Is Combination Therapy Recommended for All High Risk Patients : When and Why Combination Therapy Is Needed?

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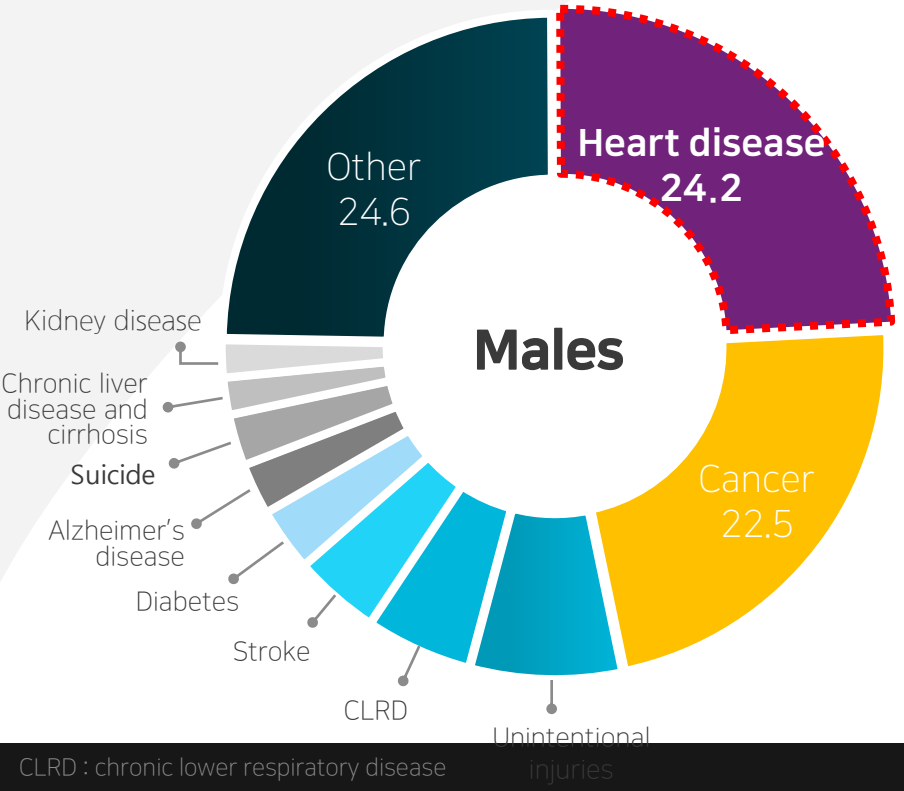
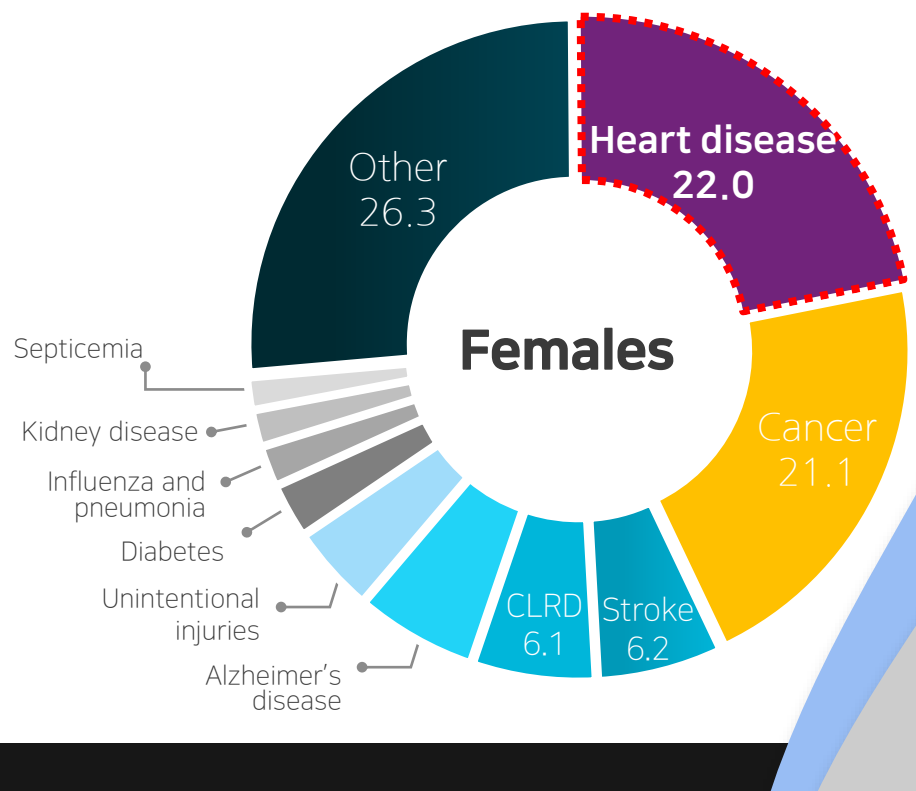
Today's Contents

- Treatment gap between real world and cholesterol lowering studies
- Residual Risk of Statin Mono-therapy and Ezetimibe outcome study
- Benefit of Atorvastatin and Ezetimibe in plaque regression

Major cause of death(United States, 2016)

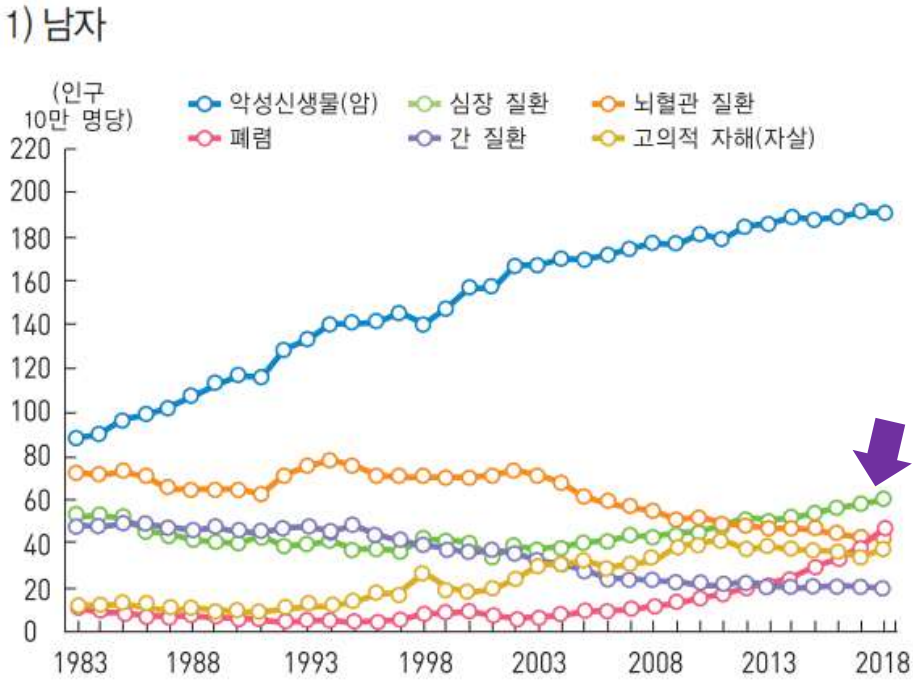


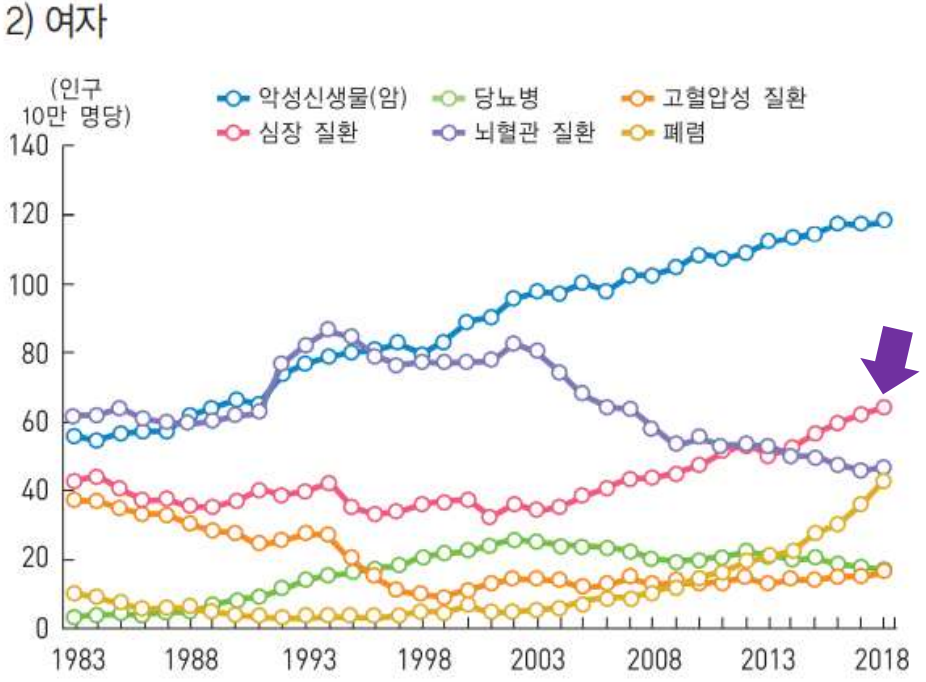


CLRD : chronic lower respiratory disease

Ref) Melonie Heron, et al. National Vital Statistics Reports, Vol. 67, No. 6, July 26, 2018

ASCVD mortality was residually increased in Korea





Reference : 2019 통계청_2018년 사망원인 통계

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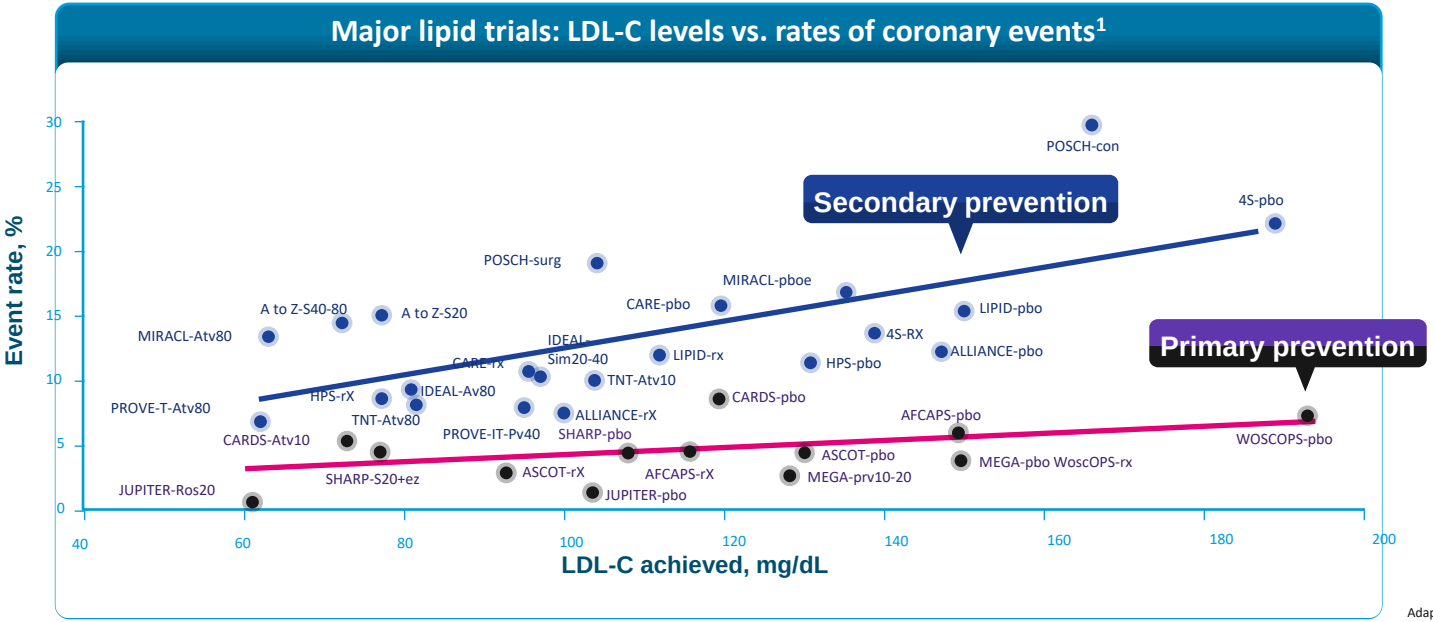
RCT of statins and other studies of cholesterol-lowering show a reproducible relationship between the LDL-C level achieved and absolute risk[1]



Adapted from Raymond C, *et al*.[1]

4S-pbo, Scandinavian Simvastatin Survival Study placebo group; 4S-X, 45 simvastatin group; A to Z-520, A to Z trial simvastatin 20 mg group; A to Z-540-80, A to Z trial simvastatin 40-80 mg group; AFCAPS-pbo Air orce/Texas Coronary Atherosclerosis Prevention Study placebo group; AFCAPS-X, AFCAPS lovastatin 20-40 mg group; ALLIANCE-pbo, Aggressive Lipichowering Initiation Abates New Cardiac Events study placebo group; ALLIANCE-X, ALLIANCE atorvastatin group; ASCOT-pbo, AngloScandinavian Cardiac Outcomes Trnal placebo group; ASCOT-X, ASCOT atorvastatn group; CARDS-pbo, Collaborative Atorvastatin Diabetes Study placebo group; CARDS-Atv10, CARDS atorvastatin 10 mg group; CARE-pbo, Cholesterol and Recurrent Events trial placebo group; CARE, CARE pravastatin group; HPS-obo, Heart Protection Stud placebo group; HPS-X, HPS simvastatin 40 mg group; IDEAL-Sim20-40, Incremental Decrease in End Points Through Aggressive Lipid Lowering trial simvastatin 20-40 mg group; IDEAL-Atv80, IDEAL atorvastatin 80 mg group; JUPITER-pbo, Justification for the use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin placebo group; JUPITER-Ros20, JUPITER rosUvastan 20 mg group; LIPIDpbo, Long-Tem Intervention With Pravastatin in ischaemic Disease placebo group; LIPD-X, LIPID pravastatin group; MEGApbo, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese study placebo group; MEGA-Pv10-20, MEGA pravastatin 10-20 mg group; MIRACL-pbo, Myocardial ischemia Reduction With Acute Cholesterol Lowering trial placebo group; MIRACL-AV80, MIRACL trial atorvastatin 80 mg group; POSCH-con, Program on the Surgical Control of the Hyperlipidemias control group; POSCH-surg, POSCH Ileal bypass group; PROVE-T-Pru40, Pravastatin or Atorvastatin Evaluation and Infection Therapy pravastatin 40 mg group; PROVE-T-Av80, PROVENIT atorvastatin 80 mg group; SHARP-pbo, Study of Heart and Renal Protection placebo group; SHARP-S20+ez, SHARP simvastatin 20 mg plus ezetimibe group; TNT-Atv10, Treating to New Targets atorvastatin 10 mg group; TNT-Atv80, TNT atorvastatin 80 mg group, WOSCOPSpbo West of Scotland Coronary Prevention Study placebo group; WOSCOPS, WOSCOPS pravastatin group LDL-C : Low density lipoprotein cholesterol, RCT : randomized controlled trials.

1. Raymond C, *et al.* New cholesterol guidelines: Worth the wait? *Cleve Clin J Med*. 2014;81(1):11-9.

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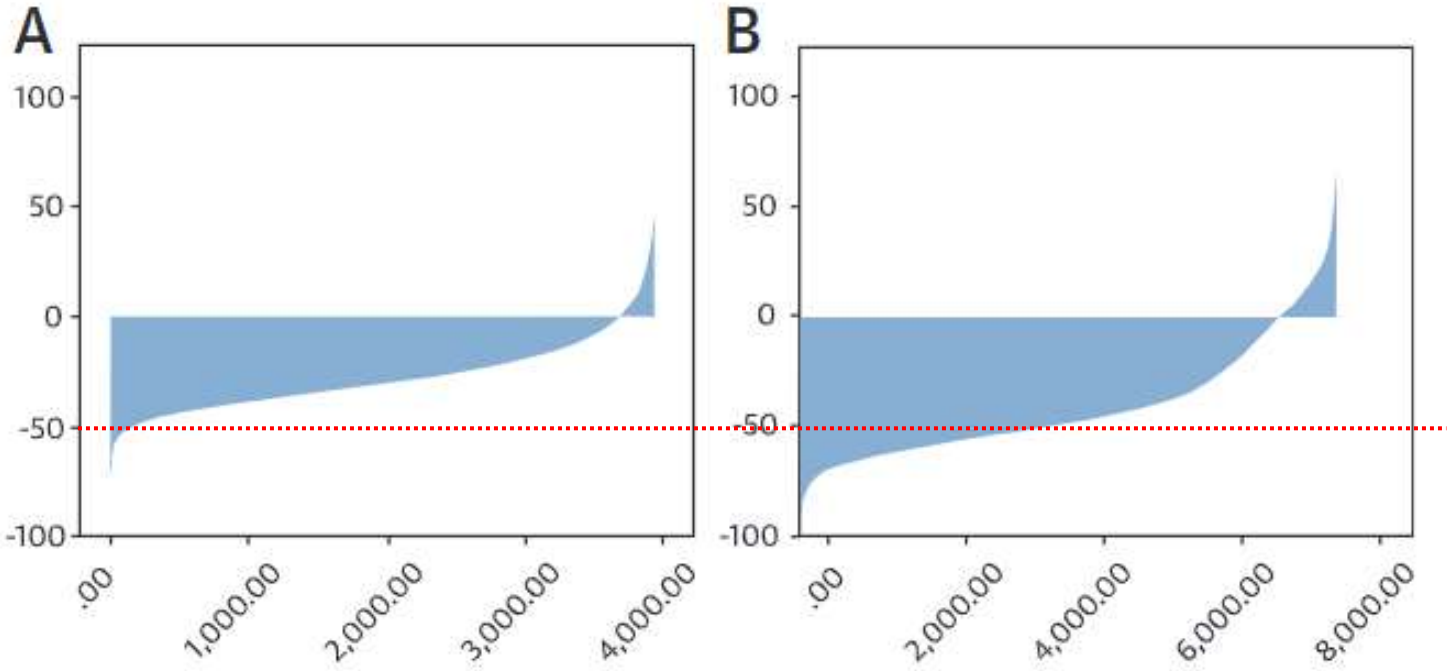
Despite intensive statin therapy, a large number of patients fail to reach the treatment target with residual risk.

Usual-dose statin therapy
Pravastatin 40 mg in the LIPID trial

High-dose statin therapy
rosuvastatin 20 mg in the JUPITER trial



DYSIS II: LDL-C Goal Attainment Rate

ACS | CHD

LDL-C Goal [<70mg/dL] Attainment Rate[1]

CHD Patients[1]

Baseline (Total N=6,792)

LDL-C at goal

29.4%

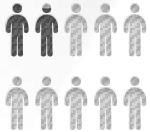
(N=1,994)

ACS Patients[1]

Baseline (N=1,071)*

LDL-C at goal

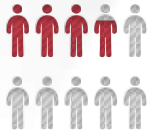
19.0%



Follow-Up (N=1,071)*

LDL-C at goal

37.0%



Conclusions[1]

- LDL-C target attainment was poor in very high-risk patients(CHD/ACS).
- Although use of LLT was widespread, potency of LLT was insufficient for reducing the CV risk of these patients.
- Atorvastatin equivalent dose was associated with better LDL-C target attainment.

*Includes only patients with lipid levels available from both baseline and 4-month follow-up.

DYSIS : Dyslipidemia International Study, CHD : Coronary heart disease, ACS : Acute coronary syndrome, LLT : Lipid-lowering therapy, LDL-C : Low-density lipoprotein cholesterol, CV : Cardiovascular

1. Gitt AK, *et al.* Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis.* 2017; 266:158-166.

Although most high-risk patients with T2D and CV disease were on lipid lowering therapy, only 1:3 had LDL-C <70 mg/dL and 1:6 had LDL-C <55 mg/dL

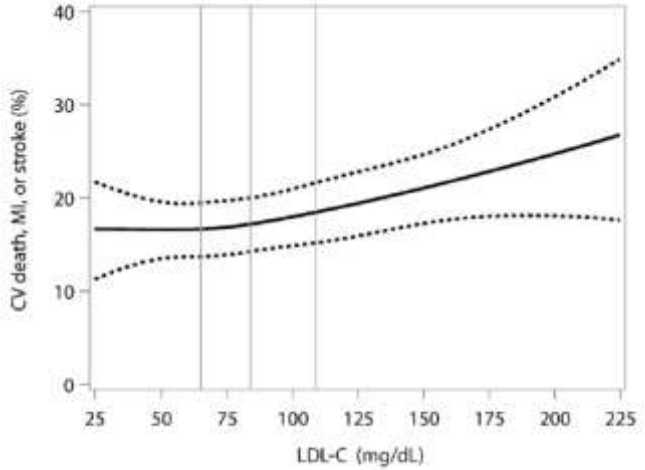


Table IV. Adjusted models for an association between LDL-C category and endpoints

	Events (events per 100 pt-yrs)				HR (95% CI)			
Endpoint	≤ 55	55.1–70	70.1–100	>100	55.1–70 vs ≤55	70.1–100 vs ≤55	>100 vs ≤55	*P*
CV death, non-fatal MI, or stroke	140 (3.1)	196 (3.4)	375 (3.4)	389 (3.9)	1.15 (0.91–1.44)	1.21 (0.99–1.49)	1.47 (1.18–1.82)	.003
CV death	65 (1.4)	81 (1.3)	161 (1.4)	220 (2.0)	0.99 (0.69–1.42)	1.09 (0.80–1.50)	1.53 (1.12–2.10)	.003

Reference group was patients with LDL-C ≤ 55 mg/dL

Predicted probability of major adverse cardiac events (CV death, nonfatal MI, or nonfatal stroke) at 5 years by baseline LDL cholesterol (LDL-C) assessed as a continuous variable. CV indicates cardiovascular; MI, myocardial infarction

Am Heart J 2020;220:82-88.

Am Heart J 2020;220:82-88

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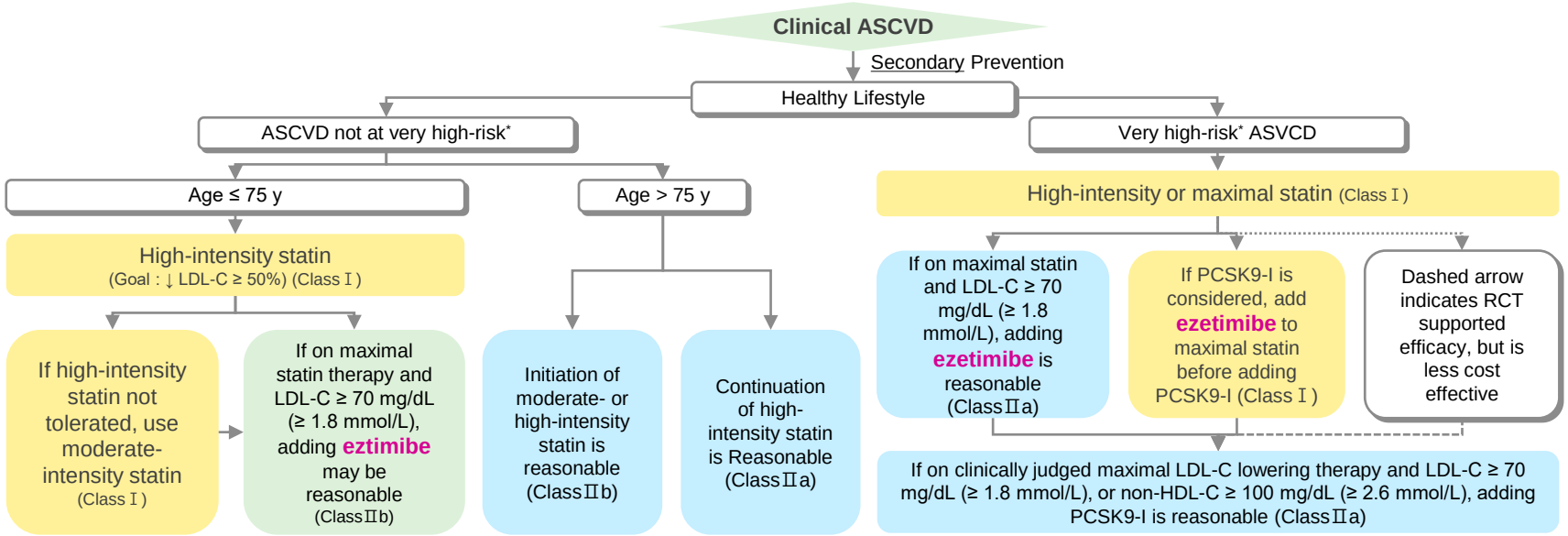
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of

Secondary Prevention in Patients With Clinical ASCVD[1]



*** Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.**

Adapted from Grundy SM, *et al.*[1]

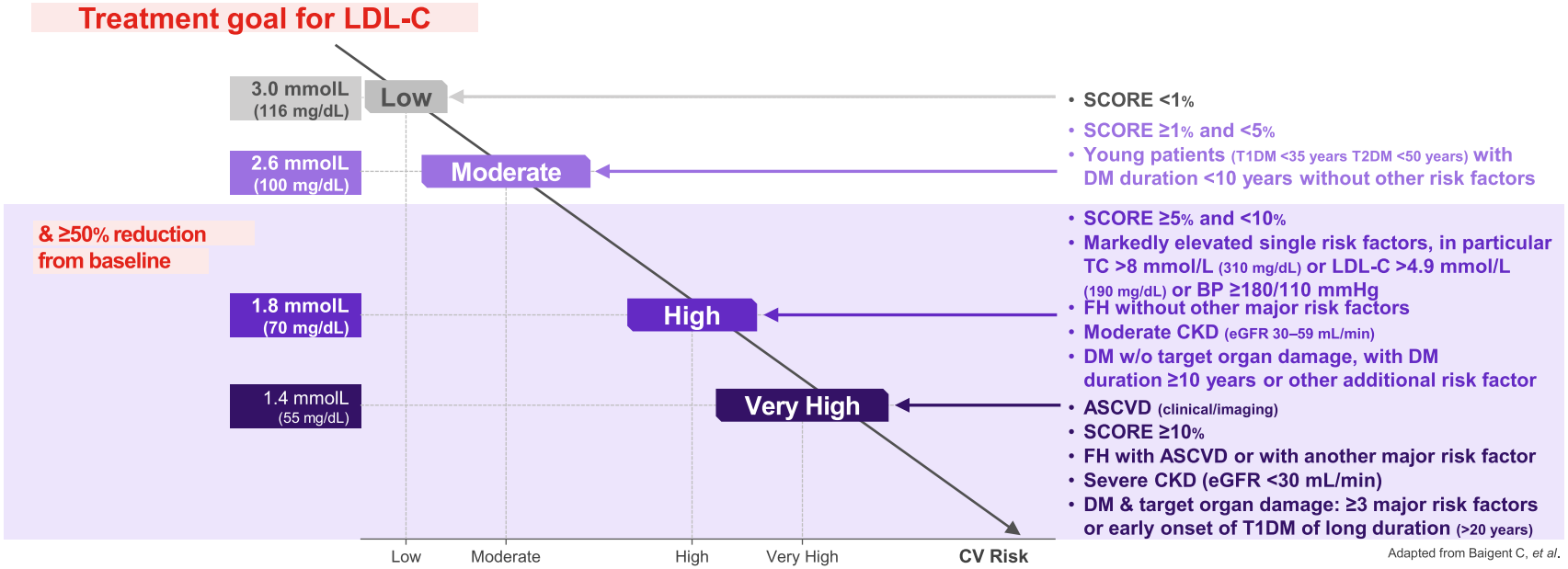
Definition of Major ASCVD events : Recent ACS (within the past 12 mo), history of MI (other than recent ACS event listed above), history of ischemic stroke, symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation.
Definition of high-Risk conditions : age ≥65 y, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes mellitus, hypertension, CKD (eGFR 15-59 mL/min/1.73 m^2), current smoking, persistently elevated LDL-C (LDL-C 100 mg/dL [2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe, history of congestive HF.

1. Grundy SM, *et al*. 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. *J Am Coll Cardiol*. 2018 Nov 8. pii: S0735-1097(18)39034-X.

2019 ESC/EAS Dyslipidemia Guideline

Treatment goals for LDL-C across categories of total cardiovascular disease risk

- **2019 ESC/EAS Guidelines recommend both a ≥50% LDL-C reduction from baseline and an absolute LDL-C treatment goal of <55 mg/dL (<1.4 mmol/L) for very high-risk patients, and <70 mg/dL (<1.8 mmol/L) for high-risk patients.**



Adapted from Baigent C, *et al*.

1. Baigent C, *et al*. 2019 ESC/EAS guidelines for the management of dyslipidaemias : lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2019:1-78.

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- **Residual Risk of Statin Mono-therapy and Ezetimibe outcome study**
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Atorvastatin has proven primary prevention of ASCVD in high risk patients

Study	Patient Population	Intervention	Outcomes Benefit
ASCOT[1]	**Hypertension**; aged 40–79 years; TOTAL-C ≤6.5 mmol/L (~251 mg/dL); and at least 3 other CV risk factors; N=10,305	Atorva 10 mg vs placebo; median 3.3 years	**36% reduction in nonfatal MI and fatal CHD;** *P*=0.0005
CARDS[2]	**Type 2 diabetes**; aged 40–75 years; LDL-C ≤4.14 mmol/L (~160 mg/dL); TG ≤6.8 mmol/L (~602 mg/dL); at least 1 additional risk factor; N=2,838	Atorva 10 mg vs placebo; median 3.9 years	**37% reduction in major CV events** (MI, acute CHD death, UA, resuscitated cardiac arrest, coronary revascularization, or stroke); *P*=0.001

The incremental benefit of ezetimibe/atorvastatin on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has not been established.

ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; TOTAL-C = total cholesterol; CV = cardiovascular; Atorva = atorvastatin; MI = myocardial infarction; CHD = coronary heart disease; CARDS = Collaborative Atorvastatin Diabetes Study;
TG = triglycerides; UA = unstable angina; TNT = Treating to New Targets; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA = Transient Ischemic Attack

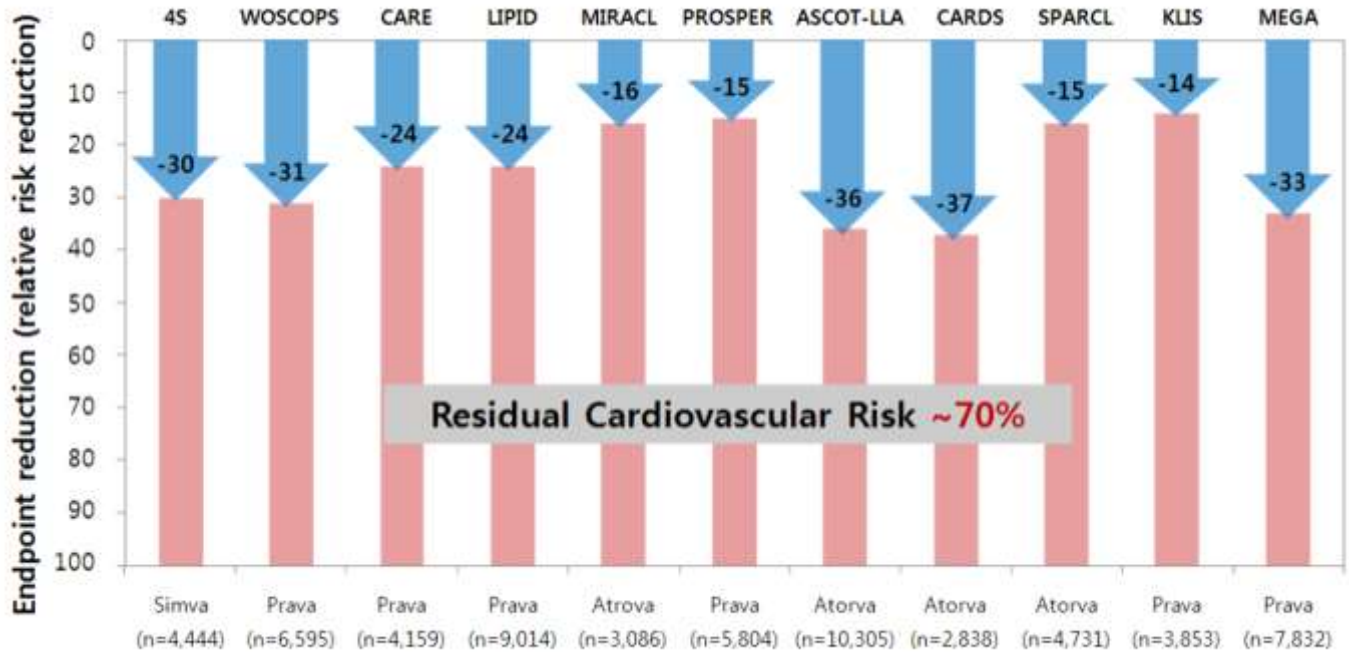
1. Sever PS et al. *Lancet.* 2003;361:1149–1158. **2**. Colhoun HM et al. *Lancet*. 2004;364:685–696. 3. Amarenco P et al., N Engl J Med 2006;355:549-59.
4. LaRosa JC et al. *N Engl J Med* 2005;352:1425–1435. **5**. Schwartz GG et al. *JAMA*. 2001;285:1711–1718. 6. Cannon C, et al. N Engl J Med. 2004;350:1495-504.

Intensity Atorvastatin saving various ASCVD patients away from 2nd events

Study	Patient Population	Intervention	Outcomes Benefit
SPARCL[3]	**Stroke or TIA**; aged >18 years; LDL-C 100-190 mg/dL; N=4,731	Atorva 80 mg vs placebo; median 4.9 years	**16% reduction in fatal/nonfatal stroke;** P=0.03
TNT[4]	**Clinically evident, stable CHD**; aged 35-75 years; LDL-C <130 mg/dL (~3.4 mmol/L); N=10,001	Atorva 10 mg vs atorva 80 mg; median 4.9 years	**22% reduction in major CV events** (death from CHD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke); in the 80-mg vs 10-mg group; *P*<0.001
MIRACL[5]	**Acute coronary syndrome (non–Q-wave MI or unstable angina)**; aged ≥18 years; N=3,086	Atorva 80 mg vs placebo; 16 weeks	**16% reduction in ischemic events** (death, nonfatal MI, cardiac arrest with resuscitation or angina pectoris with evidence of myocardial ischemia requiring hospitalization); *P*=0.048
PROVE IT – TIMI[6]	**Acute coronary syndrome (<10days, Hosptalization for acute MI or high-risk UA)**; mean age(year) 58; TOTAL-C ≤240mg/dL; n=4,162	Atorva 80mg vs. Prava 40mg; mean 2years	**16% reduction in all-cause death or major CV event** [Death, MI, Documented UA requiring hospitalization, revascularization (>30days after randomization), or Stroke]; *P*=0.005

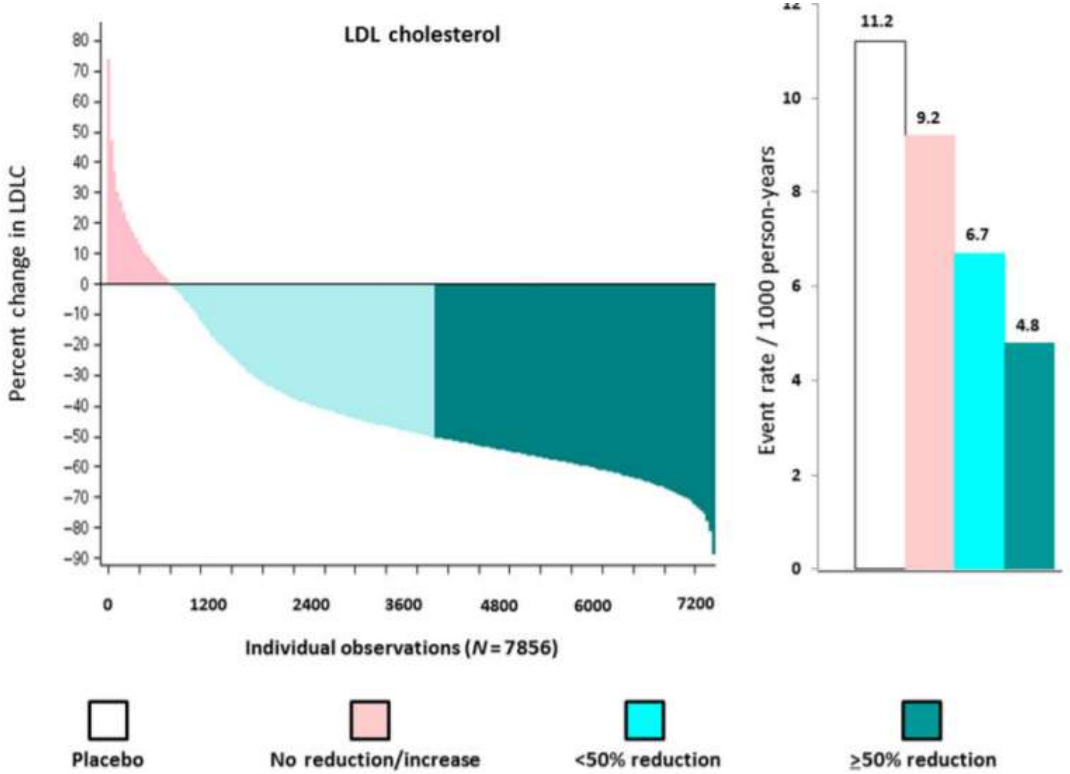
1. Sever PS et al. *Lancet.* 2003;361:1149–1158. **2**. Colhoun HM et al. *Lancet*. 2004;364:685–696. 3. Amarenco P et al., N Engl J Med 2006;355:549-59.
4. LaRosa JC et al. *N Engl J Med* 2005;352:1425–1435. **5**. Schwartz GG et al. *JAMA*. 2001;285:1711–1718. 6. Cannon C, et al. N Engl J Med. 2004;350:1495-504.

Statin Effects on CV Event Reduction and Residual Risk



Statin is Effective, However…

As documented for low- and moderate-intensity regimens, variability in % LDLC reduction following high-intensity statin therapy is wide yet the magnitude of this % reduction directly relates to efficacy



European Heart Journal (2016) 37, 1373–1379

Waterfall plot for individual trial participants allocated to rosuvastatin 20 mg for the per cent change in low-density lipoprotein cholesterol (left) and concordant incident event rates (per 1000 person-years) for the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin primary endpoint (right). Data are shown for the placebo group (white bars) and for those allocated to rosuvastatin who had no reduction or an increase in low-density lipoprotein cholesterol (pink), a .0 but ,50% reduction in low-density lipoprotein cholesterol (light green), and a ≥50% reduction in low-density lipoprotein cholesterol (dark green).

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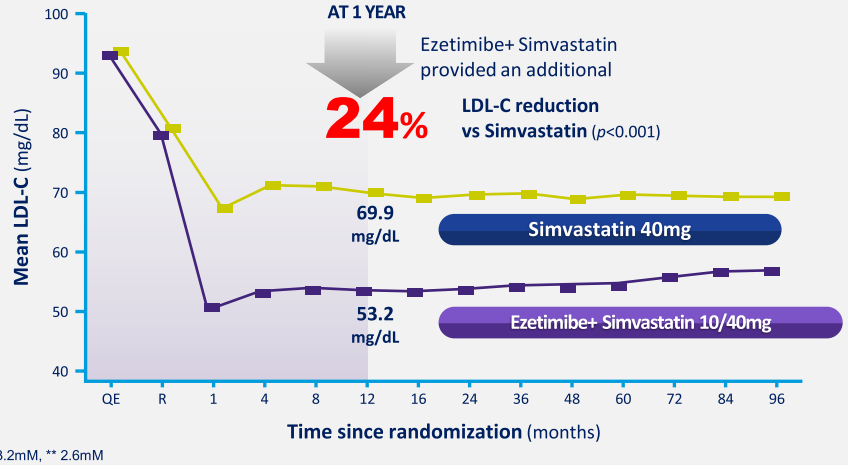
IMProved Reduction of Outcomes : Vytorin Efficacy International Trial[1-5]

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

- **Ezitimibe/simvastatin 10/40 mg**
- **Simvastatin 40 mg**

Primary Endpoint:
CV death, MI, hospital admission for UA, coronary revascularization
(≥ 30 days after randomization), **or stroke**
Duration: Minimum 2½--year follow-up (at least 5250 events)

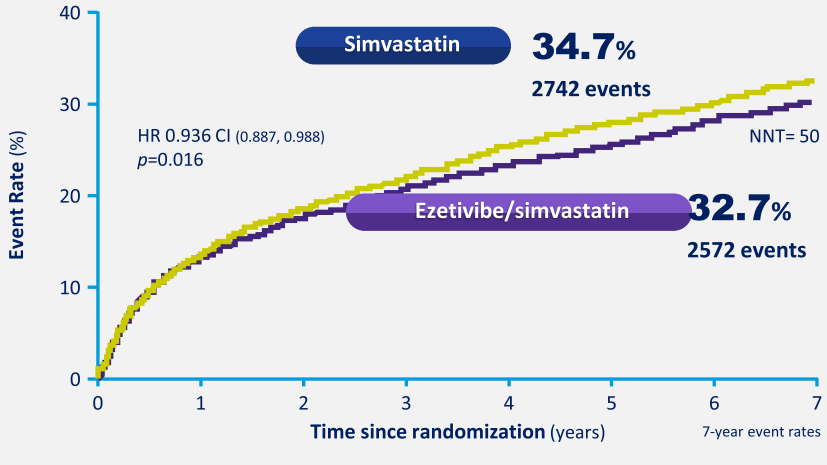
Change of LDL-cholesterol[4,5]



* 3.2mM, ** 2.6mM

Adapted from Cannon CP, *et al.*[4]

Primary Endpoint[4]



Adapted from Cannon CP, *et al.*[4]

Adapted From Cannon CP, *et al.* N Engl J Med. 2015;372(25):2387–2397;
IMPROVE-IT Main Study Results.5

1. Cannon CP, *et al.* Rationale and design of IMPROVE-IT. *AHJ.* 2008;156:826-32 **2.** Califf RM, *et al.* Premature Release of Data from Clinical Trials of ezetimibe. *New England Journal of Medicine*. 2009;361:712-717 **3.** Blazing MA, *et al.* Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: Final baseline characteristics of the IMPROVE-IT study population. *AHJ.* 2014;168:205-12 **4.** 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 **5.** Cannon CP, *et al. N Engl J Med.* 2015;372(25):2387–2397; IMPROVEIT Main Study Results. http://www.timi.org/index.php?page=improve-it-timi-40-slide-sets. Accessed July 20, 2015.

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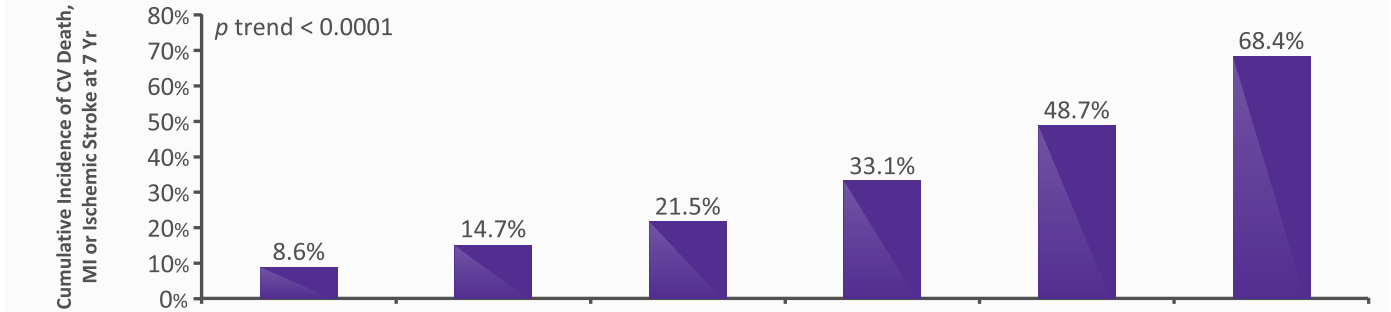
Atherothrombotic risk stratification using the TRS 2ºP risk indicators showed a strong graded relationship with the rate of CV death, MI, or ischemic stroke at 7 years in IMPROVE-IT

Risk Stratification of CV Death, MI, or Ischemic Stroke in the Control Arm (Placebo/Simvastatin)

TRS 2°P Risk Indicators	CHF	HTN	Age ≥ 75	DM	Prior Stroke	Prior CABG	PAD	eGFR < 60	Smoking	Maximum Possible
Points	1	1	1	1	1	1	1	1	1	9



# Risk Indicators	0	1	2	3	4	≥5
At Risk	1070	2957	2642	1418	534	248
% Population	12	33	30	16	6	2
Simva Events	79	381	471	377	200	128

TRS 2ºP : TIMI(Thrombolysis in myocardial infarction) risk score for secondary prevention, **Study design** This study tested the hypothesis that atherothrombotic risk stratification may be useful to identify post-ACS patients who have the greatest potential for benefit from the addition of ezetimibe to statin therapy. The TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention (TRS 2P) is a simple 9-point risk stratification tool, previously developed in a large population with atherothrombosis to predict CV death, myocardial infarction (MI), and ischemic stroke (CV death/MI/ischemic cerebrovascular accident [iCVA]). The current study applied this tool prospectively to 17,717 post-ACS patients randomized either to ezetimibe and simvastatin or to placebo and simvastatin in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Treatment efficacy was assessed by baseline risk for CV death/MI/iCVA, the IMPROVE-IT composite endpoints (CE), and individual component endpoints at 7 years.

1. Bohula EA, *et al.* Atherothrombotic risk stratification and Ezetimibe for secondary prevention. *Journal of the american college of cardiology*. 2017;69(8):911-921

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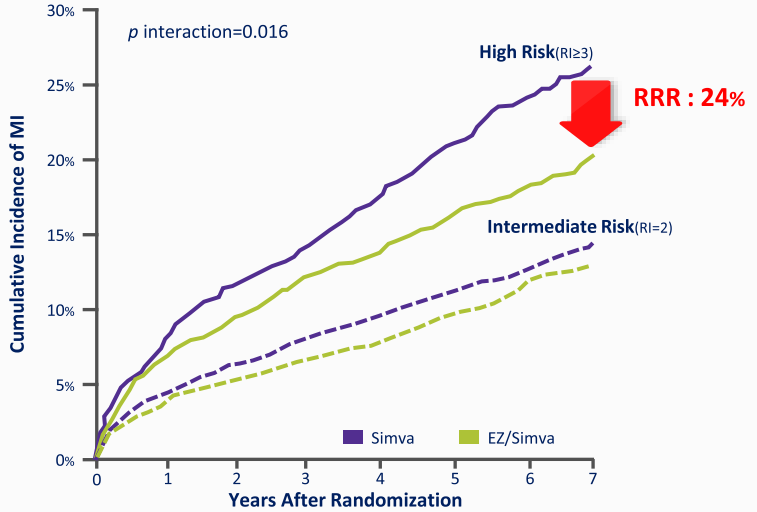
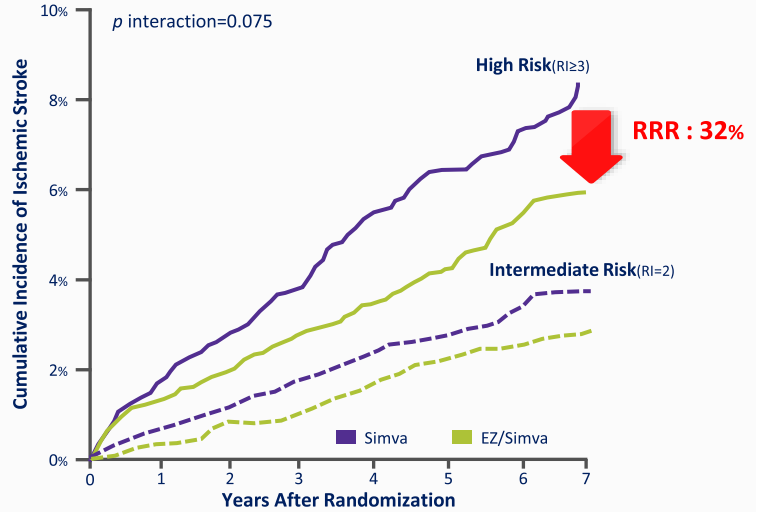
Ezetimibe demonstrated 24% In MI & 32% in Ischemic Stroke when added to statin therapy in high risk patients

Outcomes by Risk Category and Randomized Treatment : MI*



		7yr KM	ARR	HR
High risk	Simva	26.2%	5.9% (2.9, 9.1)	0.76 (0.66, 0.88)
	Ez/Simva	20.3%		
Intermediate risk	Simva	14.4%	1.5% (-0.5, 3.7)	0.87 (0.74, 1.02)
	Ez/Simva	12.9%		

Outcomes by Risk Category and Randomized Treatment : Ischemic stroke**



		7yr KM	ARR	HR
High risk	Simva	8.4%	2.4% (0.4, 4.4)	0.68 (0.52, 0.88)
	Ez/Simva	6.0%		
Intermediate risk	Simva	3.8%	1.0% (-0.2, 2.1)	0.75 (0.54, 1.05)
	Ez/Simva	2.8%		

1. Bohula EA, *et al.* Atherothrombotic risk stratification and Ezetimibe for secondary prevention. *Journal of the american college of cardiology*. 2017;69(8):911-921/

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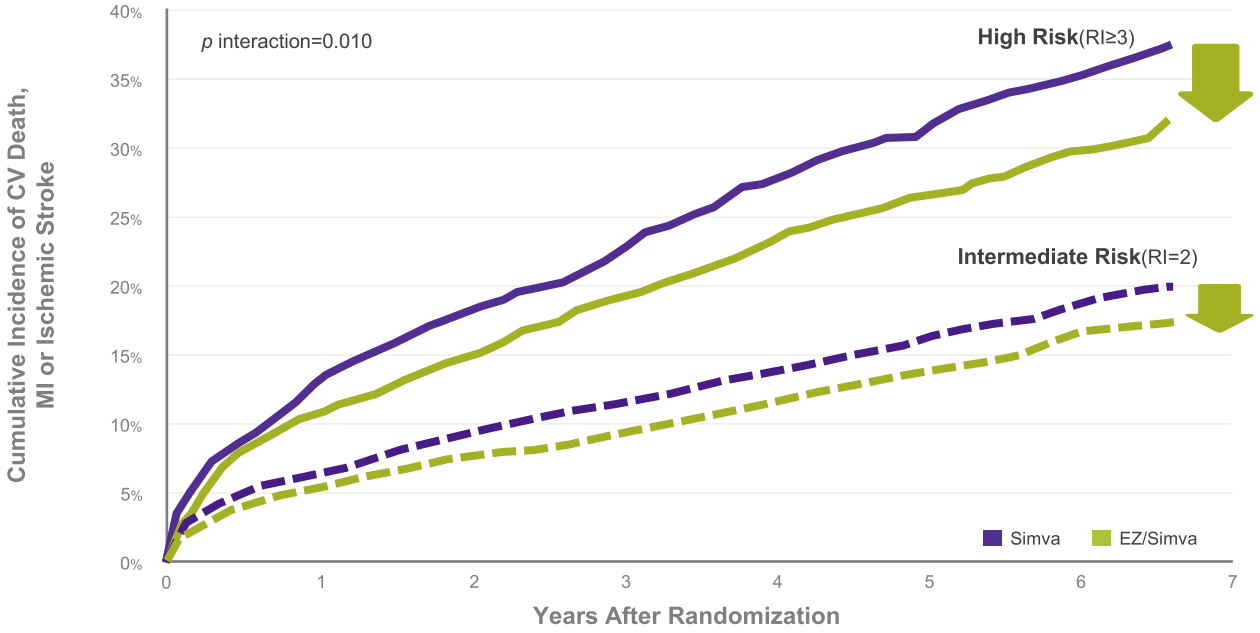
[IMROVE-IT sub-analysis]

Addition of ezetimibe to Simvastatin demonstrated a significant 19% relative risk reduction with a NNT of 16 in high risk patients

Outcomes by Risk Category and Randomized Treatment : CV death, MI or ischemic stroke



NNT=16

RRR : 19%

7yr KM	ARR	HR
Simva 40.2%	6.3% (2.9, 9.7)	0.81 (0.73, 0.90)
Ez/Simva 33.9%		

NNT=44

RRR : 11%

7yr KM	ARR	HR
Simva 21.5%	2.2% (-0.3,4.6)	0.89 (0.78, 1.01)
Ez/Simva 19.3%		

1. Bohula EA, *et al*. Atherothrombotic risk stratification and Ezetimibe for secondary prevention. *Journal of the American college of cardiology*. 2017;69(8):911-921.

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[IMROVE-IT sub-analysis]

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

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

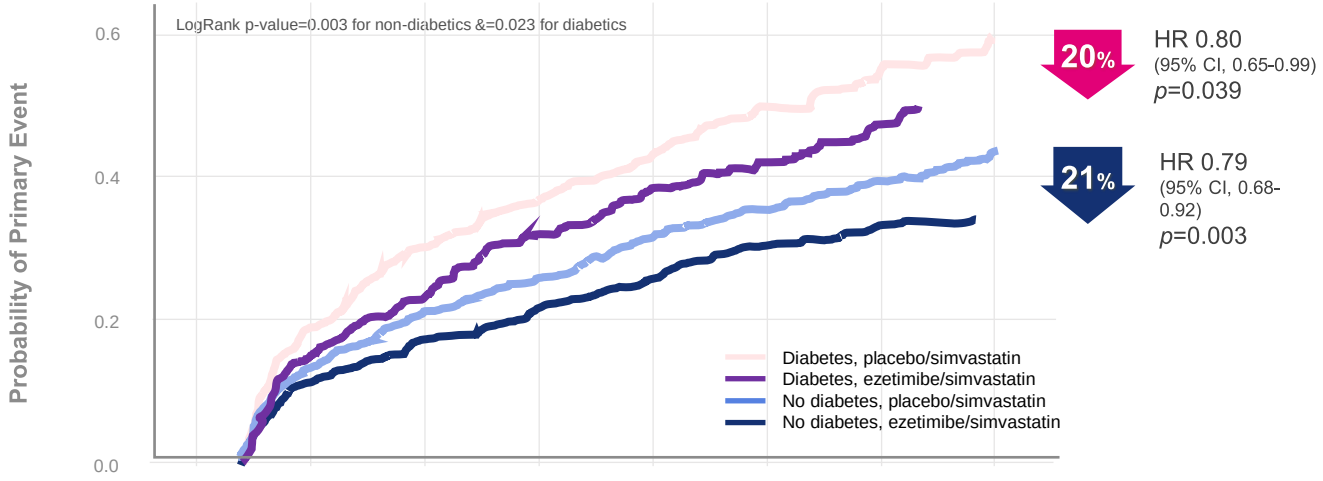
LLT : Lipid lowering treatment, **LDL-C** : Low density lipoprotein Cholesterol, DM : diabetes mellitus, **CV** : Cardiovascular, **EZ/Simva** : Ezetimibe/Simvastatin

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.

ORGANON

[IMROVE-IT subgroup]
The CV benefit of Ezetimibe add-on therapy in elderly patients ≥75 years old with DM or non-DM

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



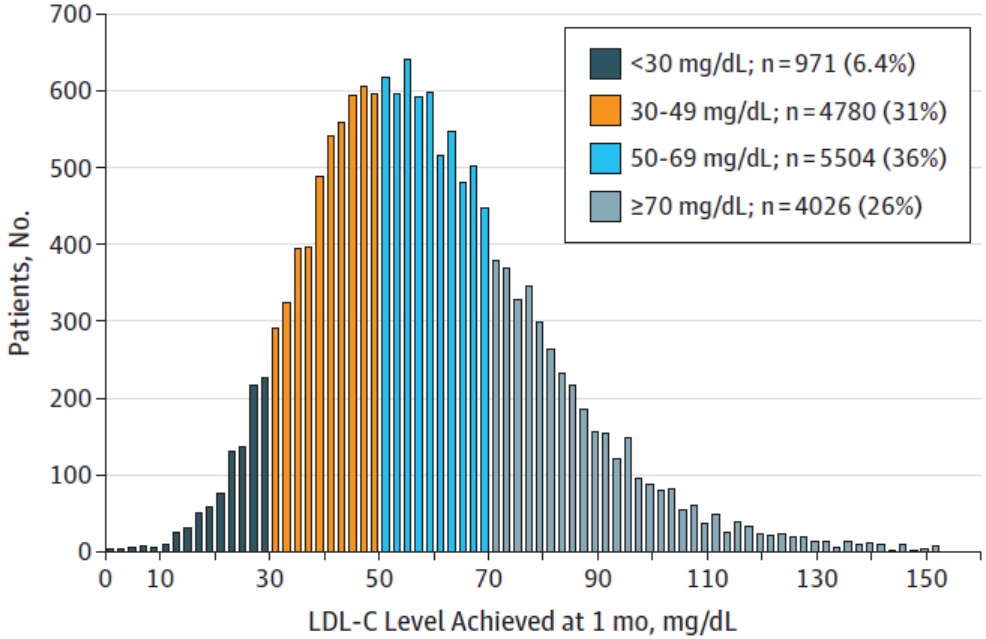
	0	1	2	3	4	5	6	7
Diabetes, placebo/simvastatin	968	778	706	645	572	394	296	177
Diabetes, ezetimibe/simvastatin	**1009**	**784**	**698**	**639**	**551**	**397**	**283**	**159**
No diabetes, placebo/simvastatin	402	300	258	228	200	133	93	48
No diabetes, ezetimibe/simvastatin	**418**	**300**	**248**	**213**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

Time (year) **post-randomization**

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.

ORGANON

IMPROVE-IT subgroup analysis : Long-term Safety and Efficacy
Low-Density Lipoprotein Cholesterol (LDL-C) Level at 1 Month



The median LDL-C level was 56 mg/dL (interquartile range, 43-70 mg/dL).
To convert LDL-C to millimoles per liter, multiply by 0.0259.

Giugliano RP, *et al*. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. *JAMA Cardiol.* 2017 May 1;2(5):547-555

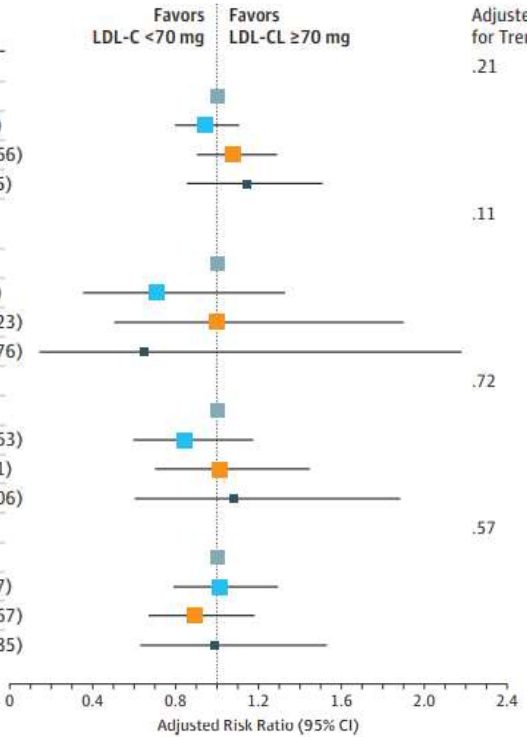
ORGANON

IMPROVE-IT subgroup analysis : Long-term Safety and Efficacy

Patients achieving an LDL-C ≥70mg/dL and < 70mg/dL at 1 month had a similar safety profile over a 6-year period

Safety events by achieved LDL-C level at 1 month

Safety Event	HR (95% CI)	Adjusted *P* Value for Trend
Adverse event → discontinuation		.21
≥70	1 [Reference]	
50-69	0.948 (0.817-1.1)	
30-49	1.076 (0.915-1.266)	
<30	1.13 (0.872-1.465)	
Rhabdomyolysis, myopathy, or myalgia with CK elevation >5x ULN		.11
≥70	1 [Reference]	
50-69	0.736 (0.417-1.3)	
30-49	1.003 (0.552-1.823)	
<30	0.682 (0.224-2.076)	
AST or ALT >3x ULN		.72
≥70	1 [Reference]	
50-69	0.859 (0.635-1.163)	
30-49	1.017 (0.733-1.41)	
<30	1.076 (0.642-1.806)	
Gallbladder adverse event		.57
≥70	1 [Reference]	
50-69	1.016 (0.813-1.27)	
30-49	0.906 (0.703-1.167)	
<30	0.995 (0.667-1.485)	



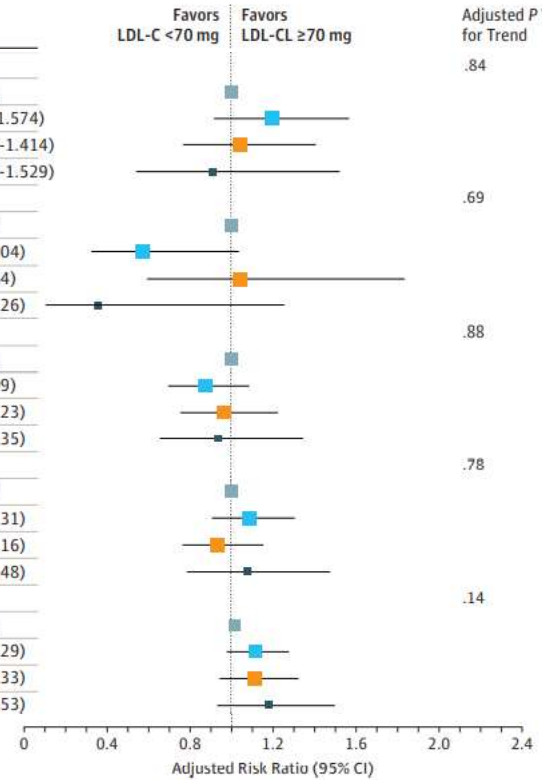
Giugliano RP, *et al*. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. *JAMA Cardiol.* 2017 May 1;2(5):547-555

ORGANON

IMPROVE-IT subgroup analysis : Long-term Safety and Efficacy

Patients achieving an LDL-C ≥70mg/dL and < 70mg/dL at 1 month had a similar safety profile over a 6-year period

Safety Event	HR (95% CI)	Adjusted *P* Value for Trend
Neurocognitive event		.84
≥70	1 [Reference]	
50-69	1.204 (0.92-1.574)	
30-49	1.045 (0.772-1.414)	
<30	0.913 (0.545-1.529)	
Hemorrhagic stroke		.69
≥70	1 [Reference]	
50-69	0.58 (0.33-1.04)	
30-49	1.05 (0.6-1.84)	
<30	0.36 (0.11-1.26)	
Hospitalized for heart failure		.88
≥70	1 [Reference]	
50-69	0.88 (0.7-1.09)	
30-49	0.97 (0.76-1.23)	
<30	0.94 (0.66-1.35)	
Noncardiovascular death		.78
≥70	1 [Reference]	
50-69	1.09 (0.91-1.31)	
30-49	0.94 (0.77-1.16)	
<30	1.08 (0.79-1.48)	
Cancer		.14
≥70	1 [Reference]	
50-69	1.11 (0.96-1.29)	
30-49	1.12 (0.95-1.33)	
<30	1.18 (0.91-1.53)	

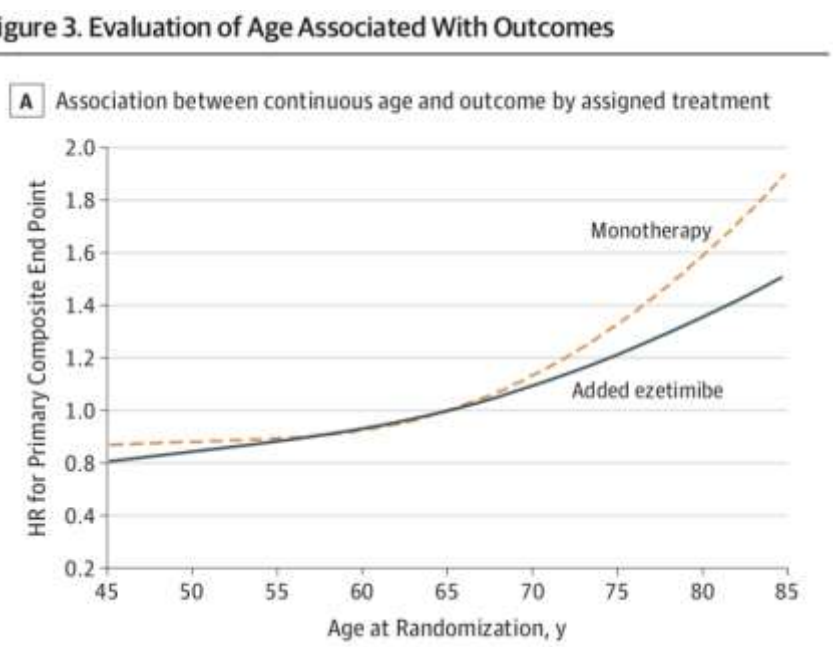


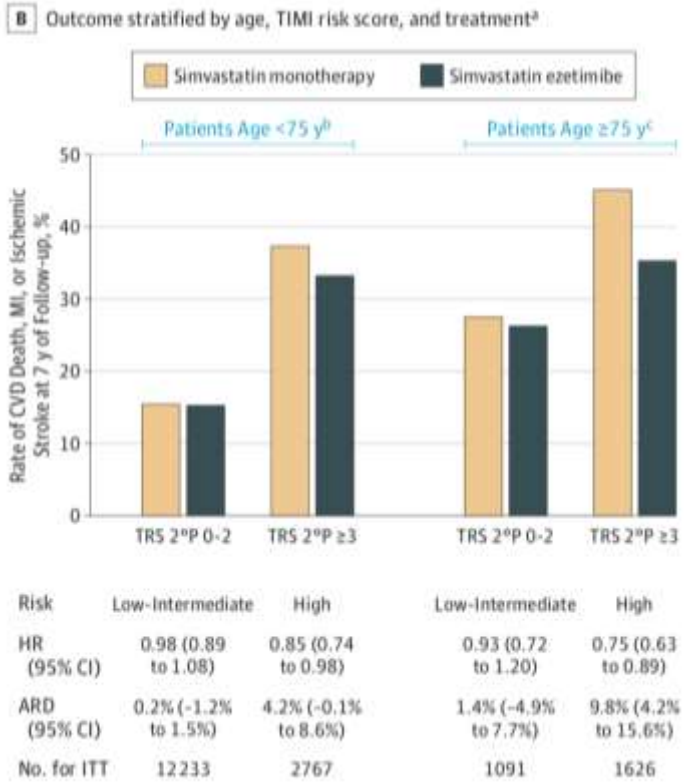
Giugliano RP, *et al*. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. *JAMA Cardiol.* 2017 May 1;2(5):547-555

ORGANON

[IMPROVE-IT : Long-term Safety]
Simva/Eze vs. Simva after ACS Among Patients ≥75 Years Starting EZE/ATV Combo

Figure 3. Evaluation of Age Associated With Outcomes





Risk	Low-Intermediate	High	Low-Intermediate	High
HR (95% CI)	0.98 (0.89 to 1.08)	0.85 (0.74 to 0.98)	0.93 (0.72 to 1.20)	0.75 (0.63 to 0.89)
ARD (95% CI)	0.2% (-1.2% to 1.5%)	4.2% (-0.1% to 8.6%)	1.4% (-4.9% to 7.7%)	9.8% (4.2% to 15.6%)
No. for ITT	12233	2767	1091	1626

Bach RG, et al. JAMA Cardiol. doi:10.1001/jamacardio.2019.2306

ORGANON

[IMPROVE-IT : Long-term Safety]
Simva/Eze vs. Simva after ACS Among Patients ≥75 Years Starting EZE/ATV Combo

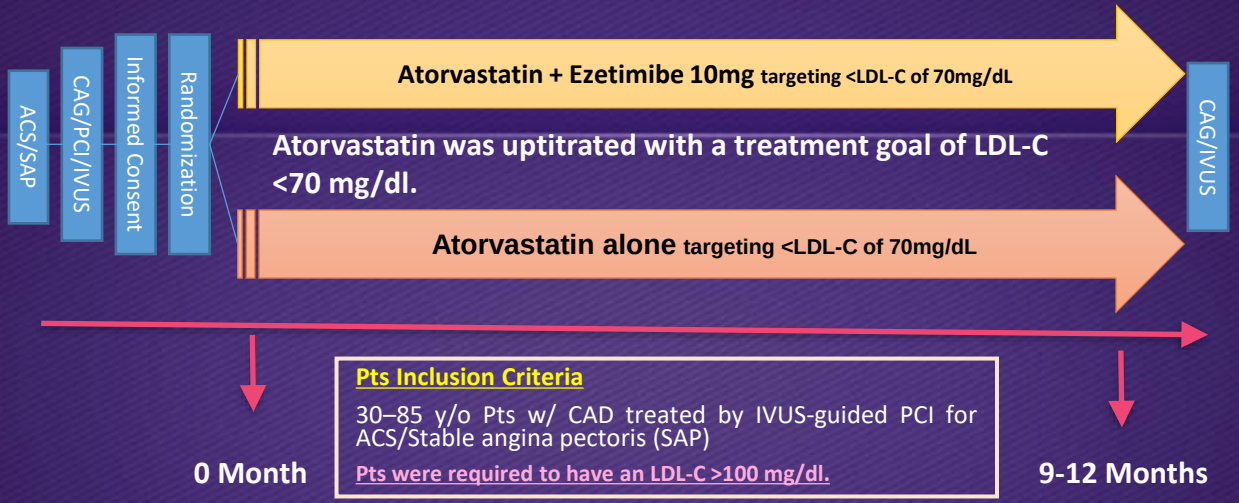
Table 2. Safety End Points According to Age at Randomization and Treatment

	Patient Age Group by Treatment, No. (%)					
	<65 y		65-74 y		≥75 y	
	Simvastatin Monotherapy (n = 5129)	Simvastatin-Ezetimibe (n = 5044)	Simvastatin Monotherapy (n = 2520)	Simvastatin-Ezetimibe (n = 2653)	Simvastatin Monotherapy (n = 1428)	Simvastatin/Ezetimibe (n = 1370)
Liver-related events						
ALT or AST level or both ≥3 × ULN	108 (2.1)	128 (2.5)	51 (2.0)	60 (2.3)	49 (3.4)	36 (2.6)
Gallbladder-related adverse events	169 (3.3)	138 (2.7)	105 (4.2)	100 (3.8)	47 (3.3)	44 (3.2)
Muscle-related events						
Rhabdomyolysis	6 (0.1)	5 (0.1)	9 (0.4)	5 (0.2)	3 (0.2)	3 (0.2)
Myopathy	4 (0.1)	7 (0.1)	5 (0.2)	7 (0.3)	1 (0.1)	1 (0.1)
Myalgia	52 (1.0)	53 (1.1)	34 (1.3)	25 (0.9)	16 (1.1)	11 (0.8)
Myalgia with CK	17 (0.3)	16 (0.3)	9 (0.4)	5 (0.2)	5 (0.4)	5 (0.4)
Myopathy/rhabdomyolysis/myalgia with CK	27 (0.5)	28 (0.6)	22 (0.9)	16 (0.6)	9 (0.6)	9 (0.7)
Any cancer	368 (7.2)	378 (7.5)	335 (13.3)	339 (12.8)	212 (14.8)	192 (14.0)
Cataracts	106 (2.1)	116 (2.3)	134 (5.3)	151 (5.7)	85 (6.0)	81 (5.9)
Cognitive impairment	110 (2.1)	107 (2.1)	61 (2.4)	72 (2.7)	68 (4.8)	64 (4.7)

Today's Contents

- Treatment gap between real world and cholesterol lowering studies
- Residual Risk of Statin Mono-therapy and Ezetimibe outcome study
- **Benefit of Atorvastatin and Ezetimibe in plaque regression**

PRECISE-IVUS Study



Eligible pts who underwent PCI were randomly assigned to atorvastatin alone or atorvastatin + ezetimibe (10 mg) daily.

Randomization was stratified by 1) gender, 2) age, 3) history of HTN, 4) history of DM, 5) history of PAD, 6) serum LDL-C level, 7) serum HDL-C level, 8) serum TG level, and 9) statin pretreatment prior to study enrollment.

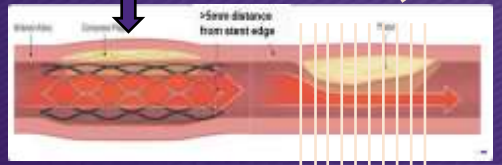
Tsujita K, Ogawa H, et al. ***J Am Coll Cardiol*** 2015;66:495–507

IVUS Acquisition & Endpoints

On the basis of expert consensus (9), the primary efficacy endpoint was the absolute change in percent atheroma volume (PAV) of the coronary selected target segment from baseline to follow-up. The PAV was calculated as follows:

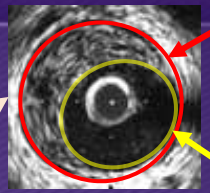
$$\text{PAV} = \frac{\Sigma\,(\text{EEM CSA} - \text{lumen CSA})}{\Sigma\,\text{EEM CSA}} \times 100$$

where EEM CSA is the cross-sectional area of the EEM border, and the lumen CSA is the cross-sectional area of the lumen border. For PAV, the summation of the EEM CSA minus the lumen CSA was performed first. This value was then divided by the summation of the EEM CSA, which was finally multiplied by 100. The absolute change in PAV was calculated as the PAV at 9- to 12-month follow-up minus the PAV at baseline.



S_0 S_1 S_2 … S_{n-1} S_n

Cross-Sectional Contour Analysis



Plaque = EEM - lumen

Volumetric Analysis

Modified Simpson's Rule

$$\text{Volume} = \sum_{i=0}^{n} S_i = S_0 + S_1 + \cdots\cdots + S_{n-1} + S_n$$

Percent Atheroma Volume (PAV)

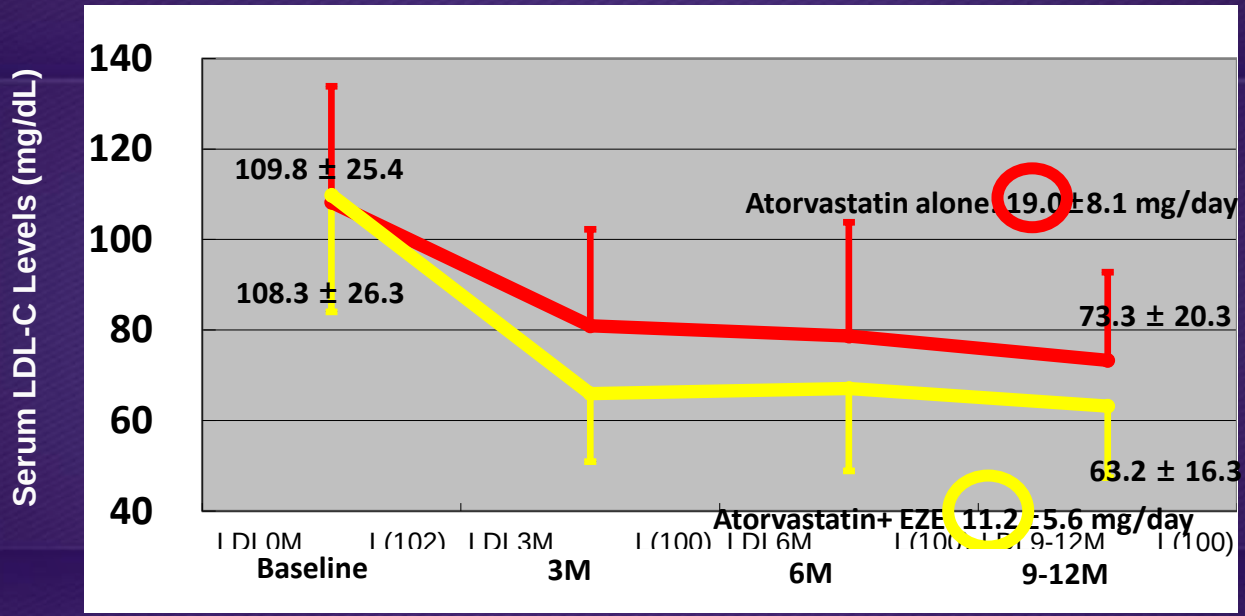
$$\text{PAV} = \sum (\text{EEM}_{CSA} - \text{lumen}_{CSA}) / \sum \text{EEM}_{CSA} \times 100$$

1st IVUS Endpoint; ΔPAV = $PAV_{follow\text{-}up} - PAV_{baseline}$
2nd IVUS Endpoint; % Change in Total Atheroma Volume

Serial volumetric IVUS was performed at baseline and again at 9-12 months to quantify the coronary plaque response.

Tsujita K, Ogawa H, et al. ***J Am Coll Cardiol*** 2015;66:495–507

Serial Change in Serum LDL-C



Whereas the f/u LDL-C values were significantly lower in LZ group than in L group (63.2±16.3 vs 73.3±20.3mg/dL), the final dosage of atorvastatin were significantly lower in LZ group than in L group. Attain rate to achieve LDL-C <70mg/dL were significantly higher in LZ group (72% vs. 47%).

Tsujita K, Ogawa H, et al. ***J Am Coll Cardiol*** 2015;66:495–507

Coronary Plaque Progression/Regression
Full Analysis Set Analysis

For superiority, the absolute change in PAV decreased by –1.4% in the Atorvastatin +EZE group and by –0.3% in the Atorvastatin group. For PAV, a significantly greater percentage of pts of the the Atorvastatin +EZE group showed coronary plaque regression (78% vs. 58%).

After classifying the entire study cohort into either an ACS or SAP cohort, the between-group difference of the plaque regression effect was greater in the ACS cohort.

With regard to vessel remodeling during f/u, the vessel volume of the target segment was negatively remodeled in the the Atorvastatin +EZE group vs the Atorvastatin group.

Similar results were confirmed even in the "per protocol set" cohort.

	LZ Group (n = 100)	p Value With Baseline	L Group (n = 102)	p Value With Baseline	p Value Between Groups
Plaque volume (mm^3)	-3.9 (-10.6-0.0)	<0.001	-1.0 (-6.8-5.7)	0.4	0.001
PAV (%)	-1.4 (-3.4--0.1)	<0.001	-0.3 (-1.9-0.9)	0.03	0.001
ACS cohort	-2.3 (-3.7--0.5)	<0.001	-0.2 (-1.3-0.5)	0.2	<0.001
SAP cohort	-1.2 (-2.2--0.1)	0.001	-0.7 (-2.3-1.1)	0.08	0.2
TAV_{norm} (mm^3)	-5.3 (-12.4-0.1)	<0.001	-1.2 (-5.7-3.3)	0.1	<0.001
Vessel volume (mm^3)	-4.1 (-12.6-3.1)	0.001	-0.6 (-11.8-10.6)	0.9	0.04

Tsujita K, Ogawa H, et al. ***J Am Coll Cardiol*** 2015;66:495–507

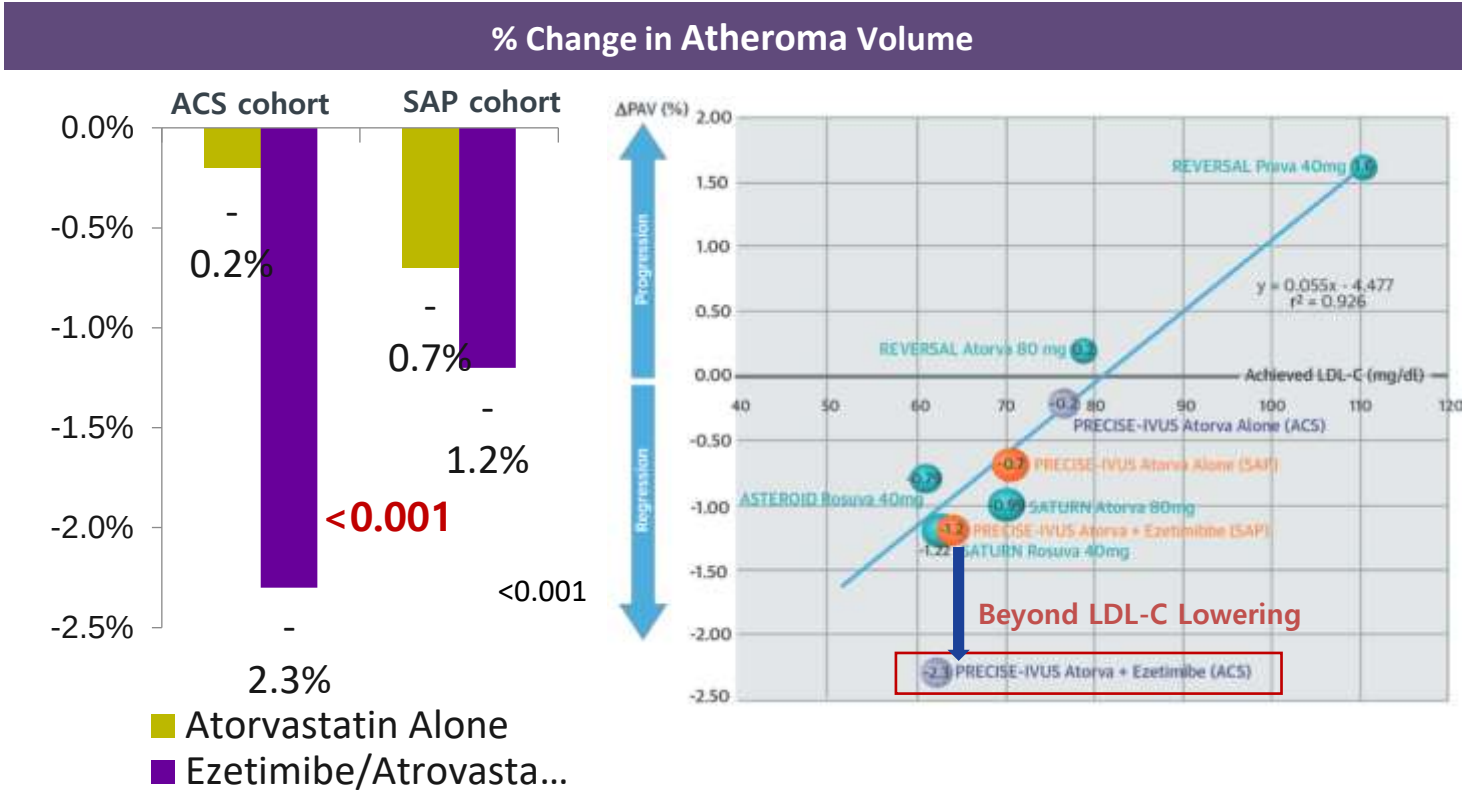
Between the Regression vs. Progression in PAV

	Regression in PAV (n = 135)	Progression in PAV (n = 67)	p Value
Total cholesterol, mg/dL	130.6 ± 24.0	141.5 ± 24.3	0.006
HDL-cholesterol, mg/dL	44.0 ± 12.2	45.3 ± 10.7	0.2
LDL-cholesterol, mg/dL	65.5 ± 17.8	74.3 ± 20.3	0.003
Ratio of LDL-C to HDL-C	1.57 ± 0.51	1.71 ± 0.54	0.08
Triglycerides, mg/dL	95.0 (76.0-126.5)	102.0 (85.0-142.0)	0.2
Apolipoprotein A-I, mg/dL	124.0 ± 25.6	130.0 ± 22.6	0.04
Apolipoprotein B, mg/dL	64.1 ± 14.6	69.3 ± 15.2	0.02
sd LDL-cholesterol, mg/dL	20.4 ± 8.6	24.1 ± 10.6	0.02
Lathosterol, µg/100mg TC	63.5 (43.5-91.2)	57.7 (44.3-85.3)	0.8
Campesterol, µg/100mg TC	225.0 (174.4-356.9)	261.9 (207.1-395.8)	0.1

Compared with pts with plaque progression (any positive change in PAV), the achieved LDL-C level was significantly suppressed in pts with plaque regression (any negative change in PAV), as well as apolipoprotein B and small-dense LDL-C. Among cholesterol absorption markers, the campesterol-to-cholesterol ratio tended to be lower in the regression group vs. the progression group.

Tsujita K, Ogawa H, et al. ***J Am Coll Cardiol*** 2015;66:495–507

Relationship Between Achieved Low -Density Lipoprotein Cholesterol Levels and the Median Change in Percent Atheroma Volume for Previous Intravascular Ultrasound Trials and the PRECISE -IVUS Trial



The ZIPANGU Study]

Effect of Ezetimibe on Stabilization and Regression of Intracoronary Plaque

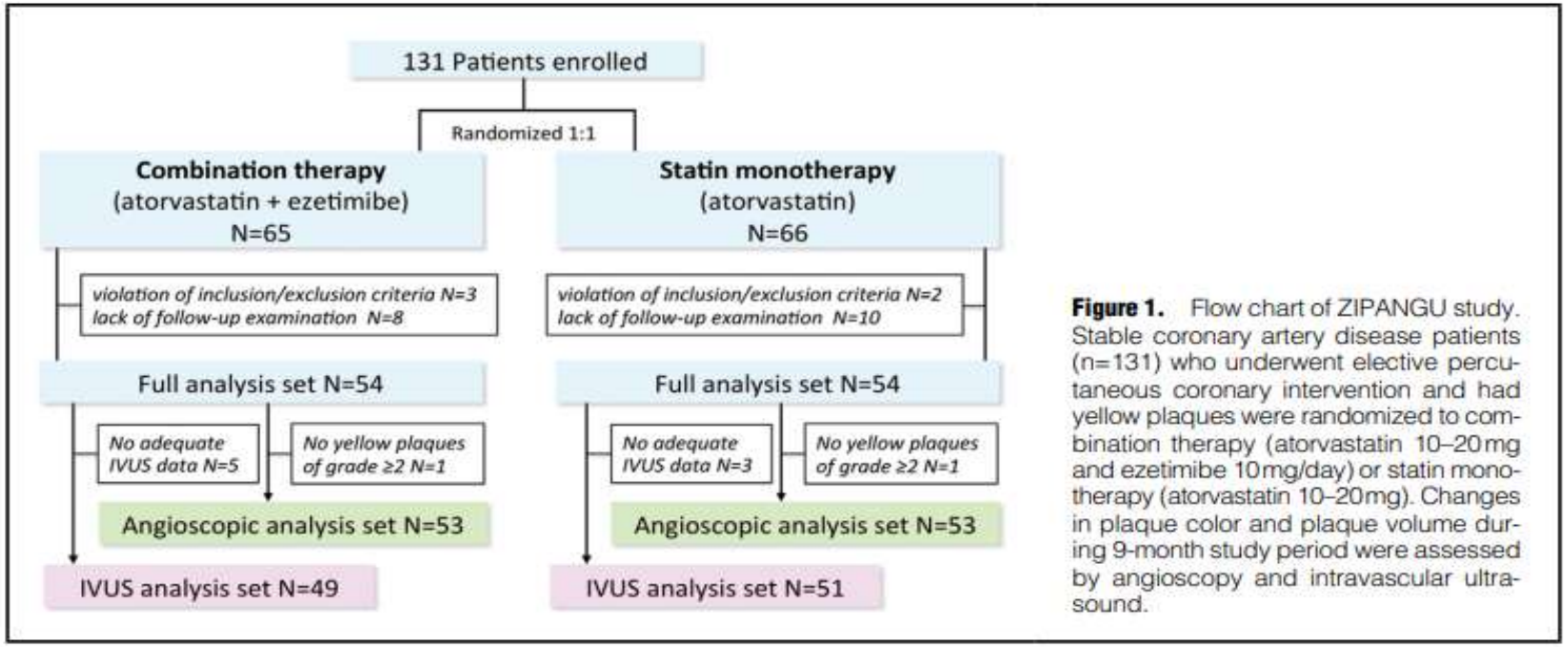


Figure 1. Flow chart of ZIPANGU study. Stable coronary artery disease patients (n=131) who underwent elective percutaneous coronary intervention and had yellow plaques were randomized to combination therapy (atorvastatin 10–20 mg and ezetimibe 10 mg/day) or statin monotherapy (atorvastatin 10–20 mg). Changes in plaque color and plaque volume during 9-month study period were assessed by angioscopy and intravascular ultrasound.

Circ J 2017; 81: 1611–1619 doi:10.1253/circj.CJ-17-0193

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The ZIPANGU Study]

Effect of Ezetimibe on Stabilization and Regression of Intracoronary Plaque

Table 2. Changes in Laboratory Data in the ZIPANGU Study

	Monotherapy group (atorvastatin 10–20 mg/day)				Combination therapy group (atorvastatin 10–20 mg/day and ezetimibe 10 mg/day)			
	Baseline	1 month	3 months	9 months	Baseline	1 month	3 months	9 months
Serum lipid profile, mg/dL								
TC	162±33	150±27	144±21*	140±21**	168±36	126±24**,††	129±23**,†	126±25**,†
LDL-C	101±27	81±19**	77±19**	75±16**	101±27	61±16**,††	63±14**,††	61±17**,††
HDL-C	45±9	46±11	46±10	45±11	47±19	46±12	47±11	44±12
Triglycerides	113±52	127±77	114±67	109±54	114±58	98±50	111±71	95±46*
Other laboratory data								
Hemoglobin A1c,%	5.5±0.7	–	–	5.6±0.7	5.7±0.7	–	–	5.9±0.9*,†
Creatinine, mg/dL	0.8±0.2	0.9±0.2	0.9±0.2*	0.9±0.2	0.9±0.3	0.9±0.2	0.9±0.3	0.8±0.2
hs-CRP, ng/dL	5,510±13,018	–	–	988±1,521**	7,653±11,370	–	–	1,699±2,830**
Campesterol, μg/mL	4.0±1.6	–	–	4.6±1.6**	4.4±2.0	–	–	2.1±0.7**,††
Sitosterol, μg/mL	2.1±0.9	–	–	2.4±0.9**	2.2±0.9	–	–	1.3±0.4**,††
Lathosterol, μg/mL	1.3±0.7	–	–	1.1±0.2*	1.5±1.0	–	–	1.2±0.4*,††
Campesterol, μg/100 mg TC	248±90	–	–	330±102**	267±107	–	–	166±46**,††
Sitosterol, μg/100 mg TC	130±54	–	–	171±58**	137±57	–	–	109±29**,††
Lathosterol, μg/100 mg TC	83±37	–	–	77±18	91±47	–	–	95±25*,††

*P<0.05 vs. baseline. **P<0.001 vs. baseline. †P<0.05 vs. monotherapy. ††P<0.001 vs. monotherapy. Significant based on a Bonferroni correction. Abbreviations as in Table 1.

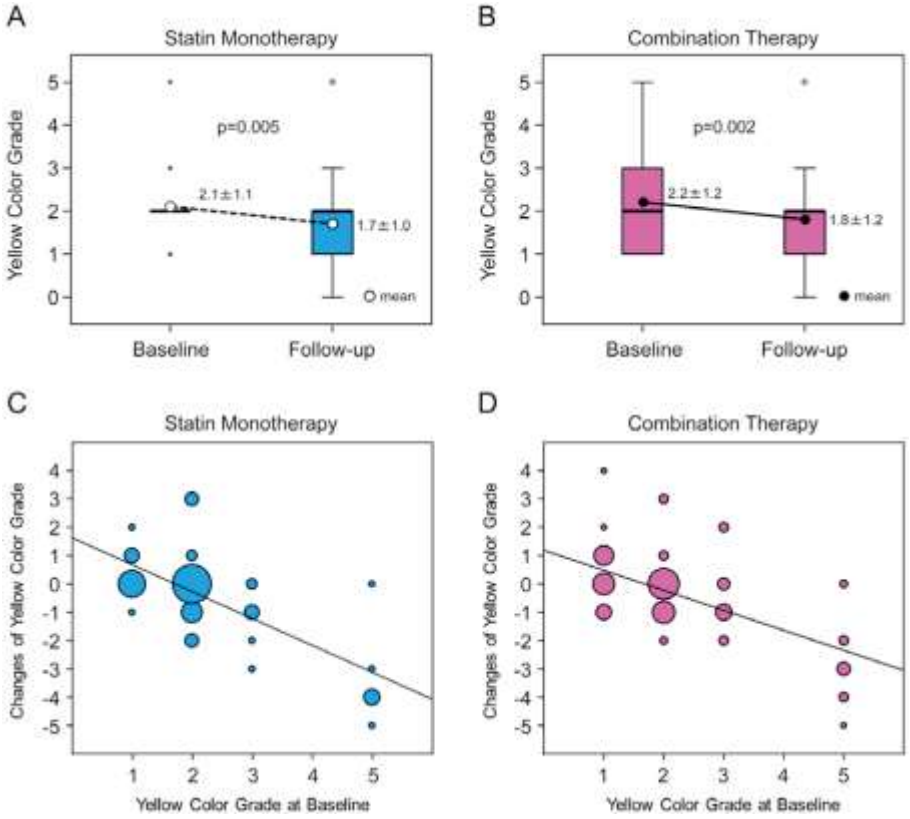
Circ J 2017; 81: 1611–1619 doi:10.1253/circj.CJ-17-0193

ORGANON

There was no significant difference in the slope of the regression lines between the monotherapy and combination therapy groups

The yellow color grade decreased significantly from baseline to follow-up in both the monotherapy group and combination group.

The change in yellow color grade was significantly associated with the yellow color grade at baseline in both the monotherapy group



The size of each circle indicates the number of yellow plaques.

Circ J 2017; 81: 1611 – 1619

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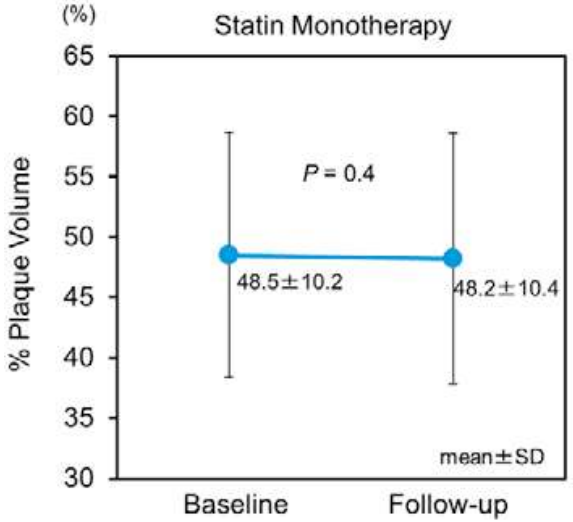
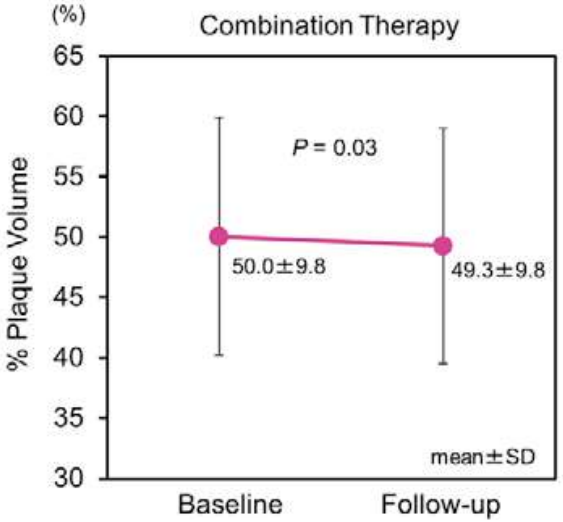
The %plaque volume did not change from baseline to follow-up in the monotherapy group, but decreased significantly in the combination therapy group (50.0±9.8% vs. 49.3±9.8%, P=0.03).



48.5±10.2% vs. 48.2±10.4%
P=0.4



50.0±9.8% vs. 49.3±9.8%
P=0.03

Ezetimibe and Atorvastatin on carotid artery plaque in patients with T2DM complicated with coronary heart disease

* Atorvastatin Group: atorvastatin 20mg, Combination Group: ezetimibe 10mg + atorvastatin 20mg

	TC	TG	LDL	hs-CRP	FPG	HbA_{1c}
Atorvastatin group						
Before	5.28±0.69	1.91±0.21	3.45±0.75	3.50±0.73	9.56±1.06	8.5±0.63
After	4.46±0.62*	1.77±0.55*	2.04±0.54*	1.23±0.86*	7.50±0.86*	6.6±0.31*
Combined treatment group						
Before	5.26±0.67	1.92±0.19	3.53±0.87	3.45±0.79	9.70±1.12	8.6±0.76
After	3.05±0.60*#	1.31±0.20*#	1.67±0.43*#	0.68±0.93*#	7.61±1.01*	6.6±0.40*

*P<0.05 compared with before treatment in the same group; #P<0.05 compared with atorvastatin group after the treatment.

	IMT (mm)	Plaque diameter (mm)	Plaque area (mm^2)	Neovascularization on plaques (N.)
Atorvastatin group				
Before	1.27±0.44	11.73±0.74	12.93±0.74	9
After	1.13±0.37*	10.53±0.64*	11.73±0.88*	8
Combined treatment group				
Before	1.26±0.43	11.98±0.84	13.12±0.79	10
After	1.06±0.32*#	9.53±0.59*#	10.94±0.89*#	8

*P<0.05 compared with before treatment in the same group; #P<0.05 compared with atorvastatin group after the treatment.

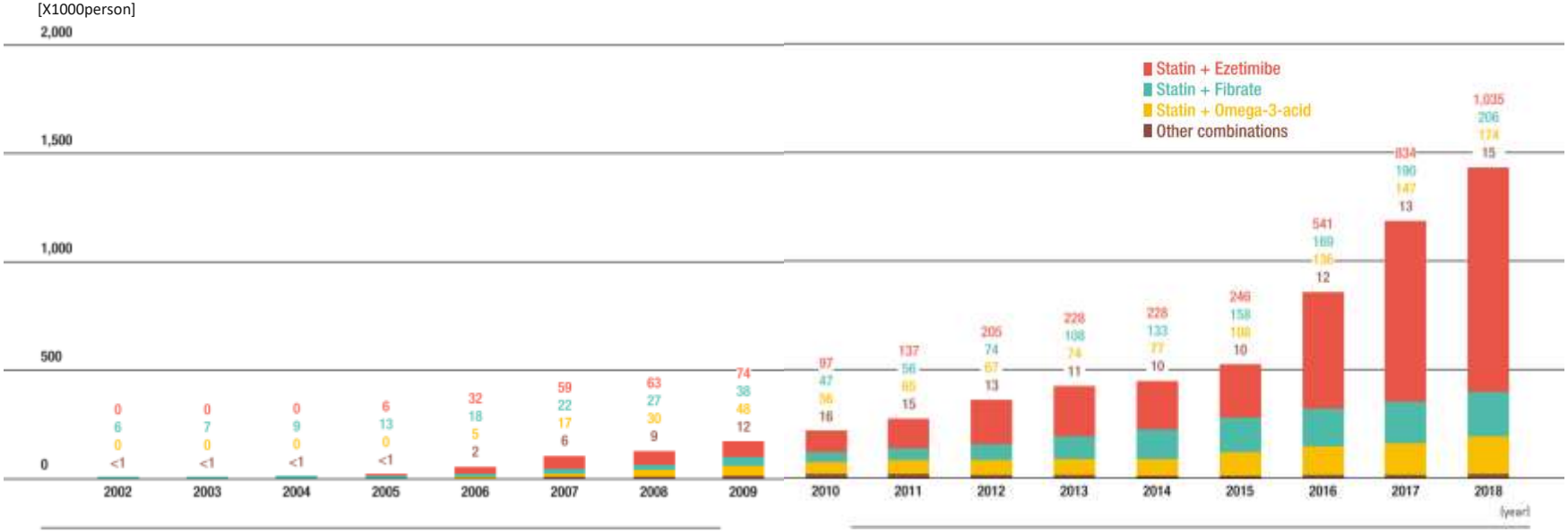
OBJECTIVES: to evaluate the efficacy of ezetimibe combined with atorvastatin in treatment of carotid artery plaque in patients with type 2 diabetes mellitus complicated with coronary heart disease.

Study Method: a multicenter, prospective, randomized trial; patients with carotid atherosclerosis with type 2 diabetes mellitus and CHD; atorvastatin 20mg + ezetimibe 10mg (n=51) vs. atorvastatin 20mg (n=49); Endpoints : serum lipid, ALT, AST, CK, hs-CRP, FBG, HbA1c, and cIMT by ultrasonography

Wang J, et al. Int Angiol. 2017 Jun 21. doi: 10.23736/S0392-9590.17.03818-4. [Epub ahead of print]

Changes in Dual Therapy Regimen

- Estimated Number of People Receiving dual Therapy by Lipid-Lowering Drugs
- Statin are included in 99% of dual therapy regimen
- Statin plus ezetimibe was the most frequently used combination, accounting for 72% of dual therapy in 2018



DYSLIPIDEMIA Fact Sheet in Korea, 2020
Data source by National Insurance Big Data 2002-2018

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Highlights from the recently published 2017 ACC Expert Consensus Decision Pathway on the role of non-statin therapies

Considerations on selecting initial non-statin add-on therapy[Ezetimibe vs. PCSK9i]1

Favors Ezetimibe	Favors PCSK9i
< 25% additional lowering of LDL-C required	**> 25%** additional lowering of LDL-C required
Patients with recent ACS < 3 months	*The clinician–patient discussion should consider the extent o f available scientific evidence for net ASCVD risk- reduction b enefit, cost, administration by subcutaneous injection, every 14-day or monthly dosing schedule, and storage requirement s (refrigeration).
Cost considerations with recent availability of generic ezetimibe and future cost savings	
Ease of use as oral agent with low pill burden	
Patients preferences	
HF, HTN, DM, Stroke, CABG, PAD, smoking	
Age > 75 yrs	
eGFR < 60 ml/min/1.73 m^2	

Adapted from Lloyd-Jones DM, *et al*.[1]

ACC : The American College of Cardiology, LDL-C : Low-density lipoprotein cholesterol, CHD : Coronary heart disease, HF : Heart failure, HTN : Hypertension, DM : diabetes mellitus, CABG : Coronary artery bypass graft surgery, PAD : Peripheral artery disease, GFR : Glomerular Filtration Rate, ASCVD : Atherosclerotic cardiovascular disease, PCSK9i : Proprotein convertase subtilisin kexin type 9 inhibitors.

1. Lloyd-Jones DM, *et al*. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017 Oct 3;70(14):1785-1822.

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Conclusion

1 Increase mortality of CVD event in Korea

The second-highest rate of death after malignant neoplasms is cardiovascular disease, so risk should be prevented based on early active treatment.

2 Treatment gap between target goal and real world

Although LDL-c management is required actively to reduce potential risks, many patients still do not reach treatment targets

3 Strategic for ASCVD patients

When Statin alone does not reach enough treatment targets, the Ezetimibe add-on therapy proved a reduction in CVD events.
As it can help the regression of Plaque, ezetimibe's combination strategy is effective early and actively