2012 대한임상건강증진학회 춘계 통합학술대회 / 연수강좌

일차진료에서 이상지질혈증 치료 Up-to-date

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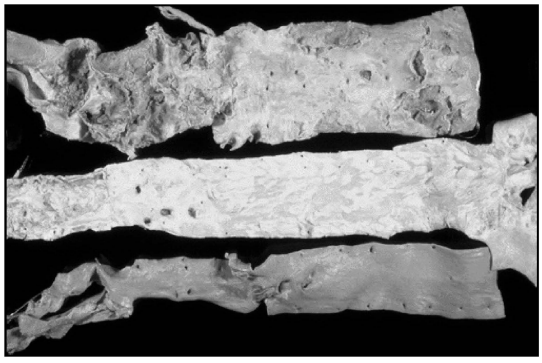
선우성



권고사항 1

- 20세 이상 성인은 5년에 1회 이상 12시간 공복상태에서 혈청 지질농도(총콜레스테롤, 중성지방, HDL콜레스테롤 및 LDL 콜레스테롤)를 측정한다.

권고사항 2

- 관상동맥질환이나 이에 상응하는 위험도를 가진 질환 군을 파악한다. 여기에는 복부 대동맥류, 말초혈관질환, 증상이 있는 경동맥 질환, 당뇨병 등이 해당한다.

권고사항 3

- LDL콜레스테롤이 높은 것 이외의 심혈관계 질환에 대한 위험요소를 파악한다.
  1. Aging (male ≥ 45 years, female ≥ 55 years),
  2. Hypertension(≥140/90mmHg or HT 치료 중)
  3. Smoking,
  4. Family history of coronary artery disease(남자55세 미만, 여자 65세 미만 직계 가족에서 관상동맥질환)
  5. Low HDL cholesterol (<40mg/dL)
  - ○ 높은 HDL 콜레스테롤 (≥60 mg/dL)은 보호인자로 간주하여 총 위험인자 수에서 하나를 감한다.

Back to the conventional risk factors!

Risk Factors for CHD

- Modifiable
  - Dyslipidemia
    - Raised LDL
    - Low HDL
    - Raised TGs
  - Smoking
  - Hypertension
  - Diabetes mellitus
  - Obesity
  - Dietary factors
  - Thrombogenic factors
  - Sedentary lifestyle
- Nonmodifiable
  - Age
  - Sex
  - Family history of premature CHD

LDL-C is the primary target to prevent CHD

Wood D, et al. *Atherosclerosis.* 1998;140:199-270.

권고사항 4

- 고LDL콜레스테롤혈증 치료목표를 위해 위험도에 따라 환자군을 분류하고 LDL 콜레스테롤 목표치를 정한다.

위험도	LDL 콜레스테롤 목표 (mg/dL)	비HDL 콜레스테롤 목표 (mg/dL)
고위험군 (관상동맥질환, 또는 그에 상당하는 위험) 관상동맥질환, 경동맥질환, 말초혈관질환, 복부동맥류, 당뇨병	<100	<130
중등도 위험군 주요 위험인자 2개 이상	<130	<160
저위험군 주요 위험인자가 없거나 1개	<160	<190

LDL Cholesterol

Remains the cornerstone of dyslipidemia therapy[1]

Strongly associated with atherosclerosis and CHD events[1]

10% increase results in a 20% increase in CHD risk[1]

Most patients with elevated LDL untreated

Only 4.5 million out of 28.4 million treated[2,3]

1. Wood D et al. Atherosclerosis. 1998;140:199-270.
2. National Centre for Health Statistics. National Health and Nutrition Examination Survey (III), 1994.
3. Jacobson TA, et al. Arch Intern Med. 2000;160:1361-1369.

NCEP ATP III LDL-C Goals

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)	≥100 mg/dL	≥100 mg/dL (<100 mg/dL: consider drug options)
Moderately high risk: 2+ risk factors (10-year risk 10% to 20%)	<130 mg/dL	≥130 mg/dL	≥130 mg/dL (100-129 mg/dL: consider drug options)
Moderate risk: 2+ risk factors (10 year risk <10%)	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0-1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

Grundy, S. et al., *Circulation* 2004;110:227-39.

2011 ESC/EAS Tightens up lipid Targets for Dyslipidemia with New Recommendations

Risk category	LDL-C goal	Evidence
Very High CV Risk: Known CVD, T2DM or T1DM with microalbuminuria, CKD, SCORE level: ≥10%	~70 mg/dl and/or ≥ 50% reduction in level when target level cannot be reached	Class I, A
High CV Risk: Very high levels of individual risk factors, SCORE level: ≥5% and <10%	~100 mg/dl	Class IIa, A
Moderate Risk: SCORE level: ≥5% and <10%	~115 mg/dl	Class IIa, C

권고사항 5

- LDL콜레스테롤이 목표치 보다 높을 때 치료적 생활양식 변화를 시작하며 3개월 이후에도 목표치 보다 높을 때는 약제를 투여한다.

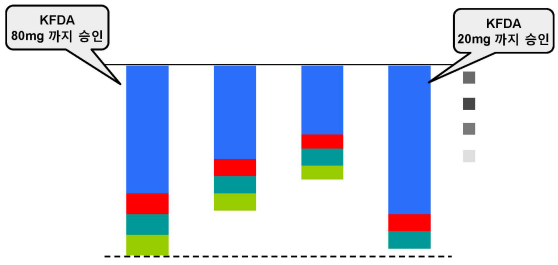
권고사항 6

- 중등도 이상의 위험요소를 가진 사람은 관상동맥질환과 뇌졸중 위험을 감소시키기 위해 생활양식 개선과 동시에 약제(스타틴)를 사용한다. 스타틴은 최소한도 LDL콜레스테롤을 30-40%이상 감소시키도록 약제를 선택한다. 또한 위험요소가 높은 고위험군은 목표에 빠른 도달을 위해 초기부터 약제의 강도가 높거나 용량을 높여 사용한다.

	Dose range (%LDL cholesterol reduction)*	Metabolism	Most important drug interaction increasing myopathy risk†
Lovastatin	20-80mg daily (30% with 40mg)	Mainly CYP3A4	Potent inhibitors of CYP3A4‡
Simvastatin	10-80mg daily (41% with 40mg)	Mainly CYP3A4	Potent inhibitors of CYP3A4
Pravastatin	20-80mg daily (34% with 40mg)	Sulphation, biliary and urinary excretion	
Fluvastatin	40-80mg daily (23% with 40mg)	CYP2C9(some CYP2C8 and CYP3A4)	Inhibitors of CYP2C9
Atorvastatin	10-80mg daily (38% with 10mg)	CYP3A4	Potent inhibitors of CYP3A4
Rosuvastatin	5-40mg daily (45% with 10mg)	Minimal metabolism(via CYP2CP and some CYP2C19), and biliary excretion	
Pitavastatin	2-4mg daily (42% with 2mg)	Minimal metabolism(via CYP2C8 and CYP2C9), lactonisation, and biliary excretion	Unclear

*Typically, doubling of a statin dose produces an additional 6% absolute decrease in LDL cholesterol—eg, simvastatin 20 mg daily reduces LDL by 35% and 40 mg daily by 41%. †With all statins, the risk of myopathy is also increased by ciclosporin and gemfibrozil, and possibly other fibrates; prescribing information will provide further details and other interactions. ‡Including itraconazole, ketoconazole, erythromycin, clarithromicin, telithromycin, nefazodone, HIV protease inhibitors, and regular ingestion of grapefruit juice. Information from relevant Data Sheets 9

LDL-C Efficacy Meta-analysis of Statins



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Source: Law et al. *BMJ*. 2003;326:1423.

CV outcomes studies demonstrating significant primary endpoint

	Primary Prevention				Secondary prevention		
	High-cholesterol with multiple risk factor	ELEVATED CRP and low/normal LDL-C	Hypertension +multiple risk factors	Type 2 Diabetes	Stable CHD	Stroke/TIA	ACS
Atorvastatin			ASCOT-LLA	CARDS	GREACE ALLIANCE TNT	SPARCL	MIRACL PROVE IT
Rosuvastatin		JUPITER					
Simvastatin				HPS-DM	4S		A TO Z
Pravastatin	WOSCOPS				CARE LIPID		

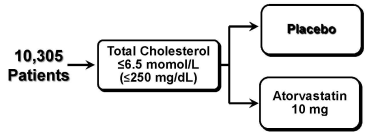
The benefit of statin: Primary & Secondary prevention

Primary Prevention

ASCOT-LLA

The Anglo-Scandinavian
Cardiac Outcomes Trial-Lipid Lowering Arm

ASCOT-LLA: Study Design



Patient Population

- Age 40–79 years
- Hypertension plus 3 or more risk factors including age, smoking, family history of CHD, or low HDL
- TC ≤6.5 mmol/L (250 mg/dL)

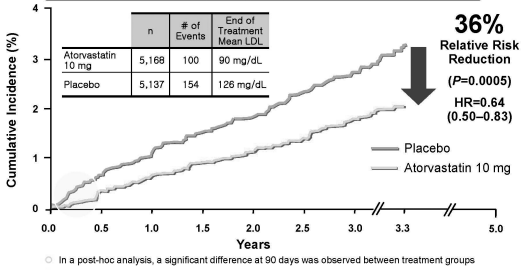
Composite Primary End Point

- Combined end point of:
  - Nonfatal MI
  - Fatal CHD

Adapted from Sever PS, et al. *Lancet.* 2003;361:1149-1158.

ASCOT-LLA Primary End Point: Nonfatal MI and Fatal CHD

The Event Curves Separate as Early as 90 Days and Diverge Over Time



	n	# of Events	End of Treatment Mean LDL
Atorvastatin 10 mg	5,168	100	90 mg/dL
Placebo	5,137	154	126 mg/dL

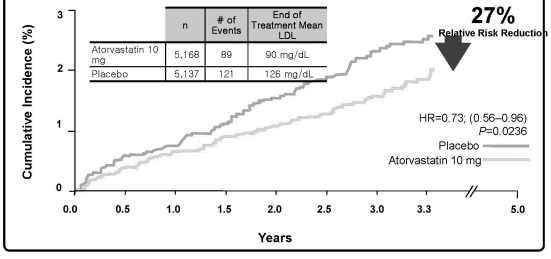
- In a post-hoc analysis, a significant difference at 90 days was observed between treatment groups
- Due to a significant reduction in the primary end point, the trial was stopped after only 3.3 years, nearly 2 years earlier than expected

HR = hazard ratio

Adapted from Sever PS, et al. *Lancet.* 2003;361:1149-1158.

ASCOT-LLA : Atrovastatin reduces significantly 27% of stroke risk

Atorvastatin Lowers Stroke Risk in Patients with Treated Blood Pressure Above and Beyond those Achieved with Antihypertensive Therapy Alone[2]



	n	# of Events	End of Treatment Mean LDL
Atorvastatin 10 mg	5,168	89	90 mg/dL
Placebo	5,137	121	126 mg/dL

- Due to a significant reduction in the primary end point, the trial was stopped after only 3.3 years

1. Data on File, Pfizer Inc.
2. Adapted from Sever PS, et al. *Lancet.* 2003;361:1149-1158.

HR = hazard ratio

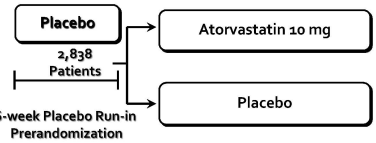
The benefit of statin: Primary & Secondary prevention

Primary Prevention

CARDS

The Collaborative AtoRvastatin Diabetes Study

CARDS : Study Design



Patient Population

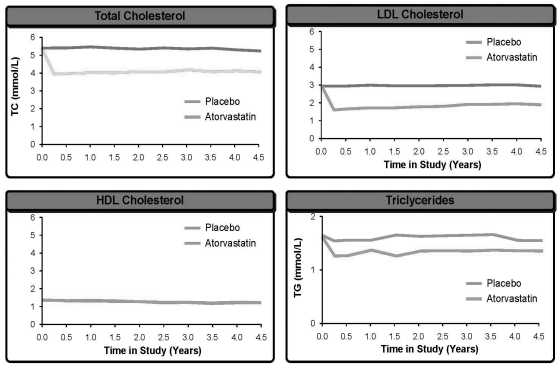
- Type 2 diabetes with no clinically evident CHD
- ≥1 other CHD risk factor (smoking, hypertension, albuminuria, retinopathy) plus LDL-C ≤ 4.1 mmol/L (160 mg/dL) and TG ≤ 6.8 mmol/L (600 mg/dL)
- Aged 40–75 years

Composite Primary End Point

- First occurrence of:
  - acute CHD event
  - coronary revascularization procedure
  - Stroke

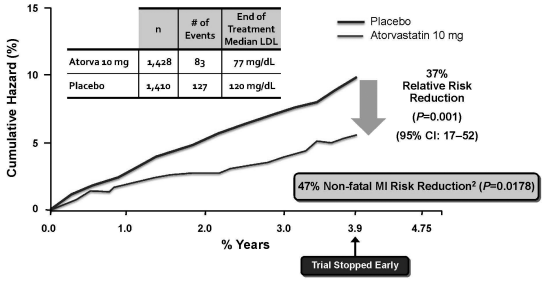
Adapted from Colhoun HM, et al. *Diabet Med.* 2002;19:201-211.

CARDS : TC, LDL-C, HDL-C and TG Levels



Adapted from Colhoun HM, et al. *Lancet.* 2004;364:685-696.

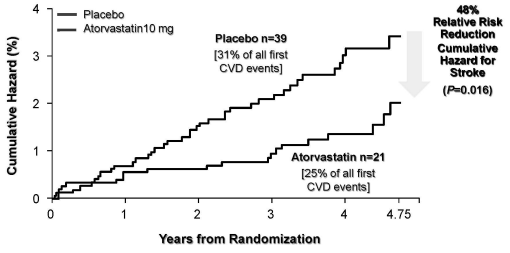
CARDS : Primary End Point – Major CV Events*
Acute Coronary Heart Disease Events, Coronary Revascularization, or Stroke



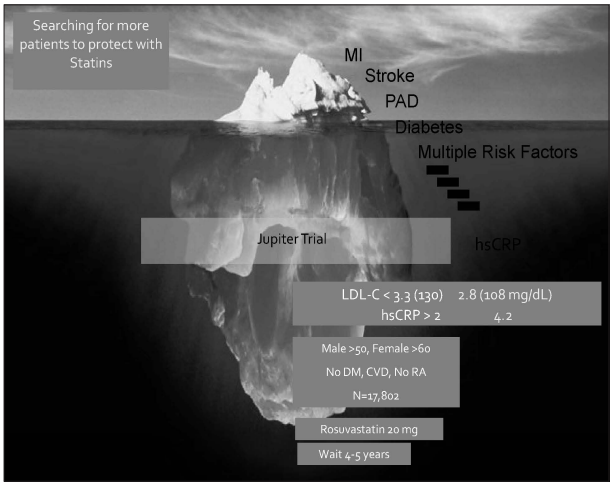
○ The study was stopped 2 years earlier than anticipated after a median follow up of 3.9 years, due to beneficial effect of atorvastatin
○ The results were similar in patients with LDL-C <120 mg/dL (3.1 mmol/L) and ≥120 mg/dL (3.1 mmol/L)

1. Adapted from Colhoun HM, et al. *Lancet*. 2004;364:685-696.
2. Data on File, Pfizer Inc.

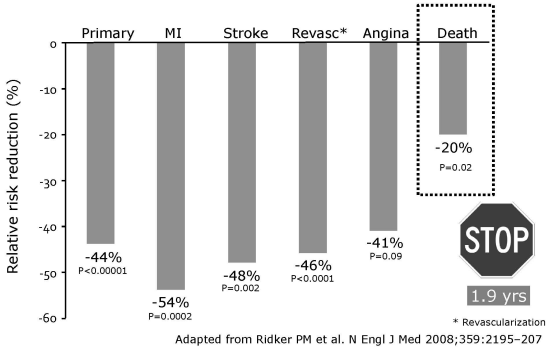
CARDS : Cumulative Hazard for Stroke



Adapted from Newman C, et al. Presented at: American Heart Association 2005 Scientific Sessions; November 13-16, 2005; Dallas, TX.



JUPITER Trial: Results



* Revascularization

Adapted from Ridker PM et al. N Engl J Med 2008;359:2195-207

The benefit of statin: Primary & Secondary prevention

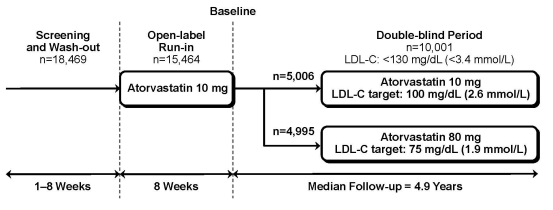
Secondary Prevention

TNT

The Treating to New Targets

The first randomized trial designed to demonstrate the benefits of lowering LDL-C well below 100 mg/dL (2.6 mmol/L) in stable CHD patients

TNT : Study Design

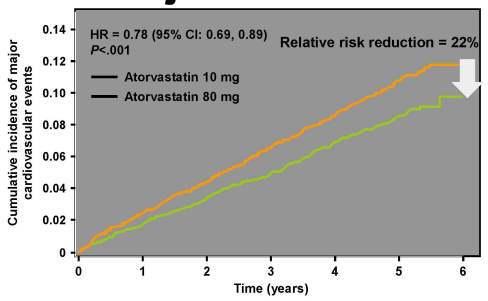


○ CHD
○ LDL-C: 130-250 mg/dL (3.4-6.5 mmol/L)
○ Triglycerides ≤600 mg/dL (≤6.8 mmol/L)

Primary Efficacy Outcome Measure

○ Time to occurrence of a major CV event:
- CHD death
- Nonfatal, non–procedure-related MI
- Resuscitated cardiac arrest
- Fatal or nonfatal stroke

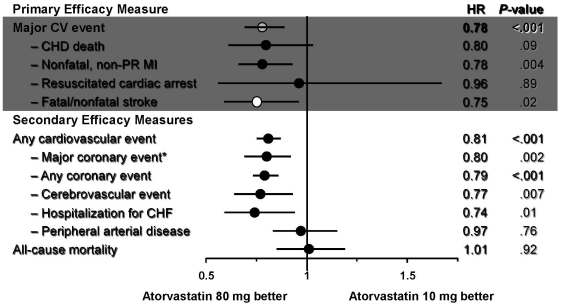
Primary Efficacy Outcome Major CV Events*



*CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

LaRosa JC et al. *N Engl J Med.* 2005;352:1425-1435.

Primary and Secondary Efficacy Outcome Measures: Hazard Ratios



TNT SAFETY

	No. of Patients (%)	
	Atorvastatin 10 mg (n=5006)	Atorvastatin 80 mg (n=4995)

AE = adverse events; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal

- No cases were considered by investigator with direct responsibility for the patients to be causally related to Atorvastatin

LaRosa JC et al. *N Engl J Med.* 2005;352:1425-1435.

Statin Clinical End-Point Trials

P: positive, N: negative

Drugs	Stable CAD	ACS	Stroke	HTN	Diabetes	High CRP
Pravastatin	P	N	-	N	-	-
Simvastatin	P	N	N	-	P	-
Fluvastatin	P	N	-	-	-	-
Pitavastatin	-	-	-	-	-	-
Rosuvastatin	-	-	-	-	-	P
Atorvastatin	P	P	P	P	P	-

MIRACL, CARDS, PROVE-IT, ALLIANCE, 4D, ASCOT-LLA, IDEAL, TNT, SPARCL...

Many medicines are used based on the fact that they improve the numbers (LDL-c, HDL-c, CRP, Plaque Volume, etc), but this doesn't mea necessarily mean there will be a reduction in the risk for disease

Adverse effects of statin use

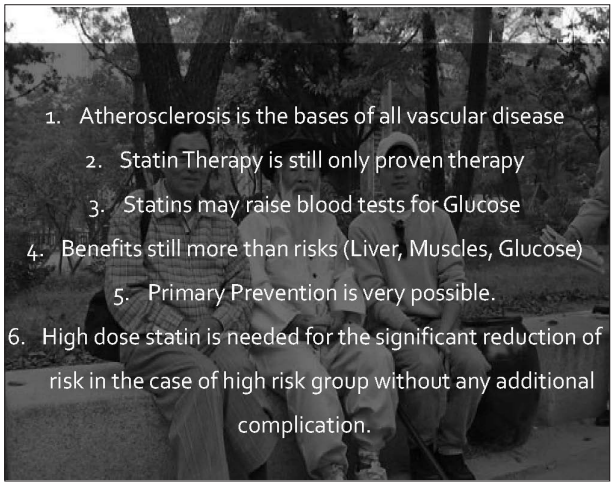
- 소화장애, 속쓰림, 복통 등의 비특이적인 증상으로 나타나며, 복용환자의 약 4%
- 간 효소치의 상승(0.5~2.0%)과 근육병증(0.1%)
- 최고 용량을 투여하지 않는다면 간기능 장애나 근육병증 등의 발생은 거의 없다.
- 그러나 80세 이상의 고령, 여러 기관의 기능저하 상태, 다양한 약물 복용을 할 때는 스타틴 투여 시 고용량 투여군에서는 안정성 확인에 더 많은 주의

스타틴 사용에 따른 부작용 대처법

- 간기능 검사는 치료 시작 전과 시작 12주 후에 시행한다. 용량이 정해지고 난 후에는 정기적으로 시행한다.
- 간기능 수치가 상한치의 3배가 넘으면 다른 원인을 찾을 동안 용량을 줄이거나 중단한다.
- CK 수치는 무증상 환자에게는 치료시작 전이나 일상적으로는 측정하지는 않는다. 간기능 검사 시 함께 측정하면 충분하다
- CK 수치가 10배 이상 또는 10,000 IU/L 이상이면 정맥수액요법을 위해 입원해서 신장기능을 관찰하고 횡문근융해증(rhabdomyolysis)을 치료한다.
- 스타틴을 사용하는 환자에서 혈청 크레아틴과 단백뇨의 일상적인 측정이 필요하지는 않다.
- 스타틴 치료하는 동안 크레아틴이 상승하면 치료 용량을 조절한다.
- 단백뇨가 검출되면 용량조절을 고려한다.

Statins 요약

- 약제: Lovastatin, Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, Rosuvastatin, Pitavastatin
- 지질개선효과
  - LDL 콜레스테롤 20 ~ 60% 감소
  - HDL 콜레스테롤 5 ~ 15% 증가
  - 중성지방 10 ~ 30% 감소
- 효과: 관상동맥질환, 뇌졸중, 심혈관계 질환 사망률 및 총 사망률의 감소
- 금기
  - 절대금기: 활동성 간질환, 임신, 수유
  - 상대금기: 타약제 병용 주의 약물 (Azol-antifungals, Macrolides, Fibrates, Cyclosporin 등)
- 안전성: 부작용은 적음
- 부작용: 간 독성, 근육병증
- 복용법:
  - Lovastatin(20 ~ 80 mg/일) 저녁식사와 함께 복용
  - Pravastatin(5 ~ 40 mg/일), Simvastatin(20 ~ 80 mg/일), Fluvastatin(20 ~ 80 mg/일) 자기 전에 복용
  - Atorvastatin(10 ~ 80 mg/일), Rosuvastatin(5 ~ 20 mg/일), Pitavastatin(1 ~ 2 mg/일) 복용시간에 큰 영향을 받지 않음



권고사항 7

- LDL콜레스테롤이 목표에 도달한 후에는 non-HDL콜레스테롤을 목표로 한다. 만일 non-HDL콜레스테롤이 목표에 도달하지 않으면 병합요법을 고려한다. 병합요법은 스타틴에 피브린산 유도체, 니코틴산, 오메가 3 지방산 등을 사용한다.

권고사항 8

- 중성지방 농도가 높은 경우에 우선 중성지방을 높일 수 있는 이차적 원인을 찾아서 교정해야 하며, 중성지방 농도에 따라 치료방침을 정한다.

Serum TG category		ATP III Treatment Goals
Borderline high	150-199 mg/dL	Achieve LDL-C goal
High	200-499 mg/dL	Primary: Achieve LDL-C goal Secondary: Achieve non-HDL-C goal (30 mg/dL above LDL-C goal)
Very high	≥500 mg/dL	Primary: Prevent pancreatitis Secondary: Prevent CHD

Effect of various pharmacologic therapies on lipoprotein levels.

Drug	TC	LDL-C	HDL-C	TG
Statin	↓15-60%	↓20-60%	↑ 3-15%	↓10-40%
Niacin	↓ 25%	↓10-15%	↑15-35%	↓20-50%
Fibrate	↓ 15%	↓0-15%	↑6-15%	↓20-50%
Fish oil	↑or neutral	↑or neutral	↑or neutral	↓20-50%
Ezetimibe	↓ 12%	↓ 18%	↑ 1%	↓ 8%

CLINICAL CONSIDERATIONS WHEN ADDING A SECOND AGENT TO STATIN THERAPY FOR TX OF MIXED DYSLIPIDEMIA

Agent	Baseline Lab. Needed	Potential Adverse Effects to Monitor
Fibrates	LFT, BUN/Cr Consider CK	Gallstone, increased AST/ALT: Myopathy/rhabdomyolysis
Niacin	LFT, glucose, Uric acid	Increased AST/ALT, DM, Gout, Flush
Ezetimibe	LFT	Increased AST/ALT
Omega-3 FA	None	GI symptoms Interaction with warfarin, aspirin?

** Omega-3 FA reduce CAD event irrespective of their effect on TG level

Nicotinic acid 요약

- 약제 : Nicotinic acid, Acipimox, ER niacin/laropiprant
- 지질개선 효과:
  - LDL 콜레스테롤 15~18% 감소
  - HDL 콜레스테롤 15~35% 증가
  - 중성지방 20~50% 감소
- 효과: 관상동맥질환의 감소
- 금기:
  - 절대금기: 간질환이나 심한 통풍
  - 상대금기: 당뇨병, 고요산혈증, 소화성 궤양질환
- 안전성: 서방형 제제(SR) 사용 시 간독성
- 부작용: 피부 홍조, 소화장애, 간독성, 통풍, 혈당 상승
- 복용법:
  - Sustained release nicotinic acid 1~2 g/일
  - Extended release nicotinic acid 1~2 g/일 취침 전, 단계적 증량
  - ER niacin/laropiprant 1 g/20 mg, 2 g/40 mg/일 저녁 또는 취침 전, 단계적 증량

Fibrates 요약

- 약제: *Bezafibrate, Ciprofibrate, Gemfibrozil,* **Fenofibrate**
- 지질개선 효과
  - LDL 콜레스테롤 10~20% 감소
  - HDL 콜레스테롤 10~15% 증가
  - 중성지방 25~50% 감소
- 효과: 관상동맥질환의 감소
- 절대금기: 심한 간질환이나 신부전, 담석
- 안전성: 부작용은 적음, 스타틴과 병용 시 주의
- 부작용: 담석, 근육병증
- 복용법:
  - Fenofibrate : 160~200 mg/일 식후 즉시

Omega-3 fatty acid 요약

- 지질개선 효과:
  - LDL 콜레스테롤 별다른 영향 없음
  - HDL 콜레스테롤 별다른 영향 없음
  - 중성지방 8~30% 감소
- 효과: 관상동맥질환의 감소
- 금기: 없음
- 안전성: 부작용은 적음
- 부작용: 생선비린내(구역 시), 피부 발진
- 복용법: omega-3 fatty acid 1~4 g/d