# 고지혈증의 치료전략

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## 가이드라인의 홍수


- 2011 ESC/EAS guideline
- 2013 AHA/ACCF guideline
- 2014 IAS position paper
- 2015 이상지혈증 치료지침 …

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## Guidelines

| | ATP III updates 2004 | ESC/EAS 2011 | ACC/AHA 2013 | 이상지질혈증 2015 |
|---|---|---|---|---|
| Risk assessment for primary prevention | Framingham risk model | SCORE model | ASCVD model | Risk factors |
| Targets (primary and secondary) | LDL, Non-HDL | LDL, Non-HDL, ApoB | LDL | LDL, Non-HDL |
| Goals | LDL < 70 | LDL < 70 or 50% ↓ | LDL 50% ↓ | LDL < 70 |

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## RISK ASSESSMENT AND TREATMENT TARGET & GOAL

## 2011 ESC/EAS guideline

| | Goals | | |
|---|---|---|---|
| | LDL-C (mg/dL) | Secondary target (IIa) Non HDL-C (mg/dL) | Secondary target (IIa) ApoB (mg/dL) |
| **Very High-risk patients**<br>• Documented CVD by invasive or non-invasive testing, previous **MI, ACS, coronary revascularization** (PCI or CABG) and other arterial revascularization procedures, **ischemic stroke, PAD.**<br>• **Patients with type 2 diabetes**, patients with type 1 diabetes with target organ damage (such as microalbuminuria).<br>• **Patients with moderate to severe CKD** [glomerular filtration rate (GFR) ,60 mL/min/1.73 m2).<br>• A calculated 10 year risk SCORE ≥10%. | <70 or ≥50% reduction from baseline LDL-C. | <100 | <80 |
| **High-risk patients**<br>•Markedly elevated single risk factors such as familial dyslipidemia and **severe hypertension**.<br>• A calculated SCORE ≥5% and ,10% for 10 year risk of fatal CVD. | <100 | <130 | <100 |

* For subjects at moderate risk, an LDL-C target of <3 mmol/L (less than ~115 mg/dL) should be considered.

*European Heart Journal (2011) 32, 1769–1818*

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## 2011 ESC/EAS guideline

Intervention strategies as a function of total CV risk and LDL-C level.

| Total CV risk (SCORE) % | LDL-C levels | | | | |
|---|---|---|---|---|---|
| | <70 mg/dL <1.8 mmol/L | 70 to <100 mg/dL 1.8 to <2.5 mmol/L | 100 to <155 mg/dL 2.5 to <4.0 mmol/L | 155 to <190 mg/dL 4.0 to <4.9 mmol/L | >190 mg/dL >4.9 mmol/L |
| <1 | No lipid intervention | No lipid intervention | Lifestyle intervention | Lifestyle intervention | Lifestyle intervention, consider drug if uncontrolled |
| Class[a]/Level[b] | I/C | I/C | I/C | I/C | IIa/A |
| ≥1 to <5 | Lifestyle intervention | Lifestyle intervention | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention, consider drug if uncontrolled | Lifestyle intervention, consider drug if uncontrolled |
| Class[a]/Level[b] | I/C | I/C | IIa/A | IIa/A | I/A |
| >5 to <10, or high risk | Lifestyle intervention, consider drug* | Lifestyle intervention, consider drug* | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention |
| Class[a]/Level[b] | IIa/A | IIa/A | IIa/A | I/A | I/A |
| ≥10 or very high risk | Lifestyle intervention, consider drug* | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention | Lifestyle intervention and immediate drug intervention |
| Class[a]/Level[b] | IIa/A | IIa/A | I/A | I/A | I/A |

*European Heart Journal (2011) 32, 1769–1818*

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Recommendations for the pharmacological treatment of hypercholesterolaemia.

| Recommendations | Class[a] | Level[b] | Ref[c] |
|---|---|---|---|
| Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level. | I | A | 15, 16, 17 |
| In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered. | IIa | B | 108, 120 |
| A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance. | IIb | C | - |
| If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered. | IIb | C | - |

Atherosclerosis 217S (2011) S1–S44

## 2013 ACC/AHA Guideline
### 4 Statin Benefit Groups

- Clinical ASCVD*
- LDL-C ≥190 mg/dL, Age ≥21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

*Atherosclerotic cardiovascular disease
†Requires risk discussion between clinician and patient before statin initiation
‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

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## 2013 ACC/AHA Guideline
### Primary Prevention Global Risk Assessment

- To estimate 10-year ASCVD* risk
  - New Pooled Cohort Risk Equations (ASCVD Risk Estimator)
  - age, sex, race, SBP, DBP, DM, TC, HDL-C, HT-treatment, smoking

*10-year ASVD: Risk of first nonfatal myocardial infarction, coronary heart disease death, nonfatal or fatal stroke

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## 2013 ACC/AHA Guideline
### Individuals Not in a Statin Benefit Group

- In those for whom a risk decision is uncertain, these factors may inform clinical decision making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL-C ≥160 mg/dL
  - hs-CRP ≥2.0 mg/L
  - CAC score ≥300 Agaston units
  - ABI <0.9
- Statin use still requires discussion between clinician and patient

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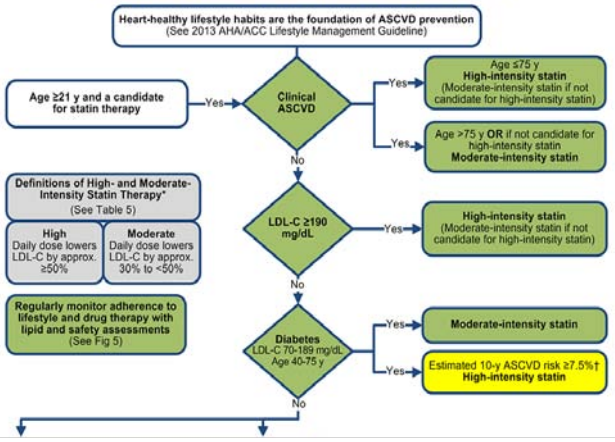
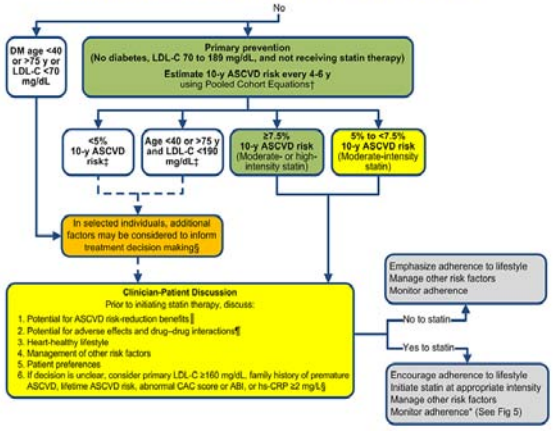
## Summary of Statin Initiation Recommendations to Reduce ASCVD Risk (Revised Figure)



## Summary of Statin Initiation Recommendations to Reduce ASCVD Risk (Revised Figure)




## Intensity of Statin Therapy

**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**<br>**Rosuvastatin 20** *(40)* **mg** | **Atorvastatin 10** *(20)* **mg**<br>**Rosuvastatin** *(5)* **10 mg**<br>**Simvastatin 20–40 mg‡**<br>**Pravastatin 40** *(80)* **mg**<br>**Lovastatin 40 mg**<br>*Fluvastatin XL 80 mg*<br>**Fluvastatin 40 mg bid**<br>*Pitavastatin 2–4 mg* | *Simvastatin 10 mg*<br>**Pravastatin 10–20 mg**<br>**Lovastatin 20 mg**<br>*Fluvastatin 20–40 mg*<br>*Pitavastatin 1 mg* |

*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 (Pedersen et al).
‡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.

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## Statin-Treated Individuals Nonstatin Therapy Considerations

- Use the maximum tolerated intensity of statin
- Consider addition of a nonstatin cholesterol-lowering drug(s)
  - If a less-than-anticipated therapeutic response persists
  - Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    - *Clinical* ASCVD <75 years of age
    - Baseline LDL-C ≥190 mg/dL
    - Diabetes mellitus 40 to 75 years of age
- Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred

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## LDL 콜레스테롤 및 non-HDL 콜레스테롤의 목표치

| 위험도 | LDL 콜레스테롤 목표 (mg/dL) | non-HDL 콜레스테롤 목표 (mg/dL) |
|---|---|---|
| 초고위험군<br>관상동맥질환<br>허혈성 뇌졸중<br>일과성 뇌허혈발작<br>말초혈관질환 | <70 | <100 |
| 고위험군<br>경동맥질환*<br>복부동맥류<br>당뇨병 | <100 | <130 |
| 중등도 위험군<br>주요위험인자 2개 이상 | <130 | <160 |
| 저위험군<br>주요위험인자 1개 이하 | <160 | <190 |

*50%가 넘는 경동맥 협착이 확인된 경우

| | 내용 | 권고 수준 | 근거 수준 |
|---|---|---|---|
| 1 | 이상지질혈증 치료의 일차 목표는 LDL 콜레스테롤이다. | I | A |
| 2 | LDL 콜레스테롤 목표 수치로 조절후 이차 목표로 non-HDL 콜레스테롤을 조절할 수 있다. | IIa | B |

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## LDL 콜레스테롤을 제외한 주요 위험인자

흡연
고혈압
  수축기혈압 140 mmHg 이상 또는 이완기혈압 90 mmHg 이상
  또는 항고혈압제 복용
저HDL 콜레스테롤(<40 mg/dL)
연령
  남자 45세 이상
  여자 55세 이상
관상동맥질환 조기 발병의 가족력
  부모, 형제자매 중 남자 55세 미만, 여자 65세 미만에서 관상동맥질환이 발병한 경우

*고HDL 콜레스테롤(60 mg/dL 이상)은 보호인자로 간주하여 총 위험인자 수에서 하나를 감하게 된다.

이상지질혈증 치료지침 3판, 2015 SNUH

## 위험도 및 LDL 콜레스테롤 농도에 따른 치료의 기준

| 위험도 | LDL 콜레스테롤 농도 | | | | |
|---|---|---|---|---|---|
| | 70–99 | 100–129 | 130–159 | 160–189 | ≥190 |
| 초고위험군*<br>관상동맥질환<br>허혈성 뇌졸중<br>일과성 뇌허혈발작<br>말초혈관질환 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 |
| 고위험군<br>경동맥질환†<br>복부동맥류<br>당뇨병 | 생활습관 개선 및 투약고려 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 |
| 중등도 위험군‡<br>주요위험인자 2개 이상 | 생활습관 개선 | 생활습관 개선 및 투약고려 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 |
| 저위험군‡<br>주요위험인자 1개 이하 | 생활습관 개선 | 생활습관 개선 | 생활습관 개선 및 투약고려 | 생활습관 개선 및 투약시작 | 생활습관 개선 및 투약시작 |

*급성심근경색 발생 시 기저치의 LDL 콜레스테롤 농도와 상관 없이 바로 스타틴을 투약한다. 급성심근경색 이외의 초고위험군의 경우 LDL 콜레스테롤 70 mg/dL 미만에서도 스타틴 투약을 고려할 수 있다.
†50%가 넘는 경동맥 협착이 확인된 경우
‡중등도 위험군과 저위험군의 경우는 수주 혹은 수개월간 생활습관 개선을 시행한 뒤에도 LDL 콜레스테롤 농도가 높을 시 스타틴 투약을 고려한다.

이상지질혈증 치료지침 3판, 2015 SNUH

## Non-LDL target

(3) 고중성지방혈증

| | 내용 | 권고 수준 | 근거 수준 |
|---|---|---|---|
| 1 | 중성지방이 500 mg/dL 이상인 경우 급성췌장염의 예방을 위한 즉각적인 중성지방을 낮추는 약물치료와 생활습관 개선이 중요하다. | I | A |
| 2 | 중성지방이 200–499 mg/dL인 경우, 먼저 일차적인 치료목표는 계산된 심혈관계 위험도에 기반하여 LDL 콜레스테롤을 목표치까지 낮추는 것이다. | I | A |
| 5 | 적응증에 해당하는 경우 중성지방 조절을 위한 약제는 피브린산 유도체를 사용한다. | I | B |
| 6 | 적응증에 해당하는 경우 중성지방 조절을 위한 약제는 니코틴산을 사용한다. | IIa | B |
| 7 | 적응증에 해당하는 경우 중성지방 조절을 위한 약제는 오메가-3 지방산을 사용한다. | IIa | B |

(4) 저HDL 콜레스테롤혈증

| | 내용 | 권고 수준 | 근거 수준 |
|---|---|---|---|
| 1 | 일차 치료목표는 LDL 콜레스테롤을 목표 수치 이하로 조절하는 것이다. | I | A |
| 2 | HDL 콜레스테롤을 높이기 위해 니코틴산을 사용할 수 있다. | IIa | A |
| 3 | HDL 콜레스테롤을 높이기 위해 피브린산을 사용할 수 있다. | IIb | B |

*이상지질혈증 치료지침 3판, 2015* SNUH

## CASE SERIES

## MONITORING AND MANAGEMENT OF ADVERSE REACTION

## Monitoring

- Adherence
- Lipid profile
- Liver enzyme: X3 ULN
- CK: x5 ULN
- Muscle symptom: mild-moderate vs. severe

- 4-12week interval

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## NEW LIPID LOWERING AGENTS

## Mipomersen

- antisense oligonucleotide inhibitor that targets apolipoprotein B-100
- an adjunct to maximally tolerated lipid-lowering medications and diet for the treatment of patients with homozygous FH
- variability in LDL lowering, worries about malignancies, immune-mediated reactions, and hepatic abnormalities

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## Lomitapide

- microsomal triglyceride transfer protein (MTP) inhibitor
- an adjunct to a low-fat diet and other lipid-lowering treatments in patients with homozygous FH
- risk of hepatotoxicity

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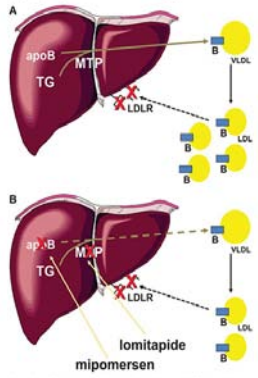
A, Very-low-density lipoprotein (VLDL) assembly involves the loading of triglycerides (TG) onto apolipoprotein B (apoB) by microsomal triglyceride transfer protein (MTP).



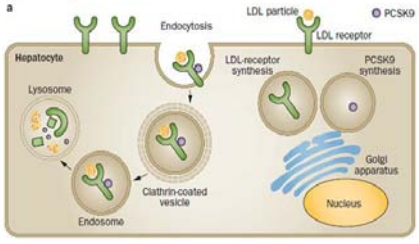

Daniel J. Rader, and John J.P. Kastelein Circulation. 2014;129:1022-1032

American Heart Association.



## PCS K9 inhibitors

- Alirocumab, Evolocumab…
  - Proprotein convertase subtilisin/kexin type 9 (PCSK9): recently discovered target (2003)
  - PCS K9: bind to LDL receptor and modulate LDL receptor cycle




Nat. Rev. Cardiol. 11, 563–575 (2014)

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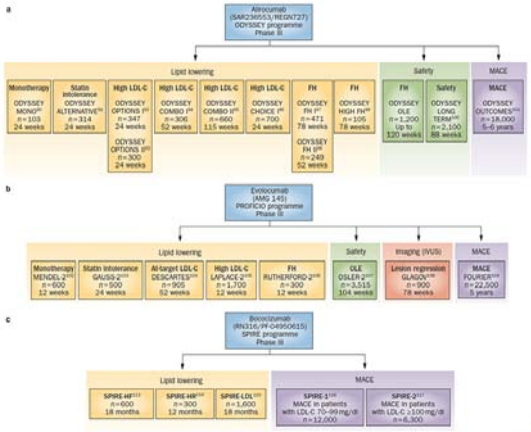
## Clinical trials of PCS K9 inhibitors

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