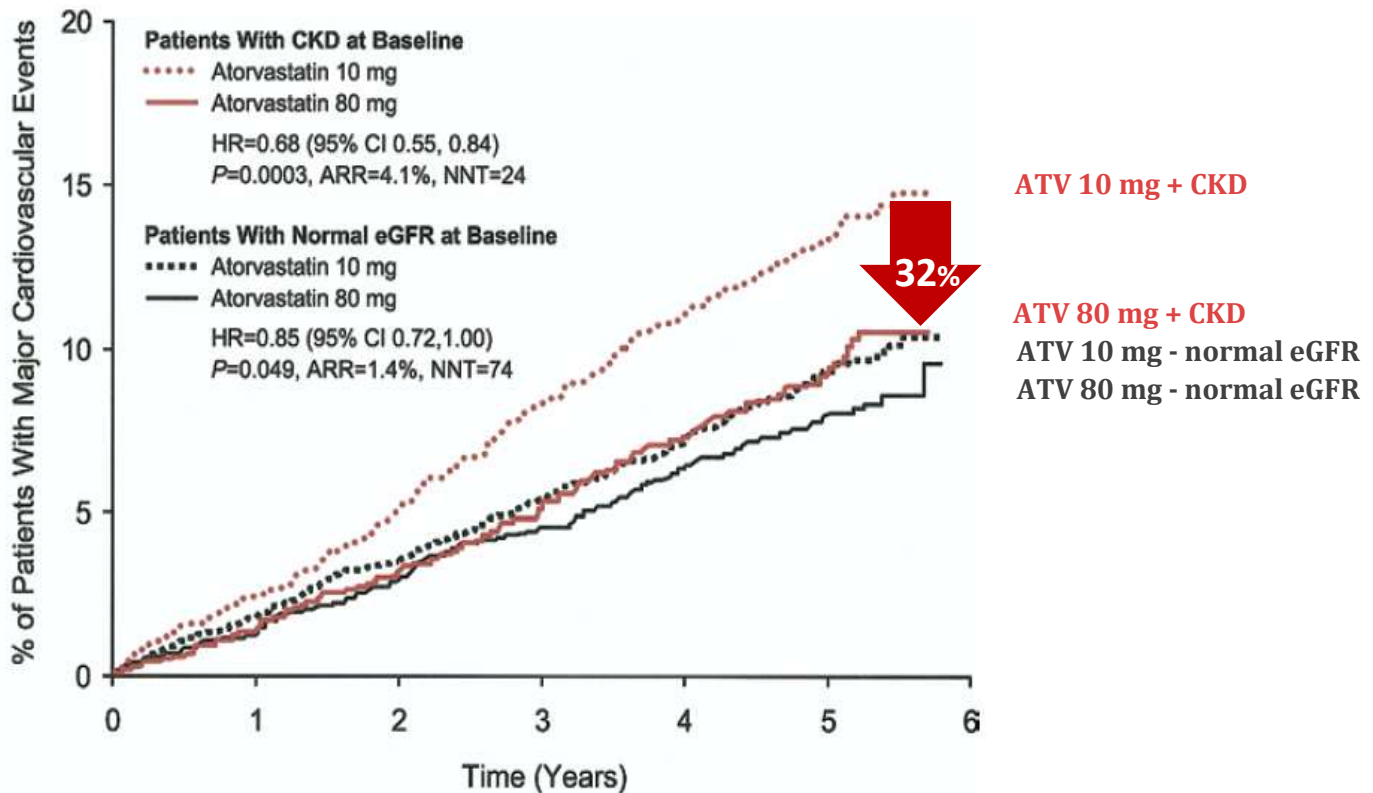
Atorvastatin 10 mg/day

Atorvastatin 80 mg/day

- Primary endpoint : major CV event
- Median follow-up = 4.9 years

\* CKD : eGFR < 60 mL/min/1.73 m2.

Time to First Major CV Event by Treatment in Patients With CKD and With Normal eGFR at Baseline



ATV 10 mg + CKD

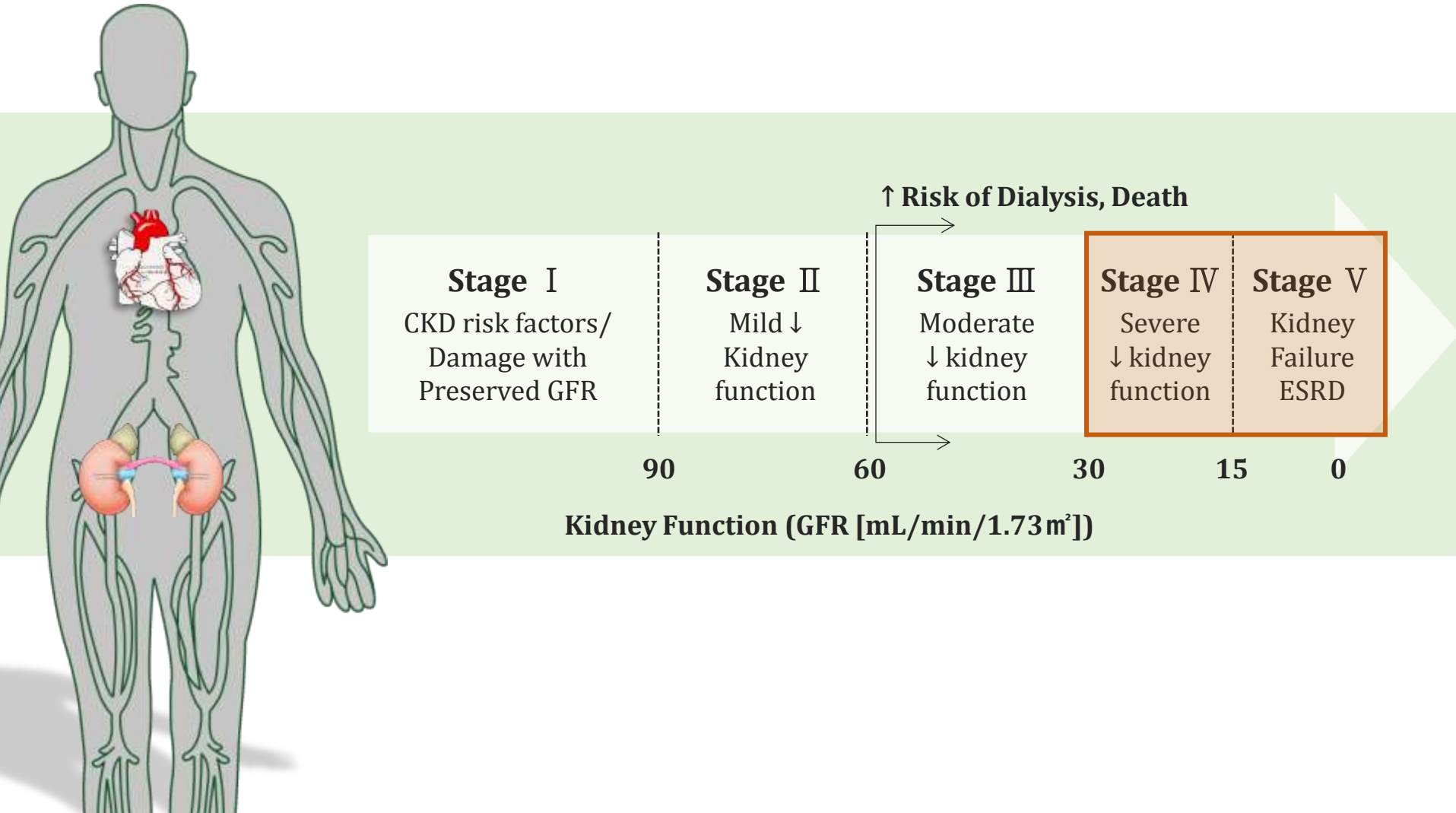
ATV 80 mg + CKD

ATV 10 mg - normal eGFR

ATV 80 mg - normal eGFR

32%

# Statin Effect on CKD stage IV-V



# 4D : Effect of Statins in Dialysis Patients

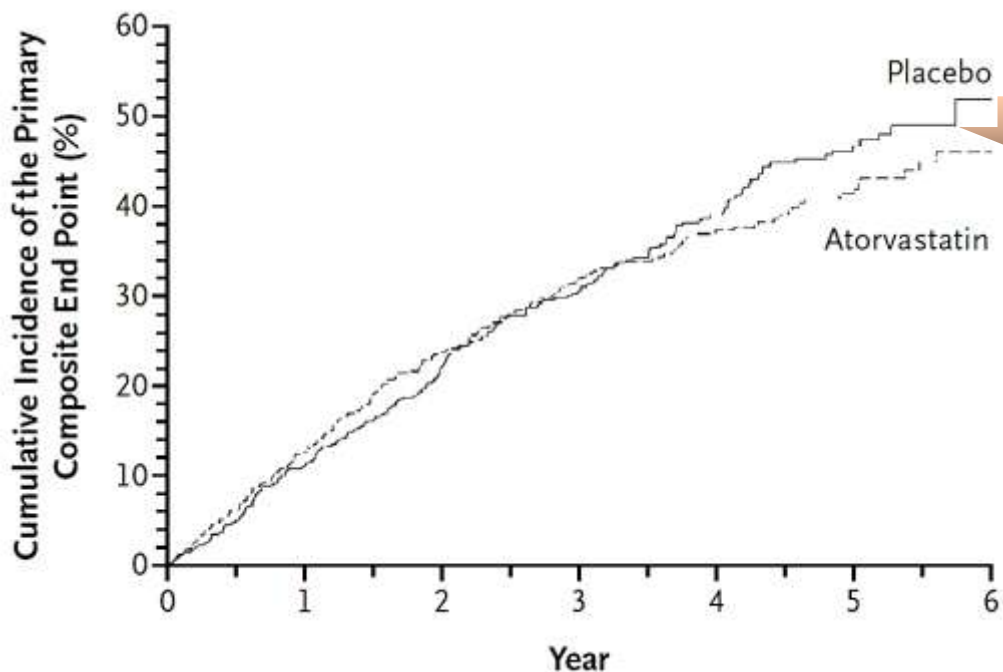
1,255 Patients  
with type 2 DM  
receiving hemodialysis

Placebo

Atorvastatin 20 mg/day

- Primary endpoint : Cardiac death, non fatal MI and stroke
- Median follow-up = 4 years

Primary endpoint



**HR=0.92(0.77-1.10),  
P=0.37**



# AURORA : Effect of Statins in Dialysis Patients

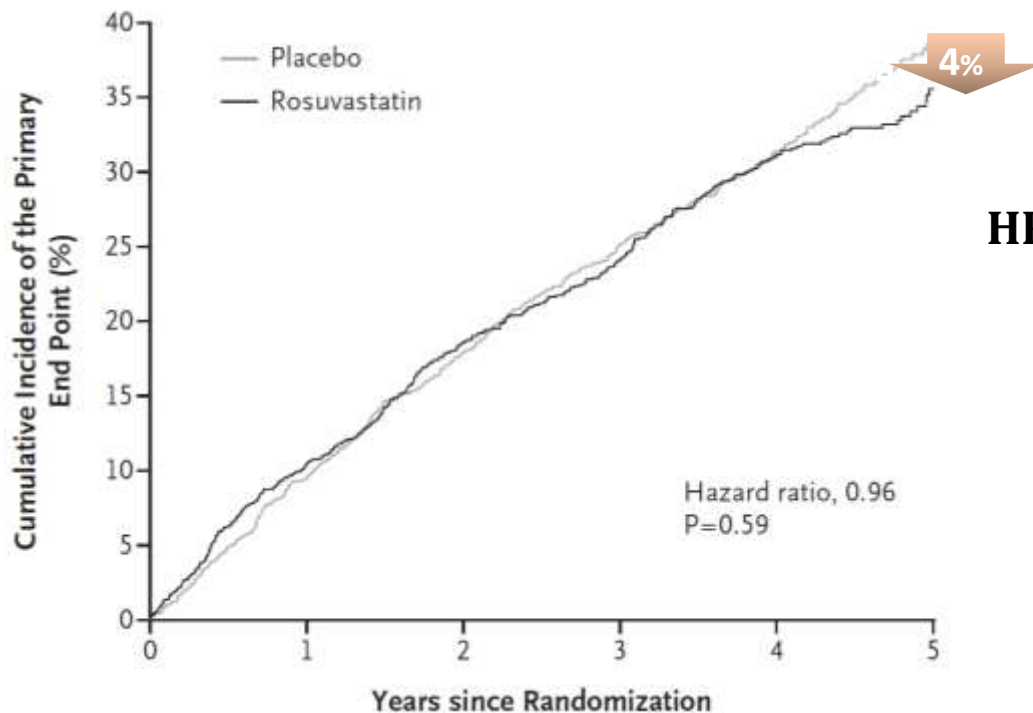
2,776 Patients  
aged 50 to 80 years  
receiving hemodialysis

Placebo

Rosuvastatin 10 mg/day

- Primary endpoint : nonfatal MI, nonfatal stroke, or CV death.
- Median follow-up = 3.8 years

## Primary endpoint



**HR=0.96(0.84-1.11),  
P=0.59**

# SHARP : Effect of Statins in CKD patients (including Dialysis Patients)

9,270 Patients  
aged  $\geq 18$  years  
with CKD

\*3023 on dialysis and 6247 not

Simvastatin plus Ezetimibe

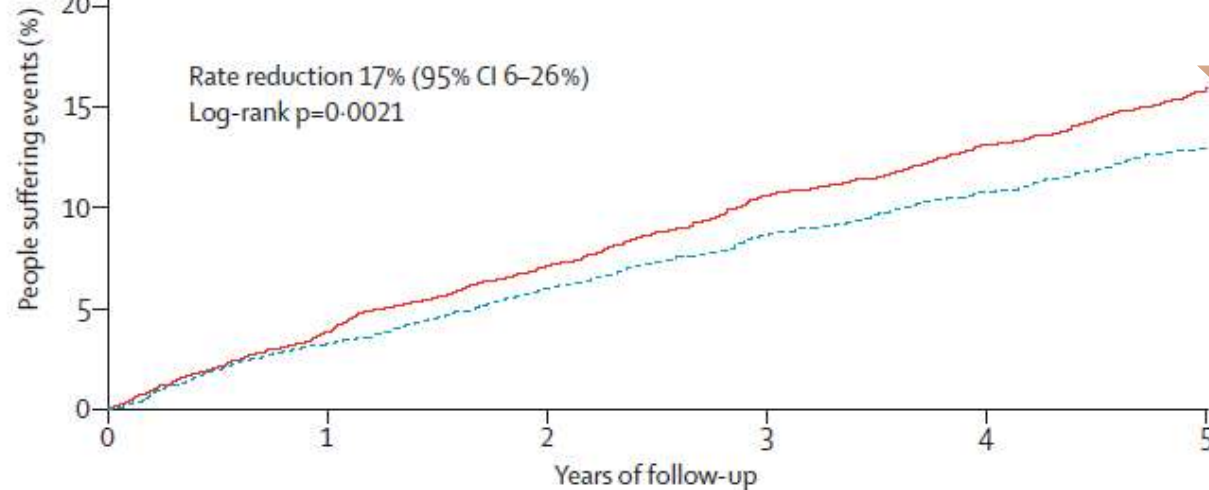
Simvastatin

Placebo

- Primary endpoint : non-fatal MI, death, non-haemorrhagic stroke, arterial revascularisation
- Median follow-up = 4.9 years

## Primary endpoint

— Placebo  
- - - Simvastatin plus ezetimibe

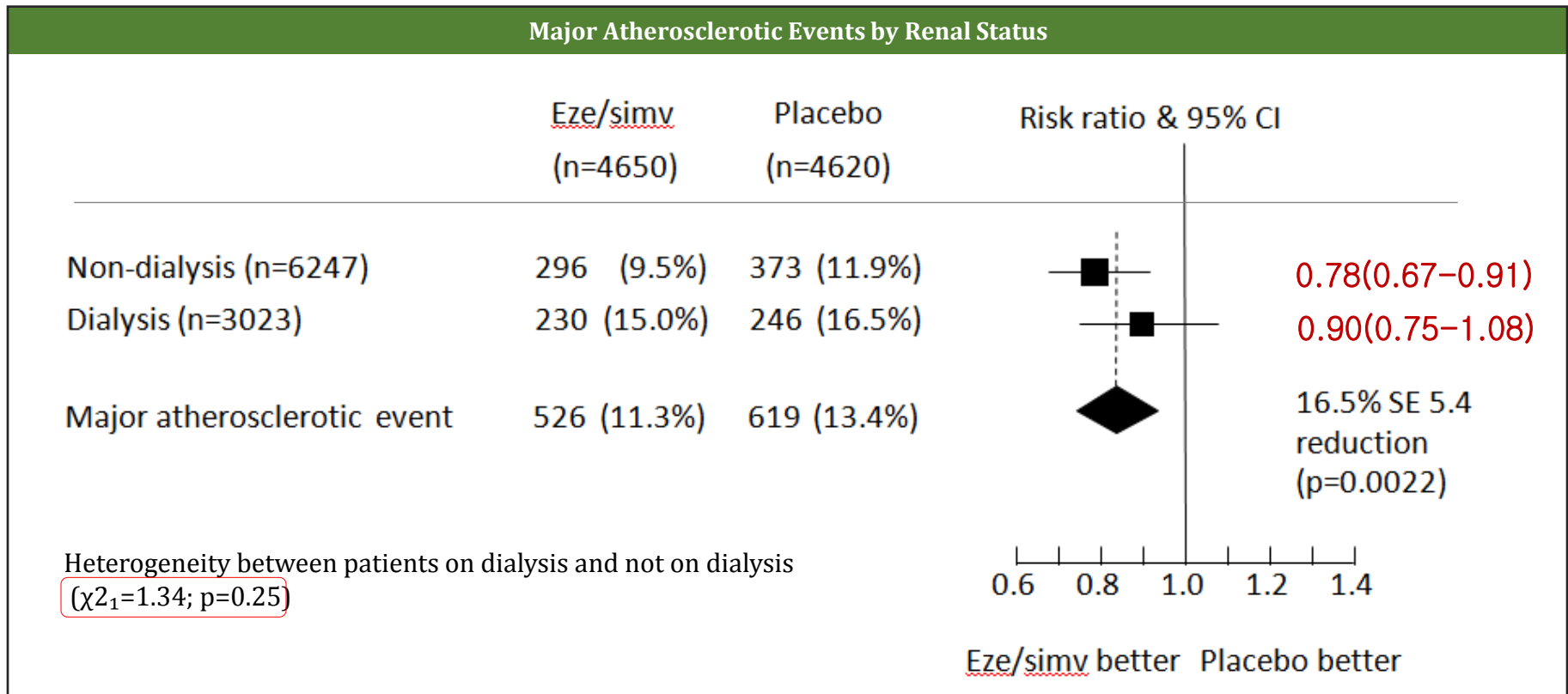


Rate reduction 17% (95% CI 6-26%)  
Log-rank p=0.0021

17%

**RR=0.83 (0.74-0.94),  
p=0.0021**

# SHARP : Major Atherosclerotic Events by Renal Status

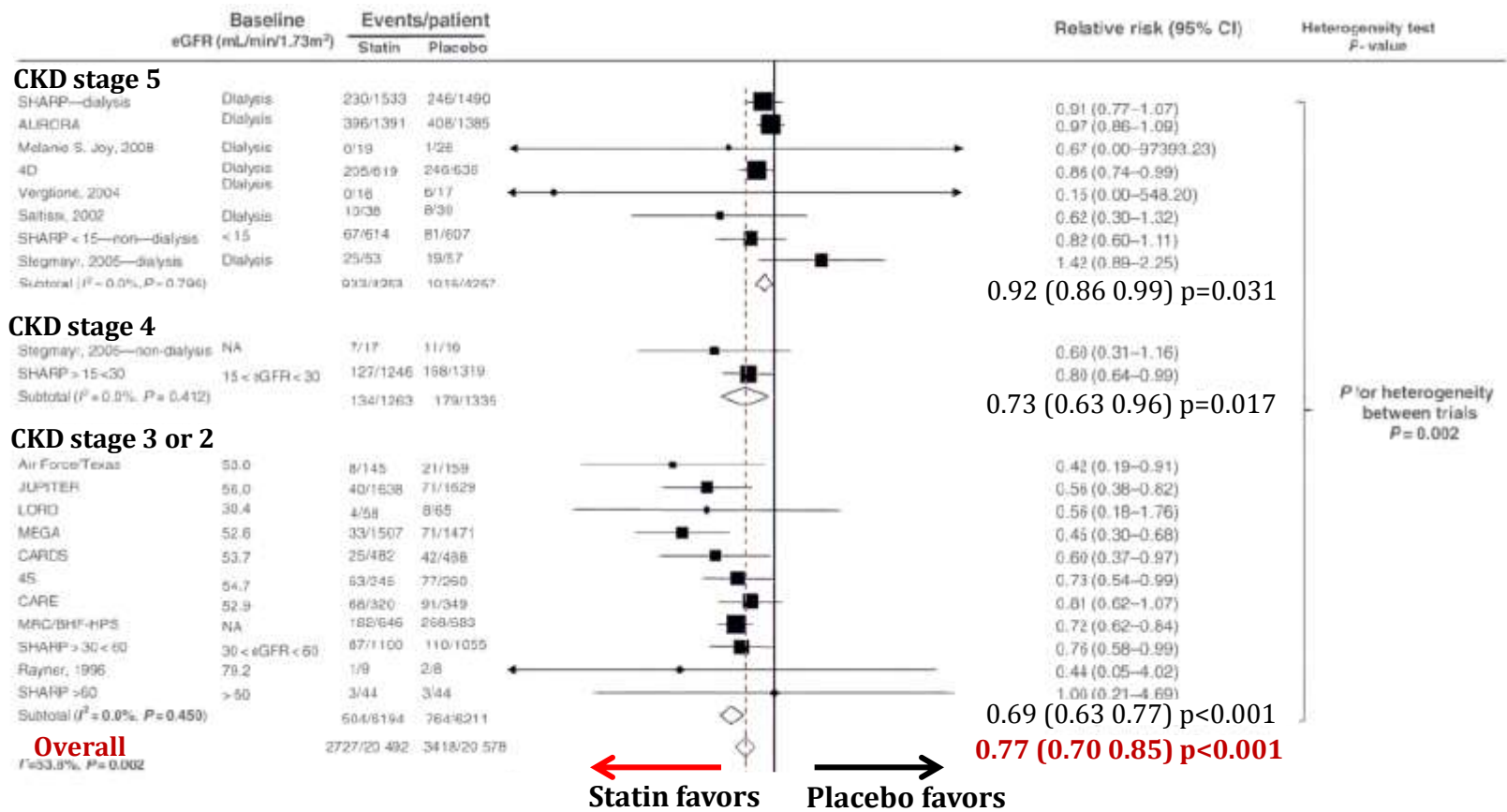




# Meta-analysis 2013

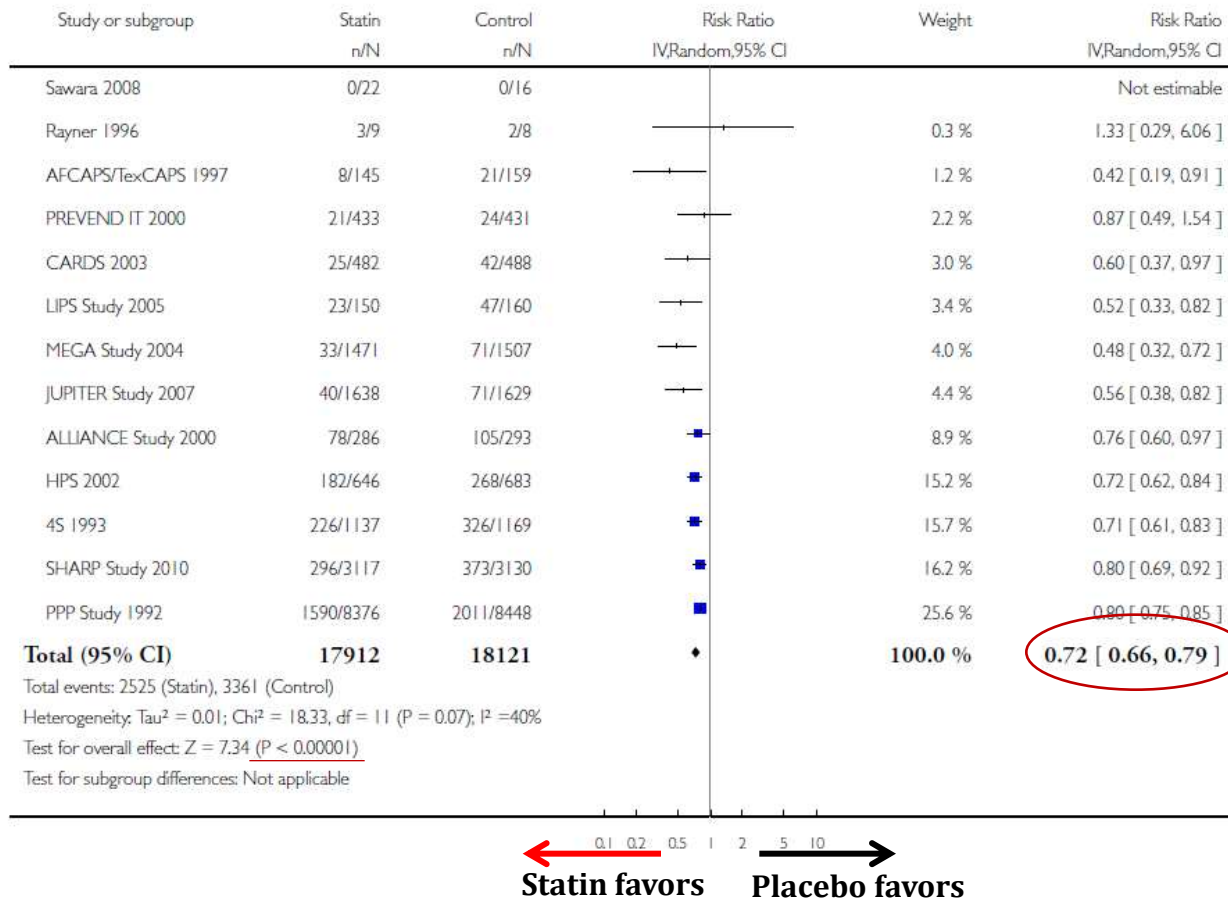
Meta-analysis : 48,429 patients with CKD, including 6690 major CV events and 6653 deaths

- Patient : CKD stages I–V
- Comparison: Statins versus placebo
- Outcome: major CV events



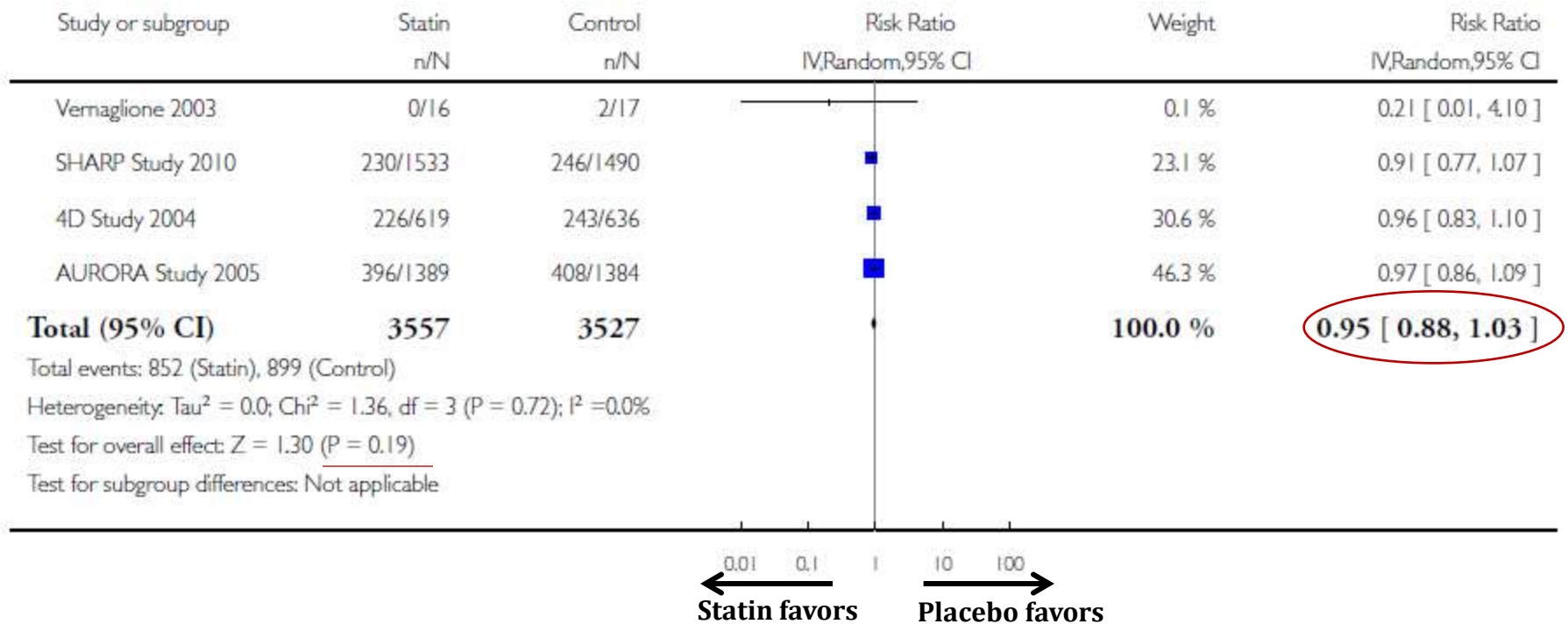
# Meta-analysis 2013 : CKD Not Requiring Dialysis

- **Patient :** CKD not requiring dialysis
- **Comparison:** Statins versus placebo or no treatment
- **Outcome:** Major cardiovascular events



# Meta-analysis 2013 : CKD Requiring Dialysis


- **Patient** : CKD requiring dialysis
- **Comparison**: Statins versus placebo or no treatment
- **Outcome**: Major cardiovascular events





## **03. Lipid Guideline in Patients with CKD**

# 2013 ACC/AHA Guideline



**2013  
ACC/AHA  
Guideline**

## **statin benefit groups**

- ✓ **with clinical ASCVD\***
- ✓ primary elevations of **LDL-C  $\geq 190$  mg/dL**
- ✓ **diabetes aged 40 to 75 years** with LDL-C 70-189 mg/dL
- ✓ without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70- 189 mg/dL and an **estimated 10-year ASCVD risk  $> 7.5\%$**

\* Clinical ASCVD - ACS, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD presumed to be of atherosclerotic origin.

# 2013 ACC/AHA Guideline



**2013  
ACC/AHA  
Guideline**

**No statin benefit  
groups**



Yes

**No recommendations regarding the initiation  
or discontinuation of statins**

**Heart Failure**

**Hemodialysis**



# Keep in Mind : 2013 ACC/AHA Guideline

Recommendation 1	NHLBI Grade	NHLBI Evidence statement	ACC/AHA COR	ACC/AHA LOE
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The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in **patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis.**

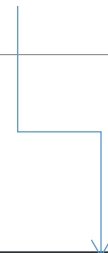
**N**  
(No recommendation)

71,72

-

-

\* NHLBI Grading the Strength of Recommendations



**No recommendation for or against (“There is insufficient evidence or evidence is unclear or conflicting.”)**

N

Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.

# 4D post hoc analysis

In dialysis diabetic patients **with high levels of LDL cholesterol levels**, atorvastatin decreased the risk of fatal and nonfatal cardiac events

Prognostic value of baseline LDL-C on risk of endpoint occurrence in atorvastatin and placebo group

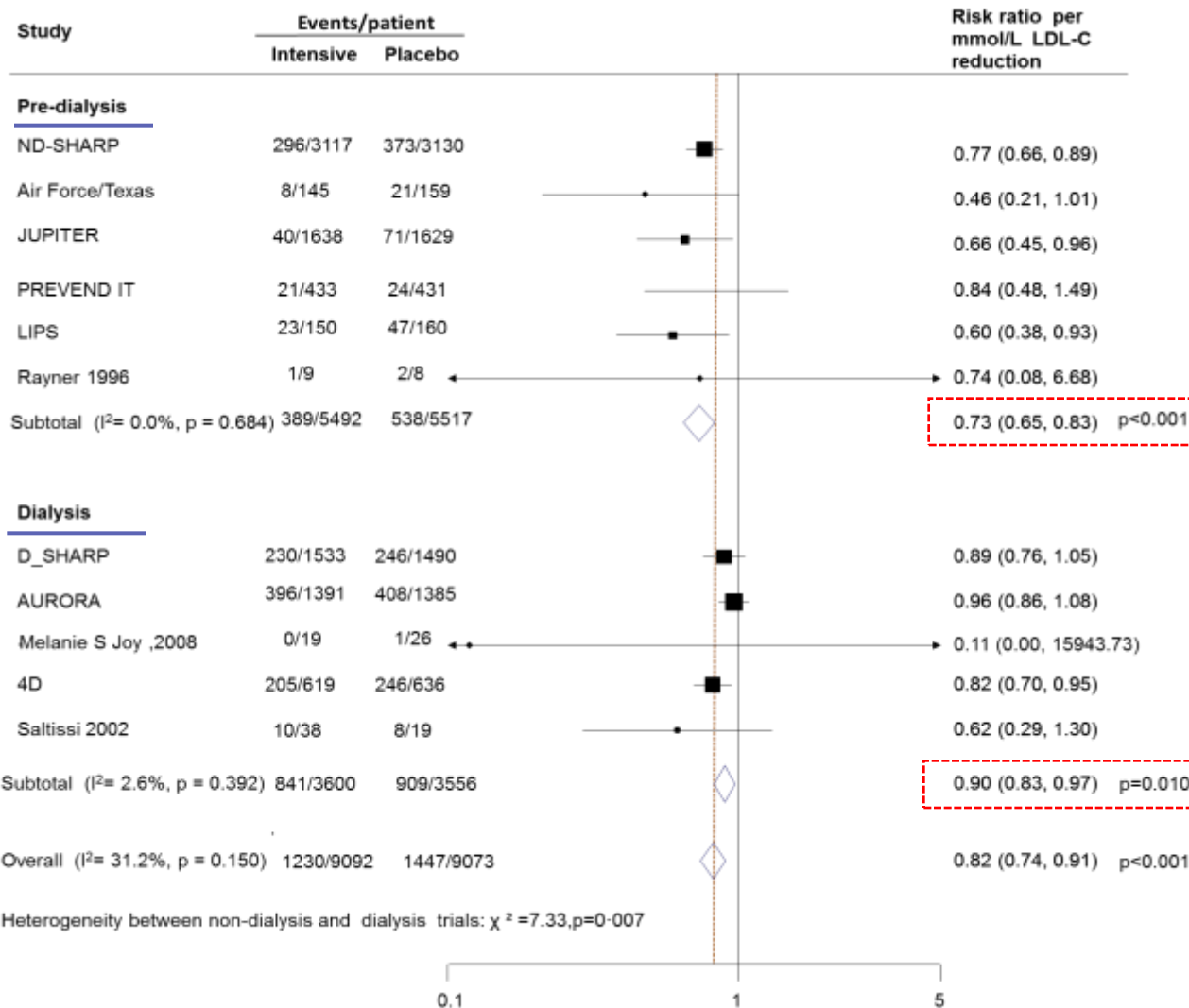
**LDL-C > 145**

Endpoint	Quartile 1 ( $\leq 104$ mg/dl) (n = 297)				Quartile 2 (104 to 123 mg/dl) (n = 328)				Quartile 3 (123 to 145 mg/dl) (n = 316)				Quartile 4 (>145 mg/dl) (n = 314)			
	Number of Events	HR	95% CI	P	Number of Events	HR	95% CI	P	Number of Events	HR	95% CI	P	Number of Events	HR	95% CI	P
Composite primary endpoint, FE	105	0.85	(0.57, 1.27)	0.433	120	1.11	(0.77, 1.61)	0.573	117	0.96	(0.66, 1.38)	0.821	127	0.69	(0.48, 1.00)	0.052
Composite primary endpoint, ME	123	0.90	(0.61, 1.33)	0.597	131	0.98	(0.69, 1.40)	0.907	145	0.99	(0.68, 1.43)	0.960	149	0.65	(0.44, 0.96)	<u>0.032</u>
Cardiac death	75	0.90	(0.57, 1.43)	0.660	65	0.99	(0.60, 1.65)	0.978	69	0.87	(0.53, 1.41)	0.563	61	0.58	(0.34, 0.99)	<u>0.044</u>
Sudden cardiac death	35	1.34	(0.68, 2.62)	0.397	43	1.05	(0.56, 1.97)	0.869	41	1.07	(0.57, 2.00)	0.840	41	0.48	(0.25, 0.94)	<u>0.033</u>
Nonfatal MI, FE	30	0.85	(0.41, 1.77)	0.663	33	1.24	(0.62, 2.51)	0.539	42	1.00	(0.54, 1.87)	0.995	44	0.62	(0.33, 1.17)	0.138
Nonfatal MI, ME	33	0.81	(0.39, 1.67)	0.572	35	0.96	(0.49, 1.87)	0.897	49	1.37	(0.74, 2.53)	0.310	49	0.50	(0.27, 0.91)	<u>0.024</u>
All cardiac events, FE	106	0.82	(0.56, 1.21)	0.323	106	0.99	(0.67, 1.45)	0.944	117	0.92	(0.63, 1.32)	0.641	122	0.68	(0.47, 0.98)	<u>0.041</u>
All cardiac events, ME	144	0.78	(0.53, 1.14)	0.201	134	0.89	(0.61, 1.30)	0.551	160	1.10	(0.76, 1.57)	0.615	147	0.54	(0.38, 0.79)	<u>0.001</u>
All cerebrovascular events, FE	28	1.00	(0.47, 2.15)	0.997	38	1.28	(0.66, 2.46)	0.466	34	0.96	(0.49, 1.90)	0.913	49	1.14	(0.64, 2.02)	0.653
All cerebrovascular events, ME	31	1.02	(0.47, 2.21)	0.958	43	1.14	(0.59, 2.22)	0.692	47	0.97	(0.47, 1.99)	0.929	55	1.32	(0.72, 2.41)	0.364
Death from all causes	139	1.02	(0.71, 1.45)	0.929	167	0.93	(0.68, 1.27)	0.642	152	0.84	(0.61, 1.17)	0.312	159	0.72	(0.52, 0.99)	<u>0.047</u>

\*Adjusted estimates of a Cox regression model (FE) and Andersen-Gill approach (ME).

# Meta-analysis 2013 : adjusted by LDL reduction

## Effects for statin therapy on major cardiovascular events risk ratio adjusted by LDL reduction



**Pre-dialysis**  
 LDL -C 1 mmol/L ↓,  
 RR for CVD event 27% ↓

**Dialysis**  
 LDL -C **1** mmol/L ↓,  
 RR for CVD event **10%** ↓



# Summary

- Dyslipidemia in patients with CKD contributes to progressive loss of kidney function and to high CV morbidity and mortality.
- Statin therapy in patients with CKD reduces the risk of major CV events, as well as mortality, across a broad range of kidney functions.
- Current lipid guideline did not recommend the initiation or discontinuation of statins for dialysis patients because benefit of statin therapy in those patient is unclear.
- Until more data are available, dialysis patients might reasonably choose statin treatment if they have elevated level of LDL of with recent CVD event.