Early for Longer : Intensive Lipid Lowering

- Moving Beyond Statins Alone-

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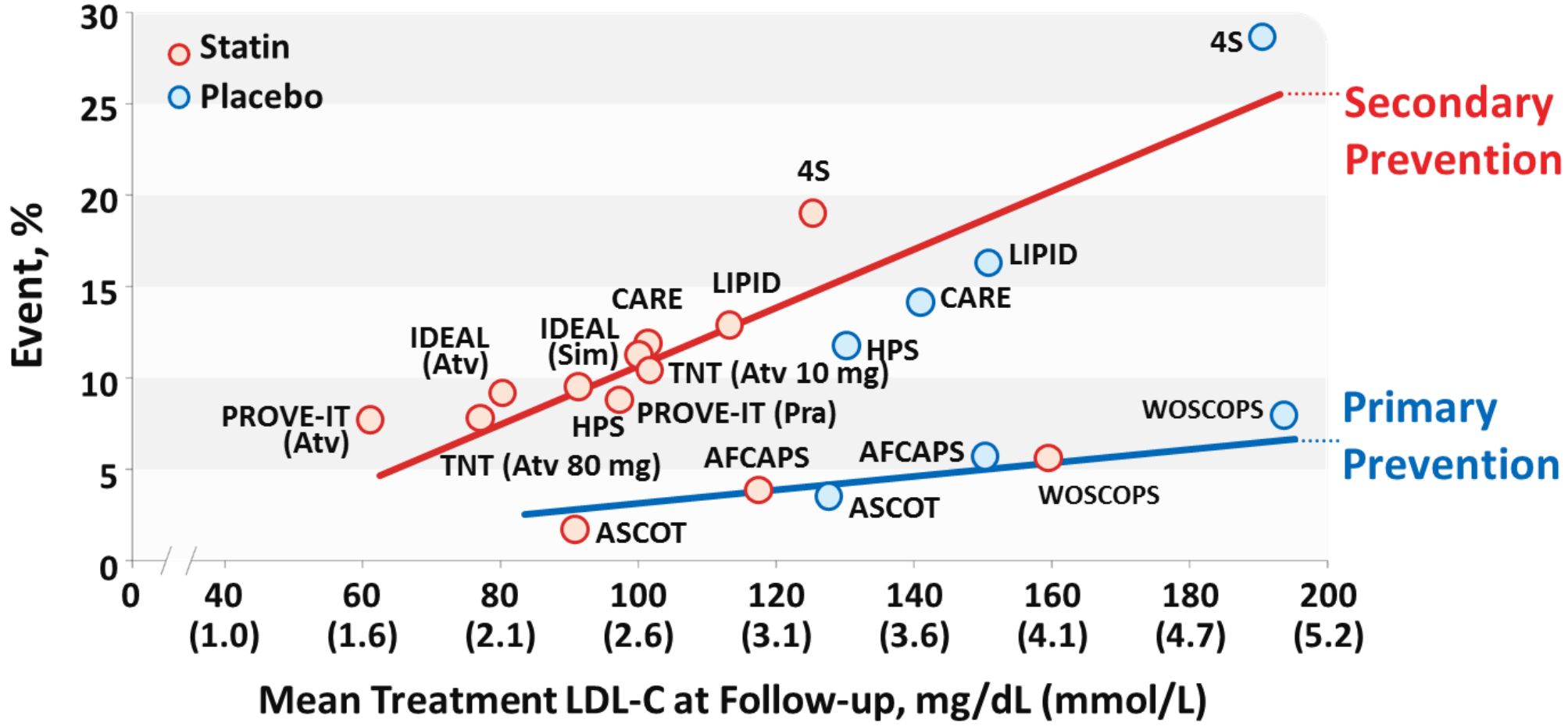
Contents

- Treatment gap between studies and real world
- Latest trend of lipid management
- Early for longer reduction for prevention of recurrent CVD event

Treatment gap between studies and real world

Primary and Secondary Prevention Trials with Statins



Results from the Dyslipidemia International Study II (DYSIS II)

Background and aims: Low-density lipoprotein cholesterol (LDL-C) is a major contributor to cardiovascular disease. In the Dyslipidemia International Study II (DYSIS II), we determined LDL-C target value attainment, use of lipid-lowering therapy (LLT), and cardiovascular outcomes in patients with stable coronary heart disease (CHD) and those suffering from an acute coronary syndrome (ACS).

Methods: DYSIS II included patients from 18 countries. Patients with either stable CHD or an ACS were enrolled if they were ≥18 years old and had a full lipid profile available. Data were collected at a physician visit (CHD cohort) or at hospital admission and 120 days later (ACS cohort).

Results: A total of 10,661 patients were enrolled, 6794 with stable CHD and 3867 with an ACS. Mean LDL-C levels were low at 88 mg/dl and 108 mg/dl for the CHD and ACS cohorts respectively, with only 29.4% and 18.9% displaying a level below 70 mg/dl. LLT was utilized by 93.8% of the CHD cohort, with a mean daily statin dosage of 25 ± 18 mg. The proportion of the ACS cohort treated with LLT rose from 65.2% at admission to 95.6% at follow-up. LLT-treated patients, who were female, obese, or current smokers, were less likely to achieve an LDL-C level of <70 mg/dl, while those with type 2 diabetes, chronic kidney disease, or those taking a higher statin dosage were more likely.

Conclusions: Few of these very high-risk patients achieved the LDL-C target, indicating huge potential for improving cardiovascular outcome by use of more intensive LLT.

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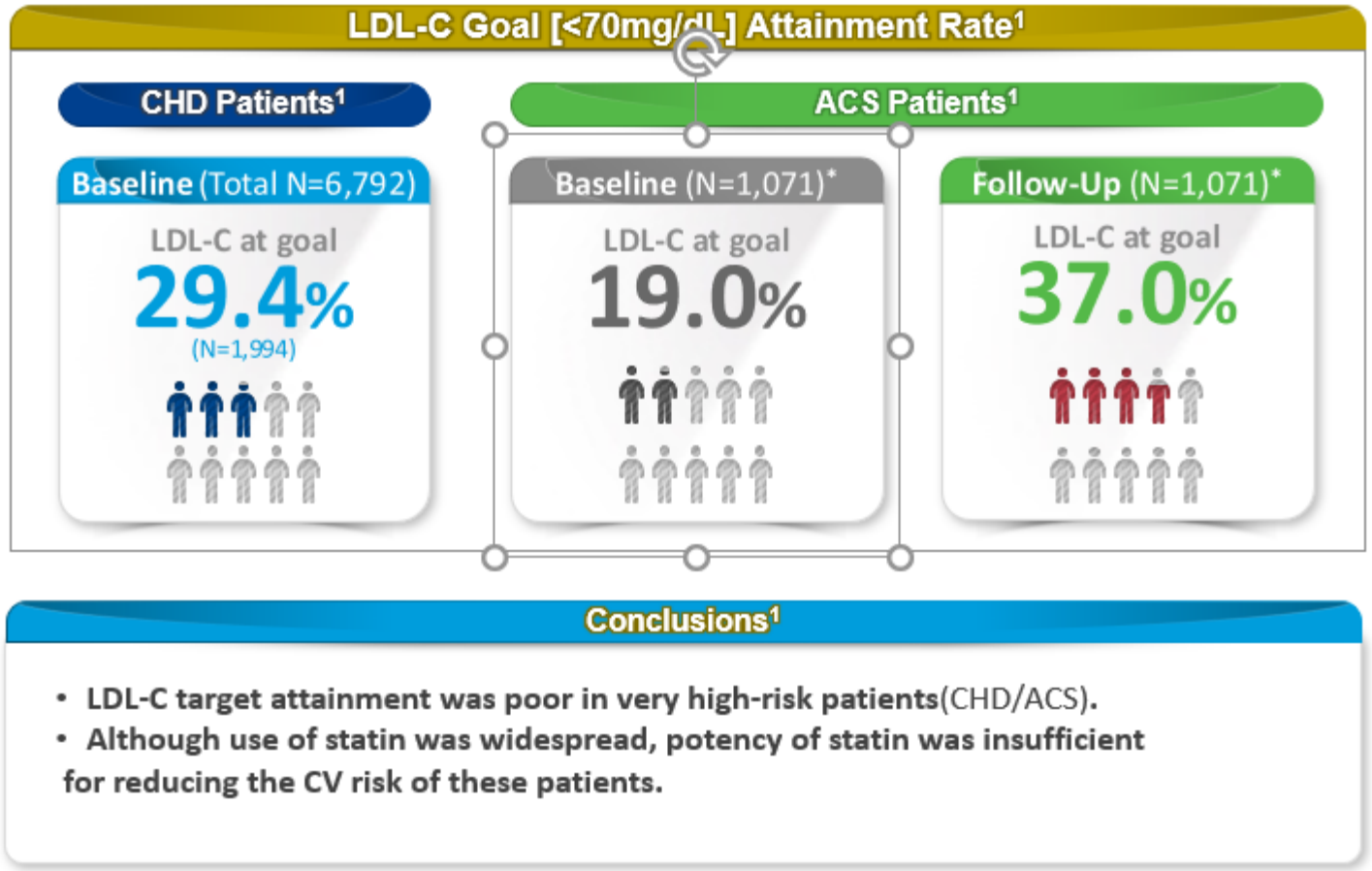
1. Gitt AK, *et al*. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis.* 2017; 266:158-166.

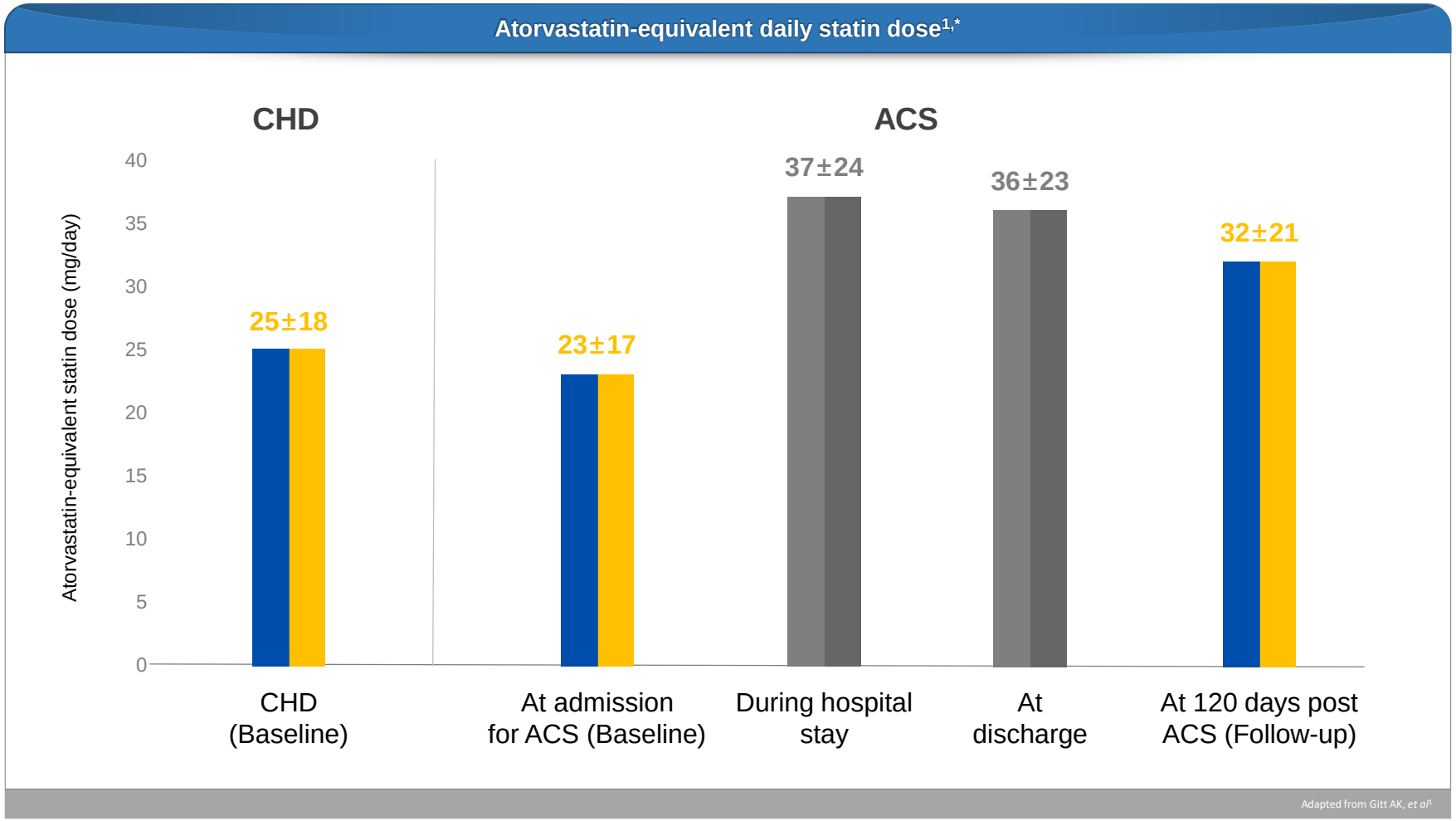
DYSIS II: LDL-C Goal Attainment Rate



DYSIS : Dyslipidemia International Study, CHD : Coronary heart disease, ACS : Acute coronary syndrome, CV : Cardiovascular

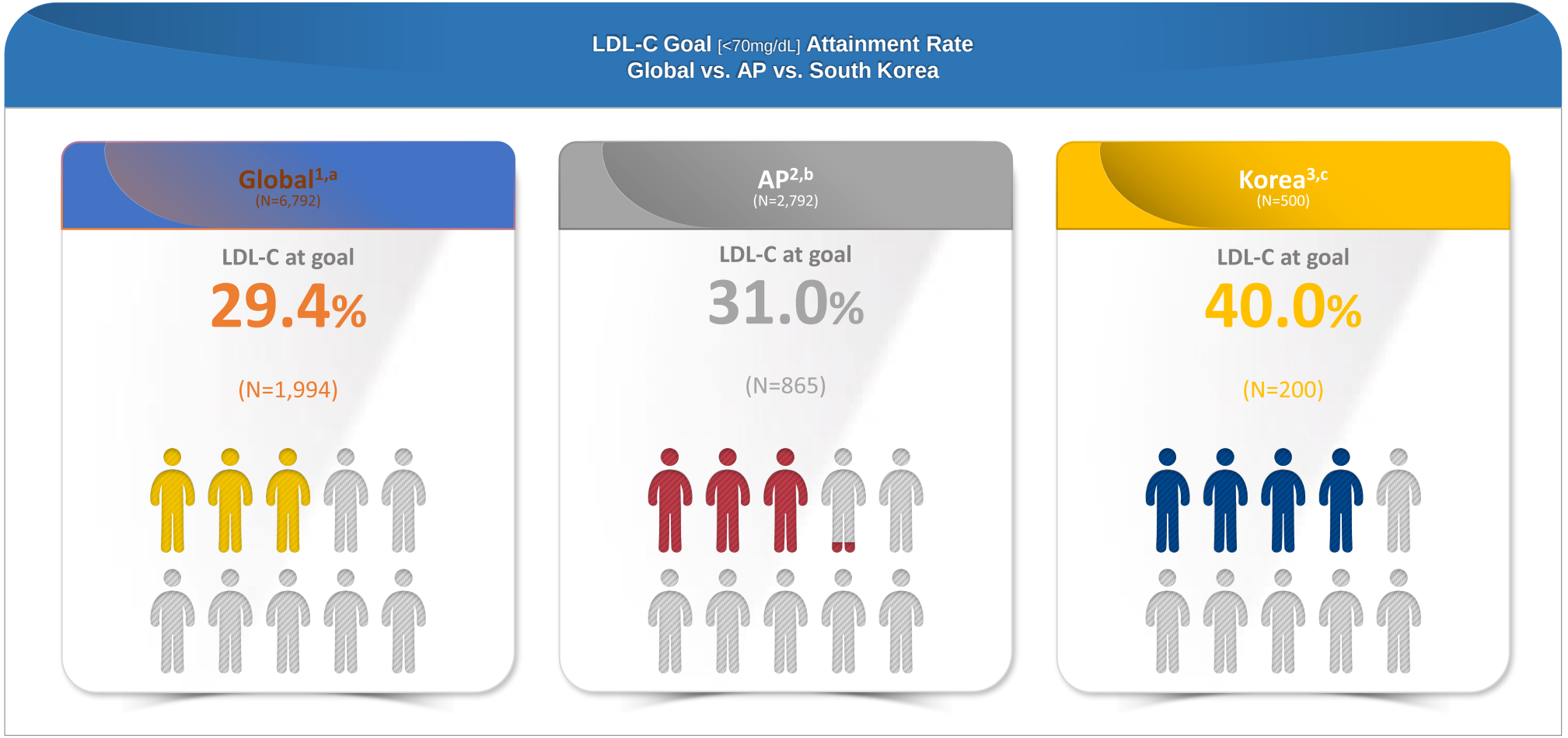
1. Gitt AK, *et al*. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis.* 2017; 266:158-166.

DYSIS II: Intensity of Statin Lipid Lowering Therapy



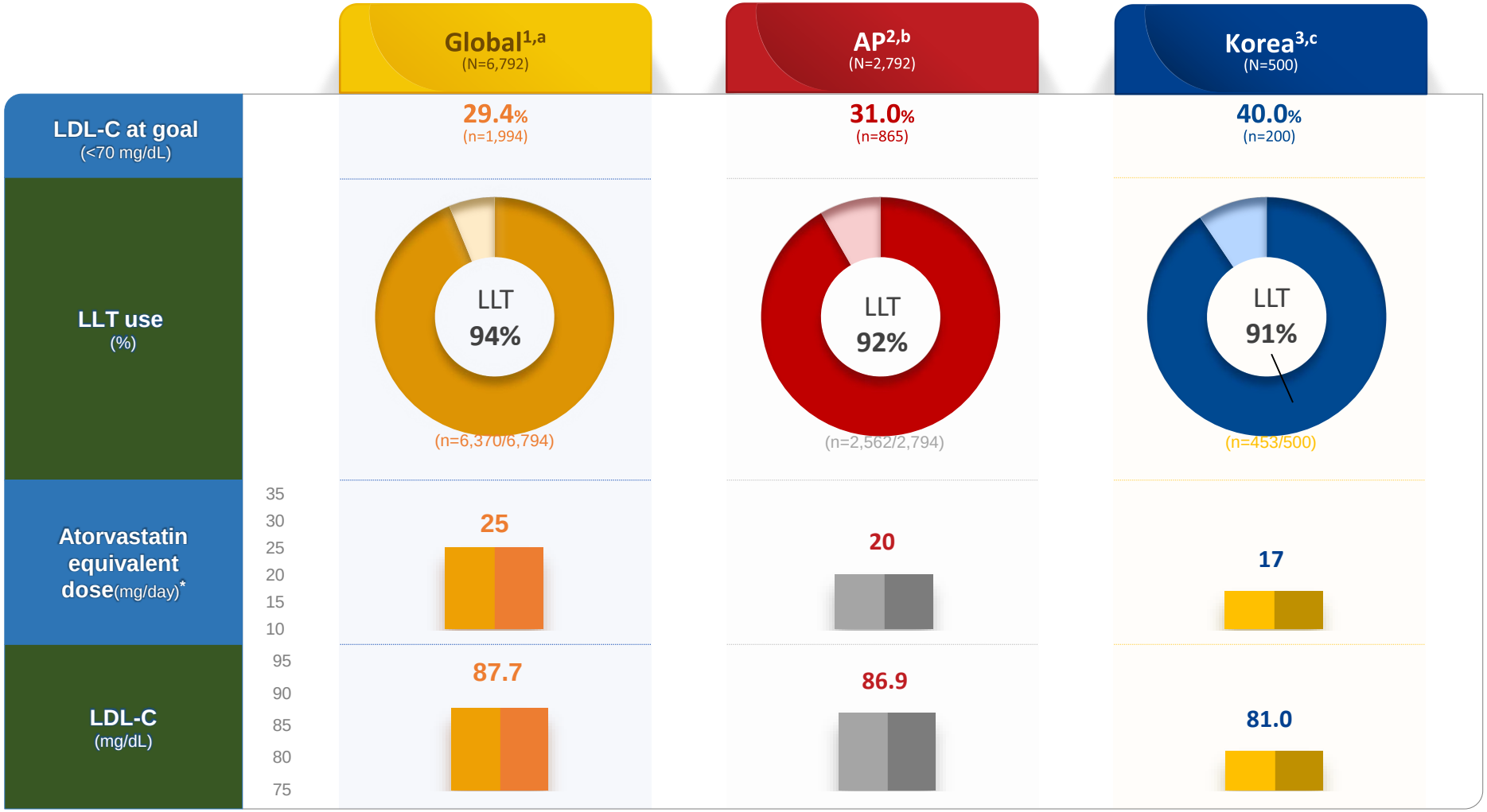
1. Gitt AK, et al. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. Atherosclerosis. 2017; 266:158-166.

LDL-C Goal Attainment Rate



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. 2. Poh KK, et al. Low-density lipoprotein cholesterol target attainment in patients with stable or acute coronary heart disease in the Asia-Pacific region: results from the Dyslipidemia International Study II. Eur J Prev Cardiol. 2018;25(18):1950-1963. 3. Lee SH, et al. Dyslipidemia and Rate of Under-Target Low-Density Lipoprotein-Cholesterol in Patients with Coronary Artery Disease in Korea. J Lipid Atheroscler. 2019;8(2):242-251.

Use of Lipid Lowering Therapy



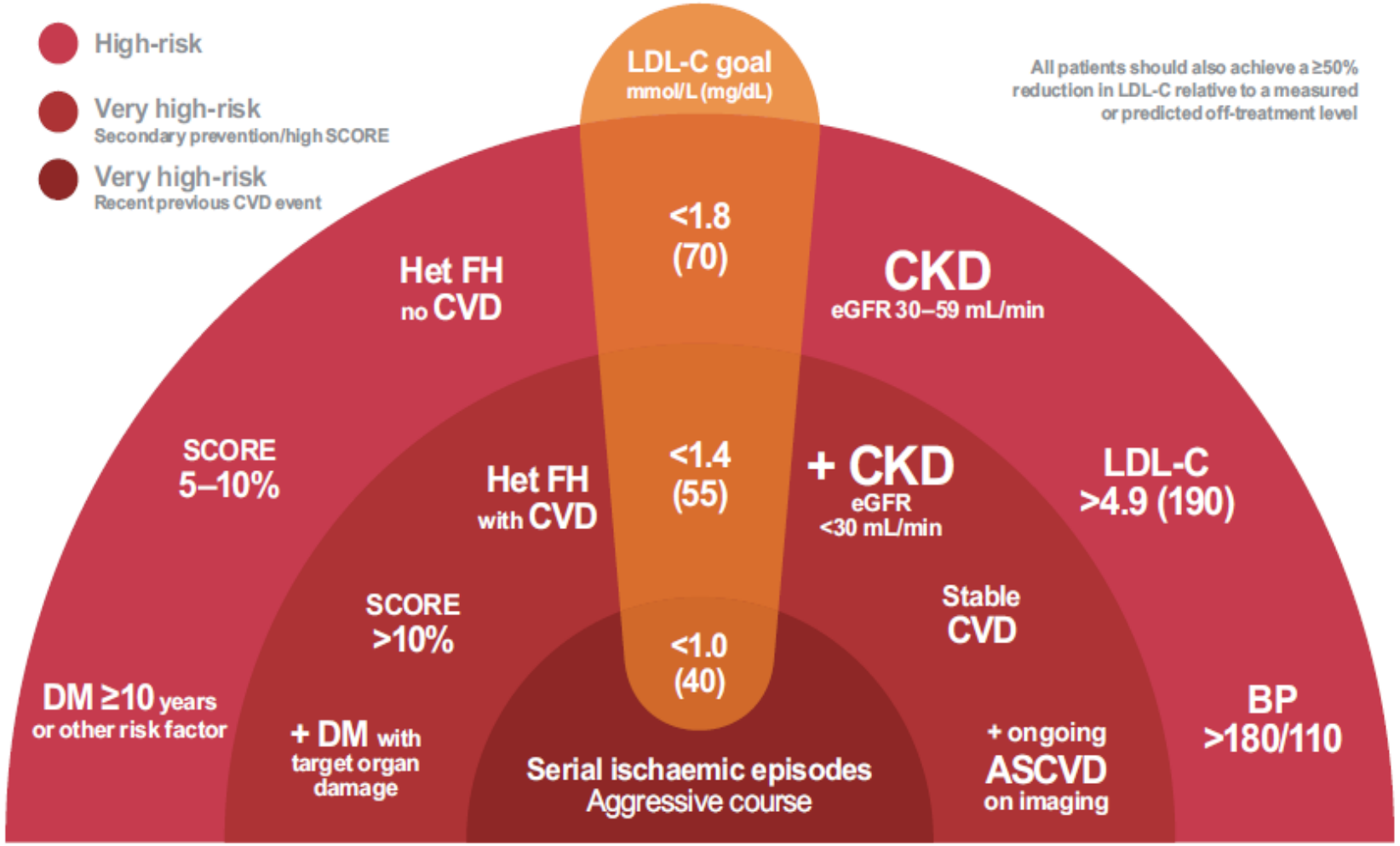
1. Gitt AK, et al. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. Atherosclerosis. 2017;266:158-166. 2. Poh KK, et al. Low-density lipoprotein cholesterol target attainment in patients with stable or acute coronary heart disease in the Asia-Pacific region: results from the Dyslipidemia International Study II. Eur J Prev Cardiol. 2018;25(18):1950-1963. 3. Lee SH, et al. Dyslipidemia and Rate of Under-Target Low-Density Lipoprotein-Cholesterol in Patients with Coronary Artery Disease in Korea. J Lipid Atheroscler. 2019;8(2):242-251.

LDL-C, The Lower is The Better

Guideline	Category	LDL-C goal
2018 AACE/ACE	**Extreme** • DM plus established clinical CVD	**<55 mg/dL**
	Very high • DM + major ASCVD risk(s) (HTN, Fam Hx, HDL-C, smoking, CKD 3,4)*	**<70 mg/dL**

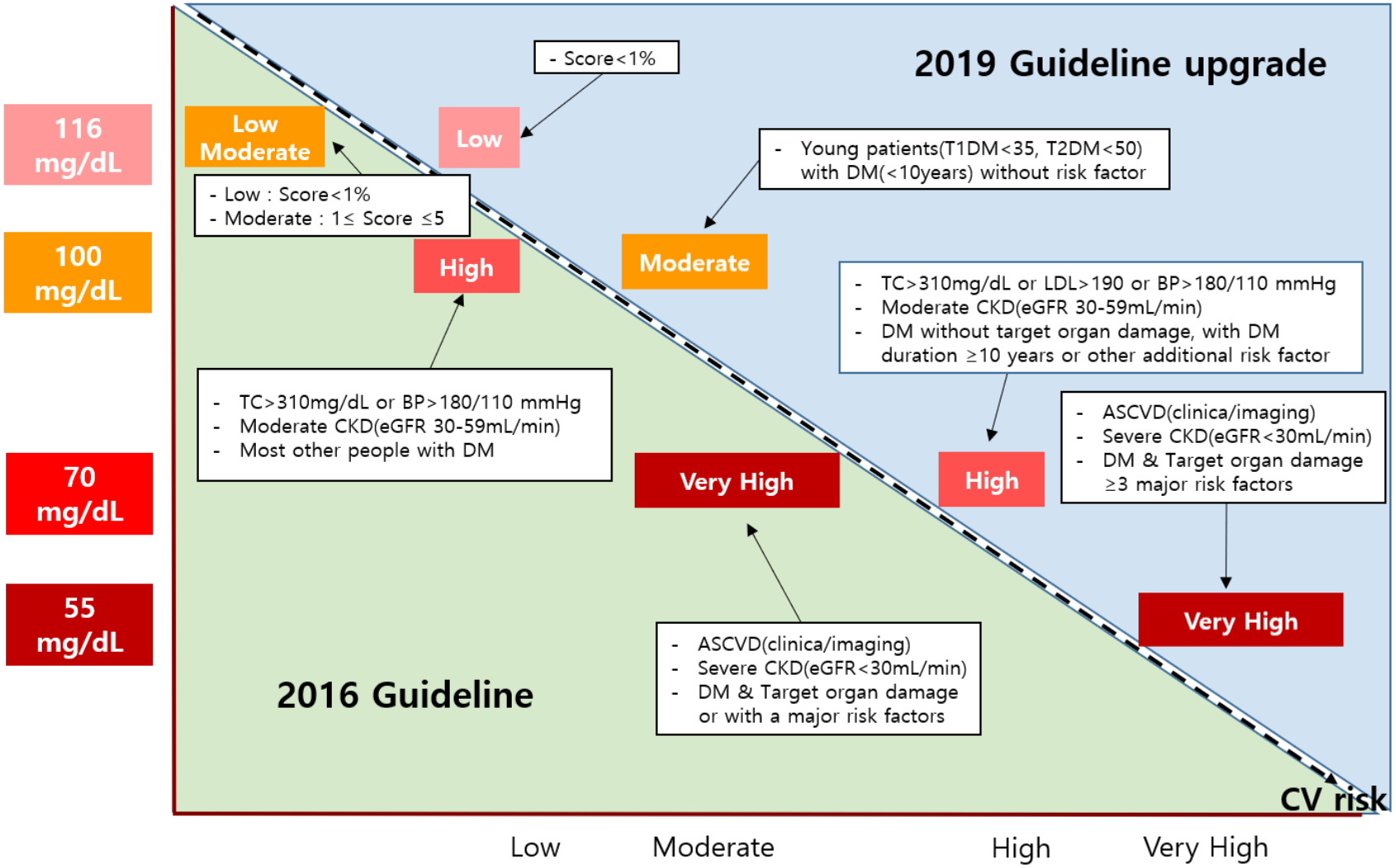
Latest trend of lipid management

Schematic diagram for intensive LDL-C therapy



Packard C, et al. Heart 2021;107:1369–1375

2019 ESC Guideline Update



2021 EAS Task force statement

Atherosclerosis 325 (2021) 99–109

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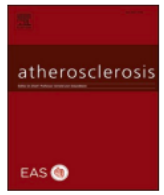


From the EAS

Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force

A B S T R A C T

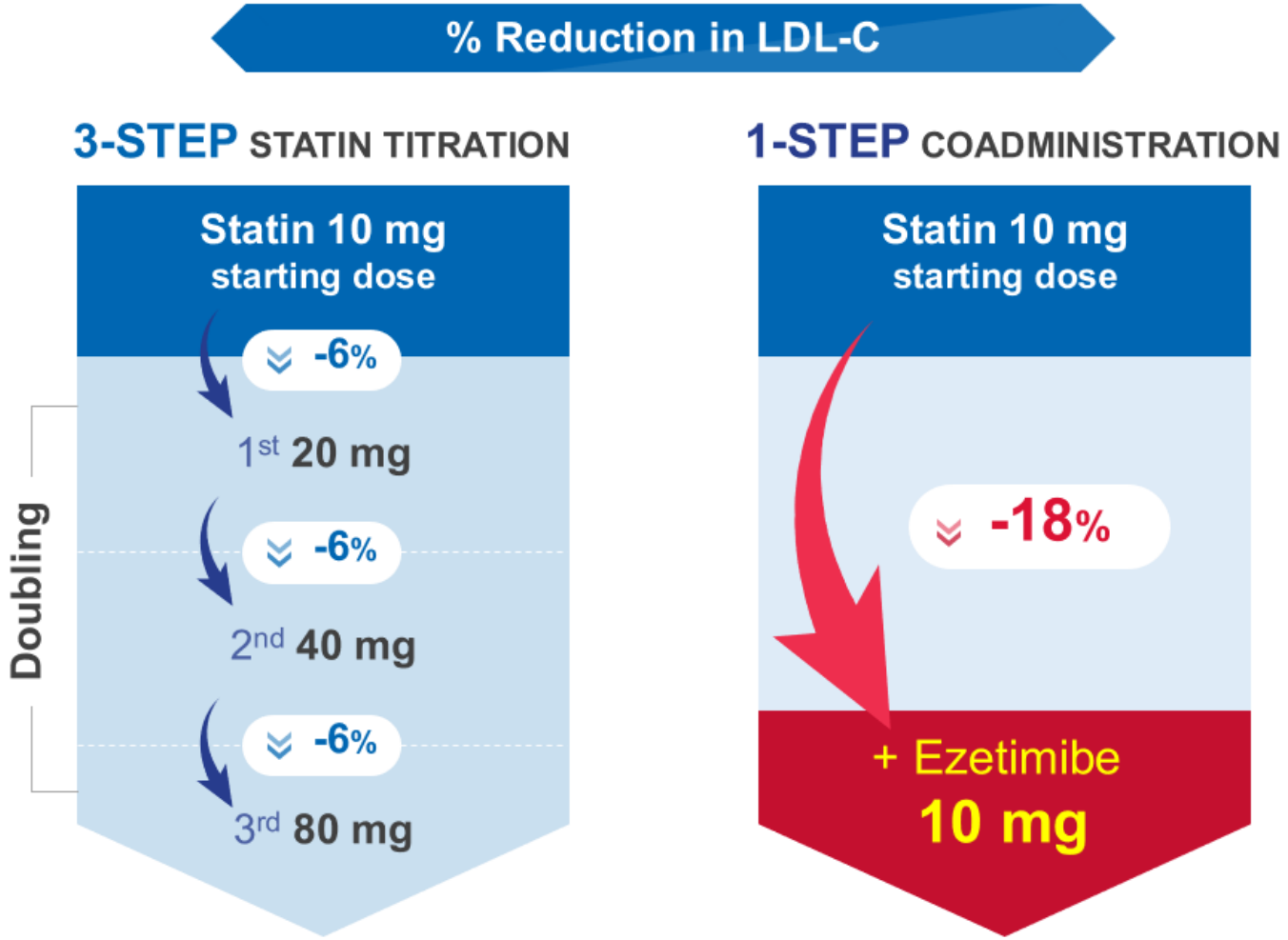
Background and aims: This European Atherosclerosis Society (EAS) Task Force provides practical guidance for combination therapy for elevated low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TG) in high-risk and very-high-risk patients.

Methods: Evidence-based review.

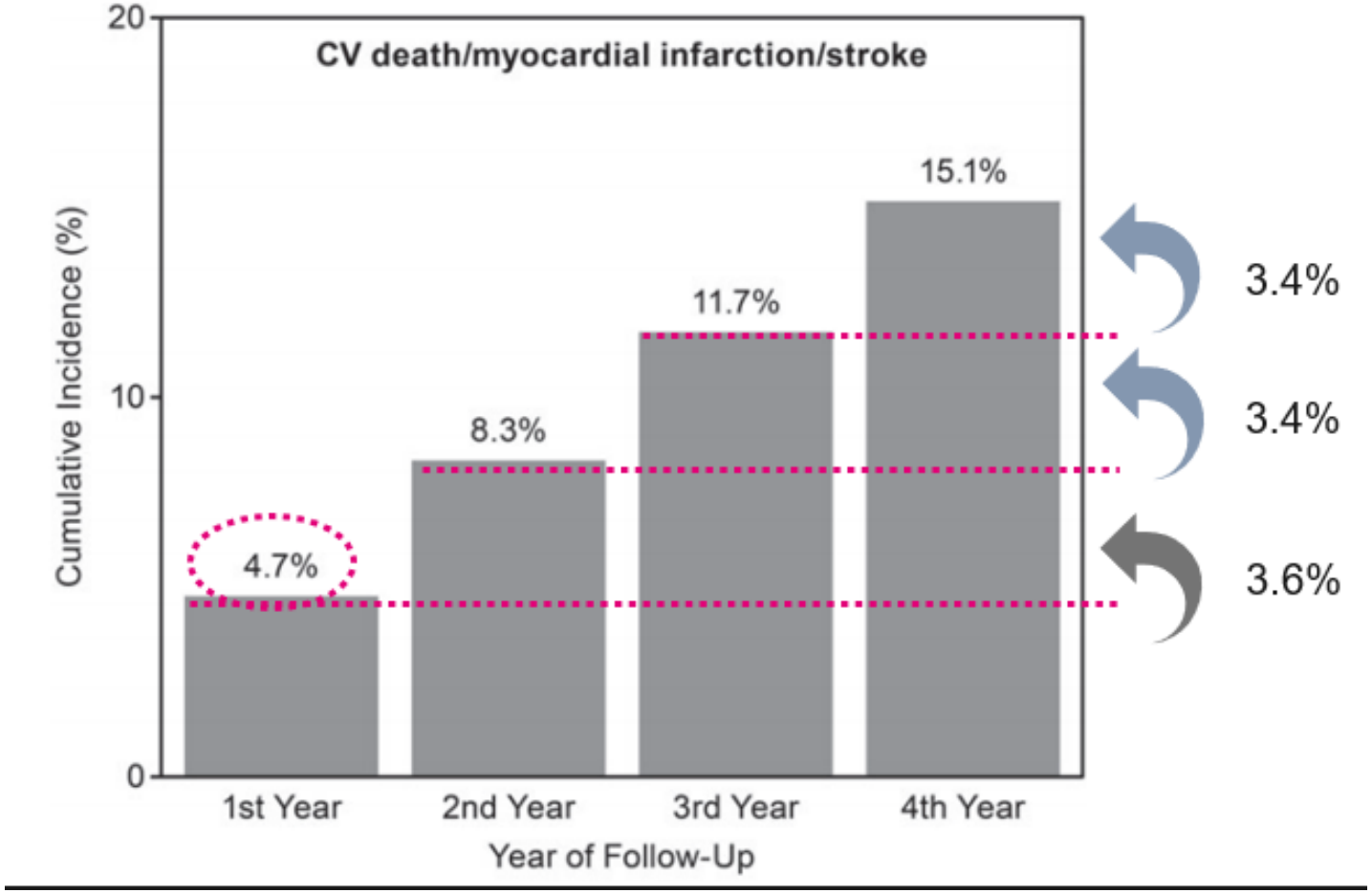
Results: Statin-ezetimibe combination treatment is the first choice for managing elevated LDL-C and should be given upfront in very-high-risk patients with high LDL-C unlikely to reach goal with a statin, and in primary prevention familial hypercholesterolaemia patients. A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be added if LDL-C levels remain high. In high and very-high-risk patients with mild to moderately elevated TG levels (>2.3 and < 5.6 mmol/L [>200 and < 500 mg/dL) on a statin, treatment with either a fibrate or high-dose omega-3 fatty acids (icosapent ethyl) may be considered, weighing the benefit versus risks. Combination with fenofibrate may be considered for both macro- and microvascular benefits in patients with type 2 diabetes mellitus.

Conclusions: This guidance aims to improve real-world use of guideline-recommended combination lipid modifying treatment.

Statin Titration vs Statin+Ezetimibe



Recurrent CV (CV death, MI or Stroke) event



Clinical Cardiology 2016; 39(11):670–677

Early for longer reduction for prevention of recurrent CVD event

Longer reduction

IMPROVE-IT

IMPROVE-IT

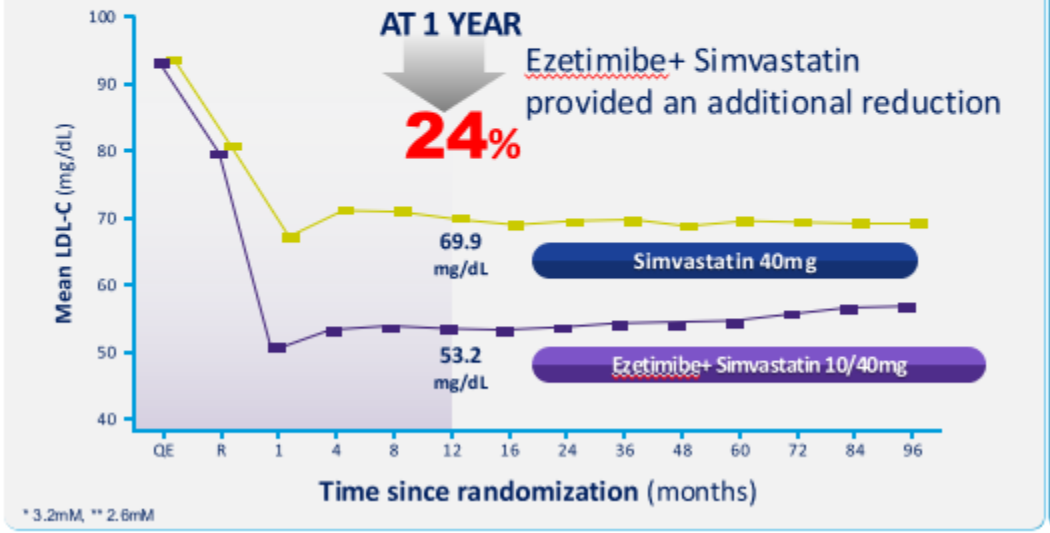
18,144 patients

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

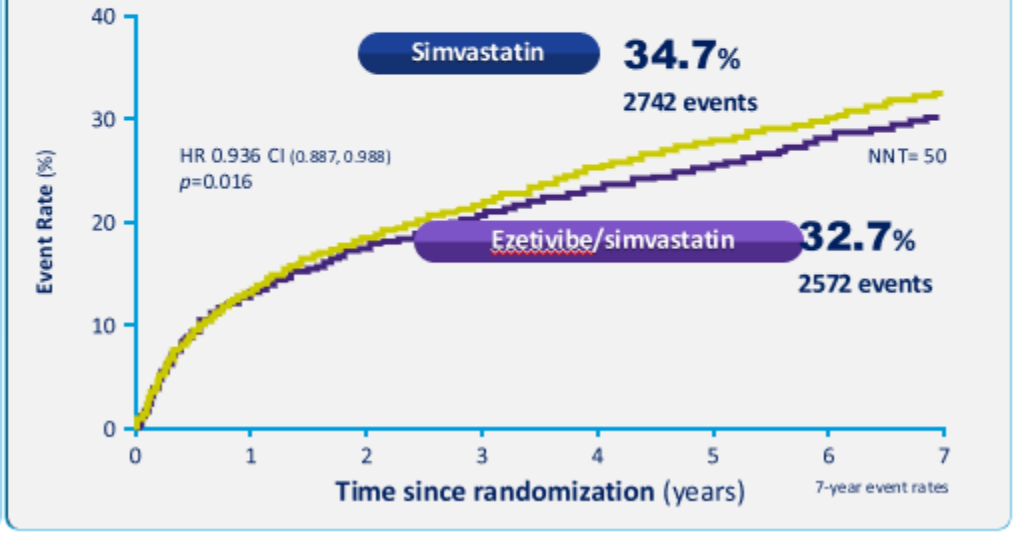
Primary Endpoint:

CV death, MI, hospital admission for UA, coronary revascularization or stroke

Change of LDL-cholesterol[4,5]

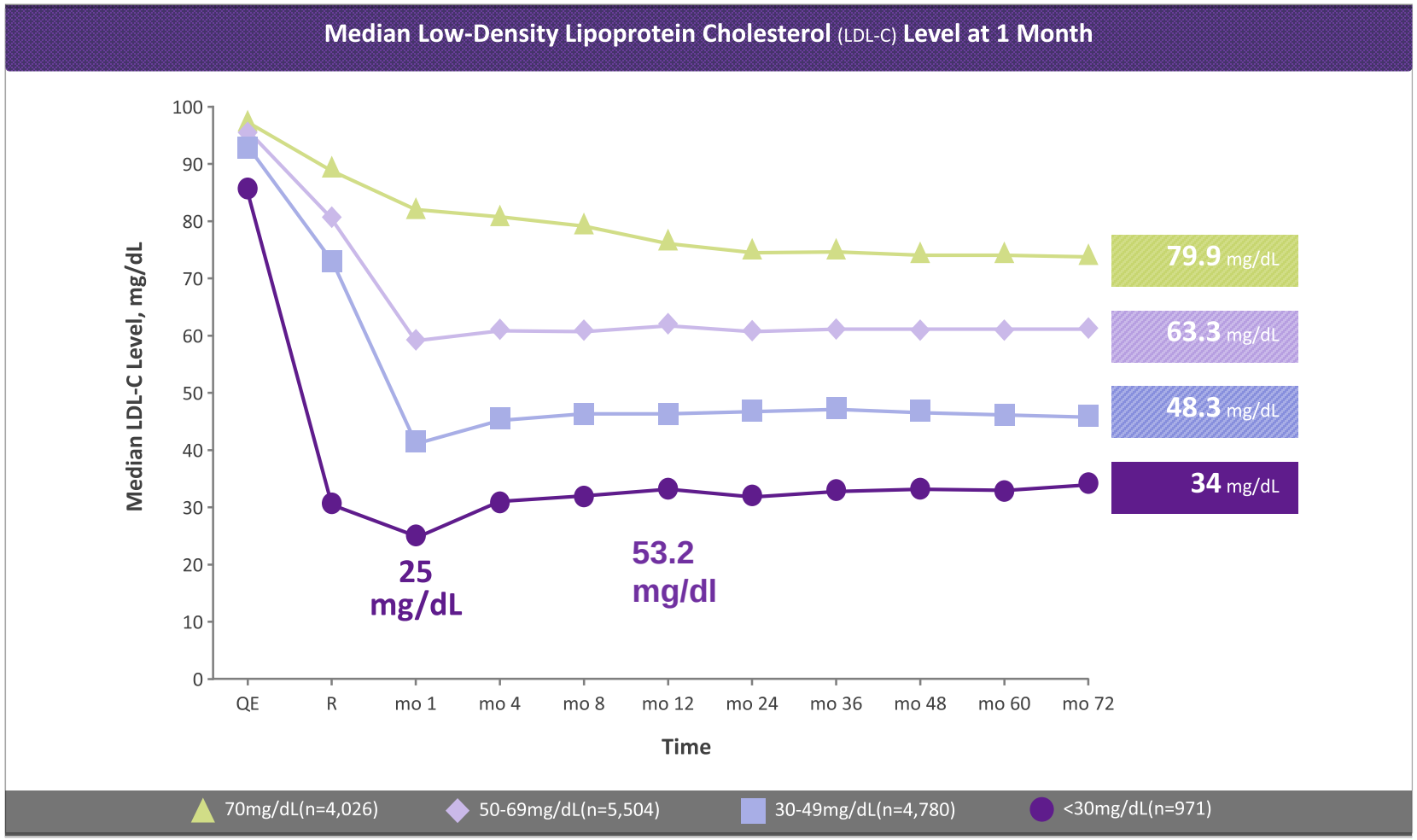


Primary Endpoint[4]



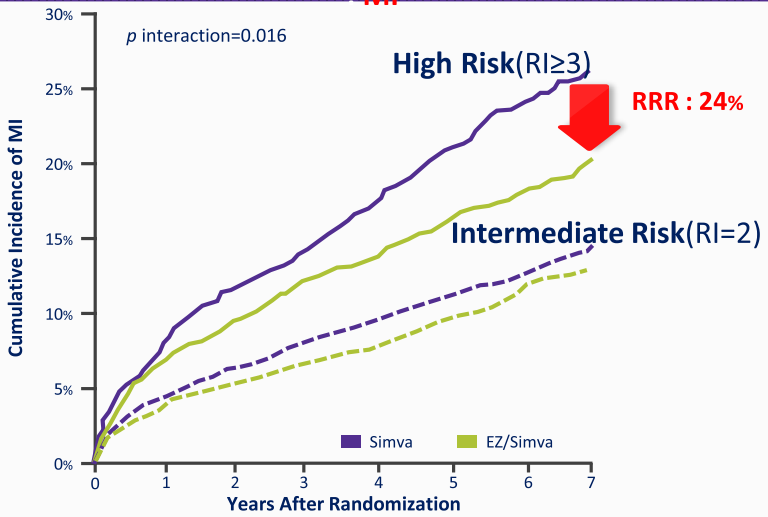
Cannon CP, *et al.* N Engl J Med. 2015;372(25):2387–2397; IMPROVE-IT

IMPROVE-IT: Median LDL-C Level



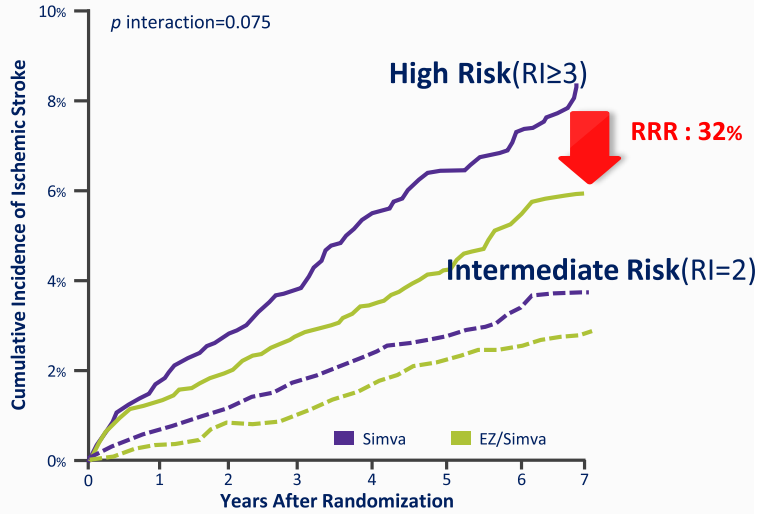
IMPROVE-IT: MI and ischemic stroke

Outcomes by Risk Category and Randomized Treatment : MI*



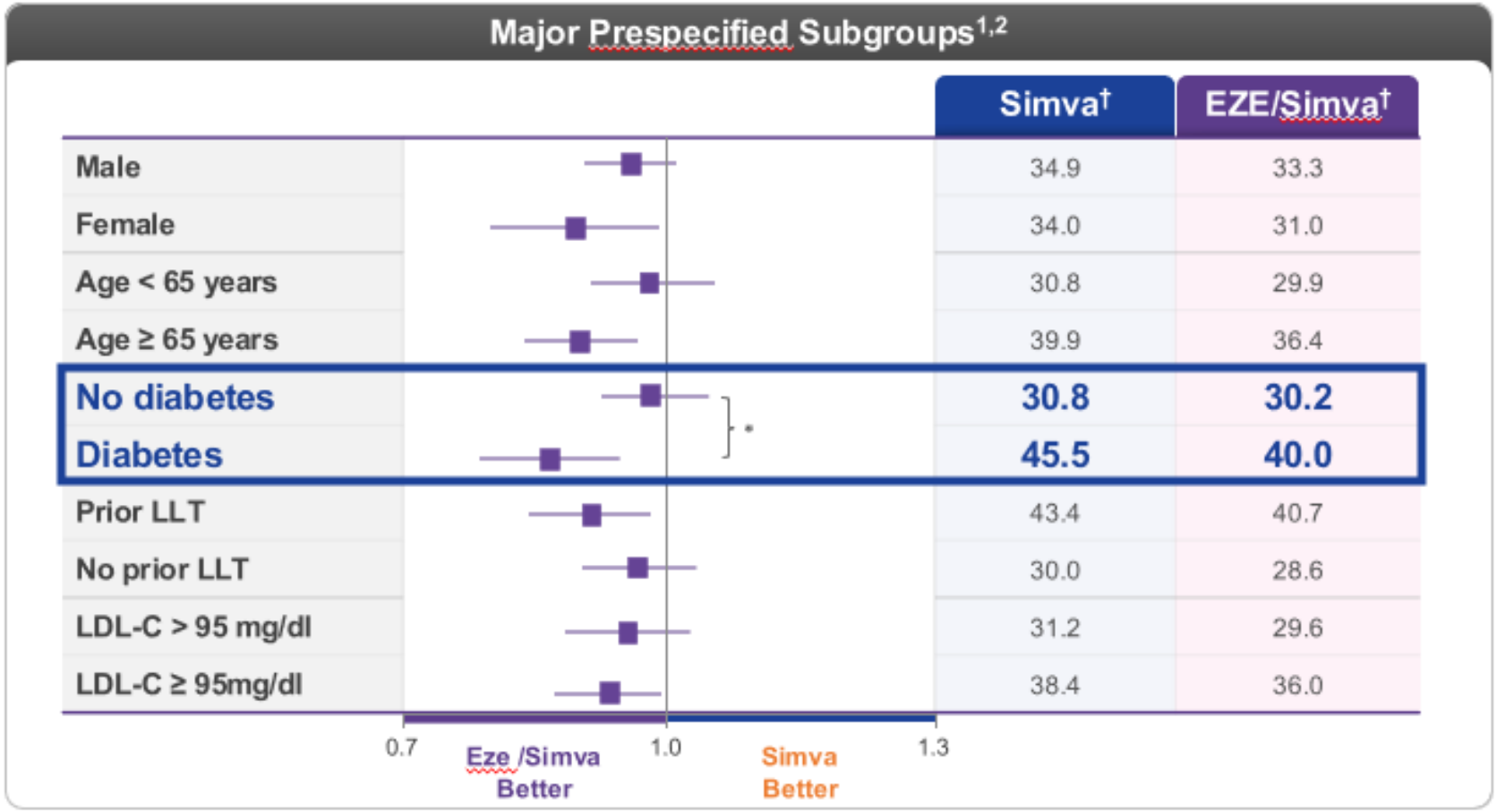
		7yr KM	ARR	HR
High risk	Simva	26.2%	5.9% (2.9, 9.1)	0.76 (0.66, 0.88)
	Ez/Simva	20.3%		
Intermediate risk	Simva	14.4%	1.5% (-0.5, 3.7)	0.87 (0.74, 1.02)
	Ez/Simva	12.9%		

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



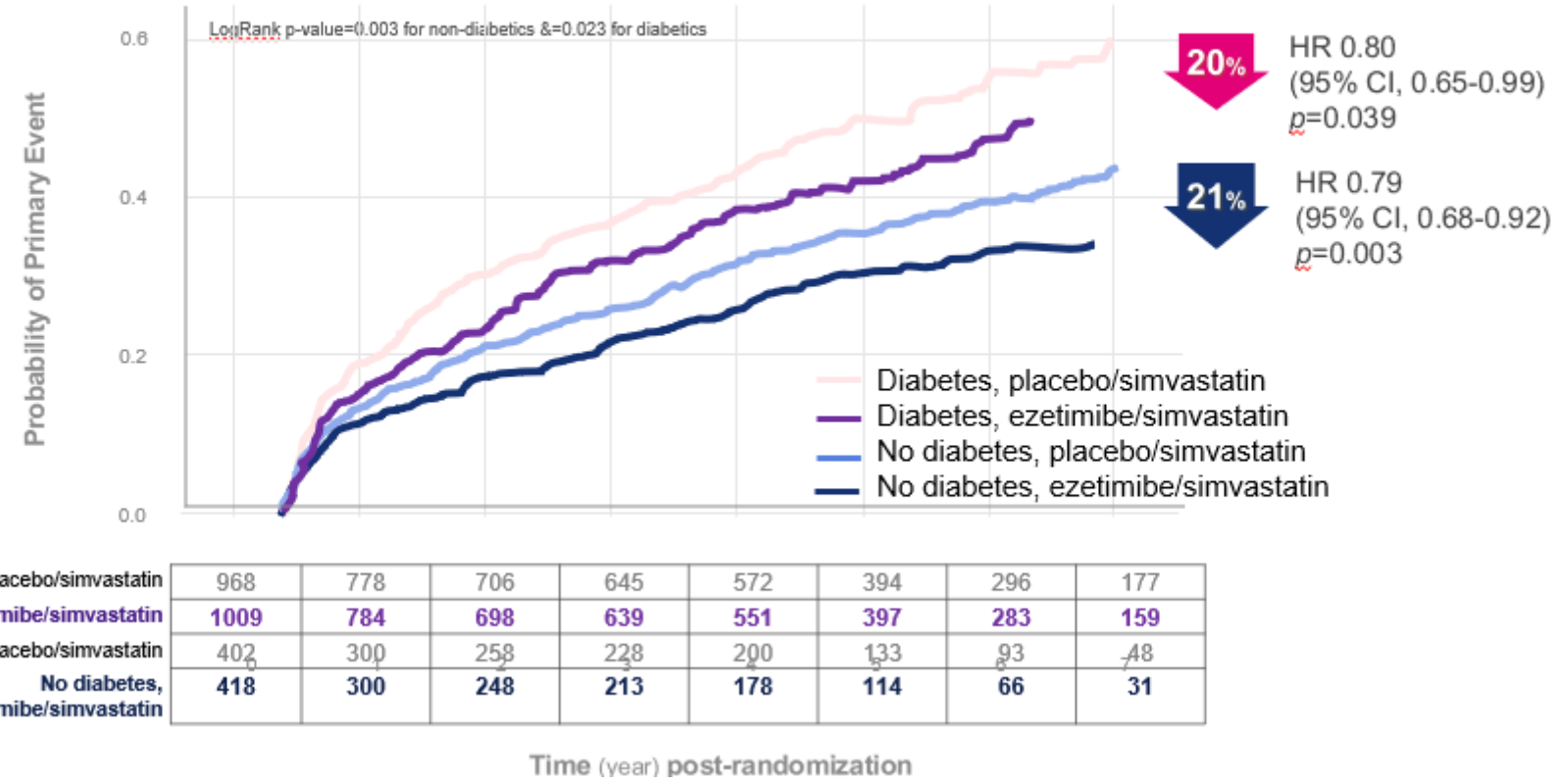
		7yr KM	ARR	HR
High risk	Simva	8.4%	2.4% (0.4, 4.4)	0.68 (0.52, 0.88)
	Ez/Simva	6.0%		
Intermediate risk	Simva	3.8%	1.0% (-0.2, 2.1)	0.75 (0.54, 1.05)
	Ez/Simva	2.8%		

IMPROVE-IT : CV benefit of ezetimibe add-on



CV benefit of Ezetimibe in elderly ≥75 years patients and DM status

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**

IMPROVE-IT : Long-term Safety

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)

Early reduction

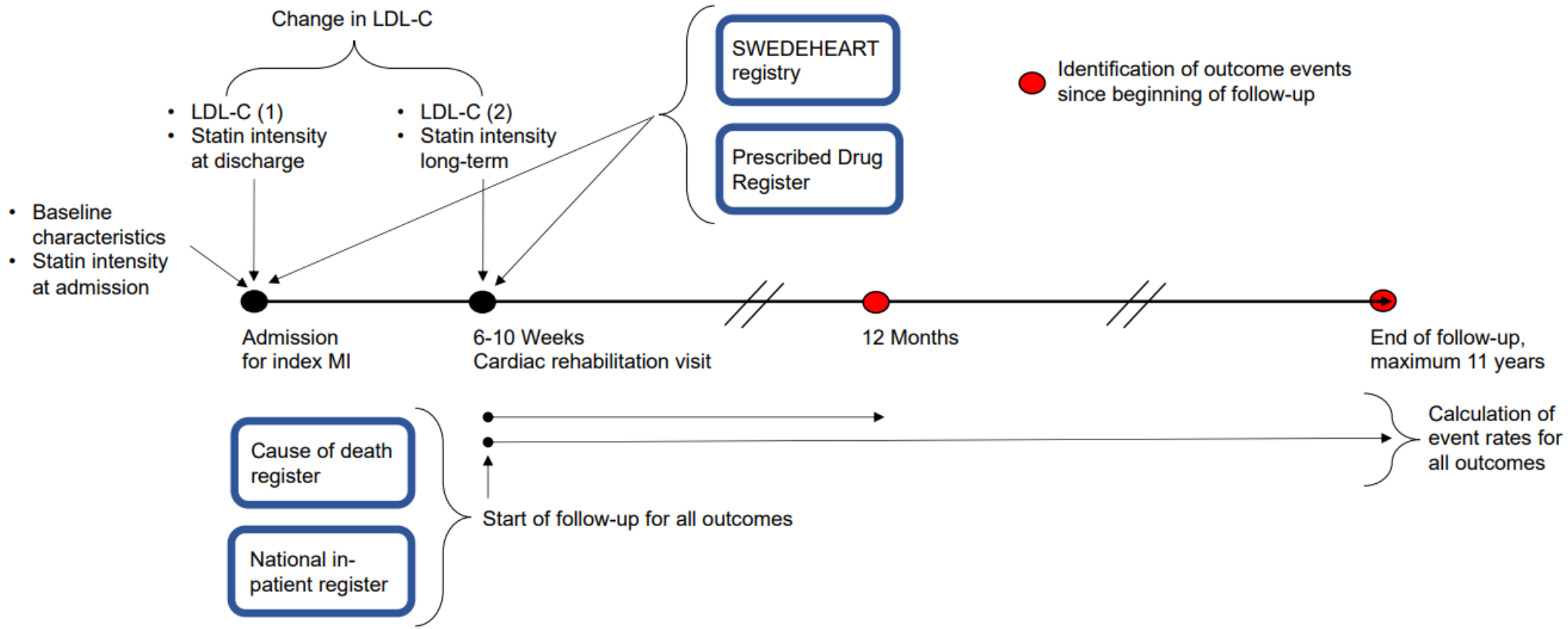
LDL reduction and statin intensity in MI - Swedish nationwide study

LDL reduction and statin intensity in MI - Swedish nationwide study

- There is a paucity of information assessing the association between early changes in LDL-C level and intensity of statin therapy after a myocardial infarction (MI) with long-term prognosis from real-life patient populations.
- Patients admitted with MI were followed for mortality and major CV events.
- Changes in LDL between the MI and a 6- to 10-week follow-up visit were analysed.

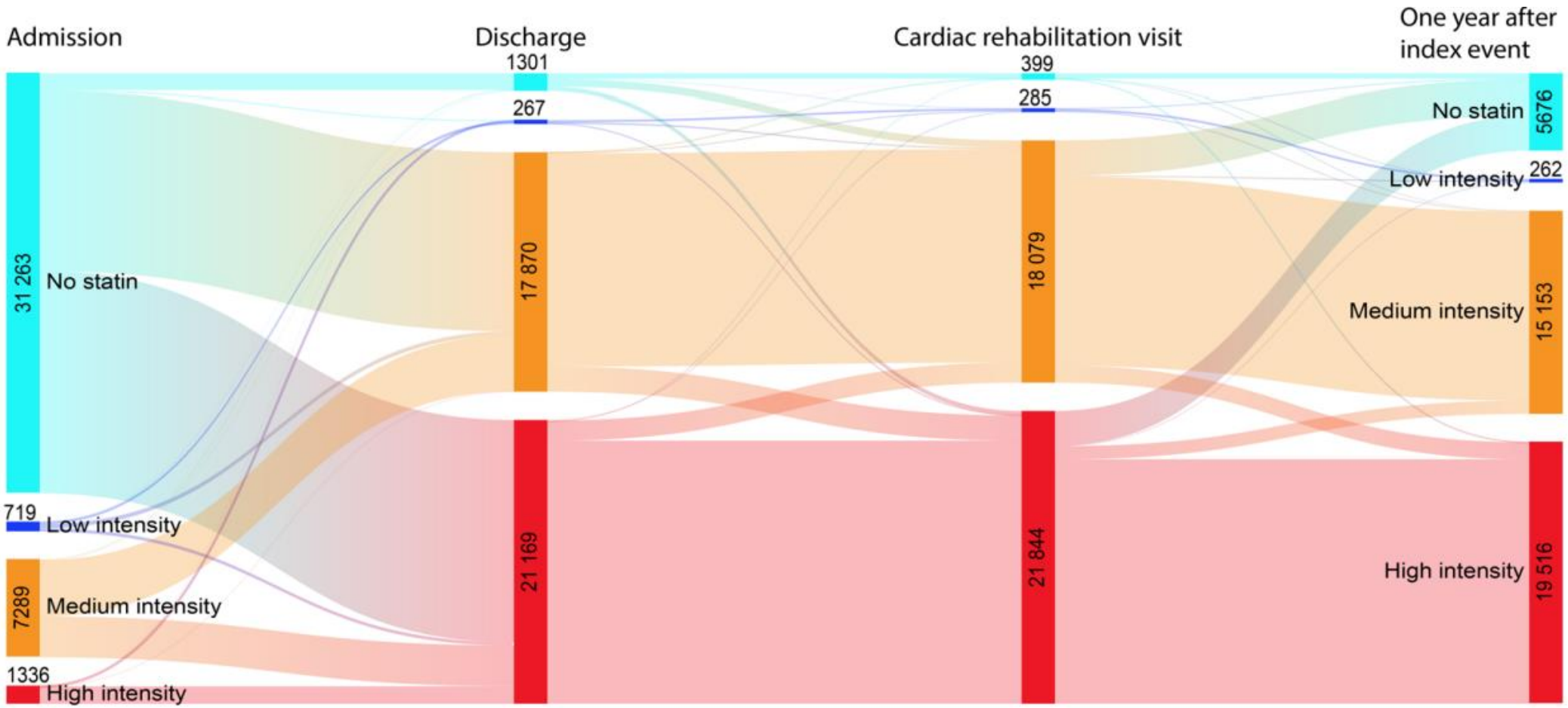
European Heart Journal (2021) 42, 243–252

Study design schema



European Heart Journal (2021) 42, 243–252

Change in statin intensity



KM curve of culmulative incidence rate by quartile LDL-C change

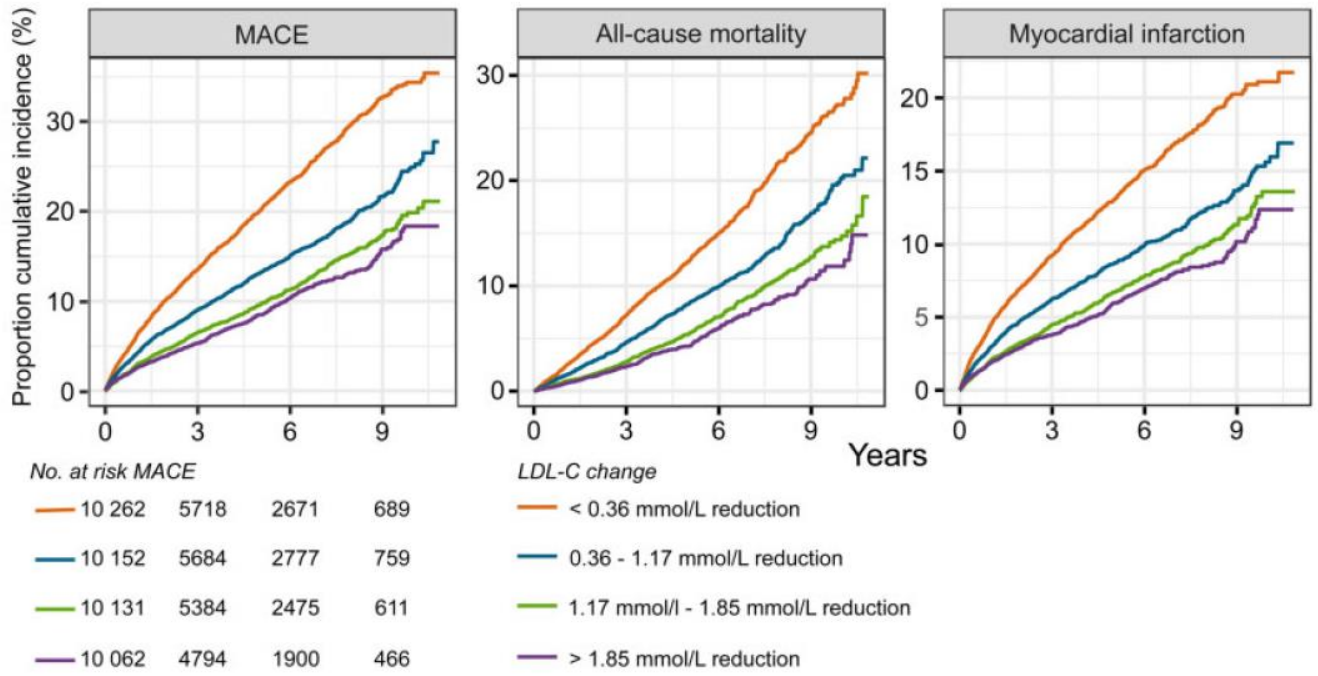
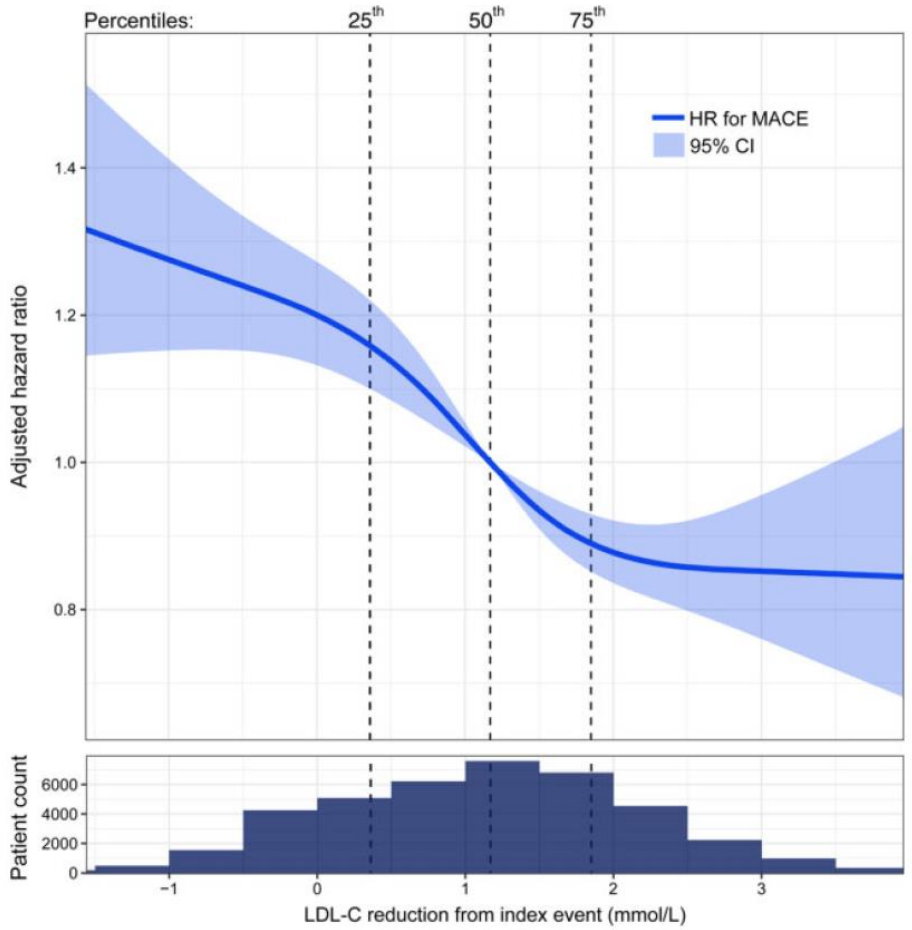
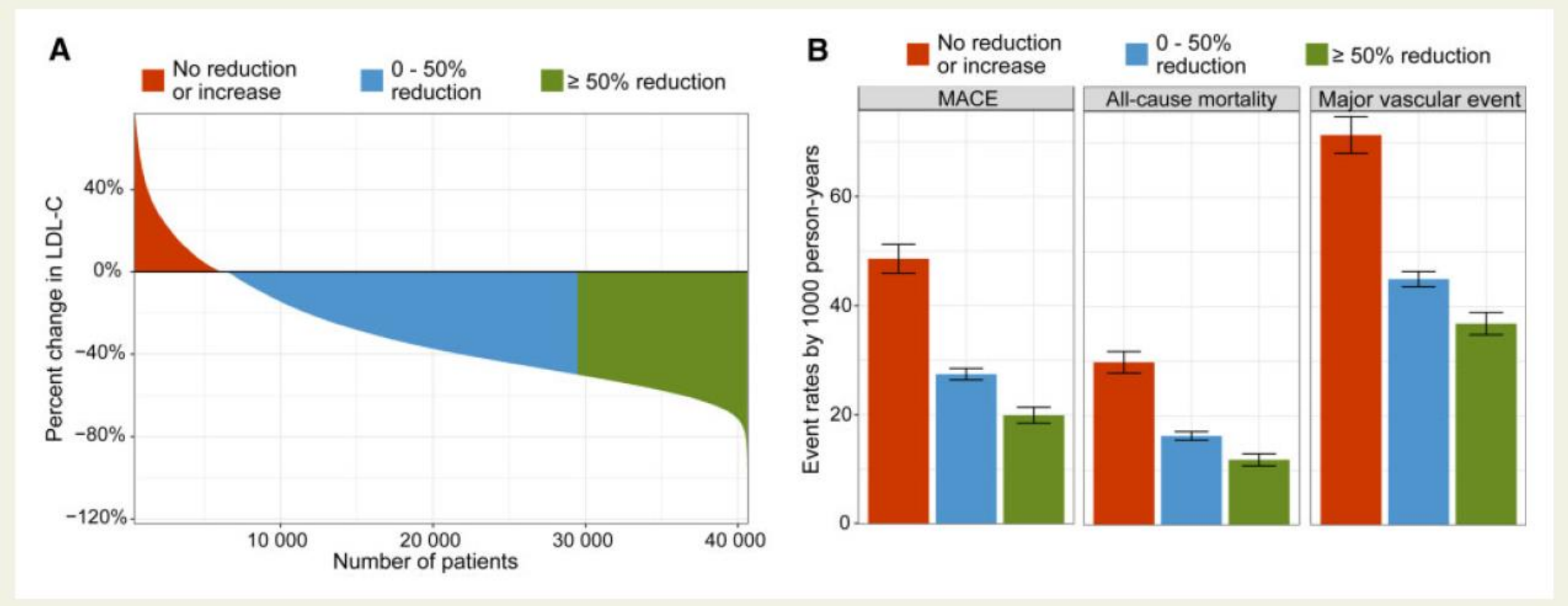


Figure 1 Kaplan–Meier curves of the cumulative incidence rates by quartile low-density lipoprotein cholesterol (LDL-C) change from index event to the cardiac rehabilitation visit. Outcomes are assessed after the cardiac rehabilitation visit. Numbers at risk shown for MACE. MACE, major adverse cardiovascular event is the composite outcome of cardiovascular mortality, myocardial infarction, and ischaemic stroke.

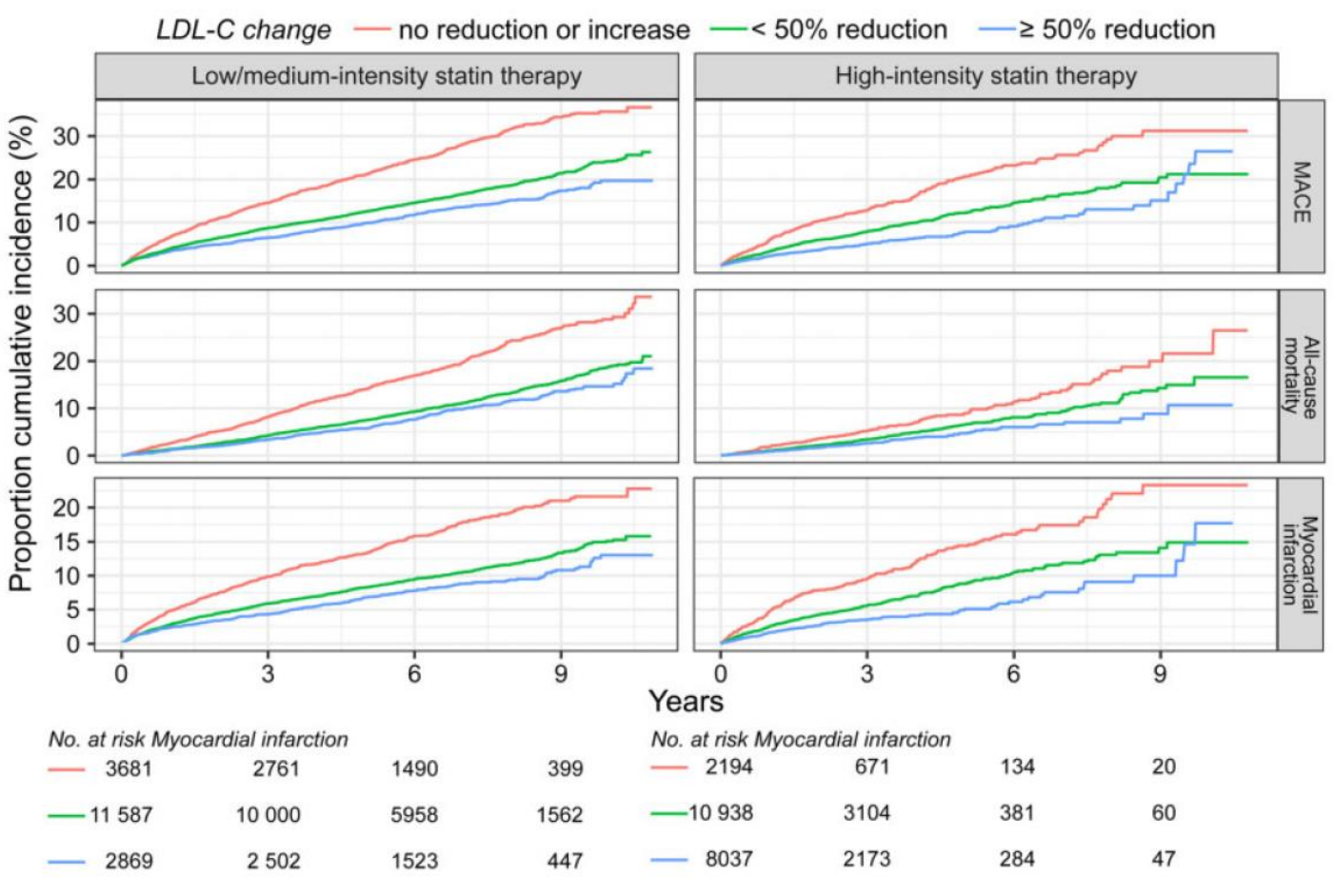
HR for the composite outcome by change in LDL



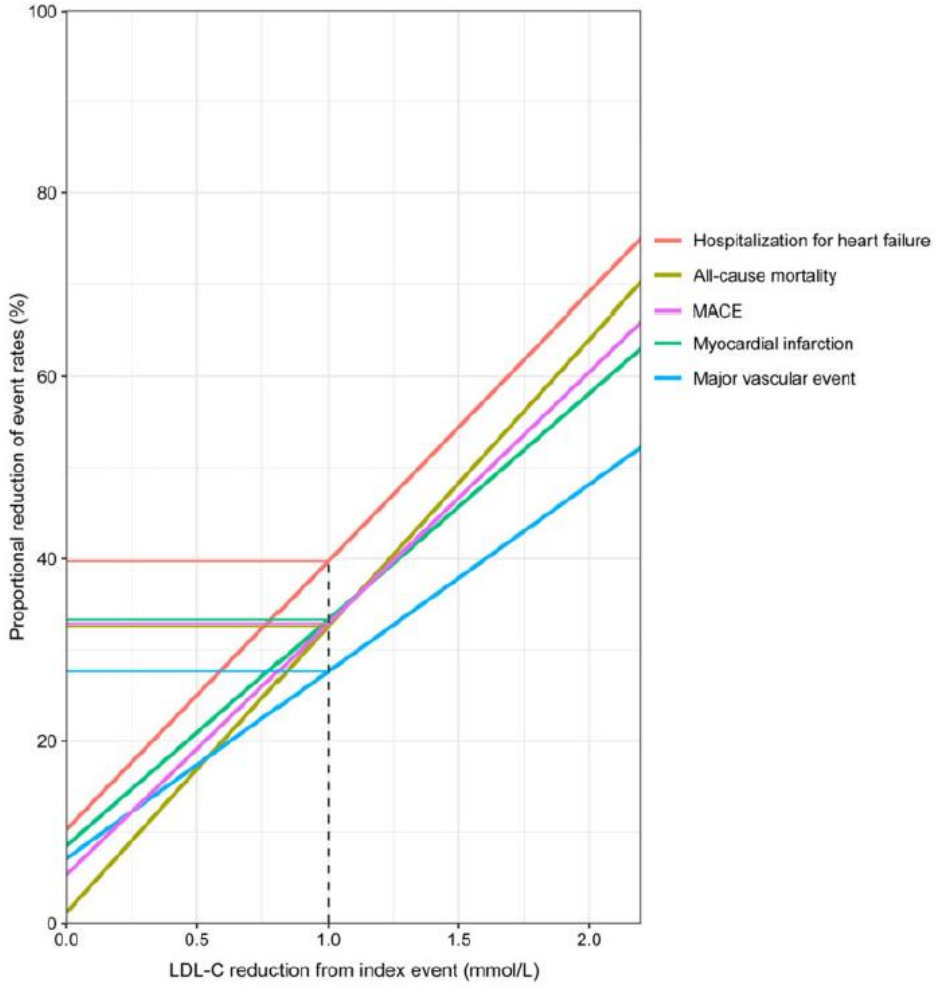
Change in LDL and incidence rate



KM curves of the cumulative incidence rates by statin therapy intensity



Proportional reduction of event rates by degree of mean absolute LDL-C reduction



Conclusion of Swedish nationwide study

- Larger early LDL-C reduction and more intensive statin therapy after MI were associated with a reduced hazard of all CV outcomes and all-cause mortality

Conclusion

- Mono statin has limitation to reach ASCVD patient's target goal
  - ✓Atorvastatin + ezetimibe combination therapy would meet target goal.
- More aggressive lipid management to prevent recurrent event
- Early for longer of intensive lipid therapy need for high risk patients
  - ✓Initial ezetimibe combination therapy is helpful

Thank you for attention