

## 이상지질혈증 치료의 최신 Update

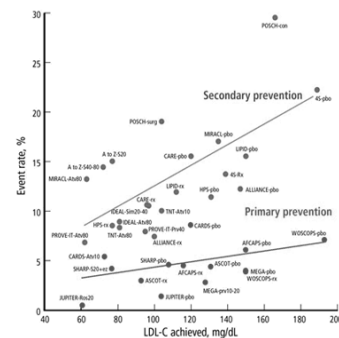
이 준 형

인제대학교 일산백병원 가정의학과

**RISK**  
**STATIN**  
**TARGET ?**  
**SAFETY!**

Lower is better !!

LDL-C levels vs rates of Coronary events



### Statin

- Statins for the primary prevention of cardiovascular disease (2013, Cochrane Database Syst Rev)



- 18 randomized control trials (19 trial arms; 56,934 Comparison 1. Mortality and Morbidity)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total Mortality	13	48060	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.79, 0.94]
2 Total Number of CHD Events	14	48049	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.67, 0.80]
3 Number of Total CHD Events	10	46094	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.70, 0.96]
4 Number of Non-fatal CHD Events	11	40977	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.59, 0.76]
5 Total Number of CVD Events	9	23805	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.70, 0.81]
6 Number of Total CVD Events	5	34012	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.96]
7 Number of Non-fatal CVD Events	2	8696	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.96]
8 Total Number of Stroke Events	10	40295	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.68, 0.89]
9 Number of Total Stroke Events	3	27238	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.38, 2.23]
10 Number of Non-fatal Stroke Events	5	28097	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.58, 0.83]
11 Total Number of Total and Non-fatal CHD, CVD and Stroke Events	4	35254	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.58, 0.73]
12 Number of Study Participants who underwent Revascularization	7	42403	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.54, 0.72]

### Statin – DM

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Summary  
Background: Trials of statin therapy have had conflicting findings on the risk of development of diabetes mellitus in patients given statins. We aimed to establish by a meta-analysis of published and unpublished data whether any relation exists between statin use and development of diabetes.

Methods: We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from 1994 to 2009.

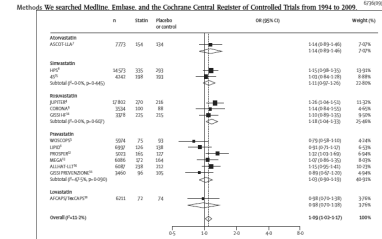
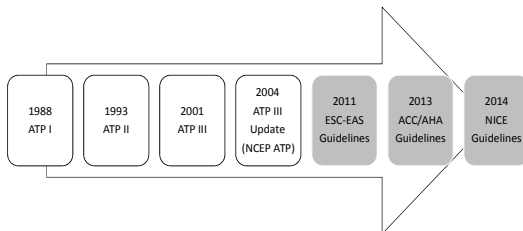


Figure 2 Association between different statins and development of diabetes

## Dyslipidemia Guideline



ESC/EASD 2007, ADA/AHA/ACC 2007, JBS2 2005, CCS 2012, JAS 2012, IAS 2013, ADA 2014.....

## ESC-EAS Guidelines(2011)



European Heart Journal (2011) 32, 1769–1818  
doi:10.1093/eurheartj/ehv158

ESC/EAS GUIDELINES

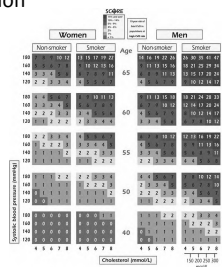
### ESC/EAS Guidelines for the management of dyslipidaemias

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

Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation†

## ESC-EAS Guidelines(2011)

- Total cardiovascular risk estimation
  - Risk group
  - SCORE system
- Risk levels & treatment goals
  - Very high risk
  - High risk
  - Moderate risk
  - Low risk
- Treatment targets
  - 1<sup>st</sup>: LDL-C
  - Alternative: apo B, non-HDL-C
  - do not provide targets: HDL-C, TG



## ESC-EAS Guidelines(2011)

- Lifestyle modifications
- Drugs for Hyperlipidemia
  - Statins: treatment of first choice
  - Other drug combinations
- Drugs for hyperTG
  - Fibrates, Nicotinic acid, n-3 fatty acids
  - Statins and combinations
- Drugs for Low HDL-C
  - Nicotinic acid
  - no clear direct evidence that raising HDL-C really results in CVD prevention
- Different clinical settings
  - DM, Metabolic syndrome, Renal disease, Stroke...
- improve adherence to lifestyle changes and compliance with drug therapy

## AHA/ACC Guidelines(2013)

**Circulation**  
JOURNAL OF THE AMERICAN HEART ASSOCIATION



2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines  
Neil J. Stone, Jennifer G. Robinson, Alice H. Lichtenstein, C. Noel Bairey Merz, Courad B. Blum, Robert H. Eckel, Anne C. Goldberg, David Gordon, Daniel Levy, Donald M. Lloyd-Jones, Patrick McBride, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Karol Watson and Peter W. F. Wilson

## AHA/ACC Guidelines(2013)

- Goal
  - Treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults
- Estimated 10-year ASCVD risk
- 4 Statin Benefit Groups
- Intensity of Statin Therapy in primary and secondary prevention
- Do not titrate to a specific LDL cholesterol target
- Statins Safety recommendations

## New 10 year ASCVD risk assessment

- Age, Gender, Race
- total Cholesterol, HDL-C, Systolic blood pressure
- Tx of HTN, DM, Smoking
- <http://my.americanheart.org/cvriskscalculator>
- <http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx>



### 2013 Prevention Guidelines Tools CV RISK CALCULATOR

The American Heart Association and the American College of Cardiology are excited to provide a series of new cardiovascular prevention guidelines for the assessment of cardiovascular risk, lifestyle modifications that reduce risk, management of elevated blood cholesterol, and management of increased body weight in adults. To support the implementation of these guidelines, the new Pooled Cohort Equations CV Risk Calculator and additional Prevention Guideline Tools are available below. Others may be developed and available in the near future.



Gender

Male Female

Age

50

Total Cholesterol (mg/dL)

250

HDL Cholesterol (mg/dL)

45

Systolic Blood Pressure

130

Treatment for Hypertension

Yes No

Diabetes

Yes No

Smoker

Yes No

Race

White

African American

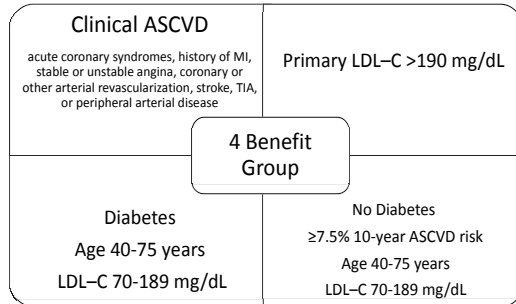
Other

Recommendation Based On Calculation

*Note: These estimates may underestimate the 10-year and lifetime risk for persons from some sociodemographic groups, especially American Indians, some Asian Americans (e.g., of South Asian ancestry), and some Hispanics (e.g., Puerto Ricans), and may overestimate the risk for others, including some Asian Americans (e.g., of East Asian ancestry) and some Hispanics (e.g., Mexican Americans).*

*Because the primary use of these risk estimates is to facilitate the very important discussion regarding risk reduction through lifestyle change, the expression introduced is small enough to justify proceeding with lifestyle change counseling informed by these results.*

## Statin Benefit Groups



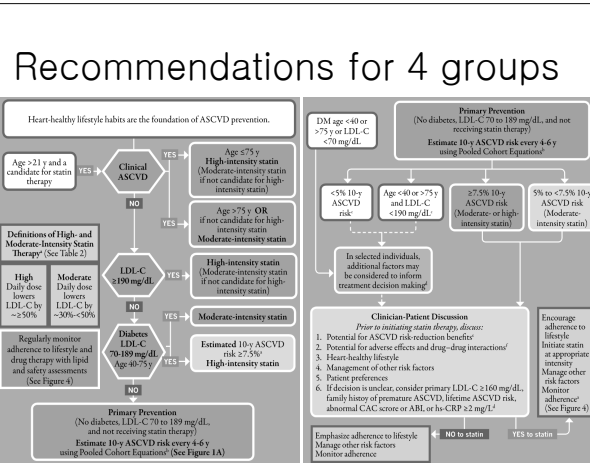
**Moderate to High-Intensity Statin Recommended**

Before initiating statin therapy, it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment (IIa-C).

Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, with no diabetes and estimated 10-year ASCVD risk ≥7.5% should be treated with moderate to high-intensity statin therapy (IIa).

**Lifestyle Recommendations**

AHA/ACC guidelines stress the importance of lifestyle modifications to lower cardiovascular disease risk. This includes eating a heart-healthy diet, regular aerobic exercises, maintenance of desirable body weight and avoidance of tobacco products.



## Do not titrate to a specific LDL cholesterol target

- Evidence is inadequate to support treatment to specific LDL-C or non-HDL-C treatment goals
- Unknown magnitude of additional ASCVD risk reduction with one target compared to another
- Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal

## Intensity of Statin Therapy

High-Intensity	Moderate-Intensity	Low-Intensity
Daily dose lowers LDL-C, on average, by approximately $\geq 50\%$	Daily dose lowers LDL-C, on average, by approximately 30% to $< 50\%$	Daily dose lowers LDL-C, on average, by $< 30\%$
Atorvastatin (40)–80 mg Rosuvastatin 20 (40) mg	Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

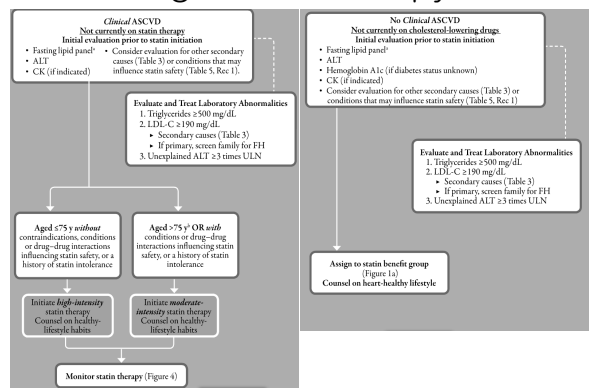
## Relative LDL-lowering Efficacy(FDA)

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Vytorin	Simva	% $\downarrow$ LDL-C
-----	40 mg	1 mg	20 mg	20 mg	-----	-----	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	-----	-----	20 mg	38%
20 mg	-----	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	-----	-----	-----	-----	10 mg	10/20 mg	80 mg	47%
80 mg	-----	-----	-----	-----	20 mg	10/40 mg	-----	55%
-----	-----	-----	-----	40 mg	10/80 mg	-----	-----	63%

Atorva=Atorvastatin; Fluva=Fluvastatin; Pitava=Pitavastatin; Lova=Lovastatin; Prava=Pravastatin; Rosuva=Rosuvastatin; Simva=Simvastatin.

<http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm>

## Initiating Statin Therapy

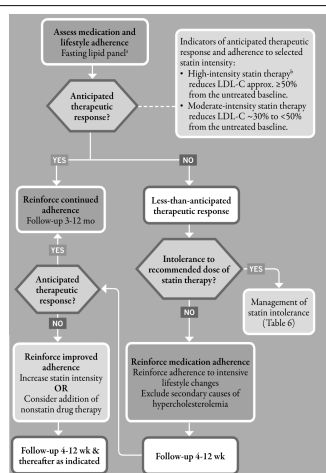


## Statins Safety recommendations

- Predisposing factor of statin-associated Adverse Effects
  - Multiple or serious comorbidities, including impaired renal or hepatic function.
  - History of previous statin intolerance or muscle disorders.
  - Unexplained ALT elevations  $\geq 3$  times ULN.
  - Patient characteristics or concomitant use of drugs affecting statin metabolism.
  - Age  $> 75$  years.
- History of hemorrhagic stroke.
- Asian ancestry.

## Monitoring

- Fasting lipid panel
- Creatinine Kinase (CK)
  - Routine monitoring of CK not recommended
  - at baseline(useful)
- Alanine Transaminase (ALT)
  - Baseline(recommended)
  - Routine hepatic monitoring not recommended



## EAS/ESC vs AHA/ACC

	EAS/ESC	AHA/ACC
Secondary prevention	Target LDL-C $< 70$ mg/dL, or at least 50% reduction. If target cannot be reached with statin, drug combination may be considered.	High-intensity statin. If 50% reduction is not reached drug combination may be considered.
Statin intolerance in secondary prevention	Reduce statin dose, consider combination therapy.	Moderate or low dose statin, consider combination therapy.
Primary prevention	Target LDL-C $< 100$ mg/dL. If target cannot be reached maximal reduction of LDL-C, using appropriate drug combinations in tolerated doses.	High-intensity statin therapy, aimed at achieving at least 50% reduction of LDL-C. If 50% reduction cannot be achieved, consider additional therapy.
Primary prevention in diabetes	Diabetes with other risk factors or organ damage: Target 70 mg/dL, or at least 50% reduction. Uncomplicated diabetes: Target LDL $< 100$ mg/dL.	Diabetes with high risk: High-intensity statin therapy. Diabetes with low risk: Moderate-intensity statin therapy.
Primary prevention High risk	SCORE $\geq 5\%$ risk of fatal CVD: Target $< 100$ mg/dL	Total risk for CVD event $> 7.5\%$ : Moderate- to high-intensity statin therapy. Risk 5-7.5% risk of CVD event: moderate-intensity statin therapy.

## NICE Guideline(2014)

- Update and replaces NICE guideline on lipid modification 2006

**NICE** National Institute for Health and Care Excellence

Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Issued: July 2014 last modified: September 2014

NICE clinical guideline 181  
guidance.nice.org.uk/cg181

## NICE Guideline(2014)

- Identifying and assessing CVD risk
  - Full formal risk assessment 10-yr risk of CVD  $\geq 10\%$
  - QRISK2 risk assessment tool [new 2014]
    - Primary prevention,  $\leq 84$
    - Type 2 DM
    - Do not use type 1 DM
    - eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> and not albuminuria
  - 1933-2010, GB
  - Age, Sex, Total-C, HDL-C, systolic BP, DM, Smoking, race, FHx. Of early CVD, CKD, Af, RA, BMI, Socioeconomic state

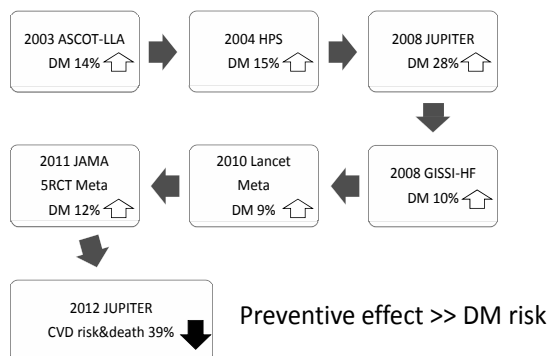
## NICE Guideline(2014)

- Primary prevention
  - QRISK2 10-yr CVD risk  $\geq 10\%$ 
    - atorvastatin 20 mg
  - Type I DM
    - Not assess CVD risk, atorvastatin 20 mg
  - Type II DM
    - UKPDS 10-yr CVD risk  $\geq 10\%$ 
      - atorvastatin 80 mg -> If needed, decrease
  - CKD
    - Without CVD, QRISK2 10-yr CVD risk  $\geq 10\%$ : atorvastatin 20 mg
    - With CVD: atorvastatin 20 mg start,  $\leq 40\%$  reduction in non-HDL-C -> increase statin (if eGFR  $> 30$  mL/min/1.73 m<sup>2</sup>)
- Secondary prevention
  - atorvastatin 80 mg start
  - Do not delay treatment to manage modifiable risk factors

## NICE Guideline(2014)

- Follow-up
  - $\leq 40\%$  reduction in non-HDL-C
  - 3mo: Total cholesterol, HDL-C, non-HDL-C check
  - medicines adherence and lifestyle modification
  - monitoring for adverse effects
    - Other drugs, foods, supplements
    - unexplained muscle pain (+) -> CK
- Fibrates for preventing CVD
  - Do not routinely offer
  - Also Nicotinic acid, Bile Acid, Omega-3 fatty acid

## Recent Issues – DM



## Recent Issues – DM

**American Diabetes Association** Diabetes Care  
Statins and the Risk of Diabetes: Evidence From a Large Population-Based Cohort Study

- In a real-world setting, the risk of new-onset diabetes rises as adherence with statin therapy increases.
- Benefits of statins in reducing cardiovascular events clearly overwhelm the diabetes risk.

## Recent Issues – Risk calculation

**The New York Times**

**Risk Calculator for Cholesterol Appears Flawed**

By GINA KOLATA

Published: November 17, 2013

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**Health**

**CASE OF RISK OVERESTIMATION**

44-year-old African American male with blood pressure 120/70 mmHg, non-diabetic, non-smoker, not on medications, BMI 22. He is active and healthy.

Total cholesterol 180 mg/dL, HDL-C 70 mg/dL, triglycerides 130 mg/dL, LDL-C 84 mg/dL

Following the new guidelines:

- His 10-year ASCVD risk is 7.5% and he would qualify for high-intensity statin therapy

Our Approach:

- In this case, starting a statin would be treating the ASCVD risk score and not the patient
- We would encourage maintenance of a healthy diet and lifestyle.
- In order to further reduce his cholesterol, we would consider additional testing such as C-reactive protein (CRP) score after discussing the risks and benefits with the patient and then decide if he would benefit from statin therapy.

**CASE OF RISK UNDERESTIMATION**

25-year-old white male with no medical problems, blood pressure 110/70 mmHg, non-smoker, non-diabetic, no medications, BMI 45

Strong family history of premature coronary artery disease (father died of myocardial infarction at age 42)

Total cholesterol 305 mg/dL, HDL-C 45 mg/dL, triglycerides 400 mg/dL, LDL-C 180 mg/dL

Following the new guidelines:

- At 40 years old, his 10-year risk per the new risk calculator is 3.3%
- He would not reach a 10-year risk of 7.5% and qualify for statin treatment until he is 45 years old. If we strictly follow the new guidelines, his patient would inappropriately wait 10 years before starting statin therapy

Our Approach:

- Advise the patient on the importance of adherence to a healthy diet
- Start the patient on a moderate to high intensity statin

Estimator

Cholesterol

Patients

About

ASCVD Risk Estimator\*

10-Year ASCVD Risk

11.8%

2.1%

Lifetime ASCVD Risk

69%

5%

Recommendation Based On Calculation

Gender

Male Female

Total Cholesterol (mg/dL)

250

HDL - Cholesterol (mg/dL)

45

Systolic Blood Pressure

130

Treatment for Hypertension

Yes No

Diabetes

Yes No

Smoker

Yes No

Age

65

Note: Lifetime risk is only calculated for the 20 to 59 year range

African American

Other

Note: These estimates may underestimate the 10-year and lifetime risk for persons from some socioeconomic groups, especially African Americans, some Asian Americans (e.g., South Asian ancestry), and some Hispanics (e.g., Puerto Ricans), and may overestimate the risk for others, including some Asian Americans (e.g., of East Asian ancestry) and some Hispanics (e.g., Mexican Americans).

Because the primary use of these risk estimates is to facilitate the very important discussion regarding lipid reduction therapy change, the expression introduced is small enough to justify proceeding with therapy change counseling informed by these results.

## Recent Issues – In Aisa?

European Heart Journal (2014) 35, N/A

CURRENT OPINION

**The ACC/AHA 2013 guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: the good the bad and the uncertain: a comparison with ESC/EAS guidelines for the management of dyslipidaemias 2011**

Kausik K. Ray<sup>1</sup>, John J. P. Kastelein<sup>2</sup>, S. Matthias Beekhof<sup>3</sup>, Kay-Tee Khaw<sup>4</sup>, Christine M. Ballantyne<sup>5</sup>, Alberto L. Cat and Thomas F. Lüscher<sup>1</sup>

- The ACC/AHA mixed pooled cohorts equation is unsuitable for most parts of the world as these populations were not included. These include south east Asia, the Indian subcontinent, Pacific islanders including Maori and Australian aboriginals.
- The reduction in the primary prevention threshold from 20 to 7.5% will result in a significantly greater number of patients offered statin therapy and in many cases higher doses. In some regions of the world, this will be simply unaffordable and among some ethnic groups will lead to a greater number of side-effects being observed.
- The 2013 ACC/AHA guidelines are impractical in the Asia-Pacific region.

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