Holistic Care for the Patients with Cardiovascular Disease

Optimal Lipid Lowering Therapy in Asia Patients

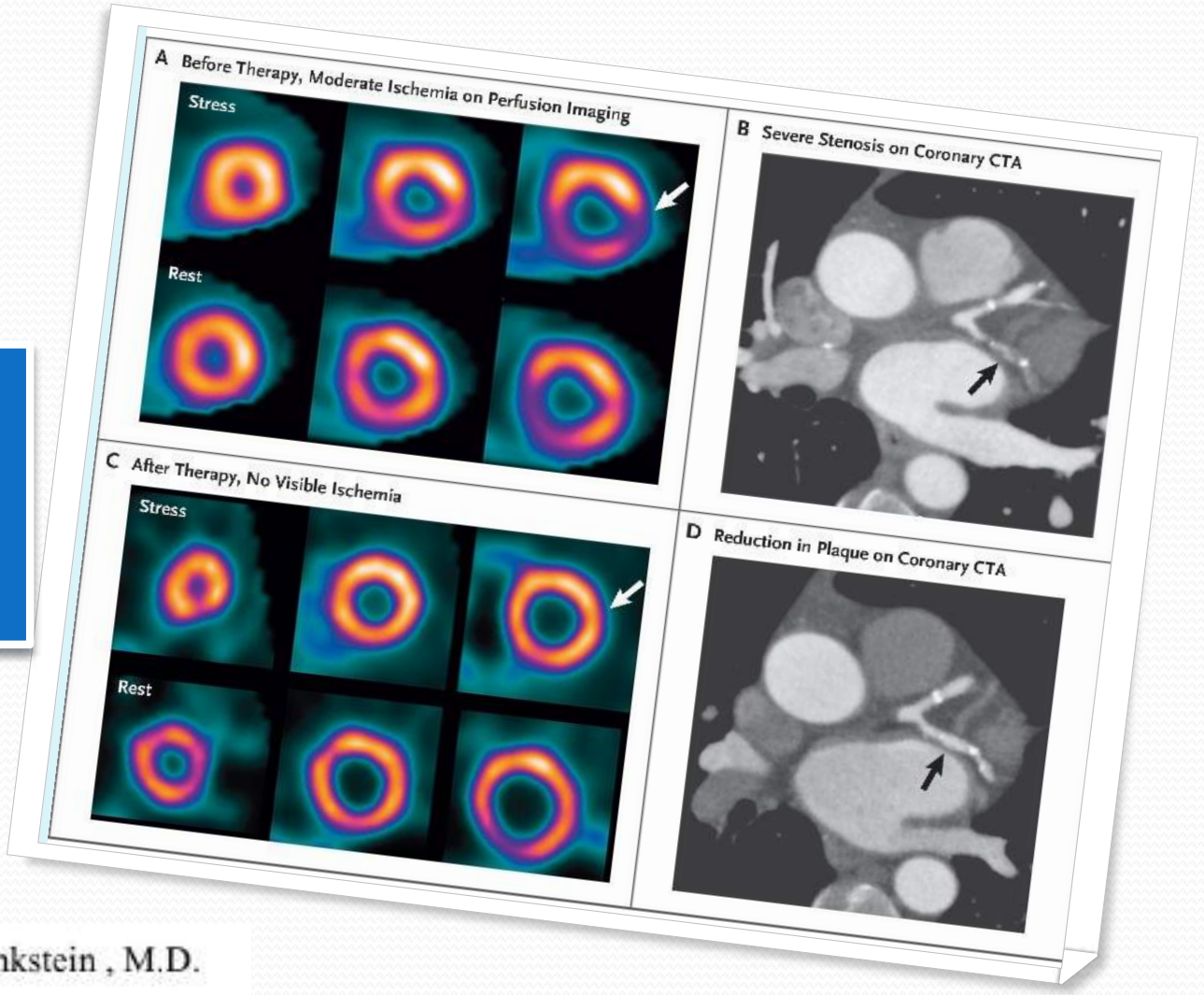
REAL-CAD vs. 2018 ACC/AHA Guideline on the Management of Blood Cholesterol

陽明大學附設醫院

心臟內科　黃嵩豪

Why should we control lipid aggressively?

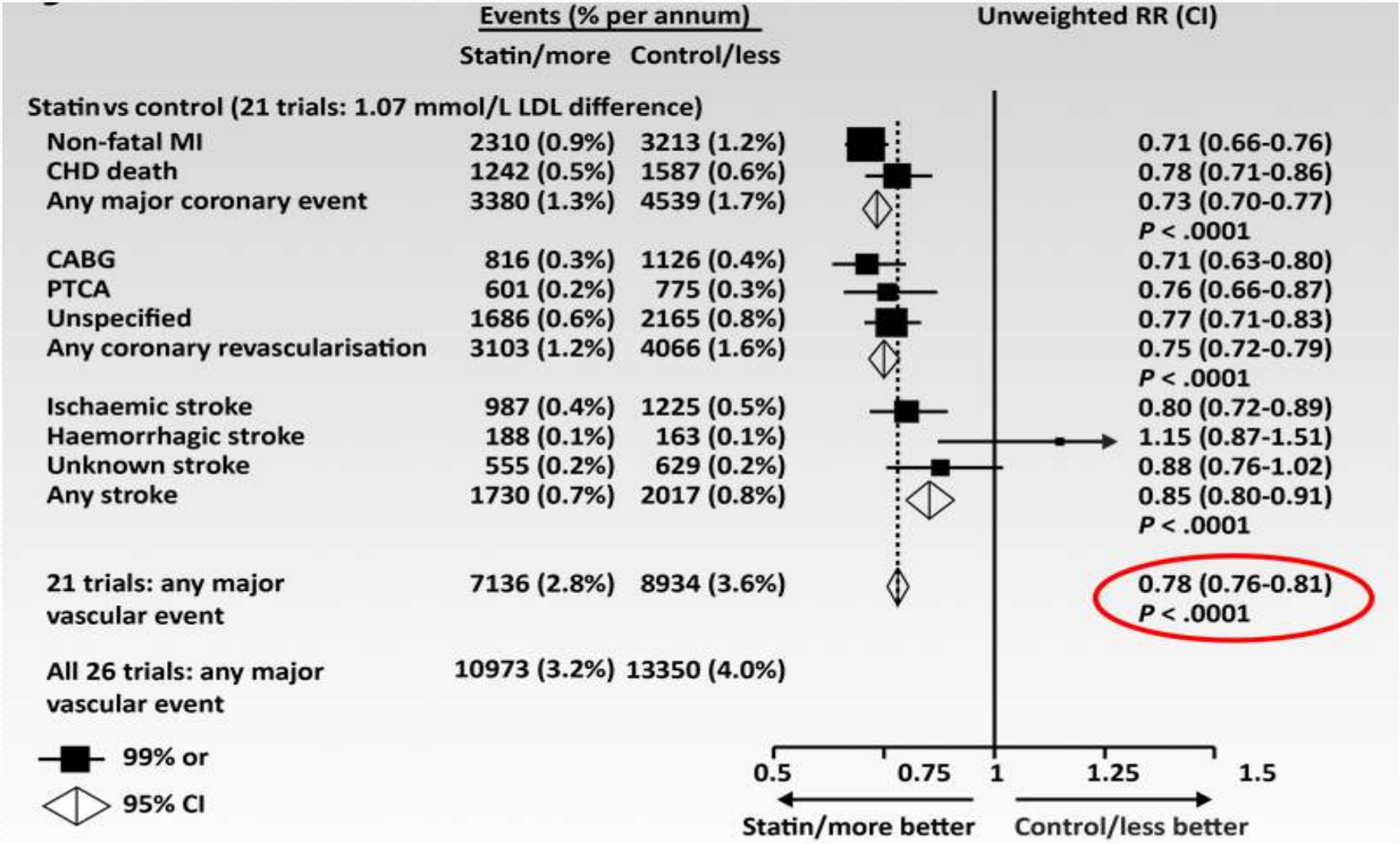
Regression of Coronary Atherosclerosis with Medical Therapy



Abhishek Keraliya , M.D. , Ron Blankstein , M.D.

N Engl J Med 376:1370 - 1370 | April 6 , 2017

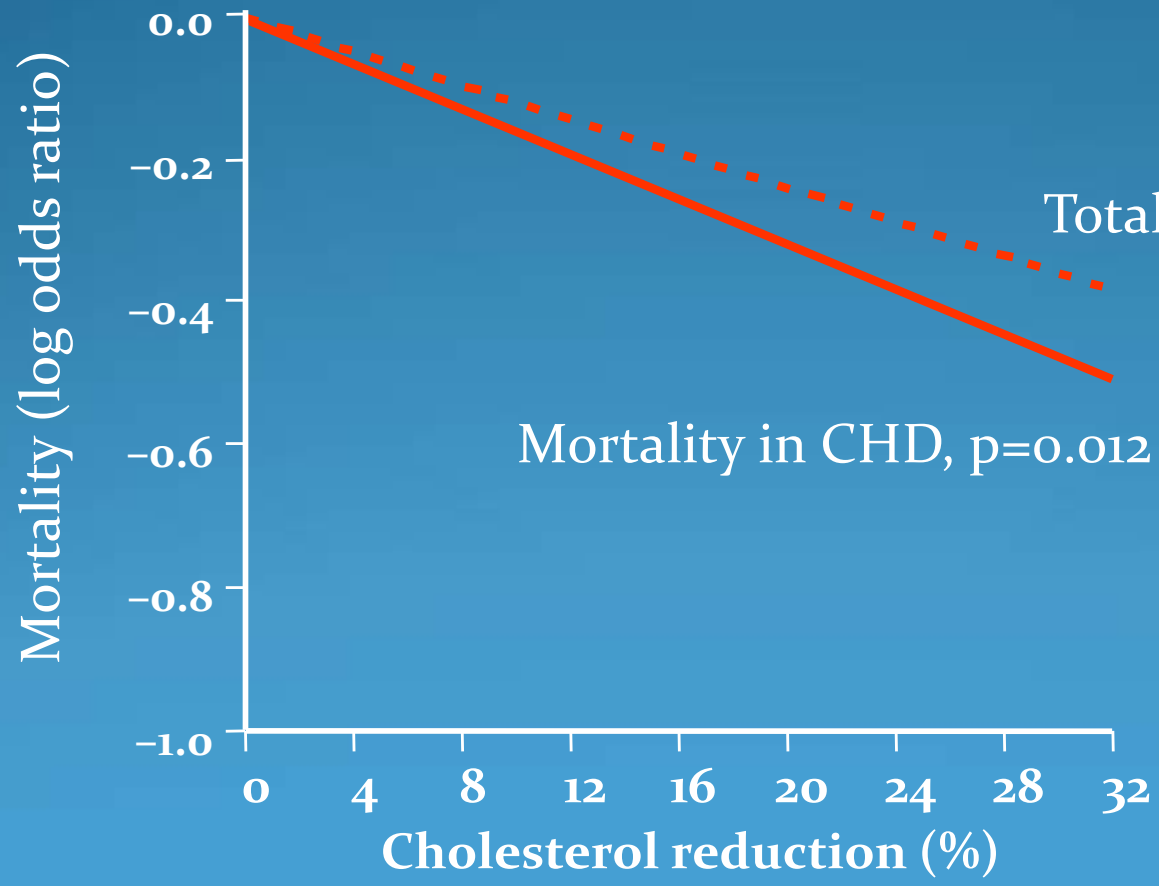
Impact of Intensive Statin Therapy on Major Vascular Events



Reproduced from Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2010;376:1670-168. © 2010, with permission from Elsevier.

Benefit of Lowering Cholesterol

Meta-analysis of 38 primary and secondary prevention trials, with more than 98,000 patients in total



Adapted from Gould AL et al. *Circulation* 1998;97:946–952

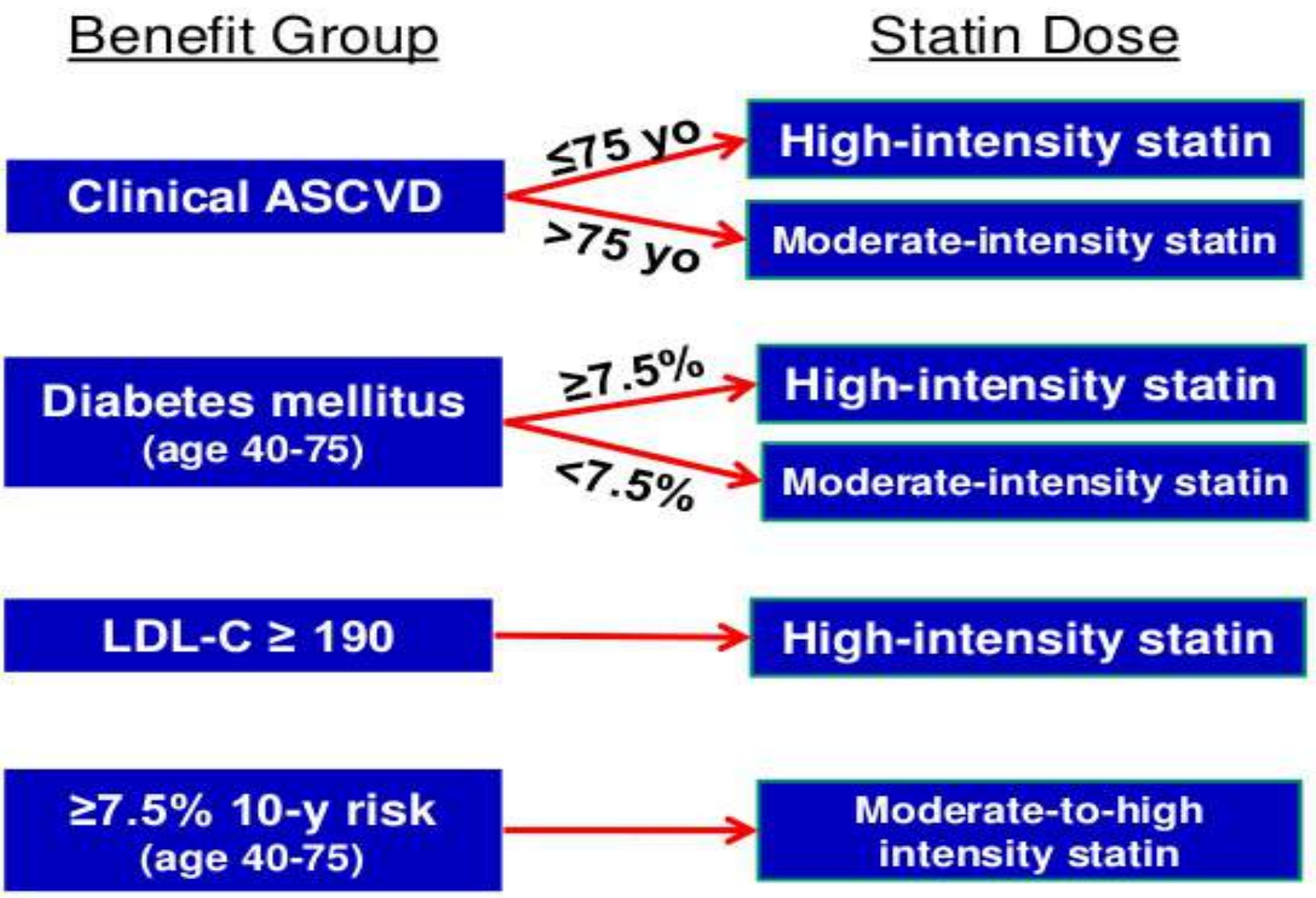
2013 ACC/AHA Cholesterol Guideline

New Perspective on LDL-C & HDL-C

- Lack of RCT evidence to support titration of drug therapy to specific LDL-C and/or non–HDL-C goals
- Strong evidence that appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit
- Quantitative comparison of statin benefits with statin risk
- Non-statin therapies – did not provide ASCVD risk reduction benefits or safety profiles comparable to statin therapy

2013 ACC/AHA Cholesterole Guidelines:

Recommendations for initiation of statin therapy



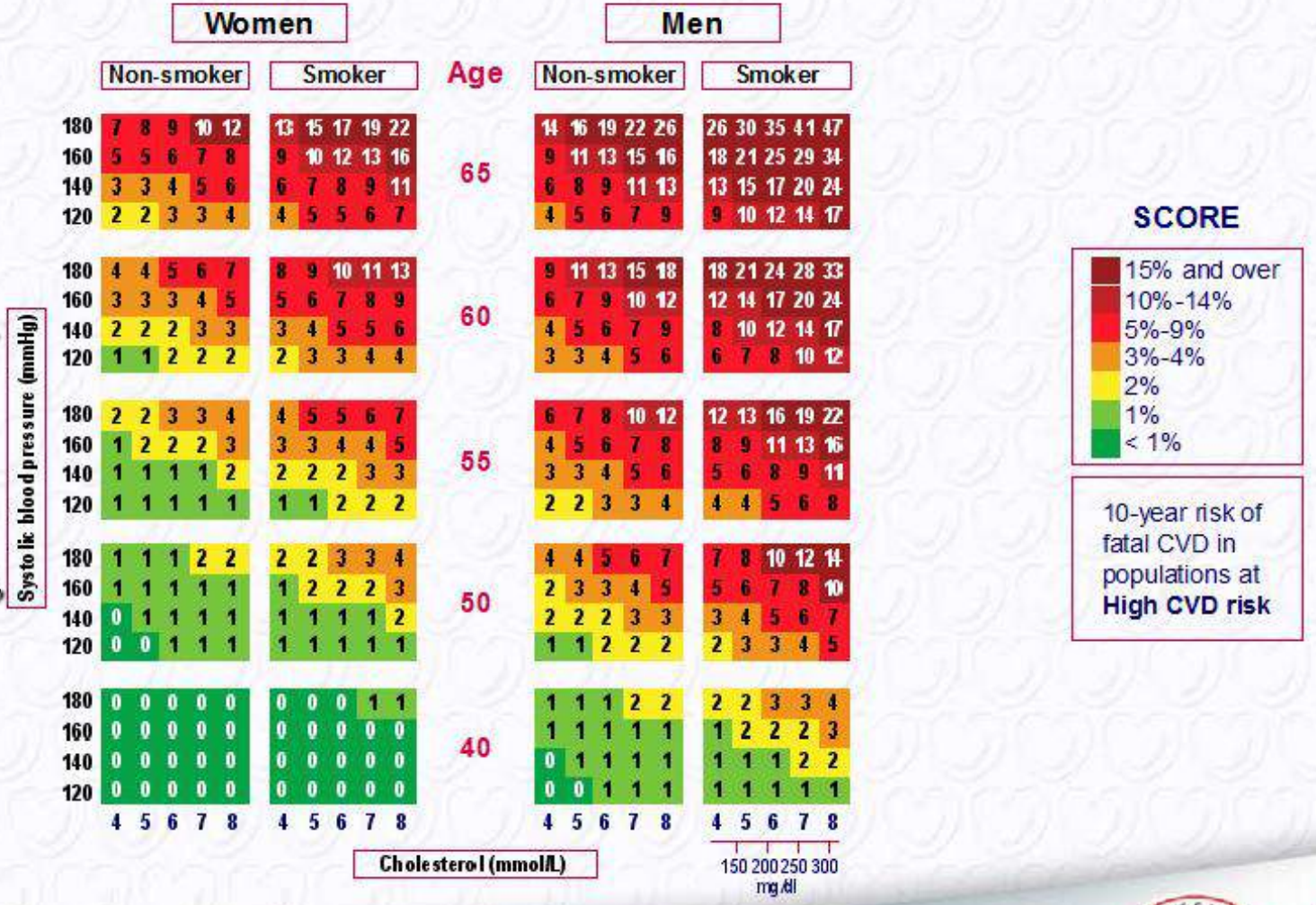
Controversies of 2013 ACC/AHA Lipid Guideline

Removal of LDL-c Goals

- Concern over message to patients and providers
  - Are cholesterol levels no longer important ?
  - Role of LDL-c goals in patients motivation
  - Providers not follow up on patients lipid response
- Do we need a target to support adherence/lifestyle changes ?
- Does a lack of RCT evidence mean lack of benefit ?
  - Decades of clinical experience with treating to target
- Effect on current performance measures
  - Will quality assurance measures follow these guidelines

SCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at high CVD risk

High CVD risk countries are all those not listed under the low risk chart. *Of these, some are at very high risk, and the high-risk c*hart may underestimate risk in these. These countries are Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Macedonia FYR, Moldova, Russia, Ukraine, and Uzbekistan.



European Heart Journal 2011;32 (14):1769–1818
Atherosclerosis 2011 Jul;217(1):3-46

www.escardio.org/guidelines

EUROPEAN SOCIETY OF CARDIOLOGY®

Lipid-lowering Drug

All hypertensive patients with established CVD or with T2DM or with an estimated 10-year risk of CV death ≥5% (based on the SCORE chart) should be considered for statin therapy aiming at goal.

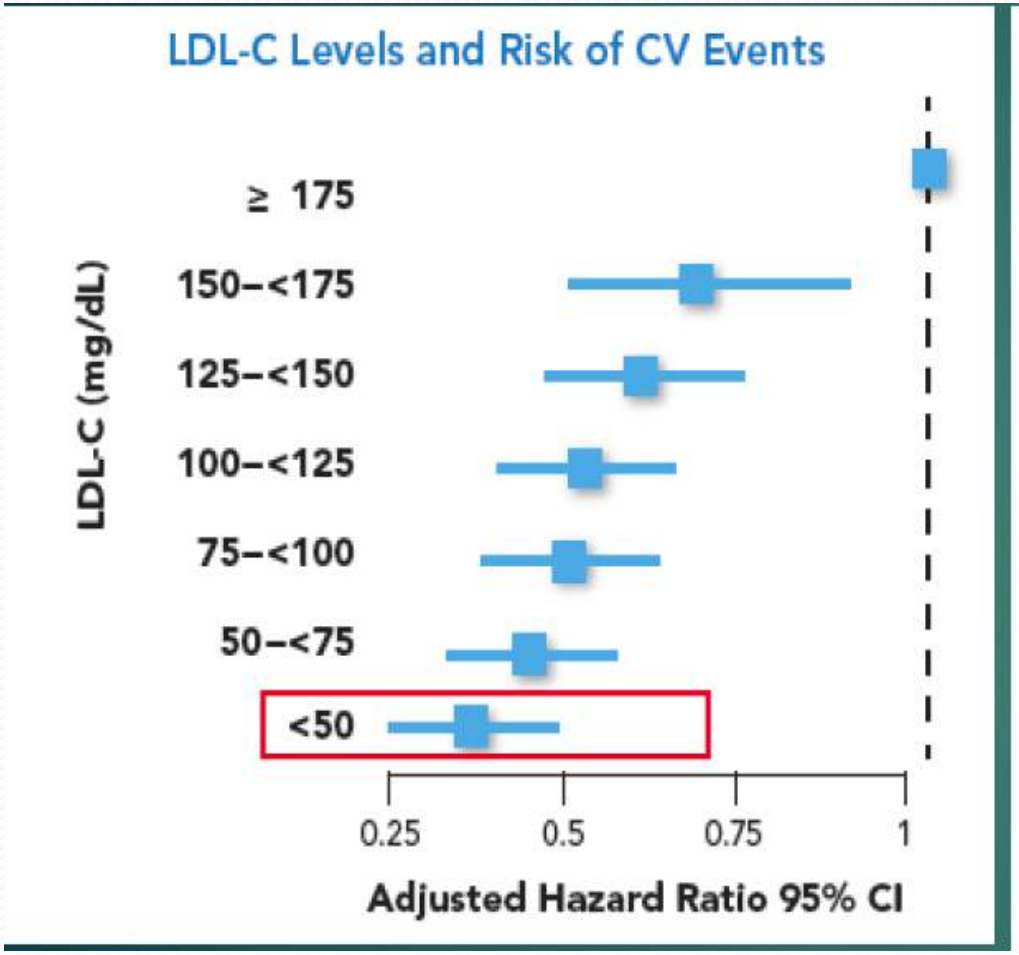
ESC CP Guidelines 2016 – Highlights: Dyslipidemia

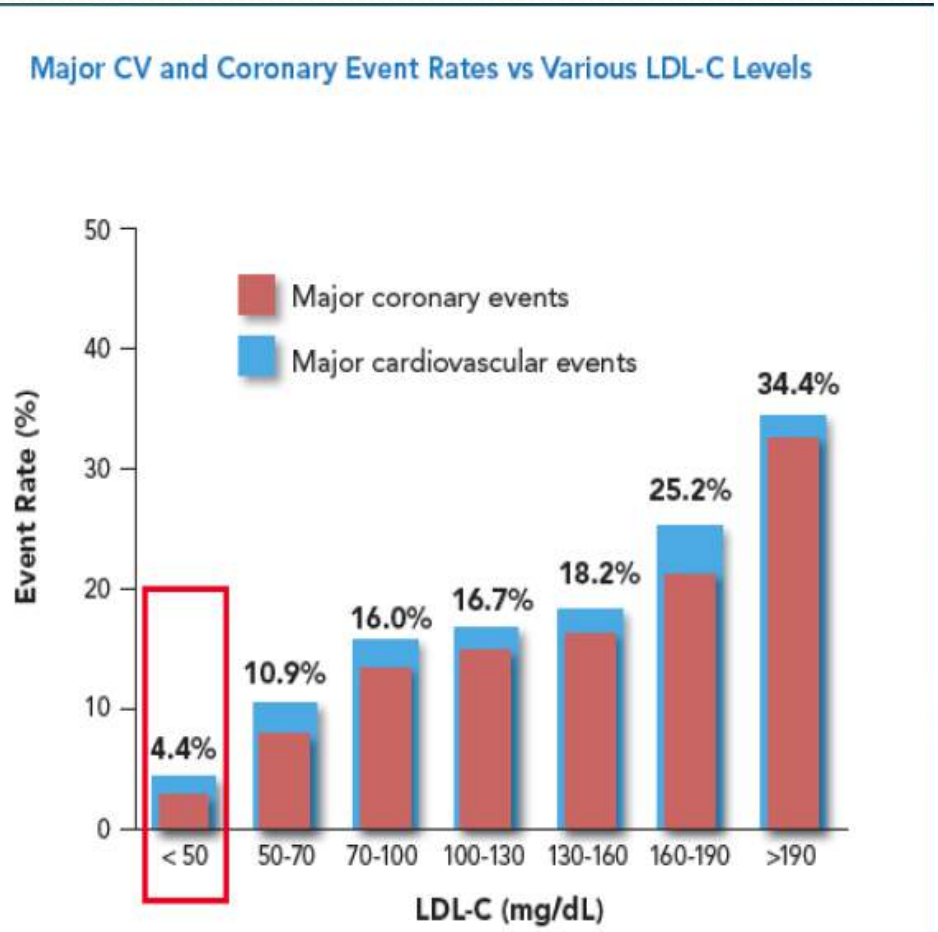
Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10%.

2016 ESC Dyslipidaemias guidelines

Recommendation	Class	Level
VERY-HIGH CV risk: LDL-c goal <70 mg/dl (1.8 mmol/L) and/or 50% reduction if baseline is 70-135 mg/dl (1.8-3.5 mmol/L)	I	B
HIGH CV risk: LDL-c goal <100 mg/l (2.6 mmol/L) or 50% reduction if baseline is 100-200 mg/dl (2.6-5.1 mmol/L)	I	B
MODERATE CV risk: LDL-c goal <115 mg/dl (3.0 mmol/L)	IIa	C

MEAN ATTAINED LDL-C ON STATIN THERAPY AND RISK OF SECONDARY EVENTS

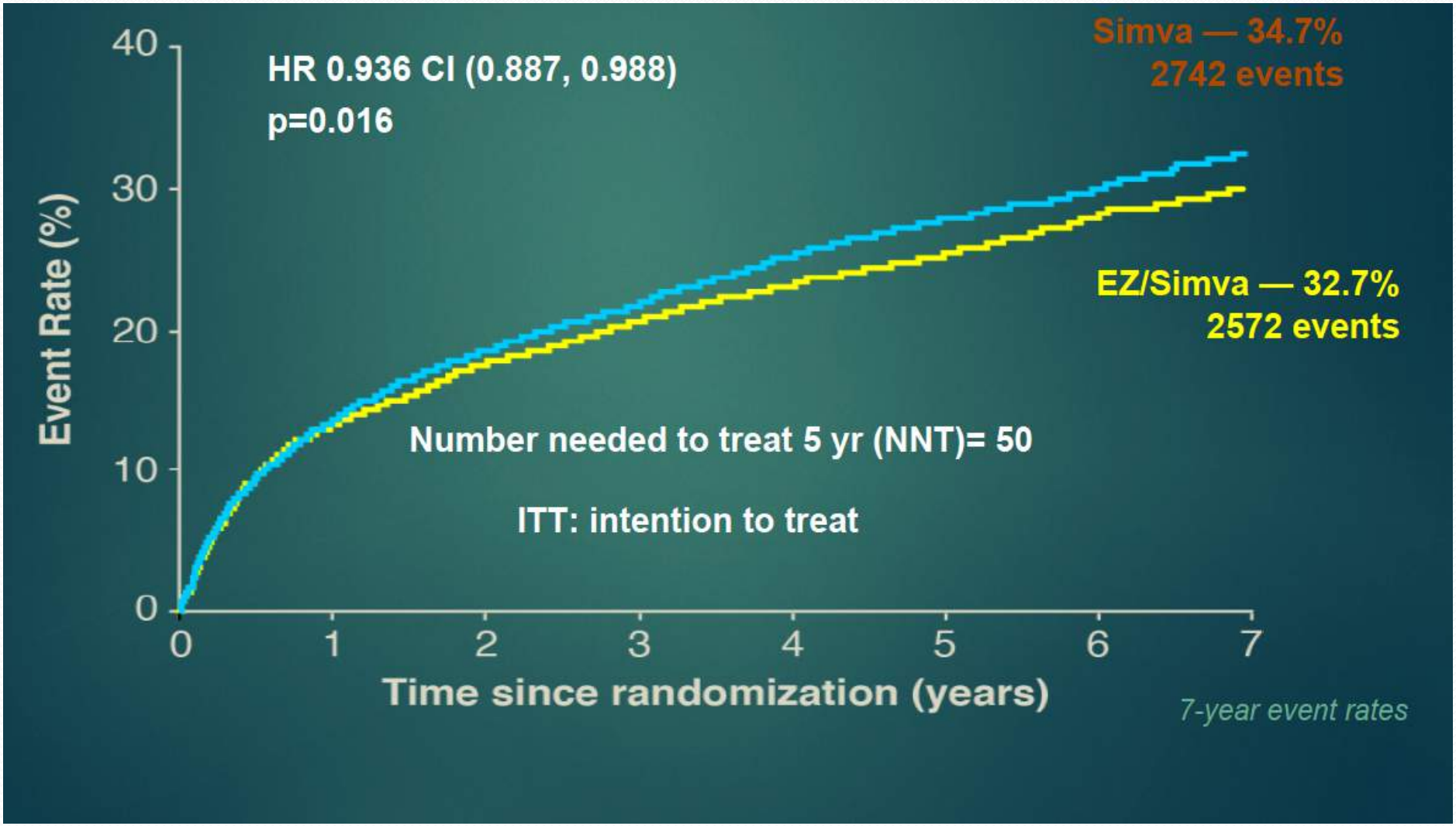




Boekholdt et al. J Am Coll Cardiol 2014;64:485–94.

IMPROVE-IT: Primary Endpoint — ITT

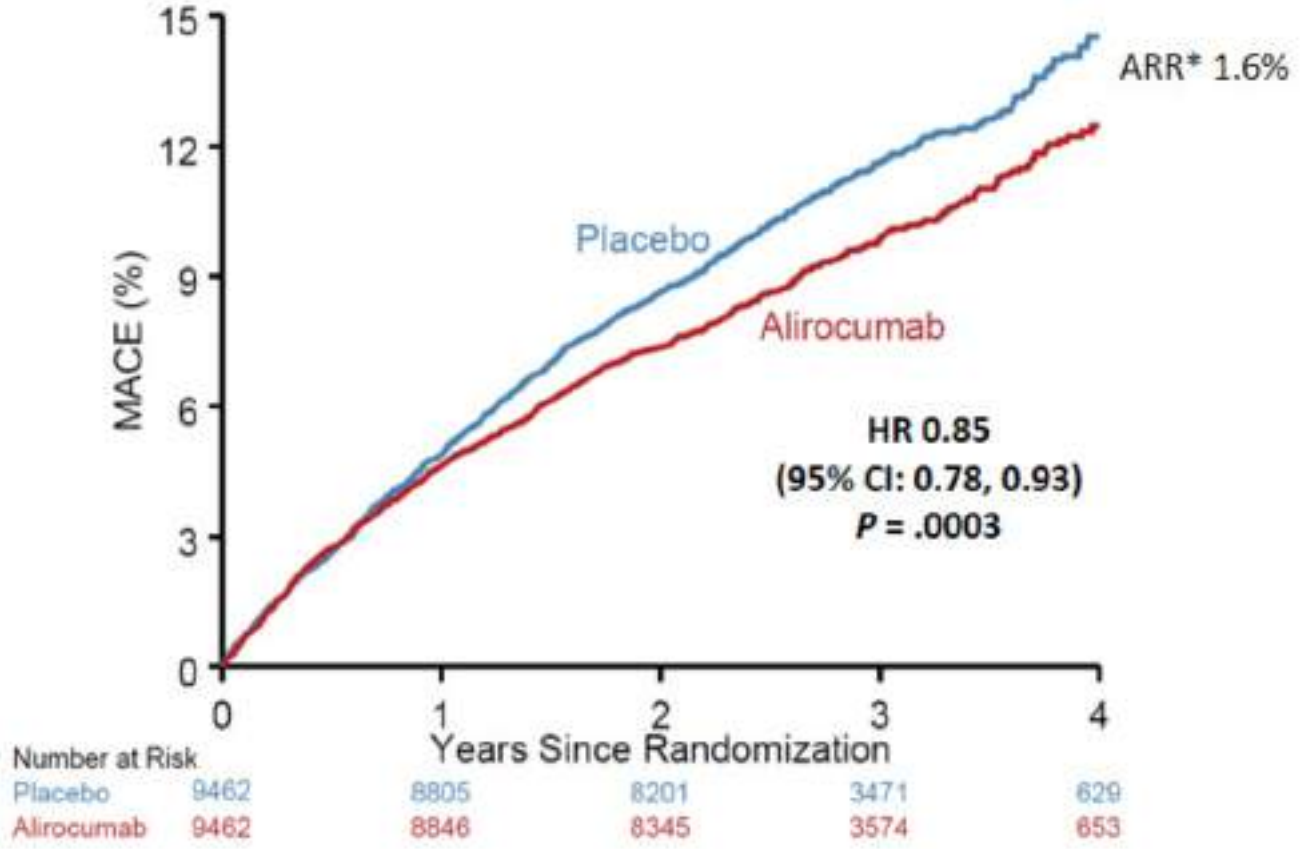
CV death, MI, documented UA requiring rehospitalization, coronary revascularization (≥30 days), or stroke



ODYSSEY ACS outcome Trials

Primary Efficacy Endpoint

MACE: CHD death, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization



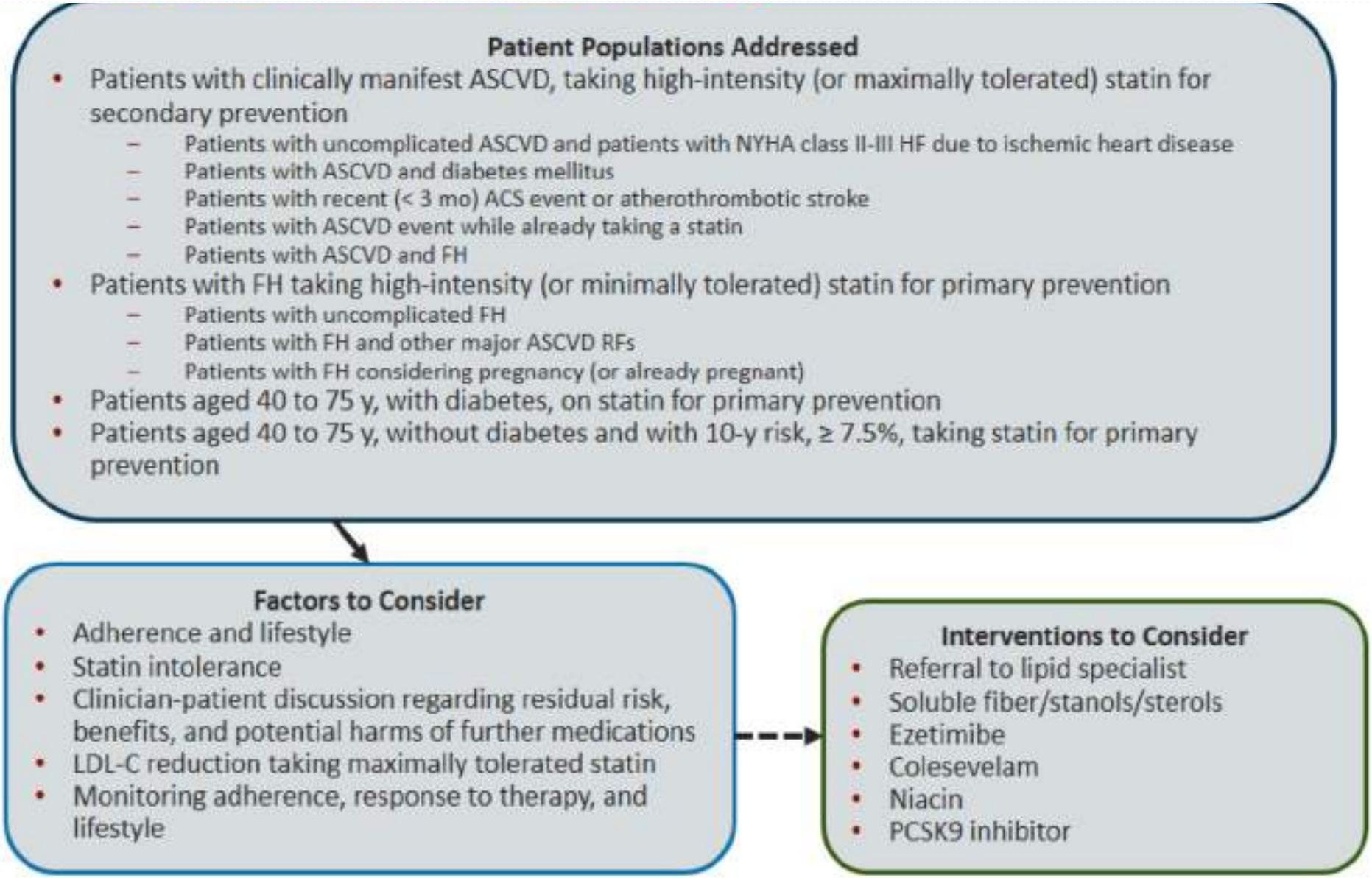
*Based on cumulative incidence.

Schwartz GG, et al. ACC.2018. Presentation 401-08.

2016 ACC consensus

2013 AHA/ACC guideline statin benefit 4 groups

Role of Non-statin Therapies in LDL-C Lowering



Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2016;68:92-125.

2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Group 1
Secondary ASCVD Prevention

ACS, MI, angina, coronary arterial revascularization, stroke, TIA or PAD

Group 2
Severe Hypercholesterolemia

LDL-C ≥190 mg/dL(4.9 mmol/L)

Group 3
Diabetes mellitus in Adults

+ age of 40–75 years

Group 4
Primary Prevention

+ age of 40–75 years & LDL-C 70–189 mg/dL
+ 10-year ASCVD risk≥7.5%(intermediate-risk)

Group 5
Other Populations at Risk

Ethnicity, Hypertriglyceridemia, CKD without dialysis or kidney transplantation & Chronic Inflammatory Disorders and HIV

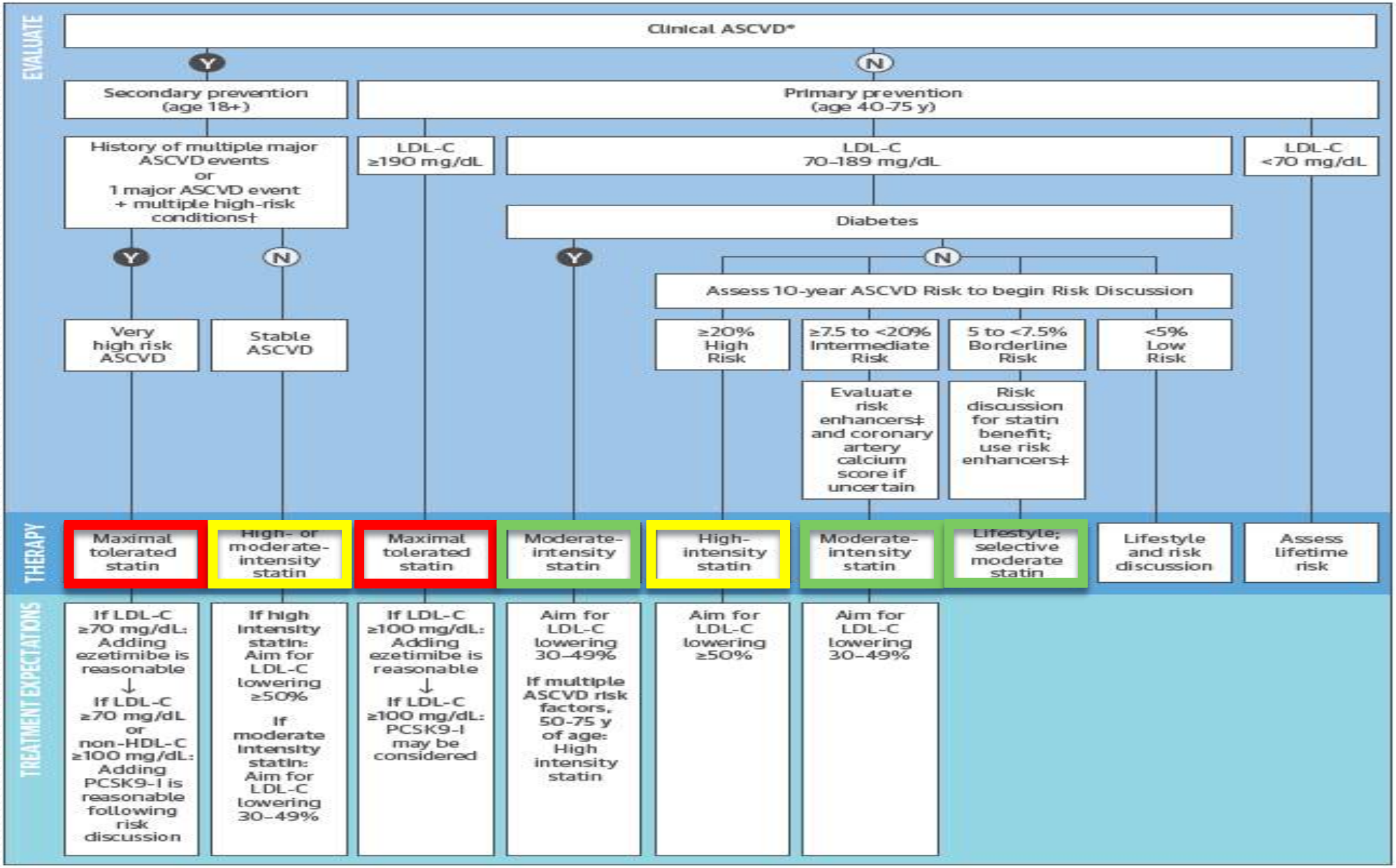
Grundy SM, et al. 2018 AHA Cholesterol Clinical Practice Guidelines

GUIDELINES MADE SIMPLE

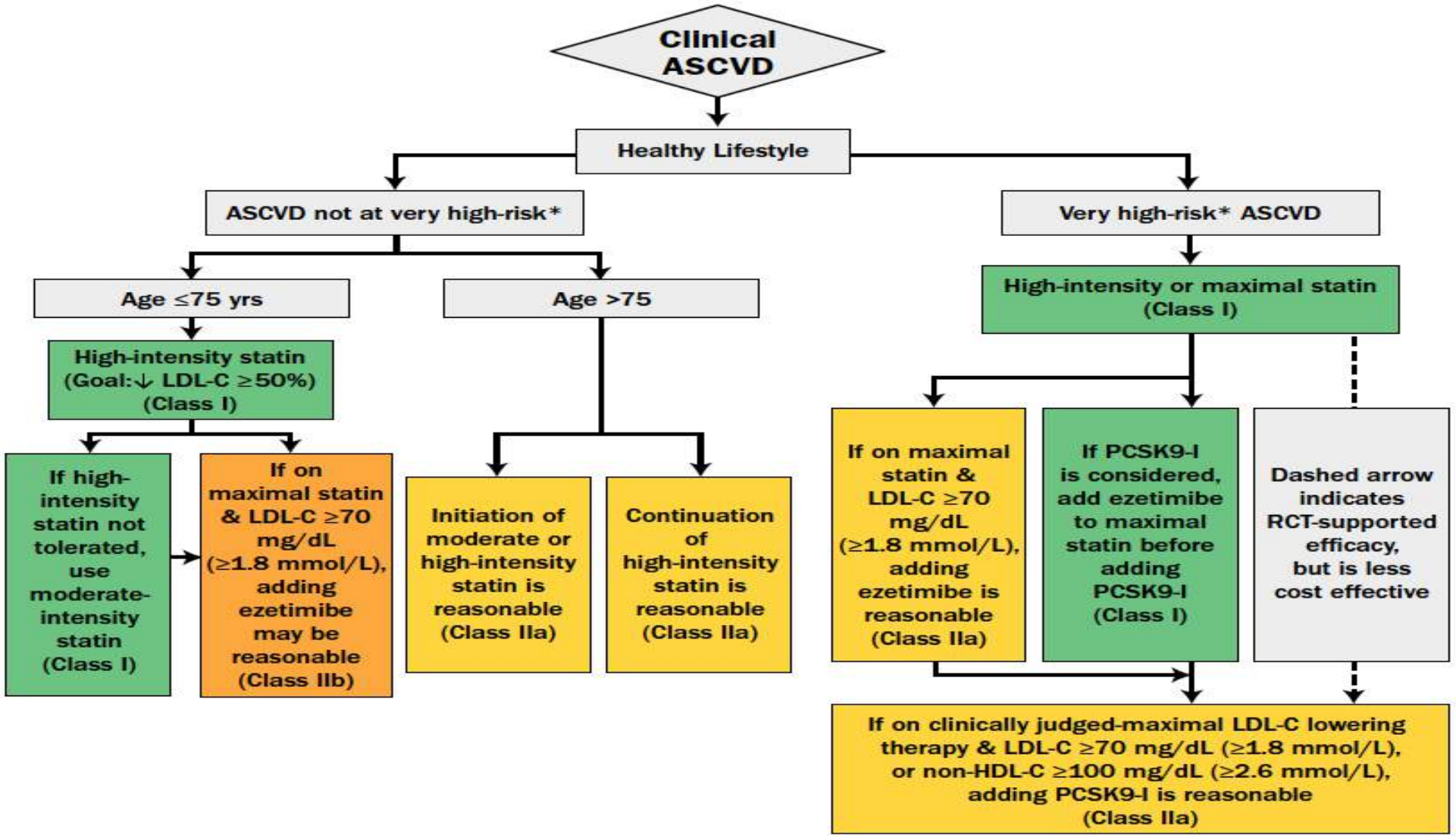
2018 Guideline on the Management of Blood Cholesterol

Overview of Primary and Secondary ASCVD Prevention

This tool provides a broad overview of the 2018 Cholesterol Guideline.
Please refer to the full guideline document for specific recommendations.



Secondary ASVCD Prevention
First Statin Benefit Group



*Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4 on following page).

GUIDELINES MADE SIMPLE
2018 Guideline on the Management of Blood Cholesterol

Primary Prevention Over The Life Span

Fourth Statin Benefit Group

Primary Prevention

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia → statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history, premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

Age 40-75 y and LDL-C ≥70 to <190 mg/dL (≥1.8 - <4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion

LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)

Age >75 y
Clinical assessment, Risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g. preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity factors (e.g. South Asian ancestory)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/mL)

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

<5% "Low Risk"	5% - <7.5% "Borderline Risk"	≥7.5% - <20% "Intermediate Risk"	≥20% "High Risk"
Risk Discussion: Emphasize lifestyle to reduce risk factors **Class (I)**	If Risk enhancers present then risk discussion regarding moderate-intensity statin therapy **Class (IIb)**	**Risk Discussion:** If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% **Class (I)**	**Risk Discussion:** initiate statin to reduce LDL-C ≥50% **Class (I)**

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

Primary Prevention Over The Life Span

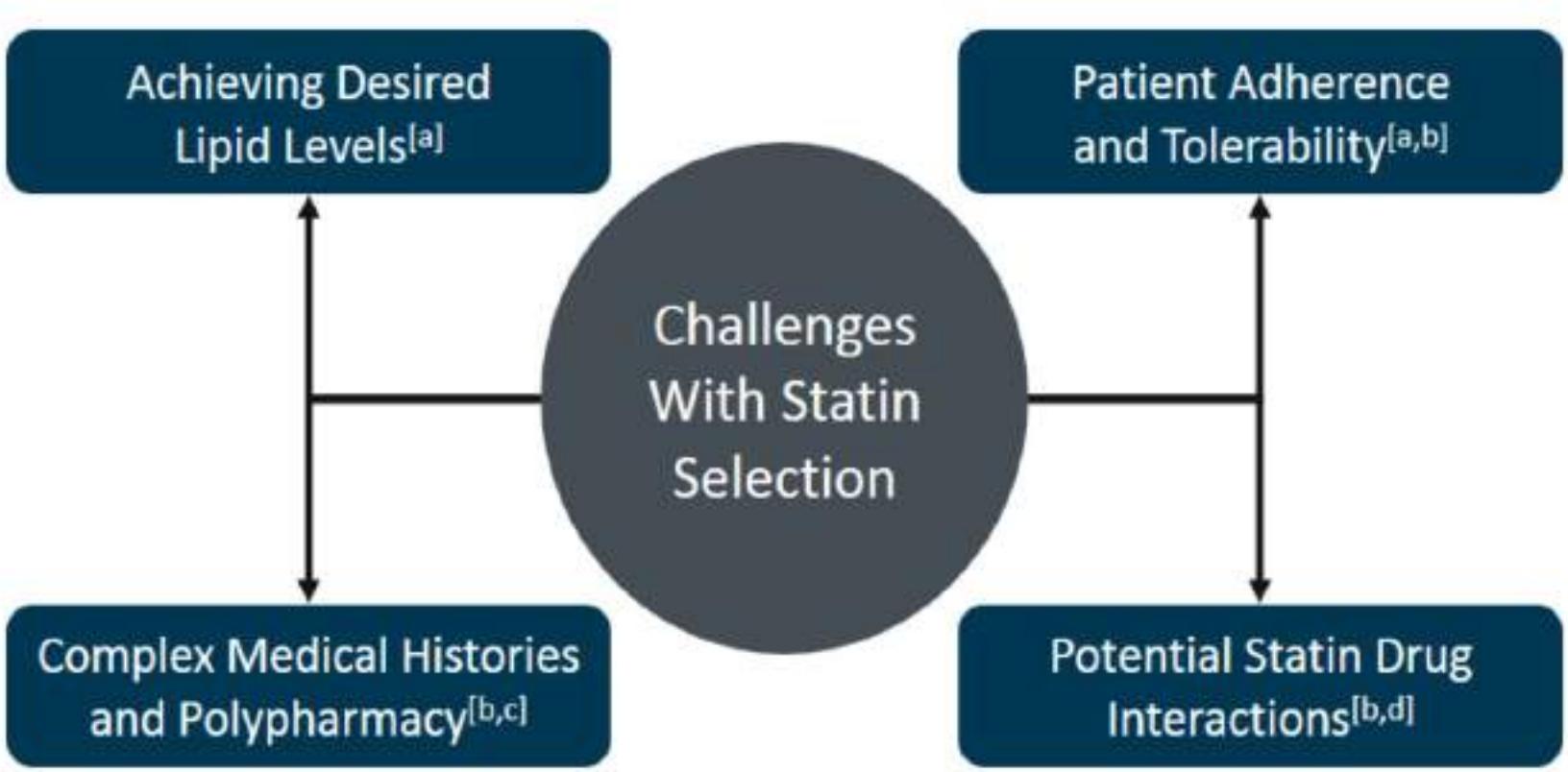
Fourth Statin Benefit Group

Checklist for Clinician-Patient Shared Decision Making for Initiating Therapy

Table 7

Checklist Item	Recommendation
ASCVD Risk Assessment	• Assign to statin treatment group; use ASCVD risk estimator plus* ◦ In lower risk primary prevention adults 40-75 years with LDL-C ≥70 mg/dL (≥1.8 mmol/L). ◦ Not needed in secondary prevention, LDL-C ≥190 mg/dL (≥4.9 mmol/L) and those 40-75 years with diabetes. • Assess other patient characteristics which influence risk. See Risk Enhancing Factors *(Section 4.4.1.3 and Table 6)* • Assess coronary artery calcium *(section 4.4.1.4)* if risk decision uncertain and additional information is needed to clarify ASCVD risk ◦ Use decision tools to explain risk (ASCVD risk estimator plus- http://tools.acc.org/ASCVD-Risk-Estimator-Plus, Mayo Clinic Statin Choice Decision Aid)
Lifestyle Modifications	• Review lifestyle habits (diet, physical activity, weight/BMI, tobacco use) • Endorse a healthy lifestyle and provide relevant advice/materials/referrals (CardioSmart, AHA Life's Simple 7, NLA Patient Tear Sheets, PCNA Clinicians' Lifestyle Modification Toolbox, cardiac rehab, dietitian, smoking cessation program)
Potential Net-Clinical Benefit of Pharmacotherapy	• Recommend statins as first-line therapy • Consider the combination of statin and non-statin therapy in select patients • Discuss potential risk reduction from lipid-lowering therapy • Discuss the potential for adverse effects/drug-drug interactions
Cost Considerations	• Discuss potential out-of-pocket cost of therapy to the patient (e.g., insurance plan coverage, tier level, copayment)
Shared Decision Making	• Encourage patient to verbalize what was heard (personal ASCVD risk, available options and their risk/benefit) • Invite the patient to ask questions, express values/preferences, state ability to adhere to lifestyle changes and medications • Refer patients to trustworthy materials to aid in their understanding of issues regarding risk decisions • Collaborate with the patient to determine therapy and follow-up plan

Multiple Challenges in Statin Selection



a. Ansell BJ. *J Manag Care Pharm.* 2008;14(suppl S-b):S9-S15; b. Meade LT. *US Pharm.* 2007;32:66-71;
c. Vogeli C, et al. *J Gen Intern Med.* 2007;22(suppl 3):391-395; d. Ito MK, et al. *J Clin Lipidol.* 2014;8:69-76.

Percentage reduction of low-density LDL-C requested to achieve goals as a function of the starting value

Starting LDL-C		Reduction to reach LDL-C goal, %		
mmol/L	~ mg/dL	< 1.8 mmol/L (~ 70 mg/dL)	< 2.6 mmol/ (~ 100 mg/dL)	< 3 mmol/L (~ 115 mg/dL)
>6.2	> 240	> 70	> 60	> 55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	< 10
2.3–2.9	90–110	22–35	< 10	–
1.8–2.3	70–90	< 22	–	–

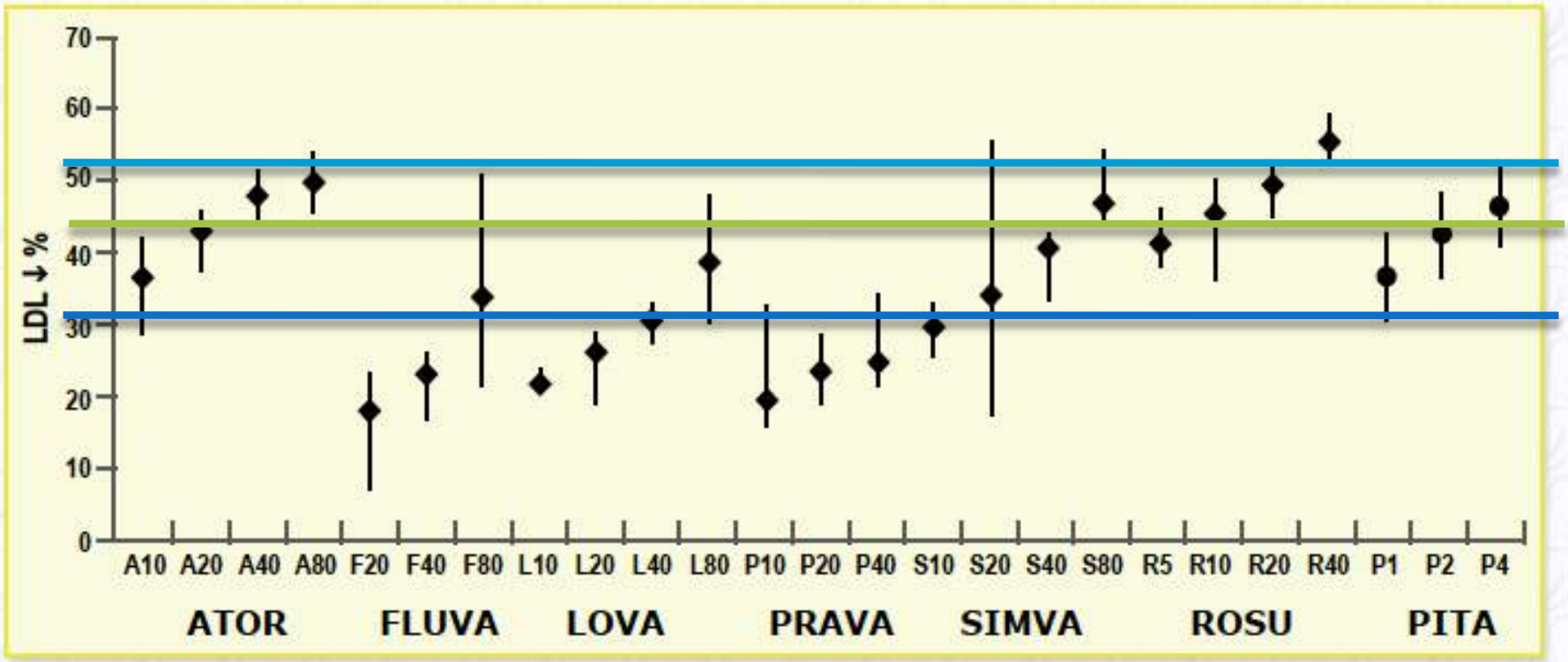
EAS

EUROPEAN SOCIETY OF CARDIOLOGY®

www.escardio.org/guidelines

European Heart Journal 2016 - doi:10.1093/eurheartj/ehv272

A systematic review and meta-analysis of the therapeutic equivalence of statins



Weng TC, et al. *J Clin Pharm Ther.* 2010;35;139-151

Mukhtar RY, et al. *Int J Clin Pract.* 2005;59(2):239-252

Statin Dosing Considerations

	Atorva	Fluva	Lova	Pitava	Prava	Simva	Rosuva
Time	Any time	PM*	AM & PM with meals	Any time	PM	PM	Any time
AUC (%)	14	24	5	~50	17	5	20
Food Effect	↓ AUC	None	↑ AUC	None	↓ AUC	None	None
Protein binding (%)	98	>99	>95	96	~50	95-98	96
Half-life (h)	14	3	3	12	1.8	2	12

*May depend on drug formulation.

Racial Differences in Response to Statins

Japanese patients have similar relative risk reduction of CV events with lower dose of statins and a shorter duration of treatment compared with Western patients[a]

Comparison in Response to Rosuvastatin[a]	Asian (N=304)	Westerner (N=869)
LDL-C reduction* (%)	44.0 ± 4.8	49.9 ± 2.6
Statin Dose	14.1 ± 4.9	40.0 ± 0
Duration (mo)	10.3 ± 3.7	24.0 ± 0

Maximum Dose of Statins: US vs Japan[a]

United States	Japan
• Atorvastatin 80 mg	• Atorvastatin 40 mg
• Fluvastatin 80 mg	• Fluvastatin 60 mg
• Pitavastatin 4 mg	• Pitavastatin 4 mg
• Pravastatin 80 mg	• Pravastatin 20 mg
• Rosuvastatin 40 mg	• Rosuvastatin 20 mg
• Simvastatin 80 mg†	• Simvastatin 20 mg

*There were no significant differences for LDL-C at baseline or follow-up between the Asian or Western populations.
†Only for patients who have been on stable dose for >12 months without history of muscle toxicity.[b]

a. Naito R, et al. *J Atheroscler Thromb*, 2017;24:19-25; b. FDA Drug Safety Communication. 2011.

Selected Drug Interactions That Increase Statin Levels

Statin	Interacting Agent[a]	Fold Increase in Statin AUC %[a]
Atorvastatin	Diltiazem	51*
Lovastatin*	Amiodarone	1.8
	Conivaptan	3.0
	Diltiazem	3.6
	Dronedarone	3.9
	Gemfibrozil	2 to 3
	Verapamil	3.6
Simvastatin*	Amiodarone	1.8
	Amlodipine	1.8
	Conivaptan	3.0
	Diltiazem	4.6
	Dronedarone	3.9
	Gemfibrozil	2 to 3
	Ranolazine	1.9
	Ticagrelor	2 to 3
	Verapamil	2.5
	Warfarin	≤ 30% change in INR
Pitavastatin	Gemfibrozil	1.5
Pravastatin	Gemfibrozil	2.0
Rosuvastatin	Gemfibrozil	1.6 to 1.9

Interpreting AUC ratio increase:[c]
- Weak: >1.25 – <2.0
- Moderate: >2.0-<4.9
- Strong: >5.0

Least CYP450 interactions[b]

*"Sensitive" statins. Up to 5-fold increase in statin AUC when administered with strong CYP3A4 inhibitors.[b] *51% increase in AUC of atorvastatin. Combination is reasonable but use caution/monitor.

a. Wiggins BS, et al. *Circulation*. 2016;134:e468-e495; b. *Pharm Lett/Prescr Lett*. 2012;28;6:280606; c. Kellick KA, et al. *J Clin Lipidol*. 2014;8:S30–S46.

Pitavastatin Extension Study

- **Core Study:** 12-wk, multicenter, double-blind study in patients ≥ 65 y old with primary hypercholesterolemia or mixed dyslipidemia[a]
  - Pitavastatin (1, 2, and 4 mg) qd
    vs
  - Pravastatin (10, 20, 40 mg) qd
- Results: noninferiority with respect to mean percentage change in LDL-C[a]
  - Both statins were well tolerated, with no reports of myopathy

- **Extension Study:** 60-wk, open-label, multicenter (N = 545)[b]
  - All patients receiving pravastatin in core study were started on pitavastatin 2 mg in extension study while taking concomitant medications
- Results: Continued use of pitavastatin lead to additional 43% reduction in LDL-C and 9.6% increase in HDL-C levels
  - 17% of patients uptitrated to 4 mg and met LDL-C targets by week 60
  - 4 patients (2 on 2-mg pitavastatin) discontinued because of myalgia but no reports of myopathy, myositis, or rhabdomyolysis

a. Stender S, et al. *Eur J Prev Cardiol*. 2013;20:40-53.
b. Stender S, et al. *Eur J Prev Cardiol*. 2013;20:29-39.

Ethnicity Issues in Evaluation, Risk Decisions, and Treatment of ASCVD Risk

Ethnic/racial groupings	Asian-Americans*	Hispanic/Latino-Americans†	Blacks	Comments
Evaluation				
ASCVD Issues informed by ethnicity	South Asian and East Asian ASCVD risk varies by country of origin; Individuals from South Asia (see below) have increased ASCVD risk	Race and country of origin together with socioeconomic status and acculturation level may explain risk factor burden more precisely. e.g. ASCVD risk is higher among individuals from Puerto Rico than from Mexico.	ASCVD risk assessment in black women shows increased ASCVD risk compared to their otherwise similar white counter-parts	Heterogeneity in risk according to racial/ethnic groups and within racial/ethnic groups. Native American/Alaskan populations have high rates of risk factors for ASCVD compared to non-hispanic whites.
Lipid issues informed by ethnicity	Lower levels of HDL-C compared to whites Higher prevalence of LDL-C among Asian Indians, Filipinos, Japanese, and Vietnamese compared to whites. An increased prevalence of high TGs was seen in all Asian American subgroups	Hispanic/Latino women have higher prevalence of low HDL-C compared to Hispanic/Latino men	Higher levels of HDL-C and lower levels of triglycerides (TG) than in Non-Hispanic Whites or Mexican-Americans.	All ethnic groups appear to be at greater risk for dyslipidemia, but important to identify those with more sedentary behavior and less favorable diet.
Metabolic issues informed by ethnicity	Increased Metabolic Syndrome (MetS) seen with lower waist circumference than in whites. DM develops at a lower lean body mass and at earlier age (19-21) Majority of risk in South Asians explained by known risk factors, especially those related to insulin resistance	DM disproportionately present compared to whites and blacks. Increased prevalence MetS, DM in Mexican Americans compared to whites & Puerto Ricans.	Increased DM and hypertension	Increased prevalence of DM. Features of MetS vary by ethnicity. Waist circumference, not weight, should be used to determine abdominal adiposity when possible

Table 10 is continued in the next page. For footnotes please refer to pages 21 and 22.

GUIDELINES MADE SIMPLE
2018 Guideline on the Management of Blood Cholesterol

Ethnicity Issues in Evaluation, Risk Decisions, and Treatment of ASCVD Risk

Ethnic/racial groupings	Asian-Americans*	Hispanic/Latino-Americans†	Blacks	Comments
Risk Decisions				
Pooled Cohort Equations (PCE)	No separate PCE available; use PCE for whites. PCE may underestimate ASCVD risk in South Asians PCE may overestimate risk in East Asians	No separate PCE available; use PCE for non-Hispanic whites. If African American ancestry also, then use PCE for blacks	Use PCE for blacks	Country specific race/ethnicity, along with socio-economic status, may affect estimation of risk of PCE
Coronary Artery Calcium (CAC) Score	In terms of CAC burden, South Asian men were similar to non-Hispanic white men, but higher CAC when compared to blacks, Latinos and Chinese Americans. South Asian women had similar CAC to whites and other ethnic women, although CAC burden higher in older age	CAC predicts similarly in whites and those who identify as Hispanic/Latino	In MESA, CAC score was highest in whites and Hispanic men, with blacks having significantly lower prevalence and severity of CAC.	Risk factor differences in MESA between ethnicities didn't fully explain variability in CAC However, CAC predicted ASCVD events over and above traditional risk factors in all ethnicities
Treatment *(will continue in the next page)*				
Lifestyle counseling (Utilize principles of Mediterranean & DASH diets)	Utilize lifestyle counseling to recommend a heart healthy diet consistent with racial/ethnic preferences to avoid weight gain, and address BP and lipids	Utilize lifestyle counseling to recommend a heart healthy diet consistent with racial/ethnic preferences to avoid weight gain, address BP and lipids	Utilize lifestyle counseling to recommend a heart healthy diet consistent with racial/ethnic preferences to avoid weight gain, address BP and lipids	Need to disaggregate Asian and Hispanic/Latino groups due to regional differences in lifestyle preferences. Challenge is to avoid increased sodium, sugar and calories as groups acculturate

Does High-Intensity Pitavastatin Therapy Further Improve Clinical Outcomes ?

The Real-CAD Study in 13,054 Patients with Stable Coronary Artery Disease

Takeshi Kimura, Teruo Inoue, Isao Taguchi, Hiroshi Iwata, Satoshi Iimuro, Takafumi Hiro, Yoshihisa Nakagawa, Yukio Ozaki, Yasuo Ohashi, Hiroyuki Daida, Hiroaki Shimokawa, Ryozo Nagai,

on behalf of the REAL-CAD Study Investigators

REAL-CAD

Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease

Backgrounds

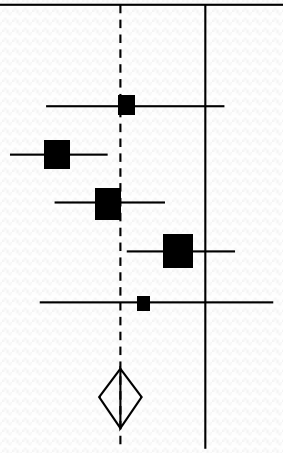
Recommendations for Lipid-lowering Therapy in Patients with Established CAD

ACC/AHA guideline: High-intensity statin therapy

atorvastatin 40/80 mg, rosuvastatin 20/40 mg, or simvastatin 80 mg

Previous "More versus Less" Statins Trials

	LDL-C Reduction (mmol/L)	Events (% per annum)		Unweighted RR (CI)
		Statin/more	Control/less	
More vs less statin				
PROVE–IT	0.65	406 (11.3%)	458 (13.1%)	
TNT	0.62	889 (4.0%)	1,164 (5.4%)	
IDEAL	0.55	938 (5.2%)	1,106 (6.3%)	
SEARCH	0.39	1,347 (3.6%)	1,406 (3.8%)	
A to Z	0.30	257 (7.2%)	282 (8.1%)	
Subtotal (5 trials)	**0.51**	**3,837/19,829 (4.5%)**	**4,416/19,783 (5.3%)**	**0.85 (0.82-0.89) p<0.0001**



Trend: χ^2_1=12.4 (p=0.0004)

Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet 2010; 376: 1670-81.

Backgrounds and Objectives

However, the high-intensity statins are not widely used in daily clinical practice, particularly in Asia. No clear evidence regarding “more versus less” statins has been established in Asian population. Most of the doses of high-intensity statin therapy defined in the ACC/AHA guideline are not approved in Japan. Furthermore, maximum approved doses of statins are prescribed only very infrequently in Japan.

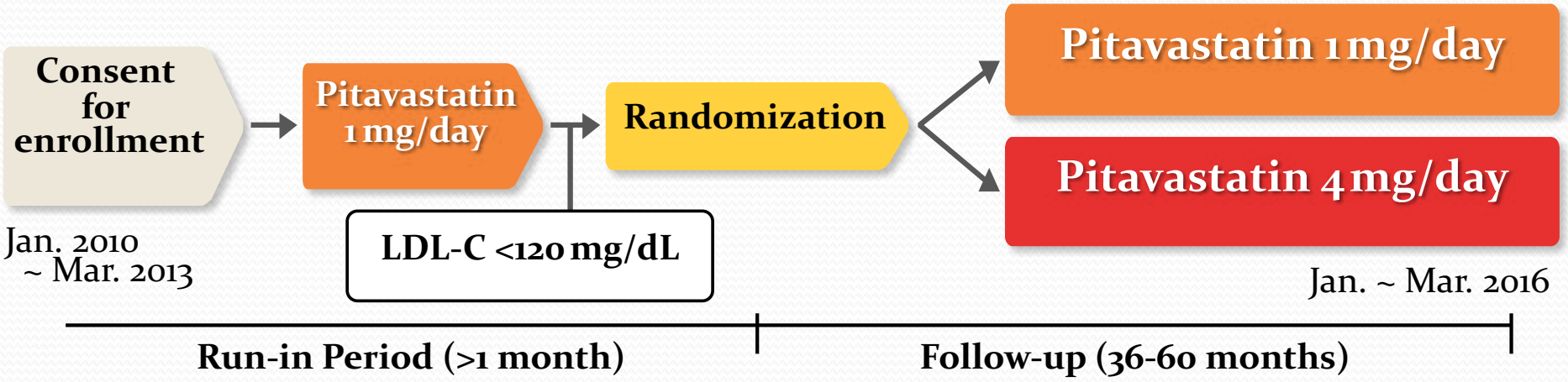
Therefore, we sought to determine whether higher-dose statin therapy would be beneficial in Japanese patients in the largest-ever trial comparing the efficacy of high-dose versus low-dose statin therapy in patients with established stable CAD.

REAL-CAD

(Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease)

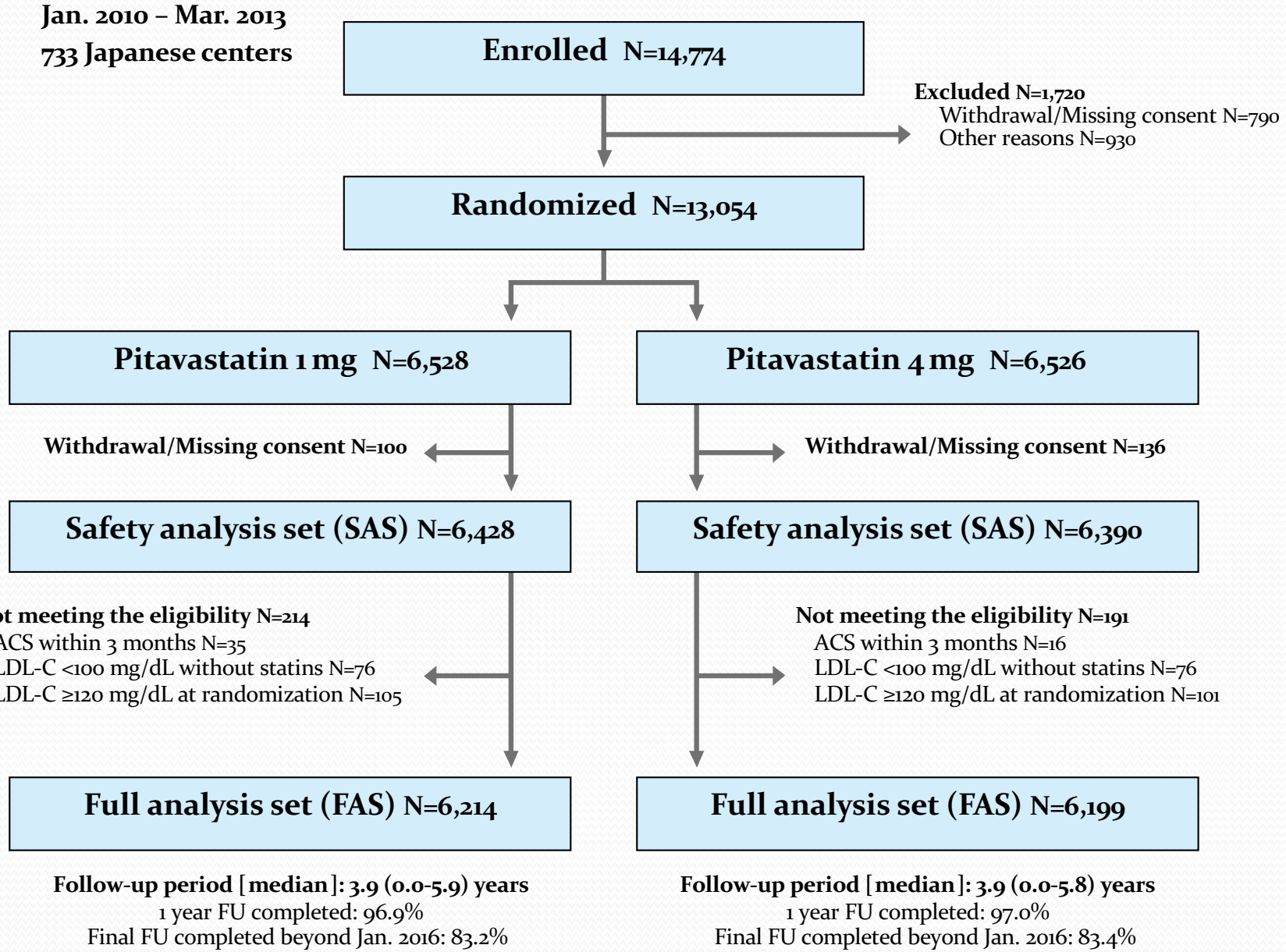
A prospective, multi-center, randomized, open-label, blinded endpoint, physician-initiated trial to determine whether high-dose as compared with low-dose pitavastatin therapy within the approved dose range could reduce CV events in Japanese patients with stable CAD.

Eligibility:
- Men and women, 20-80 years of age
- Stable CAD:
  - ACS or PCI/CABG >3 months
  - Clinical diagnosis of CAD with coronary stenosis ≥50 % diameter stenosis
- LDL-C <120 mg/dL on pitavastatin 1 mg/day during the run-in period



Pitavastatin 1 mg and 4 mg have LDL-C lowering effect comparable to atorvastatin 5 mg and 20 mg, respectively.

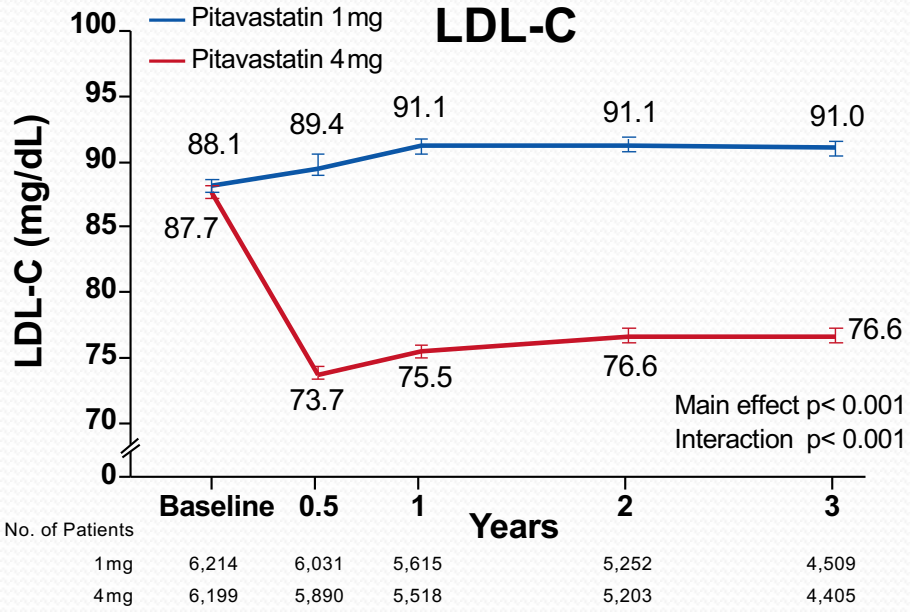
Study Patient Flow



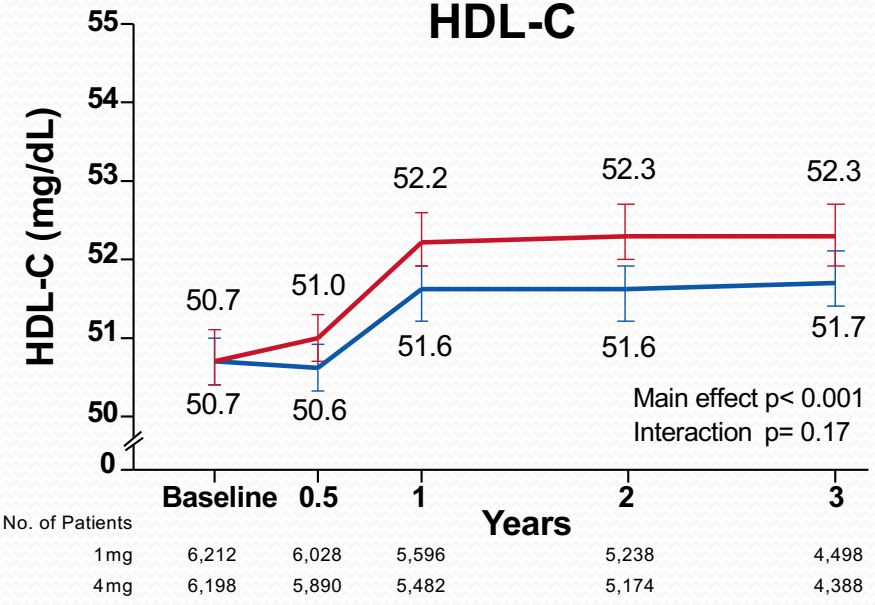
Baseline Characteristics

Variables	Pitavastatin 1 mg (N=6,214)	Pitavastatin 4 mg (N=6,199)
Age — years	68.1±8.3	68.0±8.3
Male sex	83%	83%
BMI — kg/m^2	24.6±3.4	24.6±3.3
Hypertension	75%	76%
Diabetes mellitus	40%	40%
Current smoking	16%	17%
History of ACS	72%	72%
ACS within 1 year before randomization	24%	24%
Coronary revascularization	91%	90%
Revascularization within 1 year before randomization	28%	28%
Ischemic stroke	7%	7%
Peripheral vascular disease	7%	7%
CKD (eGFR <60 mL/min/1.73m^2)	36%	35%
Aspirin	93%	92%
DAPT	45%	44%
Statins before enrollment	91%	91%

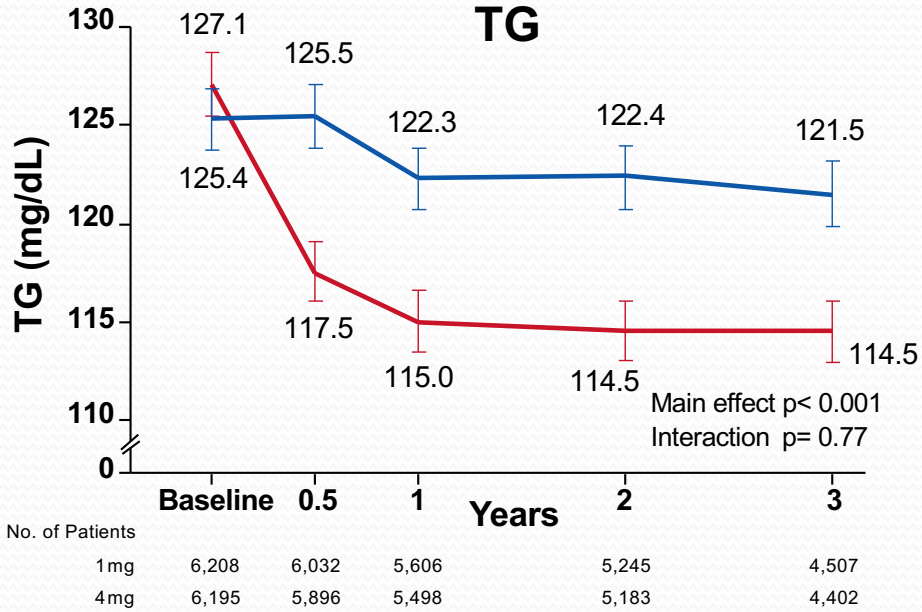
Serial Changes in Lipid Parameters and hs-CRP



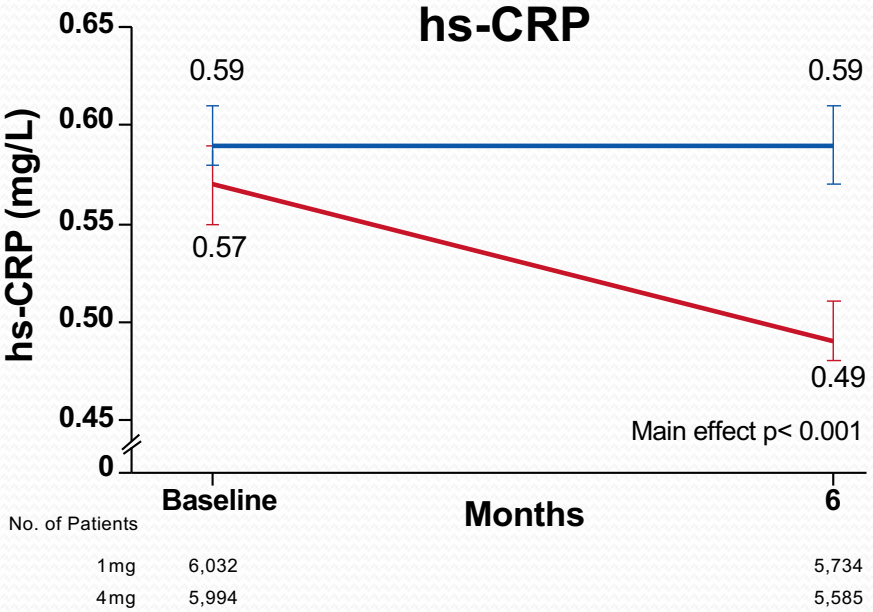
No. of Patients	Baseline	0.5	1	2	3
1mg	6,214	6,031	5,615	5,252	4,509
4mg	6,199	5,890	5,518	5,203	4,405



No. of Patients	Baseline	0.5	1	2	3
1mg	6,212	6,028	5,596	5,238	4,498
4mg	6,198	5,890	5,482	5,174	4,388



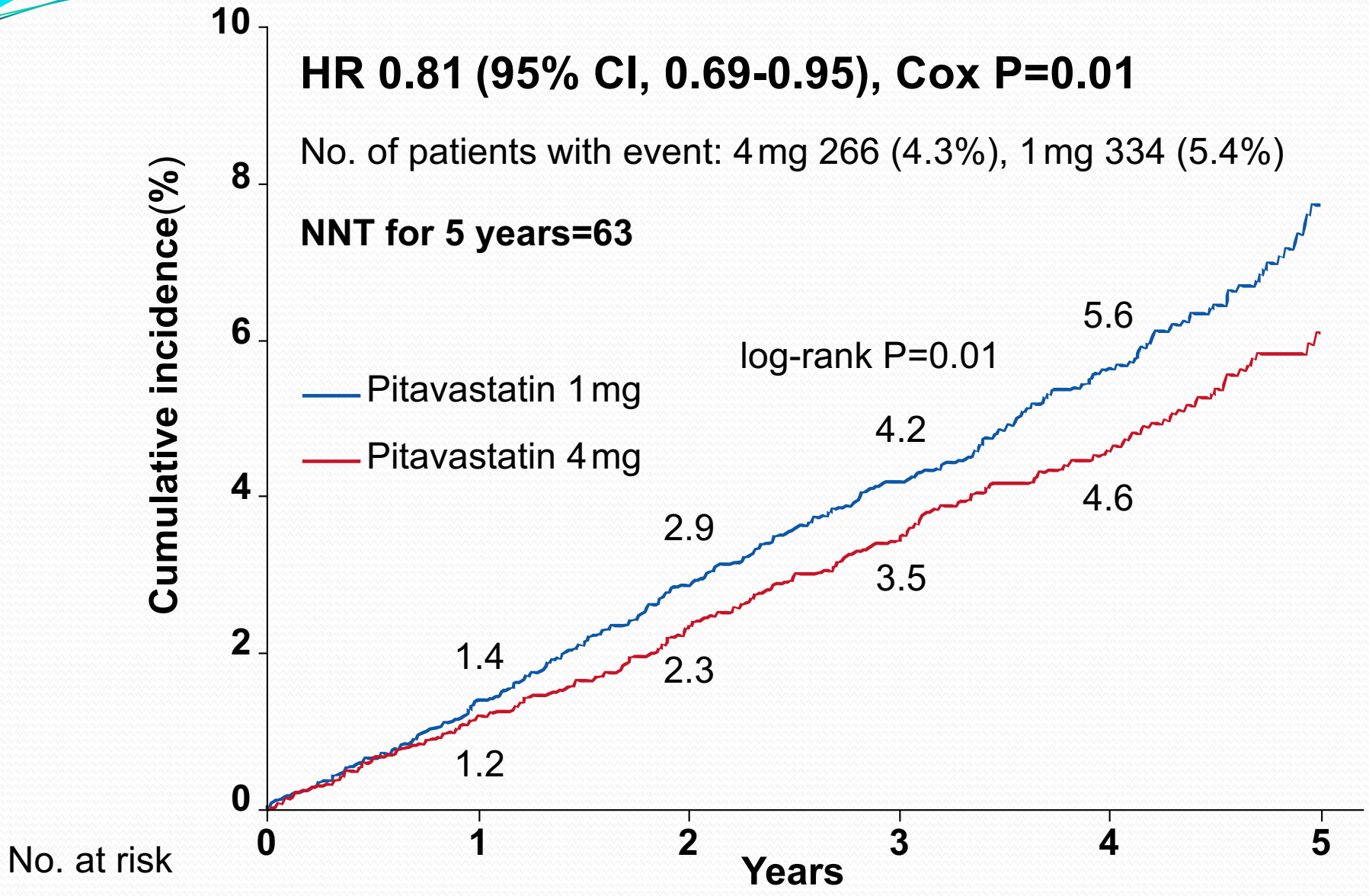
No. of Patients	Baseline	0.5	1	2	3
1mg	6,208	6,032	5,606	5,245	4,507
4mg	6,195	5,896	5,498	5,183	4,402



No. of Patients	Baseline	6
1mg	6,032	5,734
4mg	5,994	5,585

Primary Endpoint

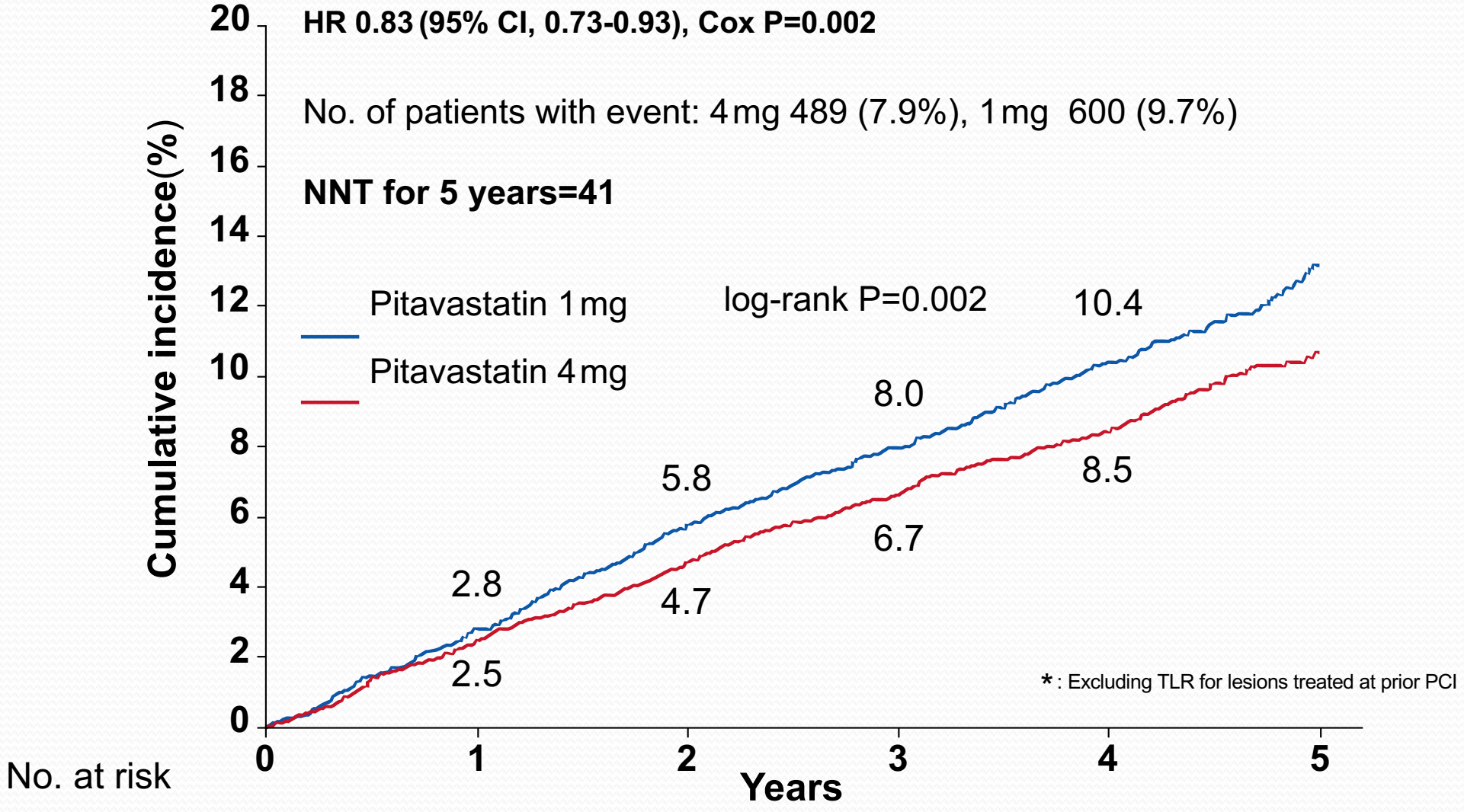
CV death/MI/Ischemic stroke/UA



No. at risk						
1 mg	6,214	5,743	5,321	4,501	2,760	593
4 mg	6,199	5,631	5,256	4,427	2,730	616

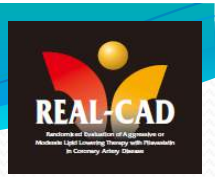
Secondary Endpoint

Primary Endpoint plus Coronary Revascularization*

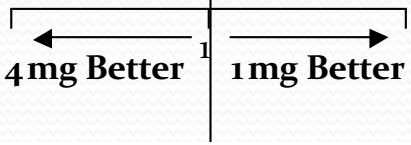


No. at risk						
1mg	6,214	5,660	5,166	4,327	2,627	561
4mg	6,199	5,556	5,131	4,277	2,617	588

Other Secondary Endpoints



Outcomes	No. of patients with event (%) 1 mg (n=6,214)	4 mg (n=6,199)	HR(95% CI)	P Value
Death from any cause	260 (4.2)	207 (3.3)	0.81 (0.68-0.98)	0.03
CV death	112 (1.8)	86 (1.4)	0.78 (0.59-1.04)	0.09
MI	72 (1.2)	40 (0.6)	0.57 (0.38-0.83)	0.004
Ischemic stroke	83 (1.3)	84 (1.4)	1.03 (0.76-1.40)	0.84
Hemorrhagic stroke	30 (0.5)	43 (0.7)	1.46 (0.92-2.33)	0.11
Unstable angina requiring emergency hospitalization	90 (1.4)	76 (1.2)	0.86 (0.63-1.17)	0.34
Coronary revascularization (All)	626 (10.1)	529 (8.5)	0.86 (0.76-0.96)	0.008
Coronary revascularization (non-TLR)	356 (5.7)	277 (4.5)	0.79 (0.68-0.92)	0.003
Coronary revascularization (TLR)	319 (5.1)	276 (4.5)	0.88 (0.75-1.03)	0.12



Safety Outcomes

Event	Pitavastatin 1 mg (N=6,428)	Pitavastatin 4 mg (N=6,390)	P value
Adverse events — N (%)			
Rhabdomyolysis	1 (0.0)	2 (0.0)	0.62
Muscle-complaints	45 (0.7)	121 (1.9)	<0.001
New onset of diabetes mellitus	279 (4.3)	285 (4.5)	0.76
Laboratory test abnormalities — N (%)			
Elevation of ALT, AST, or both ≥3ULN	174 (2.7)	187(2.9)	0.46
Elevation of CK ≥5ULN	40 (0.6)	42 (0.7)	0.83
Study drug discontinuation— N (%)	503 (8.1)	610 (9.8)	<0.001

REAL-CAD vs. TNT

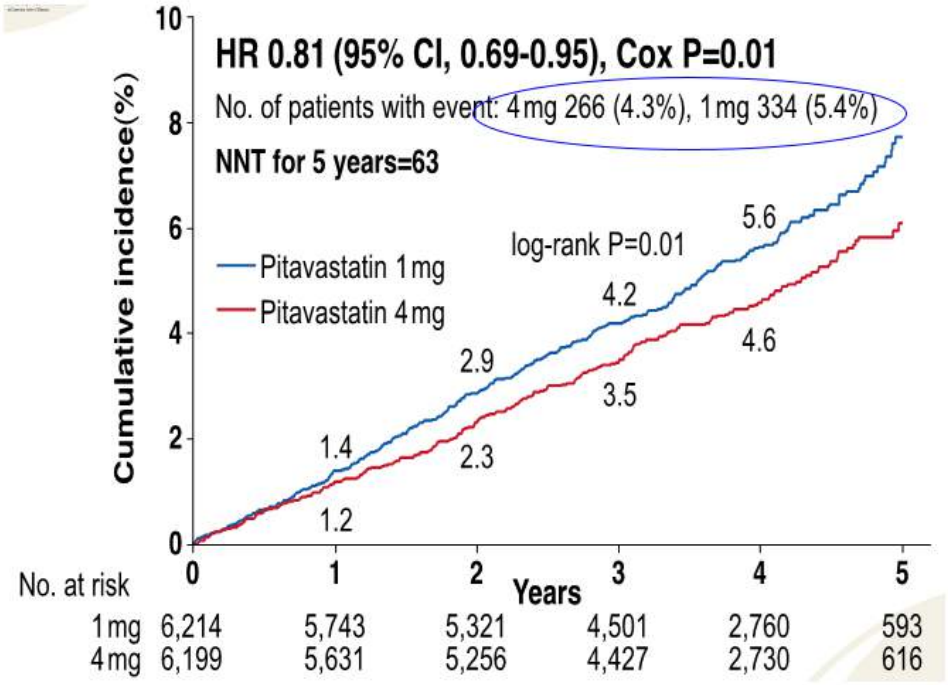
Trial	REAL-CAD (n=13,054)	TNT (n=10,001)
Race	Japanese(100%)	White(94.1%)
Age	68y	61y
DM/HT/Smoking	40%/75%/16%	15%/54%/13%
BMI	24	28
Baseline LDL-C	<120 mg/dL (run-in) : 88 mg/dL	<130 mg/dL (run-in) : 98 mg/dL
Baseline HDL-C	50.7 mg/dL	47 mg/dL
Baseline TG	126 mg/dL	151 mg/dL
Coronary revascularization	83.5%	54%
Primary Endpoint	CV death, non-fatal MI, non-fatal ischemic stroke, unstable angina	CHD death Nonfatal, non–procedure-related MI Resuscitated cardiac arrest Fatal or nonfatal stroke
Follow-up period [median]	3.9y	4.9y

Primary Endpoint

REAL-CAD

Moderate-Intensity Statin

CV death/MI/Ischemic stroke/UA



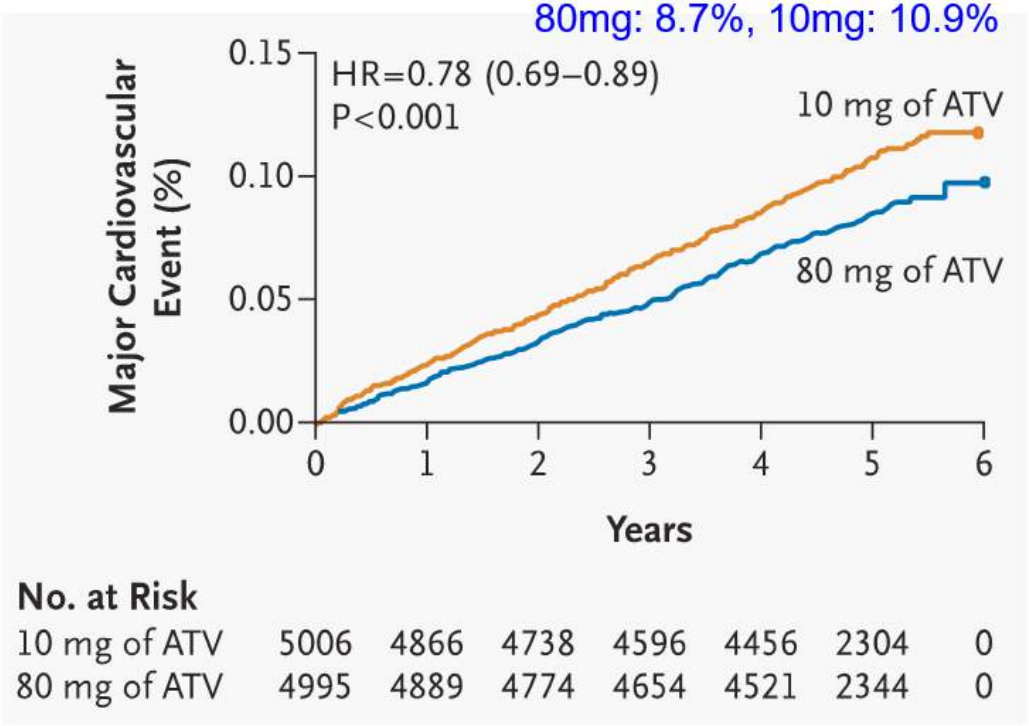
LDL: 91 mg/dL versus 76 mg/dL (-15 mg/dL)

vs.

TNT

High-Intensity Statin

CHD death/MI/Stroke/Resuscitation



LDL: 101 mg/dL versus 77 mg/dL (-24 mg/dL)

REAL-CAD vs. TNT

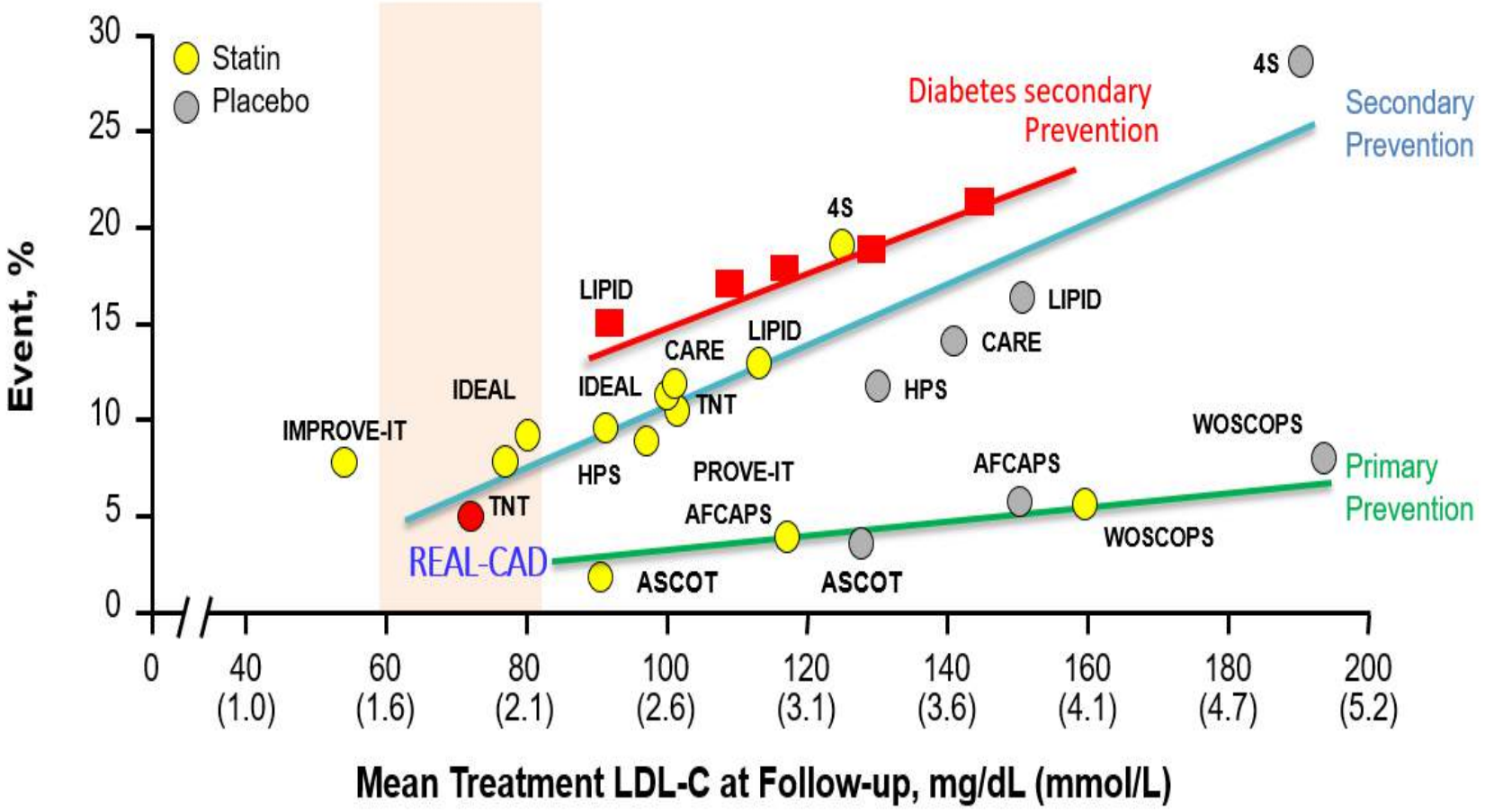
Trial	REAL-CAD (n=13,054)	TNT (n=10,001)
Major Cardiovascular Event	-19%	-22%
CV death	-22%	-20%
Non-fatal MI	-43%	-22%
Safety		
Adverse events	5.0% vs. 6.4%	5.8% vs. 8.1%
Muscle	Muscle-complaints 0.7% vs. 1.9%	Treatment-related myalgia 4.7% vs. 4.8%
New onset of diabetes mellitus	4.3% vs. 4.5%	10.0% vs. 10.0%
Elevation of ALT, AST, or both ≥3ULN	2.7% vs. 2.9%	0.2% vs. 1.2%
Study drug discontinuation	8.1% vs. 9.8%	5.3% vs. 7.2%

Deaths in Trials of More vs. Less LDL-c Lowering Therapy

Trial	Therapy	Follow-Up, y	Mean LDL-C in Less Aggressive Arm, mg/dL	Mean LDL-C Reduction in Aggressive Arm, rmg/dL	Primary End Point* in Aggressive Relative to Less Aggressive Arm	No. of Deaths	Deaths in Aggressive Relative to Less Aggressive Arm
TNT	Atorvastatin 80 mg vs 10 mg	4.9	101	24	–22% *P*<0.001	566	+1.0% *P*=0.92
IDEAL	Atorvastatin 80 mg vs simvastatin 20–40 mg	4.8	104	23	–11% *P*=0.07	740	–2% *P*=0.81
PROVE-IT	Atorvastatin 80 mg vs pravastatin 40 mg	2	95	33	–16% *P*=0.005	240	–28% *P*=0.07
IMPROVE-IT	Simvastatin vs simvastatin + ezetimibe	6	70	16	–6.4% *P*=0.016	2446	–1% *P*=0.78
FOURIER	Statin vs statin + evolocumab	2.2	90	56	–15% *P*<0.001	870	+4.0% *P*=0.54
REAL-CAD	Pitavastatin 4 mg vs 1 mg	3.9	88	15	–19% *P*=0.01	467	–19% *P*=0.03

Circulation. 2018;137:2013–2015.

LDL-c Lowering and Decreased CHD Risk

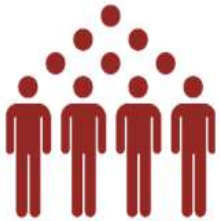


It is estimated that 1% reduction in LDL-C levels, the relative risk for major CHD events is reduced by approximately 1%

IDEAL=Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS=Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS=West of Scotland Coronary Prevention Study.

Adapted from Rosenson RS. *Expert Opin Emerg Drugs*. 2004;9(2):269–279; LaRosa JC, et al. *N Engl J Med*. 2005;352(14):1425–1435; Pedersen TR, et al. *JAMA*. 2005;294(19):2437–2445.

Conclusions and Implications



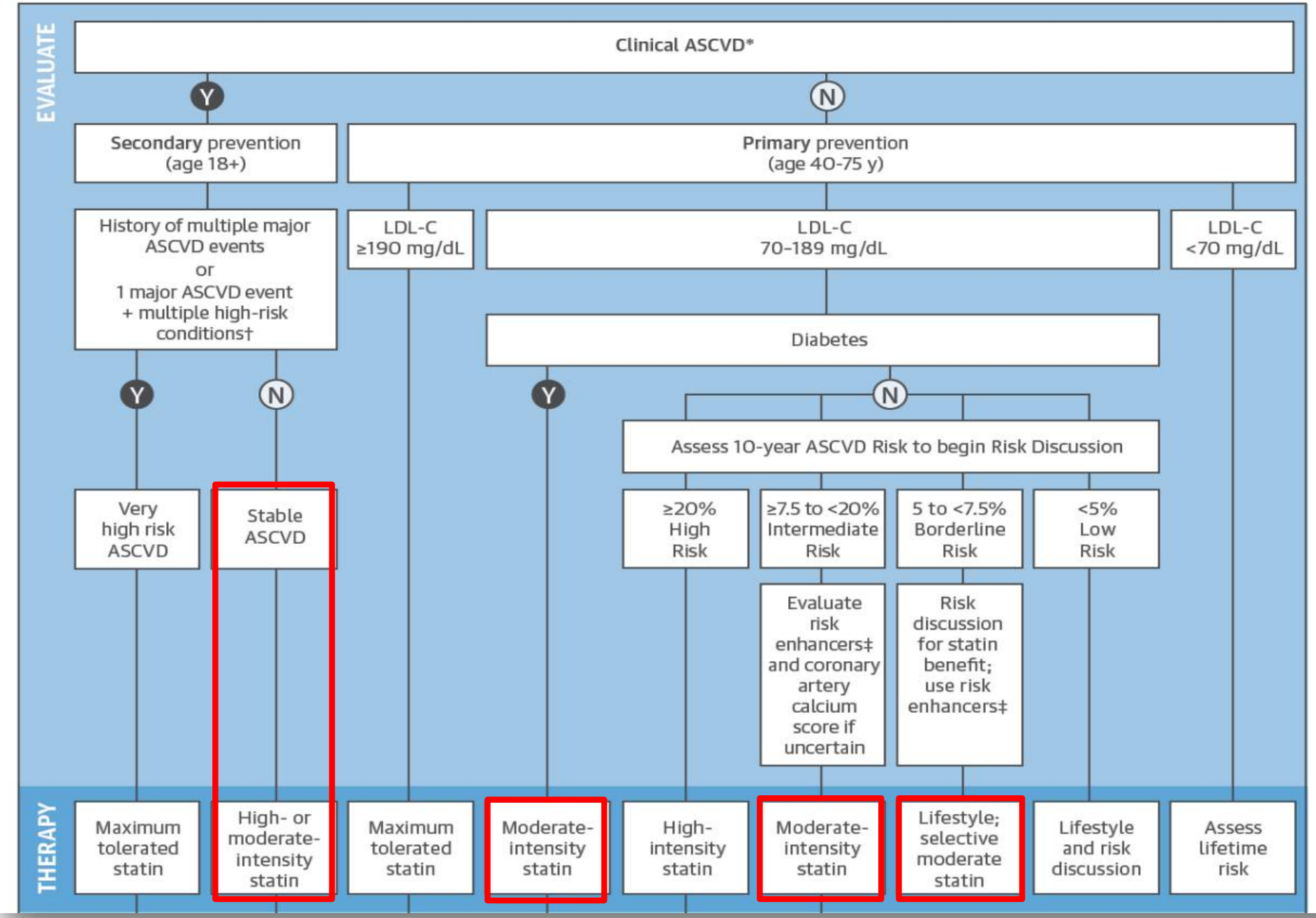
The largest-ever trial comparing the efficacy of high-dose versus low-dose pitavastatin therapy in Japan patients with established stable CAD

The REAL-CAD trial showed that High-dose is superior to low-dose in reducing cardiovascular events among patients with established stable CAD (Dose-dependent)

The present study suggests that the administration of maximum tolerable doses of pitavastatin would be the preferred statins therapy in Asia patients with established CAD regardless of the baseline LDL-C levels

Overview of Primary and Secondary ASCVD Prevention

This tool provides a broad overview of the 2018 Cholesterol Guideline.
Please refer to the full guideline document for specific recommendations.



GUIDELINES MADE SIMPLE
2018 Guideline on the Management of Blood Cholesterol

Ethnicity Issues in Evaluation, Risk Decisions, and Treatment of ASCVD Risk

Ethnic/racial groupings	Asian-Americans*	Hispanic/Latino-Americans†	Blacks	Comments
Treatment *(continued)*				
Intensity of Statin therapy and Response to LDL-C lowering	Japanese patients may be sensitive to statin dosing. In an open-label, randomized primary prevention trial, Japanese participants had a reduction in CVD events with low-intensity doses of pravastatin as compared to placebo. In a secondary prevention trial, Japanese participants with CAD benefitted from a moderate-intensity doses of pitavastatin.	No sensitivity to statin dosage compared to non-Hispanic white or black individuals	No sensitivity to statin dosage compared to non-Hispanic white individuals	Using a lower statin intensity in Japanese patients may give results similar to those seen with higher intensities in non-Japanese patients
Safety	Higher rosuvastatin plasma levels in Japanese, Chinese, Malay, and Asian-Indians compared to whites. FDA recommends a lower starting dose (5 mg of rosuvastatin in Asians vs. 10 mg in whites). Caution urged as dose uptitrated.	No specific safety issues with statins related to Hispanic/Latino ethnicity	Baseline serum CK values are higher in blacks than in whites. The 95th percentile race/ethnicity specific and sex-specific serum CK normal levels are available for assessing changes in serum CK.	Clinicians should take Asian ethnicity into account when prescribing dose of rosuvastatin (see package insert). In adults of East Asian descent, other statins should be used preferentially over simvastatin.

* The term Asian characterizes a diverse portion of the world's population. Individuals from Bangladesh, India, Nepal, Pakistan, and Sri Lanka make up most of the South Asian group. Individuals from Japan, Korea, and China make up most of the East Asian group.

† The term Hispanics/Latinos in the United States characterizes a diverse population group. This includes white, black, and Native American races. Their ancestry goes from Europe to America, including among these, individuals from the Caribbean, Mexico, Central and South America

AMERICAN COLLEGE of CARDIOLOGY

2018 ACC/AHA Guideline on the Management of Blood Cholesterol

Racial/ethnic issues in intensity of statin therapy & response to LDL-C lowering

- Japanese patients may be sensitive to statin dosing. In an open-label, randomized primary- prevention trial, Japanese participants had a reduction in CVD events with low-intensity doses of pravastatin as compared with placebo (S4.5.1- 33)

- In a secondary prevention trial, Japanese participants with CAD benefitted from a [moderate-intensity] dose of pitavastatin (S4.5.1-34)

- Using a lower statin intensity in Japanese patients may give results similar to those seen with higher intensities in non- Japanese patients

PLOS ONE

RESEARCH ARTICLE

Lipid lowering therapy in patients with atherosclerotic cardiovascular diseases: Which matters in the real world? Statin intensity or low-density lipoprotein cholesterol level? – Data from a multicenter registry cohort study in Taiwan

Yen-Ting Yeh[1], Wei-Hsian Yin[2,3], Wei-Kung Tseng[4,5], Fang-Ju Lin[6,7,8], Hung-I Yeh[9], Jaw-Wen Chen[10,11], Yen-Wen Wu[1,10,12]*, Chau-Chung Wu[12,13]*, on behalf of the Taiwanese Secondary Prevention for Patients with AtheRosCLErotic Disease (T-SPARCLE) Registry Investigators[¶]

Received: May 8, 2017

Accepted: October 9, 2017

Published: October 26, 2017

Conclusions

For patients with ASCVD on statin therapy guided by a target-driven strategy, failure to control LDL-C levels to < 100 mg/dL was associated with higher risk of MACEs. Statin intensity alone had no significant impact on the risk of MACEs after multivariate adjustment.

SCIENTIFIC REPORTS

OPEN

Residual Risk Factors to Predict Major Adverse Cardiovascular Events in Atherosclerotic Cardiovascular Disease Patients with and without Diabetes Mellitus

Received: 3 April 2017
Accepted: 18 July 2017
Published online: 23 August 2017

Fang-Ju Lin[1,2,3], Wei-Kung Tseng[4,5], Wei-Hsian Yin[6,7], Hung-I Yeh[8], Jaw-Wen Chen[9,10] & Chau-Chung Wu[11,12]

A prospective observational study was conducted to investigate the residual risk factors to predict recurrence of major adverse cardiovascular events (MACE) in atherosclerotic cardiovascular disease (ASCVD) patients with a high prevalence under lipid-lowering therapy, particularly in the subpopulations of diabetic and nondiabetic individuals. A total of 5,483 adults (with a mean age of 66.4 and 73.3% male) with established coronary heart disease, cerebrovascular disease, or peripheral artery disease were identified from the T-SPARCLE multi-center registry. Of them, 38.6% had diabetes. The residual risk factors for MACE are divergent in these atherosclerotic patients with and without diabetes. In diabetic subpopulation, the risk of MACE was significantly increased with heart failure (HF), chronic kidney disease (CKD) stage 4–5 (vs. stage 1–2), without beta blocker use, and higher non-HDL-C, after controlling for covariates including statin use and the intensity of therapy. Increased LDL-C and TG levels were also associated with increased risk, but to a much less extent. Among nondiabetic individuals, HF, CKD stage 4–5, and history of myocardial infarction were the significant independent predictors of MACE. It is suggested that ASCVD patients with concomitant diabetes need stricter control of lipid, particularly non-HDL-C levels, to reduce cardiovascular risk when on statin therapy.

European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

7.4 Statins

Since statins have significant effects on mortality as well as most CVD outcome parameters, these drugs are the first choice to reduce both total CVD risk and moderately elevated TG levels. More potent statins (atorvastatin, rosuvastatin and pitavastatin) demonstrate a robust lowering of TG levels, especially at high doses and in patients with elevated TGs. In subgroup analyses from statin trials, the risk reduction is the same in subjects with HTG as in normotriglyceridaemic subjects.

GUIDELINES MADE SIMPLE
2018 Guideline on the Management of Blood Cholesterol

Statin Associated Side Effects (SASE)

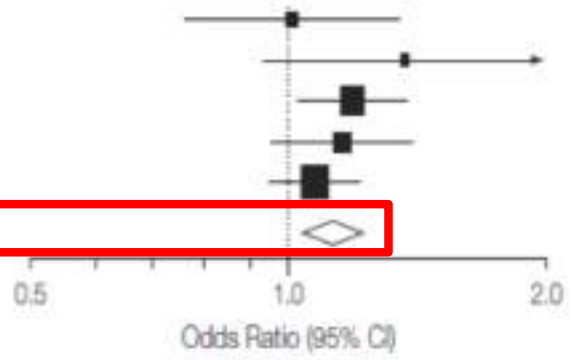
Statin Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Statin Associated Muscle Symptoms (SAMS) • Myalgias (CK normal)	Infrequent (1%–5%) in RCTs/frequent (5%–10%) in observational studies and clinical setting	Age, female, low BMI, high- risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, pre-existing myopathy), Asian descent, excess alcohol, high levels of physical activity and trauma.	RCTs cohorts/observational
• Myositis/Myopathy (CK >ULN) with concerning symptoms/objective weakness	Rare		RCTs cohorts/observational
• Rhabdomyolysis (CK >10xULN + renal injury)	Rare		RCTs Cohorts/observational
• Statin-associated autoimmune myopathy (SAAM) (HMGCR Ab's, incomplete resolution)	Rare		Case reports
New onset Diabetes Mellitus	Depends on population; more frequent if diabetes mellitus risk factors such as BMI ≥30, fasting blood sugar ≥100 mg/dL; metabolic syndrome or A1c ≥6% are present	Diabetes risk factors/ metabolic syndrome High-intensity statin therapy	RCTs/Meta-analyses

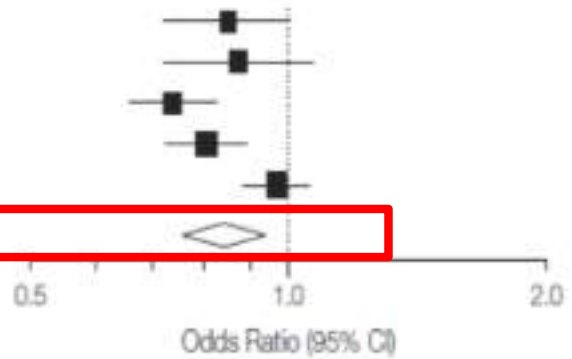
Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy

A Meta-analysis

Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident Diabetes			
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16408 (8.8)	1300/16344 (8.0)	1.12 (1.04-1.22)
Heterogeneity: $I^2 = 0\%$; $P = .60$			
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT,[15] 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL,[16] 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH,[5] 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	3134/16408 (19.1)	3550/16344 (21.7)	0.84 (0.75-0.94)
Heterogeneity: $I^2 = 74\%$; $P = .004$			





JAMA. 2011;305(24):2556-2564

Statin Associated Side Effects (SASE)

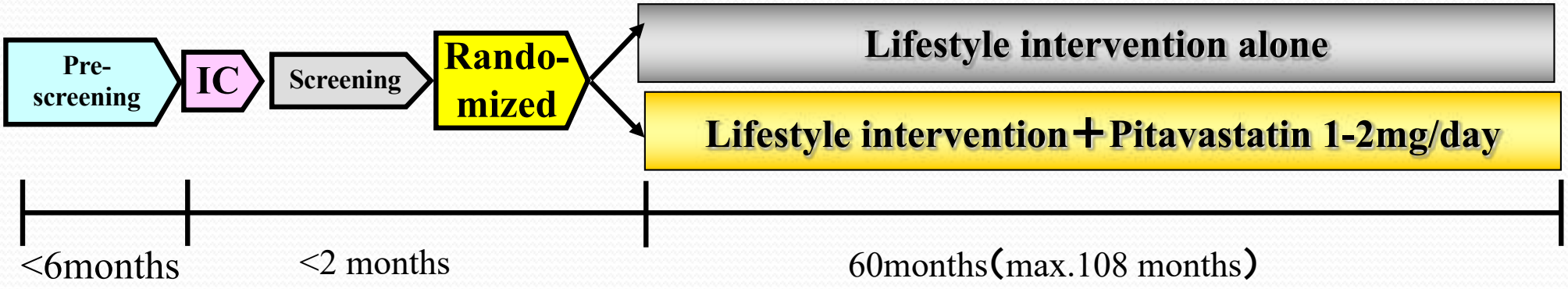
Statin Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Liver • Transaminase elevation 3xULN	Infrequent		RCTs/cohorts/observational Case reports
• Hepatic Failure	Rare		
CNS • Memory/Cognition	Rare/Unclear		Case reports; no increase in memory/cognition problems in three large scale RCTs
Cancer	No definite association		RCTs/meta-analyses
Other • Renal Function • Cataracts • Tendon Rupture • Hemorrhagic Stroke • Interstitial Lung Disease • Low Testosterone	 Unclear/unfounded Unclear Unclear/unfounded Unclear Unclear/unfounded Unclear/unfounded		

J-PREDICT

Japan PREvention Trial of Diabetes by PItavastatin in Patients With Impaired GluCose Tolerance

Study population	**IGT**
Primary endpoints	**Cumulative incidence of diabetes**
Secondary endpoints	**Incidence of any cardiovascular disease , etc**
Study drug	**Pitavastatin 1-2mg/day vs Control**
Target No. of patients	**1,240（620 in each group）**
Study period	**Apr.1 2004～MAR. 31, 2015(registration until Mar.31 2010)**
Principal investigator	**Prof. Takashi Kadowaki（Tokyo university）**

Open-label, randomized, parallel-group comparison study



Diabetol Int (2011) 2: 134-140

JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Pitavastatin improves glycated hemoglobin in patients with poorly controlled type 2 diabetes

Chung-Huei Huang, Yu-Yao Huang, Brend Ray-Sea Hsu*

Division of Endocrinology and Metabolism, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan

Keywords
Glycemic control, Statin, Type 2 diabetes mellitus

***Correspondence**
Brend Ray-Sea Hsu
Tel.: +886-3-328-1200 ext. 8821
Fax: +886-3-328-8257
E-mail address: bh0658@cloud.cgmh.org.tw

J Diabetes Investig 2016

doi: 10.1111/jdi.12483

ABSTRACT

Aims/Introduction: To investigate the effect of pitavastatin on glucose control in patients with type 2 diabetes.

Materials and Methods: Medical records of 340 patients with type 2 diabetes treated with pitavastatin or atorvastatin between 1 August 2013 and 31 May 2014 were reviewed. A total of 96 patients who had not received statins were treated with pitavastatin (N to P group). A total of 100 patients who had previously used atorvastatin were switched to pitavastatin (A to P group). A total of 144 patients continued with atorvastatin treatment. Data were collected at baseline, 3 and 6 months of treatment. Changes in glycated hemoglobin (HbA1c) level were analyzed in 222 patients who did not change their antidiabetic agent during 6 months of treatment.

Results: A negative correlation between baseline HbA1c and delta HbA1c at 6 months was found in the pitavastatin-treated patients (N to P group: $\rho = -0.329$, $P = 0.006$; A to P group: $\rho = -0.480$, $P < 0.001$). The correlation remained similar after adjusting for age, body mass index, dose of pitavastatin, estimated glomerular filtration rate and high-density lipoprotein cholesterol. After 6 months of treatment, the benefit of pitavastatin on HbA1c in the patients with poorly controlled diabetes was significant in both the N to P (8.1 vs 7.4%, $P = 0.018$) and A to P (9.7 vs 9.0%, $P = 0.015$) groups.

Conclusions: Pitavastatin decreases HbA1c in patients with type 2 diabetes with a higher baseline HbA1c level. The benefit on HbA1c was also observed in patients with previous use of atorvastatin.

EXPERT OPINION ON PHARMACOTHERAPY
https://doi.org/10.1080/14656566.2018.1544243

Taylor & Francis
Taylor & Francis Group

DRUG EVALUATION

An evaluation of pitavastatin for the treatment of hypercholesterolemia

Paul Chan[a*], Li Shao[b*], Brian Tomlinson [c,d], Yuzhen Zhang [c] and Zhong-Min Liu[e]

[a]Division of Cardiology, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei City, Taiwan.; [b]The VIP Department, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China; [c]Research Center for Translational Medicine, Shanghai East Hospital Affiliated to Tongji University School of Medicine, Shanghai, China; [d]Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong; [e]Department of Cardiac Surgery, Shanghai East Hospital, Tongji University, Shanghai, China

ABSTRACT

Introduction: Statins are the first line of therapy to reduce low-density lipoprotein cholesterol (LDL-C) in order to decrease cardiovascular events. Pitavastatin is the latest statin to be introduced to the market.

Areas covered: In this article, the authors review the efficacy, safety, and tolerability of pitavastatin. The authors also review a recent cardiovascular outcome study.

Expert opinion: Pitavastatin produces dose-dependent reductions in LDL-C at lower doses than other statins. The maximum approved dose of 4 mg reduces LDL-C by about 40–49% in different patient groups and is equivalent to atorvastatin 20 mg in this effect. Pitavastatin undergoes minimal metabolism so drug–drug interactions are less likely than with many other statins, but it can interact with some drugs that inhibit drug transporters. Compared with other statins, it has been associated with greater increases in high-density lipoprotein cholesterol and it was found to be less likely to cause new onset diabetes. In a recent study in Japanese patients with stable coronary artery disease, pitavastatin 4 mg was more effective than pitavastatin 1 mg in reducing cardiovascular events. Therefore, the highest dose may be preferred in high-risk patients.

ARTICLE HISTORY
Received 30 July 2018
Accepted 31 October 2018

KEYWORDS
Hypercholesterolemia; pharmacokinetics; pharmacodynamics; pitavastatin; statins

Take Home Messages

- Know your patients and understand the risks of the population your are treating
- In patients with high risk or very high risk clinical ASCVD, reduce LDL-c with high-intensity statin therapy or maximally tolerated statin therapy is recommended.
- Ethnicity issues impact on risk decisions and treatment of ASCVD risk
  - Current pooled cohort equations may overestimate risk in East Asians
  - Japanese patients may be sensitive to statin dosing.
- Real-CAD trial demonstrated Japanese participants with CAD benefitted from a moderate-intensity doses of pitavastatin.