

# SEAS

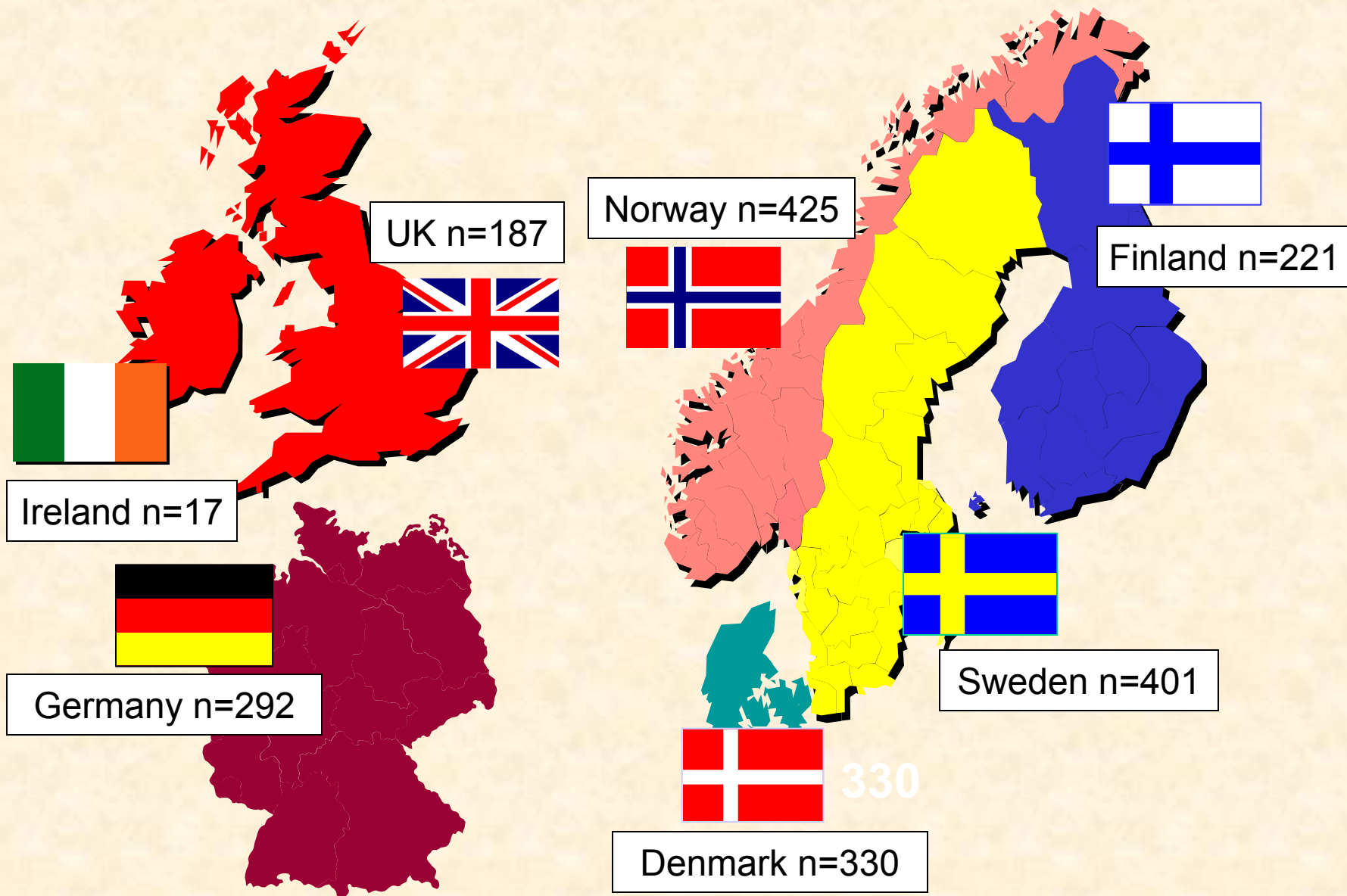
**Simvastatin + Ezetimibe in Aortic Stenosis**

**Presented by  
Terje R. Pedersen  
Oslo**

Disclosure:

Research grants and/or speaker- / consulting fees from  
Merck, MSP, Astra-Zeneca, Pfizer

# Patients Randomized by Country



# SEAS Steering Committee



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**Kristian Wachtell**

**Ronnie Willenheimer**

***Nonvoting members:***

**Philippe Brudi (MSP),**

**William Malbecq (MSD statistician)**

# Study Design



- **Randomized**
- **Double blind**
- **Placebo controlled**
- **Multicenter**
- **4 Weeks placebo/diet run-in**
- **Simvastatin 40 mg + ezetimibe 10 mg or placebo**
- **Median duration: 4.5 year (minimum follow-up 4 years)**

# Primary Endpoint

## Major Cardiovascular Events:

- Cardiovascular death
- Aortic valve replacement surgery (AVR)
- CHF as a result of progression of AS
- Non-fatal myocardial infarction
- CABG
- PCI
- Hospitalized unstable angina
- Non-hemorrhagic stroke

PCI = percutaneous coronary intervention  
CHF= congestive heart failure  
CABG = coronary-artery bypass grafting

# Secondary Endpoints

## Aortic Valve Events

- Aortic Valve Replacement
- CHF as a result of progression of AS
- Cardiovascular death

## Ischemic Cardiovascular Events

- Cardiovascular death
- Nonfatal MI
- CABG
- PCI
- Hospitalized unstable angina
- Nonhemorrhagic stroke

# Other Objectives

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**Echocardiography**

**Safety**

# Patient Definition



- Men and Women
- Age 45 - 85 years
- Asymptomatic
- Valvular AS:
  - Aortic valve thickening on echocardiographic evaluation
  - Doppler jet velocity  $\geq 2.5$  -  $\leq 4.0$  m/sec
- Normal LV systolic function



# Exclusion Criteria

- **Statin therapy or indication for statins**
- **Coronary heart disease**
- **Other important valvular disease**
  - **Significant mitral valve stenosis or regurgitation**
  - **Severe or predominant aortic regurgitation**
  - **Rheumatic valvular disease or AV prosthesis or subvalvular (hypertrophic, obstructive cardiomyopathy) or supravalvular AS**
- **Diabetes Mellitus**
- **Other conditions precluding participation**

# Baseline Characteristics

	Placebo n= 929	Simva + Ezetimibe n= 944
<b>Age (years)</b>	<b>67.4</b>	<b>67.7</b>
<b>Women (%)</b>	<b>38.8</b>	<b>38.5</b>
<b>SBP (mm Hg)</b>	<b>144</b>	<b>146</b>
<b>DBP (mm Hg)</b>	<b>82</b>	<b>82</b>
<b>Smoker (%)</b>	<b>18</b>	<b>20</b>
<b>Ex-smoker (%)</b>	<b>37</b>	<b>35</b>
<b>Never smoker (%)</b>	<b>45</b>	<b>45</b>
<b>BMI (kg/m<sup>2</sup>)</b>	<b>26.8</b>	<b>26.9</b>

# Baseline Medications

	Placebo n= 929	Simva + Ezetimibe n= 944
<b>ACE inhibitors</b>	<b>16.0</b>	<b>14.7</b>
<b>A-II blockers</b>	<b>10.5</b>	<b>10.1</b>
<b>Ca antagonists</b>	<b>17.2</b>	<b>16.6</b>
<b>Beta-blockers</b>	<b>28.8</b>	<b>25.6</b>
<b>Aspirin</b>	<b>28.0</b>	<b>25.0</b>
<b>Diuretics</b>	<b>24.7</b>	<b>22.1</b>

# Baseline Lipids and Lipoproteins

## Fasting Serum Lipid and Lipoprotein Levels at Baseline (n=1,873)

	Concentration (mmol/L)	Concentration (mg/dl)
<b>Total Cholesterol</b>	<b>5.74</b>	<b>222</b>
<b>LDL Cholesterol</b>	<b>3.60</b>	<b>139</b>
<b>HDL Cholesterol</b>	<b>1.49</b>	<b>58</b>
<b>Triglycerides</b>	<b>1.42</b>	<b>126</b>
<b>Apolipoprotein B</b>	<b>-</b>	<b>1.31 (g/L)</b>

Values given as mean  $\pm$  SD; LDL = low-density lipoprotein; HDL = high-density lipoprotein

# Baseline Echocardiography

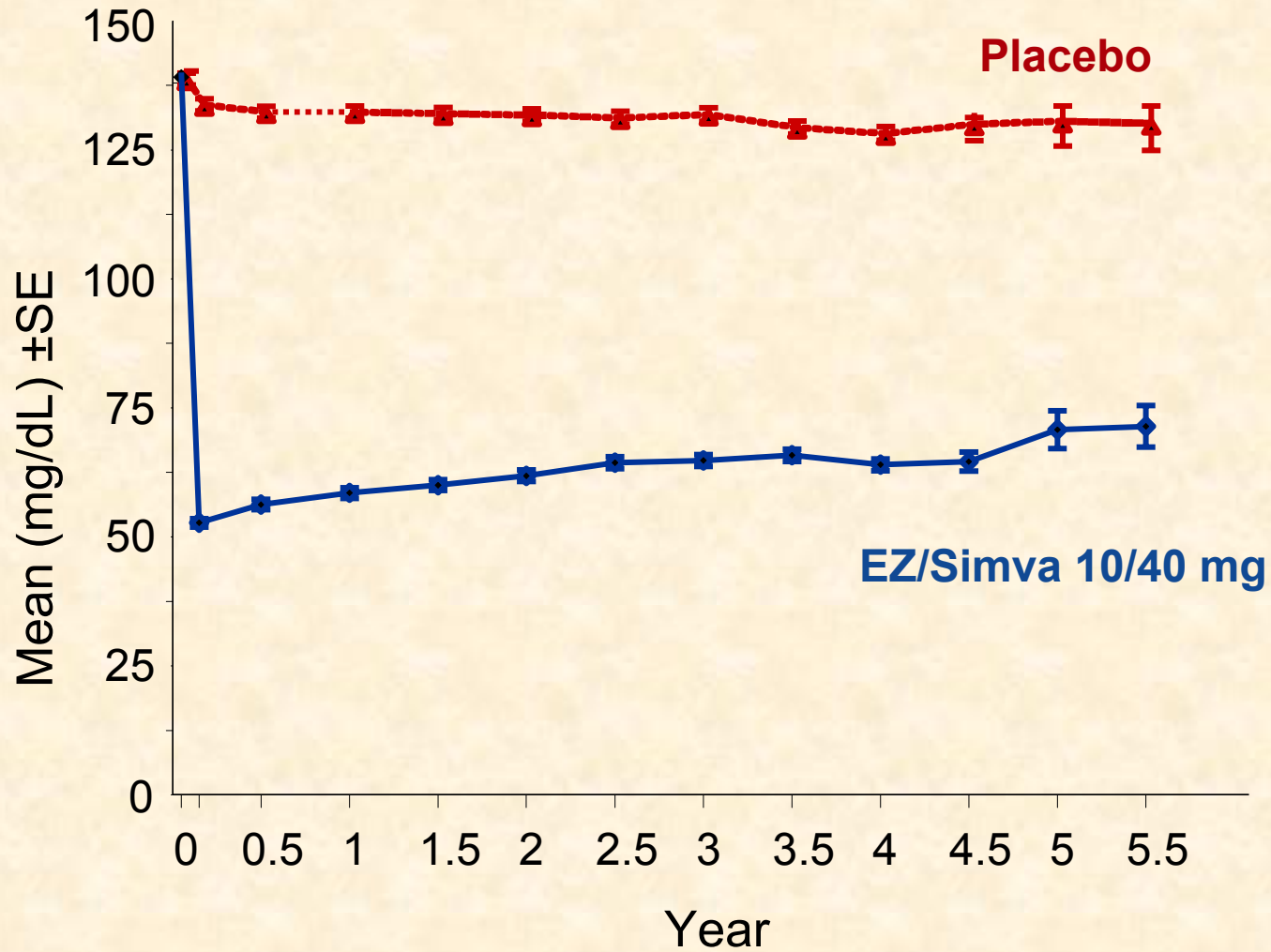


	Mean Values	
	Placebo	Simva + Ezetimibe
	n= 929	n= 944
<b>Transaortic</b>		
<b>Peak velocity (m/sec)</b>	<b>3.10</b>	<b>3.09</b>
<b>Peak gradient (mmHg)</b>	<b>39.6</b>	<b>39.3</b>
<b>Mean gradient (mmHg)</b>	<b>23.0</b>	<b>22.7</b>
<b>Aortic valve area (cm<sup>2</sup>)</b>	<b>1.27</b>	<b>1.29</b>
<b>Bicuspid valve (%)</b>	<b>6.3</b>	<b>5.0</b>

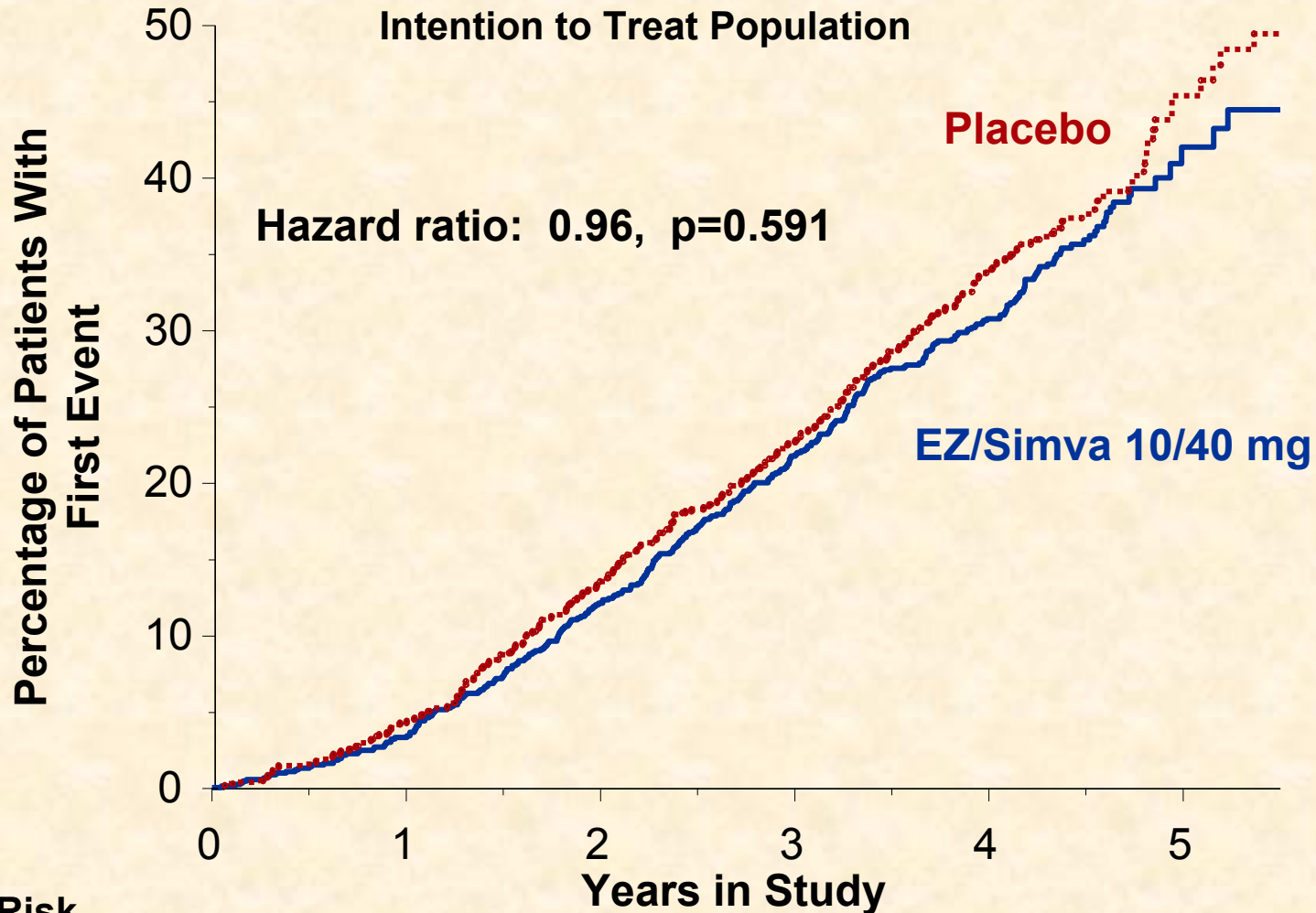
# LDL-Cholesterol



Intention to Treat Population



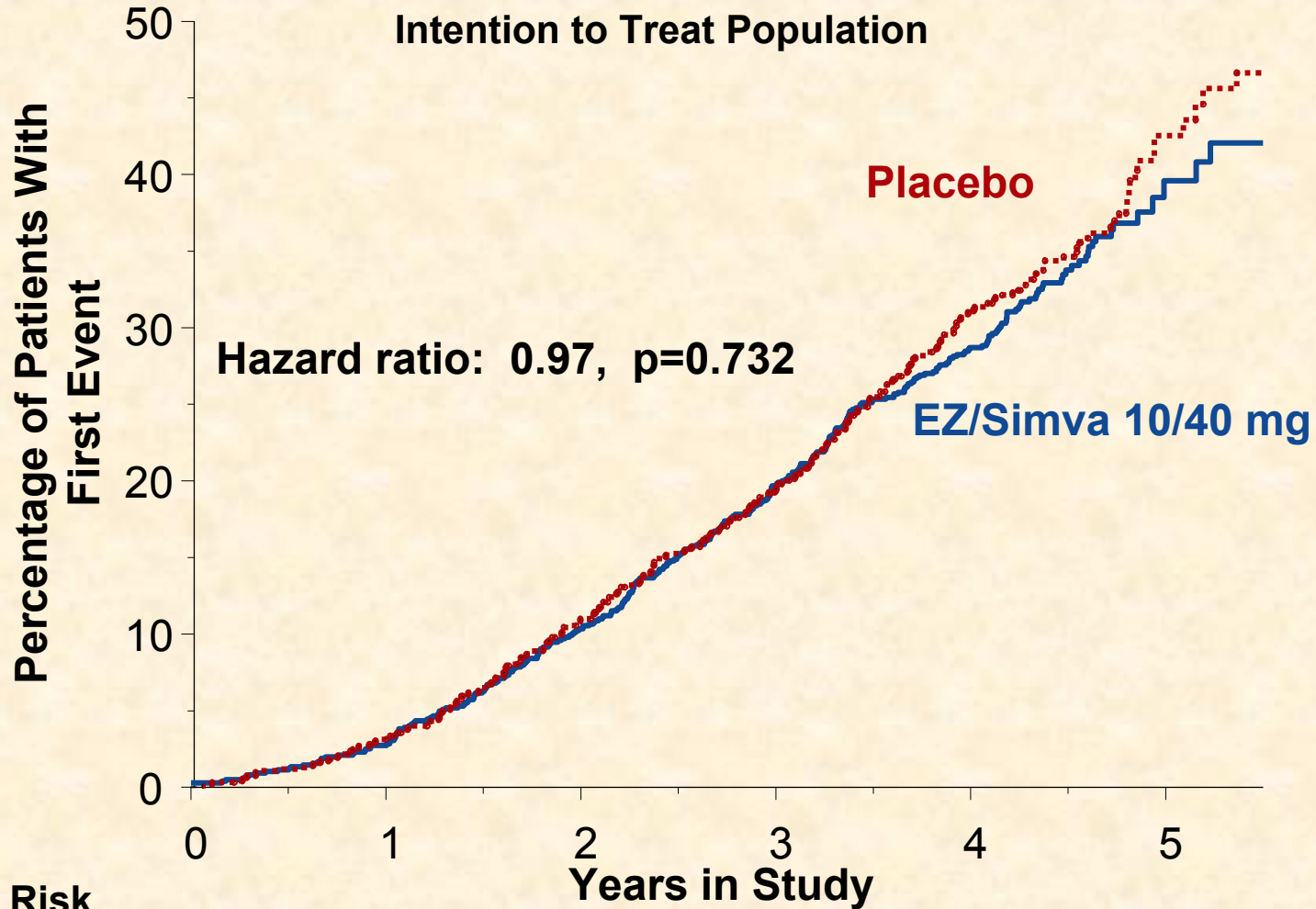
# Primary Endpoint MCE



**No. at Risk**

	0	1	2	3	4	5
<b>EZ/Simva 10/40 mg</b>	<b>906</b>	<b>817</b>	<b>713</b>	<b>618</b>	<b>538</b>	<b>53</b>
<b>Placebo</b>	<b>884</b>	<b>791</b>	<b>696</b>	<b>586</b>	<b>586</b>	<b>56</b>

# 2nd EP: Aortic Valve Events

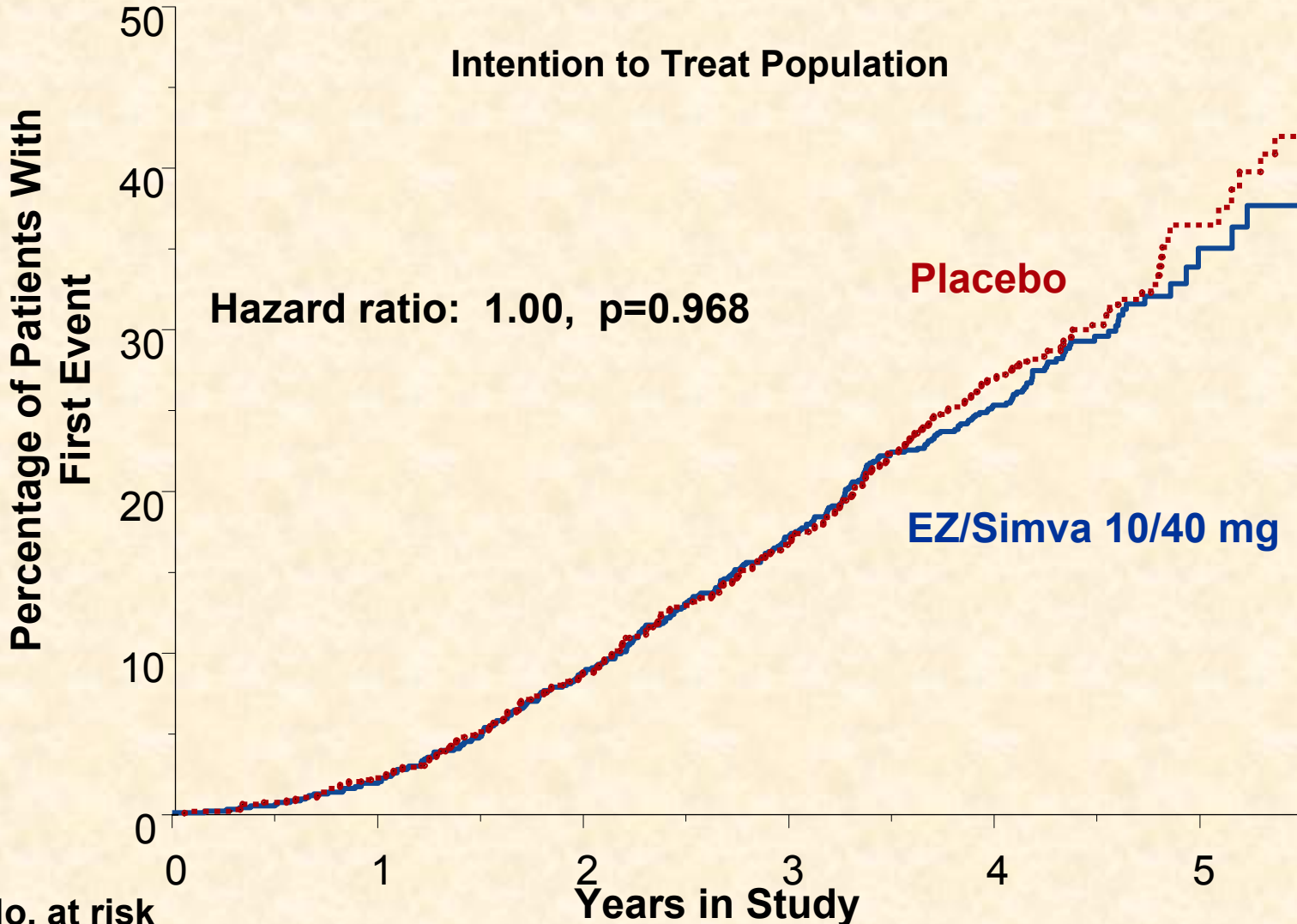


No. at Risk

EZ/Simva 10/40 mg	914	836	732	635	55
Placebo	895	814	725	611	58



# Aortic Valve Replacement

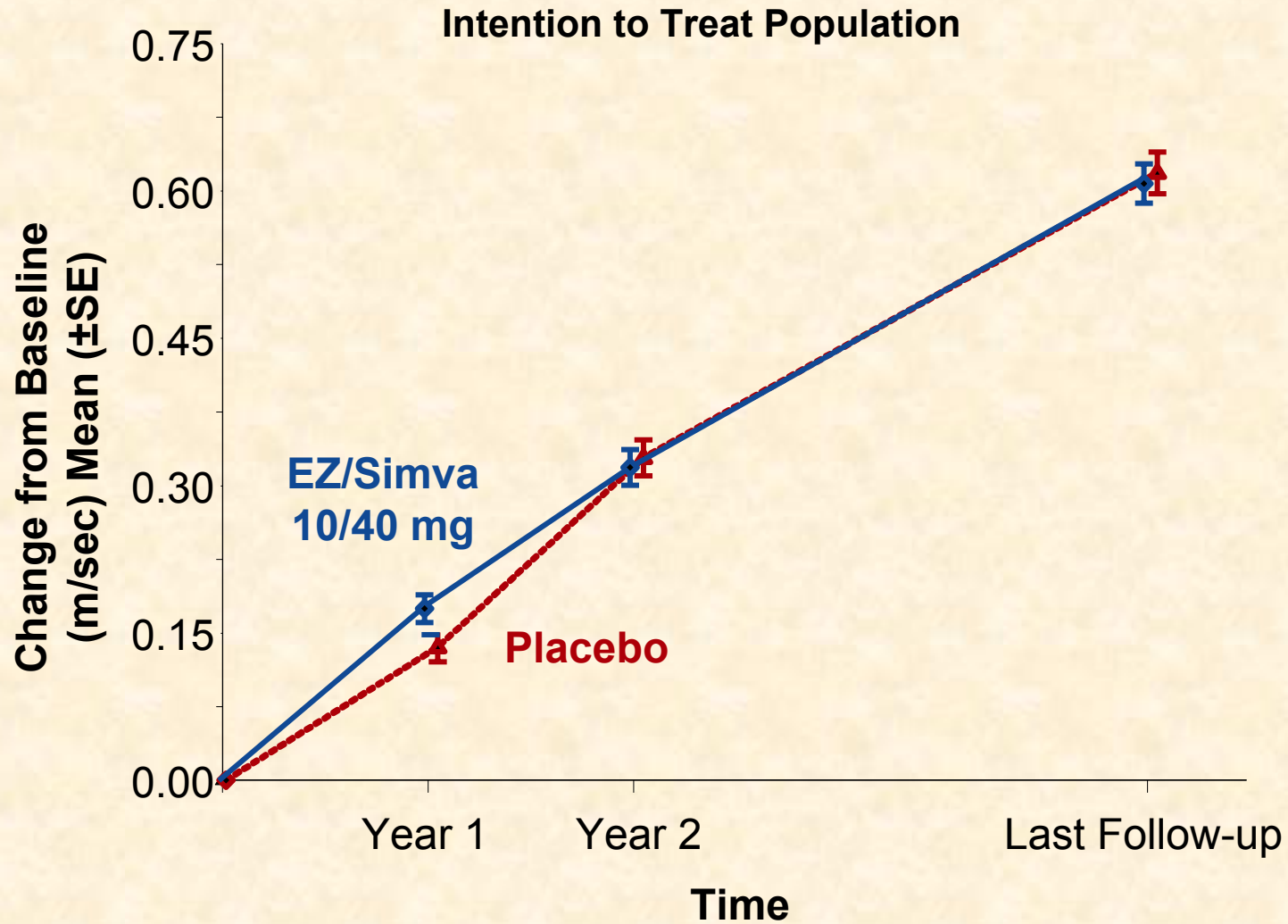


No. at risk

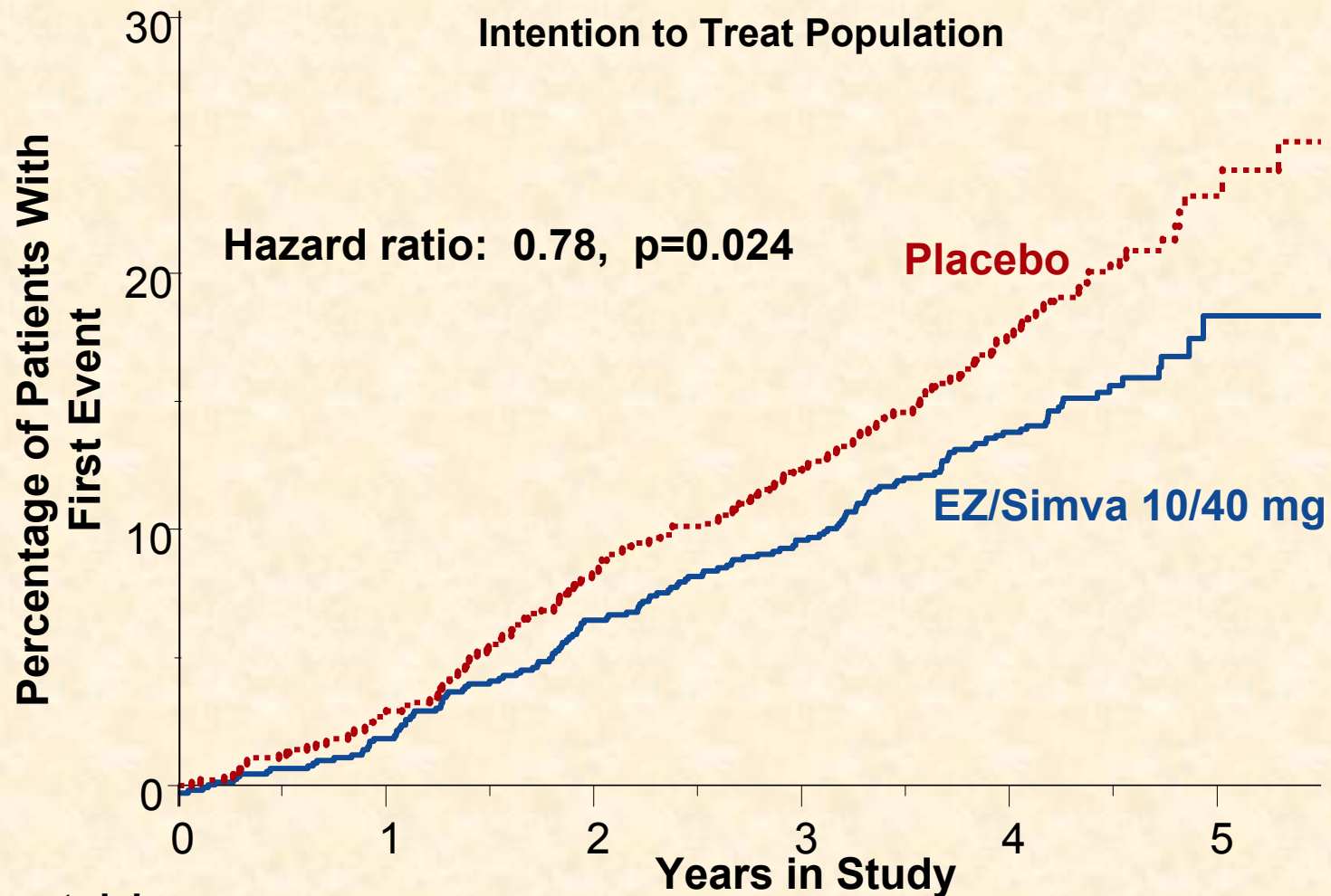
EZ/Simva 10/40 mg	915	837	734	640	55
Placebo	896	816	728	618	61

Rossebo et al. NEJM. 2008;359

# Peak Aortic - Jet Velocity



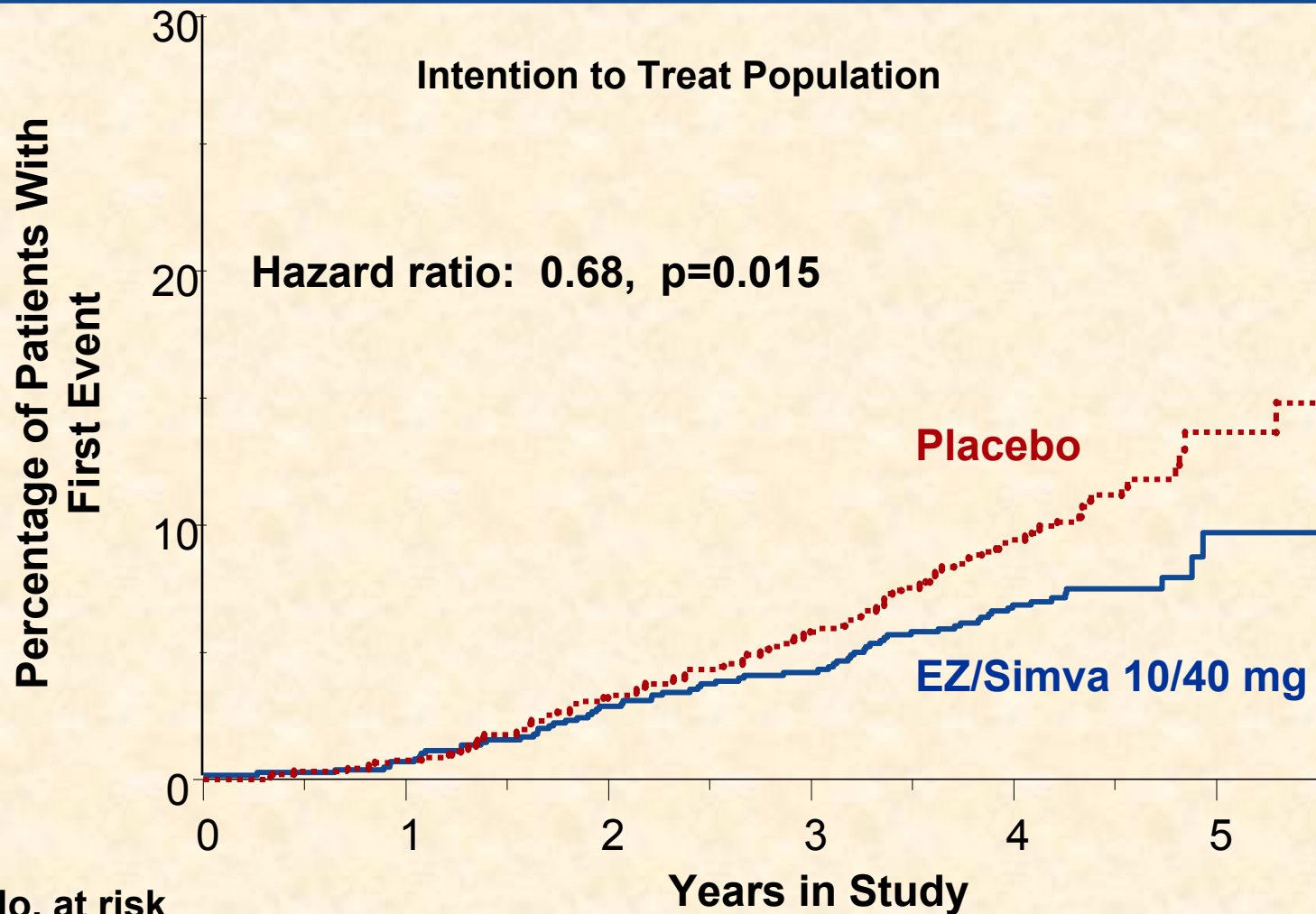
# 2nd EP: Ischemic CV Events



No. at risk

EZ/Simva 10/40 mg	917	867	823	769	76
Placebo	898	838	788	729	76

# Coronary Artery Bypass Grafting (CABG)



No. at risk

EZ/Simva 10/40 mg	925	887	848	797	80
Placebo	909	862	819	761	80

# Clinical Adverse Events (AE)

All Patients as Treated Population

	Placebo N=929	EZ/ Simva N=943*	p=
	n	n	
<b>Any serious AE (SAE)</b>	<b>463</b>	<b>468</b>	
<b>Drug discon. due to SAE</b>	<b>79</b>	<b>77</b>	

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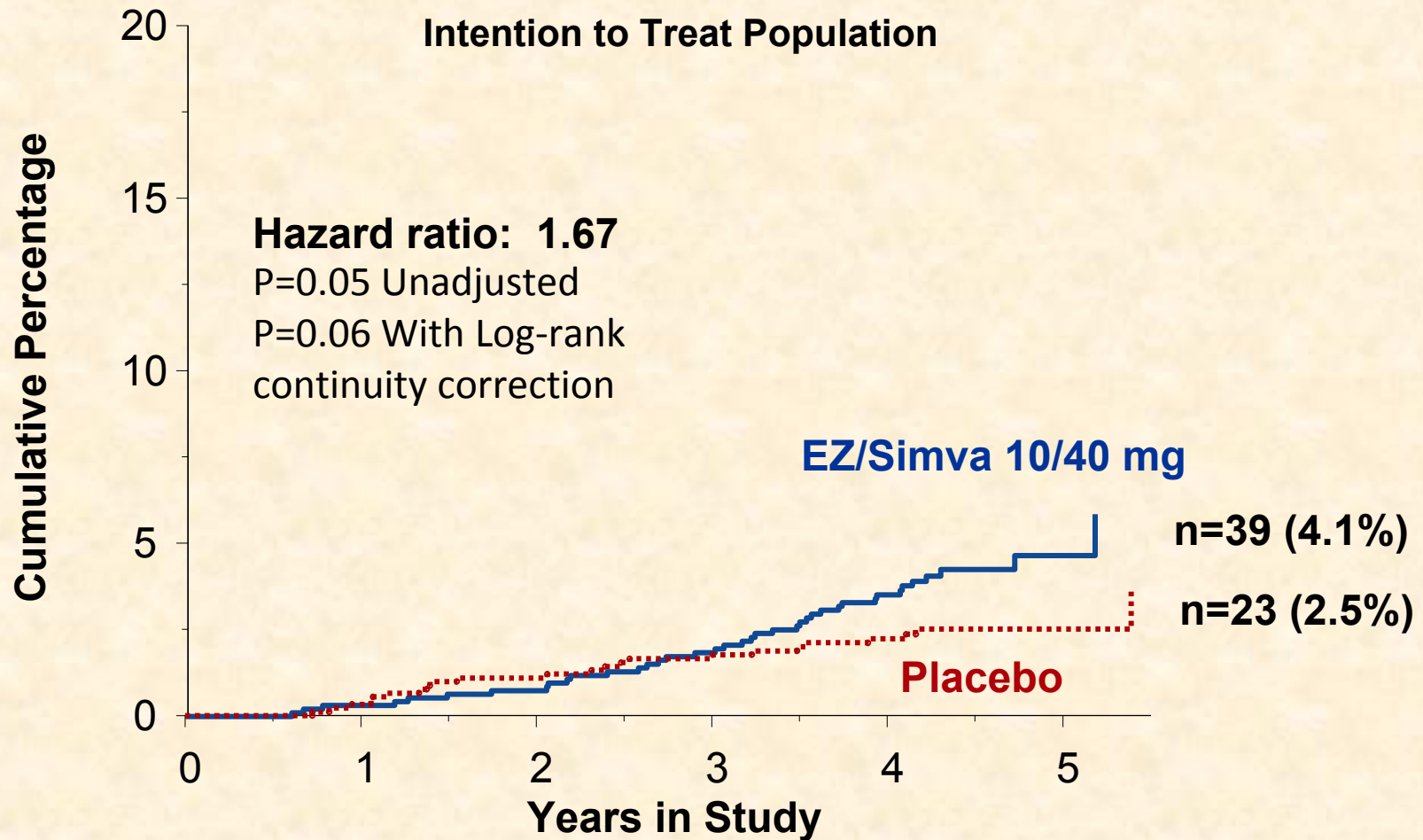
	Placebo	EZ/ Simva		p=
	N=929	N=943*		
	n	n		
<b>Any serious AE (SAE)</b>	<b>463</b>	<b>468</b>		
<b>Drug discon. due to SAE</b>	<b>79</b>	<b>77</b>		
<b>Musculoskeletal AE</b>	<b>181</b>	<b>165</b>		<b>0.28</b>
<b>Myopathy / Rhabdo</b>	<b>0</b>	<b>0</b>		

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<b>Drug discon. due to SAE</b>	<b>79</b>	<b>77</b>		
<b>Musculoskeletal AE</b>	<b>181</b>	<b>165</b>		<b>0.28</b>
<b>Myopathy / Rhabdo</b>	<b>0</b>	<b>0</b>		
<b>New cancer</b>	<b>65</b>	<b>102</b>		<b>0.01</b>
<b>Recurrent, same site</b>	<b>5</b>	<b>3</b>		
<b>Cancer, total</b>	<b>70</b>	<b>105</b>		<b>0.01</b>

# Fatal Cancer



**No. at risk**

<b>EZ/Simva 10/40 mg</b>	<b>930</b>	<b>912</b>	<b>884</b>	<b>855</b>	<b>89</b>
<b>Placebo</b>	<b>916</b>	<b>890</b>	<b>865</b>	<b>835</b>	<b>94</b>



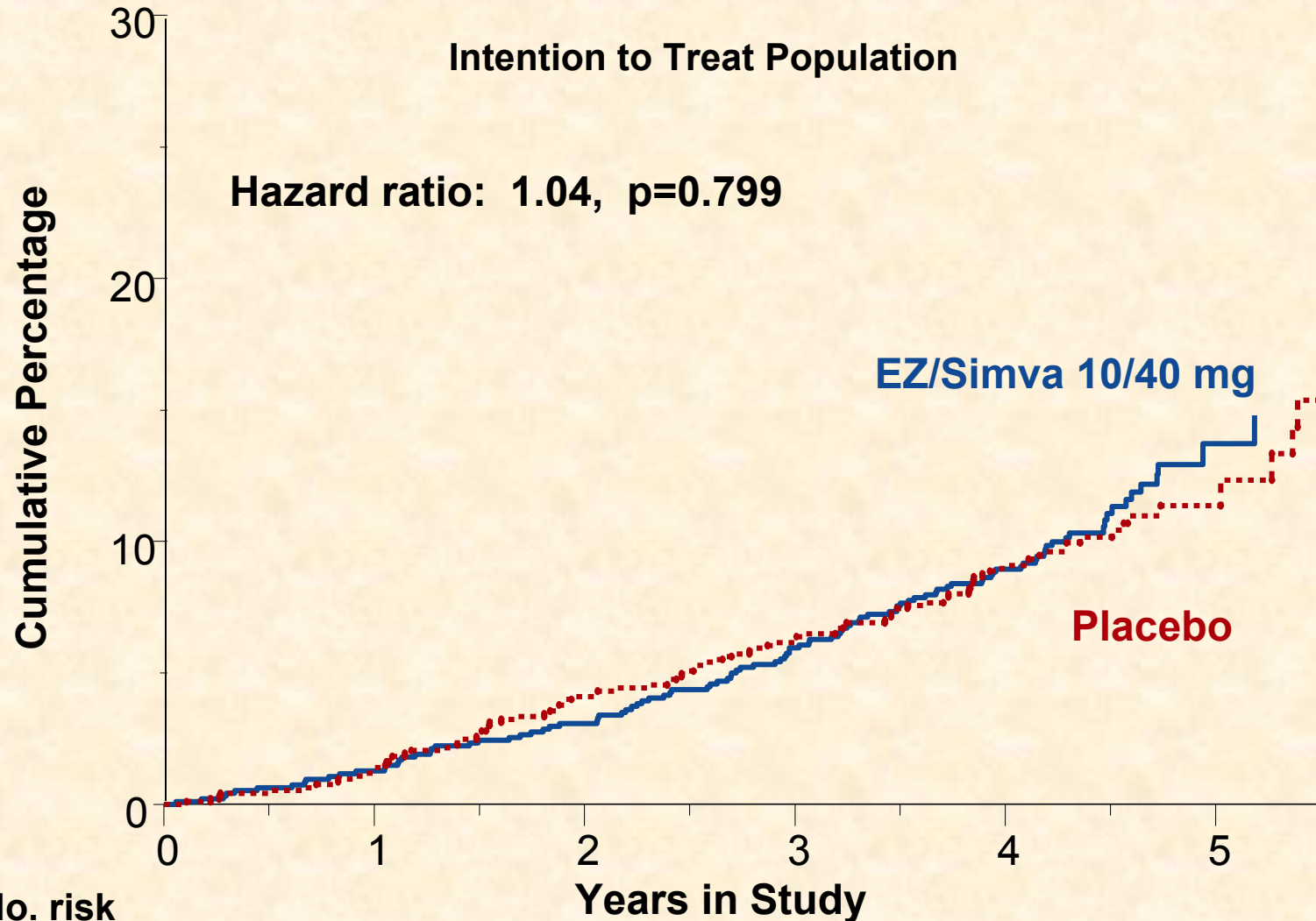
# Incident Cancer

All Patients as Treated Population



Site	Placebo (N=929)	EZ/simva (N=943)
	n	n
Lip, oral pharynx, Oesophagus	1	1
Stomach	1	5
Large bowel / intestine	8	9
Pancreas	1	4
Liver gallbladder, bile ducts	3	2
Lung	10	7
Other respiratory	0	1
Skin (any)	8	18
Breast	5	8
Prostate	13	21
Kidney	2	2
Bladder	7	7
Genital	4	4
Hemathological	5	7
Other/unspecified	7	12

# All Cause Mortality



No. risk

<b>EZ/Simva 10/40 mg</b>	<b>930</b>	<b>912</b>	<b>884</b>	<b>855</b>	<b>89</b>
<b>Placebo</b>	<b>916</b>	<b>890</b>	<b>865</b>	<b>835</b>	<b>94</b>

# Major CV Events - Components

ITT Population

