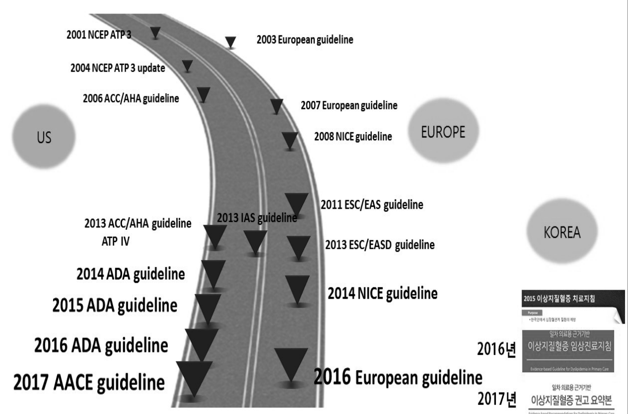
고지혈증 치료의 최신지견

박 상 민

서울대학교 의과대학 가정의학교실/ 의과학과, Health System Data Science Lab

최근 고지혈증 관련 가이드라인 변화

고지혈증 관련 가이드라인의 변화



ATP Ⅲ vs ATP Ⅳ vs NICE

Factor	ATP Ⅲ	ATP Ⅳ	NICE
Goal	Lower LDL	Lower CVD risk	Lower CVD risk
Determination of treatment	Based on risk factors (+/-risk of hard CHD events) and LDL	Based on risk of hard ASCVD events and LDL	QRISK2 to assess CVD
Lifestyle versus meds in high risk	Lifestyle first, then meds (unless CHD equivalent)	Meds on foundation of lifestyle	Meds on foundation of lifestyle (with Informed discussion)
Choice of meds	Any	Focus on statins	Focus on statins
Dosing of statins	----	Based on risk	Based on risk
Monitoring of effect	To various LDL goals	To expected effect—30% or 50% reduction in LDL from baseline	To expected effect—40% reduction in non HDL from baseline

ATP Ⅲ

치료원칙: Based on **CVD Risk** and **LDL-C level**

- **공복 지질 및 지단백 측정**
- **Framingham Risk Score : LDL-C 외에 2개 이상의 위험 요인이 있는 경우 10-year risk assess**
  -> 관상동맥질환 발생확률을 추정
- **CHD risk equivalent : DM 포함**

Risk Category	LDL-C	Non HDL-C
CHD and CHD risk equivalent (10-year risk for CHD>20%)	<100	<130
Multiple(2+) risk factors and **10-year risk<20%**	<130	<160
0-1 risk factor	<160	<190

- **치료의 1차적 목표 : LDL-C 강하(treat-to-goal paradigm)**
- **Non-HDL-C Goal (2차 목표) : TG ≥ 200 mg/dL인 경우**

- **약물 치료**
  - **10-year risk 10-20% : LDL-C >130 mg/dL**
  - **10-year risk >20% (CHD risk equivalent): LDL-C >100 mg/dL**

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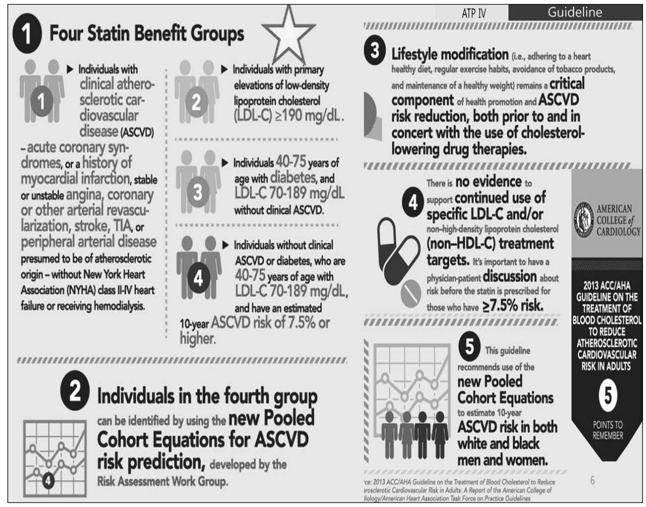
ATP IV: 2013 ACC/AHA guideline

- **치료의 1차적 목표 : ASCVD (Atherosclerotic Cardiovascular Disease) 의 예방**

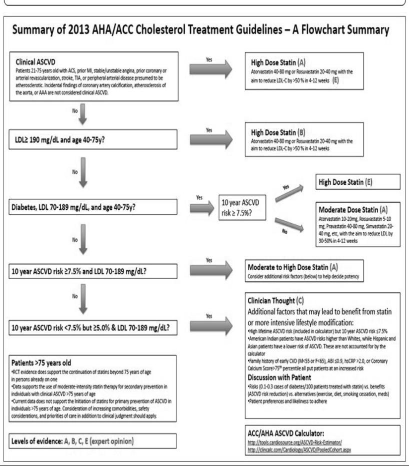
  - ACS, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin

- Pooled Cohort Equation : 10-year risk assess의 tool로 Framingham Risk Score 대신 사용
  - 10-year risk ≥ 7.5% 에서 약물치료
- ASCVD risk equivalent : DM 미포함

- **LDL-C 감소** : 치료 목표가 아니라, Statin **치료에 대한 반응이나 순응도(adherence)**를 보기 위한 목적으로 사용
- Non-HDL-C, Apo B, Lp(a), LDL particles 등의 on-treatment marker 들의 임상적 유용성이나 조절목표도 근거 부족으로 제시하지 않음



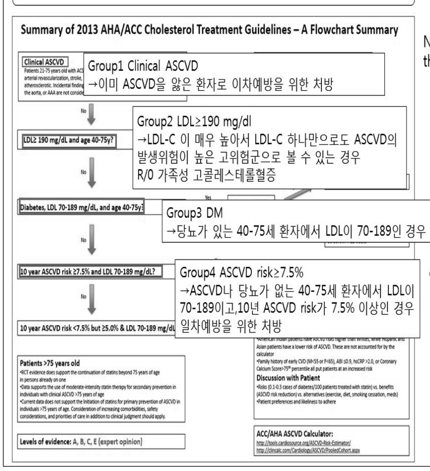
Focus on ASCVD Risk Reduction



No recommendation of statin therapy in 2 specific groups:
- HF (NYHA class II-IV)
- undergoing hemodialysis

diabetes (40-75yr) with LDL-C 70-189 mg/dL

Focus on ASCVD Risk Reduction



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고지혈증 환자에서 LDC-C 의 target goal

	2013 ACC/AHA guideline	2014 NICE guideline	2016 ADA guideline	2016 European guideline
Secondary prevention	No target	No target	No target	LDL-C <70mg/dL or LDL-C↓≥ 50% (if LDL 70-135)
Primary prevention	No target	No target	No target	• DM w/ TOD • Severe CKD • SCORE ≥10% LDL-C <70mg/dL or LDL-C↓≥ 50% (if LDL 70-135)
				• TC>310 mg/dL or BP≥180/110 mmHg • DM w/o TOD • Moderate CKD • SCORE 5~ 10% LDL-C <100mg/dL or LDL-C↓≥ 50% (if LDL 100-200)

2017 AACE/ACE Guideline: The Most Aggressive LDL-C Target Goal

Table 1
AACE Lipid Targets for Patients with Type 2 Diabetes (188,189,197,200,240-251)

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals: LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme Risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3,4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very High Risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease – Diabetes or CKD 3, 4 with 1 or more risk factor(s) – Heterozygous familial hypercholesterolemia	<70	<100	<80
High Risk	≥2 risk factors and 10-year risk >10% **or** CHD risk equivalent[c], including diabetes or CKD 3, 4 with no other risk factors	<100	<130	<90
Moderate Risk	≥2 risk factors and 10-year risk <10%	<100	<130	<90
Low Risk	≤1 risk factor	<130	<160	NR

Ref. Endocrine prictice. 2017;23(2):207-238.

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Risk category	Risk factors[a]/10-year risk[b]	Treatment goals LDLC	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme Risk	DM+ASCVD – Established clinical cardiovascular disease in patients with DM, CKD 3,4, or HeFH – History of premature ASCVD (<55 male, <65 female)	< 55	<80	<70
Very High Risk	DM+RFs – Diabetes or CKD 3, 4 with 1 or more risk factor(s) – Heterozygous familial hypercholesterolemia	< 70	<100	<80
High Risk	DM	<100	<130	<90
Moderate Risk	≥2 risk factors and 10-year risk <10%	<100	<130	<90
Low Risk	≤1 risk factor	<130	<160	NR

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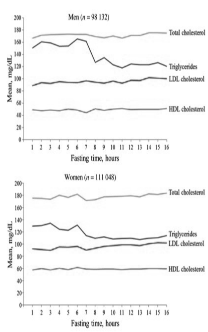
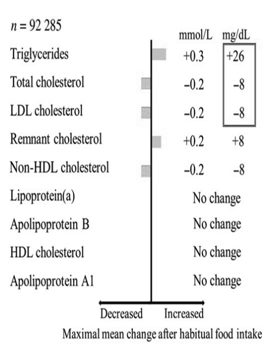
2016 ESC/EAS Guideline

Fasting or non-fasting?





공복시에 비해 비공복시 차이:
임상적으로 유의한 차이는 없음

Eur Heart J. 2016 Jul 1;37(25):1944-58

2016 ESC/EAS Guideline

Table 5 Abnormal plasma lipid, lipoprotein, and apolipoprotein concentration values that should be flagged in laboratory reports based on desirable concentration cut-points

Abnormal concentrations	Non-fasting mmol/L	Non-fasting mg/dL[a]	Non-fasting g/L	Fasting mmol/L	Fasting mg/dL[a]	Fasting g/L
Triglycerides[b]	≥2	≥175	≥1.75	≥1.7	≥150	≥1.50
Total cholesterol	≥5	≥190	≥1.90	≥5	≥190	≥1.90
LDL cholesterol	≥3	≥115	≥1.15	≥3	≥115	≥1.15
Remnant cholesterol[c]	≥0.9	≥35	≥0.35	≥0.8	≥30	≥0.30
Non-HDL cholesterol[d]	≥3.9	≥150	≥1.50	≥3.8	≥145	≥1.45
Lipoprotein(a)	[e]	≥50[f]	≥0.50	[e]	≥50[f]	≥0.50
Apolipoprotein B		≥100	≥1.00		≥100	≥1.00
HDL cholesterol[g]	≤1	≤40	≤0.40	≤1	≤40	≤0.40
Apolipoprotein A1		≤125	≤1.25		≤125	≤1.25

Non-fasting
In most patients, including:
- Initial lipid profile testing in any patient
- For cardiovascular risk assessment
- Patients admitted with acute coronary syndrome[a]
- In children
- If preferred by the patient
- In diabetic patients[b] (due to hypoglycaemic risk)
- In the elderly
- Patients on stable drug therapy

Eur Heart J. 2016 Jul 1;37(25):1944-58

- 지질검사중 LDL-C는 혈액 채취 전 반드시 공복상태일 필요는 없으나, 중성지방은 최소 12시간의 공복이 필요하다. 이상지질혈증의 진단 또는 치료 과정에서 LDL-C 수치를 가장 중요하게 고려하는 경우 공복상태가 아니라고 혈액 채취를 다음 방문 시로 미루어 시행할 필요는 없다.[152]

2016년 일차 의료용 근거기반 이상지질혈증 임상진료지침 대한의학회·질병관리본부

2014 NICE Guideline

- Before starting therapy with statins, doctors should take a full lipid profile of the patient. This should include measuring total cholesterol, HDL ("good") cholesterol and non-HDL cholesterol, as well as levels of other fats called triglycerides.
- The main difference from current guidance here is that a **fasting sample is no longer needed.**

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이상지질혈증의 1차 약물치료

2013 ACC/AHA guideline[3]	• **The appropriate intensity of statin therapy** should be initiated to reduce ASCVD risk.
2014 NICE guideline[4]	• **Offer atorvastatin 20 mg for the primary prevention** of CVD to people who have a 10% or greater 10-year risk of developing CVD • Start statin treatment in people with CVD with **atorvastatin 80 mg.**
2015 이상지질혈증 치료지침[5]	• 스타틴은 고콜레스테롤혈증 치료의 1차 선택약
2016 European guideline on CVD prevention[6]	• **Statins should be used as the drugs of first choice** in patients with hypercholesterolaemia or combined hyperlipidaemia.

Ref 3. Stone NJ, et al. Circulation. 2014 Jun 24;129:S1-45. 4. Cardiovascular disease: risk assessment and reduction, including lipid modification. NICE Clinical Guidelines(2014) 5. 이상지질혈증 치료지침 제정위원회. J Lipid Atheroscler 2015;4(1):61-92. 6. Piepoli MF, et al. Eur Heart J. 2016;37(29):2315-81.

스타인의 강도

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥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*

Specific statins and doses are noted in bold that were evaluated in RCTs (17,18,46-48,64-67,69-78) included in CQ1, CQ2 and the CTT 2010 meta-analysis included in CQ3 (20). All of these RCTs demonstrated a reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (47).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

bid indicates twice daily; FDA, Food and Drug Administration; IDEAL, Incremental Decrease through Aggressive Lipid Lowering study; LDL–C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

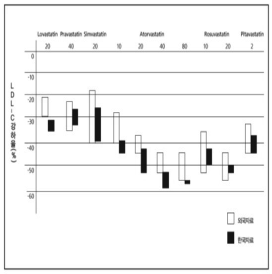

그림 1. 외국인과 한국인에서 각 스타틴에 의한 LDL-C 강하율 비교

[출처. 한국지질·동맥경화학회, 2015 이상지질혈증 치료지침]

한국인에게는 중등도 강도의 스타틴 용량도 적합 가능성(+)

Atorvastatin 10mg, Rosuvastatin 5mg, Simvastatin 20mg: 40% 이상의 LDL-C ↓

➢ **Natural Statins**
- Lovastatin
- Simvastatin
- Pravastatin
- Pitavastatin

➢ **Synthetic Statins**
- Fluvastatin
- Atorvastatin
- Rosuvastatin
- Cerivastatin

Drug	(%) Reduction in			Dosage Form(mg)	Metabolism	$T_{1/2}$,h	수용성
	TC	LDL-C	TG				
Atorvastatin	25-45	26-60	17-53	10,20,40,80	**CYP3A4**	15-30	No
Fluvastatin	16-27	22-36	12-25	20,40,80	CYP2C9	0.5-2.3	No
Lovastatin	16-34	21-42	6-27	10,20,40	**CYP3A4**	2.9	No
Pravastatin	16-25	22-34	15-24	10,20,40,80	Sulfation	1.3-2.8	**Yes**
Rosuvastatin	33-46	45-63	10-35	5,10,20,40	CYP2C9	19	**Yes**
Simvastatin	19-36	26-47	12-34	5,10,20,40,80	**CYP3A4**	2-3	No
Pitavstatin		31-51		1-4mg	CYP2C9	12	**Yes**

•**Cytochrome P450 3A4에 의해 대사** : atorvastatin, simvastatin, lovastatin 등은 다양한 약물과 상호작용의 가능성이 있어 사용에 주의를 요함

•**Rosuvastatin, pitavastatin** : 다양한 경로를 통해 대사 → 다른 스타틴에 비해 약물 상호작용이 적어 상대적으로 안전

- **Rosuvastatin, Atorvastatin, Simvastatin** : LDL-C감소가 가장 큼
  - Potent 한 statin이 필요할 때,
  - LDL-C 감소 >35% 필요할 때
- **Pravastatin** : 만성 간 질환 환자에서 사용가능
- **Pravastatin, Rosuvastatin** : 수용성. 55%만이 혈중 단백과 결합하므로 BBB 잘 통과. 주로 신장을 통해 배설.
  → 신부전 환자에서 용량 감소필요
- **Atorvastatin , Fluvastatin** : 신부전 환자에서 용량 조절이 필요하지 않음

스타틴 치료 후 추적 관찰

2016년 일차 의료용 근거기반 이상지질혈증 임상진료지침

이상지질혈증 치료 4~12주 후 환자 대상 권고 내용	권고 등급	근거 수준
이상지질혈증 약물 치료 4-12주 후, 혈중 지질 농도 측정 고려	IIb	C
(간기능 이상이 발생할 가능성이 높은 경우) 이상지질혈증 약물 치료 4-12주 후, 혈중에서 간효소 수치 측정 고려 → 스타틴 복용 후 AST/ALT 수치가 정상 상한치의 3배 이상 증가하면 수 일 또는 수 주 이내 재검사 시행하고 계속 증가하면 투약 중단	IIb	B
이상지질혈증 약물 치료 과정 중 근육 관련 증상(근육통, 근쇠약감)을 호소할 경우 근육효소(CK) 수치 측정 고려 → CK 수치가 정상 상한치의 4배 미만: 스타틴 중단 후 2~4주 후 다시 투여, 스타틴 변경, 저용량, 2일 1회, 1주 2회 등의 방법 고려 CK 수치가 정상 상한치의 4~10배: 증상 및 CK 수치 정상화될 때 까지 투약 중단 이 후 저용량의 다른 스타틴, 투여 횟수 조정 고려 CK 수치가 정상 상한치의 10배 이상: 투약 중단	IIa	C

Ref 14. 2016년 일차 의료용 근거기반 이상지질혈증 임상진료지침 대한의학회·질병관리본부

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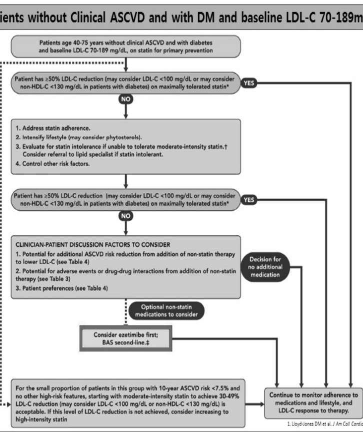
환자가 LDL-C 감소 목표치에 도달하지 못하면? : 50% LDL-C Reduction (or LDL-C< 100mg/dL)

Patients without Clinical ASCVD and with DM and baseline LDL-C 70-189mg/dL



Ezetimibe or 2차 약제

2016 American College of Cardiology
Expert Consensus
Decision Pathway :

1. Lloyd-Jones DM et al. *J Am Coll Cardiol* 2016 April 1 [E-pub ahead of print]

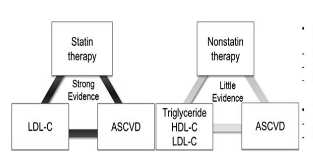
ATP IV Guideline

A New Perspective on LDL–C and/or Non-HDL–C Treatment Goals

•unable to find RCT evidence for use of specific LDL–C and/or non-HDL–C treatment targets

•Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits

- LDL–C and non-HDL–C Goals in Secondary Prevention
  - 19 RCTs
  - none of these RCTs compared titration to different LDL–C or non-HDL–C goals in individuals with clinical ASCVD
- LDL–C and non-HDL–C Goals in Primary Prevention
  - 6 RCTs
  - no evidence regarding dose titration to achieve a specific LDL–C goal in primary prevention
  - not identified any trials reporting on-treatment non-HDL–C levels



- Dyslipidemia treatment goal is to reduce ASCVD risk
- Nonstatin therapies 는 권고하지 않음

▪ Statin + Fenofibrate

ACCORD subgroup analysis

당뇨 환자에서 Statin 치료 (simvastatin 20-40 mg 사용)에도 불구하고 high triglycerides, low HDL-C 일 경우 fenofibrate 추가가 ASCVD 예방에 도움이 될 수 있다

moderate-intensity statin+fenofibrate 병합요법은 ASVDC 예방에 도움이 된다 -> 그러나 high-intensity statin 과의 비교 필요

▪ Statin + Niacin

- **AIM-HIGH** (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes)
  - 3414 pts
  - LDL–C : 40 to 80 mg
  - Primary endpoint : ASCVD events
- **Incidence of primary endpoint**
  - Statin + niacin : 16.4 %
  - Statin + placebo : 16.2%

		At Year 3	
	baseline	+Niacin	+Placebo
LDL-C	75.8	65.2	68.3
HDL – C	35.3	44.1	39.1
TG	162	120	152

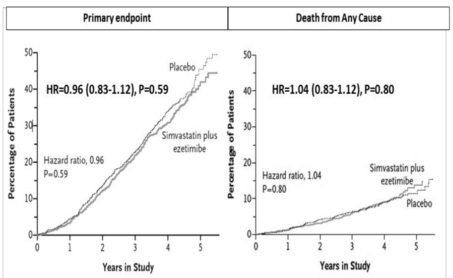
statin+niacin 병합요법이 non-HDL을 20% 정도 감소시키기는 하지만 궁극적으로 ASCVD 발생을 낮추지는 못 한다

N Engl J Med 2011;365:2255–2267

SEAS : In patients with aortic stenosis, combination of Ezetimibe plus Simvastatin did not reduce the RR for CVD.

1,873 Patients with mild-to moderate, asymptomatic aortic stenosis. → Ezetimibe 10 mg + Simvastatin 40 mg / Placebo

- Primary endpoint : major cardiovascular events
- Follow-up : 52.2 months



Reference. Rossebø AB, et al. N Engl J Med 2008;359.

SEAS : In patients with aortic stenosis, combination of Eze plus Simva increased new cancer and liver enzyme levels.

Adverse Events (Safety Population)

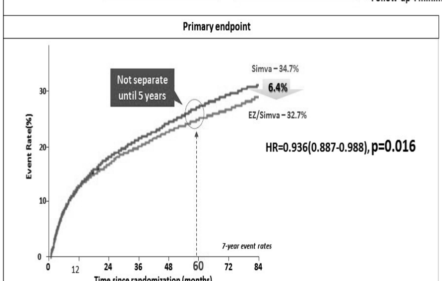
Event	Placebo (N=929)	Simvastatin plus Ezetimibe (N=943)	P Value†
	no./total no. (%)		
Clinical			
Any event	852 (91.7)	854 (90.6)	
Any serious event‡	463 (49.8)	468 (49.6)	
Incident cancer§	70 (7.5)	105 (11.1)	0.01
Recurrent cancer	5 (0.5)	3 (0.3)	
New cancer	65 (7.0)	102 (10.8)¶	0.01
New cancer after ezetimibe	65 (7.0)	101 (10.7)	0.01
Laboratory findings			
Creatine kinase			
>10 times ULN without muscle-related symptoms	2/915 (0.2)	2/925 (0.2)	1.00
>10 times ULN with muscle-related symptoms	0	0	NA
>10 times ULN with muscle-related symptoms and drug relationship	0	0	NA
Liver enzymes			
Alanine aminotransferase or aspartate aminotransferase ≥3 times ULN (consecutive)**	5/915 (0.5)	16/925 (1.7)	0.03

Reference. Rossebø AB, et al. N Engl J Med 2008;359.

IMPROVE-IT : In patients with ACS, combination of Ezetimibe plus Simvastatin reduce the RR for CVD.

18,144 patients with post ACS ≤ 10 days, Standard medical & Interventional therapy → Ezetimibe 10 mg + Simvastatin 40 mg / Placebo + Simvastatin 40 mg

- Primary endpoint : CV death, nonfatal MI, nonfatal stroke, rehospitalization for UA, and coronary revascularization (≥ 30 days postrandomization)
- Follow-up : minimum 2½-year



- No statistically significa nt differences in cancer or muscle- or gallbladd er-related events

Ref. Blazing MA, et al. Am Heart J 2014;168:205-212.e1.

Niacin in Patients with Low HDL Cholesterol Receiving Intensive Statin Therapy

- The AIM-HIGH study :

Table 3. Reductions and Discontinuation of Study Drugs and Levels of Statins.

Variable	Placebo plus Statin (N=1696)	Extended-Release Niacin plus Statin (N=1718)	P Value
Reduction of study-drug dose after randomization			
Patients requiring dose reduction — no. (%)	58 (3.4)	109 (6.3)	<0.001
Primary reason for dose reduction — no. (%)			
Flushing or itching	23 (1.4)	57 (3.3)	
Abnormality on liver-function test	0	1 (0.1)	
Request by patient	11 (0.6)	13 (0.8)	
Request by nonstudy physician	3 (0.2)	1 (0.1)	
Other clinical reason	10 (0.6)	21 (1.2)	
Increased glucose level	5 (0.3)	10 (0.6)	
Gastrointestinal symptoms	4 (0.2)	4 (0.2)	
Reason not specified	2 (0.1)	0	
Discontinuation of study drug after randomization			
Patients discontinuing study drug — no. (%)	341 (20.1)	436 (25.4)	<0.001
Time to discontinuation — days	579.6±463.5	568.1±480.2	
Primary reason for discontinuation — no. (%)			
Flushing or itching	43 (2.5)	104 (6.1)	
Abnormality on liver-function test	5 (0.3)	5 (0.3)	

NEJM 2011:365:2255-67

Variable	Placebo plus Statin (N=1696)	Extended-Release Niacin plus Statin (N=1718)	P Value
Reduction of study-drug dose after randomization			
Patients requiring dose reduction — no. (%)	58 (3.4)	109 (6.3)	<0.001
Primary reason for dose reduction — no. (%)			
Flushing or itching	23 (1.4)	57 (3.3)	
Abnormality on liver-function test	0	1 (0.1)	
Request by patient	11 (0.6)	13 (0.8)	
Request by nonstudy physician	3 (0.2)	1 (0.1)	
Time to discontinuation — days	579.6±463.5	568.1±480.2	
Primary reason for discontinuation — no. (%)			
Flushing or itching	43 (2.5)	104 (6.1)	
Abnormality on liver-function test	5 (0.3)	5 (0.3)	
Request by patient	137 (8.1)	126 (7.3)	
Request by nonstudy physician	35 (2.1)	49 (2.9)	
Other clinical reason	95 (5.6)	96 (5.6)	
Increased glucose level	14 (0.8)	29 (1.7)	
Gastrointestinal symptoms	12 (0.7)	26 (1.5)	
Reason not specified	0	1 (0.1)	

Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and may increase the risk of stroke and is not generally recommended.

2016 ADA guideline Diabetes care

NEJM 2011:365:2255-67

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

Praluent™ 75 mg (alirocumab) Repatha® 140 mg (evolocumab)

2017 American College of Cardiology Expert Consensus Decision Pathway (ECDP) Focused Update

Section	2016 ECDP	2017 ECDP Focused Update
	Included consideration of evidence from cardiovascular outcomes trials of ezetimibe, niacin, and niacin/laropiprant.	Includes consideration of new randomized clinical trial (RCT) data with the PCSK9 inhibitors, evolocumab and bococizumab.

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER)

The NEW ENGLAND JOURNAL of MEDICINE

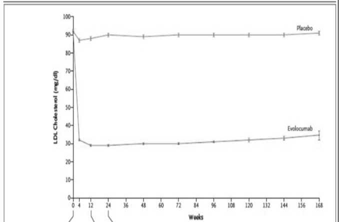
ESTABLISHED IN 1812 MAY 4, 2017 VOL. 376 NO. 18

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Criteria

Inclusion Criteria:
- Male or female ≥ 40 to ≤ 85 years of age
- History of clinically evident cardiovascular disease at high risk for a recurrent event
- Fasting LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L) or non-HDL-C ≥ 100 mg/dL (> 2.6 mmol/L)
- Fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L)

Exclusion Criteria:
- NYHA class III or IV, or last known left ventricular ejection fraction < 30%
- Uncontrolled hypertension
- Uncontrolled or recurrent ventricular tachycardia
- Untreated hyperthyroidism or hypothyroidism
- Homozygous familial hypercholesterolemia
- LDL or plasma apheresis



No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.
Shown are median values in the two study groups; I bars indicate 95% confidence intervals. Below the graph, the absolute and percentage reductions in LDL cholesterol level in the evolocumab group are compared with those in the placebo group and are presented as least-squares means or means (details are provided in the Methods section in the Supplementary Appendix). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

2017 American College of Cardiology Expert Consensus Decision Pathway (ECDP) Focused Update

Section	2016 ECDP	2017 ECDP Focused Update
	Included consideration of evidence from cardiovascular outcomes trials of ezetimibe, niacin, and niacin/laropiprant.	Includes consideration of new randomized clinical trial (RCT) data with the PCSK9 inhibitors, evolocumab and bococizumab.

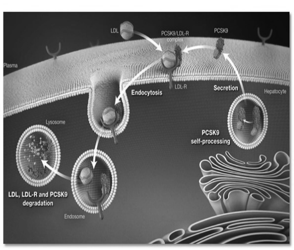
	Alirocumab	Evolocumab	Bococizumab
Mechanism of action	Human monoclonal antibody to PCSK9. Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL.		
Dose and route of administration	75 mg SQ every 2 weeks	140 mg SQ every 2 weeks or 420 mg SQ once monthly	
Adverse effects: No evidence of increase in cognitive adverse effects	URI, influenza, injection site reactions	URI, influenza, injection site reactions, back pain	
CV outcomes trials	ODYSSEY (not completed)	FOURIER	SPIRE-1 and -2
Considerations in prescribing:	Cost, SQ administration, robust LDL-C reduction		

- LDL or plasma apheresis

least-squares means or means (details are provided in the Methods section in the Supplementary Appendix). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

Proprotein convertase subtilisin/kexin type 9 (PCSK9)
- Chaperones LDL-R to destruction → ↑ circulating LDL-C
- Loss-of-fxn genetic variants → ↑ LDL-R → ↓ LDL-C & ↓ risk of MI



Evolocumab
- Fully human anti-PCSK 9 mAb
- ~60% ↓ LDL-C
- Safe & well-tolerated in Ph 2 & 3 studies
- Exploratory data suggested ↓ CV events

암젠 '레파타(Repatha, evolocumab)'

Sever P & Mackay J. *Br J Cardiol* 2014;21:91-3
Giugliano RP, et al. *Lancet* 2012;380:2007-17
Sabatine MS, et al. *NEJM* 2015;372:1500-9

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

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- Chaperones LDL-R to destruction → ↑ circulating LDL-C
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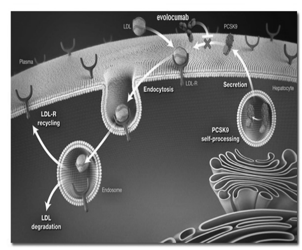

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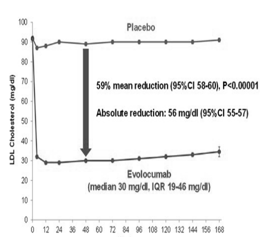
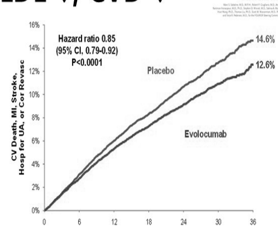
Sabatine MS, et al. *NEJM* 2015;372:1500-9

Anti-PCSK9 mAb => LDL ↓, CVD ↓

The NEW ENGLAND JOURNAL of MEDICINE
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease





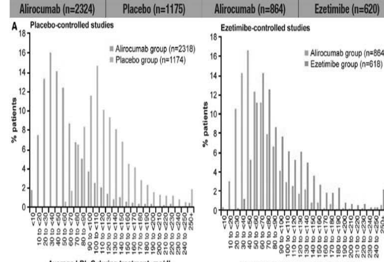
- ↓ LDL-C by 59%
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)
- ↓ CV outcomes in patients already on statin therapy
  - 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 25% reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C

ODYSSEY 의 post-hoc analysis

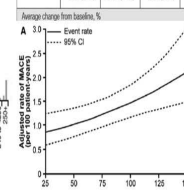
LDL-C<50 - alirocumab 44.7~52.6%
- ezetimibe 6.5%
- placebo 0%
→ Lower incidence of MACE(major adverse cardiac events)

Circulation
Reductions in Atherogenic Lipids and Major Cardiovascular Events
A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control

Placebo-Controlled Trials		Ezetimibe-Controlled Trials*	
Alirocumab (n=2324)	Placebo (n=1175)	Alirocumab (n=864)	Ezetimibe (n=620)



	Placebo-Controlled Trials		Ezetimibe-Controlled Trials	
	Alirocumab (n=2318)	Placebo (n=1174)	Alirocumab (n=864)	Ezetimibe (n=618)
Average achieved, mg/dL				
LDL-C	56.9 (38.8)	126.5 (43.9)	64.0 (42.4)	100.9 (50.8)
Non-HDL-C	82.0 (41.8)	156.0 (47.2)	91.1 (45.6)	128.5 (55.2)
ApoB	57.1 (29.1)	104.1 (28.1)	64.9 (28.1)	89.2 (31.0)
Average change from baseline, %				

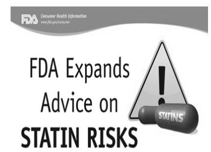


임상에서 흔한 질문

1) 고지혈증 검사를 꼭 공복에만 해야 하나요?
2) 어떤 스타틴을 처방해야 하나요?
3) 약물치료 중 LDL-C 목표에 도달하지 못할 때는 어떻게 하나요?
4) **스타틴 약이 해롭다는데 꼭 먹어야 하나요?**
5) 약을 끊으면 어떻게 되나요?

Unexpected health effects of statin use

a) Diabetes
b) Cognitive function
c) 노인



FDA mandates new safety warnings for statin drugs due to risks of memory loss, diabetes and muscle pain (May 6, 2016)

Risk of incident DM among patients treated with statin

Population based cohort study
471, 250 patients with no history of diabetes.
Median age at the outset of treatment : 73 years
Atorvastatin accounted for more than half of all new statin (about 57%)

[Analysis of primary outcome of diagnosis of diabetes by drug and dose in new users of statin]

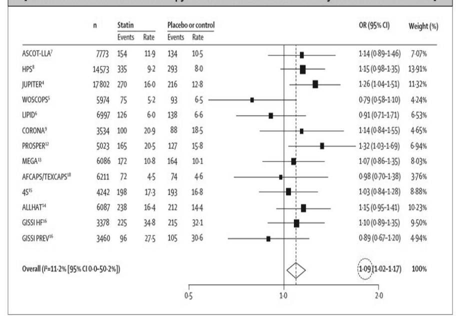
Statin	New statin user : 471,250 (100%)	Unadjusted	Adjusted*
Pravastatin	38,470 (8.1%)	Reference	Reference
Atorvastatin	**268,254 (56.9%)**	1.21 (1.15 to 1.28)	1.12 (1.05 to 1.18)
Fluvastatin	11,923,(2.5%)	0.94 (0.80 to 1.10)	0.94 (0.80 to 1.11)
Lovastatin		0.96 (0.83 to 1.11)	0.99 (0.85 to 1.14)
Rosuvastatin	76,774 (16.3%)	1.21 (1.13 to 1.30)	1.01 (0.94 to 1.09)
Simvastatin	75,826 (16.0%)	1.16 (1.09 to 1.24)	1.11 (1.04 to 1.18)
Dose grouping:			
Low dose†		Reference	Reference
Moderate dose‡		1.26 (1.22 to 1.30)	1.22 (1.19 to 1.26)
High dose§		1.39 (1.29 to 1.50)	1.30 (1.20 to 1.40)

Ref. Cartet AA, et al. BMJ. 2013;346:f2610.

Statin => DM

Statin Therapy was Associated with a 9% Increased Risk for Incident Diabetes
Meta analyses
91,140 patients with diabetes from 13 RCTs of statin therapy

[Association Between Statin Therapy and Incident Diabetes in 13 Major Cardiovascular Trials]



Ref. Sattar N, et al. Lancet. 2010;375(9716):735-42.

스타틴 사용과 당뇨병 위험도에 대한 비교효과 연구

표 4-4 스타틴 종류와 당뇨병 발생과의 관련성

변수	비스타틴군 (N=518,491)	스타틴 종류				
		아토바스타틴	로슈바스타틴	심바스타틴	프라바스타틴	기타 스타틴
당뇨병 신환자 발생 (명)	15,682	12,989	1,678	10,216	846	3,661
총 관찰 기간-Person years	2,006,261	804,895	105,919	619,385	51,143	223,740
당뇨병 발생 -per 1,000 person years	6.85	14.15	14.16	15.07	15.07	14.79
Hazard Ratio (95% CI)*	[Reference]	2.17 (2.12, 2.22)	2.15 (2.04, 2.26)	1.99 (1.94, 2.04)	1.94 (1.80, 2.07)	2.02 (1.95, 2.09)

* 보정 변수: 체질량지수 (Body Mass Index), 공복혈당, 총콜레스테롤, 찰스동반상병지수 (Charlson Comorbidity Index, CCI)

표 4-7 스타틴 종류와 심혈관계 질환 발생과의 관련성

	비스타틴군 (N=518,491)	스타틴 종류				
		아토바스타틴	로슈바스타틴	심바스타틴	프라바스타틴	기타스타틴
심혈관계질환 신환자 발생 (명)	1,061	251	39	214	19	75
총 관찰 기간-Person years	2,038,092	832,804	110,236	649,310	53,594	234,006
심혈관계질환 발생 -per 1,000 person years	0.45	0.27	0.33	0.30	0.33	0.30
Hazard ratio (95%CI)*	1 [Reference]	0.69 (0.60, 0.79)	0.81 (0.58, 1.11)	0.61 (0.53, 0.71)	0.70 (0.45, 1.11)	0.66 (0.52, 0.83)

Reference. 한국보건의료 연구원 (NECA)

Unexpected health effects of statin use

a) Diabetes
b) Cognitive function
c) 노인

JGIM

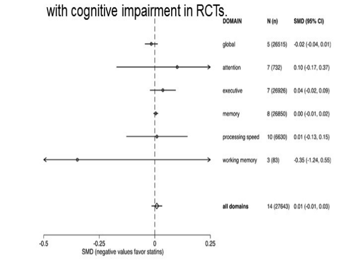
REVIEWS

Do Statins Impair Cognition? A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Brian R. Ott, MD[1], Lori A. Daiello, PharmD, ScM[1], Issa J. Dahabreh, MD, MS[2,3], Beth A. Springate, PhD[4], Kimberly Bixby, BS[1], Manjari Murali, PhD[1], and Thomas A. Trikalinos, MD[2,3]

[1]Rhode Island Hospital, Department of Neurology, Alpert Medical School of Brown University, Providence, RI, USA; [2]Center for Evidence-based Medicine, School of Public Health, Brown University, Providence, RI, USA; [3]Department of Health Services, Policy & Practice, School of Public Health, Brown University, Providence, RI, USA; [4]Department of Psychiatry and Human Behavior, Rhode Island Hospital, Providence, RI, USA.

Statin therapy was not associated with cognitive impairment in RCTs.



Negative SMD values indicate better cognition in statin compared to no statin arms.
CI = confidence interval; N = number of studies; n = number of patients included in analyses; SMD = standardized mean difference.

Figure 2 Forest plot of treatment effect of statins on global cognition and cognitive domains in cognitively normal subjects.

NEWS ACC 2017

High-Dose Atorvastatin Does Not Impact Cognition, but Small Changes Observed on Brain MRI

Researchers say the findings are far from definitive and require validation.

mean age of 48 years

In the STOMP trial, they included 66 patients treated with atorvastatin 80 mg and 84 patients treated with placebo.

Unexpected health effects of statin use

a) Diabetes

b) Cognitive function

c) 노인

입력 : 2017.09.20 07:30

JAMA 논문 "고령자 사망률 높여"

사망 원인 모든 질환 포함돼 한계... 당뇨병 증가, 우려할 정도는 아냐

스타틴 제제는 이상지질혈증 환자에게 쓰이는 약이다. 국내에서 가장 많이 팔린 약 1~2위를 다툴 정도로 많은 사람들이 복용한다. 스타틴 제제는 LDL콜레스테롤 수치를 낮추고 심장마비 예방 효과가 있어 출시된 지 30년이 됐지만 여전히 거의 모든 이상지질혈증 환자가 복용하고 있다. 그러나 많이 복용하는 약인 만큼 부작용에 대한 연구도 지속적으로 나오고 있다.

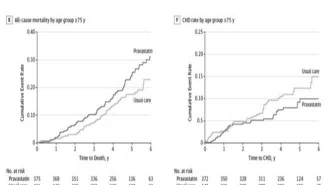
최근 고령의 이상지질혈증 환자에게는 스타틴 제제의 효과가 미미하고, 오히려 스타틴 제제를 복용하지 않은 그룹보다 사망률이 더 높다는 연구결과가 나왔다. 지난 7월 세계적으로 권위 있는 학술지 'JAMA(미국의사협회지)'에 발표된 이 논문에서 연구진은 고혈압·이상지질혈증이 심하지 않은 65세 이상 노인 2867명을 대상으로 1400명에게는 운동·식이조절만으로 질환을 관리하게 하고, 나머지 1467명에게는 스타틴을 투여했다. 그 결과, 약을 복용한 그룹과 복용하지 않은 그룹의 심장병 발작 빈도는 별 차이가 없는 것으로 나타났다. 사망률은 스타틴을 복용한 환자가 64~74세의 경우 1.08배, 75세 이상의 경우 1.34배로 더 높았다.

Research

JAMA Internal Medicine | Original Investigation

Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults
The ALLHAT-LLT Randomized Clinical Trial

Benjamin H. Han, MD, MPH; David Sutin, MD; Jeff D. Williamson, MD; Barry R. Davis, MD, PhD; Linda B. Piller, MD, MPH; Hannah Pervin, PhD; Sara L. Pressel, MS; Caroline S. Blaum, MD; for the ALLHAT Collaborative Research Group



No benefit was found when pravastatin was given for primary prevention to older adults with moderate hyperlipidemia and hypertension, and a nonsignificant direction toward increased all-cause mortality with pravastatin was observed among adults 75 years and older.

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3. 뇌혈관질환에서의 이상지질혈증

권고 내용	권고등급	근거수준	참고문헌
• 모든 허혈성 뇌졸중 및 일과성 허혈 발작 환자에서 이차예방을 위해 스타틴 사용을 권고한다.	I	A	10, 56, 107, 108, 109, 110
• 출혈성 뇌졸중 환자에서의 일괄적인 스타틴 사용은 권고하지 않는다.			
• 출혈성 뇌졸중의 병력이 있는 환자에서의 스타틴 사용은 재발위험을 증가시킬 가능성이 있으므로, 용량선택에 주의가 필요하다.			
• 혈관성 치매환자에서 스타틴의 투여가 인지기능 악화 방지에 효과적인가에 대한 근거는 부족하다.			

4. 노인과 이상지질혈증

권고 내용	권고등급	근거수준	참고문헌
• 심뇌혈관질환을 동반한 75세 이하 노인 환자에서 이차예방을 위한 스타틴 사용은 젊은 환자와 동일한 방식으로 할 것을 권고한다.	I	A	9, 10, 29, 101, 111, 112, 113, 114, 115, 116, 117
• 심뇌혈관질환을 진단받지 않은 75세 이하 노인 환자에서 일차예방을 위한 스타틴 사용은 젊은 환자와 동일한 방식으로 할 것을 권고한다.	I	B	9, 10, 29, 101, 111, 114, 117
• 노인 환자에서는 다른 질환들이 동반되어 있을 수 있고 약동학적 특성의 변화가 있을 수 있으므로, 지질강하제를 사용하는 경우 소량부터 시작하여 증량할 것을 권고한다.	I	D	9, 26

진료시 고려할 점 혹은 특수 상황에서의 권고 사용법 (연령별 적용, 동반이환(Comorbidity) 환자인 경우, 근거가 불충분한 권고의 적용 등)
• 노인 환자는 심뇌혈관질환의 고위험군이 많으므로 스타틴 사용에 따른 비용 대비 효과는 젊은 환자에 비해 더 크다.

권고 내용	권고등급	근거수준	참고문헌
• 심뇌혈관질환을 동반한 75세 초과 노인 환자에서 이차예방을 위해 스타틴 사용을 고려한다.	IIa	B	26, 101, 112, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136
• 심뇌혈관질환을 동반하지 않은 75세 초과 노인 환자에서 당뇨병이 있는 경우 일차예방을 위해 스타틴 사용을 고려한다.	IIa	C	26, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146
• 노인 환자에서는 다른 질환들이 동반되어 있을 수 있고, 약동학적 특성의 변화가 있을 수 있으므로, 지질강하제를 사용하는 경우 소량부터 시작하여 증량할 것을 권고한다.	I	D	9, 26

진료시 고려할 점 혹은 특수 상황에서의 권고 사용법 (연령별 적용, 동반이환(Comorbidity) 환자인 경우, 근거가 불충분한 권고의 적용 등)
• 심뇌혈관질환 및 당뇨병을 동반하지 않은 75세 초과 노인 환자에서 심뇌혈관질환의 일차예방을 위한 스타틴의 효과에 대한 근거는 부족하다.
• 심뇌혈관질환 및 당뇨병을 동반하지 않은 75세 초과 노인 환자에서 심뇌혈관질환의 일차예방을 위한 스타틴의 사용은 심뇌혈관질환 위험도 감소에 따른 이득, 이상약물반응, 약제상호작용, 환자의 선호도 등을 평가하여 고려할 수 있다.

5. 임신부 및 수유부에서의 이상지질혈증

권고 내용	권고등급	근거수준	참고문헌
• 임신부 또는 수유중인 여성의 이상지질혈증 치료를 위해 스타틴을 투여하지 않도록 권고한다.	I	D	26, 29, 50, 57, 147
• 임신 계획이 있는 여성 이상지질혈증 환자에서는 적어도 3개월 이전에 스타틴 복용 중단을 권고한다.	I	D	9, 51

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3. 뇌혈관질환
- stroke, TIA: statin
- 출혈성: 권고 안됨
- 인지기능 악화 방지는 근거 부족

4. 75세 이상 노인
- 노인은 소량부터 증량
- 심혈관 질환 있으면 이차예방
- 당뇨가 있는 경우는 일차예방
- 심혈관질환, 당뇨 없으면 일차예방은 benefit 고려하여

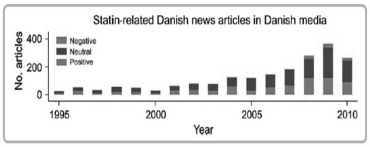
5. 임신 수유시
스타틴 투여 안함
임신 계획시 3개월 전에 중단

임상에서 흔한 질문

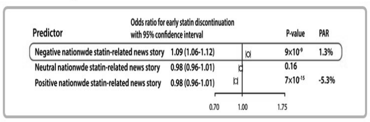
1) 고지혈증 검사를 꼭 공복에만 해야 하나요?
2) 어떤 스타틴을 처방해야 하나요?
3) 약물치료 중 LDL-C 목표에 도달하지 못할 때는 어떻게 하나요?
4) 스타틴 약이 해롭다는데 꼭 먹어야 하나요?
5) 약을 끊으면 어떻게 되나요?

Negative News => Statin discontinuation

- The number of statin news increased from 30 stories/year in 1995 to 400 stories/year in 2009



- Odds ratio for early statin discontinuation vs. continued use were 1.09 for negative statin-related news stories.



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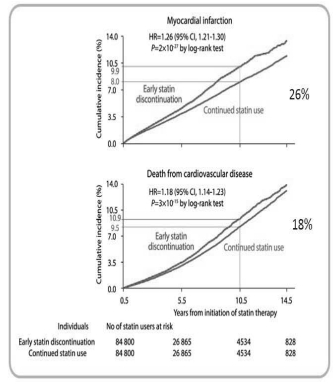
Early statin discontinuation => increase in CV risk



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3. 약제의 투여기간

권고 내용	권고등급	근거수준	참고문헌
• 이상지질혈증의 스타틴 치료는 평생 지속적으로 하도록 권고한다.	I	A	9, 10, 26, 27, 28, 29, 45
• 금연이나 10% 이상의 체중 감량 등 위험인자의 유의한 변화가 있는 경우에는 약물의 감량을 고려할 수 있다.	IIb	D	30

권고 내용	권고등급	근거수준	참고문헌
• 2회 연속 측정한 LDL-C 농도가 40 mg/dL 이하이면 스타틴 감량을 고려할 수 있다.	IIb	C	26

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