Statins and Prevention of Renal Function Loss

ISA Xchange Session 20:

Cardiovascular Disease in Chronic Kidney Disease

Amsterdam, Netherlands

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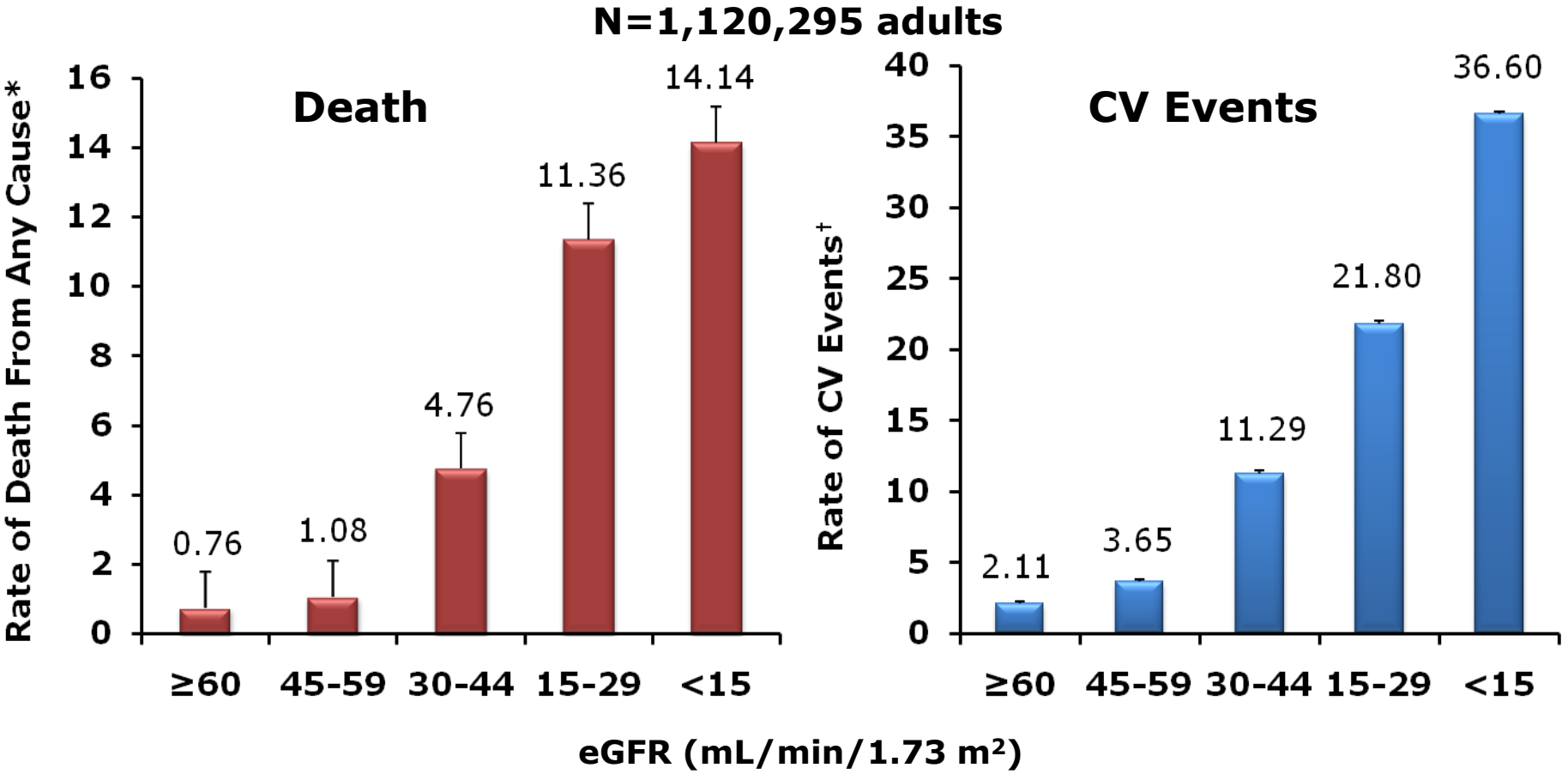
Kidney Disease Outcomes Quality Initiative: Stages of Chronic Kidney Disease

Stage	Description	eGFR (mL/min/1.73m^2)	Action
1	Kidney Damage with Normal or Increased GFR	≥90	Diagnose and treat comorbidities, slow progression, CVD risk reduction
2	Mild	60-89	Estimating progression
3	Moderate	30-59	Evaluating and treating complications
4	Severe	15-29	Preparation for renal replacement therapy
5	End Stage Renal Disease	<15	Renal replacement therapy

NKF. *Am J Kidney Dis*. 2002;39(2 Suppl 1)S1-S266.

Rates of Death and CV Events According to Severity of CKD



*Age-standardized rates per 100 person-years; †CV event defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease per 100 person-years.

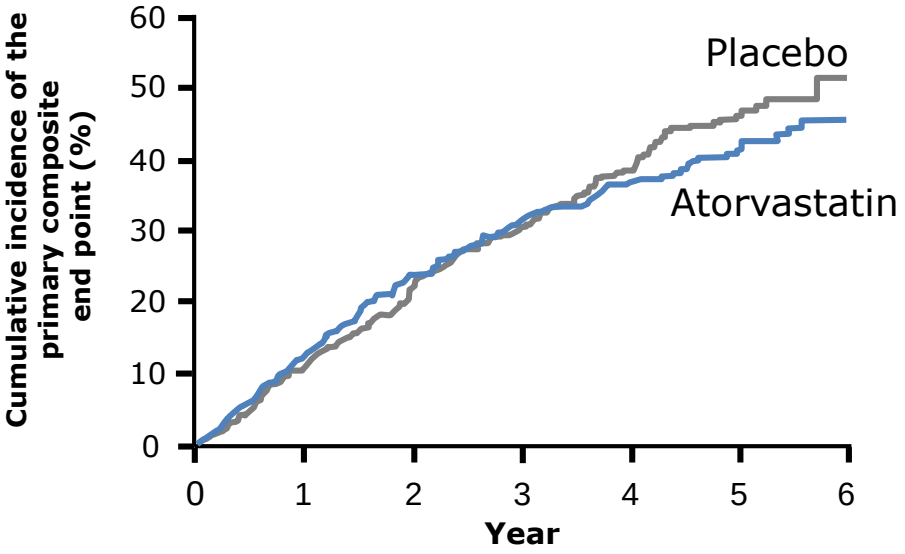
Go et al. *N Engl J Med.* 2004;351:1296-1305.

Clinical Trials of Statins in CKD

4D and AURORA:

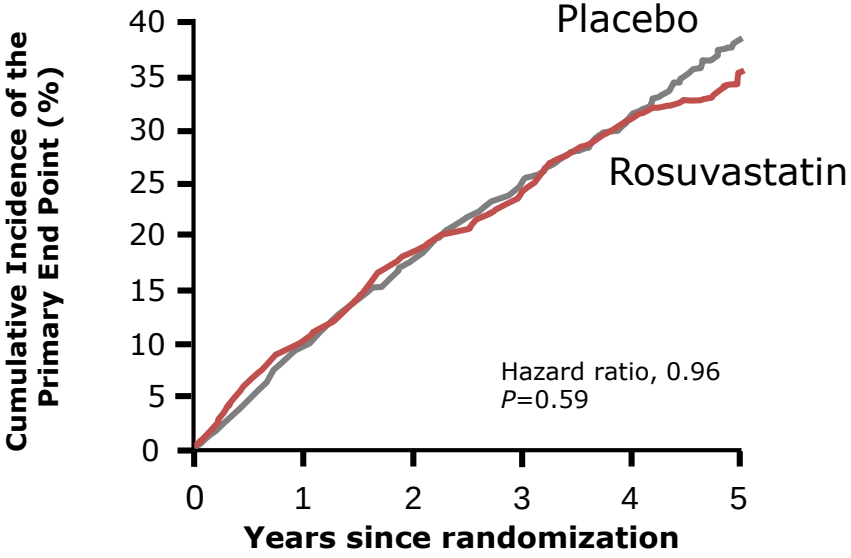
Kaplan-Meier estimate of time to first major CV event

4D



No. at Risk							
Placebo	636	532	383	252	136	51	19
Atorvastatin	619	515	378	252	136	58	29

AURORA



No. at Risk						
Placebo	1384	1163	952	809	534	153
Rosuvastatin	1390	1152	962	826	551	148

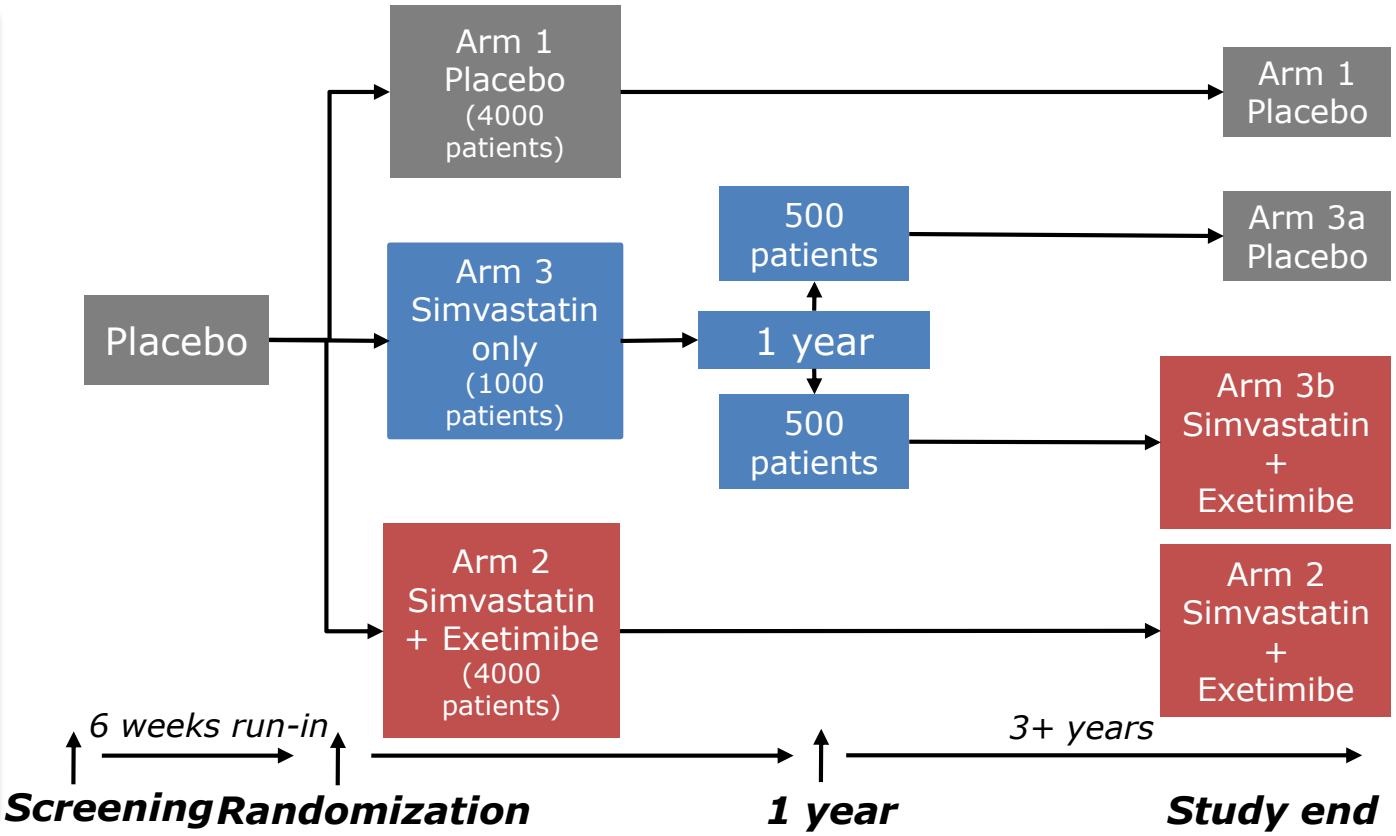
Wanner. *N Engl J Med*. 2005;353:238-248; Fellstrom, *N Engl J Med*. 2009;360:1395-1407.

SHARP Trial Design

Estimated N=9000
- **6000 predialysis**
- **3000 dialysis**

Inclusion Criteria:
- History of CKD
- Predialysis or dialysis
- Both genders
- Age >40 years

Exclusion Criteria:
- History of MI or coronary revascularization



Primary end point: Major vascular events (composite of nonfatal MI or cardiac death, nonfatal or fatal stroke or revascularization).
Secondary end points: Various vascular events and renal disease progression.
SHARP Final Protocol vs5. July 12, 2005.

SHARP: Eligibility

- History of chronic kidney disease
  - not on dialysis: elevated creatinine on 2 occasions
    - Men: ≥1.7 mg/dL (150 µmol/L)
    - Women: ≥1.5 mg/dL (130 µmol/L)
  - on dialysis: haemodialysis or peritoneal dialysis
- Age ≥40 years
- No history of myocardial infarction or coronary revascularization
- Uncertainty: LDL-lowering treatment not definitely indicated or contraindicated

SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Baseline Characteristics

Characteristic	Mean (SD) or %
Age	62 (12)
Men	63%
Systolic BP (mm Hg)	139 (22)
Diastolic BP (mm Hg)	79 (13)
Body mass index	27 (6)
Current smoker	13%
Vascular disease	15%
Diabetes mellitus	23%
Non-dialysis patients only	**(n=6247)**
eGFR (ml/min/1.73m^2)	27 (13)
Albuminuria	80%

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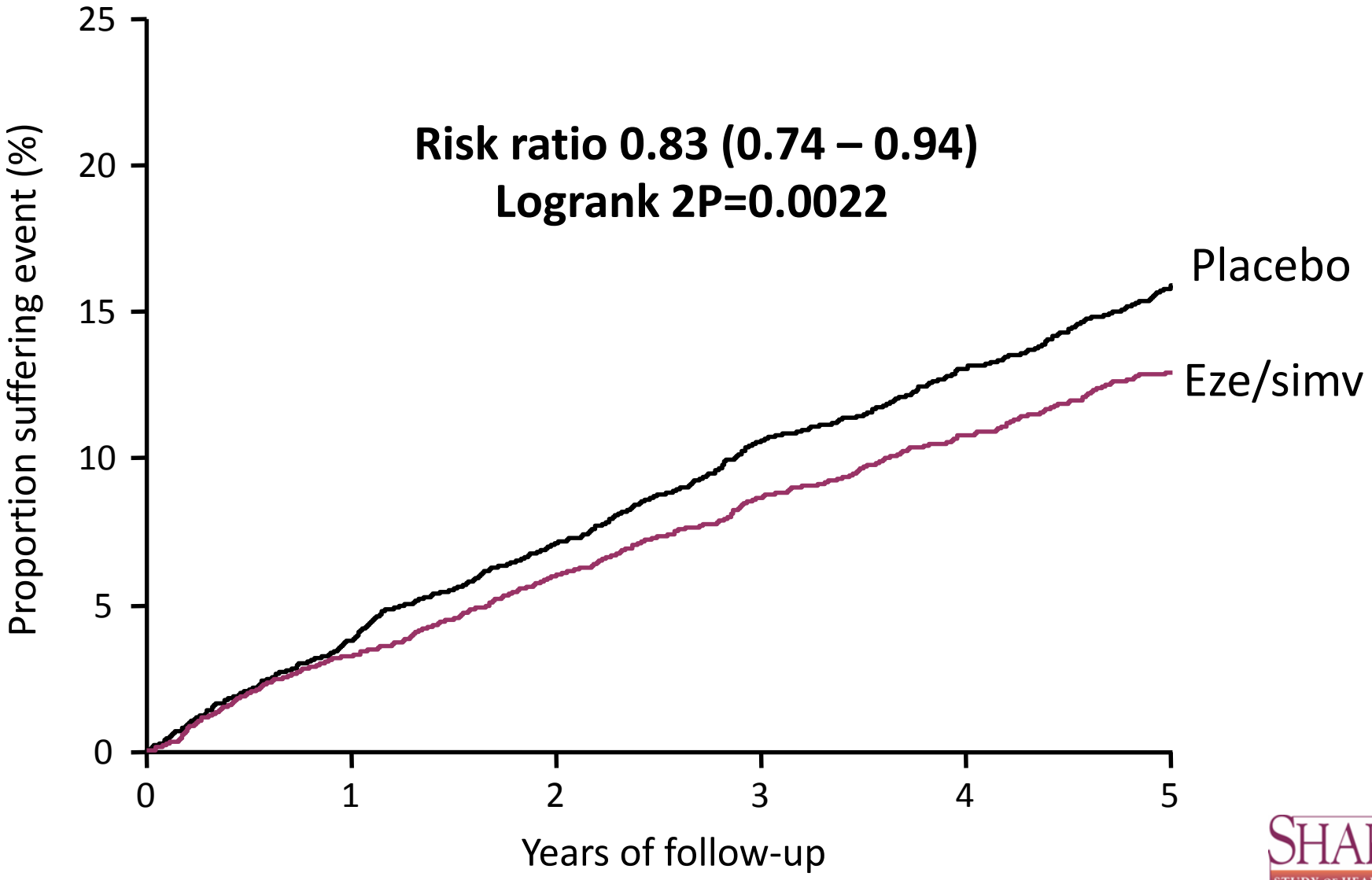
STUDY OF HEART AND RENAL PROTECTION

SHARP: Main Outcomes

- **Key outcome**
  - Major atherosclerotic events (coronary death, MI, non-haemorrhagic stroke, or any revascularization)
- **Subsidiary outcomes**
  - Major vascular events (cardiac death, MI, any stroke, or any revascularization)
  - Components of major atherosclerotic events
- **Main renal outcome**
  - End stage renal disease (dialysis or transplant)

SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Major Atherosclerotic Events



SHARP
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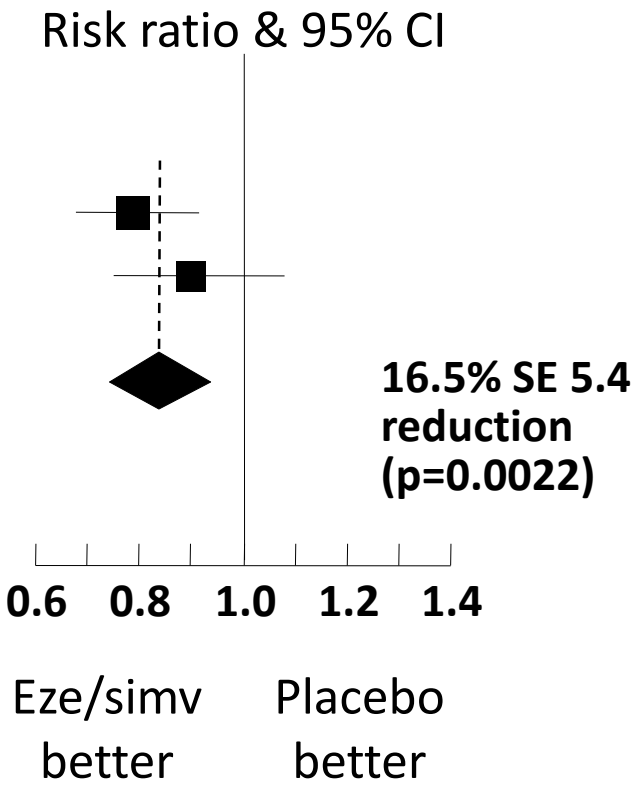
SHARP: Major Atherosclerotic Events by Renal Status at Randomization

	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)



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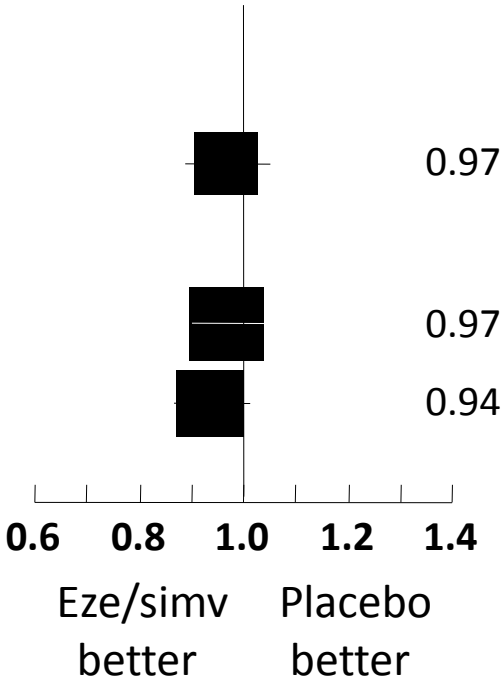
SHARP: Renal Outcomes

Event	Eze/simv (n=3117)	Placebo (n=3130)	Risk ratio & 95% CI
Main renal outcome			
End-stage renal disease (ESRD)	1057 (33.9%)	1084 (34.6%)	0.97 (0.89-1.05)
Tertiary renal outcomes			
ESRD or death	1477 (47.4%)	1513 (48.3%)	0.97 (0.90-1.04)
ESRD or 2 x creatinine	1190 (38.2%)	1257 (40.2%)	0.94 (0.86-1.01)



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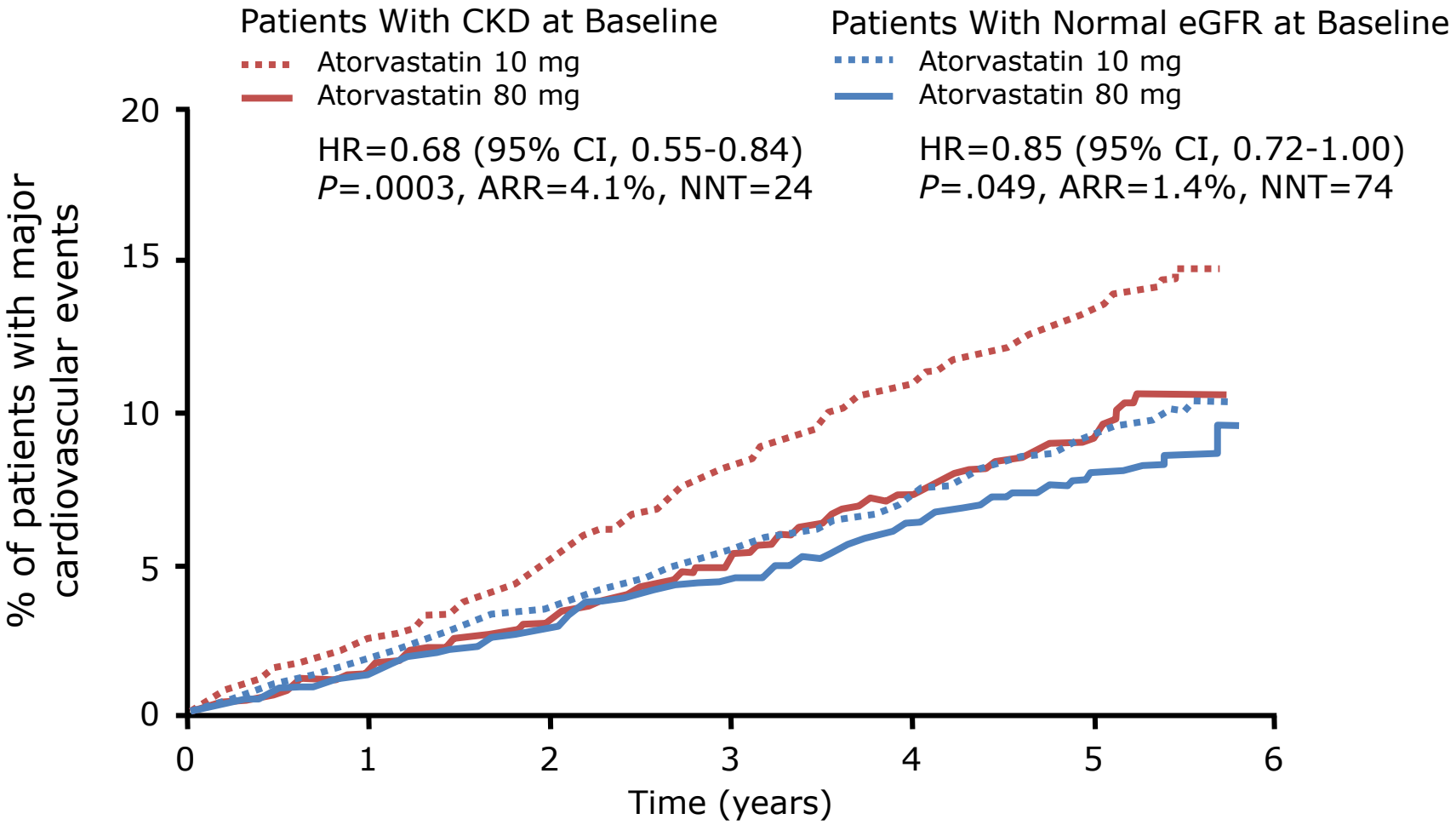
SHARP: Conclusions

- No increase in risk of myopathy, liver and biliary disorders, cancer, or nonvascular mortality
- No substantial effect on kidney disease progression
- Two-thirds compliance with eze/simv reduced the risk of major atherosclerotic events by 17% (consistent with meta-analysis of previous statin trials)
- Similar proportional reductions in all subgroups (including among dialysis and non-dialysis patients)
- Full compliance would reduce the risk of major atherosclerotic events by one quarter, avoiding 30–40 events per 1000 treated for 5 years

SHARP
STUDY OF HEART AND RENAL PROTECTION

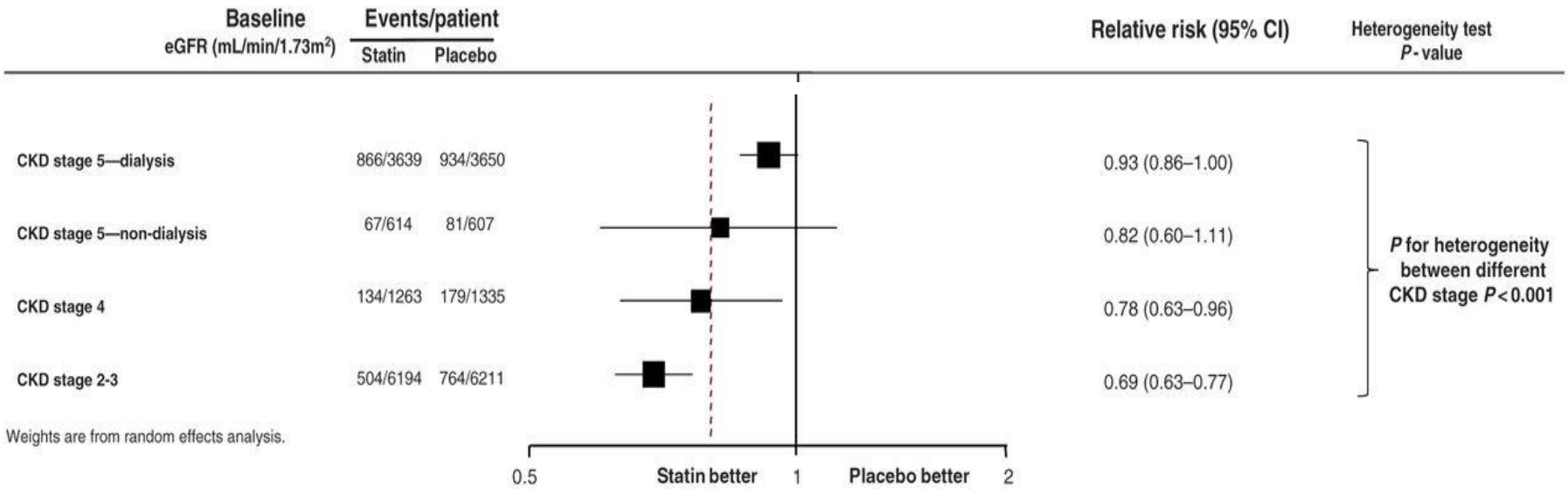
TNT: Intensive Atorvastatin Therapy in Patients With CKD*



*This analysis was not prespecified in the study protocol.

Shepherd J et al. *J Am Coll Cardiol.* 2008;51:1448-1454.

Effect of Statins on Major CV Events Stratified by Kidney Function



Absolute risk is higher with higher stages of CKD, but RRR is much better with lower stages of CKD

NNT per study duration to prevent a major CV event: 46 for stage 5, 36 for stage 4, and 24 for stage 2-3.

Hou W et al, *Eur Heart J* 2013;34:1807

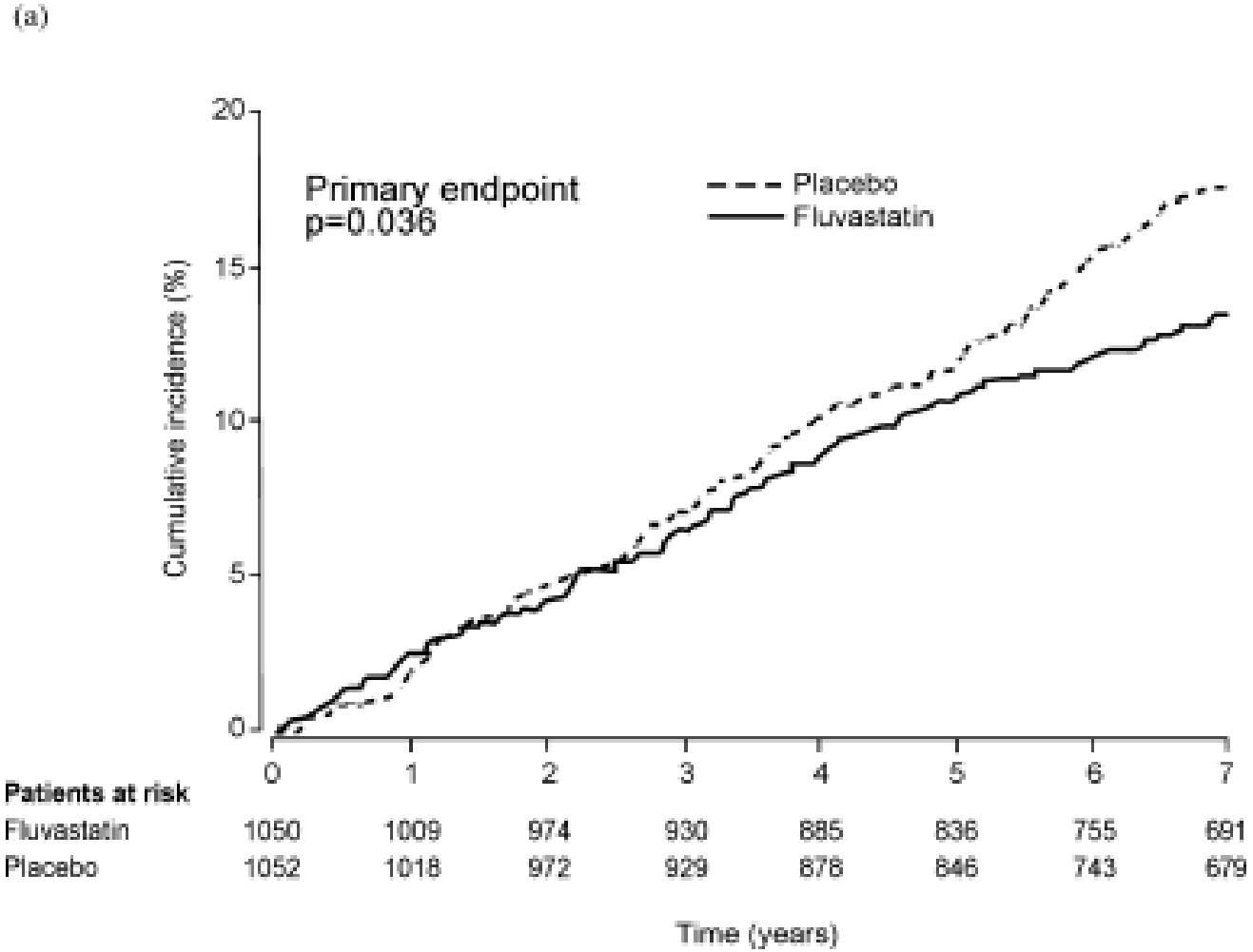
ALERT Trial: Fluvastatin to Prevent Coronary Events in Renal Transplant Recipients

- 2,102 renal transplant recipients with total cholesterol of 4.0-9.0 mmol/L randomized to fluvastatin 40, then 80 mg/day or placebo and followed for 5.1 years
- Primary endpoint = cardiac death, myocardial infarction or coronary intervention
- Fluvastatin lowered LDL-C by 32%
- Non-significant reduction in primary endpoint: RR 0.83, 95% CI 0.64-1.06
- Cardiac death + MI reduced in the fluvastatin group: 70 vs 104, RR 0.65, 95% CI 0.48-0.88, *p*=0.005
- Among pts starting treatment <4.5 years after renal transplant, fluvastatin reduced CV events: 4.6% vs 9.2%, *p*=0.007

Holdaas H et al, *Lancet* 2003;361:2024

Holdass H et al, *Nephrol Dial Transplant* 2005;20:974

Long-term Cardiac Outcomes in Renal Transplant Recipients Receiving Fluvastatin: The ALERT Extension Study



Holdass H et al, *Am J Transplant* 2005;5:2929

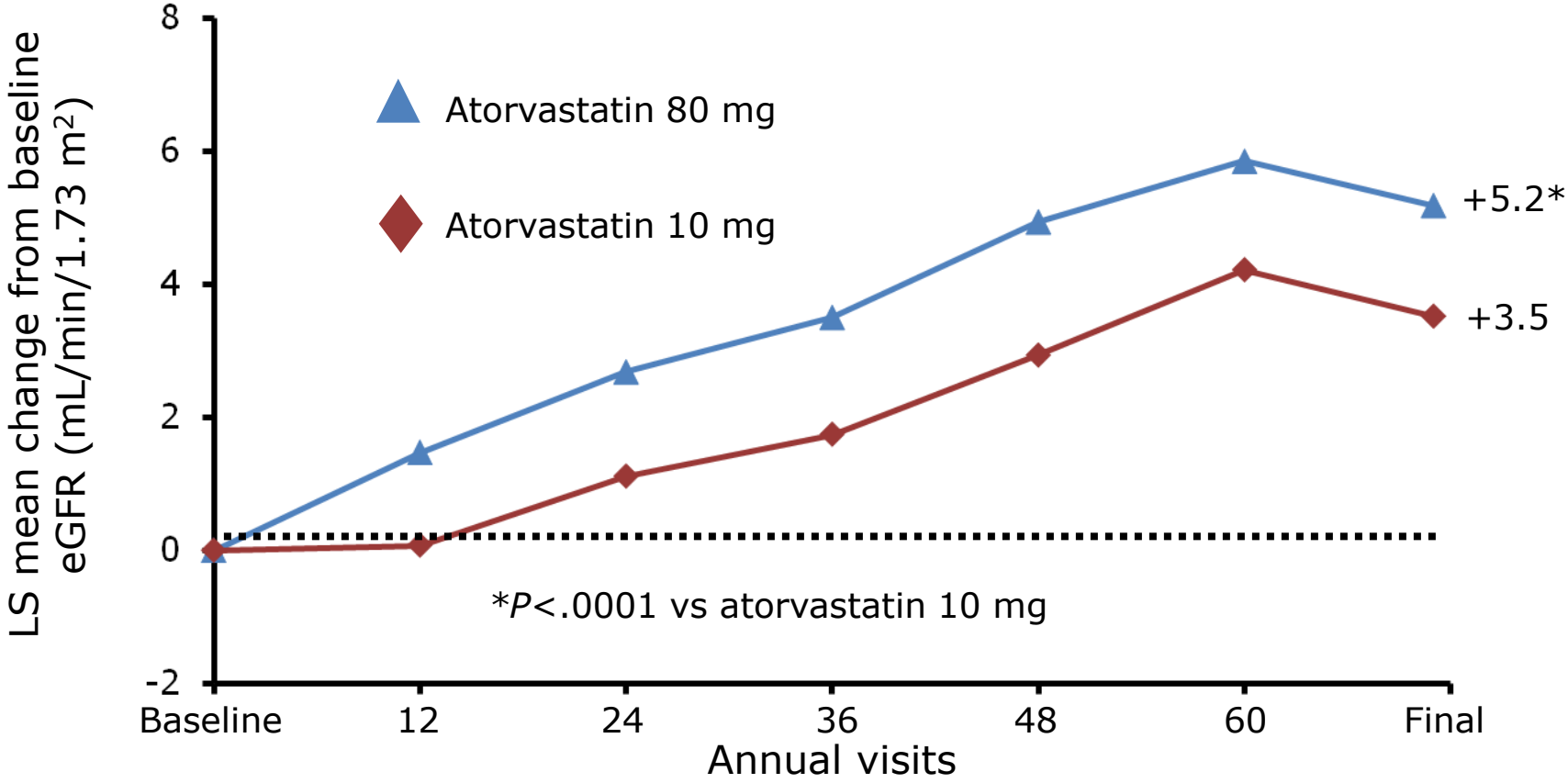
Changes in Renal Function with Statins

Changes in eGFR in Randomized Trials With Statins

- JUPITER
  - At 1 year, eGFR had declined by 6.5 and 7.0 mL/min/1.73 m^2 in rosuvastatin and placebo groups
- 4S
  - eGFR declined by 0.34 and 0.41 mL/min/1.73 m^2 per year in the simvastatin and placebo groups, respectively ($P = 0.02$)
- Pooled pravastatin trials
  - Pravastatin reduced the decline in eGFR by 8% ($P < 0.05$)

Ridker PM et al. *N Engl J Med*. 2008;359:2195-2207.
Huskey J et al. *Atherosclerosis*. 2009;205:202-206.
Tonelli M et al. *Circulation*. 2005;112:171-178.

Changes in eGFR with High and Low Dose Atorvastatin in TNT



Atorva 80 mg 4827	4700	4580	4400	4240	3659	4827
Atorva 10 mg 4829	4727	4582	4386	4220	3635	4829

eGFR=estimated glomerular filtration rate.
This analysis was not prespecified in the study protocol.
Shepherd J et al. *Clin J Am Soc Nephrol.* 2007;2:1131-1139

Changes in eGFR with High Dose Atorvastatin and Placebo in SPARCL

- 4,731 patients with recent stroke or TIA randomized to atorvastatin 80 mg or placebo and followed for 5 yrs
- 3,119 had eGFR <60 mL/min/1.73 m^2
- eGFR increased 3.46±0.33 mL/min/1.73 m^2 in the atorvastatin group and 1.42±0.34 mL/min/1.73 m^2 in the placebo group (p<0.001)
- In those with diabetes, eGFR increased 1.12±0.92 mL/min/1.73 m^2 in the atorvastatin group and decreased 1.69±0.92 mL/min/ 1.73 m^2 in placebo group (p=0.016)

Amarenco P et al, *Stroke* 2014;45:2974

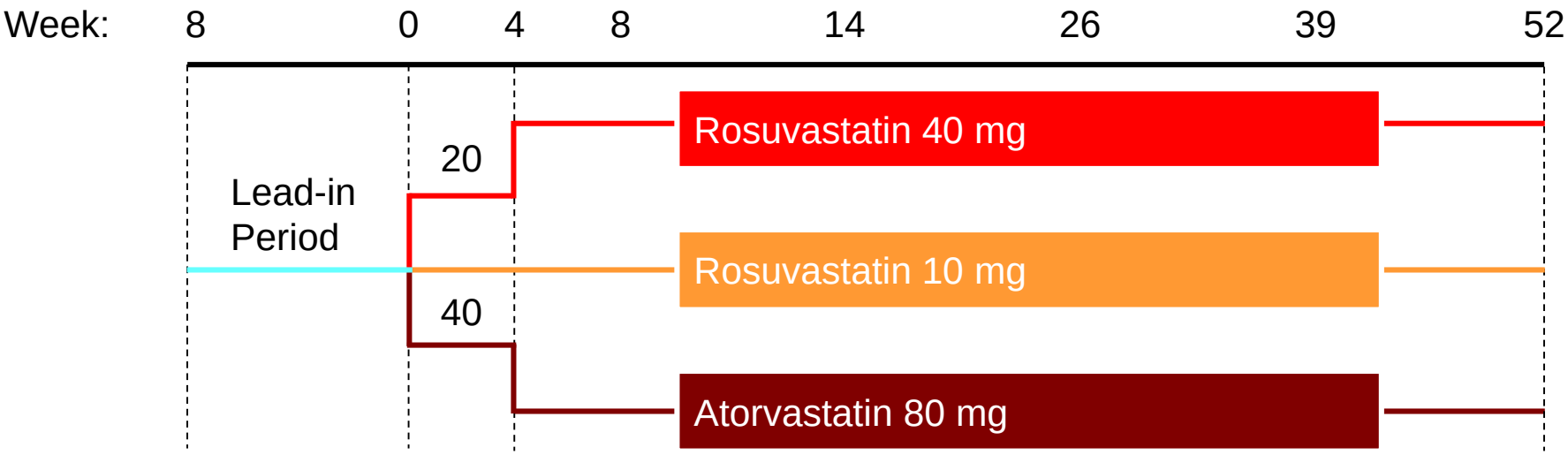
PLANET Trials: Study Design

PLANET I: 325 patients with type I or II diabetes

PLANET II: 220 patients without diabetes

Inclusion criteria

- Moderate proteinuria (urinary protein / creatinine ratio 500–5000 mg/g)
- Hypercholesterolaemia (fasting LDL-C ≥90 mg/dL (2.33 mmol/L)
- ACE inhibitors or ARBs for ≥3 months prior to screening



de Zeeuw D et al, *Lancet Diabetes Endocrinol* 2015;3:181

PLANET I: Summary

	Rosuva 10 (n=116)	Rosuva 40 (n=123)	Atorva 80 (n=110)
Proteinuria (1° endpoint)	No change	No change	↓15% (p=0.033)
GFR (ml/min/1.73m^2)	↓3.7 (p=0.0098)	↓7.3 (p0.0002)	↓1.6 (p=NS)
Renal AE's:			
Acute RF	0	5	1
Creatinine ↑x2	0	6	0
Either	0	9	1

de Zeeuw D et al, *Lancet Diabetes Endocrinol* 2015;3:181

PLANET I and II: Conclusions

- In diabetic and non-diabetic patients with proteinuria, atorvastatin 80 mg reduced proteinuria whereas rosuvastatin 10 or 40 mg had no effect
- Rosuvastatin 10 mg and 40 mg significantly decreased eGFR in patients with diabetes, whereas atorvastatin 80 mg showed no change
- Rosuvastatin should not be used in diabetic patients with CKD

Guidelines for Statin Use in Patients with CKD

NKF Guidelines Recognize CKD Patients Are at High CV Risk and Recommend Aggressive LDL Management

Year	2003	2007
Lipid management guidelines	K/DOQI Clinical Practice Guidelines for the Management of Dyslipidemias in Patients With Kidney Disease	KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease
LDL-C goal	<100 mg/dL in all CKD patients: •in patients with LDL-C of 100-129 mg/dL, initiate therapy with therapeutic lifestyle change (TLC) and add low-dose statin if needed •in patients with LDL-C ≥130 mg/dL, initiate therapy with TLC and low-dose statin	<100 mg/dL in patients with diabetes and CKD stages 1-4; **<70 mg/dL is a therapeutic option** Patients with diabetes, CKD stages 1-4, and LDL-C ≥100 mg/dL should be treated with a statin

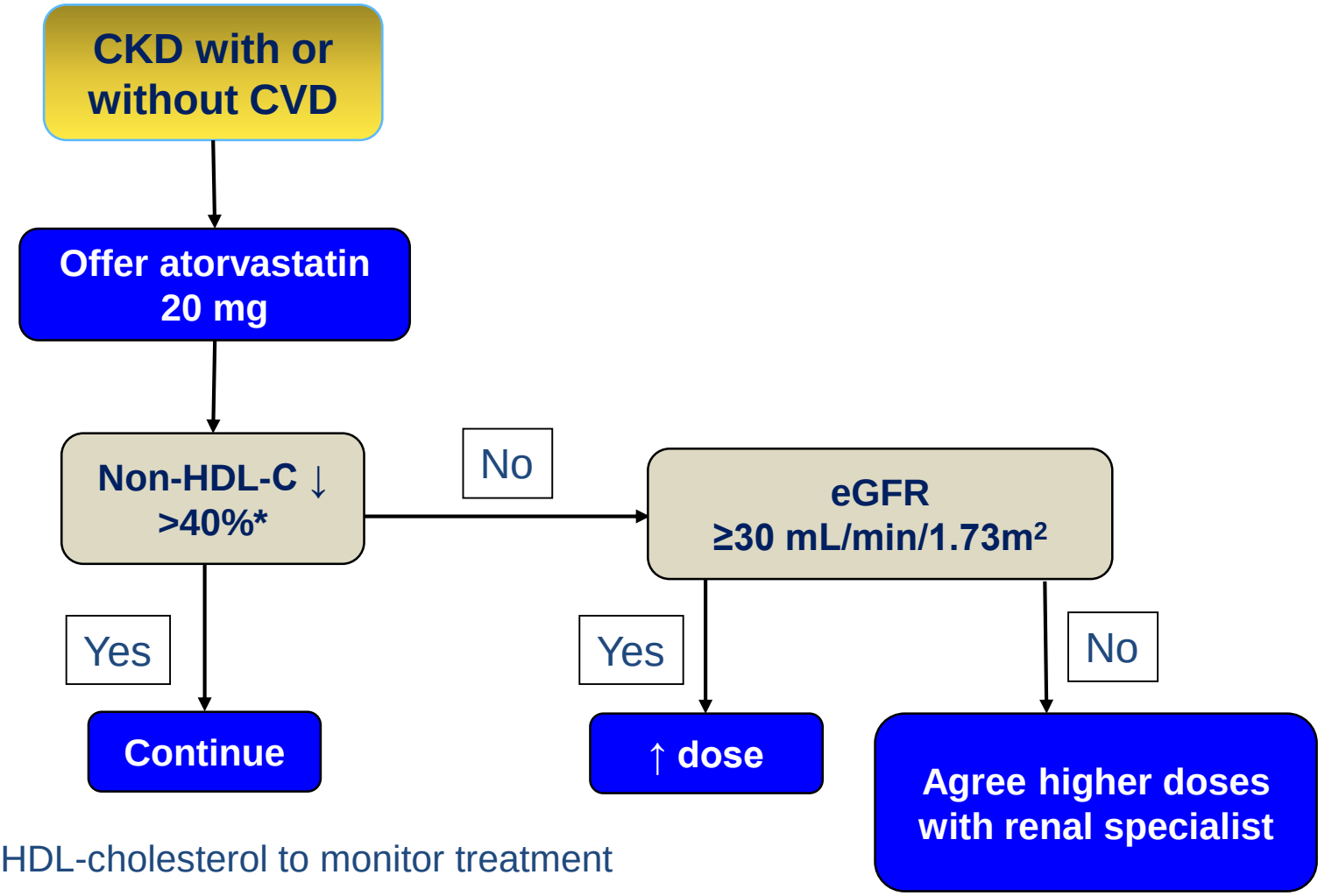
National Kidney Foundation (NKF). *Am J Kidney Dis*. 2003;41(4 suppl 3):S1-91; NKF. *Am J Kidney Dis.* 2007;49(2 suppl 2):S12-154.

Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines, 2014

- LDL-C is not an accurate predictor of CV risk in CKD patients and should not be used to determine who should receive treatment
- statin or statin + ezetimibe recommended for adults aged ≥50 years with an eGFR <60 mL/min/1.73 m^2
- Also for those aged 18-49 years with a 10-year risk >10%, including patients with known CAD, previous stroke, or diabetes
- Statins are recommended for adult renal transplant recipients
- Statins not recommended for dialysis patients

Tonelli M et al, *Ann Int Med* 2014;160:182

NICE Lipid Guidelines: Patients with CKD



*Note use of non-HDL-cholesterol to monitor treatment

eGFR, estimated glomerular filtration rate
Patients receiving renal replacement therapy are outside the scope of the guidelines

National Institute for Health and Care Excellence
Lipid modification July 2014 http://www.nice.org.uk/Guidance/CG181

Conclusions

- CKD increases the risk of CV events
- Statins reduce risk in CKD patients; the absolute risk reduction is higher than in patients without CKD
- Atorvastatin improves eGFR
- Statins do not reduce CV risk in patients receiving dialysis but do in renal transplant recipients