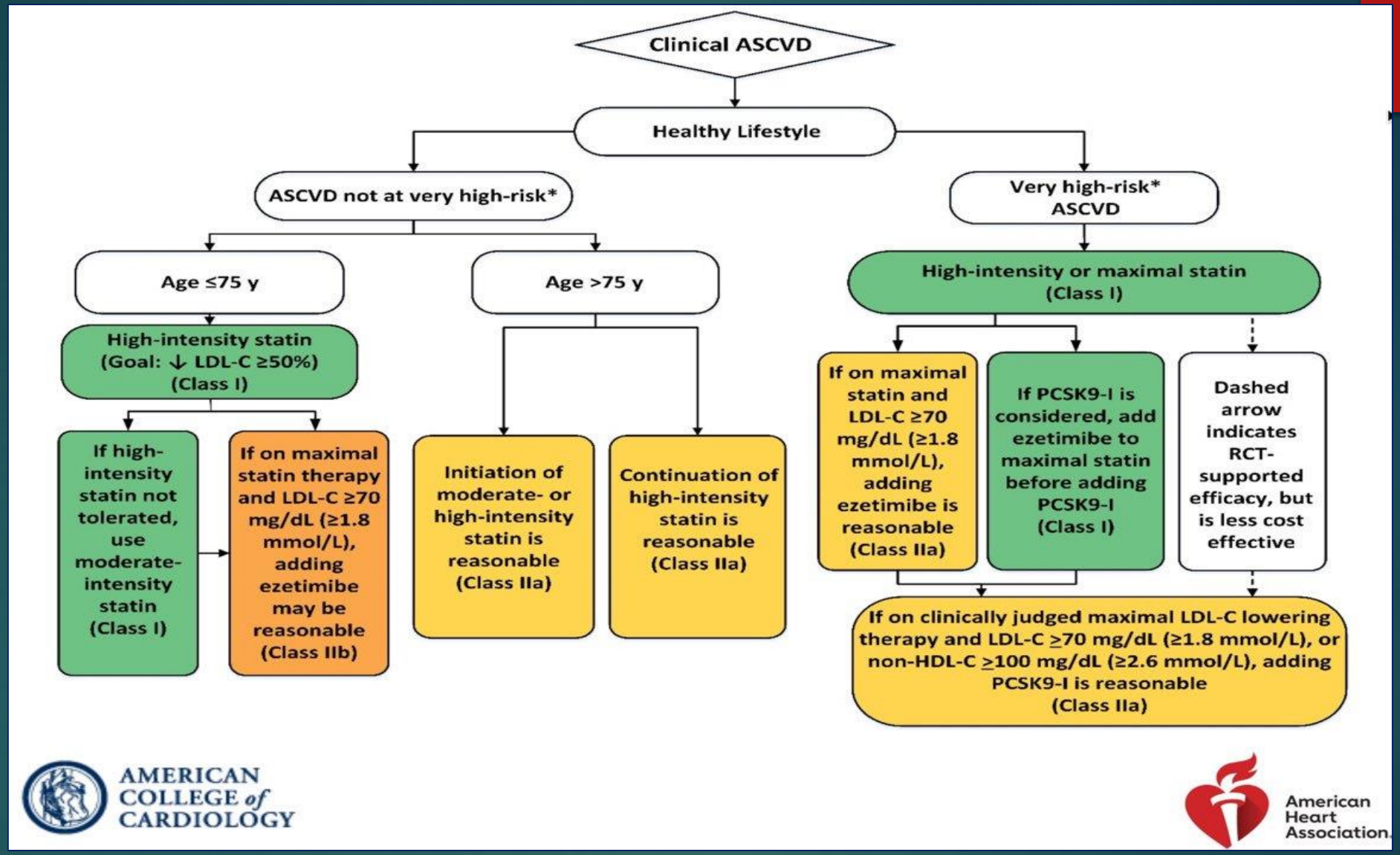
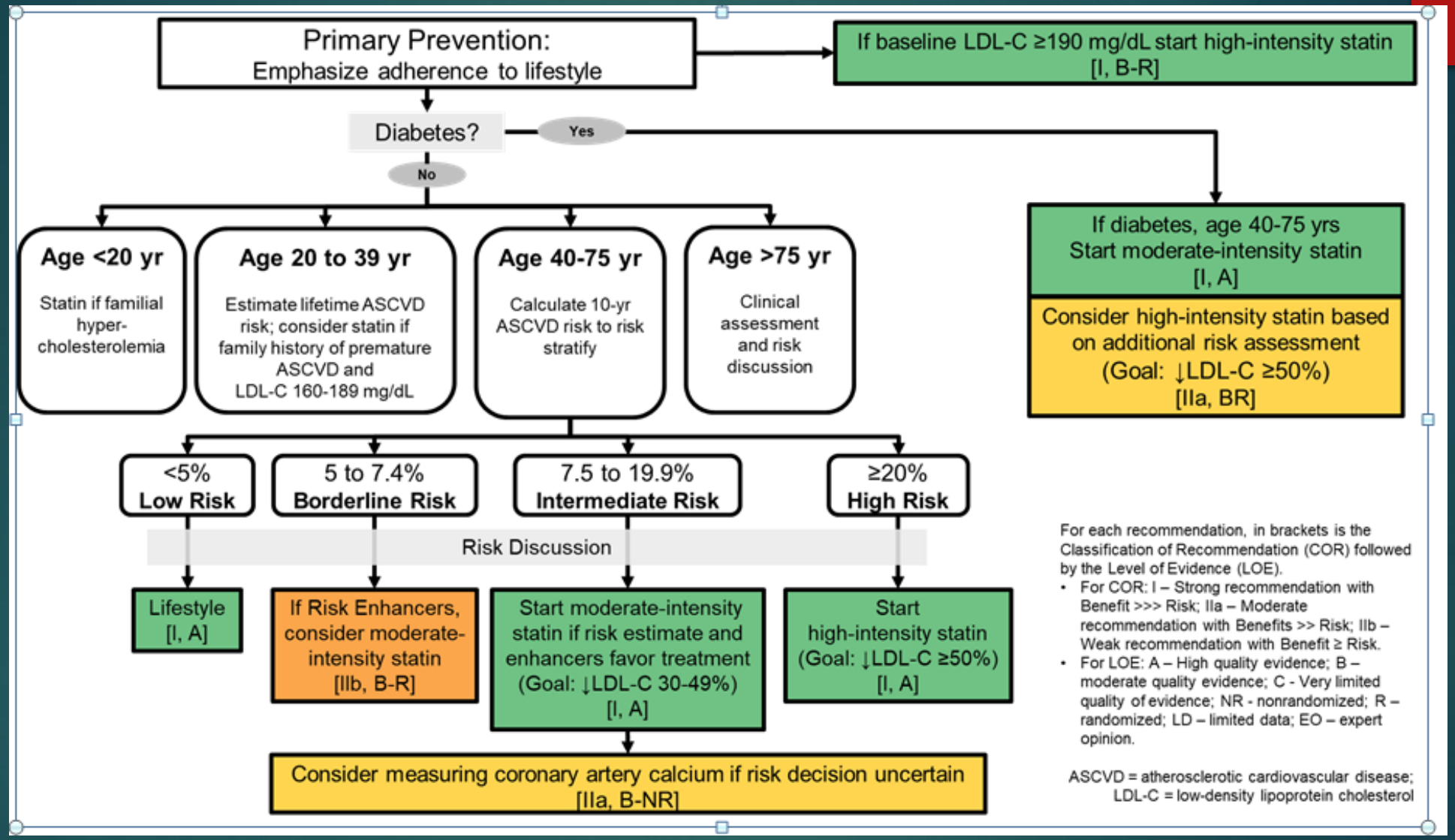
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

۴شهریورماه ۱۴۰۲



2018 AHA/…. Guideline on the Management of Blood Cholesterol



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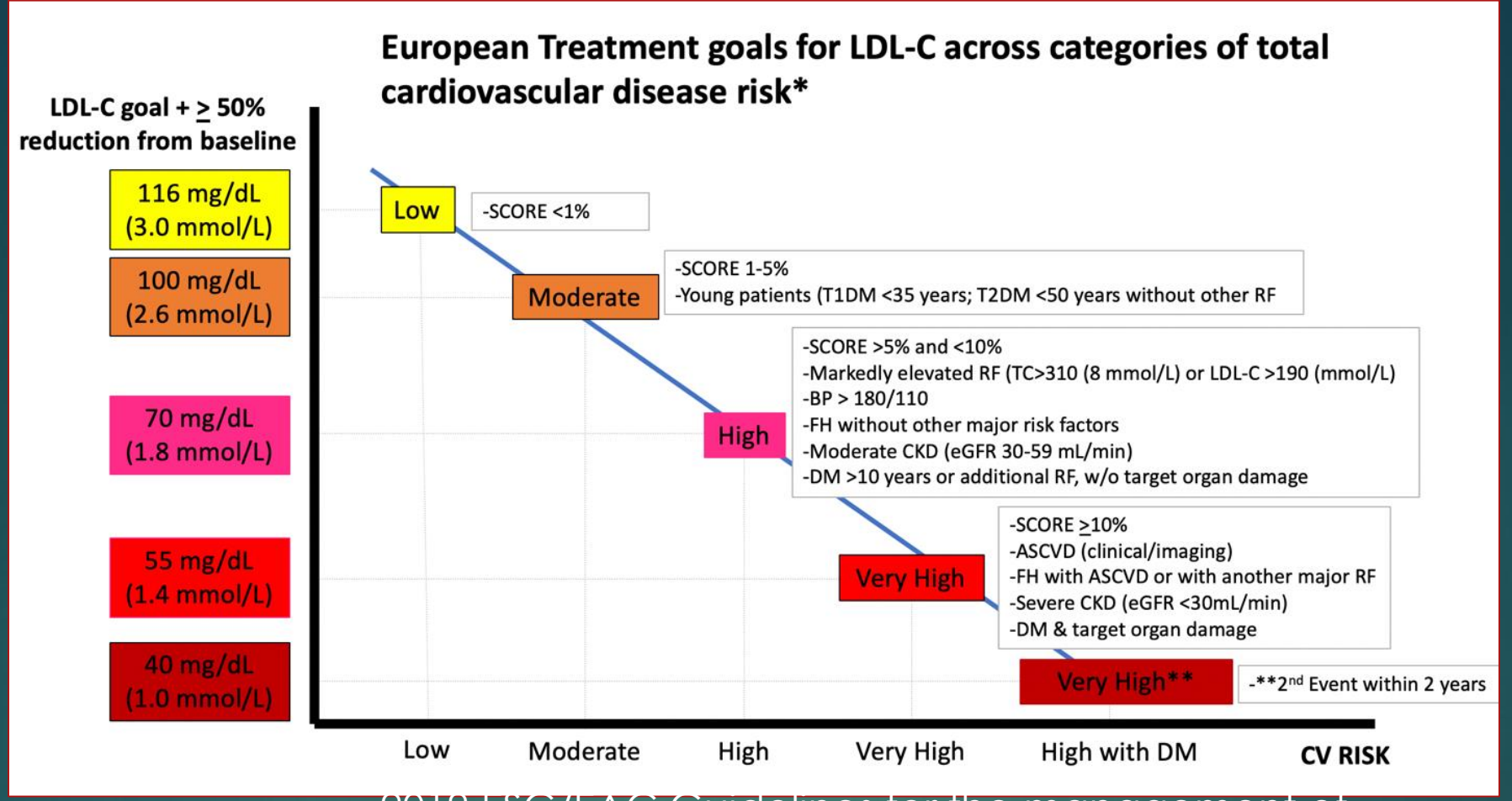
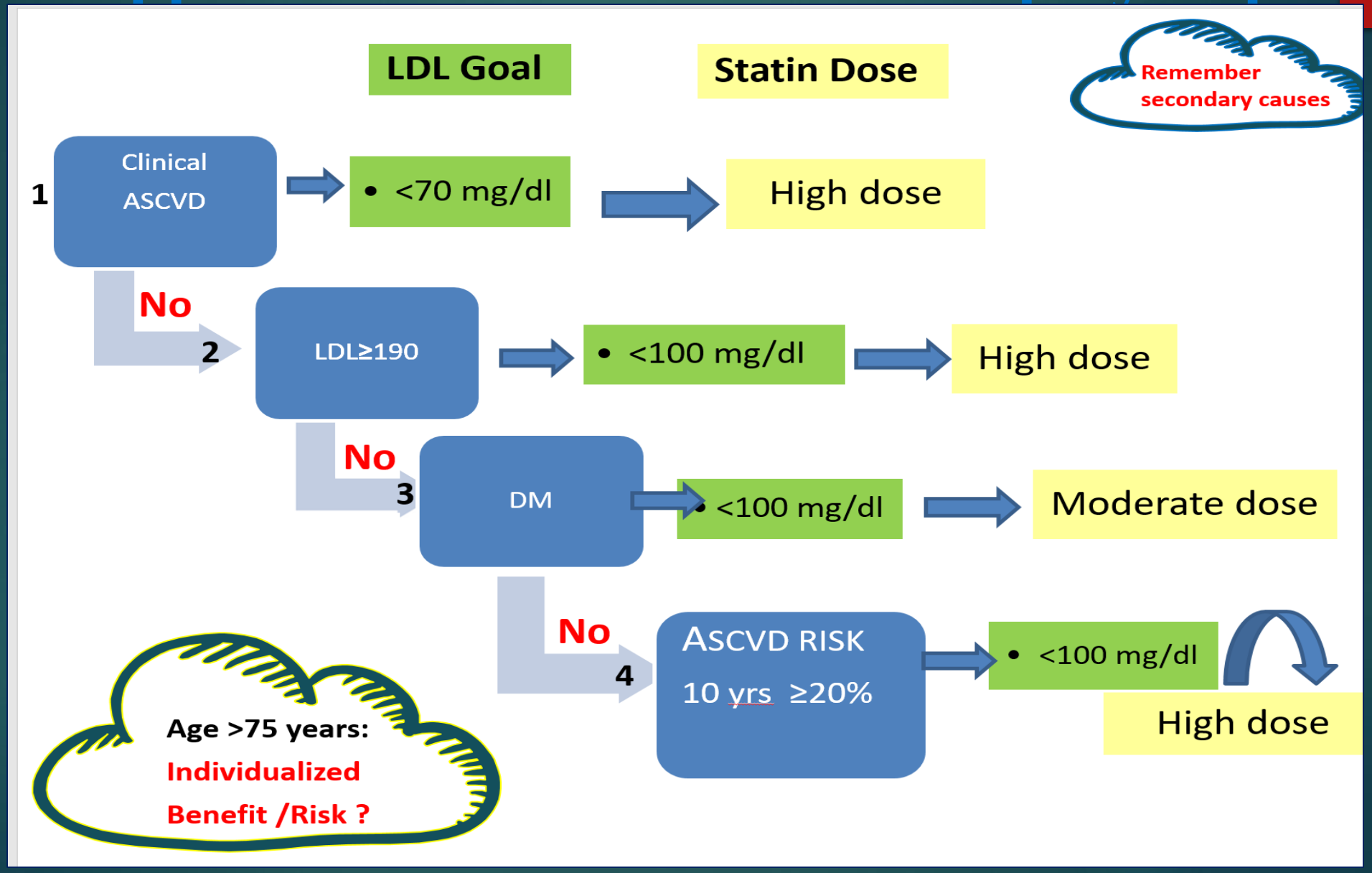


2019 ESC/EAC Guidelines for the management of dyslipidemia : lipid modification to reduce cardiovascular risk

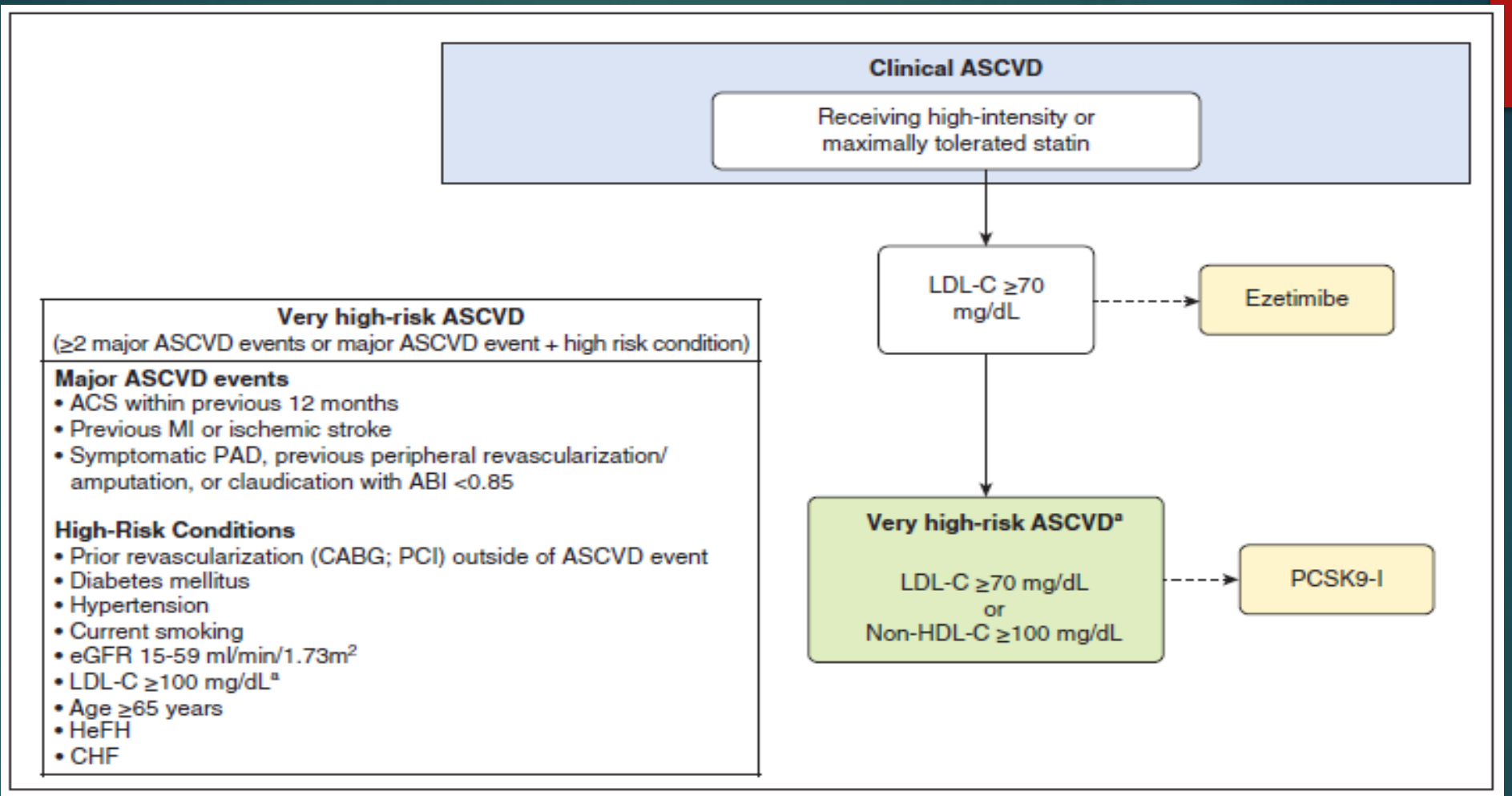
https://www.heartscore.org/en_GB

Risk group	Risk group Definition	LDL Goal mg/dl	Statin Dose
Very Very High	▪ ASCVD 2th Event during 2 years ▪ Score ≥ 10%	< 40	High
Very High	▪ ASCVD ▪ Familial Hyperchol with ASCVD or other RF ▪ Severe CKD (GFR <30 cc/min) ▪ DM + TOD	<55	High
High	▪ 5% <Score >10% ▪ LDL > 190 mg/dl or Chol > 310 mg/dl ▪ BP > 180/110 ▪ Familial Hyperchol . W/O other RF ▪ Moderate CKD (GFR 30-59 ml/min) ▪ DM > 10yr / with other RF /without TOD	<70	High
Moderate	▪ Score : 1-5% ▪ Young Patients (T1DM <35 yrs ;T2DM <50 yrs)without other RF	<100	moderate
Low	▪ Score <1%	<116	???

Approach LDL Treatment : Step by step



Step 1



Clinical ASCVD

ACS (AMI ,UA)

Chronic Stable Angina

CABG ,PCI

Stroke ,TIA

PAD

Aortic Aneurysm

LDL Goal
<70 mg/dl

High dose
Statin

STATIN

- **Rosuvastatin** Tab:5,10,20,40
- **Atorvastatin** Tab:10,20,40
- **Simvastatin** Tab:10,20
-

Statin intensity dose

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%-49%	<30%
Statins	Atorvastatin (40 mg‡) 80 mg Rosuvastatin 20 mg (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20-40 mg§	Simvastatin 10 mg
	…	Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1-4 mg	Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

Ezetimibe

- Inhibits absorption of cholesterol at the **brush border of the small intestine**

- Decreased total C, LDL-C, apoB, TG ,Increased HDL-C

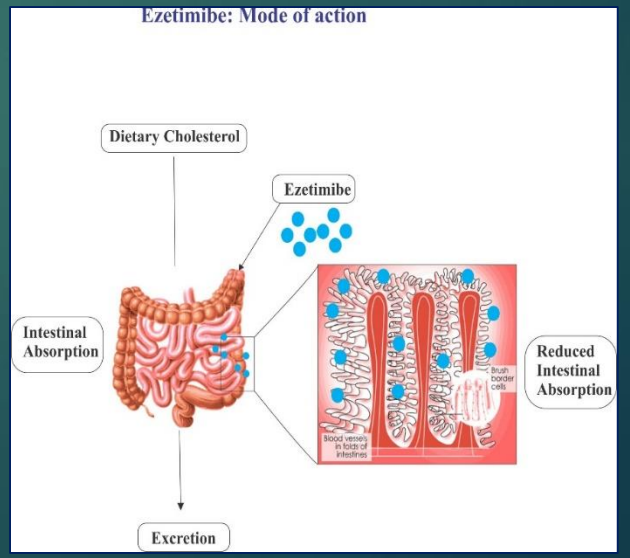
❖Onset of action: Within 1 week; Maximum effect: 2-4 weeks
❖Half-life elimination: 22 hours
❖**Absorption is not affected by food**
❖No dose adjustment **in renal and liver impairment**

✓ **ADR**

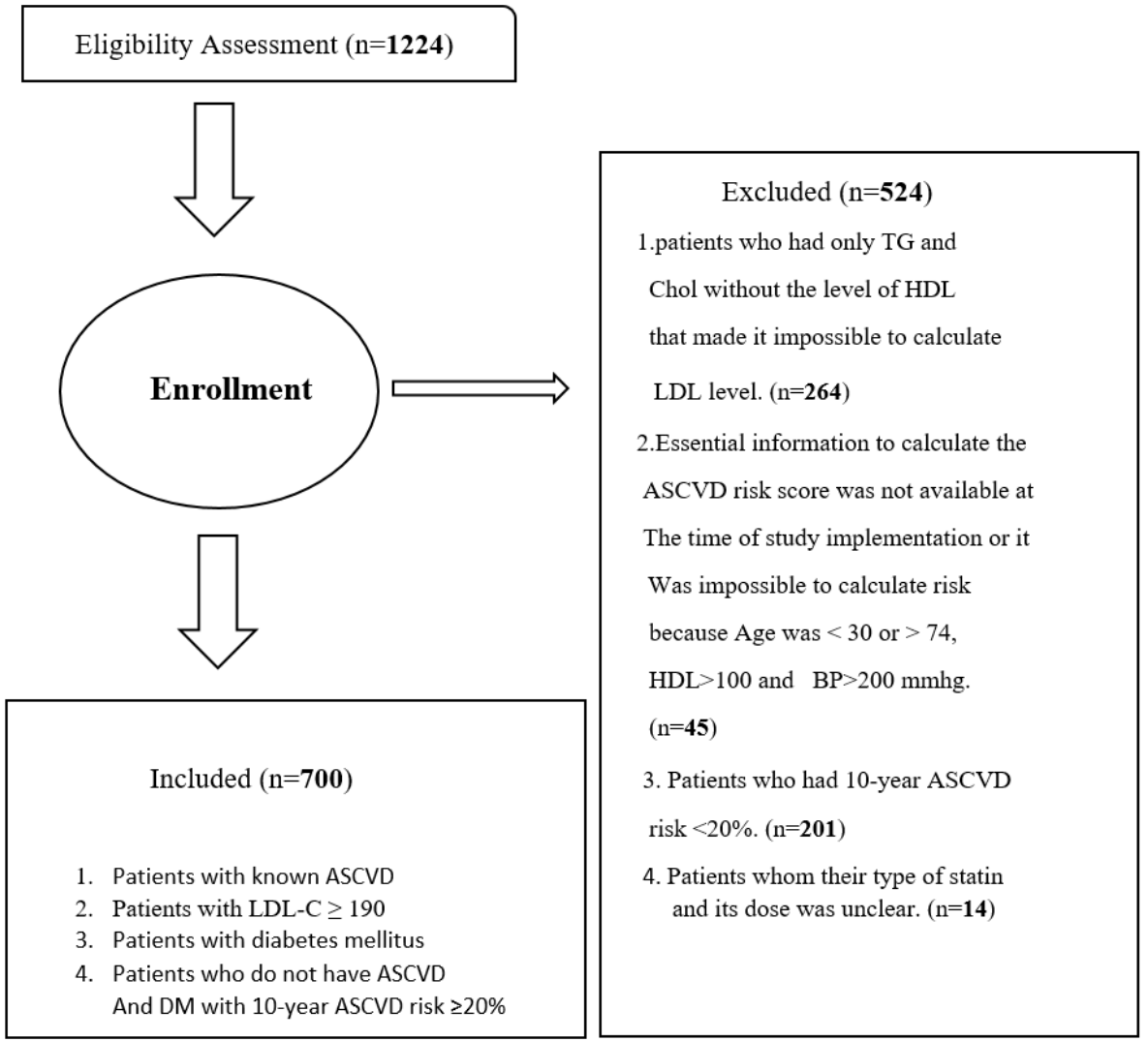
Diarrhea ,Arthralgia,Cough,Fatigue,Abdominal pain,Back pain
Increased serum transaminases

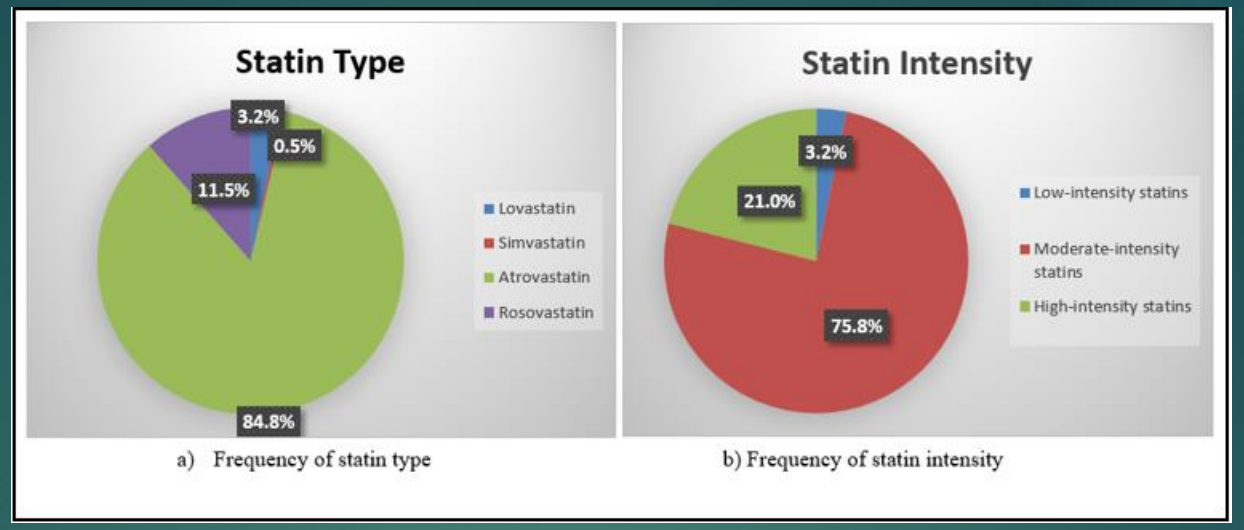
❖ Ezetimibe should be administered at least 2 h prior or 4 h following the administration of cholestyramine

✓ Dosage : 10 mg/day



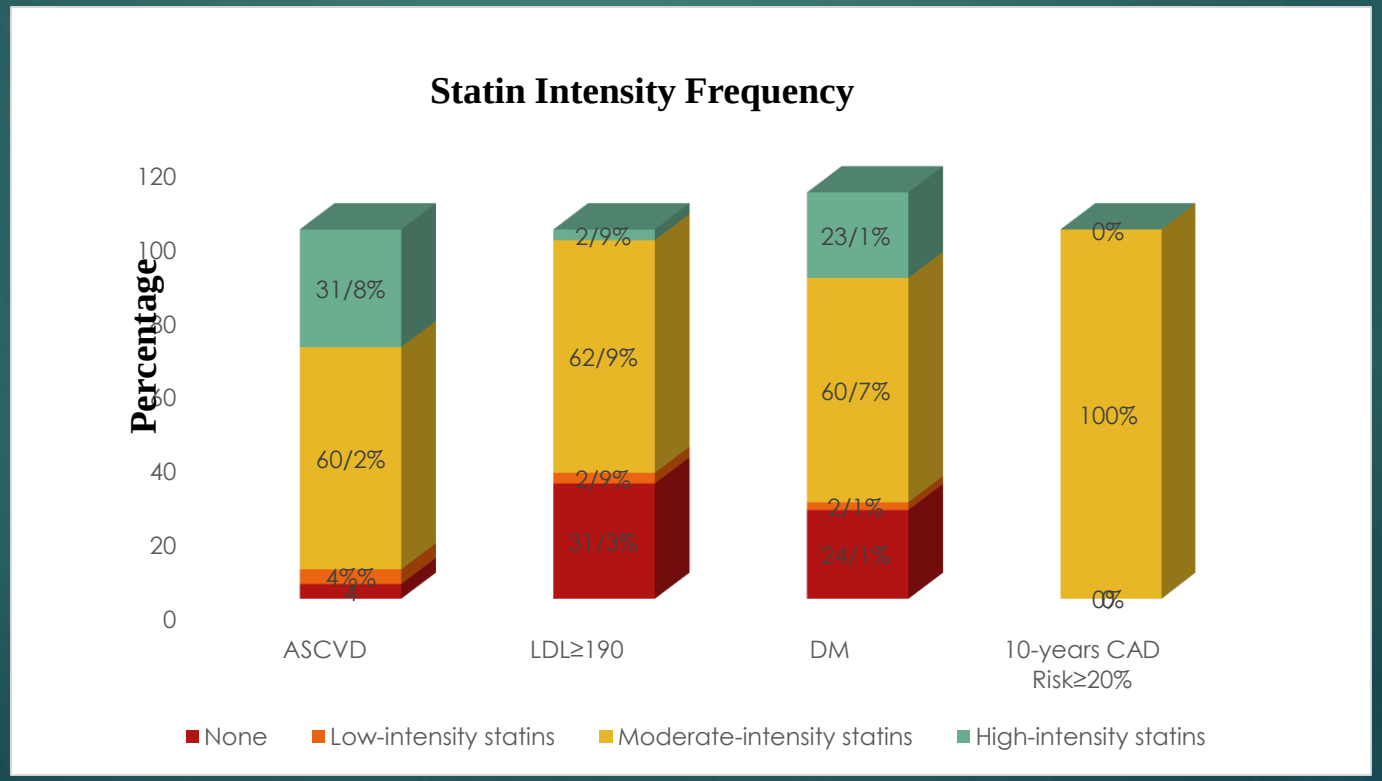
Compliance to the Statin Therapy among Patients with High Levels of Low-Density Lipoprotein in Birjand, East of Iran: A population-based study 2022-2023





a) Frequency of statin type

b) Frequency of statin intensity



Moderate-Intensity Statin With Ezetimibe Combination Therapy vs High-Intensity Statin Monotherapy in Patients at Very High Risk of Atherosclerotic Cardiovascular Disease A Post Hoc Analysis From the RACING Randomized Clinical Trial

JAMACARDIOLOGY

AUGUST 2, 2023.

INTRODUCTION

- 2018 AHA/ ACC guideline: the initial use of high-intensity statin in very high–risk (VHR) patients with atherosclerotic cardiovascular disease (ASCVD) because this population is associated with a greater risk of recurrent ASCVD events.
- Drug related adverse effects cause underuse of the guideline-recommended therapy
- the Randomized Comparison of Efficacy and Safety of Lipid-Lowering With Statin Monotherapy vs Statin/Ezetimibe Combination for High-Risk Cardiovascular Disease (RACING) trial demonstrated the noninferiority of a moderate-intensity statin with ezetimibe combination therapy compared with high-intensity statin monotherapy for the 3-year composite cardiovascular outcomes in patients with ASCVD

- whether the effect is preserved among VHR patients is not known
- investigate the outcome of ezetimibe combination with moderate-intensity statin therapy in VHR patients with ASCVD

METHODS:

- post hoc analysis of the multicenter, open-label, RACING randomized clinical trial
- February 2017 to December 2018 at 26 centers in Korea
- every patient provided written informed consent
- Race and ethnicity data were self reported which enrolled only Korean patients of East Asian ethnicity
- Adults with documented ASCVD were randomly assigned (1:1) to either receive ezetimibe/moderate–intensity statin combination therapy (rosuvastatin, 10mg plus ezetimibe, 10mg)or high-intensity statin monotherapy (rosuvastatin, 20mg)

METHODS:

- VHR patients: a history of multiple major ASCVD events or 1 major ASCVD event in addition to various high risk conditions in accordance with the 2018 AHA/ACC guidelines
- The primary end point: the occurrence of cardiovascular death, coronary or peripheral revascularization, hospitalization for cardiovascular events, or nonfatal stroke within 3 years after randomization

METHODS:

- Cardiovascular death: death owing to myocardial infarction, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, sudden cardiac death, and any case of death in which a cardiovascular cause could not be excluded as adjudicated by a clinical end point committee
- Myocardial infarction: based on symptoms, electrocardiographic changes, or abnormal imaging findings, combined with a creatine kinase MB fraction above the upper normal limits or a troponin T or troponin I level greater than the 99th percentile of the upper normal limit

METHODS:

- Coronary or peripheral revascularization: Percutaneous and surgical revascularization of the coronary, carotid, or lower-extremity arteries
- Hospitalization for cardiovascular events: hospitalization for ischemic heart disease, heart failure, or peripheral artery disease management

METHODS:

- Hospitalization for ischemic heart disease: hospitalization due to the need for coronary revascularization based on typical symptoms and signs of myocardial ischemia documented by electrocardiography, exercise, or pharmacologic stress study; angiographic findings suggestive of new or worsening coronary artery disease; or hospitalization requiring at least an overnight stay due to substantial worsening of ischemic symptoms and signs
- Nonfatal stroke: an acute cerebrovascular event resulting in a neurologic deficit for longer than 24

METHODS:

- Secondary efficacy end points: individual components of the primary end point, serial changes in low-density lipoprotein cholesterol (LDL-C) level, and a proportion of participants with LDL-C level less than 70 mg/dL at 1, 2, and 3 years
- Safety end points: the discontinuation or dose reduction of the study drug due to intolerance or the occurrence of adverse events

Statical Analysis:

- Categorical variables: as counts and percentages and compared using the $\chi 2$ test or Fisher exact test
- Continuous variables: reported as the mean and SD and compared using *t* test or Mann-Whitney *U* test
- Event rates were plotted using Kaplan-Meier survival analysis and compared using the log-rank test
- Hazard ratios (HRs) with 95% CIs were computed using Cox regression analysis
- 2-sided *P* value <.05 was considered significant.
- Statistical analyses were conducted from April to June 2022 using R, version 4.0.3 (R Foundation).

Table. Baseline Characteristics According to Treatment Assignment in Very High-Risk (VHR) and Non-VHR Patients With Atherosclerotic Cardiovascular Disease (ASCVD)

Characteristics	VHR group (n = 1511)			Non-VHR group (n = 2269)		
	Moderate-intensity statin with ezetimibe (n = 757)	High-intensity statin monotherapy (n = 754)	*P* value	Moderate-intensity statin with ezetimibe (n = 1137)	High-intensity statin monotherapy (n = 1132)	*P* value
Age, mean (SD), y	63.6 (9.9)	64.3 (10.3)	.19	63.5 (9.3)	63.9 (9.2)	.37
Sex, No. (%)						
Female	141 (18.6)	154 (20.4)	.41	333 (29.3)	326 (28.8)	.83
Male	616 (81.4)	600 (79.6)		804 (70.7)	806 (71.2)	
Body mass index, mean (SD)[a]	25.0 (3.2)	25.0 (3.0)	.82	25.1 (3.1)	25.1 (3.1)	.58
Prior myocardial infarction, No. (%)	650 (85.9)	631 (83.7)	.57	94 (8.2)	114 (10.0)	.18
Prior percutaneous coronary intervention, No. (%)	648 (85.6)	632 (83.8)	.37	610 (53.6)	607 (53.6)	<.99
Prior coronary bypass graft surgery, No. (%)	58 (7.7)	47 (6.3)	.35	74 (6.5)	68 (5.9)	.65
History of ischemic stroke, No. (%)	93 (12.3)	101 (13.4)	.57	8 (0.7)	11 (1.0)	.64
Chronic kidney disease, No. (%)[b]	106 (14.0)	106 (14.1)	<.99	87 (7.7)	93 (8.2)	.68
End-stage kidney disease receiving hemodialysis, No. (%)	11 (1.5)	12 (1.6)	.97	2 (0.2)	4 (0.3)	.69
Hypertension, No. (%)	569 (75.2)	574 (76.1)	.71	677 (59.5)	700 (61.8)	.28
Peripheral artery disease, No. (%)	54 (7.1)	56 (7.4)	.90	12 (1.1)	13 (1.1)	.99
Diabetes, No. (%)	334 (44.1)	327 (43.4)	.81	367 (32.3)	370 (32.7)	.87
Insulin treatment	26 (3.4)	34 (4.5)	.35	24 (2.1)	36 (3.2)	.15
Current smoker, No. (%)	172 (22.7)	164 (21.8)	.70	156 (13.7)	146 (12.9)	.61
Dyslipidemia treatment before randomization, No. (%)						
Drug naive	48 (6.3)	53 (7.0)	.78	112 (9.9)	103 (9.1)	.42
Low-intensity statin	4 (0.5)	3 (0.4)		2 (0.2)	2 (0.2)	
Moderate-intensity statin	243 (32.3)	262 (34.7)		438 (38.5)	423 (37.4)	
Moderate-intensity statin with ezetimibe	101 (13.3)	89 (11.8)		150 (13.2)	159 (14.0)	
High-intensity statin	324 (42.8)	316 (41.9)		387 (34.0)	413 (36.5)	
High-intensity statin with ezetimibe	37 (4.9)	31 (4.1)		48 (4.2)	32 (2.8)	
Heart failure, No. (%)	46 (6.1)	45 (6.0)	<.99	25 (2.2)	24 (2.1)	<.99
Baseline serum LDL-C, median (IQR), mg/dL	78 (63-98)	77 (62-97)	.60	82 (65-102)	82 (65-102)	.61
No. of patients with LDL-C <70 mg/dL, No. (%)	272 (35.9)	278 (36.9)	.75	371 (32.6)	338 (29.9)	.17

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert LDL-C level to millimoles per liter, multiply by 0.0259.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL per minute per 1.73 m^2 of body surface area.

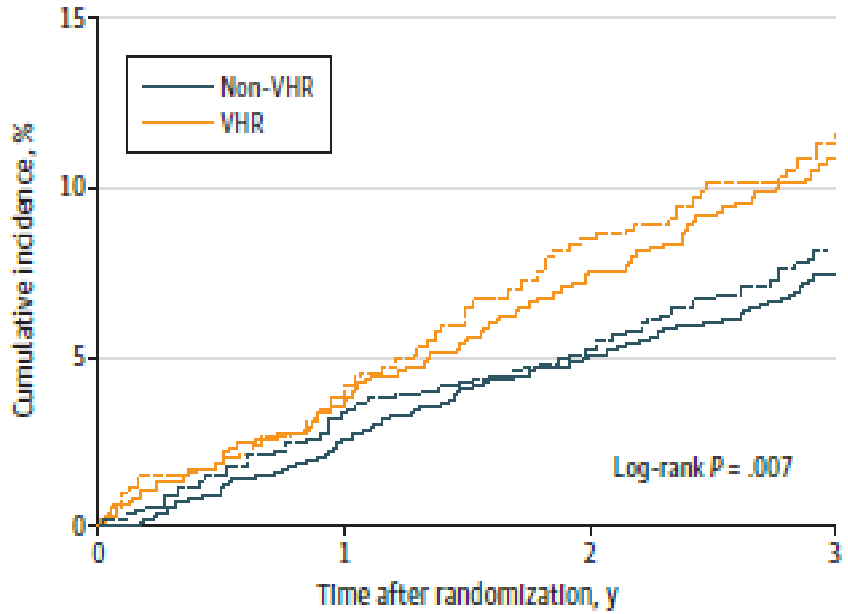
Results:

- 3780 patients enrolled in the RACING trial
- mean [SD] age, 64 years; 2826 male [75%]; 954 female [25%]
- 1511 patients (40.0%) in the VHR group had a higher frequency of comorbidities and high intensity statin medication before randomization
- Of the 1511 VHR patients:
  - 757 (50.1%) were allocated to moderate-intensity statin with ezetimibe combination therapy
  - 754 (49.9%) to high-intensity statin monotherapy,
  - the baseline characteristics were well-balanced between the groups (Table)

Results:

- Compared with non-VHR patients, VHR patients: a higher incidence of the primary end point (173 of 1511 [11.4%] vs 185 of 2269 [8.3%]; HR: 1.42; 95% CI, 1.15-1.75; *P* < .001)
- no significant difference: in the primary end point between the combination therapy and high-intensity statin monotherapy groups for both groups
  - VHR patients (85 of 757 [11.2%] vs 88 of 754 [11.7%]; HR: 0.96, 95% CI, 0.71-1.30)
  - non-VHR patients (87 of 1137 [7.7%] vs 98 of 1132 [8.7%]; HR: 0.88, 95%CI,0.66-1.18)
  - without statistical heterogeneity (*P* for interaction = .67)

Figure 1. Primary End Point According to Assigned Treatment in Very High-Risk (VHR) and Non-VHR Patients With Atherosclerotic Cardiovascular Disease (ASCVD)



No. at risk				
VHR				
Combination therapy	757	718	683	646
High-intensity statin	754	718	673	648
Non-VHR				
Combination therapy	1137	1078	1046	1010
High-intensity statin	1132	1071	1043	994

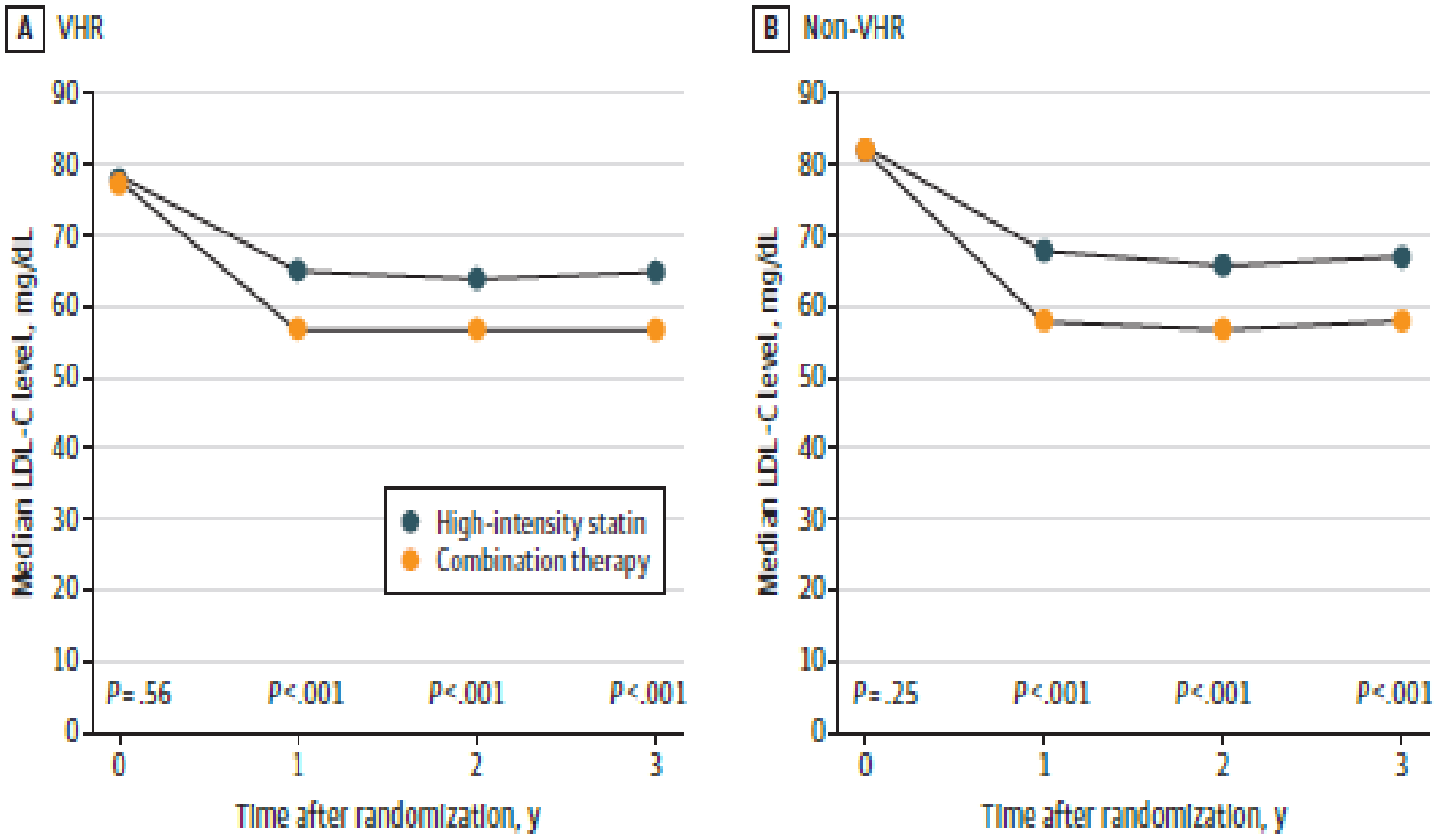
	Moderate-Intensity statin with ezetimibe, %	High-Intensity statin monotherapy, %	HR (95% CI)	*P* for Interaction
VHR	11.2	11.7	0.96 (0.71-1.30)	.67
Non-VHR	7.7	8.7	0.88 (0.66-1.18)	.67

The cumulative incidences of the primary end point at 3 years after randomization (intention-to-treat population) comparing moderate-intensity statin with ezetimibe combination vs high-intensity statin monotherapy in VHR and non-VHR patients. The interaction *P* value shows no evidence of significant heterogeneity for the treatment outcomes of the primary endpoint among VHR and non-VHR. HR indicates hazard ratio.

Results:

- no significant difference: in the occurrence of each clinical end point between the 2 treatment strategies in both VHR and non-VHR patients

Figure 2. Serial Changes of Low-Density Lipoprotein Cholesterol (LDL-C) Level According to Assigned Treatment in Very High-Risk (VHR) and Non-VHR Patients With Atherosclerotic Cardiovascular Disease



Serial median values of LDL-C level among VHR patients (A) and non-VHR patients (B) with ASCVD. To convert LDL-C level to millimoles per liter, multiply by 0.0259.

Results:

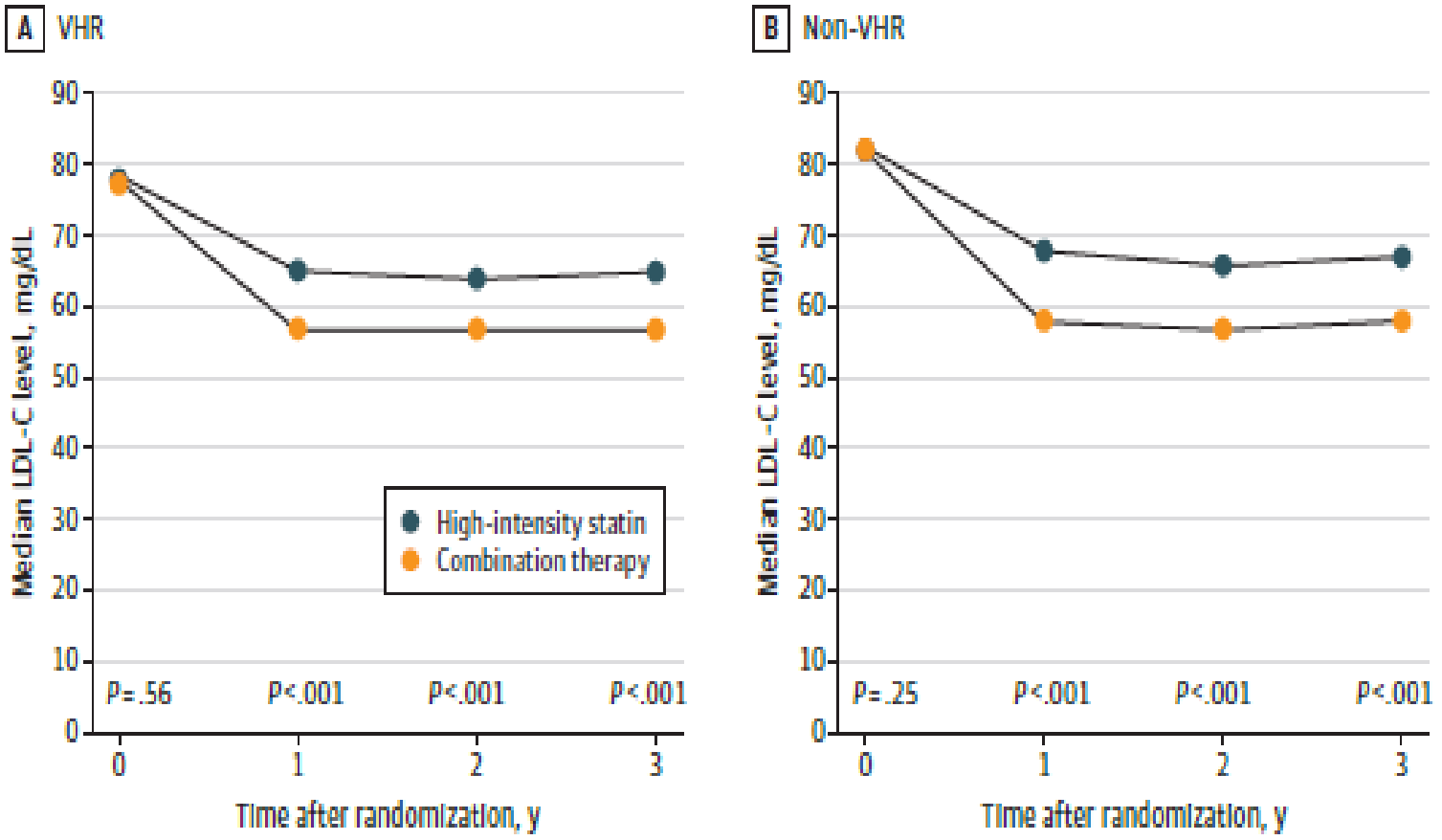
- no significant difference between the groups receiving combination therapy and high-intensity statin therapy in the median (IQR) baseline LDL-C level
  - VHR, 78 [63-98]mg/dL vs 77 [62-97]mg/dL;
  - non-VHR, 82 [65-102]mg/dL vs 82[65-102]mg/dL)
  - proportion of patients with LDL-C level less than 70 mg/dL

Characteristics	VHR group (n = 1511)			Non-VHR group (n = 2269)		
	Moderate-intensity statin with ezetimibe (n = 757)	High-intensity statin monotherapy (n = 754)	*P* value	Moderate-intensity statin with ezetimibe (n = 1137)	High-intensity statin monotherapy (n = 1132)	*P* value
Baseline serum LDL-C, median (IQR), mg/dL	78 (63-98)	77 (62-97)	.60	82 (65-102)	82 (65-102)	.61
No. of patients with LDL-C <70 mg/dL, No. (%)	272 (35.9)	278 (36.9)	.75	371 (32.6)	338 (29.9)	.17

Results:

- In the combination therapy group during follow-up, the median (IQR) LDL-C level was significantly lower
- VHR:
  - 1 year: 57 [47-71] mg/dL vs 65 [53-78] mg/dL;
  - 2 years: 57 [45-69] mg/dL vs 64 [51-78] mg/dL;
  - 3 years: 57 [46-72] mg/dL vs 65 [51-79] mg/dL
- non-VHR:
  - 1 year: 58 [47-71] mg/dL vs 68 [56-81] mg/dL;
  - 2 years: 57 [46-70] mg/dL vs 66 [53-79] mg/dL;
  - 3 years: 58 [47-70] mg/dL vs 67 [56-81]mg/dL;
- all $P < .001$

Figure 2. Serial Changes of Low-Density Lipoprotein Cholesterol (LDL-C) Level According to Assigned Treatment in Very High-Risk (VHR) and Non-VHR Patients With Atherosclerotic Cardiovascular Disease



Serial median values of LDL-C level among VHR patients (A) and non-VHR patients (B) with ASCVD. To convert LDL-C level to millimoles per liter, multiply by 0.0259.

Results:

- For both VHR and non-VHR patients, the mean (SD) change in LDL-C level from baseline was significantly greater in the combination group
- VHR,
  - 1 year: −19.1 [30.0]mg/dL vs −10.1 [31.4]mg/dL;
  - 2 years: −22.3 [33.3]mg/dL vs −13.0 [33.8] mg/dL;
  - 3 years: −18.8 [32.2]mg/dL vs −9.7 [34.5]mg/dL
- non-VHR,
  - 1 year: −23.7 [29.1]mg/dL vs −12.5 [33.6]mg/dL;
  - 2 years: −25.2 [28.5]mg/dL vs −15.1 [35.4]mg/dL;
  - 3 years: −23.5 [29.4] mg/dL vs −12.6 [31.9]mg/dL;
- all $P < .001$

Results:

- The proportion of patients with LDL-C level less than 70mg/dL was significantly higher in combination group
- VHR,
  - 1 year: 492 of 673 [73%] vs 393 of 671 [58%];
  - 2 years: 467 of 617 [76%] vs 377 of 618 [61%];
  - 3 years: 380 of 530 [72%] vs 323 of 536 [60%]
- non-VHR,
  - 1 year: 725 of 1002 [72%] vs 530 of 1002 [53%];
  - 2 years: 701 of 941 [75%] vs 547 of 921 [59%];
  - 3 years: 598 of 819 [73%] vs 436 of 779 [56%];
- all $P < .001$

Results:

- Discontinuation or dose reduction of lipid-lowering drugs due to intolerance occurred less frequently in the combination group
- VHR,
  - 34 of 732 [4.6%] vs 56 of 731 [7.7%]; *P* = .02;
- non-VHR,
  - 57 of 1114 [5.0%] vs 100 of 1105 [8.7%]; *P* = .001

Discussion:

- Despite the guideline recommendation of high-intensity statin treatment in VHR, studies have reported substantial underuse of high intensity statins **in practice**
- In a cohort of 601 934 patients with ASCVD in the US,
  - the prescription rate of a high-intensity statin was 22.5%,
  - strikingly, 49.9% of patients with prior ASCVD were not taking statin therapy
- Swedish national registry with 192 435 VHR patients
  - initially treated with a moderate intensity statin,
  - up titration to a high-intensity statin was observed in only 28%
- **drug-associated adverse effects** could be a plausible explanation for physicians' reluctance to prescribe high-intensity statins

Discussion:

- initial combination of ezetimibe, instead of up titration of the statin until intolerance develops, could be a promising strategy
- the current study results suggest that early ezetimibe combination could be a reasonable therapeutic approach for VHR patients with ASCVD

- در این مطالعه به روی افراد با خطر بالای بیماریهای اترواسکلروتیک عروق کرونر
- استاتین با دوز متوسط در ترکیب با ازتیمب در مقایسه با استاتین با دوز بالا در پیگیری ۳ ساله:
  - ۱- از نظر خطرات عمده قلبی عروقی (مرگ و میر، بستری شدن، نارسایی قلبی،...) با هم دریک میزان قرار دارند
  - ۲- استاتین با دوز متوسط در ترکیب با ازتیمب توسط بیماران بهتر تحمل می شود و کمتر عدم ادامه درمان داریم
  - ۳- میزان کاهش LDL-C در گروه استاتین با دوز متوسط در ترکیب با ازتیمب نسبت به استاتین با دوز بالا بیشتر است
  - ۴- LDL-C کمتر از ۷۰ در گروه استاتین با دوز متوسط در ترکیب با ازتیمب بیشتر دیده می شود