What to know when treating your high risk elderly patients

Kosin University Gospel Hospital

Cardiologist

Jung Ho Heo

Today's Contents

1. **The need for prevention of cardiovascular diseases in elderly patients**

2. **LDL-C management guidelines for elderly patients**

3. **Difficulty of active statin prescription for elderly patients**

4. **Benefits of using Ezetimibe**

Rapid aging of Korean society

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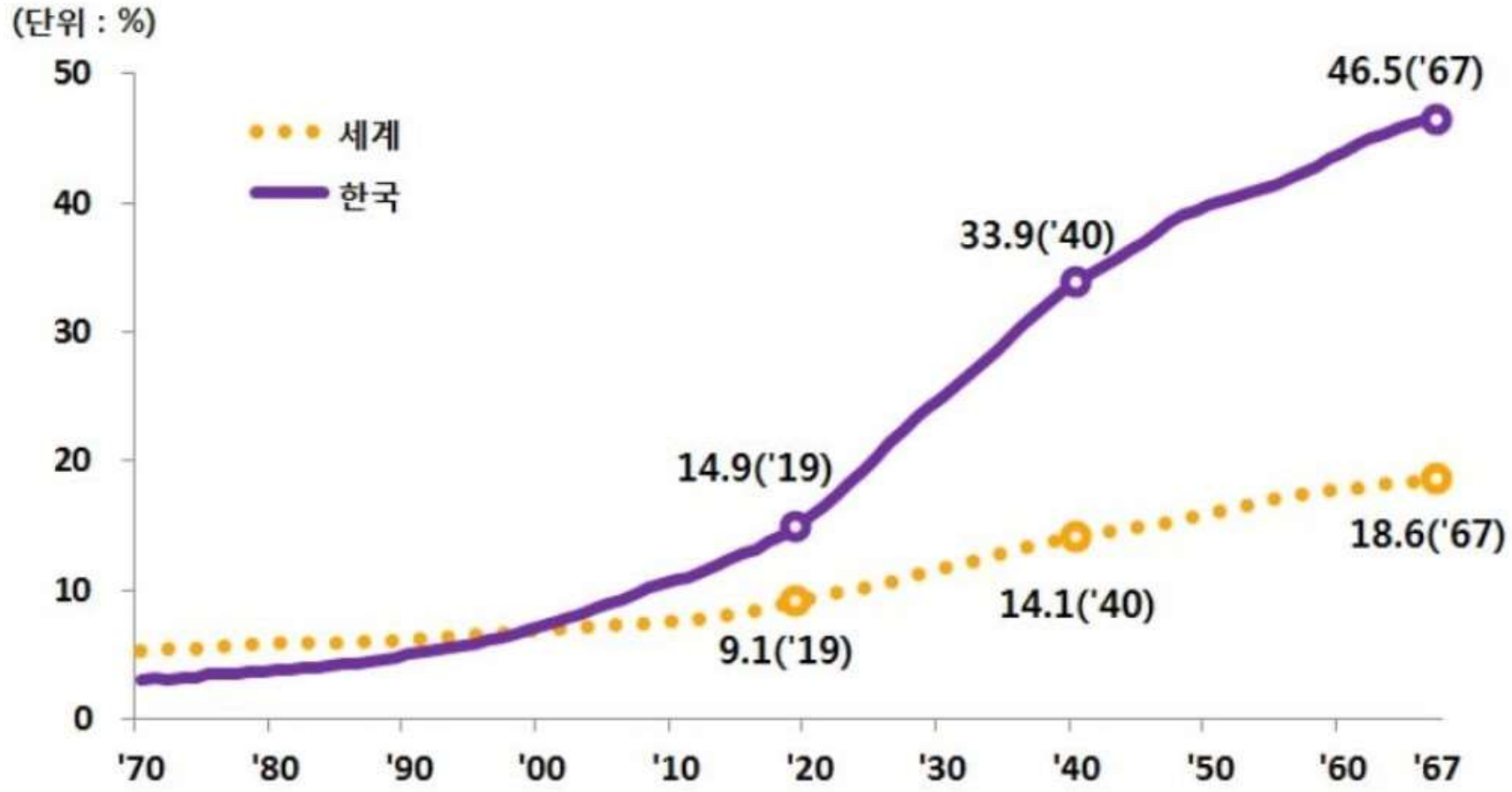
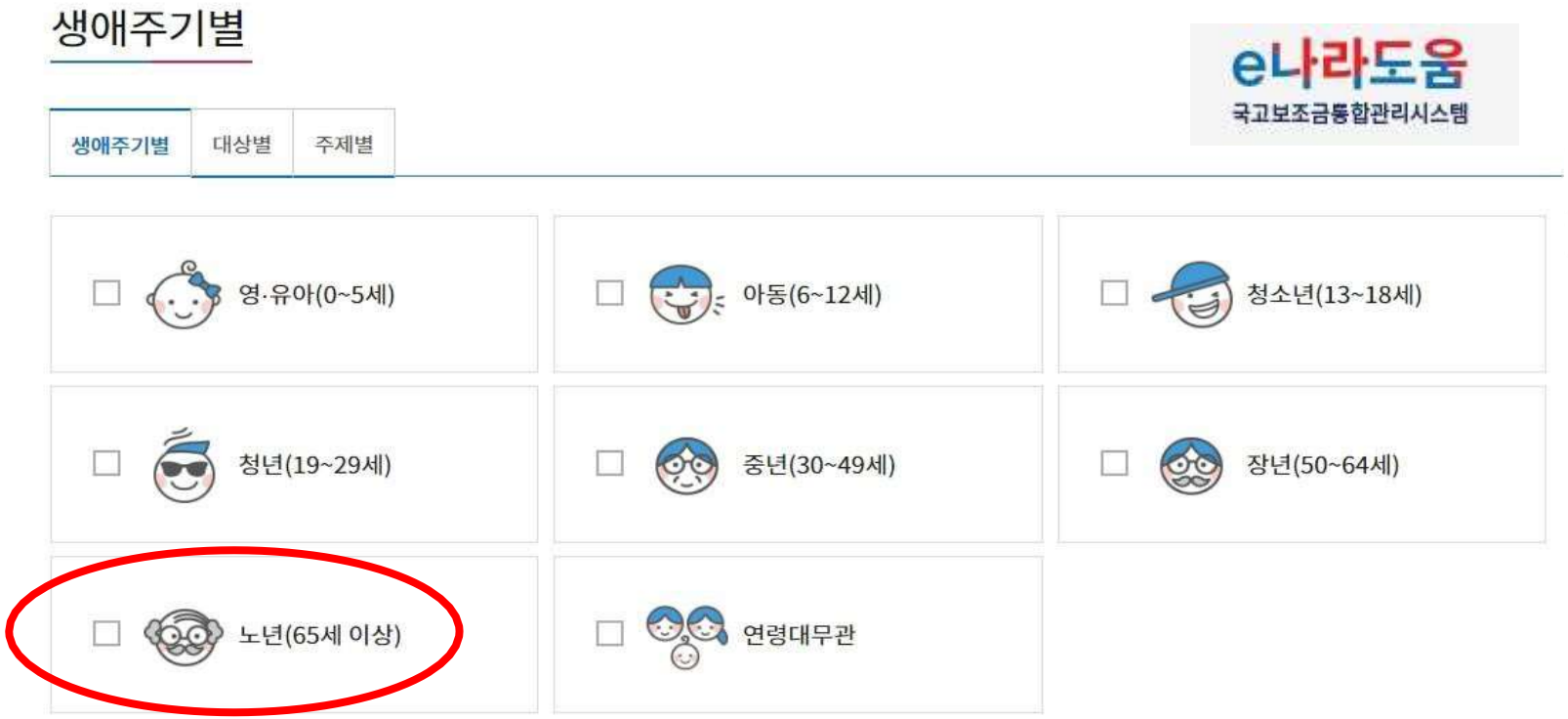


1. 통계청 2019

Definition of elderly people



Young age : 20 – 39 yrs
Middle age : 40 – 65 yrs
Old age : 65 – 75 yrs
Eldery : > 75 yrs (> 80 yrs)

- **Old age : > 65 yrs**
  - 2018 : 14.0%
  - 2026 : >20%

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Prevalence of Dyslipidemia

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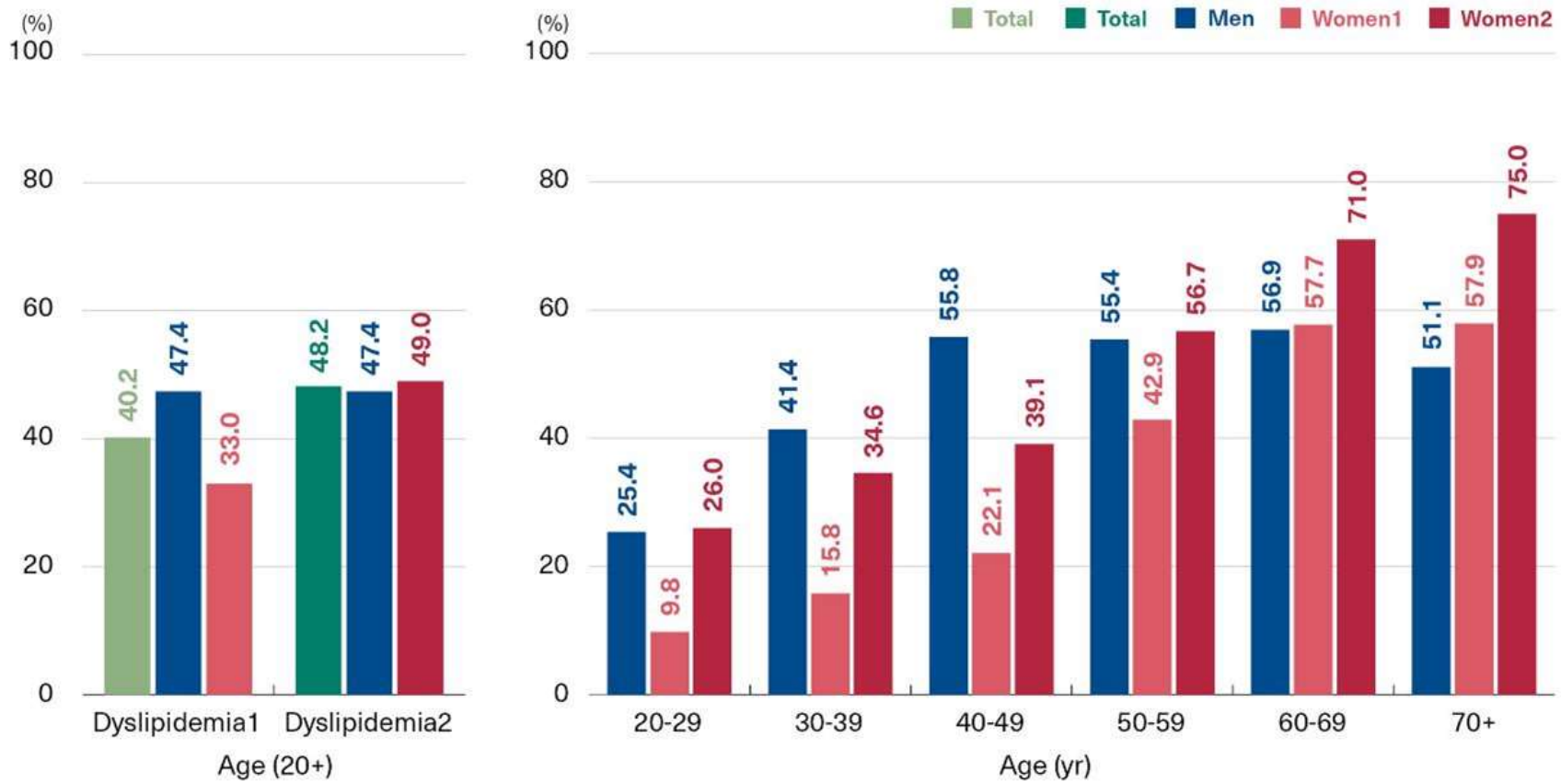

Data: 2016-2020 KNHANES; adults aged 20+ years
Dyslipidemia 1: hyper-LDL-cholesterolemia, hypertriglyceridemia, or hypo-HDL-cholesterolemia (<40 mg/dL in men and women).
Dyslipidemia 2: hyper-LDL-cholesterolemia, hypertriglyceridemia, or hypo-HDL-cholesterolemia (<40 mg/dL in men; <50 mg/dL in women).

Hyper-LDL cholesterolemia

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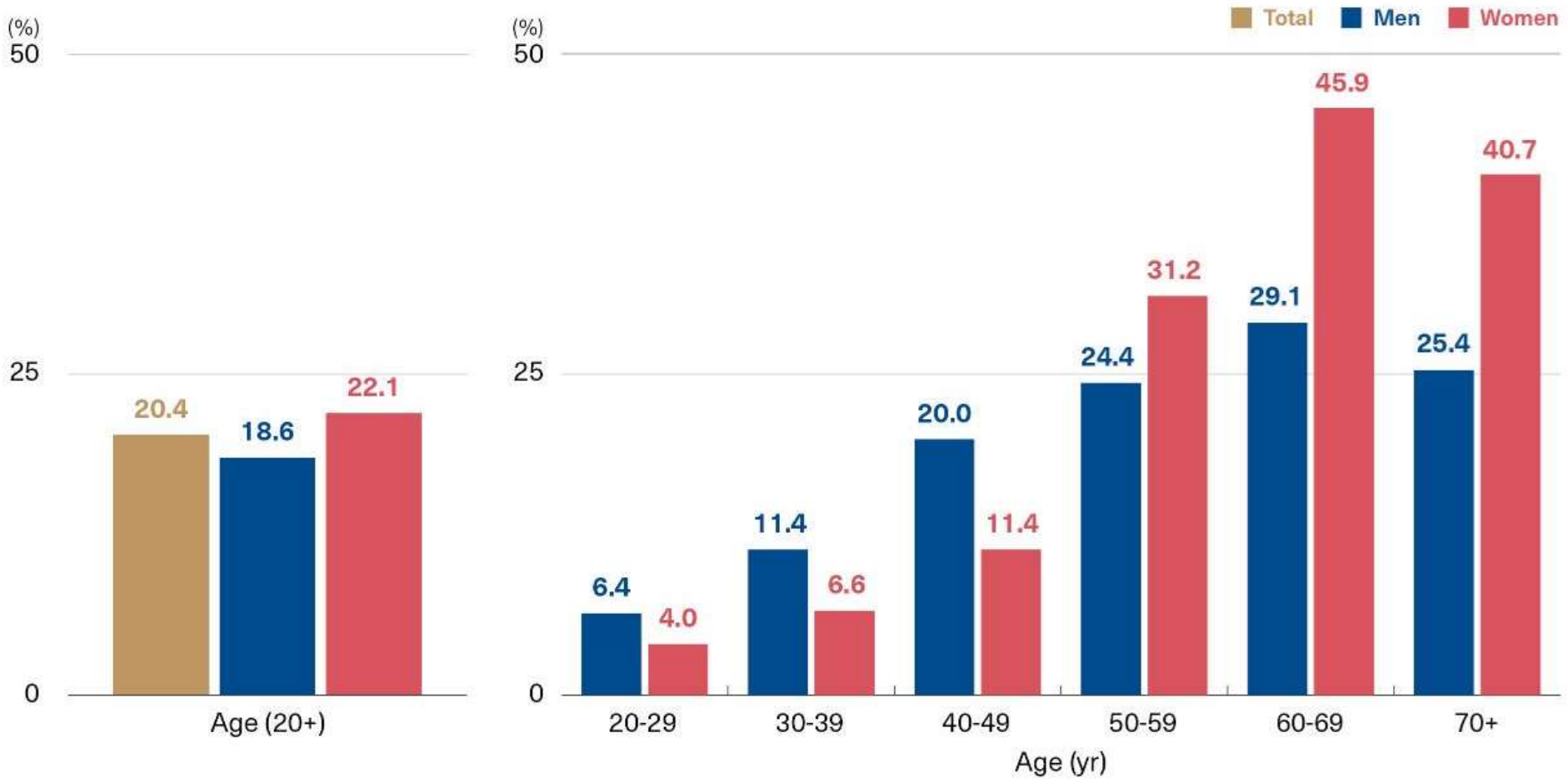


Data: 2016-2020 KNHANES; adults aged 20+ years
Hyper-LDL-cholesterolemia: LDL-cholesterol ≥160 mg/dL or taking a lipid-lowering drug

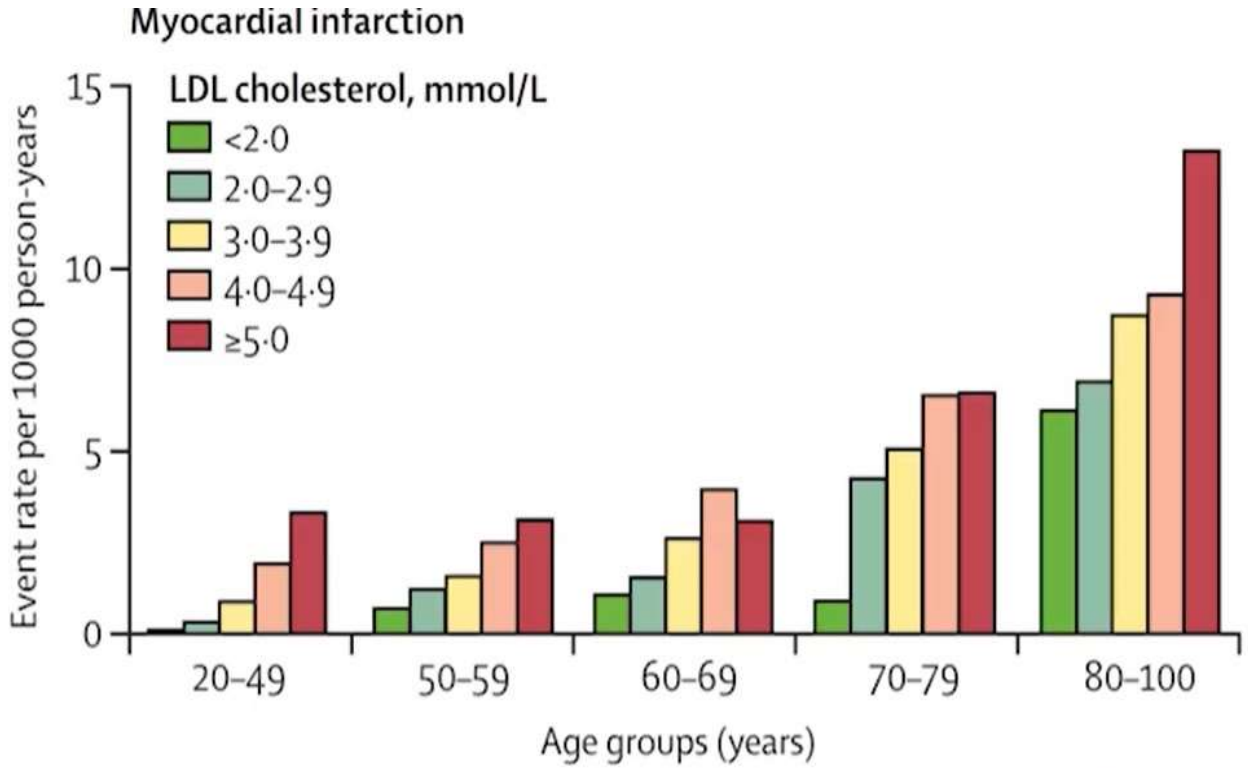
The importance of preventing cardiovascular disease in elderly patients

KR-ATO-00075 04/2021

Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort

Martin Bødtker Mortensen, Børge Grønne Nordestgaard

Copenhagen General Population Study
91,131 individuals without ASCVD, diabetes and statin use
During 8-years follow-up, 1515 MI and 3389 ASCVD events occured



1. LANCET. 2020 NOV 21;396(10263):1644-1652. DOI: 10.1016/S0140-6736(20)32233-9

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PROSPER TRIAL

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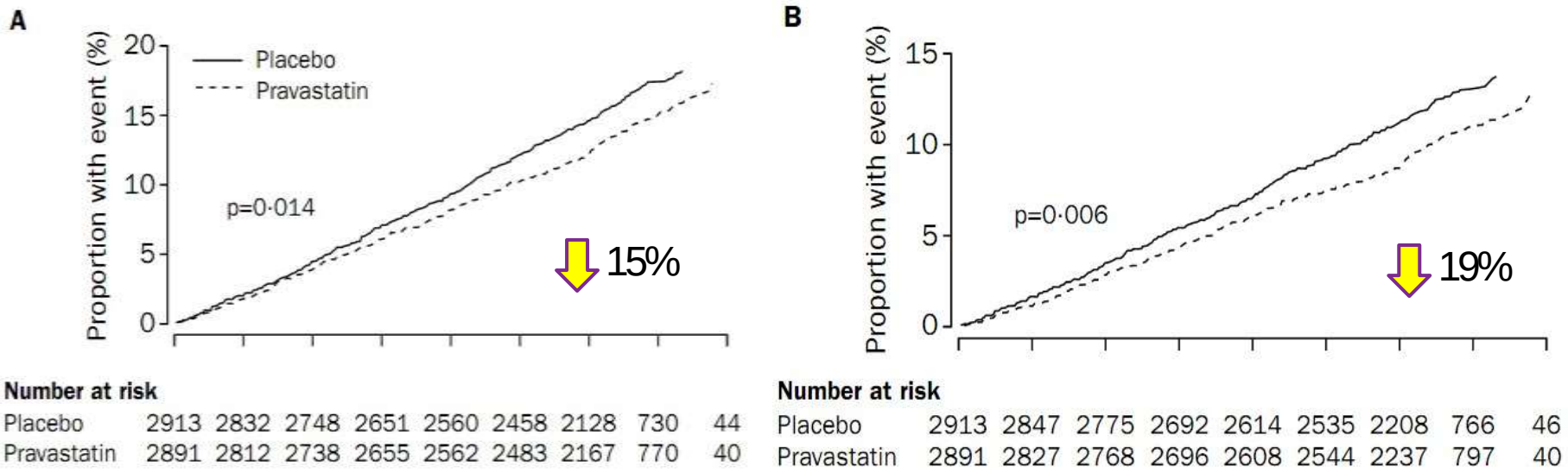
Pravastatin 40 mg vs. Placebo



CV death, MI, stroke

CV death, MI

Lancet. 2002;360:1623-30.

PROSPER TRIAL

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	Pravastatin	Placebo
Secondary prevention	**(n=1306)**	**(n=1259)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	227	273
CHD death, non-fatal MI	166	211
Fatal and non-fatal stroke	74	69
TIA	47	64
Primary prevention	**(n=1585)**	**(n=1654)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	181	200
CHD death, non-fatal MI	126	145
Fatal and non-fatal stroke	61	62
TIA	30	38

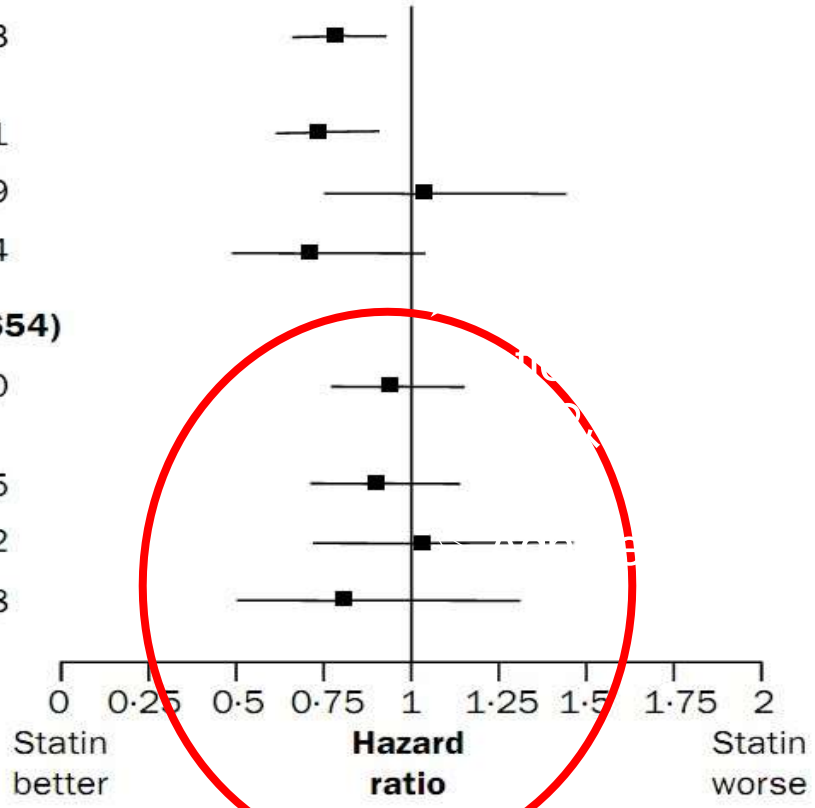

Figure 4: **Major cardiovascular outcomes, according to primary or secondary prevention status of participants**

Lancet. 2002;360:1623-30.

TNT TRIAL

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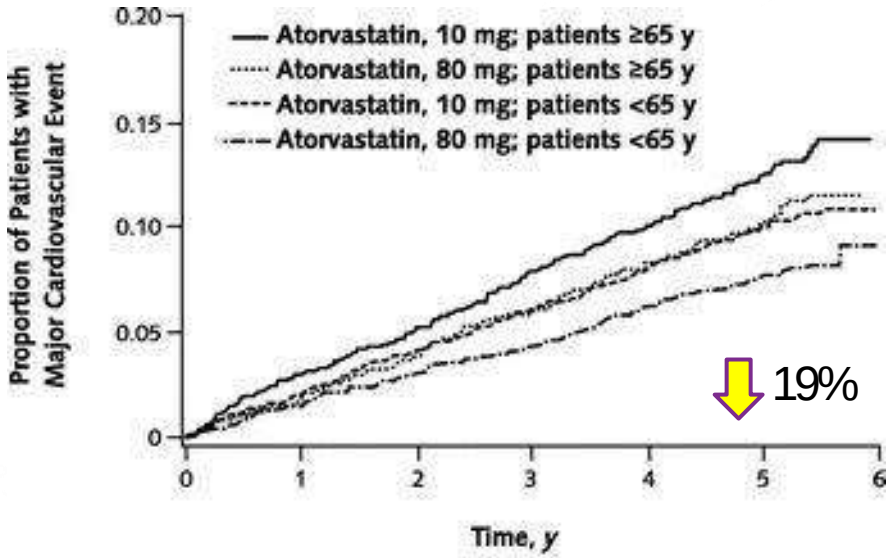
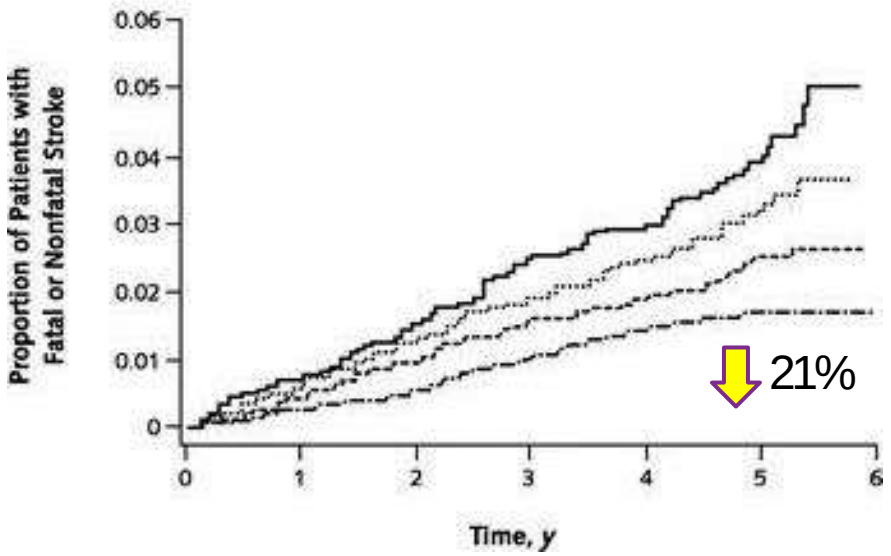


Major CV event



Fatal or nonfatal Stroke

Ann Intern Med. 2007;147:1-9.

JUPITER TRIAL – SECONDARY ANALYSIS

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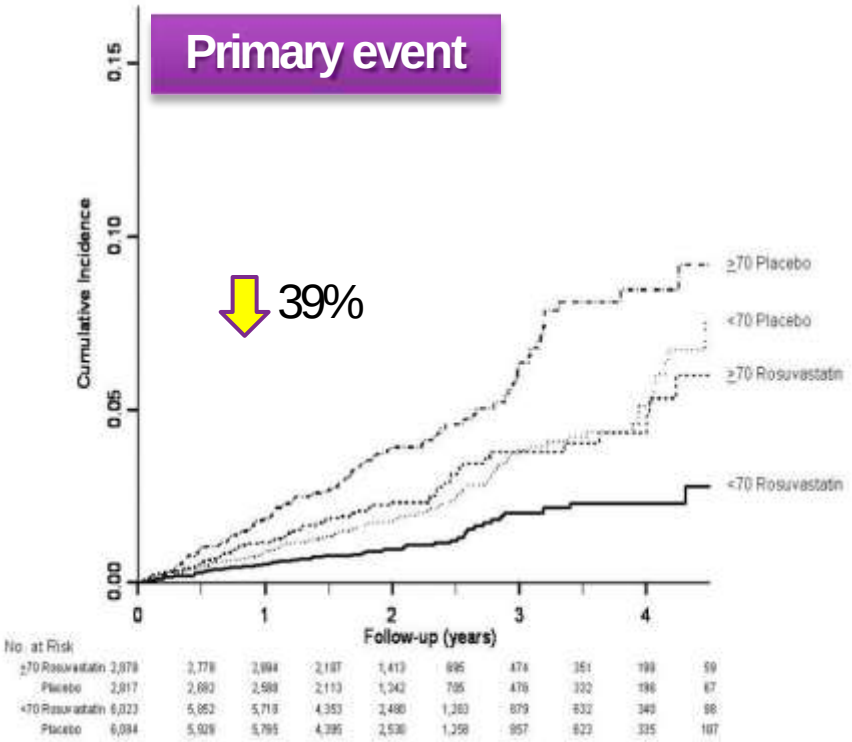
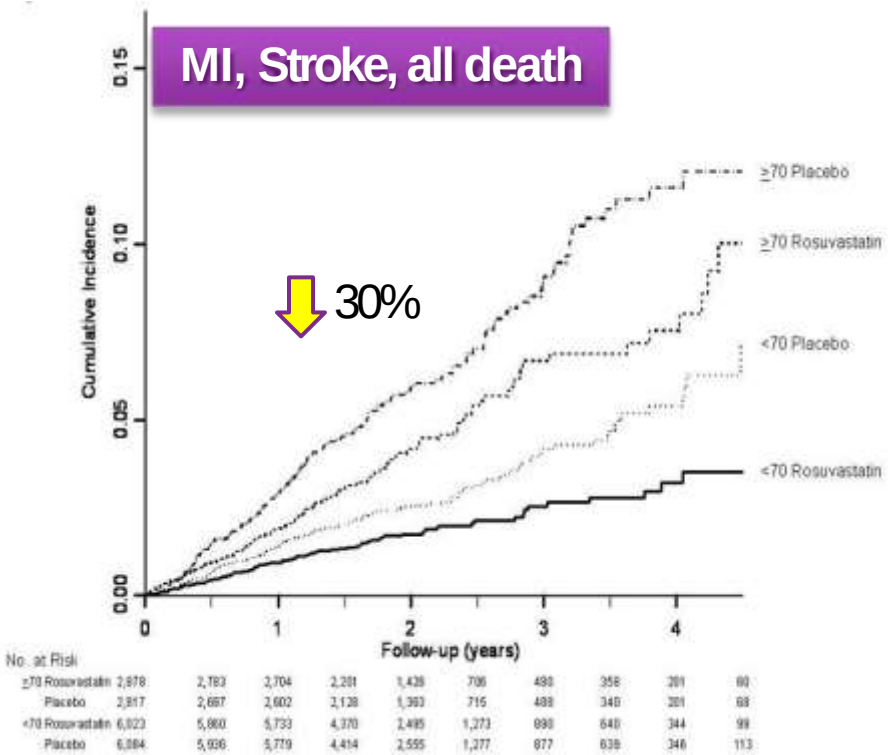
Primary event



MI, Stroke, all death



Ann Intern Med. 2010;152:488-96.

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CLINICAL PRACTICE GUIDELINE

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Recommendations for Older Adults
Referenced studies that support recommendations are summarized in Online Data Supplements 18 and 19.

COR	LOE	RECOMMENDATIONS
IIb	B-R	1. In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable (S4.4.4.1-1–S4.4.4.1-8)
IIb	B-R	2. In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy (S4.4.4.1-9).
IIb	B-R	3. In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy (S4.4.4.1-10, S4.4.4.1-11).

ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

KR-ATO-00075 04/2021

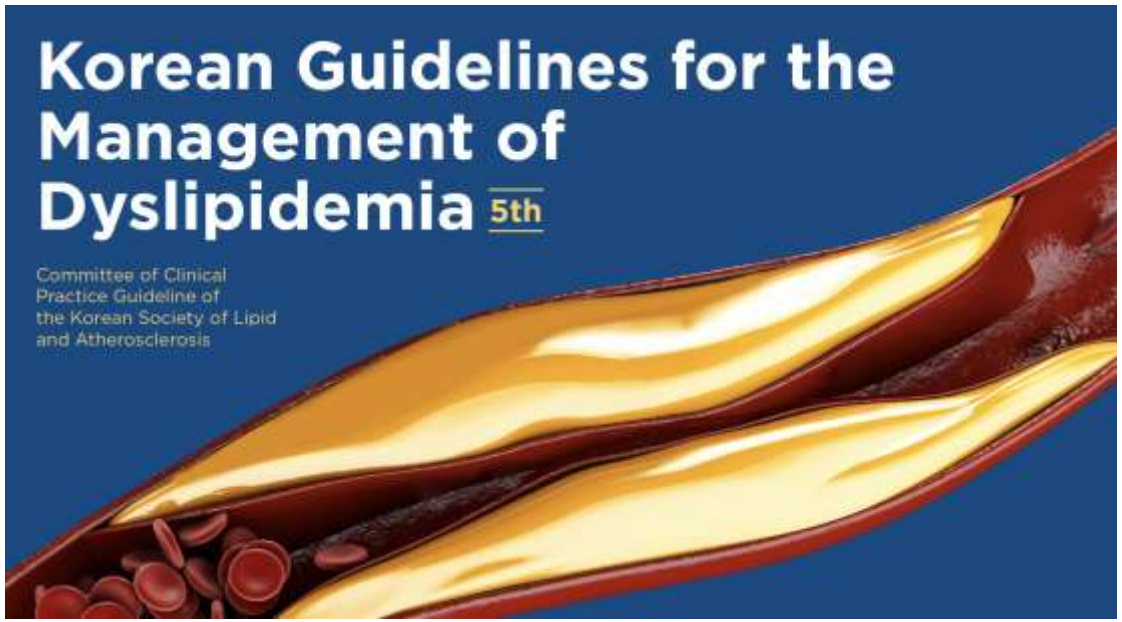
2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)

Recommendations	Class[a]	Level[b]
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.[217]	I	A
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75 years.[217]	I	A
Initiation of statin treatment for primary prevention in older people aged >75 years may be considered, if at high-risk or above.[217]	IIb	B
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C

©ESC 2019



5. 노인의 이상지질혈증

권고안

내용	권고 등급	근거수준
심뇌혈관 질환이 있는 노인에서 스타틴 치료를 권고한다	I	A
75세 이하의 노인에서 심혈관 위험도에 따라 일차예방 목적으로 스타틴을 권고한다	I	A
75세 초과 노인에서의 일차예방 목적의 스타틴 치료는 고위험군에서 고려할 수 있다	II	B
신기능의 저하, 스타틴과의 약물 상호작용이 있는 약물의 복용, 또는 취약한 노인에서는 저용량의 스타틴으로 시작하며 LDL 콜레스테롤 목표에 도달하도록 증량할 것을 권고한다	I	C

KR-ATO-00075 04/2021

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

*Cholesterol Treatment Trialists' Collaboration**

Summary

Background Statin therapy has been shown to reduce major vascular events and vascular mortality in a wide range of individuals, but there is uncertainty about its efficacy and safety among older people. We undertook a meta-analysis of data from all large statin trials to compare the effects of statin therapy at different ages.

Methods In this meta-analysis, randomised trials of statin therapy were eligible if they aimed to recruit at least 1000 participants with a scheduled treatment duration of at least 2 years. We analysed individual participant data from 22 trials (n=134 537) and detailed summary data from one trial (n=12 705) of statin therapy versus control, plus individual participant data from five trials of more intensive versus less intensive statin therapy (n=39 612). We subdivided participants into six age groups (55 years or younger, 56–60 years, 61–65 years, 66–70 years, 71–75 years, and older than 75 years). We estimated effects on major vascular events (ie, major coronary events, strokes, and coronary revascularisations), cause-specific mortality, and cancer incidence as the rate ratio (RR) per 1·0 mmol/L reduction in LDL cholesterol. We compared proportional risk reductions in different age subgroups by use of standard χ^2 tests for heterogeneity when there were two groups, or trend when there were more than two groups.

Findings 14 483 (8%) of 186 854 participants in the 28 trials were older than 75 years at randomisation, and the median follow-up duration was 4·9 years. Overall, statin therapy or a more intensive statin regimen produced a 21% (RR 0·79, 95% CI 0·77–0·81) proportional reduction in major vascular events per 1·0 mmol/L reduction in LDL cholesterol. We observed a significant reduction in major vascular events in all age groups. Although proportional reductions in major vascular events diminished slightly with age, this trend was not statistically

Lancet 2019; 393: 407–15

See Comment page 379

*Members are listed at the end of the Article

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Lancet. 2019;393:407-15.

CTT COLLABORATION – META ANALYSIS

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more than 75 years

- Median 4.9 yrs f/up

ALL

	Statin or more intensive	Control or less intensive	
≤55 years	2217 (2·7%)	2778 (3·4%)	0·75 (0·70–0·81)
>55 to ≤60 years	1741 (2·6%)	2107 (3·2%)	0·80 (0·74–0·87)
>60 to ≤65 years	2238 (2·8%)	2723 (3·5%)	0·80 (0·74–0·86)
>65 to ≤70 years	2263 (3·0%)	2867 (3·9%)	0·76 (0·71–0·82)
>70 to ≤75 years	1993 (3·8%)	2339 (4·5%)	0·81 (0·74–0·88)
>75 years	1051 (4·5%)	1153 (5·0%)	0·87 (0·77–0·99)
Total	**11 503 (3·0%)**	**13 967 (3·7%)**	**0·79 (0·77–0·81)**

Trend test χ^2_1=3·56 (p=0·06)

99% CI 95% CI

B

Exclude HF & dialysis

≤55 years	2129 (2·7%)	2680 (3·4%)	0·75 (0·69–0·81)
>55 to ≤60 years	1637 (2·5%)	2018 (3·2%)	0·78 (0·72–0·85)
>60 to ≤65 years	2083 (2·7%)	2549 (3·4%)	0·79 (0·74–0·86)
>65 to ≤70 years	2065 (2·9%)	2666 (3·8%)	0·74 (0·69–0·80)
>70 to ≤75 years	1802 (3·7%)	2134 (4·5%)	0·80 (0·73–0·87)
>75 years	802 (4·1%)	893 (4·7%)	0·82 (0·70–0·95)
Total	**10 518 (2·9%)**	**12 940 (3·7%)**	**0·77 (0·75–0·79)**

Trend test χ^2_1=0·98 (p=0·3)

99% CI 95% CI

0·5 0·75 1 1·5

Statin or more intensive better

Control or less intensive better

Statin effect by age Quitile (for major vascular events – MI, revascularization, stroke, coro nary death)

- all → 21%
- >75 → 13%

- all → 23%
- >75 → 18%

Lancet. 2019;393:407-15.

CTT COLLABORATION – META ANALYSIS

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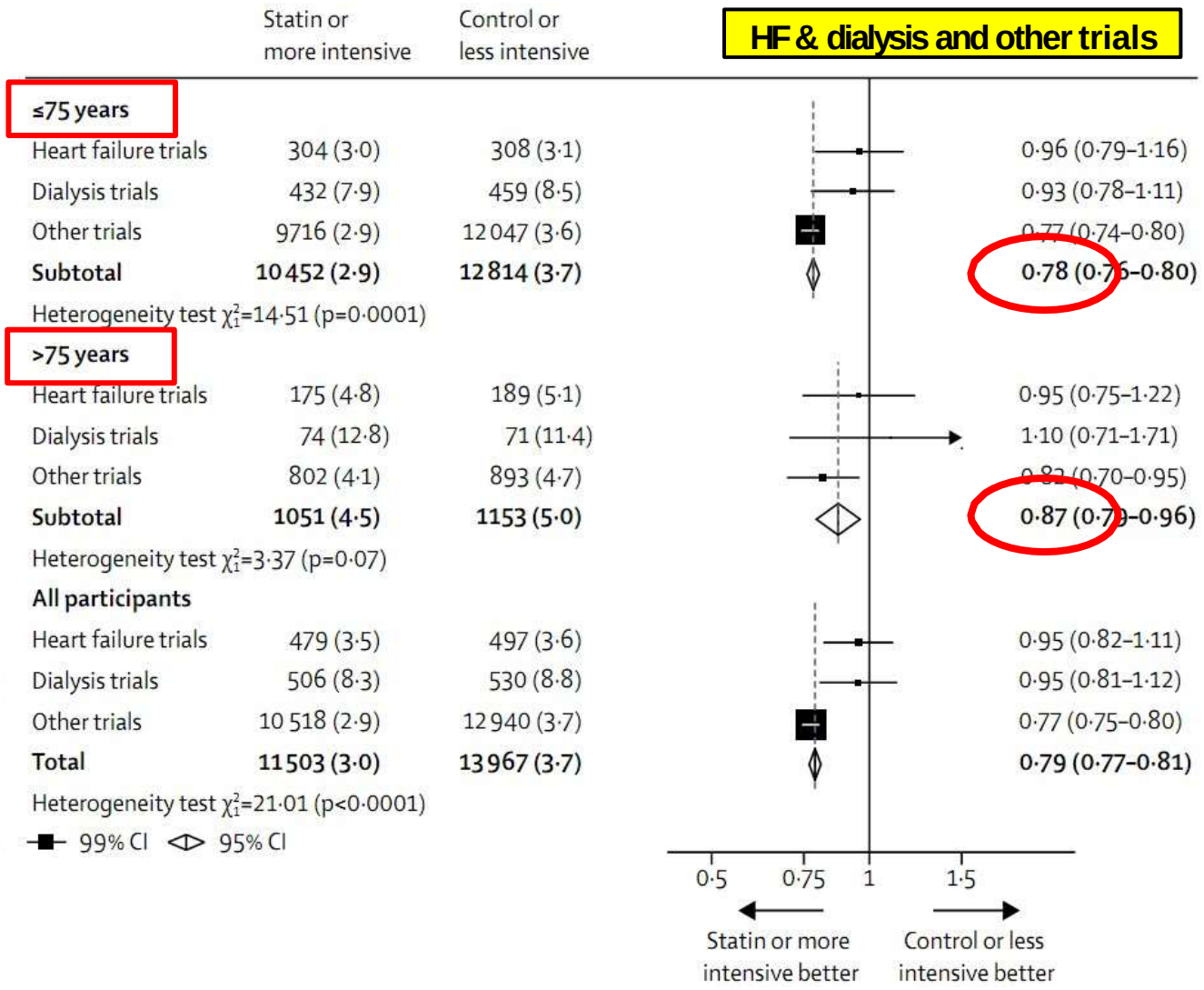
	Statin or more intensive	Control or less intensive	
≤75 years			
Heart failure trials	304 (3·0)	308 (3·1)	0·96 (0·79–1·16)
Dialysis trials	432 (7·9)	459 (8·5)	0·93 (0·78–1·11)
Other trials	9716 (2·9)	12 047 (3·6)	0·77 (0·74–0·80)
Subtotal	**10 452 (2·9)**	**12 814 (3·7)**	**0·78 (0·76–0·80)**
Heterogeneity test χ^2_1=14·51 (p=0·0001)			
>75 years			
Heart failure trials	175 (4·8)	189 (5·1)	0·95 (0·75–1·22)
Dialysis trials	74 (12·8)	71 (11·4)	1·10 (0·71–1·71)
Other trials	802 (4·1)	893 (4·7)	0·82 (0·70–0·95)
Subtotal	**1051 (4·5)**	**1153 (5·0)**	**0·87 (0·79–0·96)**
Heterogeneity test χ^2_1=3·37 (p=0·07)			
All participants			
Heart failure trials	479 (3·5)	497 (3·6)	0·95 (0·82–1·11)
Dialysis trials	506 (8·3)	530 (8·8)	0·95 (0·81–1·12)
Other trials	10 518 (2·9)	12 940 (3·7)	0·77 (0·75–0·80)
Total	**11 503 (3·0)**	**13 967 (3·7)**	**0·79 (0·77–0·81)**
Heterogeneity test χ^2_1=21·01 (p<0·0001)			



Above 75 years

Lancet. 2019;393:407-15

CTT COLLABORATION – META ANALYSIS

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	Statin or more intensive	Control or less intensive	
Participants without vascular disease			
≤55 years	290 (0·8)	408 (1·2)	0·68 (0·56–0·83)
>55 to ≤60 years	350 (1·0)	415 (1·2)	0·81 (0·67–0·99)
>60 to ≤65 years	416 (1·1)	545 (1·5)	0·73 (0·61–0·87)
>65 to ≤70 years	374 (1·2)	581 (1·8)	0·61 (0·51–0·73)
>70 to ≤75 years	400 (2·1)	462 (2·4)	0·84 (0·70–1·01)
>75 years	295 (2·7)	308 (2·8)	0·92 (0·7[illegible]–1·16)
Total	**2125 (1·3)**	**2719 (1·6)**	**0·75 (0·71–0·80)**
Trend test χ^2_1=3·85 (p=0·05)			
Participants with vascular disease			
≤55 years	1927 (4·0)	2370 (5·1)	0·77 (0·71–0·83)
>55 to ≤60 years	1391 (4·2)	1692 (5·2)	0·80 (0·73–0·88)
>60 to ≤65 years	1822 (4·4)	2178 (5·3)	0·81 (0·75–0·88)
>65 to ≤70 years	1889 (4·3)	2286 (5·5)	0·79 (0·73–0·86)
>70 to ≤75 years	1593 (4·8)	1877 (5·8)	0·80 (0·73–0·88)
>75 years	756 (6·0)	845 (6·8)	0·85 (0·7[illegible]–0·98)
Total	**9378 (4·4)**	**11248 (5·4)**	**0·80 (0·77–0·82)**
Trend test χ^2_1=1·42 (p=0·2)			

99% CI ◇ 95% CI

0·5 0·75 1 1·5

Statin or more intensive better

Control or less intensive better

Lancet. 2019;393:407-15

KR-ATO-00075 04/2021

Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials

TIMI study group

Baris Gencer, Nicholas A Marston, KyungAh Im, Christopher P Cannon, Peter Sever, Anthony Keech, Eugene Braunwald, Robert P Giugliano, Marc S Sabatine

Lancet 2020; 396: 1637–43
Published Online
November 10, 2020

Summary

Background The clinical benefit of LDL cholesterol lowering treatment in older patients remains debated. We aimed to summarise the evidence of LDL cholesterol lowering therapies in older patients.

Findings Data from six articles were included in the systematic review and meta-analysis, which included 24 trials from the Cholesterol Treatment Trialists' Collaboration meta-analysis plus five individual trials. Among 244 090 patients from 29 trials, 21 492 (8·8%) were aged at least 75 years of whom 11 750 (54·7%) were from statin trials, 6209 (28·9%) from ezetimibe trials, and 3533 (16·4%) from PCSK9 inhibitor trials. Median follow-up ranged from 2·2 years to 6·0 years. LDL cholesterol lowering significantly reduced the risk of major vascular events (n=3519) in older patients by 26% per 1 mmol/L reduction in LDL cholesterol (RR 0·74 [95% CI 0·61–0·89]; p=0·0019), with no statistically significant difference with the risk reduction in patients younger than 75 years (0·85 [0·78–0·92]; $p_{interaction}$=0·37). Among older patients, RRs were not statistically different for statin (0·82 [0·73–0·91]) and non-statin treatment (0·67 [0·47–0·95]; $p_{interaction}$=0·64). The benefit of LDL cholesterol lowering in older patients was observed for each component of the composite, including cardiovascular death (0·85 [0·74–0·98]), myocardial infarction (0·80 [0·71–0·90]), stroke (0·73 [0·61–0·87]), and coronary revascularisation (0·80 [0·66–0·96]).

Lancet. 2020;396:1647-43.

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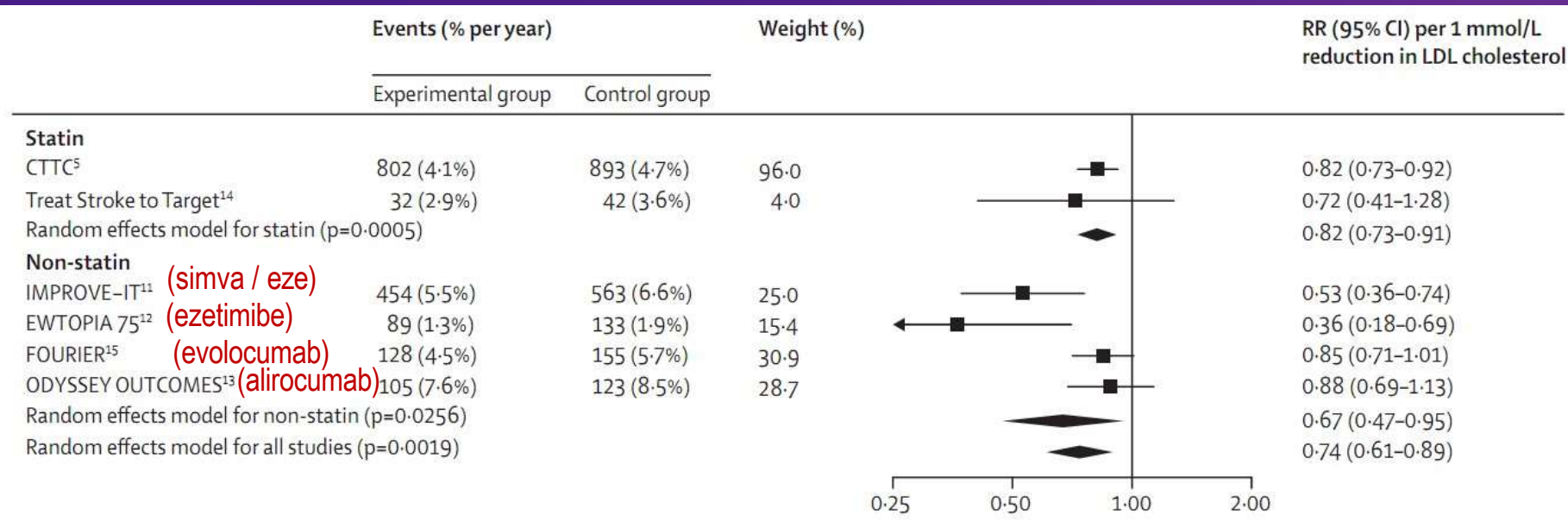

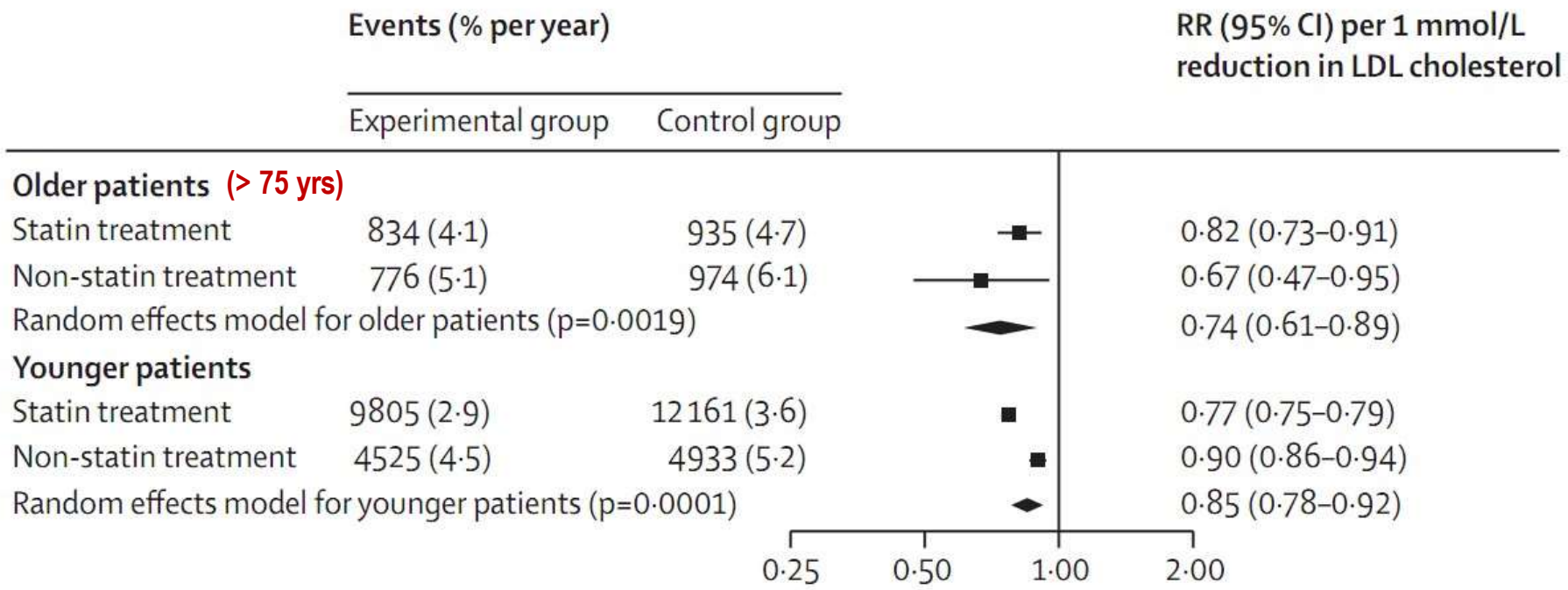

Lancet. 2020;396:1647-43.

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	Events (n)		RR (95% CI) per 1 mmol/L reduction in LDL cholesterol
	Experimental group	Control group	
Major vascular events	1610	1909	0·74 (0·61–0·89)
Cardiovascular death	723	799	0·85 (0·74–0·98)
Myocardial infarction	813	971	0·80 (0·71–0·90)
Any stroke	401	486	0·73 (0·61–0·87)
Coronary revascularisation	428	513	0·80 (066–0·96)

	Events n/N (%)		RR (95% CI) per 1 mmol/L reduction in LDL cholesterol
	Experimental group	Control group	
Statin and non-statin			
Cancer	878	807	1·07 (0·96–1·20)
Non-statin			
Haemorrhagic stroke	27/6589 (0·4%)	26/6677 (0·4%)	0·94 (0·23–3·85)
New-onset diabetes	257/3449 (7·5%)	286/3505 (8·2%)	0·89 (0·77–1·04)
Neurocognitive adverse events	165/5155 (3·2%)	179/5239 (3·4%)	0·93 (0·75–1·16)

Lancet. 2020;396:1647-43.

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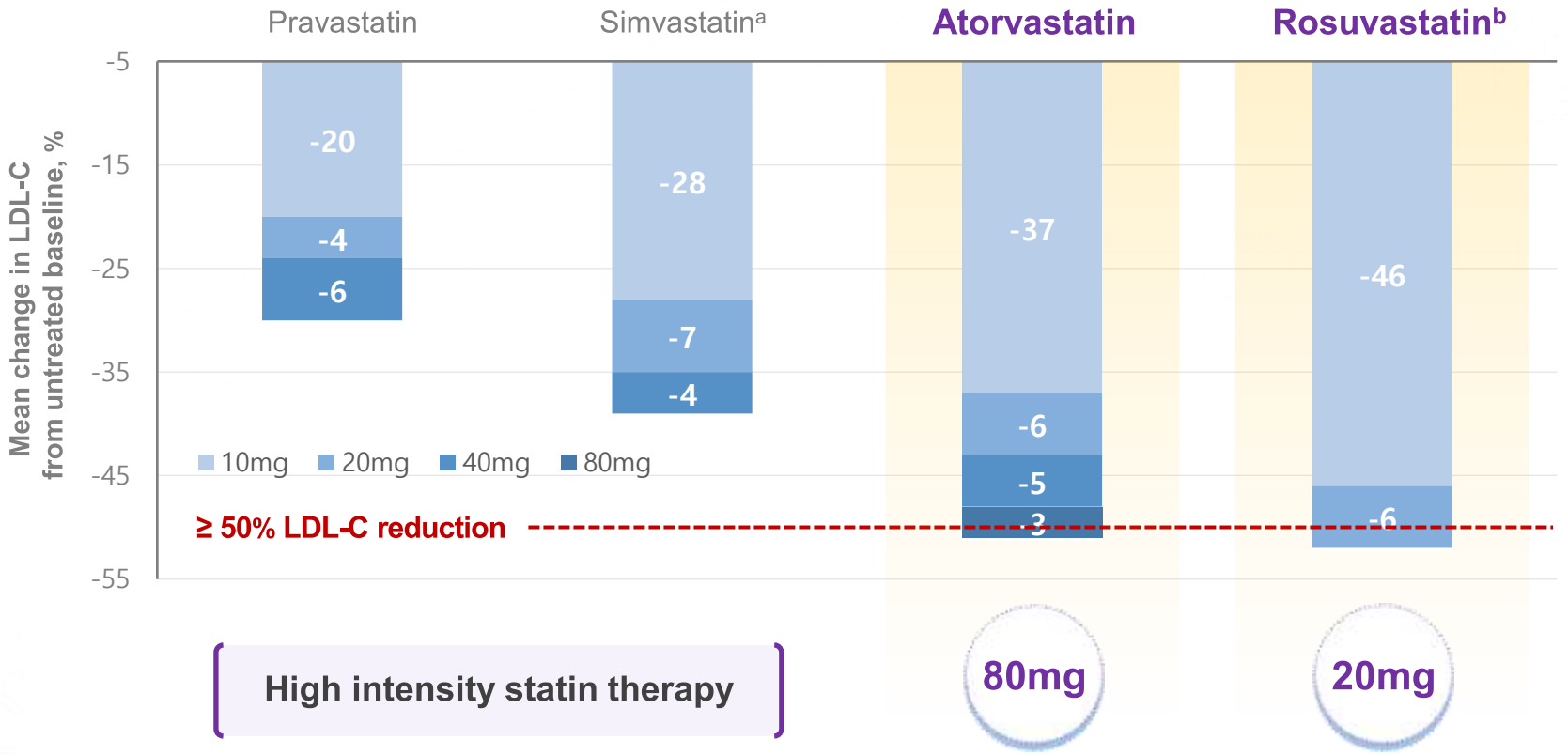
Only high intensity statins such as Atorvastatin 80mg and Rosuvastatin 20mg could achieve ≥50% reduction in LDL-C

KR-ATO-00075 04/2021

Mean change in LDL-C from baseline in four different statins



Adapted from Jones, *et al.*[1]

a. Mean change in LDL-C from untreated baseline after 6 weeks for simvastatin 80 mg was 46%.1 The 80-mg dose of simvastatin is only recommended in patients at high CV risk who have not achieved treatment goals on lower doses and when the benefits are expected to outweigh the risks.[1] **b.** Across the dose range: P<0.001 for the difference between rosuvastatin vs pravastatin, simvastatin, and atorvastatin.[1]

STELLAR : Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin, LDL-C : Low-density lipoprotein cholesterol

study design A 6-week, parallel-group, open-label, randomized, multicenter study comparing LDL-reducing efficacy of rosuvastatin vs atorvastatin, simvastatin, and pravastatin across the dose ranges in adults with hypercholesterolemia (n=2,431; per dose group, n=156–167), after dietary lead-in.

1. Jones, *et al.* Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR* Trial). *Am J Cardiol.* 2003;92:152-160.

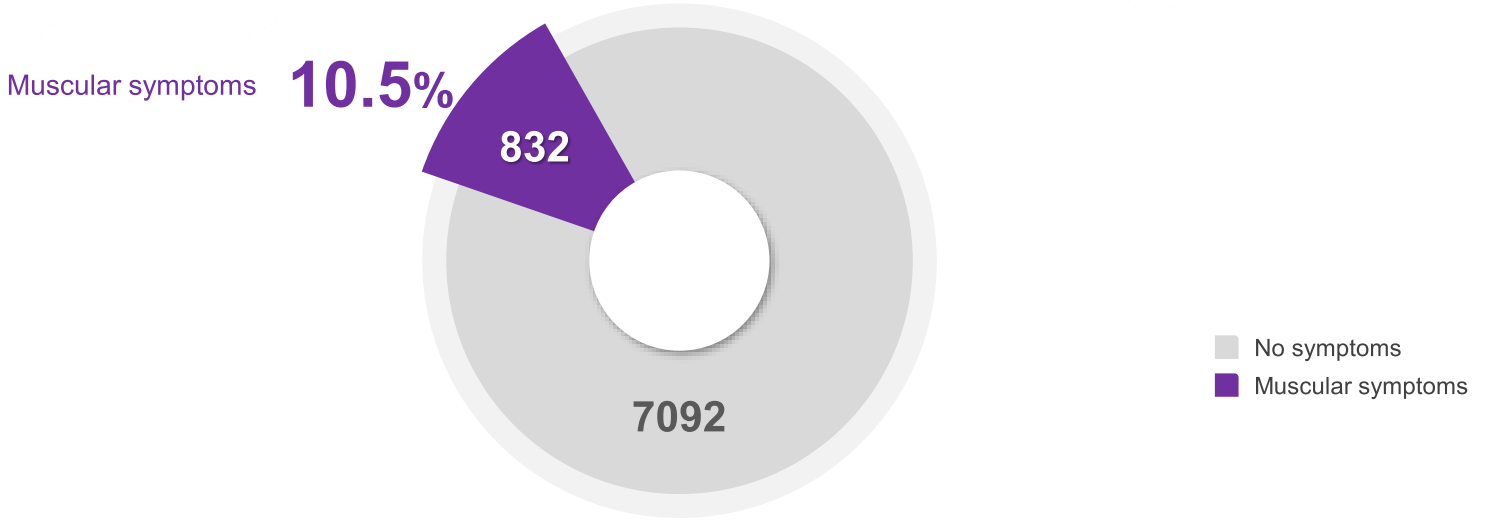
Safety issues can not be neglected in patients using high intensity statin

KR-ATO-00075 04/2021

Muscular symptoms[1]

About 11% of hyperlipidemic patients suffer from **muscular symptoms** with high dose statin[1]

1 month following initiation of statin therapy[1]



Adapted from Bruchert, *et al.*[1]

Study design Prediction of Muscular Risk in Observational conditions(PRIMO) study was a countrywide observational study conducted in a large, unselected population of hyperlipidemic patients receiving high-dosage statin therapy in a usual care, outpatient setting in France. The main objectives of the study were to identify the risk factors associated with muscular symptoms, establish the rate of occurrence of muscular symptoms with individual statins and to characterize the onset, nature and management of the symptoms. In total, 7924 hyperlipidemic patients aged 18–75 years who were seen in regular outpatient visits with their general practitioners (GPs) were entered in the study.[1]

1. Bruckert *et, al,* Mild to moderate muscular sympoms with high-dosage statin therapy in hperlipidemic patients-The PRIMO study. *Cardiovascular Drugs and Therapy.* 2005;19:403-414.

Safety Issues can not be Neglected in Patients Using High Intensity Statin

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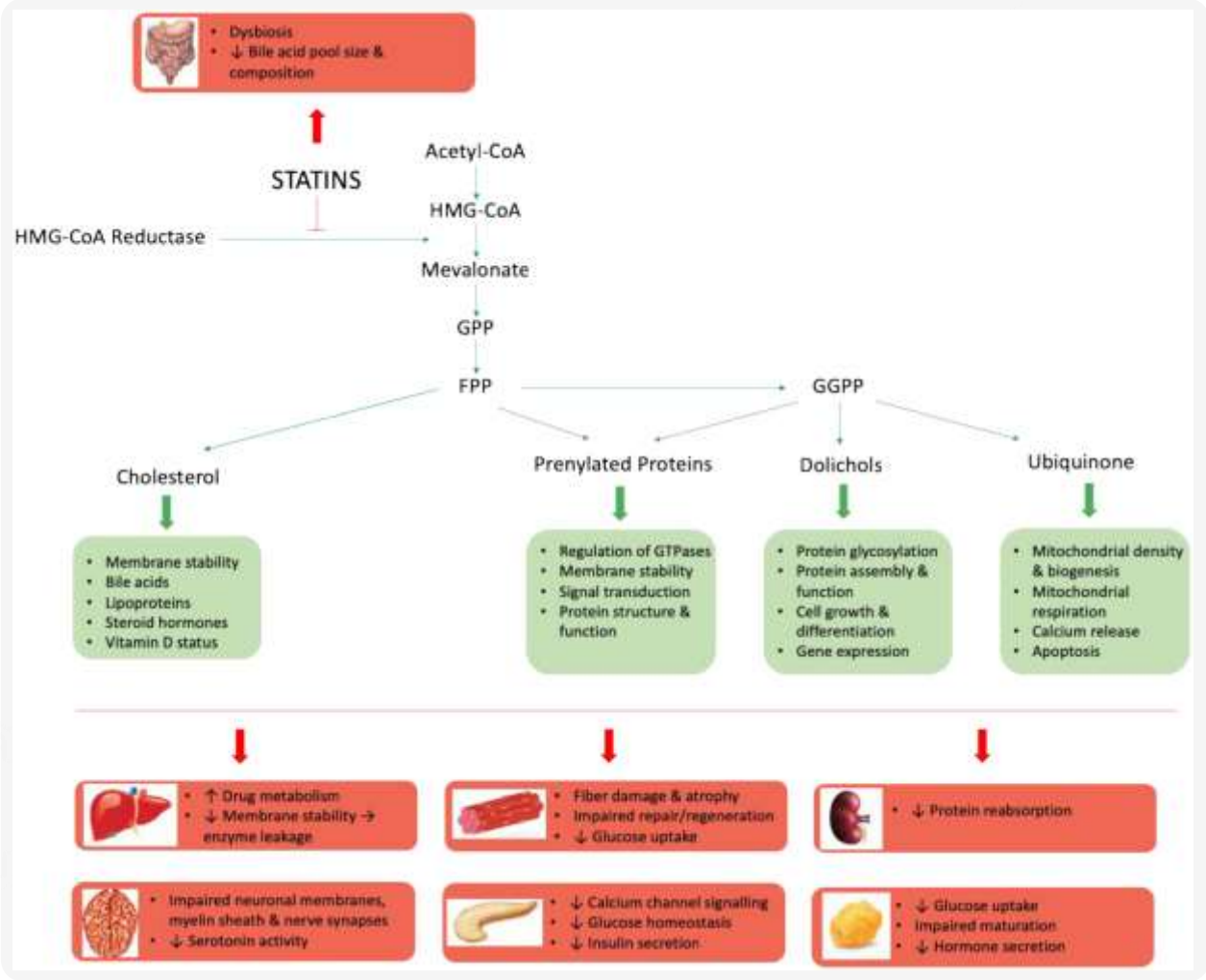
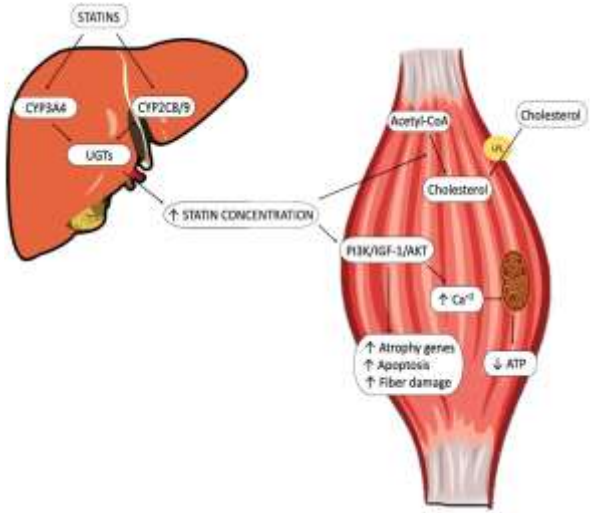


Statin-Associated Muscle Symptoms



New-Onset Type 2 Diabetes Mellitus

Neurological and Neurocognitive Conditions

Renal Toxicity

6 Jun 2019https://doi.org/10.1161/CIRCRESAHA.119.315233Circulation Research. 2019;124:e121–e122

Risk factors for statin myotoxicity[1]

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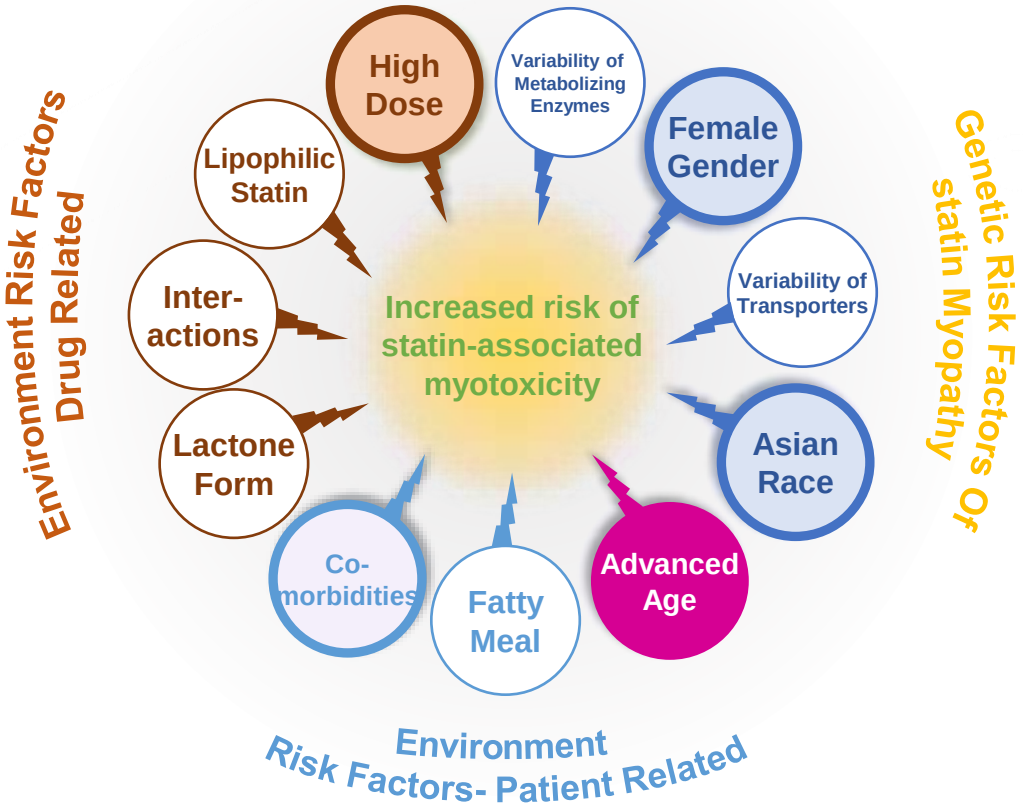
Such risk factors can be classified broadly into environmental and genetic risk factors. Although most environmental risk factors are modifiable, genetic factors appear to be unavoidable predisposing factors to statin myotoxicity[1]



Adapted from Taha A, *et al.* [1]

1. Taha A, *et al.* Translational insight into statin-induced muscle toxicity: from cell culture to clinical studies. *Translational Research* 2014;164:85–109

Statin-associated muscle symptoms(SAMS) frequently cause statin non-adherence, switching and discontinuation, contributing to adverse cardiovascular(CV) outcomes.[1]

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The management of SAMS is key in the effective treatment of patients with cardiovascular disease(CVD).[1]

NLA recommendation of use of statin therapy in specific patient population[1]

	Recommendations	Strength	Quality
Older patients	If SAMS is an issue, consideration should be given to the use of alternate regimens such as low-intensity statin therapy or non-daily, moderate-intensity statin therapy**; low-dose statin combination therapy with ezetimibe**, bile acid sequestrants or niacin*; or non-statin monotherapy (i.e., **ezetimibe** or bile acid sequestrant) or their combination, with a goal of at least a 30% reduction in LDL-C	B	Moderate
Women's health	First-line cholesterol-lowering drug therapy, unless contraindicated, is a moderate- to high-intensity statin. The statin dosage may be increased or the patient switched to a more efficacious agent if goal levels of atherogenic cholesterol are not achieved	A	High
African Americans	Clinicians should not withhold statin therapy from at-risk African American patients with asymptomatic CK levels that exceed, but are <5.0 times, the standard ULN	E	Moderate
South Asians	Due to the possibility of genetic variation in drug metabolism (as demonstrated mainly in studies of Chinese and Japanese patients), starting with a moderate-intensity statin dosage and titrating upward to reach atherogenic cholesterol goals, or downward if intolerance occurs, is recommended for patients of Asian ethnicity	B	Moderate
HIV-infected persons	First-line statin therapy is for elevated LDL-C and non-HDL-C; however, interactions between statins and anti-retroviral agents and other medications must be considered prior to initiating lipid-lowering therapy. The NLA Expert Panel recommends using atorvastatin, rosuvastatin or pitavastatin as the generally preferred agents in HIV-infected patients	A	Moderate

Adapted from Ulrich Laufs, *et al*. [1]

* Note: niacin is not recommended by the current ESC/EAS guidelines for the management of dyslipidemia

CK : Creatine kinase, **HDL-C** : High-density lipoprotein cholesterol, **HIV** : Human immunodeficiency virus, **LDL-C** : Low-density lipoprotein cholesterol, **NLA** : National Lipid Association, **SAMS** : Statin-associated muscle symptoms, **ULN** : upper level of normal, **CVD** : Cardiovascular disease, **ESC** : European Society of Cardiology , **EAS** : European Atherosclerosis Society

Reproduced with permission from Jacobson TA, Maki KC, Orringer CE, *et al.* National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. *J Clin Lipidol* 2015;9 Suppl 6:S1–122

Study design The aim of this article is to provide practical, focused advice for healthcare professionals on the management of patients with SAMS. The primary objective was to suggest best practice approaches to common and complex clinical situations. They considered a series of questions on SAMS and made recommendations on how to best assess and manage this condition. This publication contains background information, evidence and guidance that supports the recommendations of the expert working group.

1. Ulrich Laufs, *et, al*, Practical aspects in the management of statin-associated muscle symptoms (SAMS). *Atheroscler Suppl.* 2017 Apr;26:45-55.

Today's Contents

1. The need for prevention of cardiovascular diseases in elderly patients

2. LDL-C management guidelines for elderly patients

3. Difficulty of active statin prescription for elderly patients

4. Benefits of using Ezetimibe

This study was conducted with ezetimibe and simvastatin.

IMProved Reduction of Outcomes : Vytorin Efficacy International Trial[1-3]

Compared to statin alone, **Ezetimibe** add-on therapy reduced LDL-C in **24%** with **NNT of 50**

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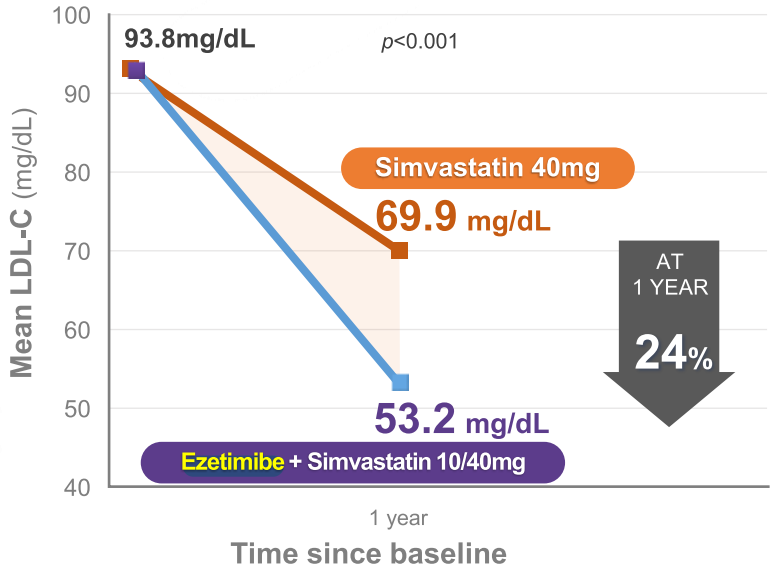
A double-blind, randomized trial,
18,144 patients stabilized post ACS ≤ 10 days: LDL-C 50–125*mg/dL
(or 50–100**mg/dL if prior lipid-lowering Rx)

- **Simvastatin 40 mg** (n=9,077)
- **Ezetimibe /simvastatin 10/40 mg** (n=9,067)

Primary Endpoint:
CV death, Nonfatal MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization)**, or Nonfatal stroke**

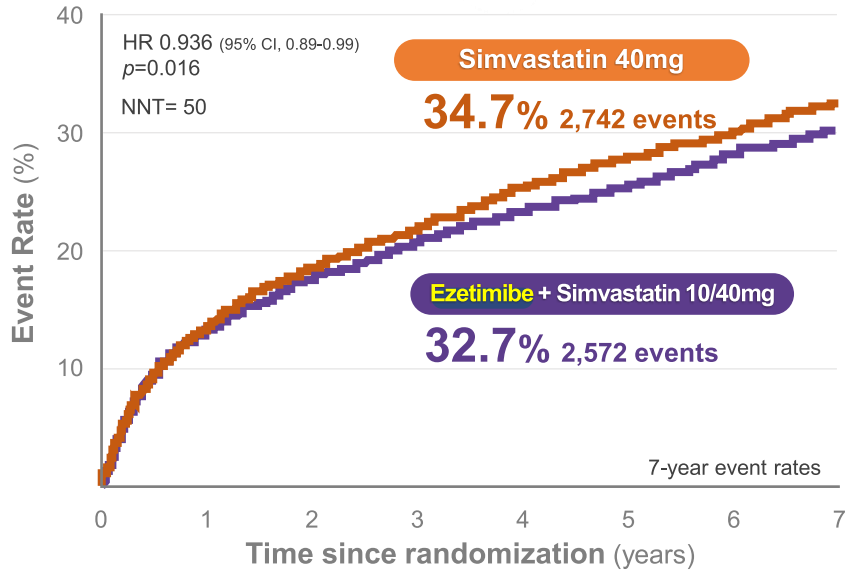
Duration: Minimum 2½--year follow-up (at least 5250 events)
The median follow-up was 6 years.

Change of LDL-cholesterol[1]



Adapted from Cannon CP, *et al.*[1]

Primary Endpoint[1]



Adapted from Cannon CP, *et al.*[1]

*3.2mM, **2.6mM

ACS : Acute Coronary Syndrome, **MI** : Myocardial infarction, **HR** : Hazard Ratio, **UA** : Unstable angina, **LDL-C** : Low density lipoprotein-cholesterol, **CI** : Confidence interval, **NNT** : Number needed to be treated, **CV** : Cardiovascular

1. Cannon CP, Blazing MA, Giugliano RP, *et al*; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387–2397.

[IMROVE-IT subgroup]

The **CV benefit** of Ezetimibe add-on therapy
in elderly patients

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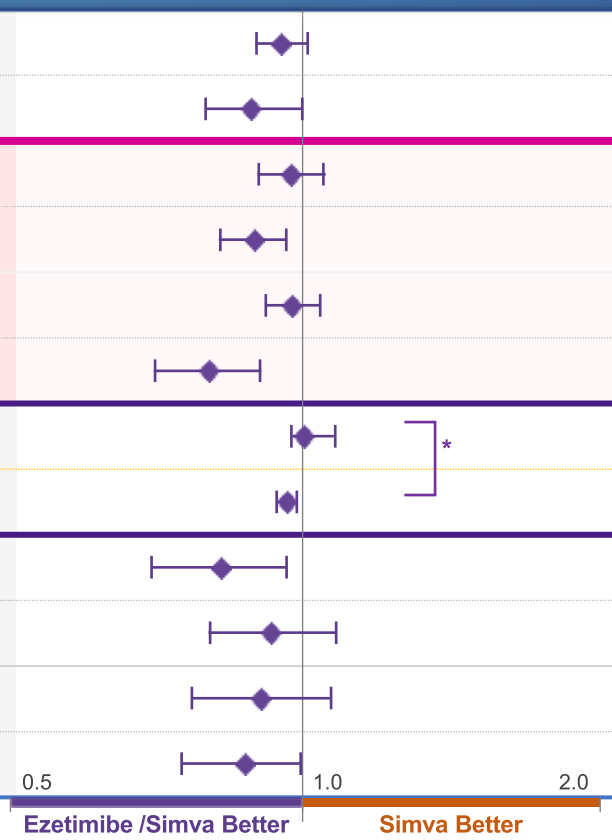
Major Prespecified Subgroups

	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	**30.8**	**29.9**
Age ≥ 65 years	**39.9**	**36.4**
Age < 75 years	**32.46**	**31.67**
Age ≥ 75 years	**47.60**	**36.95**
No diabetes	**30.8**	**30.2**
Diabetes	**45.5**	**40.0**
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
Baseline LDL-C > 95 mg/dL	31.2	29.6
Baseline LDL-C ≤ 95 mg/dL	38.4	36.0



†7-year event rates, *p-interaction = 0.023, otherwise > 0.05
LLT : Lipid lowering treatment, **LDL-C** : Low density lipoprotein Cholesterol, DM : diabetes mellitus, **CV** : Cardiovascular, **EZ/Simva** : Ezetimibe/Simvastatin

1. Cannon, *et al*. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *The New England Journal of Medicine.* 2015;372(25):2387–2397. **2.** Cannon CP, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. Supplementary Appendix. *N Engl J Med.* 2015;372:2387-97.

[IMROVE-IT subgroup]

The **CV benefit** of Ezetimibe add-on therapy
in elderly patients ≥75 years old with DM or non-DM

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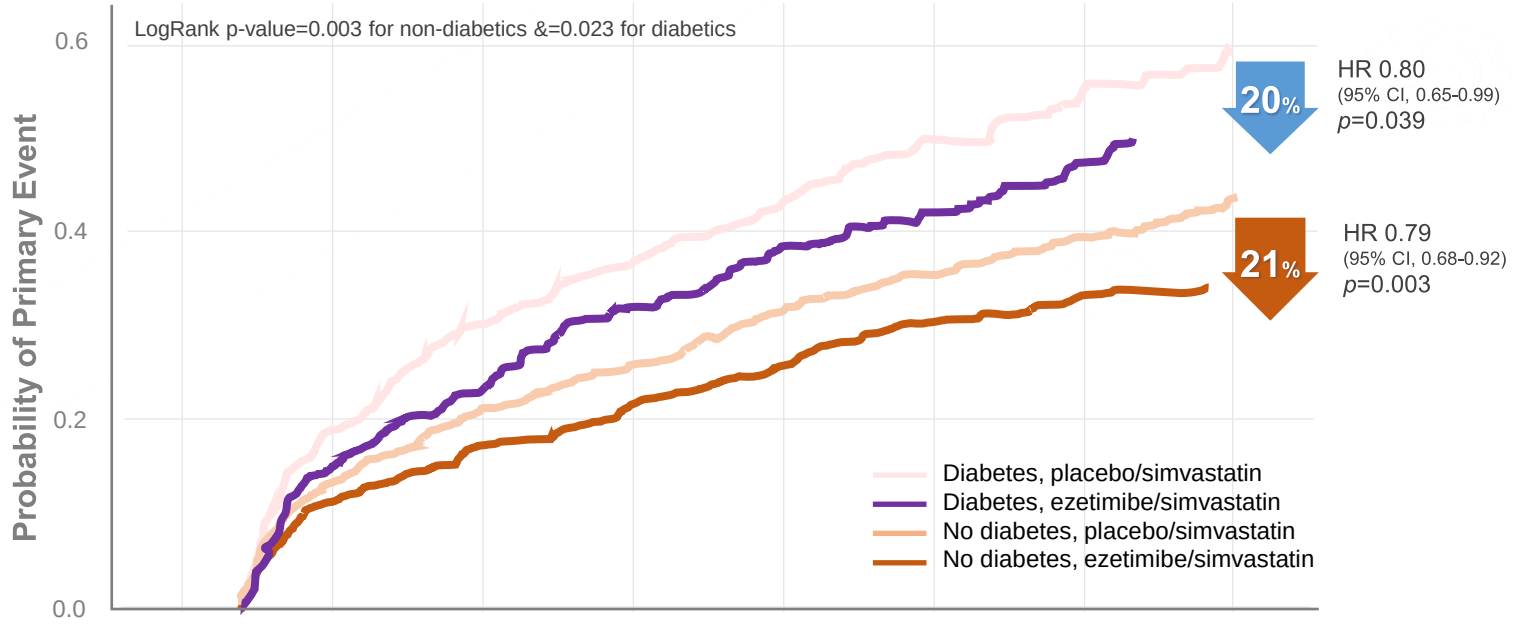
KM curves for the primary efficacy endpoint* in subjects with age ≥75years of age stratified by DM status[1]



Diabetes, placebo/simvastatin	968	778	706	645	572	394	296	177
Diabetes, ezetimibe/simvastatin	**1009**	**784**	**698**	**639**	**551**	**397**	**283**	**159**
No diabetes, placebo/simvastatin	402	300	258	228	200	133	93	48
No diabetes, ezetimibe/simvastatin	**418**	**300**	**248**	**213**	**178**	**114**	**66**	**31**
	0	1	2	3	4	5	6	7

Time (year) **post-randomization**

*Shown are the cumulative event rates for the primary composite endpoint of cardiovascular death, major coronary event (nonfatal myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization occurring ≥ 30 days post randomization), or nonfatal stroke in the intention-to treat population during the overall study period (i.e., from randomization to the first occurrence of a primary endpoint event or last contact with the patient).

IMPROVE-IT : Improved reduction of outcomes: Vytorin Efficacy International Trial, **HR** : Hazard ratio, **CI** : confidence interval, **KM** : Kaplan–Meier, **DM** : diabetes mellitus

Study design In IMPROVE-IT, 18,144 patients post ACS with LDL-C 50-125 mg/dL were randomized to ezetimibe/simvastatin-40mg (E/S) or placebo/simvastatin-40mg (P/S). The primary composite endpoint was cardiovascular death, major coronary events, and stroke. DM was a prespecified subgroup.

1. Giugliano RP,*et al*. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With vs. Without Diabetes: Results from IMPROVE-IT. *Circulation.* 2018;137:1571–1582.

Study Design of EWTOPIA 75

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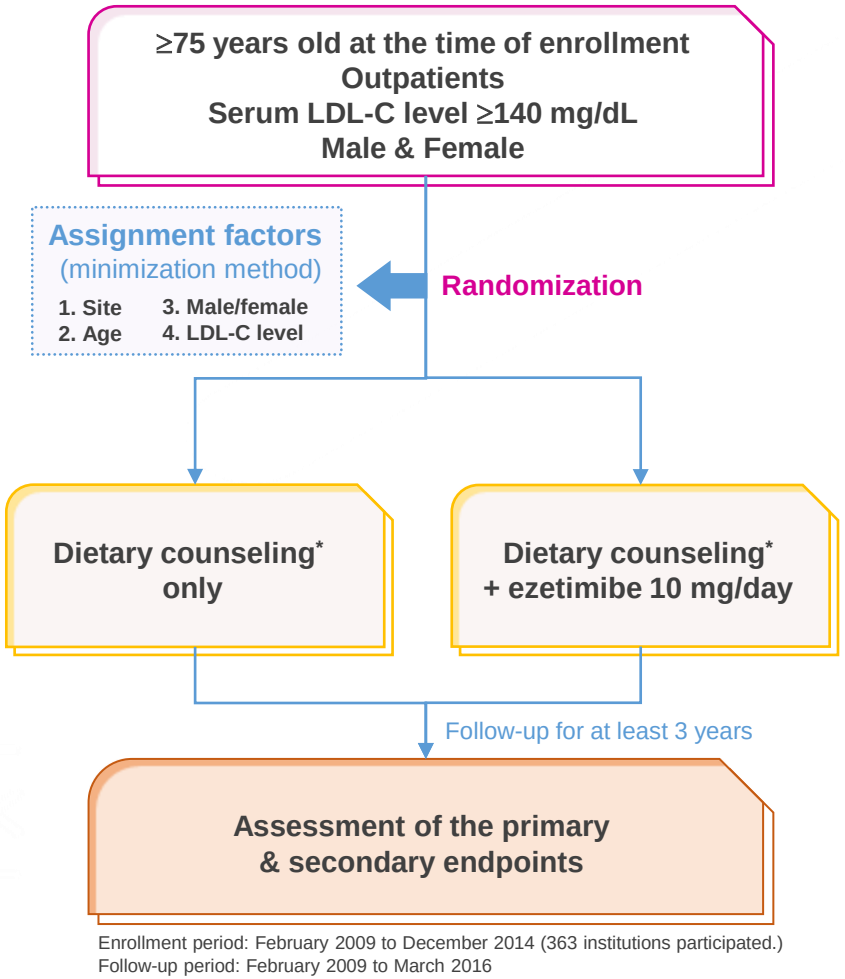

Enrollment period: February 2009 to December 2014 (363 institutions participated.)
Follow-up period: February 2009 to March 2016

PROBE design

Prospective **R**andomized **O**pen-label
Blinded- **E**ndpoint

Inclusion criteria

Patients with at least 1 of 7 conditions

1. Diabetes mellitus
2. Hypertension
3. Low HDL-cholesterolemia
4. Hypertriglyceridemia
5. Smoking
6. Previous history of cerebral infarction documented by apparent clinical symptoms and CT/MRI scanning
7. Peripheral artery disease

* Dietary counseling should be conducted based on 2007 Guideline for Prevention of ASCVD by Japan Atherosclerosis Society.
LDL-C : Low-density lipoprotein cholesterol, **HDL** : High-density lipoprotein, **CT : Computed tomography, MRI : Magnetic resonance imaging**

1. Arai H, *et al*. Ezetimibe in Prevention of Cerebro- and Cardiovascular Events in Middle- to High-Risk, Elderly (75 Years Old or Over) Patients With Elevated LDL-Cholesterol: A Multicenter, Randomized, Controlled, Open-Label Trial. Presented at the AHA congress 2018.

Lipid profile changes in Ezetimibe and Control groups

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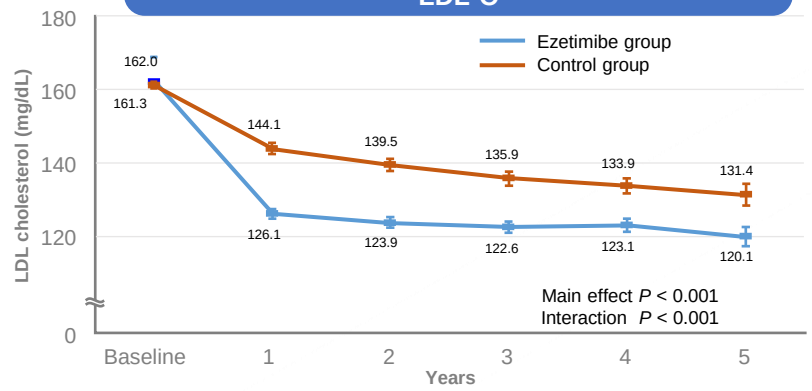
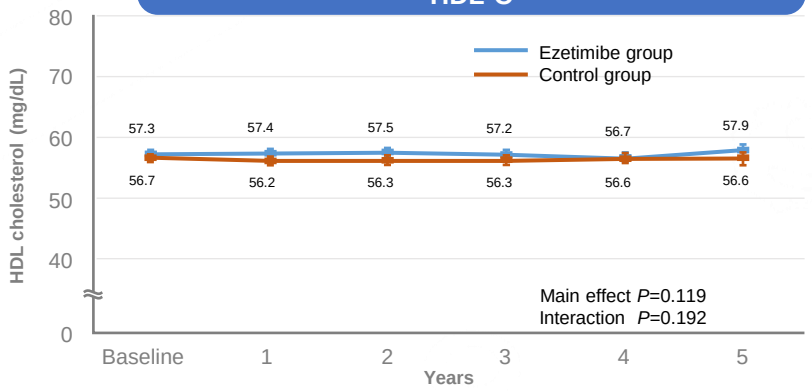
LDL-C



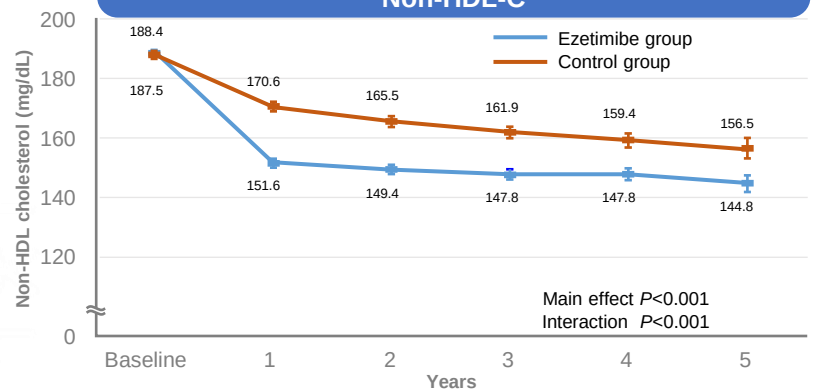
Number of Patients						
Treated by ezetimibe	1700	1489	1245	1009	685	311
Not treated by ezetimibe	1685	1464	1227	1023	706	314

HDL-C



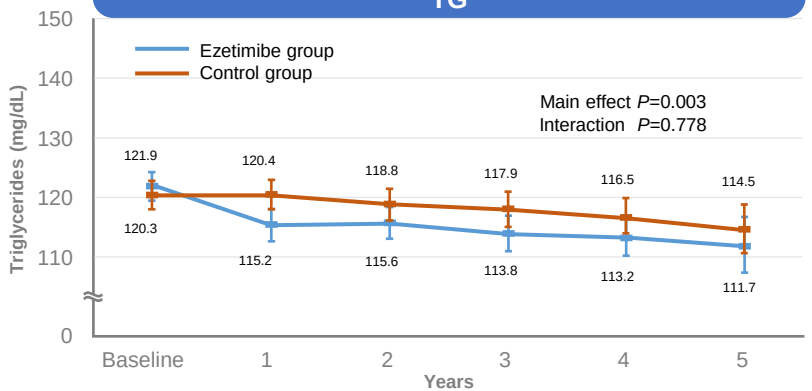
Number of Patients						
Treated by ezetimibe	1700	1508	1259	1018	701	318
Not treated by ezetimibe	1685	1484	1244	1028	718	319

Non-HDL-C



Number of Patients						
Treated by ezetimibe	1700	1490	1247	1009	687	311
Not treated by ezetimibe	1685	1466	1230	1024	707	314

TG



Number of Patients						
Treated by ezetimibe	1700	1507	1258	1019	699	317
Not treated by ezetimibe	1685	1484	1242	1029	717	321

HDL : Highdensity lipoprotein, **LDL** : Low-density lipoprotein

1. Arai H, *et al.* Ezetimibe in Prevention of Cerebro- and Cardiovascular Events in Middle- to High-Risk, Elderly (75 Years Old or Over) Patients With Elevated LDL-Cholesterol: A Multicenter, Randomized, Controlled, Open-Label Trial. Presented at the AHA congress 2018.

Effect of ezetimibe treatment on the primary end-point

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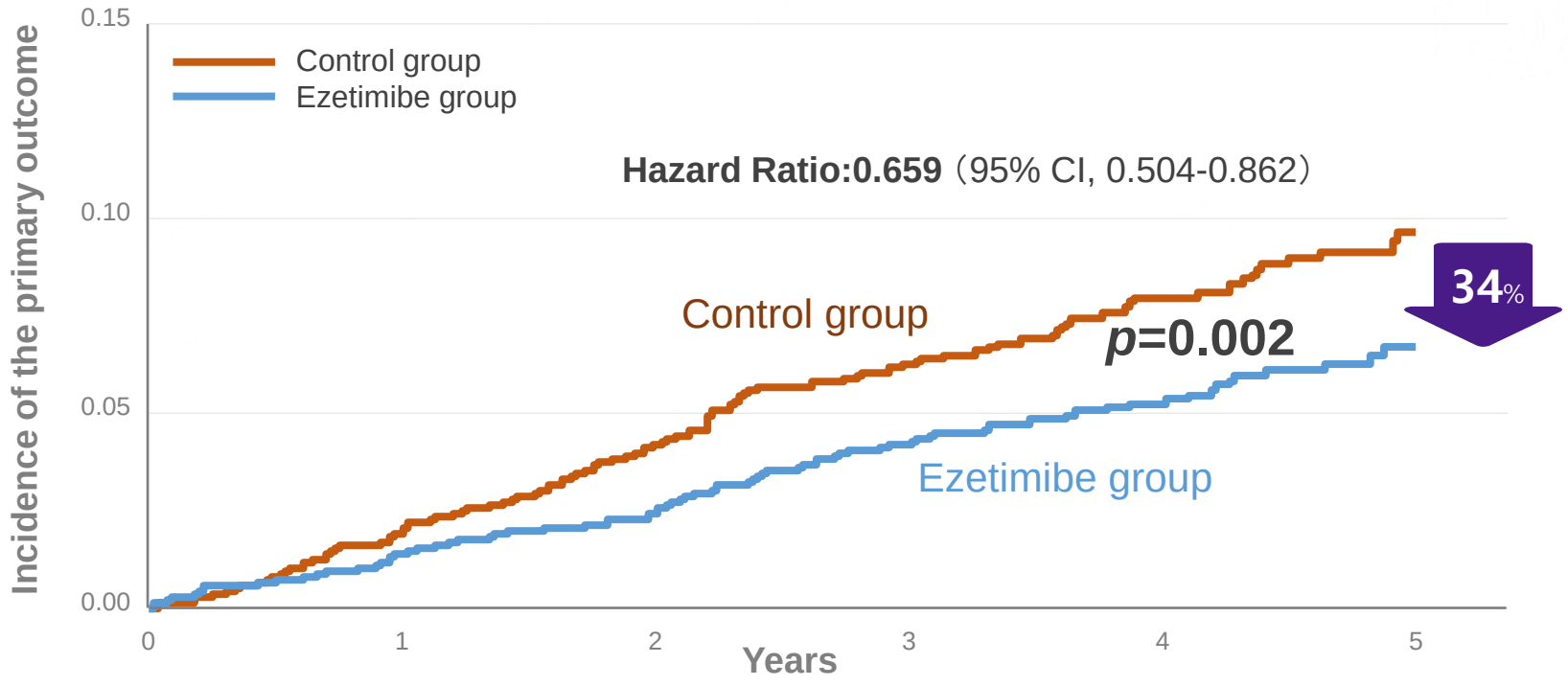
A composite of the atherosclerotic cardiovascular events (Sudden cardiac death, myocardial infarction, PCI or CABG, and/or stroke)



No. at Risk						
Control	1695	1582	1418	1217	887	383
Ezetimibe	1716	1617	1445	1219	897	387

PCI : Percutaneous coronary intervention, **CABG** : Coronary artery bypass grafting, **CI** : Confidence interval

1. Arai H, *et al.* Ezetimibe in Prevention of Cerebro- and Cardiovascular Events in Middle- to High-Risk, Elderly (75 Years Old or Over) Patients With Elevated LDL-Cholesterol: A Multicenter, Randomized, Controlled, Open-Label Trial. Presented at the AHA congress 2018.

Safety and Effects of Atozet 10/10mg versus titration to atorvastatin 40 mg in patients ≥65 years with hypercholesterolemia

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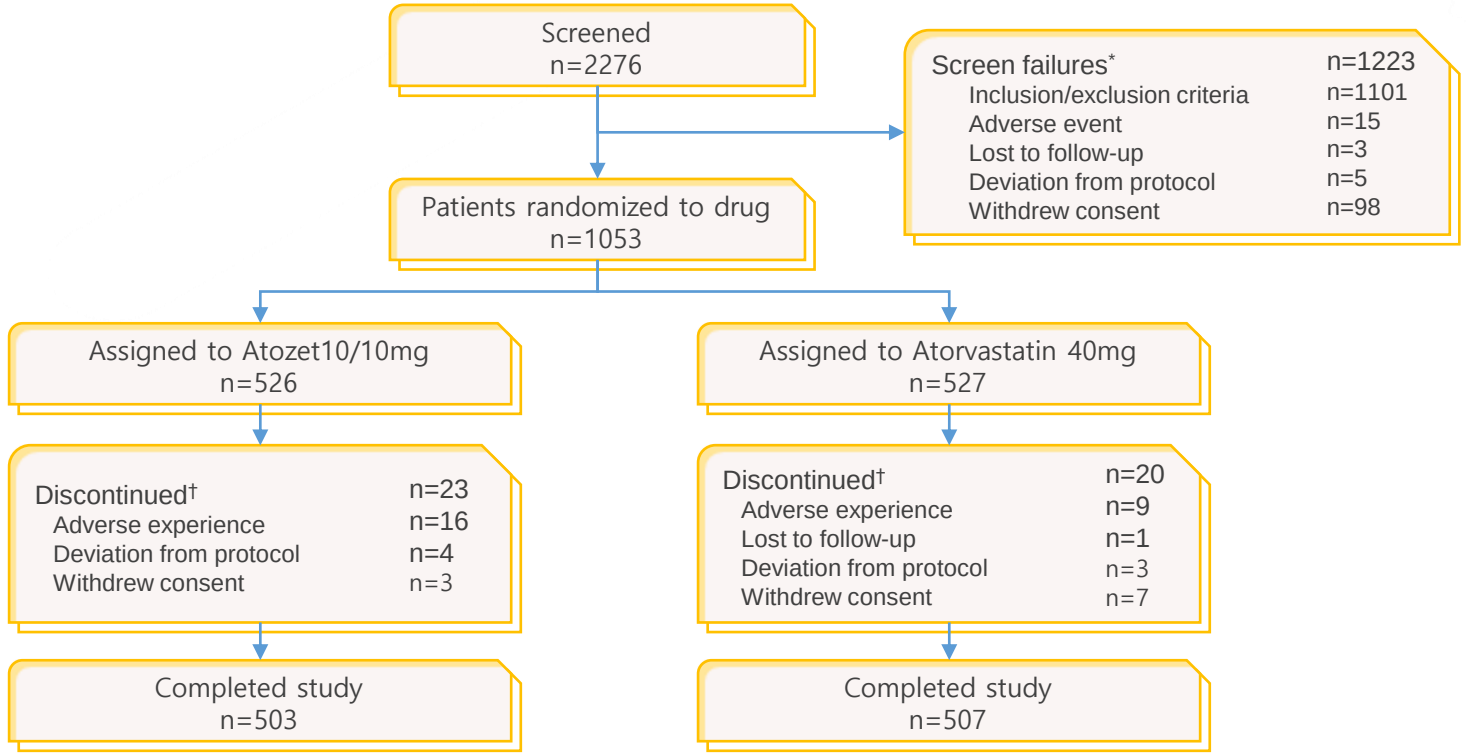
ZETELD study (12-week multicenter, randomized, double-blind, parallel-arm)

The mean age was 71 years (±5), 53% were women, approximately 30% were obese (body mass index ≥30 kg/m^2), ≥80% had CHD or AVD, and the mean treated baseline LDL-C levels ranged from 2.62 and 2.67 mmol/L.



*atorvastatin disposition record did not exist at the time of reporting for 1 patient
†includes all patients who were randomized

Adapted from Zieve F, *et al.*[1]

This study was not conducted with the fixed dose combination of ezetimibe with atorvastatin.
LDL-C : Low-density lipoprotein cholesterol, **CHD : Coronary heart disease, AVD** : Atherosclerotic vascular disease, **ZETELD** : ZETia in the ELDerly

1. Zieve F, *et al*. Safety and Efficacy of Ezetimibe Added to Atorvastatin Versus Up Titration of Atorvastatin to 40 mg in Patients >65 Years of Age (from the ZETia in the ELDerly [ZETELD] Study). *Am J Cardiol.* 2010;105:656–663. **2.** Constance C, *et al.* Atorvastatin 10 mg plus ezetimibe versus titration to atorvastatin 40 mg: attainment of European and Canadian guideline lipid targets in high-risk subjects ≥65 years Lipids in Health and Disease. 2014;13:1-8.

ZETELD study

Safety and Effects of Atozet 10/10mg versus titration to atorvastatin 40 mg in patients ≥65 years with hypercholesterolemia

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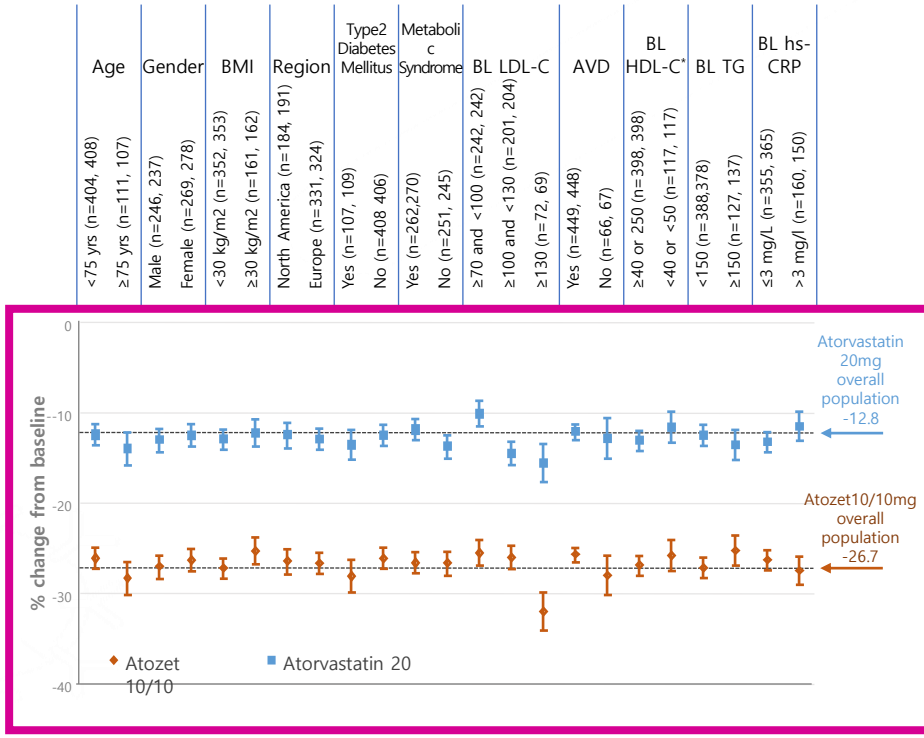
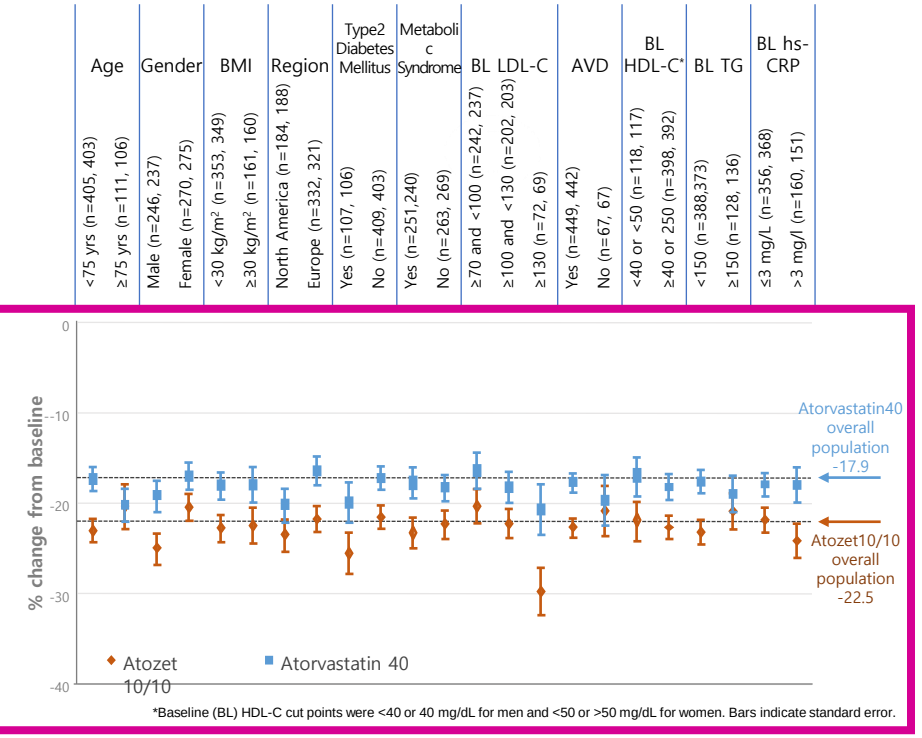
Atozet 10/10 mg resulted in significantly greater reductions at weeks 6 and 12 in LDL cholesterol and most other lipids compared to up titration to atorvastatin 20 and 40 mg, respectively, **in patients ≥65 years**

a Percentage of change from baseline in LDL cholesterol at week 6



b Percentage of change from baseline in LDL cholesterol at week 12



*Baseline (BL) HDL-C cut points were <40 or 40 mg/dL for men and <50 or >50 mg/dL for women. Bars indicate standard error.

Adapted from Zieve F, *et al*.[1]

This study was not conducted with the fixed dose combination of ezetimibe with atorvastatin.

LDL-C : Low-density lipoprotein cholesterol, **CHD : Coronary heart disease, AVD** : Atherosclerotic vascular disease, **HDL-C** : High density lipoprotein cholesterol, **BL** : Baseline, **BMI** : Body mass index, **hs-CRP** : High-sensitivity C-reactive protein, **TG** : Triglycerides, **ZETELD** : ZETia in the ELDerly

1. Zieve F, *et al*. Safety and Efficacy of Ezetimibe Added to Atorvastatin Versus Up Titration of Atorvastatin to 40 mg in Patients >65 Years of Age (from the ZETia in the ELDerly [ZETELD] Study). *Am J Cardiol.* 2010;105:656–663.

2. Constance C, *et al.* Atorvastatin 10 mg plus ezetimibe versus titration to atorvastatin 40 mg: attainment of European and Canadian guideline lipid targets in high-risk subjects ≥65 years Lipids in Health and Disease. 2014;13:1-8.

ZETELD study

Safety and Effects of Atozet 10/10mg versus titration to atorvastatin 40 mg in patients ≥65 years with hypercholesterolemia

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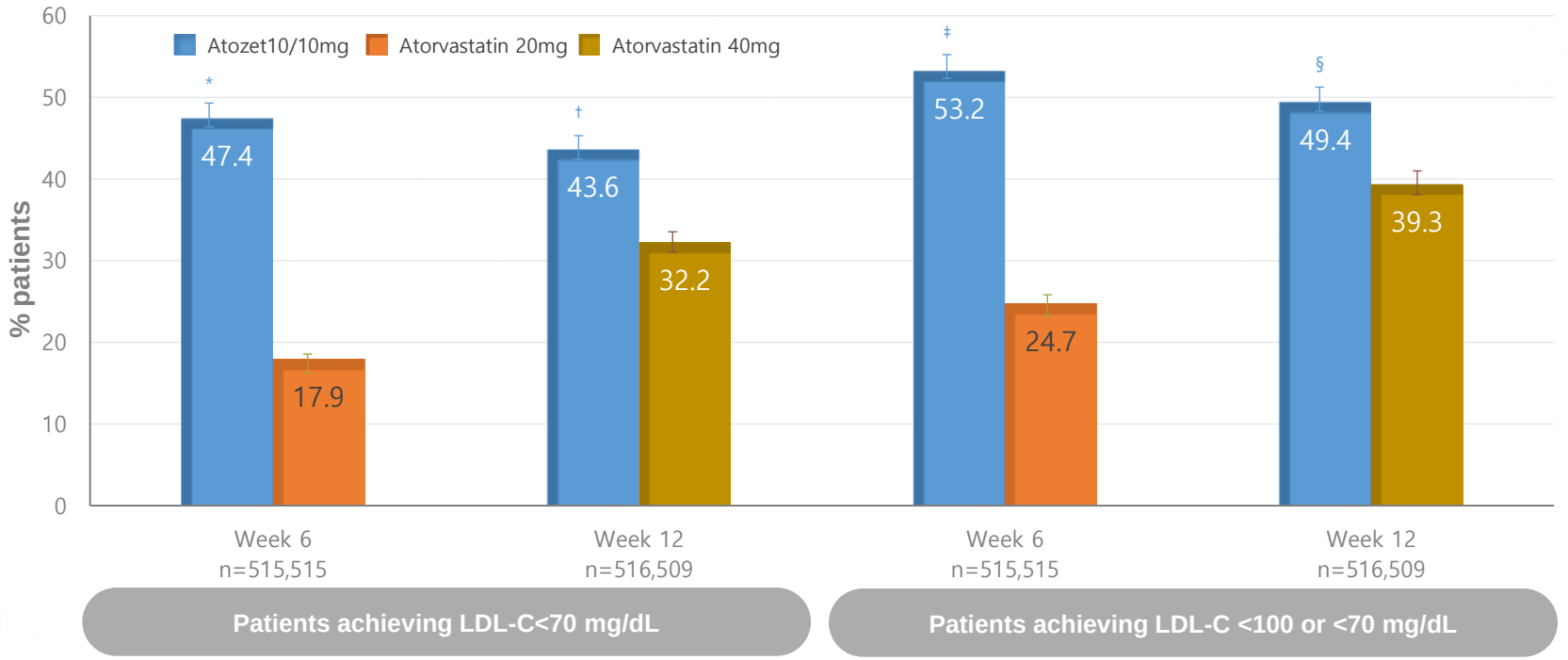
Proportion of patients achieving prespecified LDL cholesterol levels at weeks 6 and 12



Adapted from Zieve F, *et al*.[1]

Ratio of the predictive odds of achieving:
*LDL-C<70 mg/dL at week 6 on A 10 mg + E versus Atorvastatin20 mg=6.32 (95% CI: 4.52, 8.84) p<0.001.
†LDL-C<70 mg/dL at week 12 on A10 mg + E versus Atorvastatin40 =1.87 (95% CI: 1.40, 2.50) p<0.001.
‡LDL-C <100 mg/dL in patients without AVD or <70 mg/dL in patients with AVD at week 6 on Atorvastatin10/10 mg versus Atorvastatin20 mg=5.48 (95% CI: 3.98, 7.55) p<0.001.
§LDL-C <100 mg/dL in patients without AVD or <70 mg/dL in patients with AVD at week 12 on Atorvastatin10/10 mg versus Atorvastatin40 =1.75 (95% CI: 1.32, 2.31) p<0.001.

This study was not conducted with the fixed dose combination of ezetimibe with atorvastatin.
LDL-C : Low-density lipoprotein cholesterol, **AVD** : Atherosclerotic vascular disease, **CI** : Confidence interval, **ZETELD** : ZETia in the ELDerly

1. Zieve F, *et al*. Safety and Efficacy of Ezetimibe Added to Atorvastatin Versus Up Titration of Atorvastatin to 40 mg in Patients >65 Years of Age (from the ZETia in the ELDerly [ZETELD] Study). *Am J Cardiol.* 2010;105:656–663. **2.** Constance C, *et al.* Atorvastatin 10 mg plus ezetimibe versus titration to atorvastatin 40 mg: attainment of European and Canadian guideline lipid targets in high-risk subjects ≥65 years Lipids in Health and Disease. 2014;13:1-8.

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Combination Moderate-Intensity Statin and Ezetimibe Therapy for Elderly Patients With Atherosclerosis

Sang-Hyup Lee, MD,[a,*] Yong-Joon Lee, MD,[a,*] Jung Ho Heo, MD, PhD,[b] Seung-Ho Hur, MD, PhD,[c] Hyun Hee Choi, MD, PhD,[d] Kyung-Jin Kim, MD, PhD,[e] Ju Han Kim, MD, PhD,[f] Keun-Ho Park, MD, PhD,[g] Jung Hee Lee, MD, PhD,[h,a] Yu Jeong Choi, MD, PhD,[i] Seung-Jun Lee, MD, PhD,[a] Sung-Jin Hong, MD, PhD,[a] Chul-Min Ahn, MD, PhD,[a] Byeong-Keuk Kim, MD, PhD,[a] Young-Guk Ko, MD, PhD,[a] Donghoon Choi, MD, PhD,[a] Myeong-Ki Hong, MD, PhD,[a] Yangsoo Jang, MD, PhD,[k] Jung-Sun Kim, MD, PhD[a]

ABSTRACT

BACKGROUND The routine use of high-intensity statins should be considered carefully in elderly patients because of their higher risk of intolerance or adverse events.

OBJECTIVES We evaluated the impact of moderate-intensity statin with ezetimibe combination therapy compared with high-intensity statin monotherapy in elderly patients with atherosclerotic cardiovascular disease (ASCVD).

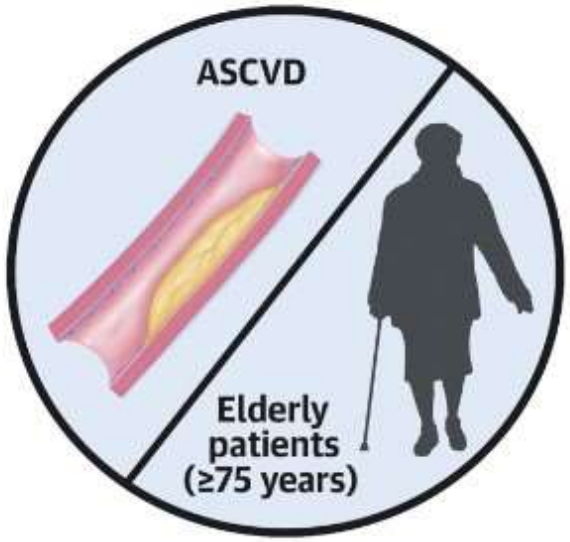
METHODS In this post hoc analysis of the RACING (RAndomized Comparison of Efficacy and Safety of Lipid-lowerING With Statin Monotherapy Versus Statin/Ezetimibe Combination for High-risk Cardiovascular Diseases) trial, patients were stratified by age (≥75 years and <75 years). The primary endpoint was a 3-year composite of cardiovascular death, major cardiovascular events, or nonfatal stroke.

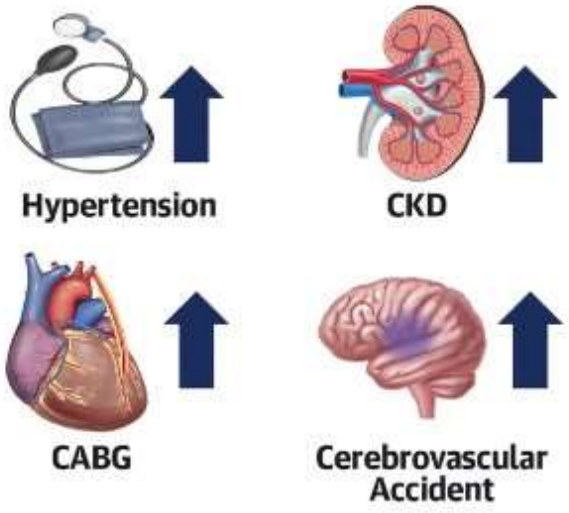
RESULTS Among the 3,780 enrolled patients, 574 (15.2%) were aged ≥75 years. The rates of the primary endpoint were not different between the moderate-intensity statin with ezetimibe combination therapy group and the high-intensity statin monotherapy group among patients aged ≥75 years (10.6% vs 12.3%; HR: 0.87; 95% CI: 0.54-1.42; $P = 0.581$) and those <75 years (8.8% vs 9.4%; HR: 0.94; 95% CI: 0.74-1.18; $P = 0.570$) (P for interaction = 0.797). Moderate-intensity statin with ezetimibe combination therapy was associated with lower rates of intolerance-related drug discontinuation or dose reduction among patients aged ≥75 years (2.3% vs 7.2%; $P = 0.010$) and those <75 years (5.2% vs 8.4%; $P < 0.001$) (P for interaction = 0.159).

CONCLUSIONS Moderate-intensity statin with ezetimibe combination therapy showed similar cardiovascular benefits to those of high-intensity statin monotherapy with lower intolerance-related drug discontinuation or dose reduction in elderly patients with ASCVD having a higher risk of intolerance, nonadherence, and discontinuation with high-intensity statin therapy. (RAndomized Comparison of Efficacy and Safety of Lipid-lowerING With Statin Monotherapy Versus Statin/Ezetimibe Combination for High-risk Cardiovascular Diseases [RACING Trial]; NCT03044665)
(J Am Coll Cardiol 2023;81:1339-1349) © 2023 by the American College of Cardiology Foundation.

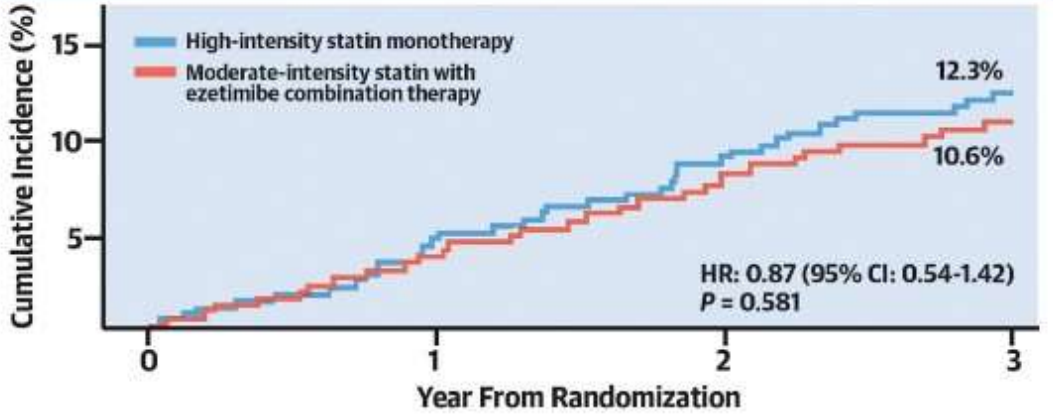
RACING Trial - Elderly post hoc analysis

Combination Moderate-Intensity Statin and Ezetimibe Therapy for Elderly Patients With Atherosclerosis

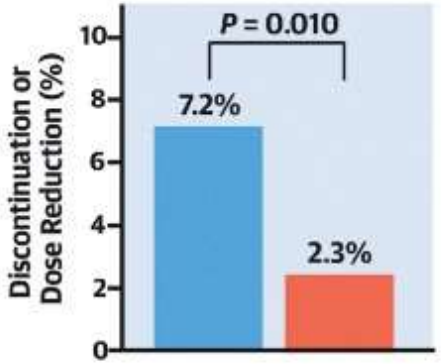




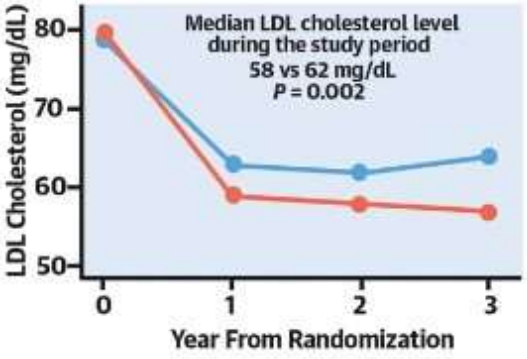
3-Year Composite Cardiovascular Events



Drug Discontinuation or Dose Reduction



LDL Cholestrol Levels



Lee S-H, et al. J Am Coll Cardiol. 2023;81(14):1339-1349.

KR-ATO-00075 04/2021

Summary

KR-ATO-00075 04/2021

1 The importance of cardiovascular disease prevention in elderly patients increases due to rapid aging

Because old age alone is a major risk factor, prevention of cardiovascular disease is essential for elderly patients. For this, it is necessary to manage well the LDL-C, which is a key correlated indicator

2 Difficulty in actively prescribing statins to elderly patients

Due to the characteristics of elderly patients, it is difficult to prescribe a sufficient dose of statin because there are many side effects and taking other drugs. Also, there are relatively few benefits through clinical trials. Active treatment has an aspect that allows it to be tailored to the situation.

3 Benefits of care for elderly patients when combined with ezetimibe

Looking at IMPROVE IT, the combined use of EZETIMIBE showed a rather relative benefit in those over 75 years of age, and EWTOPIA 75 showed that EZETIMIBE also showed results in the prevention of primary cardiovascular disease in the 75-year-old through EWTOPIA 75. In addition, as seen with ZETELD STUDY, a sufficient LDL-C lowering effect can be seen, so it can be used in elderly patients. Also in Racing Sub analysis , combined moderate intensity statin and ezetimibe showed good compliance.
For LDL-C lowering, a method using EZETIMIBE can be considered.