



## Endocrinologic and Metabolic Drugs Advisory Committee

# VYTORIN / ZETIA NDAs 21-687 and 21-445

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Silver Spring, Maryland

# VYTORIN & ZETIA

- ZETIA (ezetimibe): selective inhibitor of the absorption of intestinal cholesterol and related phytosterol
  - U.S. approval in October 2002
- VYTORIN: combination of ezetimibe and the HMG-CoA reductase inhibitor simvastatin
  - U.S. approval in July 2004
  - Simvastatin approval in December 1991

# VYTORIN & ZETIA

- Both are approved for individuals with primary hyperlipidemia, mixed hyperlipidemia, homozygous familial hypercholesterolemia
- Currently indicated to alter various lipid parameters

# Limitations of Use

- No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.
- The effect of ZETIA on cardiovascular morbidity and mortality has not been determined.



# Recent Ezetimibe/Simvastatin Clinical Trials

# ENHANCE

- 720 adults with heterozygous familial hypercholesterolemia
- Simvastatin 80 mg + random assignment to either ezetimibe 10 mg or placebo
- Primary outcome: change in mean carotid intima-media thickness (cIMT) from baseline at 2 years
- At 2 years, LDL-C ↓56% in the combination group vs. ↓39% in simvastatin-only group
- Change in mean cIMT: 0.011 mm (combination) vs. 0.006 mm (simvastatin alone),  $p=0.29$ .

# ENHANCE

- Possible explanations include:
  - enrollment of a patient population who had received prior lipid-altering or statin therapy and had relatively normal cIMT values at baseline
  - the 2-year duration may have been too short to see a favorable effect of cholesterol lowering on cIMT
  - unknown properties of ezetimibe may negate the beneficial effects of LDL lowering on cIMT

# SEAS

- 1873 adults with mild-to-moderate aortic stenosis
- Randomized to daily ezetimibe/simvastatin (10/40 mg) or placebo for median 4.4 years
- Primary composite endpoint: major cardiovascular events
- By 8 weeks, mean LDL-C ↓61% in ezetimibe/simvastatin group
- No statistically significant difference in primary outcome (HR 0.96; 95% CI 0.83-1.12; p=0.59).
- Incident cancer and cancer-related deaths more frequent in the ezetimibe/simvastatin group:
  - Incident cancer: 105 (11.1%) vs. 70 (7.5%) patients
  - Cancer-related deaths: 39 vs. 23 patients

# SEAS

- “FDA believes it is unlikely that Vytorin or Zetia increase the risk of cancer or cancer-related death.”
  - Preclinical studies did not find an association between ezetimibe and cancer incidence
  - Large body of clinical data does not suggest an association between simvastatin and risk of cancer
  - Reported increase in cancer and cancer-related deaths was the result of combining a wide variety of cancer types. It is biologically less likely that a single drug increases the risk of a wide variety of cancer types.
  - No consistent patterns of cancer risk compared with interim SHARP and IMPROVE-IT data
  - Analysis of cancer findings was not pre-specified in SEAS and was performed without statistical correction for multiple comparisons.

# IMPROVE-IT

- Randomized, double-blind study of subjects with stabilized high-risk acute coronary syndrome
- ezetimibe/simvastatin (10/40 mg) vs. simvastatin (40 mg)
- Primary outcome: death due to any CV events, non-fatal coronary events, non-fatal stroke
- Study start: October 2005
- Estimated study completion: June 2013



# Chronic Kidney Disease (CKD)

# CKD Definition & Stages

- At least 3 months of evidence of kidney damage (includes proteinuria) or GFR <60 mL/min/1.73m<sup>2</sup>

Stage	Description	GFR
1	Kidney damage with normal or ↑GFR	≥90
2	Kidney damage with mild ↓GFR	60-89
3	Moderate ↓GFR	30-59
4	Severe ↓GFR	15-29
5	Kidney failure	<15 (or dialysis)

# U.S. CKD Burden

<b>Stage</b>	<b>Estimated % of US Population</b>
1	4.1%
2	3.2%
3	6.5%
4 or 5	0.6%
<b>Total</b>	<b>14.4% (~30 million)</b>

Data from NHANES 2003-2006.

# Cardiovascular & Renal Disease

- Most patients with CKD die before reaching end-stage renal disease (ESRD), ~50-60% from cardiovascular (CV) disease
- Severity of CKD is a graded and independent risk factor for CV morbidity & mortality
- Most prevalent abnormality: Left ventricular hypertrophy
- In ESRD, arrhythmias and congestive heart failure (CHF) contribute to the majority of cardiac mortality



# Lipid-Lowering in CKD

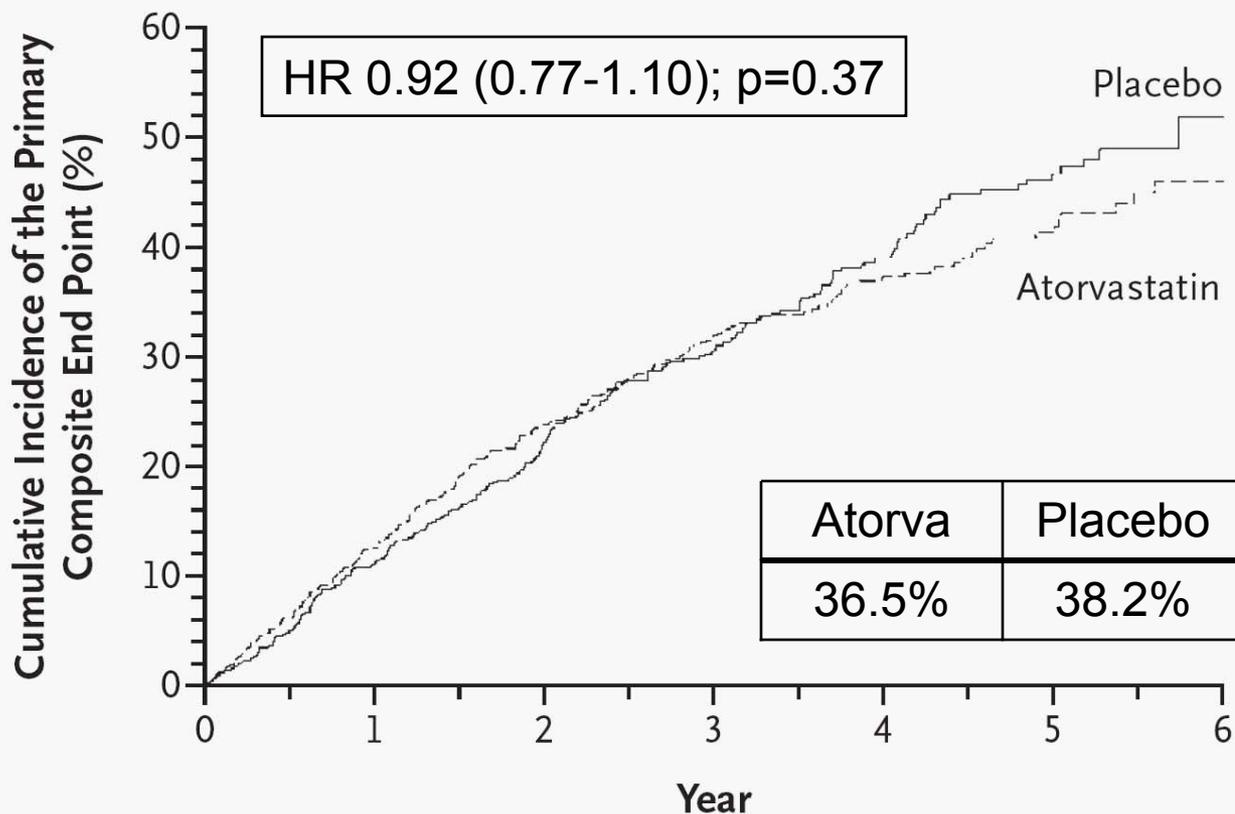
# Dyslipidemia: Practice Guidelines

- Consider CKD a coronary heart disease risk equivalent (i.e., target LDL-C < 100 mg/dL)
  - NKF Taskforce on CVD (2000)
  - NKF Kidney Disease Outcomes Quality Initiation (KDOQI) Dyslipidemia Guidelines (2002)
  - AHA Councils on Kidney in CVD, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention (2003)

## 4D

- Years of trial: 1998 to 2004
- Type 2 diabetes, on hemodialysis < 2 years
  - May have had history of CVD; 19% used statins
- 1255 randomized to atorvastatin 20mg or placebo for median 4 years
- Primary endpoint: non-fatal myocardial infarction (MI), stroke, cardiac death
  
- At 4 weeks, the median LDL-C was 72 mg/dL in the atorvastatin group, a median placebo-subtracted change from baseline of -41%.

# 4D: Primary Endpoint



**No. at Risk**

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

# 4D: Components of Primary

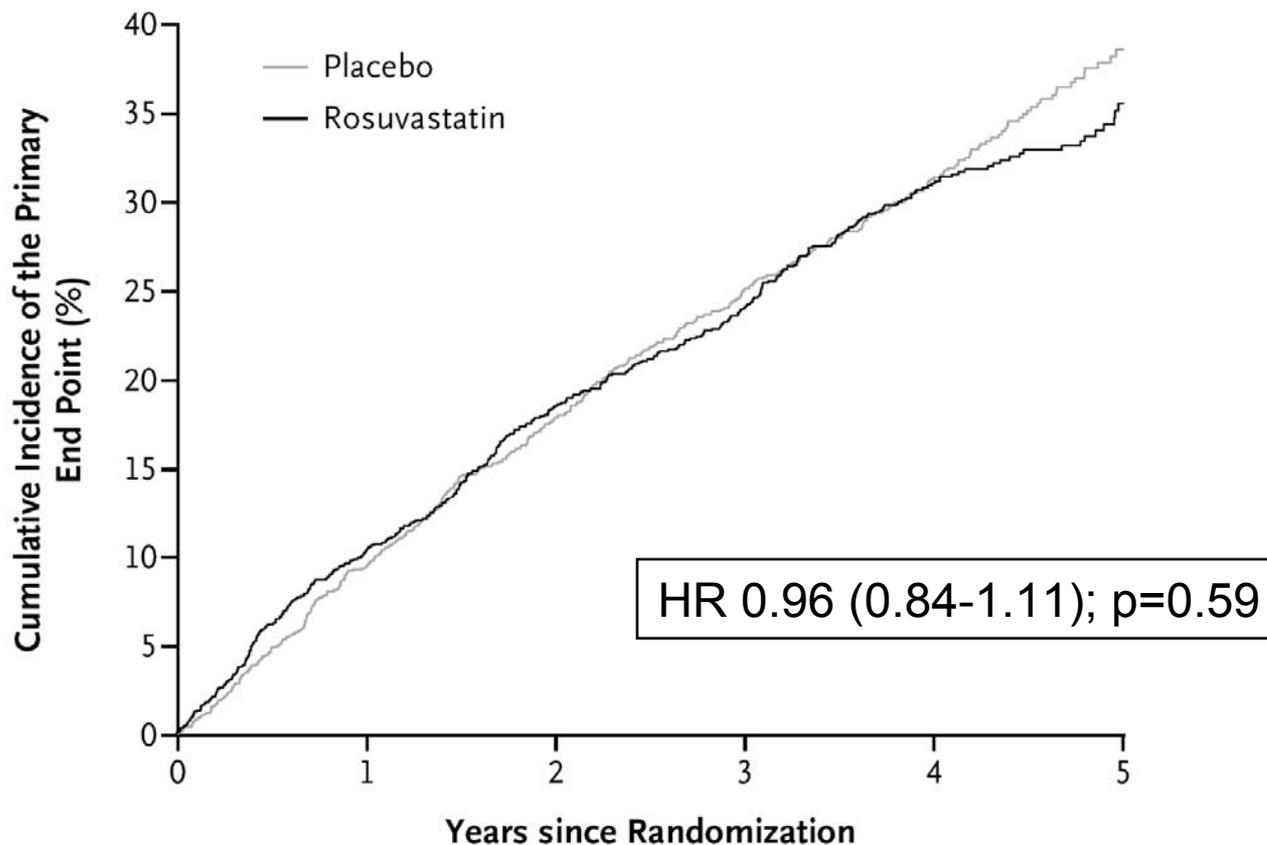
Endpoint	Atorva (n=619)	Placebo (n=636)	RR (95% CI)	P
Cardiac death	121 (20%)	149 (23%)	0.81 (0.64-1.03)	0.08
Nonfatal MI	70 (11%)	79 (12%)	0.88 (0.64-1.21)	0.42
Fatal stroke	27 (4%)	13 (2%)	2.03 (1.05-3.93)	0.04
Nonfatal stroke	33 (5%)	32 (5%)	1.04 (0.64-1.69)	0.89
<b>Secondary (2°) Endpoint:</b>				
All cardiac events*	205 (33%)	246 (39%)	0.82 (0.68-0.99)	0.03

\* Includes cardiac death, nonfatal MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG), other coronary interventions

# AURORA

- Years of trial: 2003 to 2008
- On hemodialysis  $\geq 3$  months
  - Excluded those who took statin within 6 months
- 2778 randomized to rosuvastatin 10mg or placebo for mean 3.2 y
- Primary endpoint: non-fatal MI, stroke, CV death
- At 3 months, the mean LDL was 58 mg/dL in the rosuvastatin group, a mean placebo-subtracted change from baseline of -41%

# AURORA: Primary Endpoint



**No. at Risk**

Placebo	1384	1163	952	809	534	153
Rosuvastatin	1390	1152	962	826	551	148

## AURORA: Components of Primary Endpoint

Endpoint	Rosuva (n=1389)	Placebo (n=1384)	RR (95% CI)	P
Cardiovascular Death	324 (23%)	324 (23%)	1.00 (0.85-1.16)	0.97
Nonfatal MI	91 (7%)	107 (8%)	0.84 (0.64-1.11)	0.23
Nonfatal Stroke	53 (4%)	45 (3%)	1.17 (0.79-1.75)	0.42
<b>Select 2° Endpoints:</b>				
Atherosclerotic cardiac event	258 (19%)	266 (19%)	0.96 (0.81-1.14)	0.64
Revascularization	148 (11%)	152 (11%)	0.98 (0.78-1.23)	0.88



# SHARP

# Study of Heart and Renal Protection

- Primary Objective
  - To compare the effects of lowering LDL-C with ezetimibe/simvastatin 10/20 mg daily to placebo on the time to first major vascular event (MVE) in patients with CKD (2/3 pre-dialysis and 1/3 ESRD)
- Main “Renal” Objective
  - To assess the effects of ezetimibe/simvastatin 10/20 mg on progression to ESRD

# SHARP: Highlights

- Primary Endpoint: Major Vascular Events (MVE)
  - Non-fatal MI or cardiac death
  - Non-fatal or fatal stroke
  - Revascularization
    - coronary or non-coronary angioplasty or grafting
    - non-traumatic amputation for arterial cause
    - excludes vascular access surgery for dialysis

# SHARP: Highlights

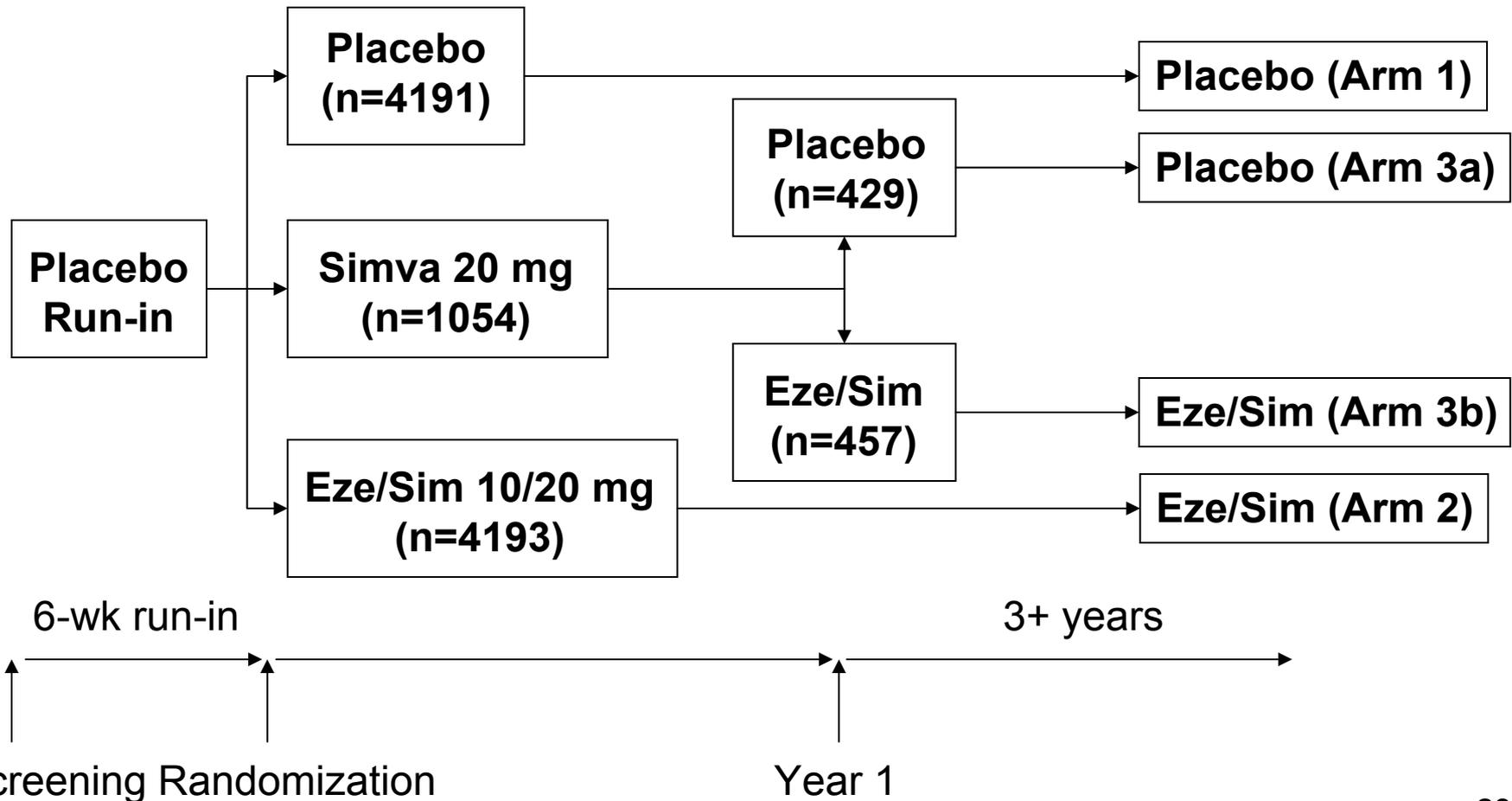
- Inclusion criteria:
  - Age  $\geq 40$ y
  - Men: Cr  $\geq 1.7$  mg/dL; Women: Cr  $\geq 1.5$  mg/dL
    - Note: Proteinuria with preserved GFR did not qualify
  - No known history of MI or coronary revascularization
  - No lipid criteria for inclusion/exclusion
  - No current use of statins, fibrates, niacin
- 380 sites, 18 countries (4% U.S.)
- 6,247 non-dialysis; 3,023 dialysis

# Eligible eGFR Based on Inclusion Criteria

	<b>40 y/o male, Cr <math>\geq</math>1.7 mg/dL</b>	<b>40 y/o female, Cr <math>\geq</math>1.5 mg/dL</b>
<b>Non-black</b>	$\leq 48$	$\leq 41$
<b>Black</b>	$\leq 58$	$\leq 50$

All values in mL/min/1.73m<sup>2</sup> and calculated using 4-variable MDRD equation. Using CKD-EPI equation yields similar values (within 2 mL/min/1.73m<sup>2</sup>).

# SHARP: Trial Design



# Primary Analysis

- Protocol: Time to first MVE
  - Population: All patients initially randomized to ezetimibe/simvastatin or placebo (i.e., Arm 2 vs. Arm 1)
    - Excludes patients initially randomized to simvastatin

# Primary Analysis

- Original assumption: 80% of non-coronary cardiac deaths would be potentially modifiable by LDL-lowering treatment
- 4D, AURORA, CORONA, GISSI-HF suggested no effect
- CTT meta-analysis suggested that LDL lowering did not favorably affect risk of hemorrhagic stroke
- Steering Committee felt that inclusion of these unmodifiable events would increase type II error

# Primary Analysis

- Major Atherosclerotic Events (MAE)
  - eliminates non-coronary cardiac deaths and hemorrhagic strokes
- Statistical Analysis Plan: Time to first MAE
  - Population: All patients *ever* randomized to ezetimibe/simvastatin or placebo (i.e., Arm 2+3b vs. 1+3a)

# Primary Analysis

- Merck declined the late-stage change in the primary endpoint and study population for the primary analysis
- FDA focus is on major vascular events
- For the purpose of today's discussion, FDA prefers to minimize discussion of these changes in analytical plan unless the choice of endpoint or study population *changes your interpretation of the trial's results.*



# SHARP

## Baseline Characteristics & Disposition

# SHARP Patient Characteristics

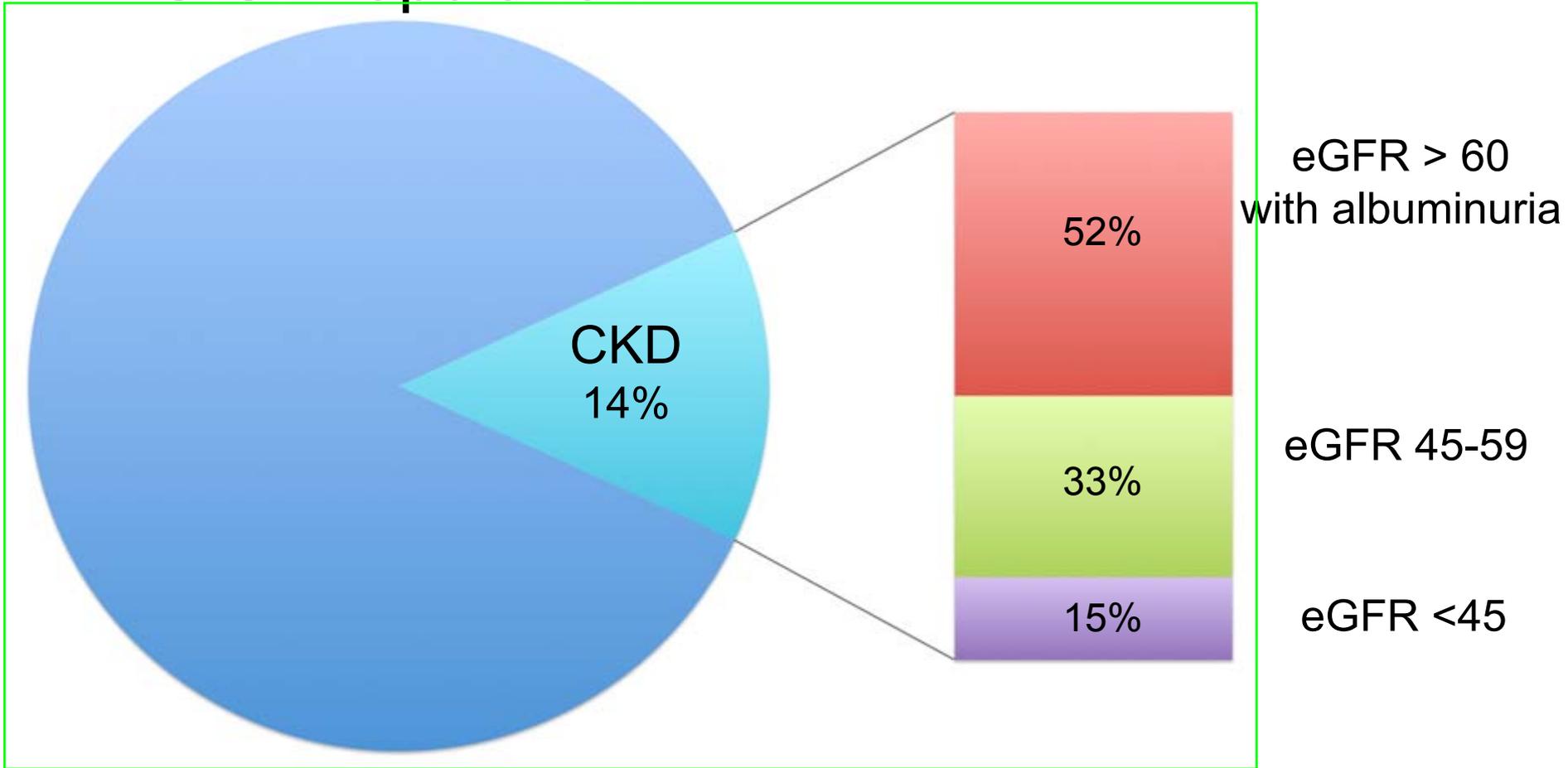
Characteristic	Study Population
Age [mean(SD)]	61 (12)
Male	63%
Race	
White	72%
Black	3%
Asian	23%
Diabetes	23%
Prior Vascular Disease	15%
Coronary disease	3%
Peripheral arterial disease	7%
Cerebrovascular disease	7%

# SHARP Baseline Renal Parameters

<b>Characteristic</b>	<b>Study Population (Pre-dialysis Only)</b>
Serum Cr (mg/dL)	2.5 [1.9-3.5]
eGFR (mL/min/1.73m <sup>2</sup> )	25.6 [16.9-34.7]
≥60 (Stage 1 or 2)	1%
≥45 and <60 (Stage 3)	5%
≥30 and <45 (Stage 3)	31%
≥15 and <30 (Stage 4)	43%
<15 (Stage 5)	20%
Normoalbuminuria	20%
Microalbuminuria	38%
Macroalbuminuria	42%

Median [interquartile range] or Frequency

# U.S. Population



# SHARP Baseline Lipids

Characteristic	Study Population
Total chol. (mg/dL)	190 (45)
LDL-C (mg/dL)	108 (34)
<70	12%
≥70 and <100	31%
≥100 and <130	33%
≥130	23%
HDL-C (mg/dL)	43 (13)
TG (mg/dL)	170 [119-249]

Mean(SD), frequency (%), or median [IQR].

# Disposition

- 11,792 screened
- 11,364 entered placebo run-in
  - 1,678 not eligible or withdrew (15%)
    - 743 by doctor's request
    - 385 by patient's request
    - 376 did not meet CKD definition
- 9,438 assigned to Arms 1, 2, 3

# Disposition

- 1,054 initially assigned to simvastatin
  - 10% stopped treatment during year 1
  - 4% died during year 1
  - 2% did not attend the second randomization visit
- 886 were re-assigned to placebo or ezetimibe/simvastatin

# Disposition

	<b>Eze/Sim</b> Arms 2+3b N=4650	<b>Placebo</b> Arms 1+3a N=4620
Complete follow-up	4547 (97.8%)	4519 (97.8%)
Median follow-up (survivors)	4.9 y	4.9 y
Total person-years follow-up	19,783	19,715

# Reasons for Discontinuing Therapy

Reason for Stopping (Incomplete List)	From Randomization to Eze/Sim or Placebo	
	Eze/Sim Arms 2+3b	Placebo Arms 1+3a
<b>Other SAE</b>	303 (6.5%)	310 (6.7%)
<b>AE (non-serious)</b>	165 (3.5%)	131 (2.8%)
<b>Abnormal safety blood result (non-serious)</b>	43 (0.9%)	28 (0.6%)
<b>Contraindicated med</b>	<b>248 (5.3%)</b>	<b>449 (9.7%)</b>
<b>Patient wishes</b>	417 (9.0%)	409 (8.9%)
<b>ANY REASON</b>	<b>1522 (32.7%)</b>	<b>1658 (35.9%)</b>

# Non-Study Statin Use

	At Year 2.5		At Final Follow-up	
	Eze/Sim N=3760	Placebo N=3735	Eze/Sim N=3512	Placebo N=3506
Any non-study statin	6%	9%	10%	15%

- Initiation of non-study lipid-lowering agents required discontinuing study treatment
- These patients were considered noncompliant with study therapy



# SHARP

## Efficacy Analyses

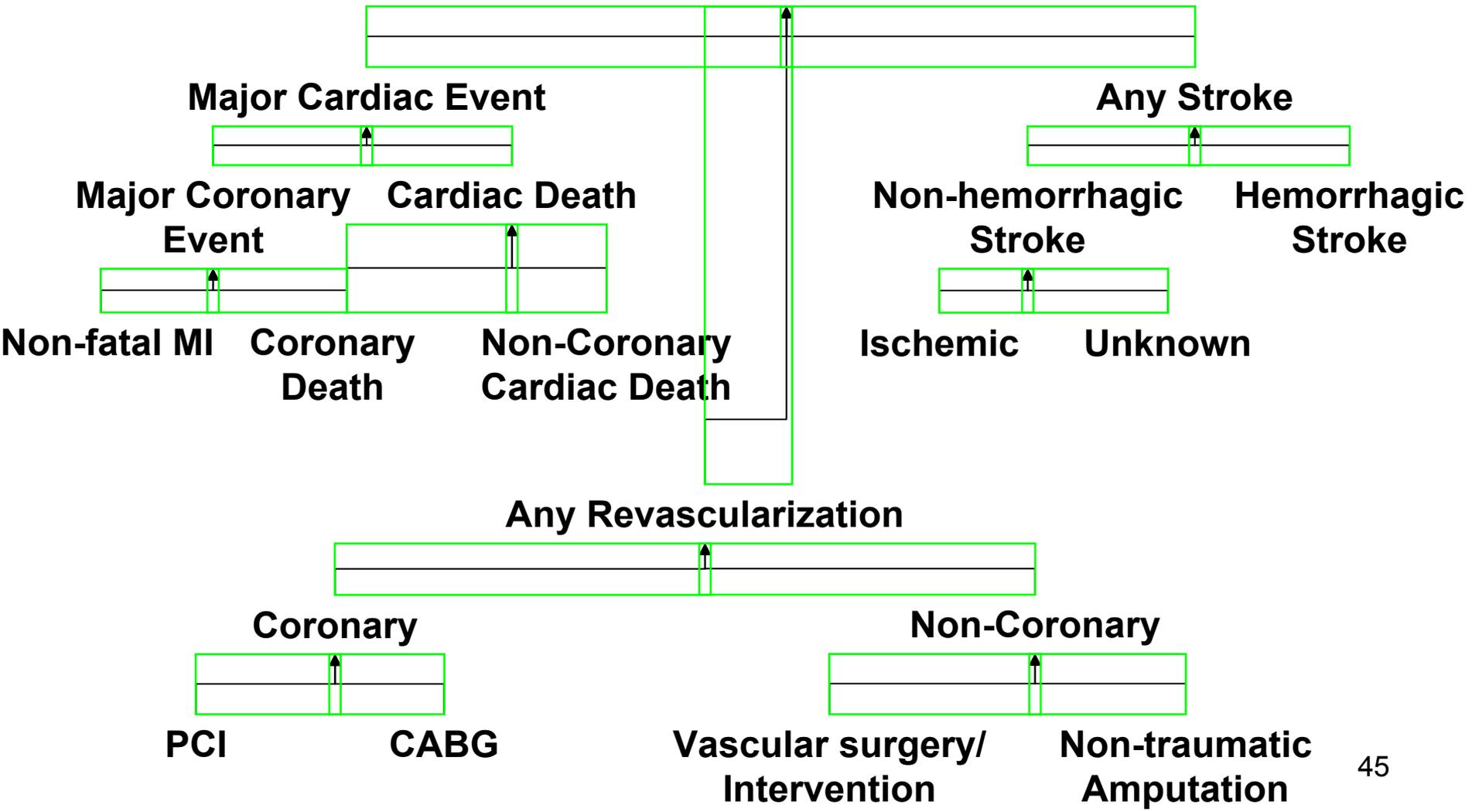
# Mean Lipid Levels at Year 2.5

	<b>Placebo (N=3455)*</b>	<b>Eze/Sim (N=3480)*</b>	<b>Relative ΔLDL</b>
Tot. chol. (mg/dL)	183	142	-23%
LDL-C (mg/dL)	103	70	-32%
HDL-C (mg/dL)	44	44	+2%
Non-HDL-C (mg/dL)	139	98	-30%
Triglycerides (mg/dL)	188	163	-13%
Apo B (mg/dL)	93	70	-24%
Apo A1 (mg/dL)	143	145	+1%

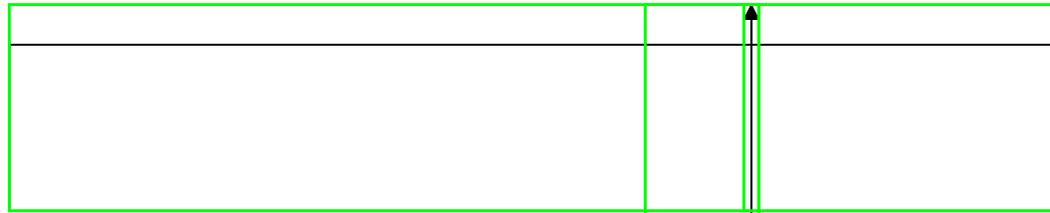
Baseline values are imputed for missing values, assuming noncompliance.

\* N ranges from 3450 to 3455 for placebo and from 3466 to 3480 for ezetimibe/simvastatin.

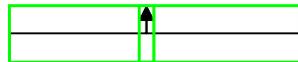
# MAJOR VASCULAR EVENT



# MAJOR **ATHEROSCLEROTIC** EVENT



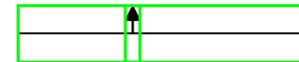
**Major Coronary Event**



**Non-fatal MI    Coronary Death**

**Non-Coronary Cardiac Death**

**Non-hemorrhagic Stroke**



**Ischemic    Unknown**

**Hemorrhagic Stroke**



**Any Revascularization**



**Coronary**

**Non-Coronary**

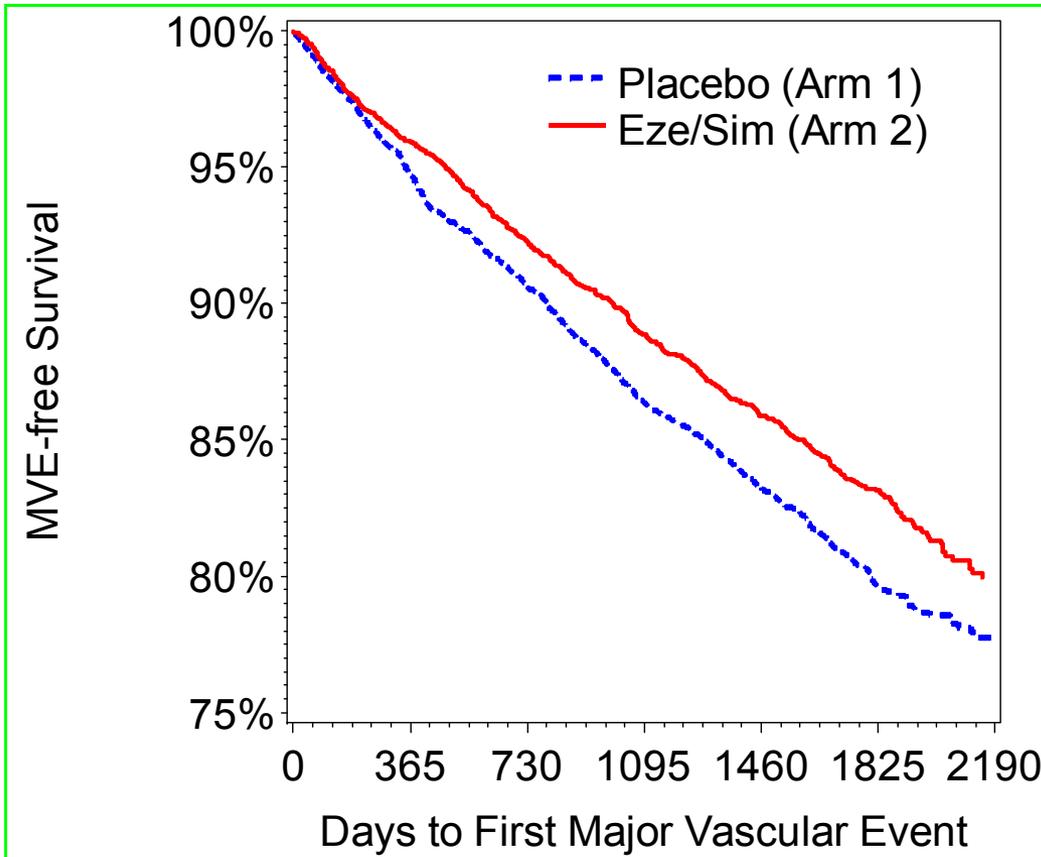


**PCI    CABG**

**Vascular surgery/  
Intervention**

**Non-traumatic Amputation**

# Protocol-Specified 1<sup>o</sup> Endpoint: Time to Major Vascular Event



Eze/Sim (Arm 2)	Placebo (Arm 1)
639/4193 (15.2%)	749/4191 (17.9%)

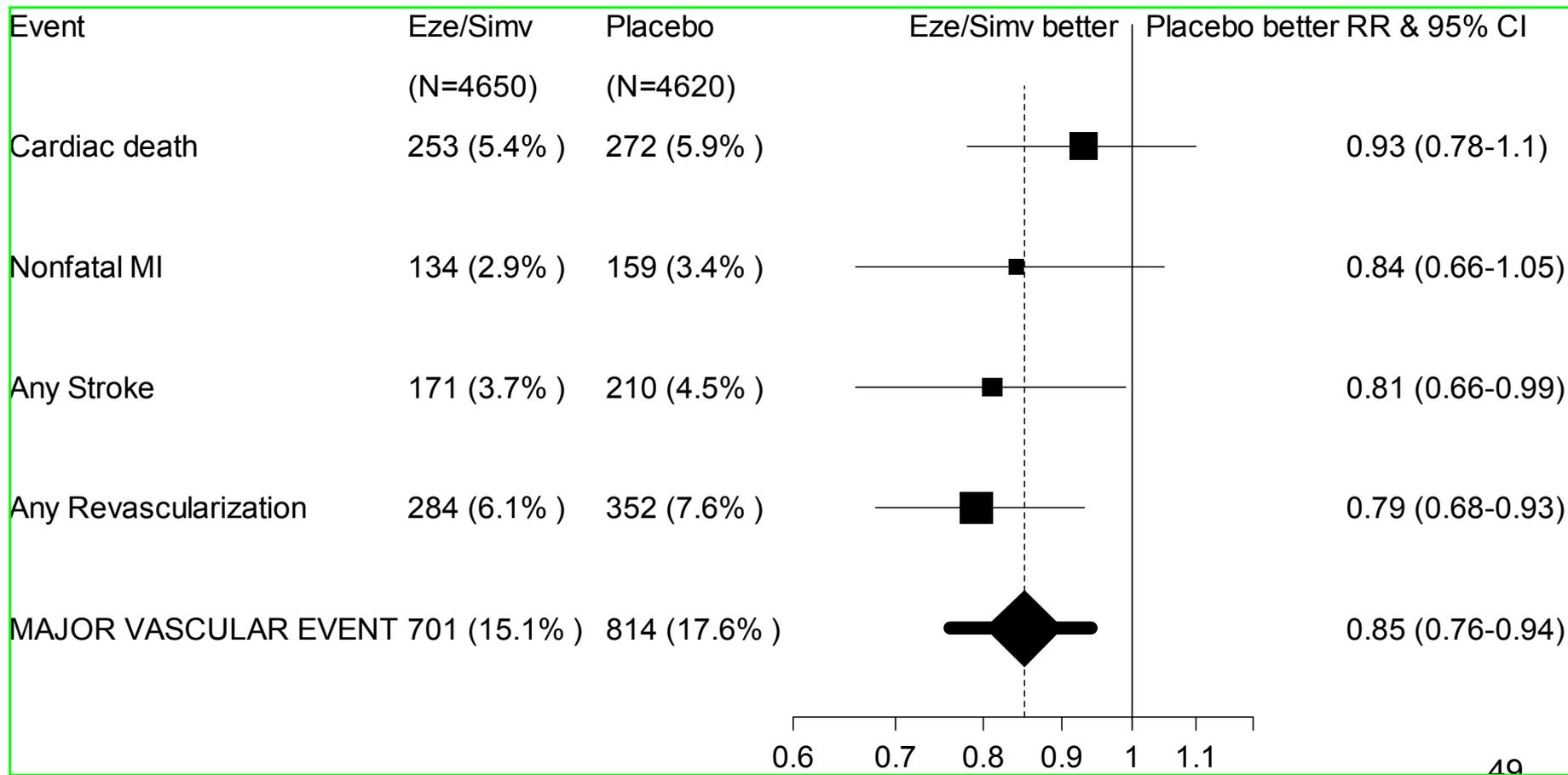
**Rate Ratio 0.84**  
**95% CI: 0.75-0.93**

**Log-rank P=0.001**

# Events Composing First MVE

	<b>Eze/Sim (Arm 2)</b>	<b>Placebo (Arm 1)</b>
Non-coronary Cardiac Death	124	143
Non-fatal MI	111	130
Ischemic CVA	96	126
Vascular Surgery/Intervention	75	99
PCI	59	75
Coronary Death	58	54
Non-traumatic Amputation	47	40
Hemorrhagic CVA	31	33
CABG	27	36
Unknown CVA	11	13
<b>TOTAL</b>	<b>639</b>	<b>749</b>

# Time to First Events: Components of MVE (Arms 1+3a vs. 2+3b)



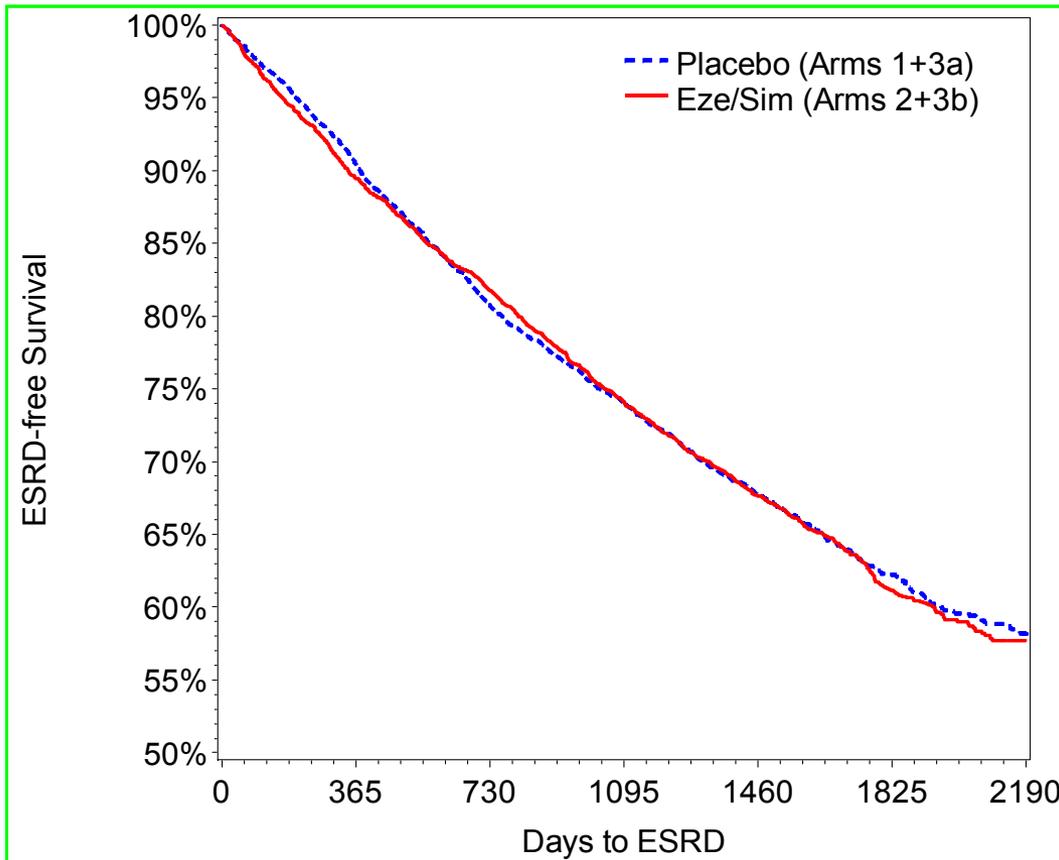
# Cardiac Death Subcomponents

	<b>Eze/Sim (Arms 2+3b)</b>	<b>Placebo (Arms 1+3a)</b>	<b>Rate Ratio (95% CI)</b>
<b>CARDIAC DEATH</b>	<b>253 (5.4%)</b>	<b>272 (5.9%)</b>	<b>0.93 (0.78-1.10)</b>
Coronary Death	91 (2.0%)	90 (1.9%)	1.01 (0.75-1.35)
Non-coronary Cardiac Death	162 (3.5%)	182 (3.9%)	0.89 (0.72-1.09)

# Stroke Subcomponents

	<b>Eze/Sim (Arms 2+3b)</b>	<b>Placebo (Arms 1+3a)</b>	<b>Rate Ratio (95% CI)</b>
<b>ANY STROKE</b>	<b>171 (3.7%)</b>	<b>210 (4.5%)</b>	<b>0.81 (0.66-0.99)</b>
<b>Non-hemorrhagic stroke</b>	<b>131 (2.8%)</b>	<b>174 (3.8%)</b>	<b>0.75 (0.60-0.94)</b>
Ischemic stroke	114 (2.5%)	157 (3.4%)	0.72 (0.57-0.92)
Unknown stroke	18 (0.4%)	19 (0.4%)	0.94 (0.49-1.79)
<b>Hemorrhagic stroke</b>	<b>45 (1.0%)</b>	<b>37 (0.8%)</b>	<b>1.21 (0.78-1.86)</b>

# Main Renal Endpoint: Time to ESRD



Eze/Sim (Arm 2+3b)	Placebo (Arm 1+3a)
1057/3117 (33.9%)	1084/3130 (34.6%)

**Rate Ratio 0.97**  
**95% CI: 0.89-1.05**

**Log-rank P=0.41**



# SHARP

## Subgroup Analyses

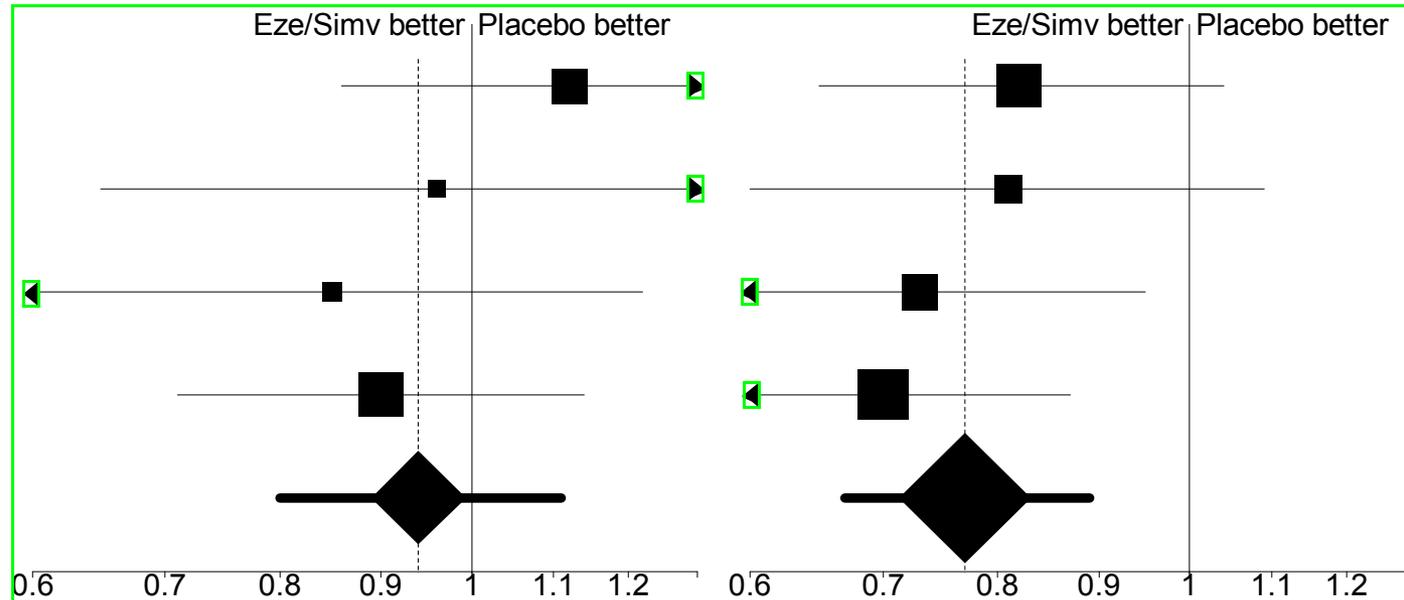
# Subgroup Analyses of MVE

- Renal Function
  - dialysis vs. non-dialysis at randomization
  - eGFR categories among non-dialysis patients
- Multiple subgroups defined by demographic or clinical criteria

# MVE and Components by Dialysis Status (Arm 2 vs. 1)

Dialysis

Not on Dialysis



P (test for heterogeneity) = 0.07

## SHARP Patient Characteristics by Dialysis Status at Randomization

Characteristic	Non-dialysis (N=6247)	Dialysis (N=3023)
Age [mean (SD)]	62 (12)	59 (12)
Male	62%	63%
Race – White	72%	72%
Black	2%	5%
Asian	24%	19%
Diabetes	23%	22%
BMI < 25 kg/m <sup>2</sup>	35%	44%
> 25 and < 30 kg/m <sup>2</sup>	38%	32%
> 30 kg/m <sup>2</sup>	25%	21%

## SHARP Patient Characteristics by Dialysis Status at Randomization

Characteristic	Non-dialysis (N=6247)	Dialysis (N=3023)
Total chol. (mg/dL)	194 (45)	180 (45)
Total chol. $\geq$ 200 mg/dL	40%	28%
LDL-C (mg/dL)	111 (33)	100 (33)
LDL-C $\geq$ 100 mg/dL	59%	44%
HDL-C (mg/dL)	44 (13)	42 (13)
Triglycerides (mg/dL)	169 [120-250]	170 [115-246]
Apo B (mg/dL)	99 (25)	92 (26)
Apo A1 (mg/dL)	136 (29)	129 (27)

Values are proportions (%), mean (SD), or median [IQR].

## Lipids at Year 2.5 by Renal Status at Randomization

eGFR	Absolute $\Delta$ LDL (mg/dL)	Relative $\Delta$ LDL	N <sub>1</sub> / N <sub>2</sub> (Eze/Sim / Pbo)
$\geq 60$	-38	-30%	39 / 40
$\geq 30$ and $< 60$	-38	-34%	1006 / 966
$\geq 15$ and $< 30$	-41	-35%	1121 / 1161
$< 15$	-28	-26%	490 / 494
<b>Non-dialysis</b>	<b>-37</b>	<b>-34%</b>	<b>2656 / 2661</b>
Hemodialysis	-24	-26%	1005 / 978
Peritoneal dialysis	-19	-20%	211 / 197
<b>Dialysis</b>	<b>-23</b>	<b>-23%</b>	<b>1216 / 1175</b>

Baseline values are imputed for missing values, assuming noncompliance.

Pbo = Placebo

## Lipids at Year 2.5 by Renal Status at Randomization

eGFR	Absolute $\Delta$ LDL (mg/dL)	Relative $\Delta$ LDL	Est. Compliance
$\geq 60$	-38	-30%	73%
$\geq 30$ and $< 60$	-38	-34%	70%
$\geq 15$ and $< 30$	-41	-35%	71%
$< 15$	-28	-26%	62%
<b>Non-dialysis</b>	<b>-37</b>	<b>-34%</b>	<b>69%</b>
Hemodialysis	-24	-26%	58%
Peritoneal dialysis	-19	-20%	47%
<b>Dialysis</b>	<b>-23</b>	<b>-23%</b>	<b>56%</b>

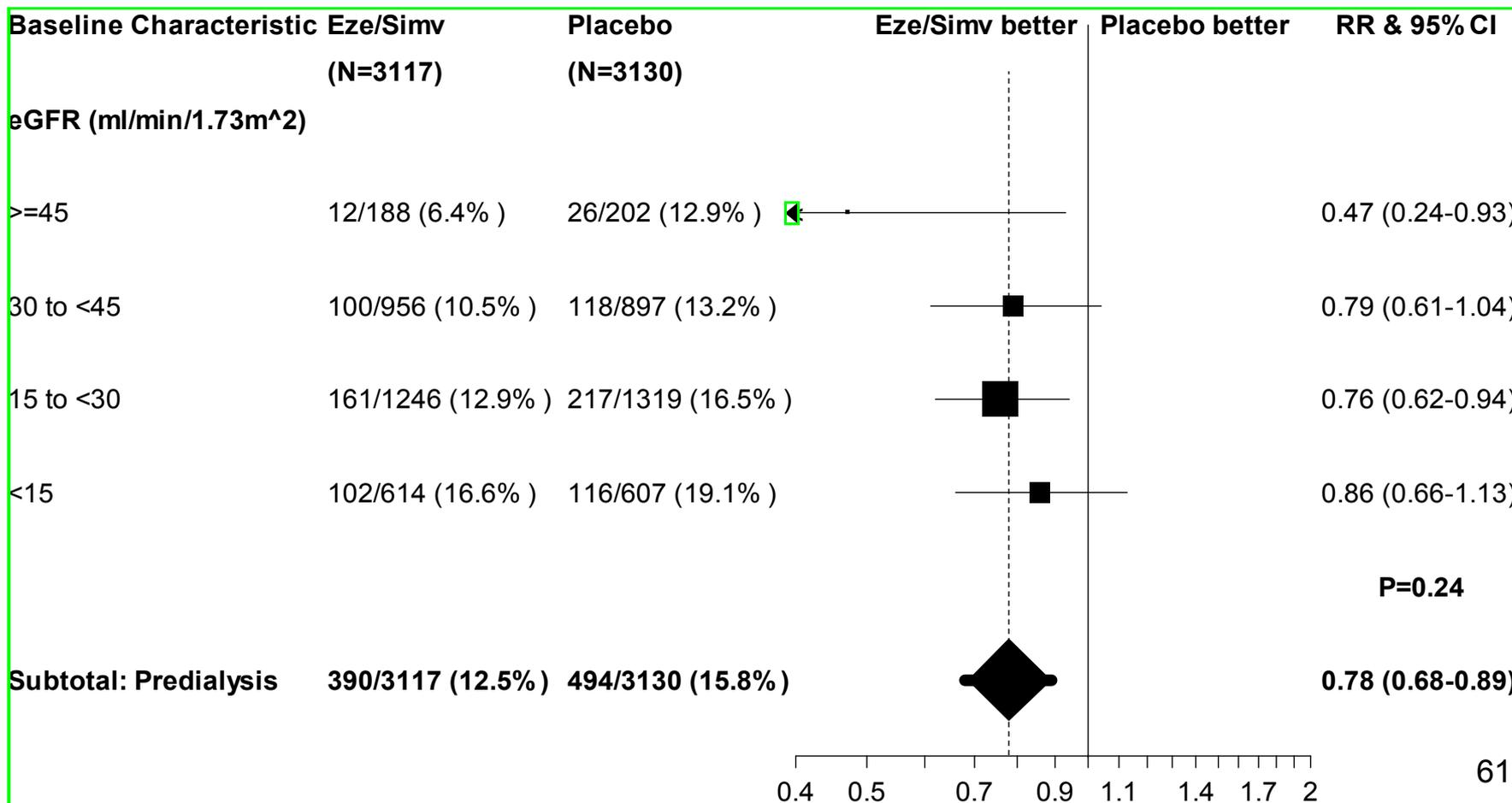
Baseline values are imputed for missing values, assuming noncompliance.

## Endpoints by Dialysis Status at Randomization

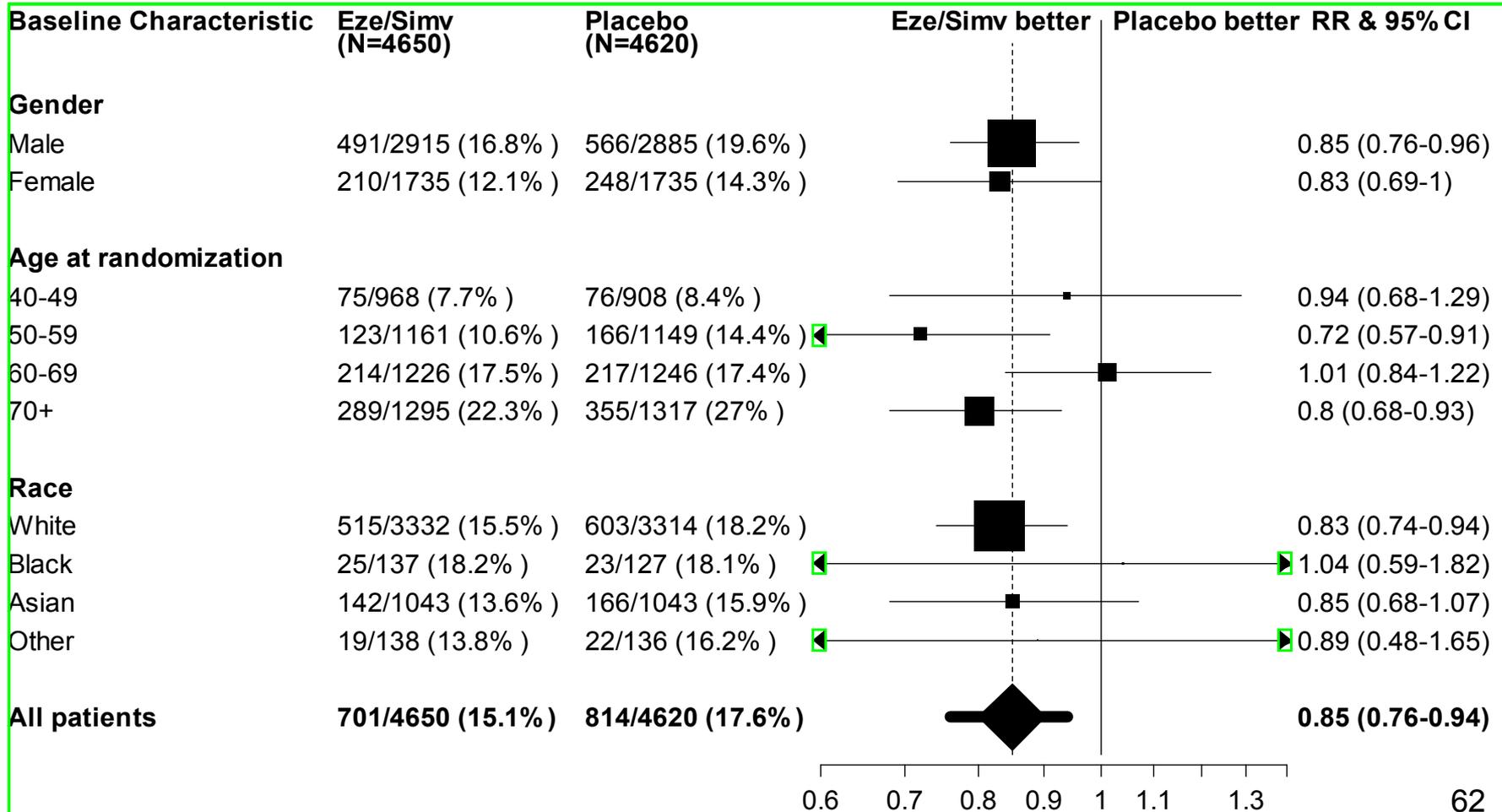
	<b>Non-dialysis RR (95% CI)</b>	<b>Dialysis RR (95% CI)</b>	<b>P (heterogeneity)</b>
<b>MVE</b> (1 vs. 2)	0.77 (0.67-0.88)	0.94 (0.80-1.11)	0.07
<b>MVE</b> (1+3a vs. 2+3b)	0.78 (0.69-0.89)	0.94 (0.80-1.09)	0.08
<b>MAE</b> (1+3a vs. 2+3b)	0.78 (0.67-0.91)	0.90 (0.75-1.08)	0.25

1. Difference between point estimates narrows, primarily as a result of removing hemorrhagic strokes.
2. Fewer MAEs than MVEs → point estimates are less precise (reflected in the wider 95% CIs).

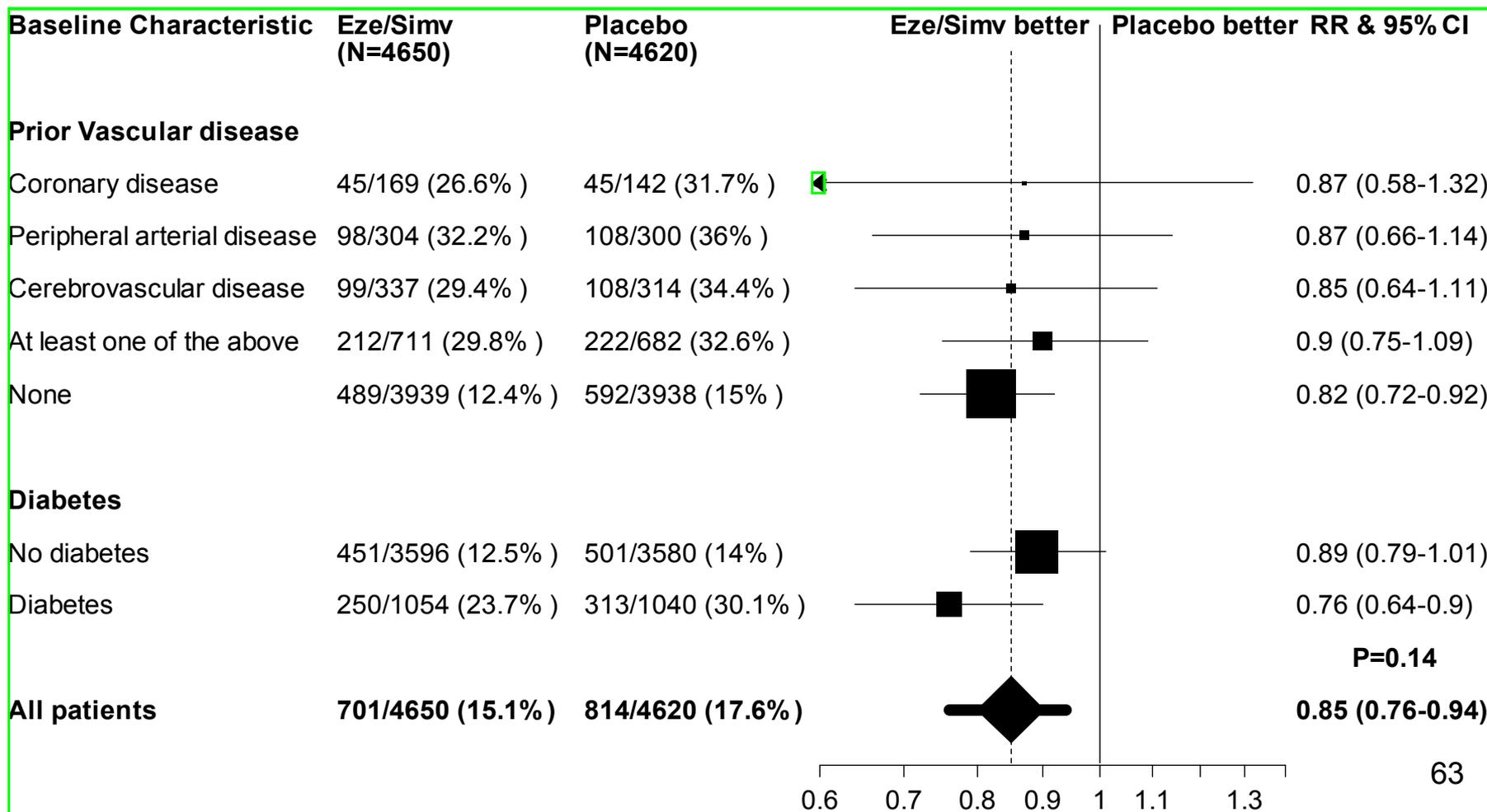
# MVE by eGFR Category (Arms 2+3b vs. 1+3a)



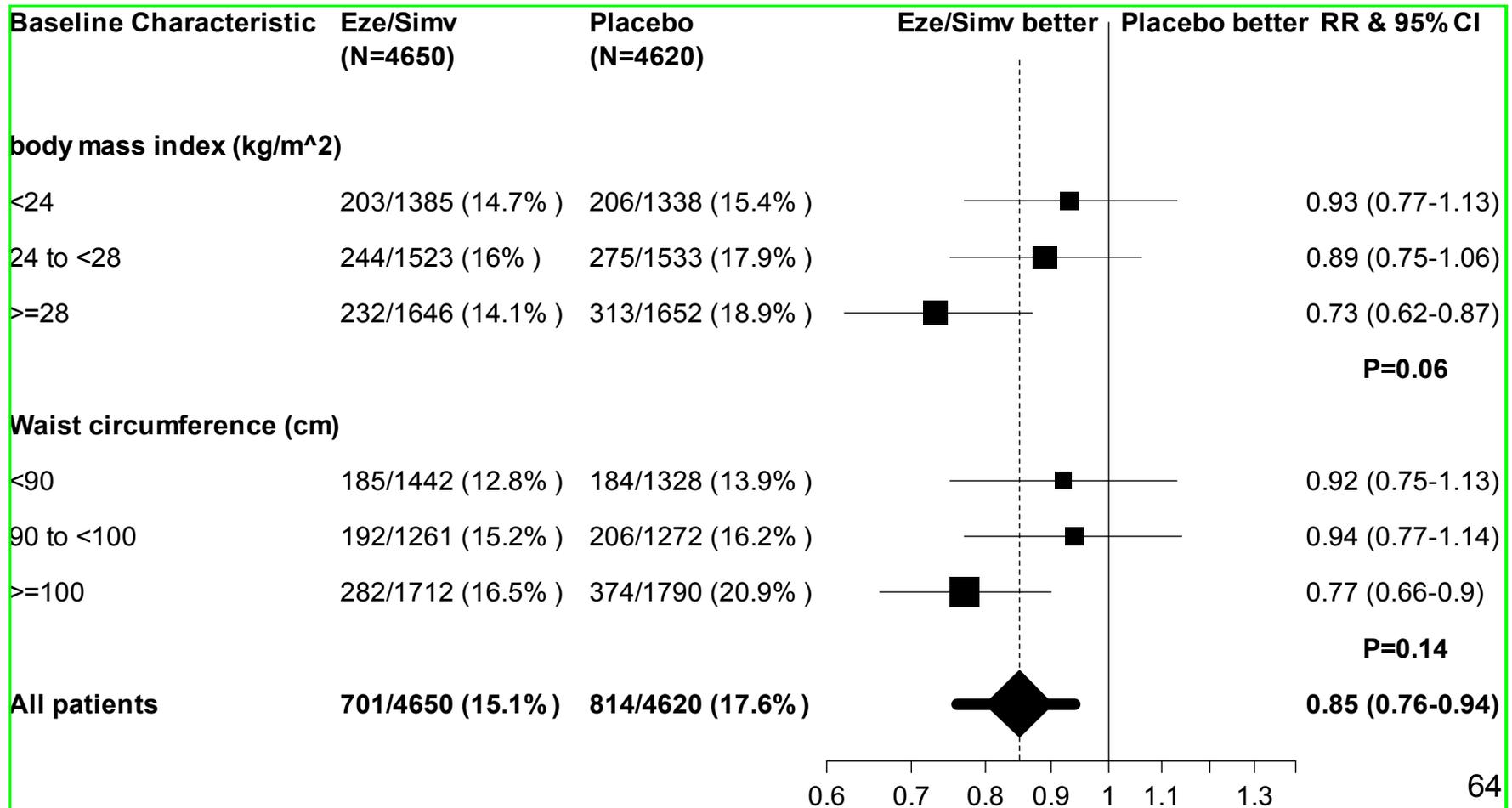
# MVE by Demographics (Arms 2+3b vs. 1+3a)



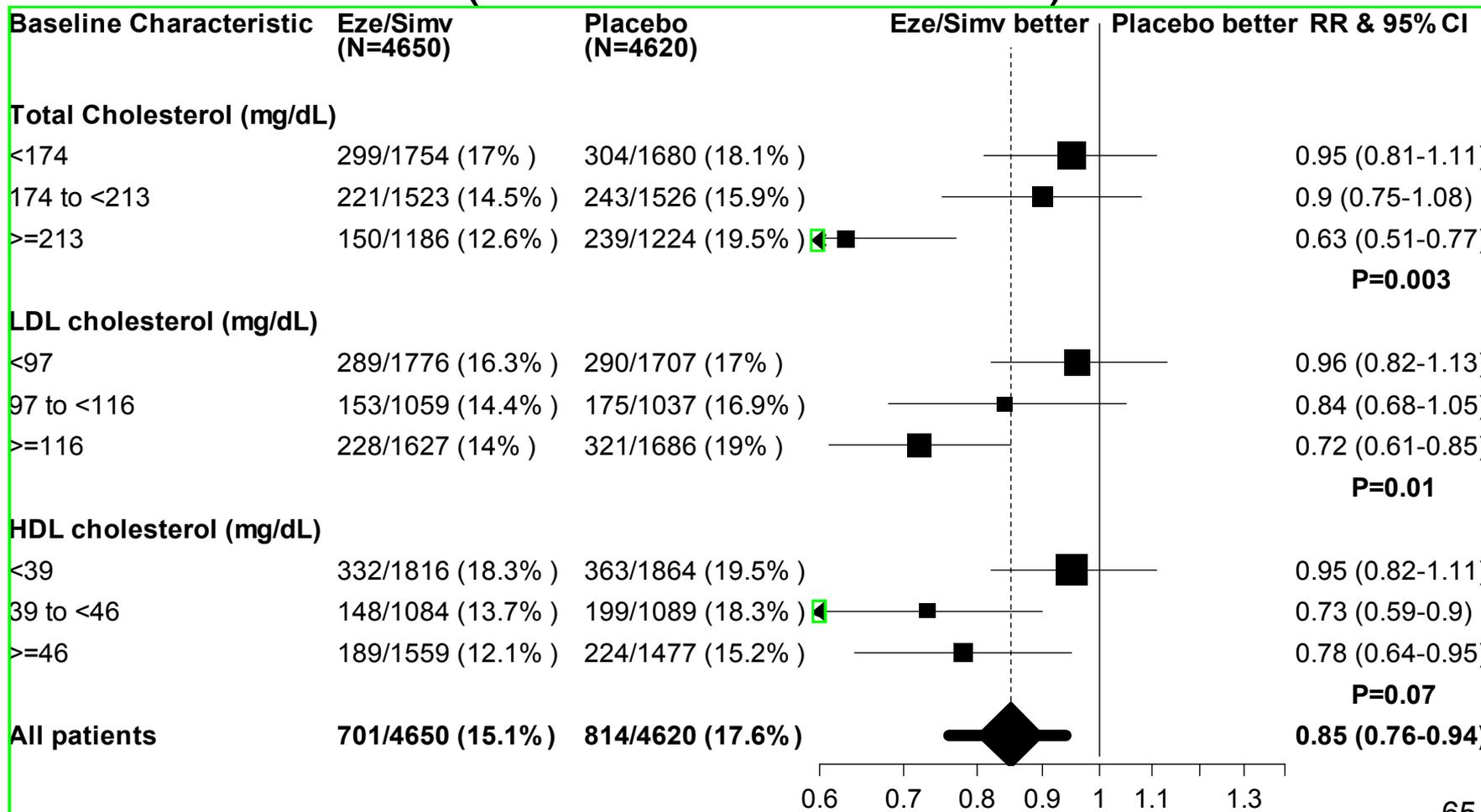
# MVE by Medical History (Arms 2+3b vs. 1+3a)



# MVE by BMI and Waist Circumference (Arms 2+3b vs. 1+3a)



# MVE by Lipid Categories (Arms 2+3b vs. 1+3a)





# 4D, AURORA, and SHARP

# 4D, AURORA, and SHARP

	4D	AURORA	SHARP
<b>Population</b>	Type 2 DM ESRD on HD $\leq$ 2y LDL 80-190 mg/dL (20% taking statins)	ESRD on HD $\geq$ 3mo No statin x 6 mo	2/3 non-dialysis; 1/3 ESRD No h/o MI or cor revasc Not on statin
<b>N</b>	1255	2773	9270
<b>Location</b>	178 centers in Germany	~300 centers, multinational, no US sites	308 centers in 18 countries (4% subjects in US)
<b>Years of trial</b>	1998-2004	2003-2008	2003-2010
<b>Intervention</b>	atorva 20 mg vs. placebo	rosuva 10 mg vs. placebo	eze/sim (10/20 mg) vs. placebo
<b>Primary Endpoint</b>	Nonfatal MI (including silent), stroke, cardiovascular death	Nonfatal MI (including silent), stroke, cardiovascular death	Nonfatal MI (not silent), stroke, cardiac death, any revascularization
<b>Median duration</b>	4.0 y	3.8 y	4.9 y

# 4D, AURORA, and SHARP Initial Assumptions

	<b>4D</b>	<b>AURORA</b>	<b>SHARP</b>
Expected treatment effect	↓27%	↓25%	↓20%
Expected event rate (placebo)	12.5% / yr	11% / yr	3.7% / yr (3% nondialysis; 5% dialysis)
Power	90%	90%	90%
Alpha	0.05	0.05	0.01
Events needed	424	620	1100
Anticipated enrollment	1200	2750	8000 (Arms 1 and 2)

# 4D, AURORA, and SHARP

	4D	AURORA	SHARP (All)	SHARP (Dialysis)
<b>Age (mean)</b>	66	64	61	59
<b>Mean Years on RRT</b>	0.7	3.7	-	3.7
<b>Diabetes</b>	100%	26%	23%	22%
<b>PVD</b>	45%	15%	7%	8%
<b>Coronary disease</b>	29%	10% h/o MI (40% with "Cardiovascular disease")	3%	3%
<b>Cerebrovascular disease</b>	18%	NR	7%	6%
<b>LDL-C (mean)</b>	126	100	108	100

NR = Not reported.

# 4D, AURORA, and SHARP

	<b>4D</b>	<b>AURORA</b>	<b>SHARP</b>
<b>Primary Endpoint</b>	0.92 (0.77-1.10)	0.96 (0.84-1.11)	0.84 (0.75-0.93)
<b>Non-fatal MI</b>	0.88 (0.64-1.21)	0.84 (0.64-1.11)	0.84 (0.66-1.05)
<b>Overall Mortality</b>	617/1255 (49%)	1296/2773 (47%)	2257/9270 (24%) [Dialysis: 33%]

# 4D, AURORA, and SHARP

- Were the competing risks for mortality too high in 4D and AURORA to observe a treatment benefit?
- Is vascular disease of dialysis patients less modifiable by lipid-lowering therapy?
- Do statins/lipid-lowering therapy have a smaller effect on CV risk reduction in dialysis patients compared with pre-dialysis patients?
- What role does compliance play in this differential treatment effect?

# SHARP Efficacy Summary

- In patients with advanced CKD and no history of MI or coronary revascularization, ezetimibe/simvastatin reduced the risk of major vascular events by 16% compared with placebo (95% CI, 7% to 25%,  $p=0.001$ ).
- In secondary and exploratory analyses, this result appears to be substantially driven by the treatment effects on non-fatal MI, ischemic stroke, and revascularization.

# SHARP Efficacy Summary

- The risk ratio for MVE was 0.94 (95% CI 0.80-1.11) for ezetimibe/simvastatin vs. placebo among those on dialysis at randomization compared with 0.77 (95% CI 0.67-0.88) among those not on dialysis (test of heterogeneity,  $P=0.07$ ).
- Patients with higher levels of total cholesterol and LDL at randomization exhibited significantly greater effects of ezetimibe/simvastatin on major vascular events.

# SHARP Efficacy Summary

- Approximately 1/3 of non-dialysis patients progressed to ESRD during the trial in both groups.

# Outcomes at Year 1

<b>Endpoint</b>	<b>Eze/Sim</b> (n=4193)	<b>Simva</b> (n=1054)	<b>Placebo</b> (n=4191)
LDL-C (Mean ± SE) (mg/dL)	66 ± 2 (n=391)	79 ± 3 (n=108)	108 ± 2 (n=365)
MVE	168 (4.0%)	51 (4.8%)	222 (5.3%)
MAE	132 (3.2%)	43 (4.1%)	162 (3.9%)



# SHARP

## Safety Analyses

# Safety

- SHARP *only* collected SAEs, pre-specified AEs, and AEs that led to discontinuation of study drug
- Blinded adjudication
- Intention-to-treat analysis.
- Safety data censored at final study visit.

# Safety: Deaths

	From Randomization to Eze/Sim or Placebo	
	Eze/Sim (N=4650)	Placebo (N=4620)
All-cause Mortality	1142 (24.6%)	1115 (24.1%)

# Muscle-related Events

Event	First Year		
	Eze/Sim	Simva	Placebo
<b>CK &gt;5x but ≤10xULN</b>	<b>18 (0.43%)</b>	<b>6 (0.57%)</b>	<b>14 (0.33%)</b>
Without symptoms	17	5	11
With symptoms	1	1	3
<b>Myopathy</b> (CK >10xULN with symptoms)	<b>1 (0.02%)</b>	<b>0</b>	<b>1 (0.02%)</b>
<b>Rhabdomyolysis</b> (CK >40xULN with symptoms)	<b>0</b>	<b>0</b>	<b>0</b>

# Muscle-related Events

Event	From Randomization to Eze/Sim or Placebo	
	Eze/Sim	Placebo
<b>CK &gt;5x but ≤10xULN</b>	<b>50 (1.1%)</b>	<b>47 (1.0%)</b>
Without symptoms	43	40
With symptoms	7	7
<b>Myopathy</b> (CK >10xULN with symptoms)	<b>9* (0.19%)</b>	<b>5†‡ (0.11%)</b>
<b>Rhabdomyolysis</b> (CK >40xULN with symptoms)	<b>4 (0.09%)</b>	<b>1‡ (0.02%)</b>

\* One subject not on study drug at the time of the event

†,‡ Each symbol designates 1 patient taking non-study statin

# Muscle-related Events by Dialysis Status at Time of Event

Event	Eze/Sim		Placebo	
	Non-dialysis	Dialysis	Non-dialysis	Dialysis
<b>CK &gt;10x but ≤40xULN</b>	9	8 (1 off drug)	11 (1 on NSS)	5
<b>CK &gt;40xULN</b>	2	2	3 (1 on NSS)	2
<b>Myopathy</b> (CK >10xULN with symptoms)	5	4 (1 off drug)	5 (2 on NSS)	0
<b>Rhabdomyolysis</b> (CK >40xULN with symptoms)	2	2	1 (on NSS)	0

NSS = Non-study statin

# Liver-related Events

Event	From Randomization to Eze/Sim or Placebo	
	Eze/Sim	Placebo
<b>Persistently elevated transaminases</b>	<b>30 (0.65%)</b>	<b>26 (0.56%)</b>
With hepatitis	14	10
With any other SAE	5	5
Without alternative explanation	11	11
<b>Hepatitis</b>	<b>21*† (0.45%)</b>	<b>18‡ (0.39%)</b>
Infective	12	12‡
Non-infective	6*	4
No cause identified	3†	2§

\* One subject stopped study drug 1.5 y before event.

† One subject with elevated transaminases (TAs) at randomization

‡ One subject initially classified as non-infective; later determined Hep C responsible

§ Elevated TAs at 2<sup>nd</sup> randomization (simva → placebo)

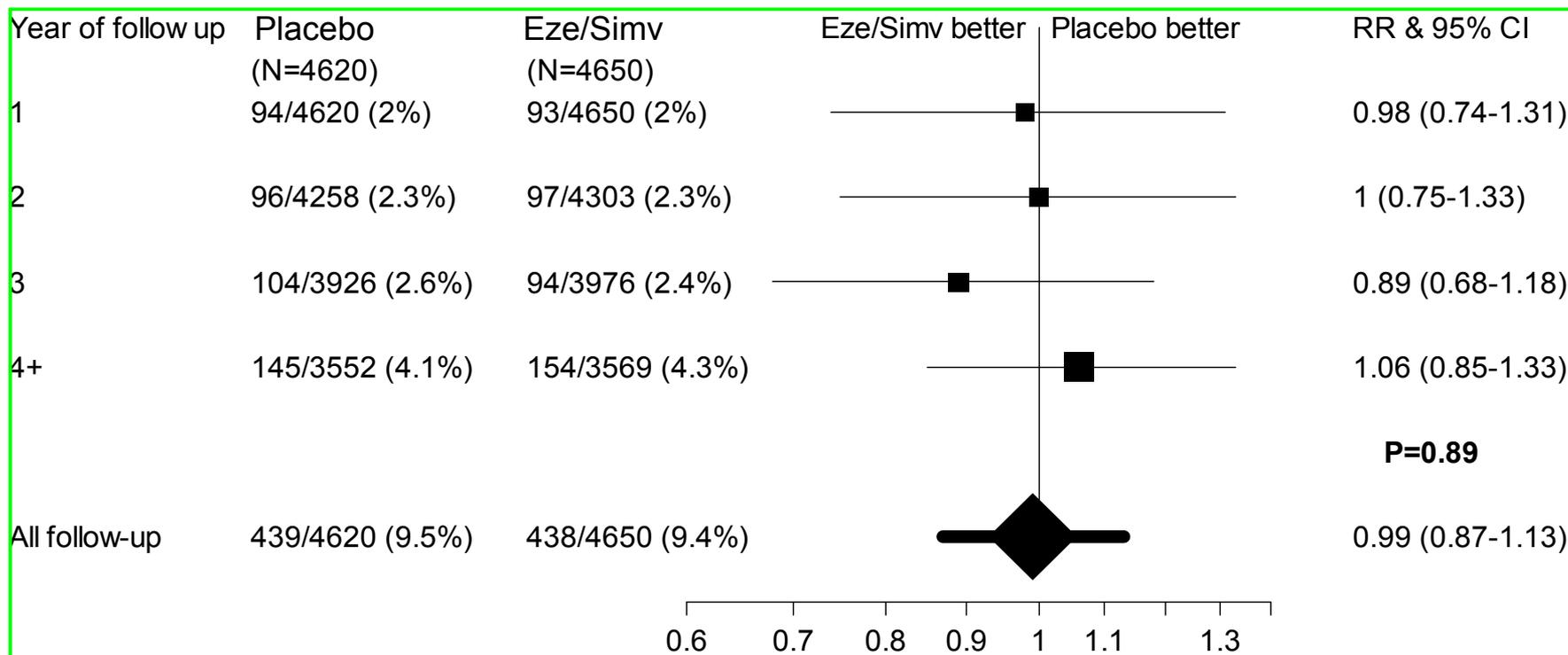
# Increases in Transaminases

Peak ALT and/or AST	From Randomization to Eze/Sim or Placebo	
	Eze/Sim	Placebo
>2x but $\leq$ 3xULN	162 (3.5%)	112 (2.4%)
>3xULN	105 (2.3%)	76 (1.7%)
>3x but $\leq$ 5xULN	66 (1.4%)	49 (1.1%)
>5x but $\leq$ 10xULN	29 (0.6%)	15 (0.3%)
>10xULN	10 (0.2%)	12 (0.3%)

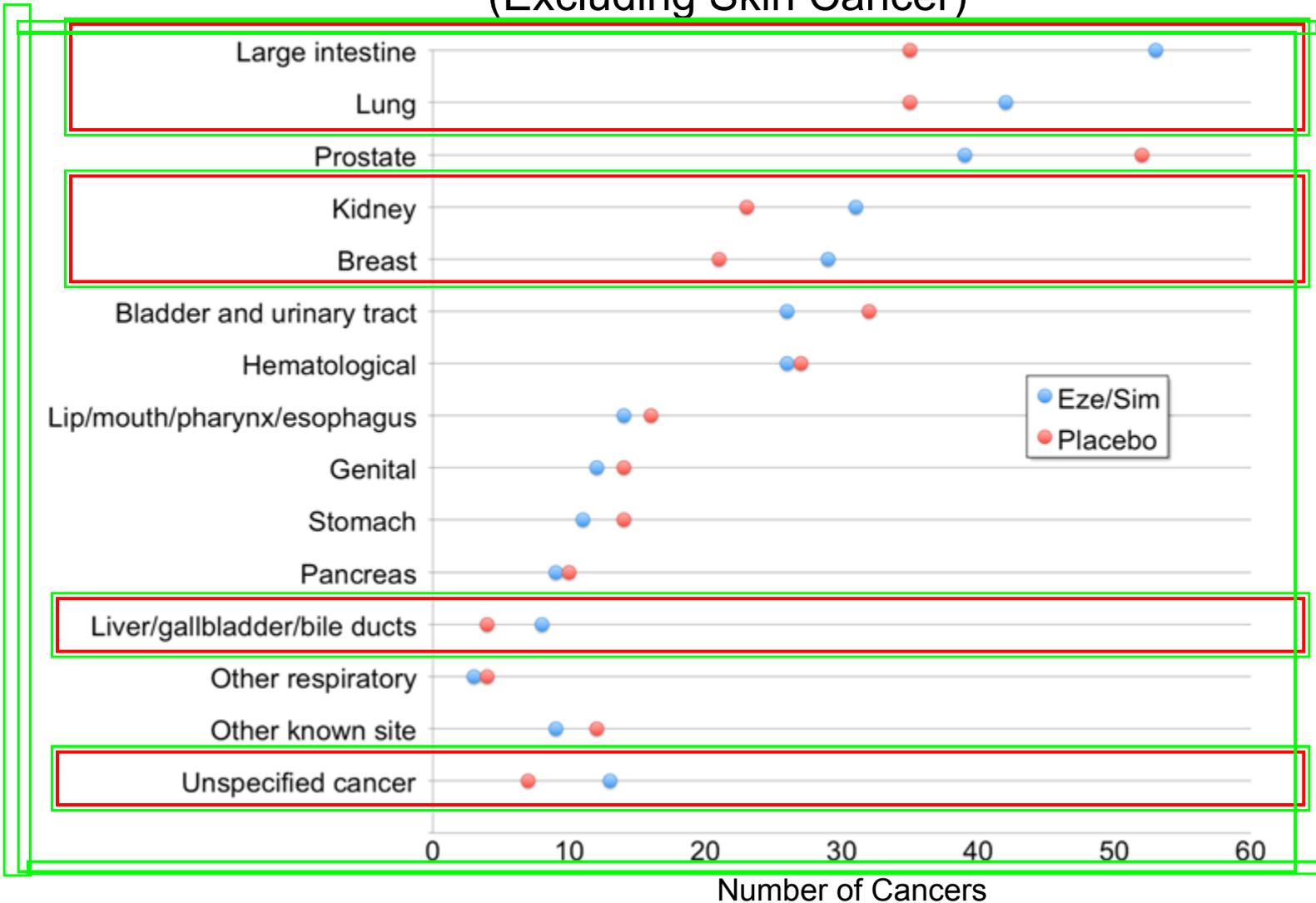
# Cancer

<b>Event</b>	<b>Eze/Sim</b>	<b>Placebo</b>	<b>Rate Ratio</b>
Any incident cancer	438 (9.4%)	439 (9.5%)	0.99 (0.87-1.13)
Excluding non-melanoma skin cancer	322 (6.9%)	307 (6.6%)	1.04 (0.89-1.22)
Deaths from incident cancer	132 (2.8%)	114 (2.5%)	1.15 (0.90-1.48)

# Cancer



# Sites of Incident Cancer (Excluding Skin Cancer)



# Incident Cancers in SEAS vs. SHARP

Site	SEAS		SHARP	
	Eze/Sim (N=944)	Placebo (N=929)	Eze/Sim (N=4650)	Placebo (N=4620)
<b>Any cancer</b>	<b>101</b>	<b>65</b>	<b>438</b>	<b>439</b>
Prostate	21	13	39	52
Skin	18	8	136	153
Breast	8	5	29	21
Hematologic	7	5	26	27
Stomach	5	1	11	14
Pancreas	3	1	9	10

Body sites in SEAS trial where the number of cases in ezetimibe/simvastatin group was  $\geq 2$  more than placebo.

# SHARP Safety Summary

- All-cause mortality was similar between patients ever randomized to ezetimibe/simvastatin or placebo (24.6% vs. 24.1%).
- Myopathy occurred in 9 vs. 5 patients assigned to ezetimibe/simvastatin and placebo, respectively. Of these, 4 vs. 1 met the definition of rhabdomyolysis.
- Persistently elevated transaminases occurred with similar frequency in both groups (0.7% vs. 0.6%).

# SHARP Safety Summary

- Incident cancers occurred with similar frequency in both groups (9.4% vs. 9.5%).
- There was a slightly higher incidence of death that the adjudication committee attributed to incident cancer among those ever randomized to ezetimibe/simvastatin (2.8% vs. 2.5%).

# Summary

- Ezetimibe/simvastatin reduced the risk of major vascular events by 16% (95% CI, 7% to 25%) relative to placebo in patients with advanced CKD without a history of MI or coronary revascularization.
- A reduction in non-hemorrhagic stroke and revascularization among non-dialysis patients substantially contributed to this result.
- The effect of ezetimibe/simvastatin among dialysis patients who are not already taking a lipid-lowering agent is less clear.