Combination Therapy for Dyslipidemia

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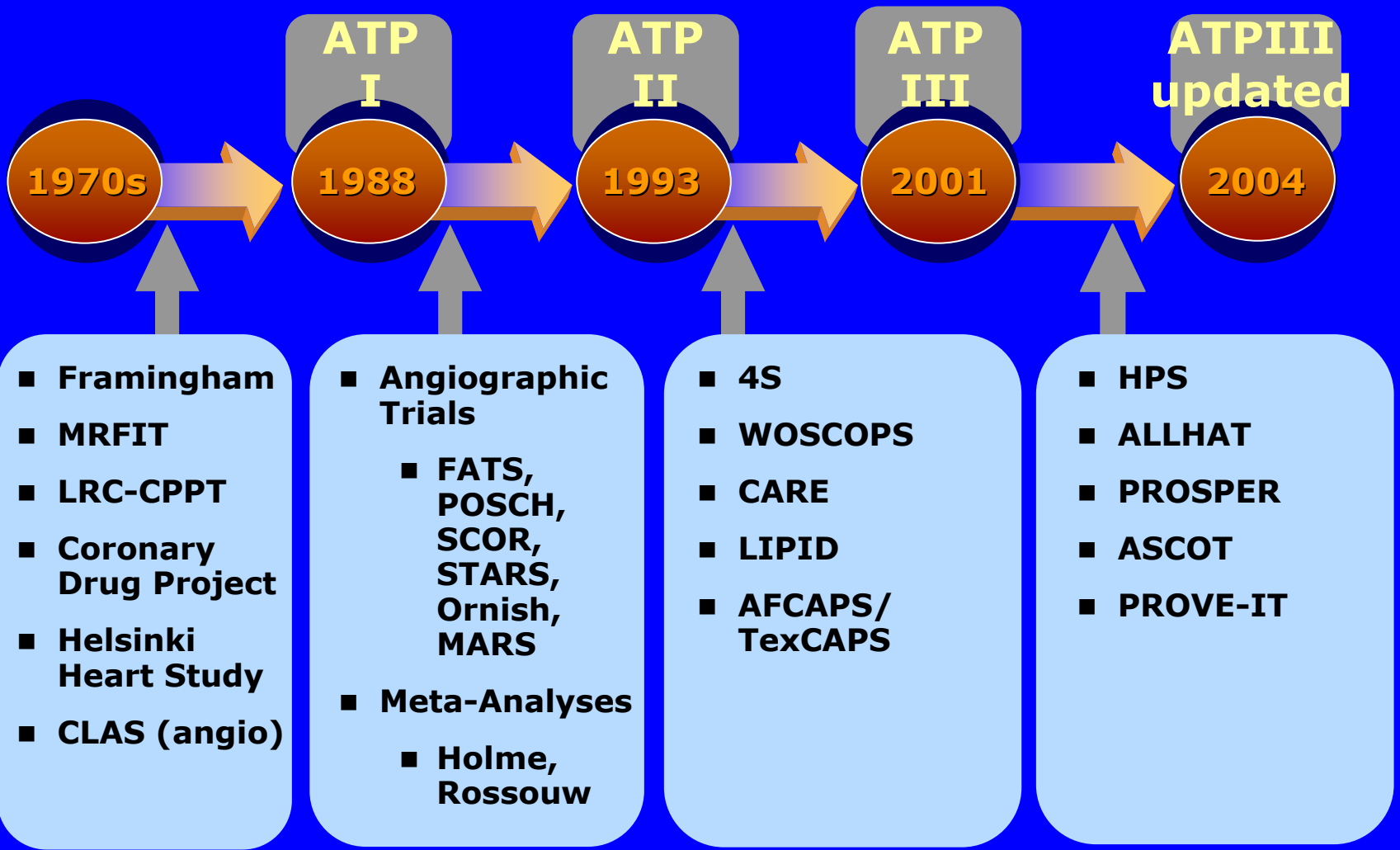
서 홍 석

Evolution of Guidelines



Determinants of Cholesterol Levels

- **Sources**
  - Intestinal cholesterol absorption
  - Peripheral cholesterol synthesis
  - Hepatic cholesterol synthesis
- **Modifying factors**
  - Genetic predisposition
  - Diet/Lifestyle
  - Drug therapies
  - Enzymatic regulation
  - Overweight
  - Smoking
  - Physical activity

Different actions of lipid-altering drugs may have complementary actions in lowering LDL-C

Options in Lipid-Lowering Therapy

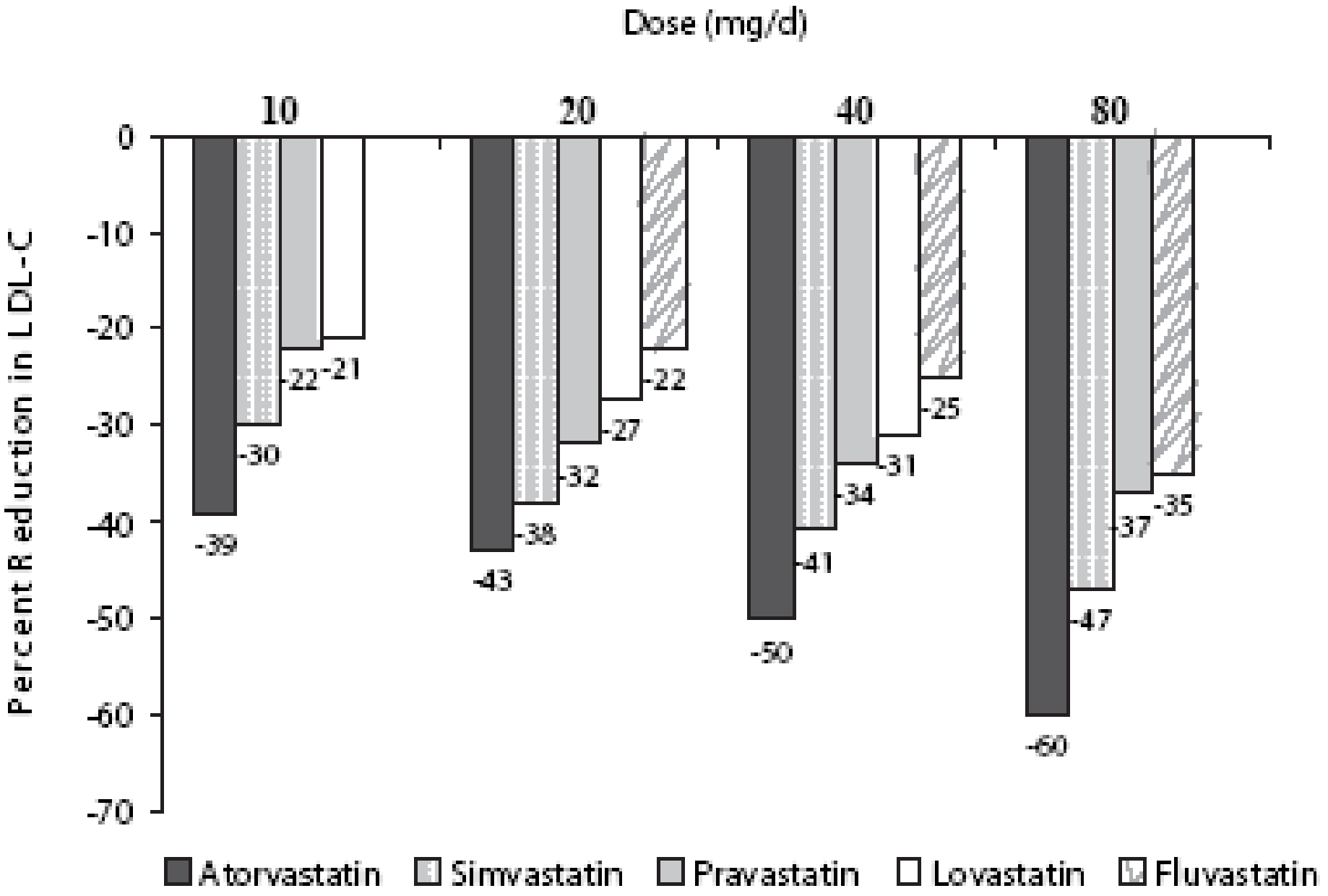
- Therapeutic lifestyle change (TLC)
  - Smoking cessation
  - Diet, including plant stanols/sterols, fish oils, and fiber
  - Weight reduction, physical activity
- Statins
  - Mainstays of drug treatment in both primary and secondary prevention

NCEP ATP III. *Circulation*. 2002;106:3143-3421.

Options in Lipid-Lowering Therapy (Cont'd)

- Bile acid sequestrants (resins)[1]
- Fibrates[1]
- Niacin[1]
- Cholesterol absorption inhibitors[2]
- Combination therapies[1]

1. NCEP ATP III. *Circulation.* 2002;106:3143-3421.
2. McKenney J. *Am J Cardiol.* 2002;90(suppl):8K-20K.



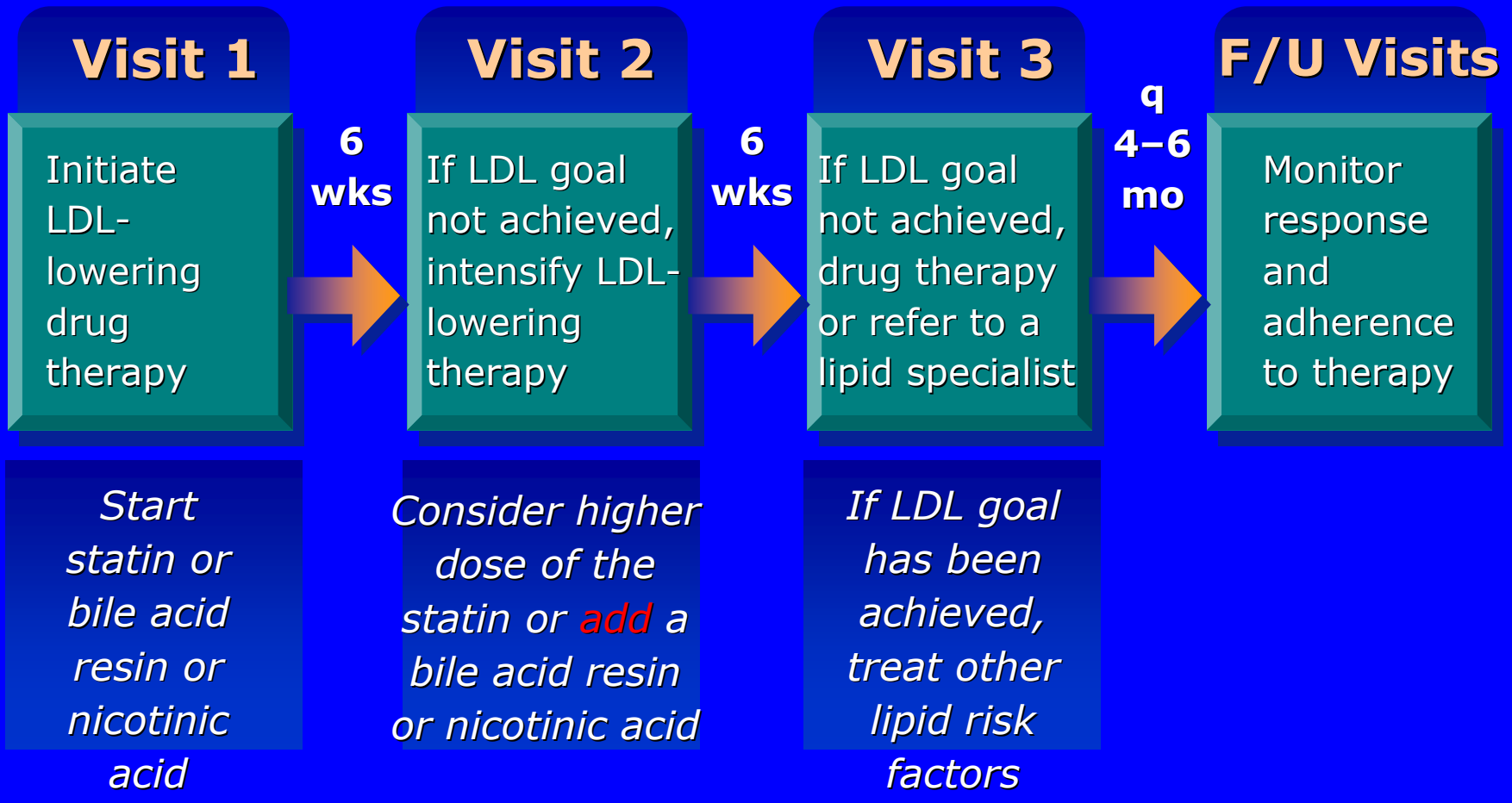
Source: Cardiovasc Rev Rep © 2004 Le Jacq Communications, Inc.

Effects of Drug Classes on Serum Lipids

	TC	LDL	HDL	TG
Resins	↓20%	↓10%–20%	↑3%–5%	Variable
Ezetimibe	↓20%	↓10%–20%	↑3%–5%	Variable
Nicotinic acid	↓25%	↓10%–15%	↑15%–35%	↓20%–50%
Fibrates	↓15%	Variable	↑6%–15%	↓20%–50%
Statins	↓15%–60%	↓20%–60%	↑3%–15%	↓10%–40%
Fish Oil (PUFA)	None	None	?? ↓ 3%	↓25%–35%

Adapted from Gotto AM Jr. Management of lipid and lipoprotein disorders. In: Gotto AM Jr, Pownall HJ, eds. Manual of lipid disorders. Baltimore: Williams & Wilkins; 1992; Rubins HB, et al. N Engl J Med. 1999;341:410–418

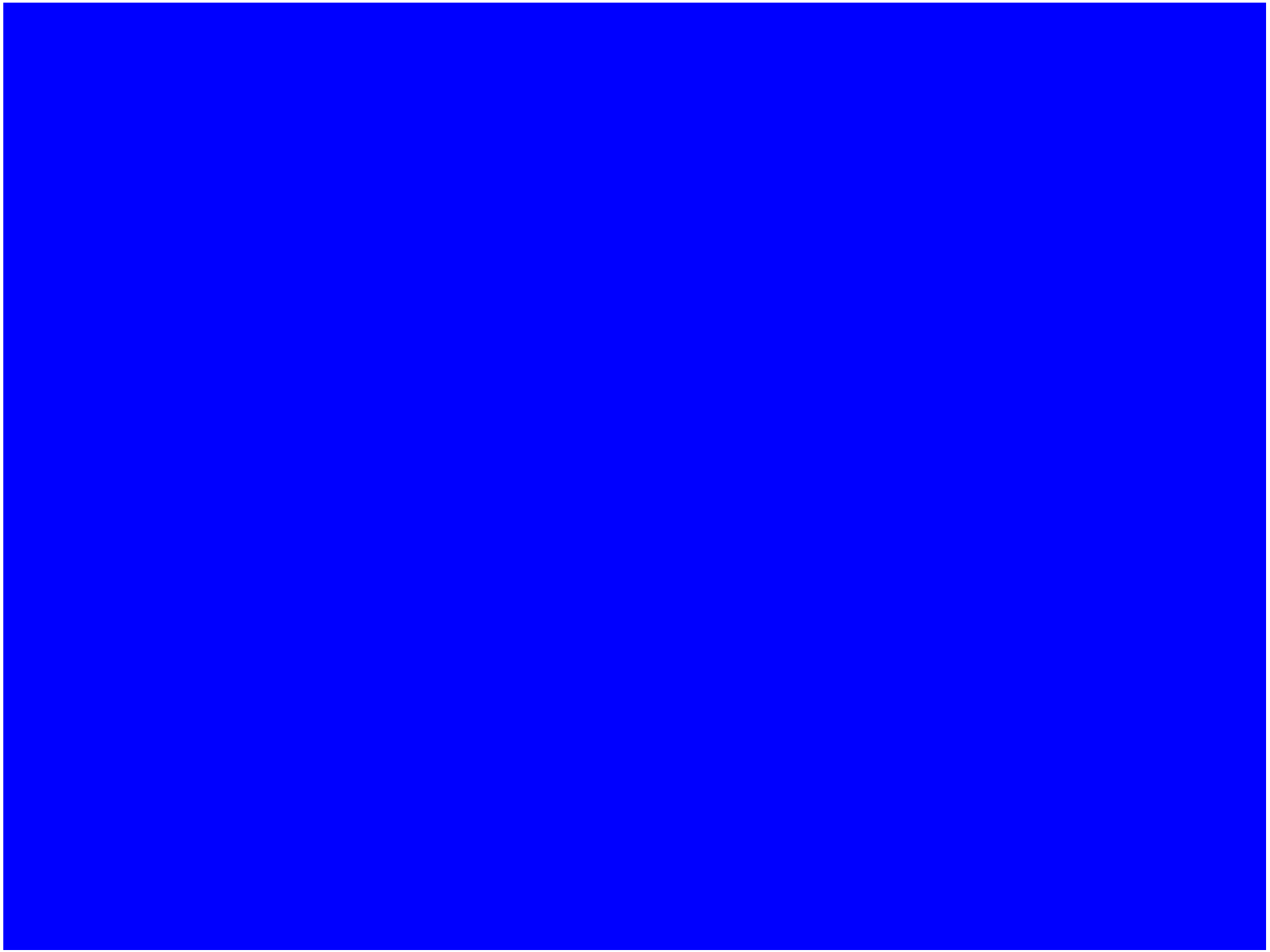
Progression of Drug Therapy for LDL-C Lowering



Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486-2497.

Candidates for Combination Therapy

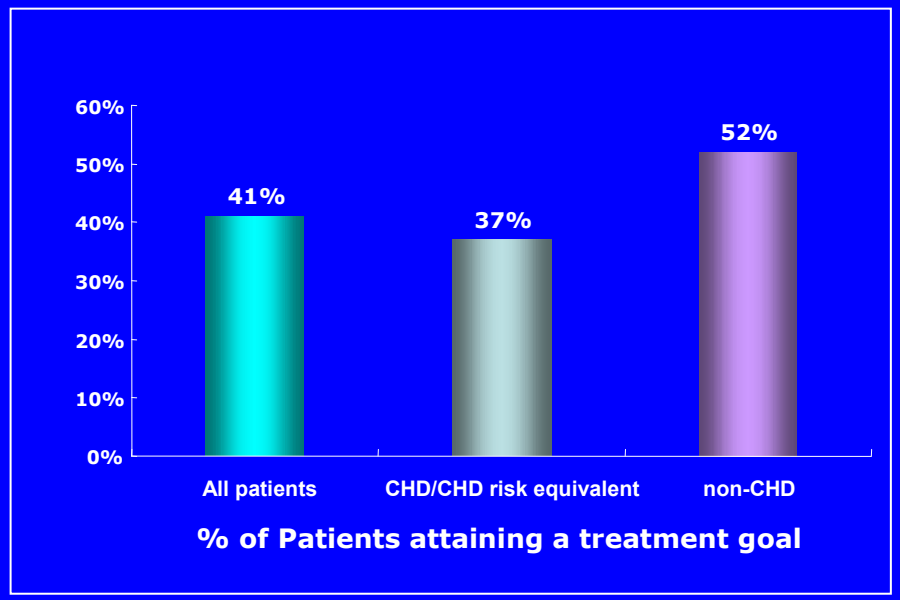
- Patients who
  - Are unable to treatment goals with a single lipid-altering drug treatment
  - Are at risk for intolerance, toxicity, or adverse drug interactions with a higher dose of a single drug therapy
  - Have mixed dyslipidemias



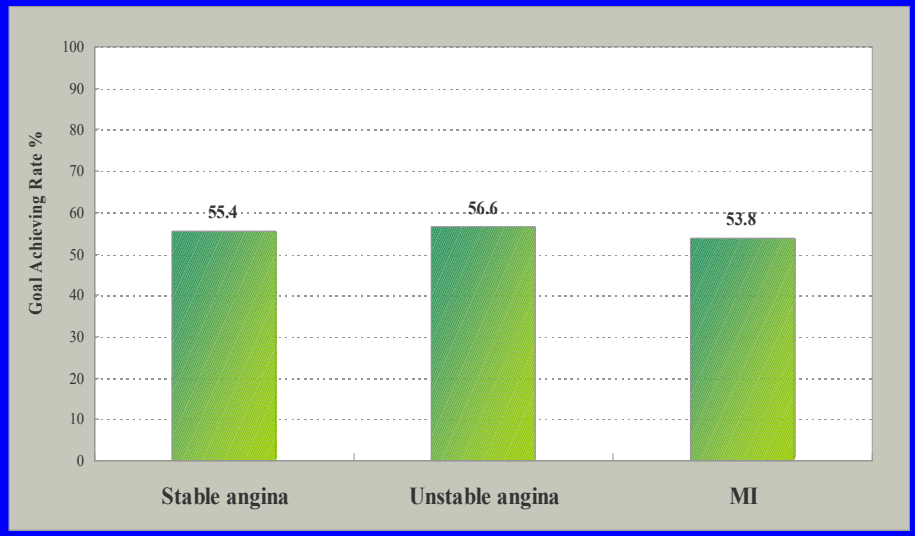
Factors that Prevent Achieving Cholesterol Goals

- Patient factors
- Provider factors
- Limitations of current lipid-lowering drugs

우리나라의 목표도달률



REALITY study

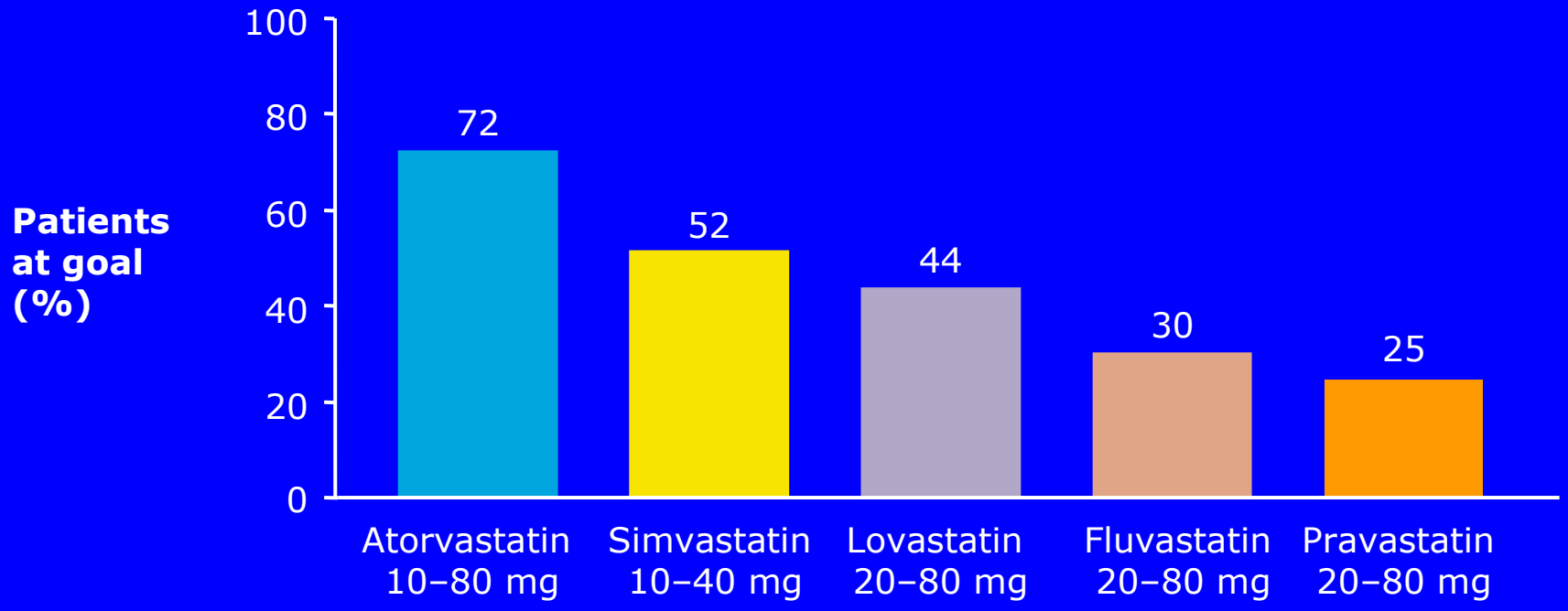


10 Center study

Design: Multi-center retrospective review of medical records, 100 investigators across Korea, total 500 patients included. Minimum 1 year follow-up

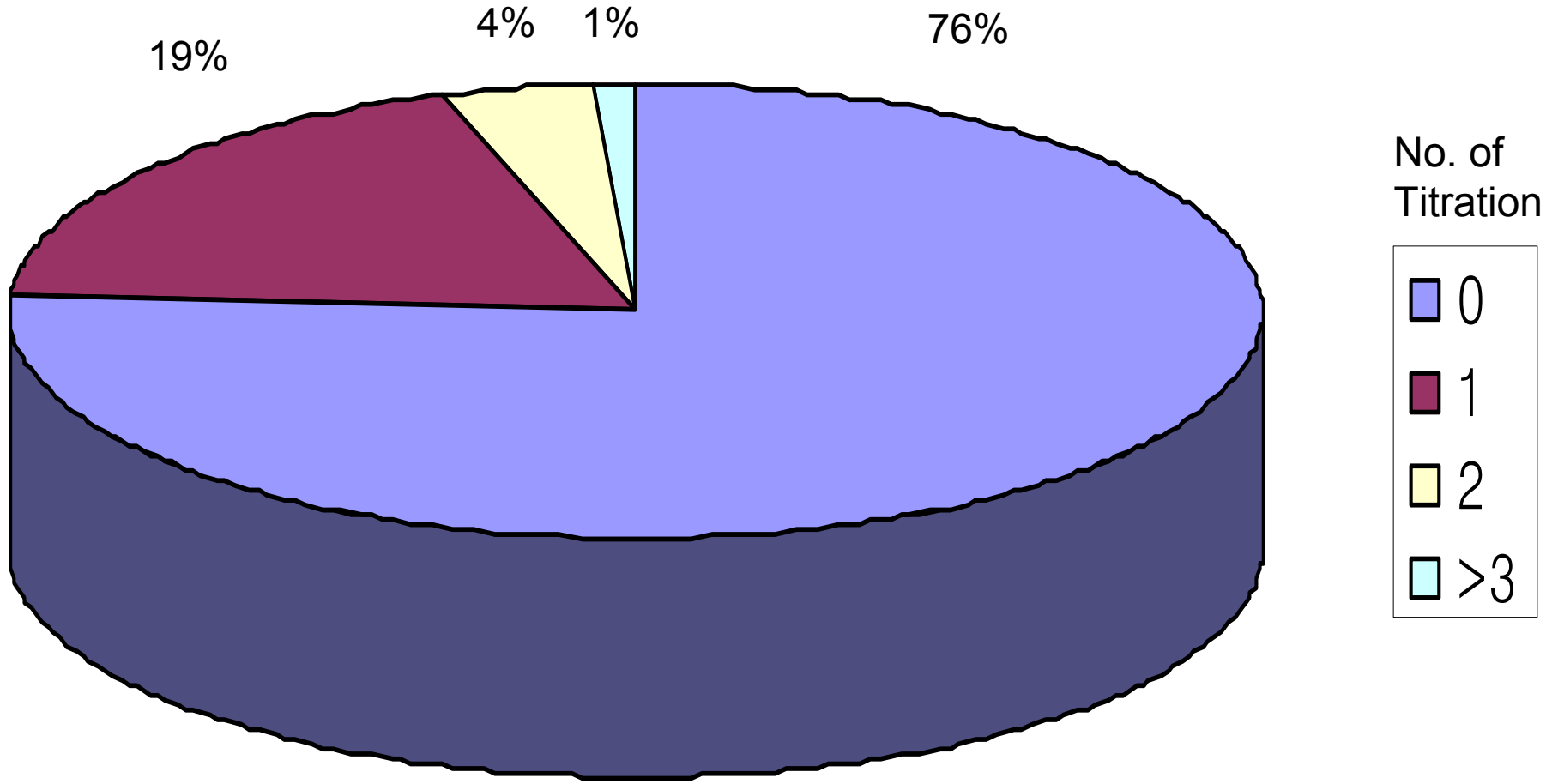
Adapted from HS Kim et al. *EAS, 2004*

약물조절후에도, 많은 환자들이 목표 저밀도 지단백 수치에 도달 못함



At week 54, n=2543 CHD patients
LDL-C=low-density lipoprotein cholesterol; CHD=coronary heart disease
Andrews TC et al. *Am J Med* 2001; 111: 185–191

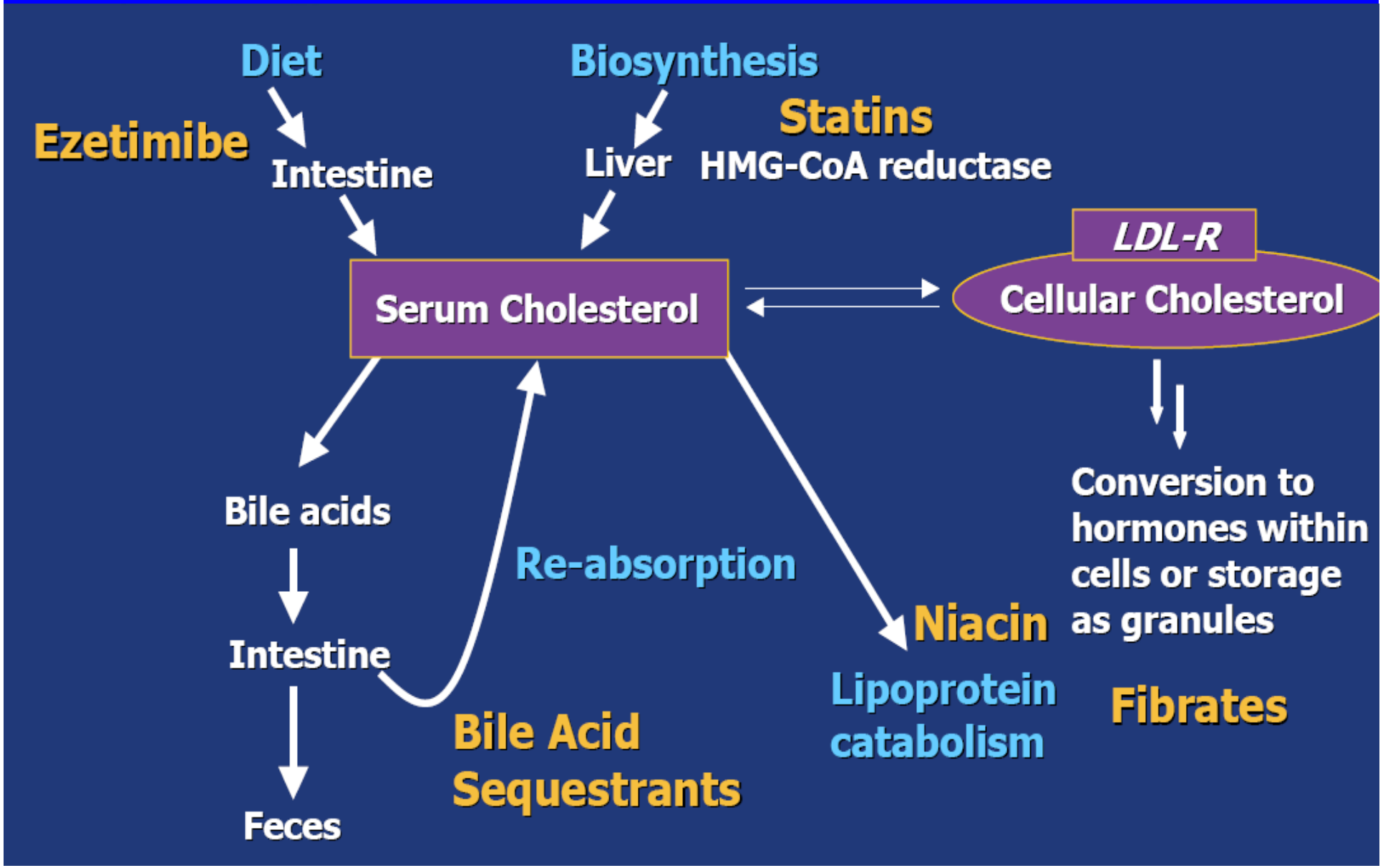
Patients tend to Stay on Initial Dose of a Statin



Rationale for Combination Therapy for Dyslipidemia

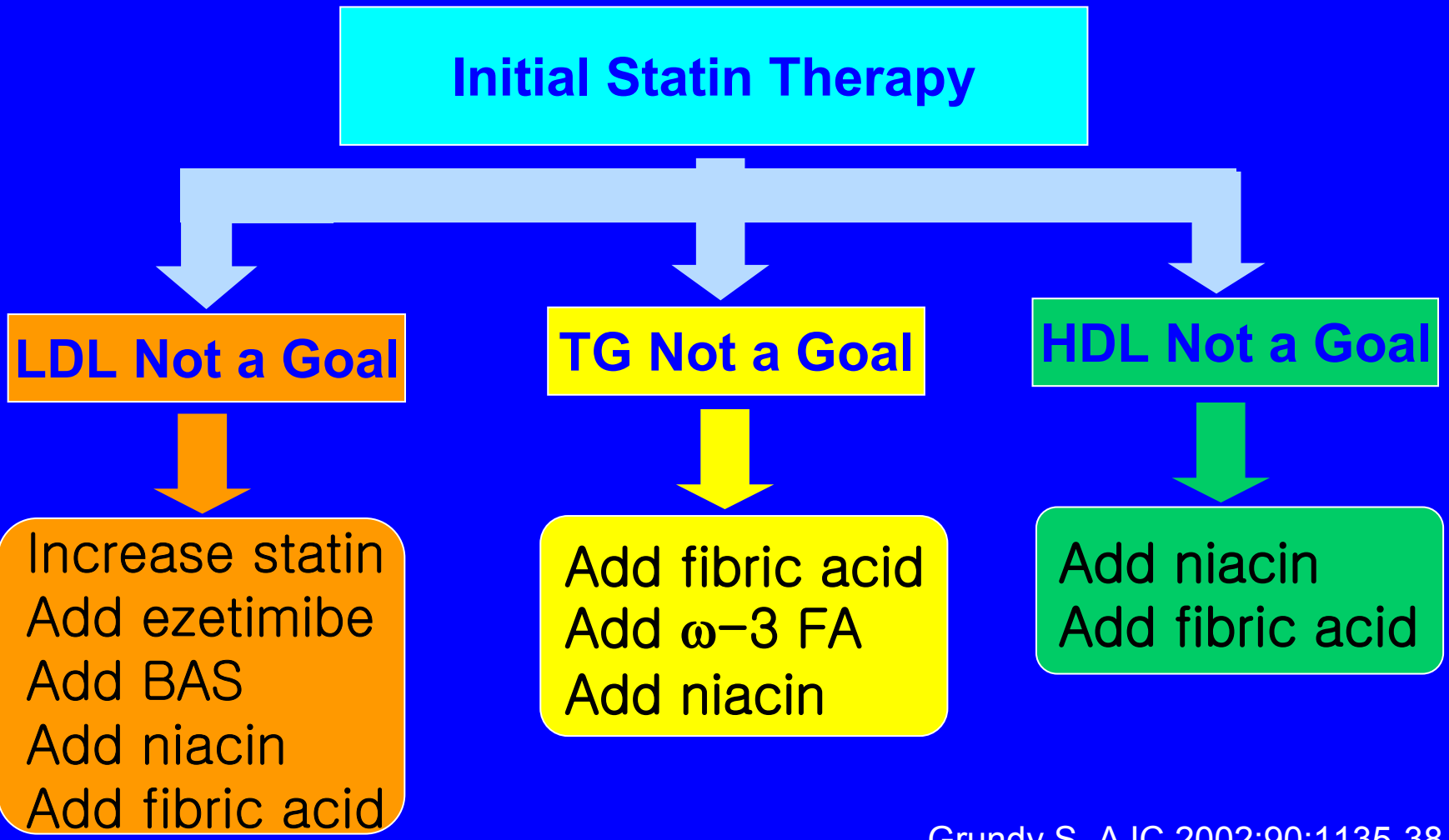
- Combination therapy
  - Enables a balanced therapeutic approach to treatment
  - Harnesses complementary metabolic drugs effects
- Build on synergies in drug combinations
  - May have mutual drug-sparing effects

Pathways for Combination Therapy of Hyperlipidemia



Selecting Combination Therapy

Treatment options after initiating statin therapy.
Some combinations increase the likelihood of myopathy



Grundy S. AJC 2002;90:1135-38

Combination Lipid-Altering Drug Therapy with Statins

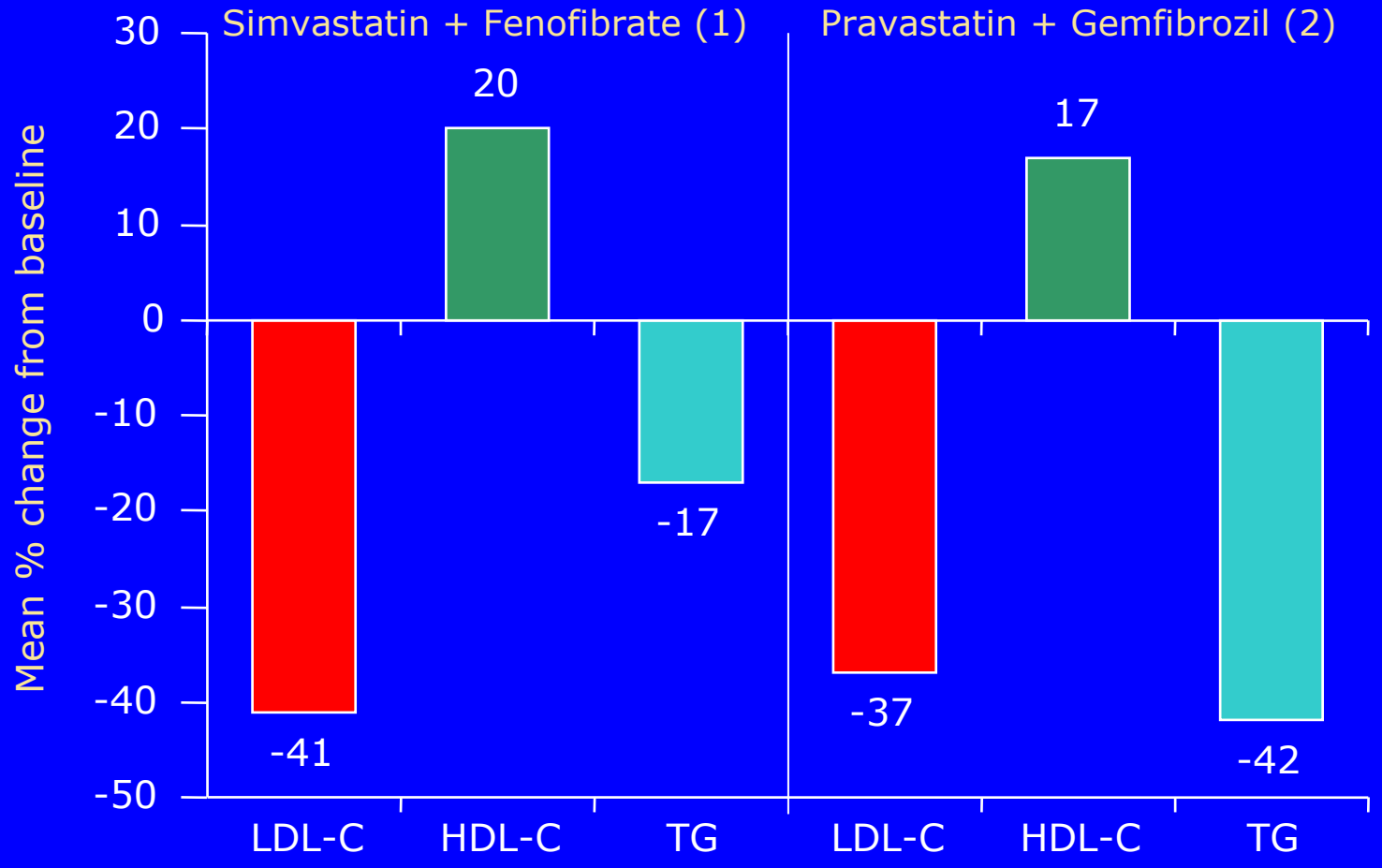
- Fibrates and statins
- Ezetimibe and statins
- Bile acid sequestrants and statins
- Fish oils and statins
- Niacin and statins
- Investigational lipid-altering drug combinations (CETP inhibition)

Combination Therapy: Statin + Fibrate

- Combination fibrate and statin therapy may significantly improve triglyceride, LDL-C, and HDL-C levels
- Fibrates plus statins are associated with increased risk for myopathy and rhabdomyolysis
  - Not thought due to cytochrome P450 drug interaction
  - High risk group: High doses of statins, Renal insufficiency (Cr > 2.0). Age > 70 years, Concomitant medications:
    Itraconazole, Ketoconazole, Cyclosporin A, Erythromycin
  - Gemfibrozil may impair glucuronidation of statins (with cerivastatin being more susceptible than other statins such as simvastatin and atorvastatin)
  - Fenofibrate appears to have less potential for impairment of statin metabolism, and thus this may account for the reduced reports of fenofibrate plus statin–induced myopathy and rhabdomyolysis compared with gemfibrozil plus statin.

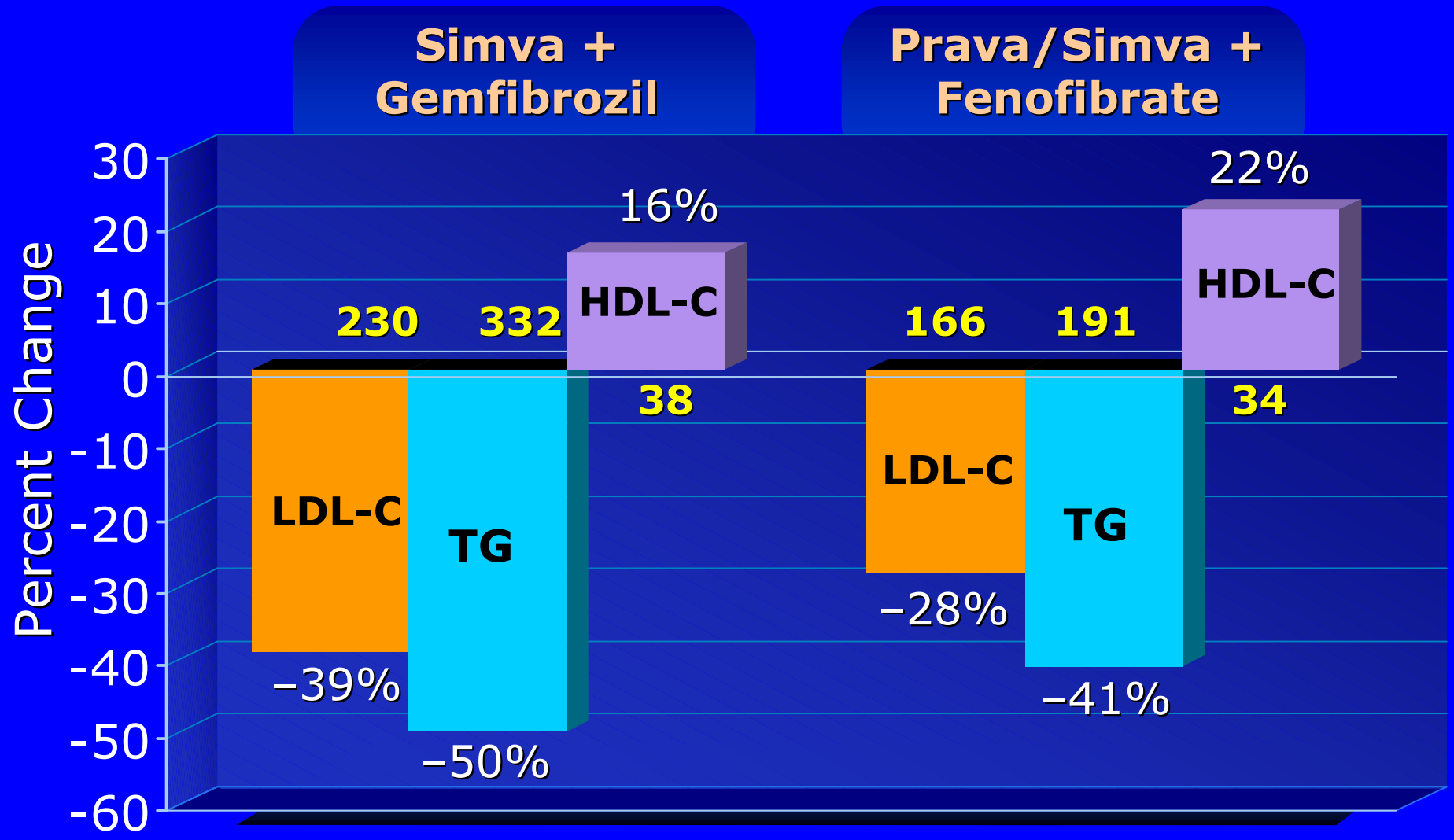
Ballantyne CM et al. *Arch Intern Med* 2003;163:553-564.
Bays H. *Am J Cardiol* 2002;90:30K-43K.

Combination Therapy
Statin Plus Fibrate



1. Wierzbicki AS et al. *QJM* 1997;90:631–634.
2. Wiklund O et al. *Am J Med* 1993;94:13–20.

Statin + Fibrate

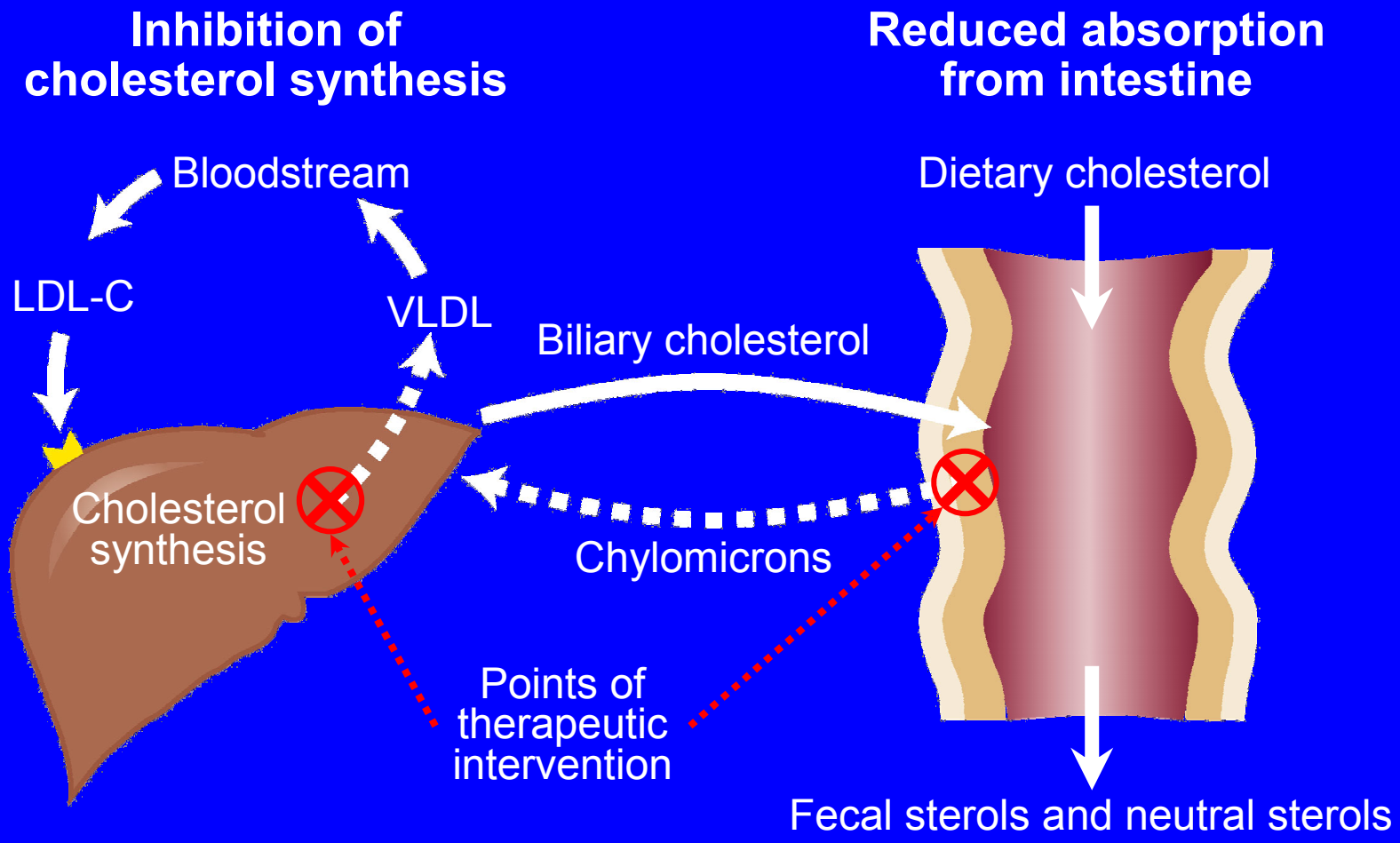


Da Col PG et al. *Curr Ther Res Clin Exp* 1973;53:473-482. | Ellen RL et al. *Am J Cardiol* 1998;81:60B-65B.

Combination Therapy With Intestinal-Acting Agents and Statins: Rationale

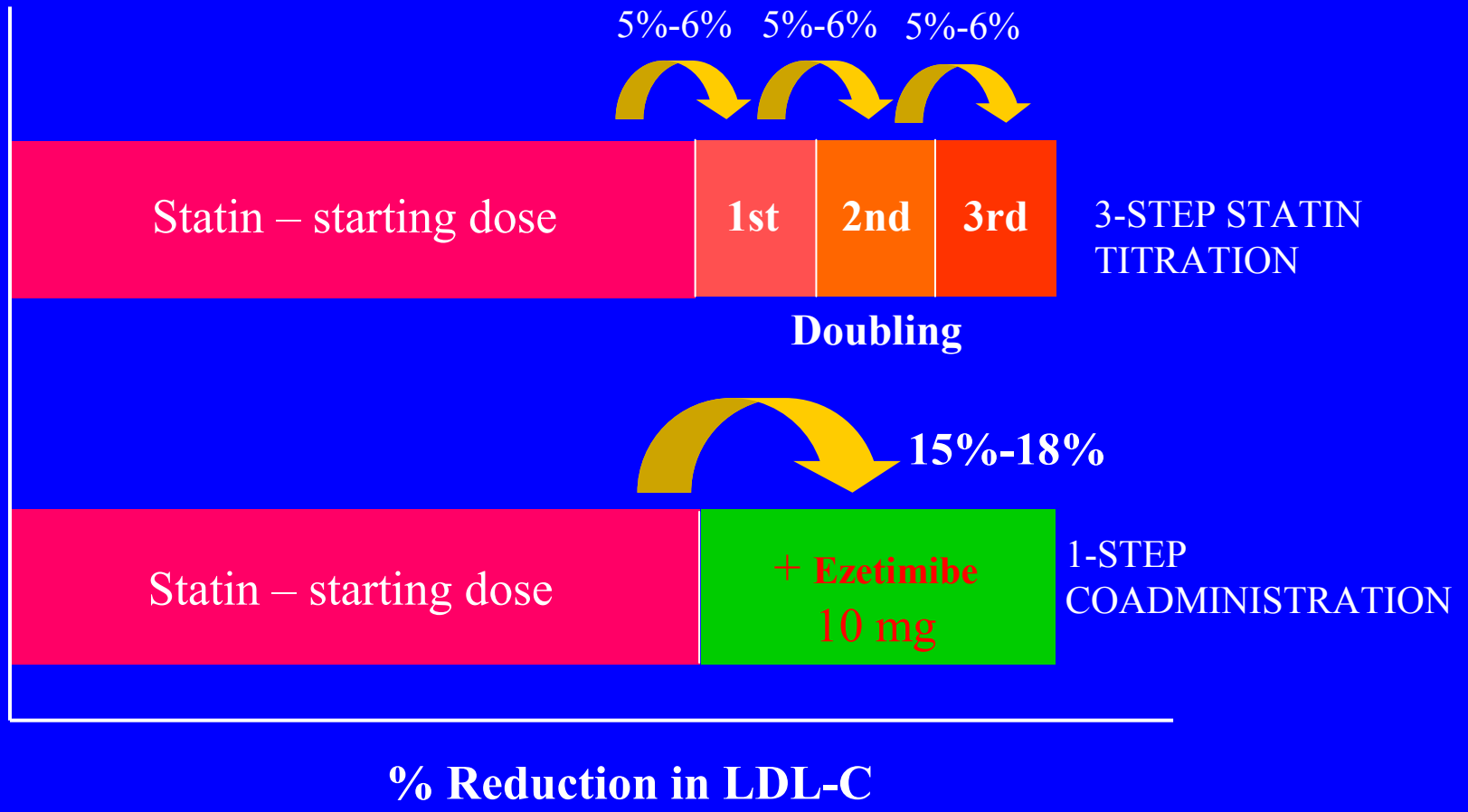
- **Intestinal-acting agents**
  - Reduce intestinal absorption of dietary/biliary cholesterol
    - May increase ability to reach LDL-C goals
    - May allow lower statin dose when the risk of high dose statins is increased due to comorbidities
- **Statins**
  - Inhibit compensatory increase in cholesterol synthesis induced by blocking cholesterol absorption

Lipid Lowering through Dual Inhibition of Both Cholesterol Production and Absorption

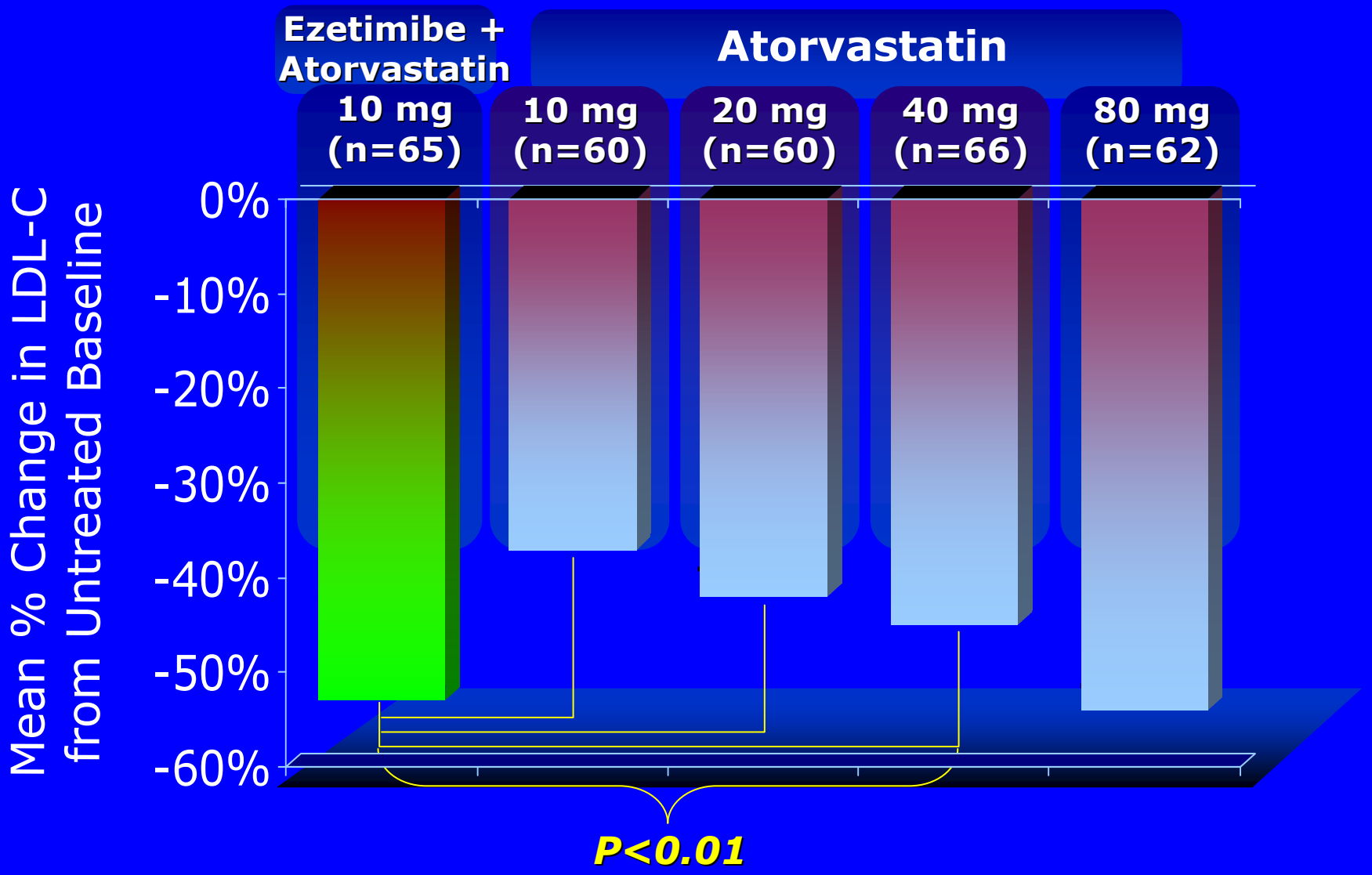


Adapted from Shepherd J *Eur J Cardiol Suppl* 2001:3(suppl E):E2–E5; Miettinen TA *Int J Clin Pract* 2001;55:710–716.

Ezetimibe + Statin vs. Statin Titrati on



Ezetimibe: Efficacy ("10 + 10 = 80")



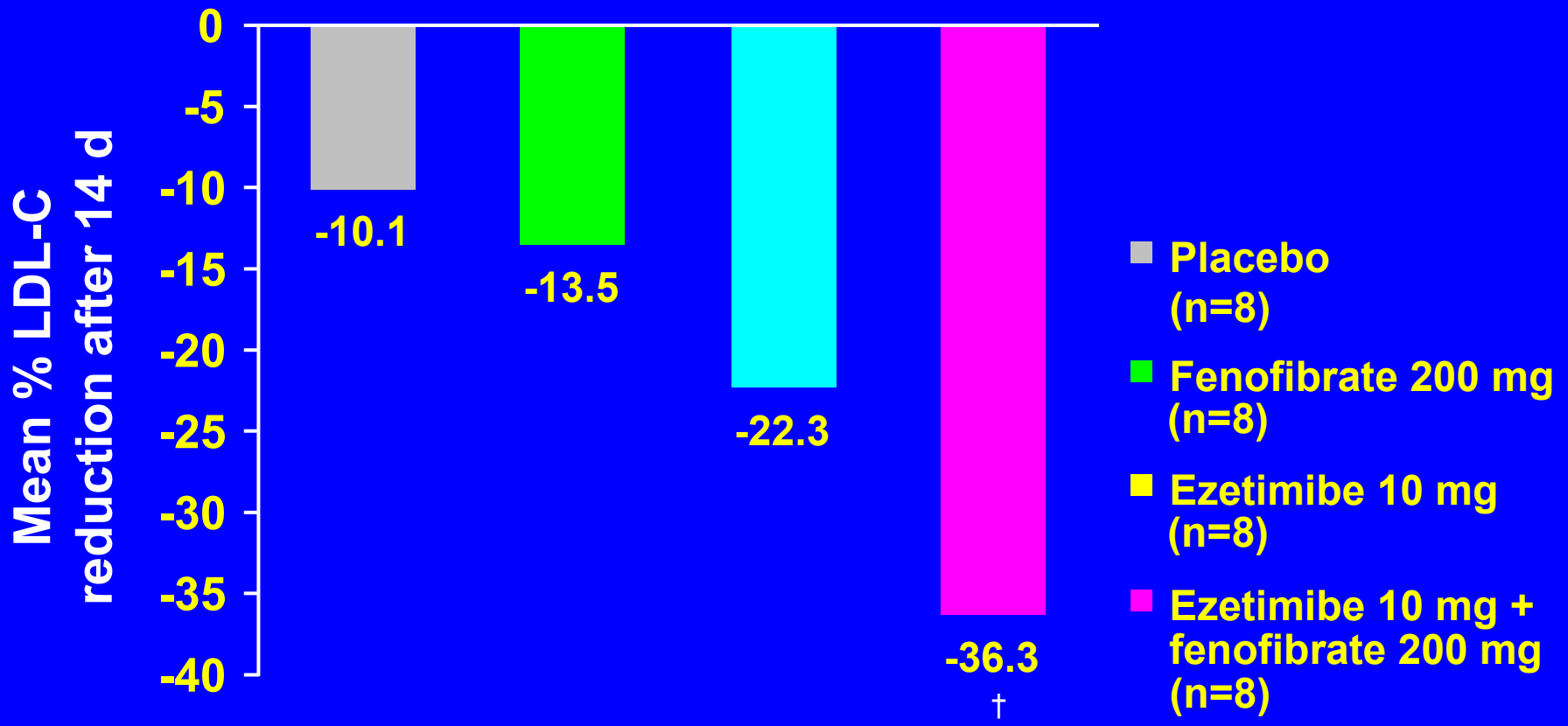
Ballantyne CM et al. *Circulation* 2003;107:2409-2415.

Candidates for Ezetimibe + Statin Therapy

- **Patients unable to tolerate high doses of statins**
- **Patients requiring further reduction in LDLC despite maximum statin dosage**
  - **Ezetimibe + statin**
    - **Further lowered LDL-C 25% vs. 4% with placebo + statin ($p<0.001$)**
    - **>70% of patients achieved ATP II LDL-C goal vs. 18.9% on placebo + statin**

Gagne, et al. Am J Cardiol. 2002 Nov 15;90(10):1084–91.

Ezetimibe in Combination With Fenofibrate*



*Hypercholesterolemic patients.

†*P*<0.03 vs placebo or either drug alone.

Kosoglou et al. European Atherosclerosis Society Meeting, Glasgow, Scotland, 2001

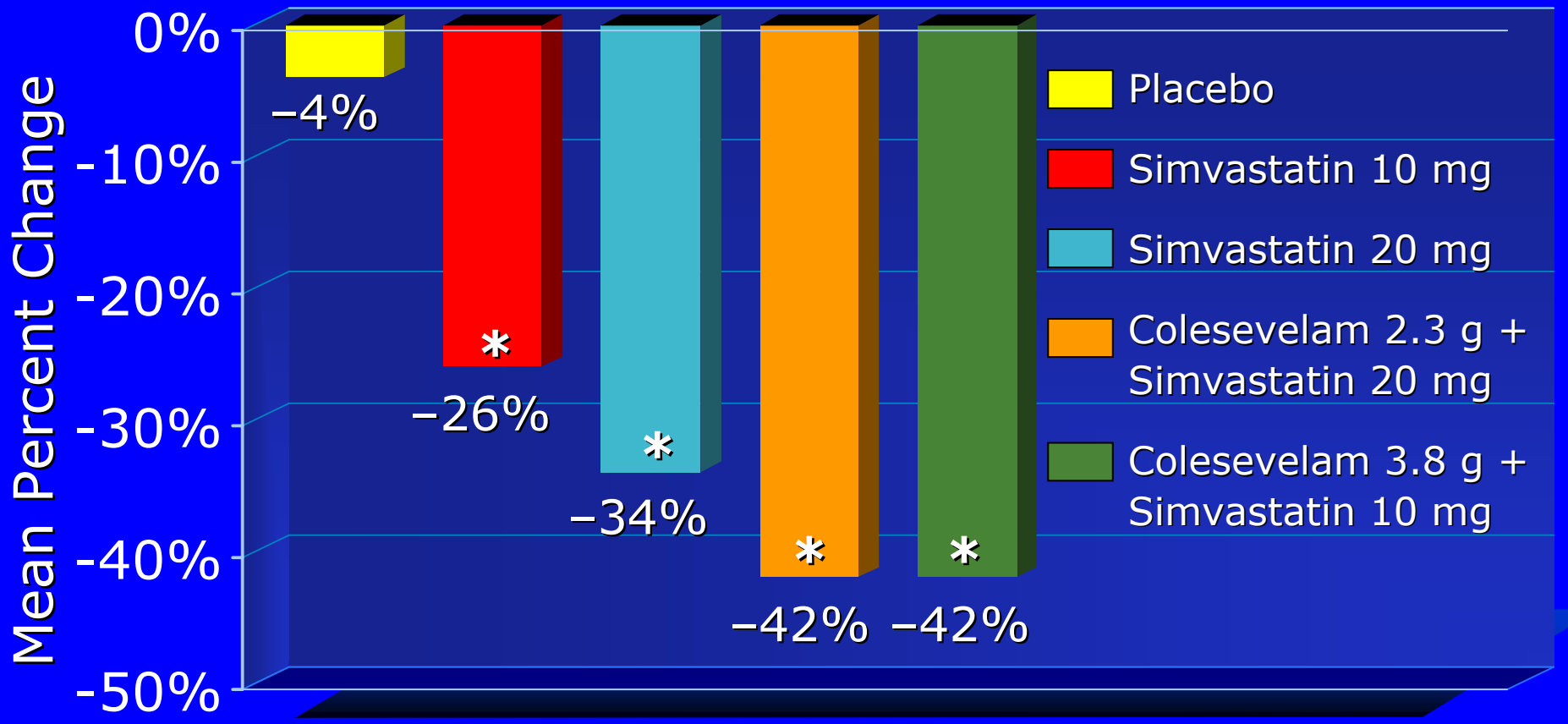
Considerations in Colesevelam + Statin Therapy

- **Colesevelam + statin**
  - Greater reduction in LDL-C vs. statins alone
  - Older bile acid sequestrants
- **Limited by GI side effects**
  - Prescribe the lowest effective dosages
- **Interaction**
  - No evidence of interactions between bile acid sequestrants and statins

Worz and Bottorff. Pharmacotherapy. 2003;23(5):625–637.

Simvastatin Alone and with Colesevelam: % Change in LDL-C

(n=258 patients with baseline LDL-C 160–220 mg/dL; treated for 6 weeks)



* $p<0.05$ vs placebo

Knapp HH et al. *Am J Med* 2001;110:352-360.

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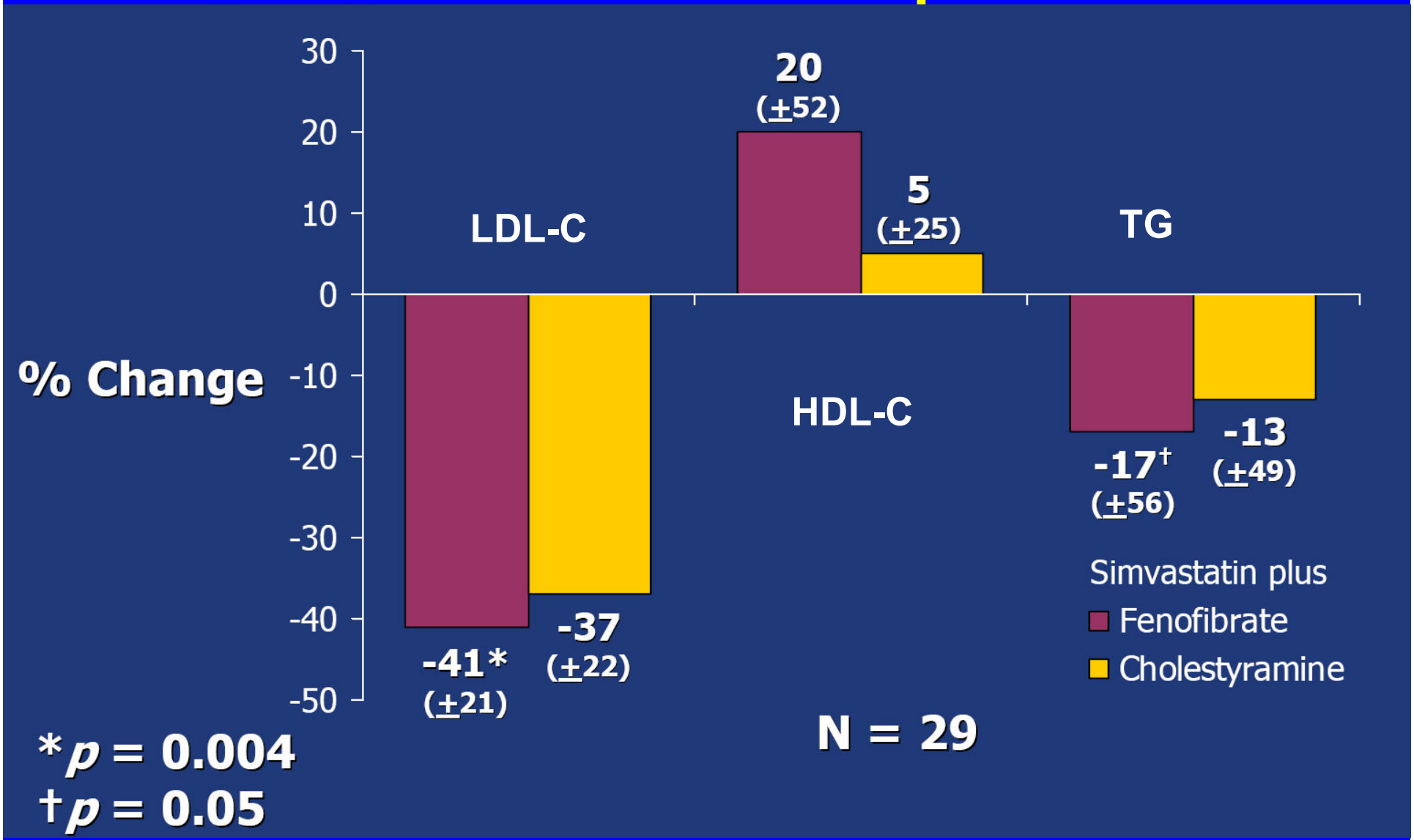
Efficacy of Statin + Fibrate vs. Statin + Bile Acid Sequestrant



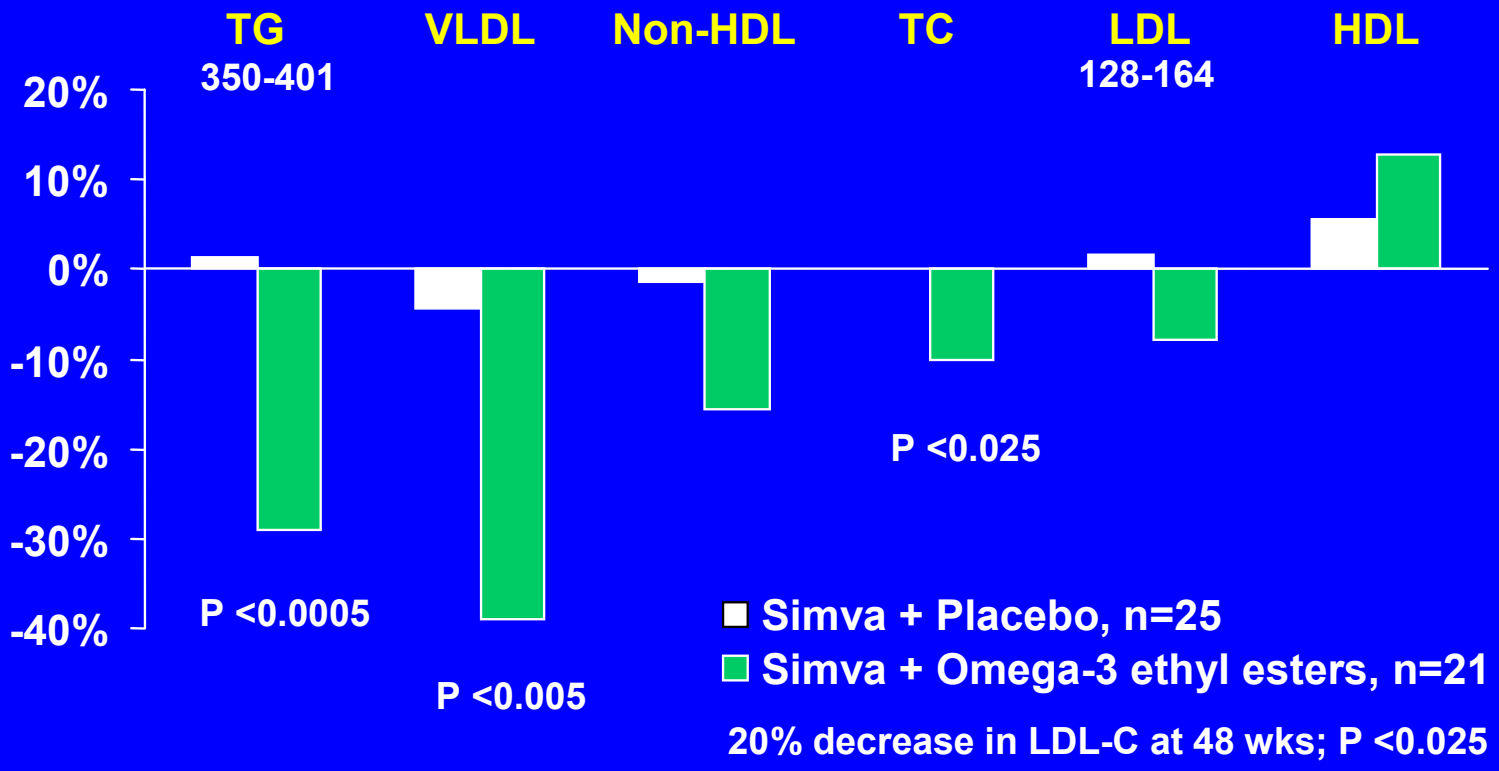
Wierzbicki et al. Q J Med. 1997;90:631–634

Omega-3 Ethyl Esters and Statins

- Omega-3 ethyl esters lower triglyceride levels significantly and may be effective with statins to treat patients with combined hyperlipidemia
- Omega-3 ethyl esters plus statin may often be an alternative to fibrate or niacin plus statin
- Omega-3 FA may have other cardiovascular effects complementary to those of statins

Bays HE, et al. *Expert Opin Pharmacother* 2003;4:1901-1938.
Kris-Etherton PM, et al. *Circulation* 2002;106:2747-2757.

Effects of Omega-3 Ethyl Esters in High TG Patients Taking Simvastatin



24 weeks treatment; Simvastatin 10-40 mg/day (average 32 mg/day)

Durrington PN, et al. *Heart*. 2001;85:544-548.

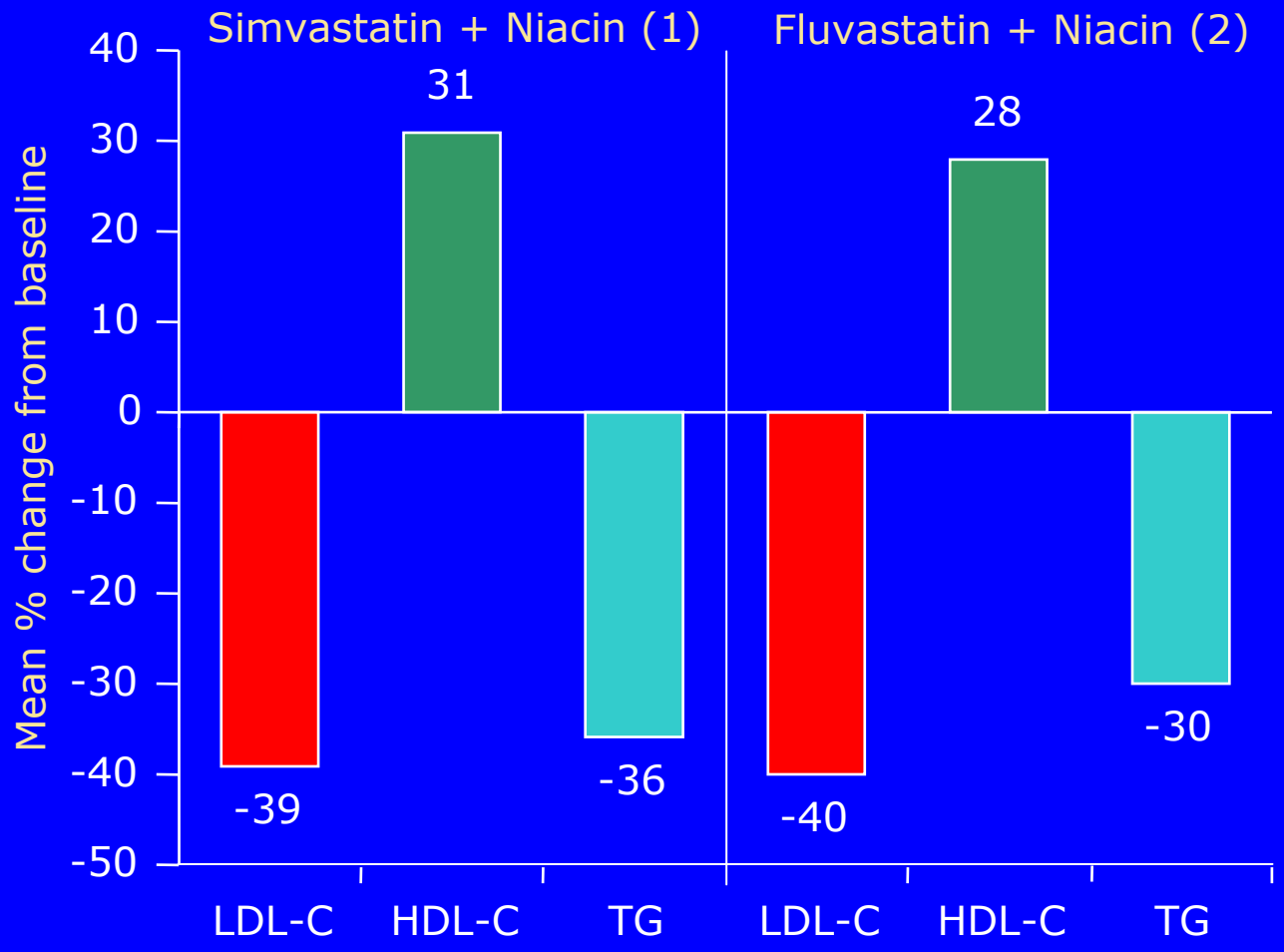
P-values all vs. baseline

Considerations in Niacin +Statin Therapy

- **Effective to treat mixed hyperlipidemia**
  - Decreased HDL-C or simple hypercholesterolemia
- **Safety**
  - Myopathy
  - Vasodilatory response
  - Gout
  - Glucose intolerance
- **Dosage**
  - **Prescribe** lowest effective dosages to increase tolerability
- **Interaction**
  - No evidence between bile acid sequestrants and statins

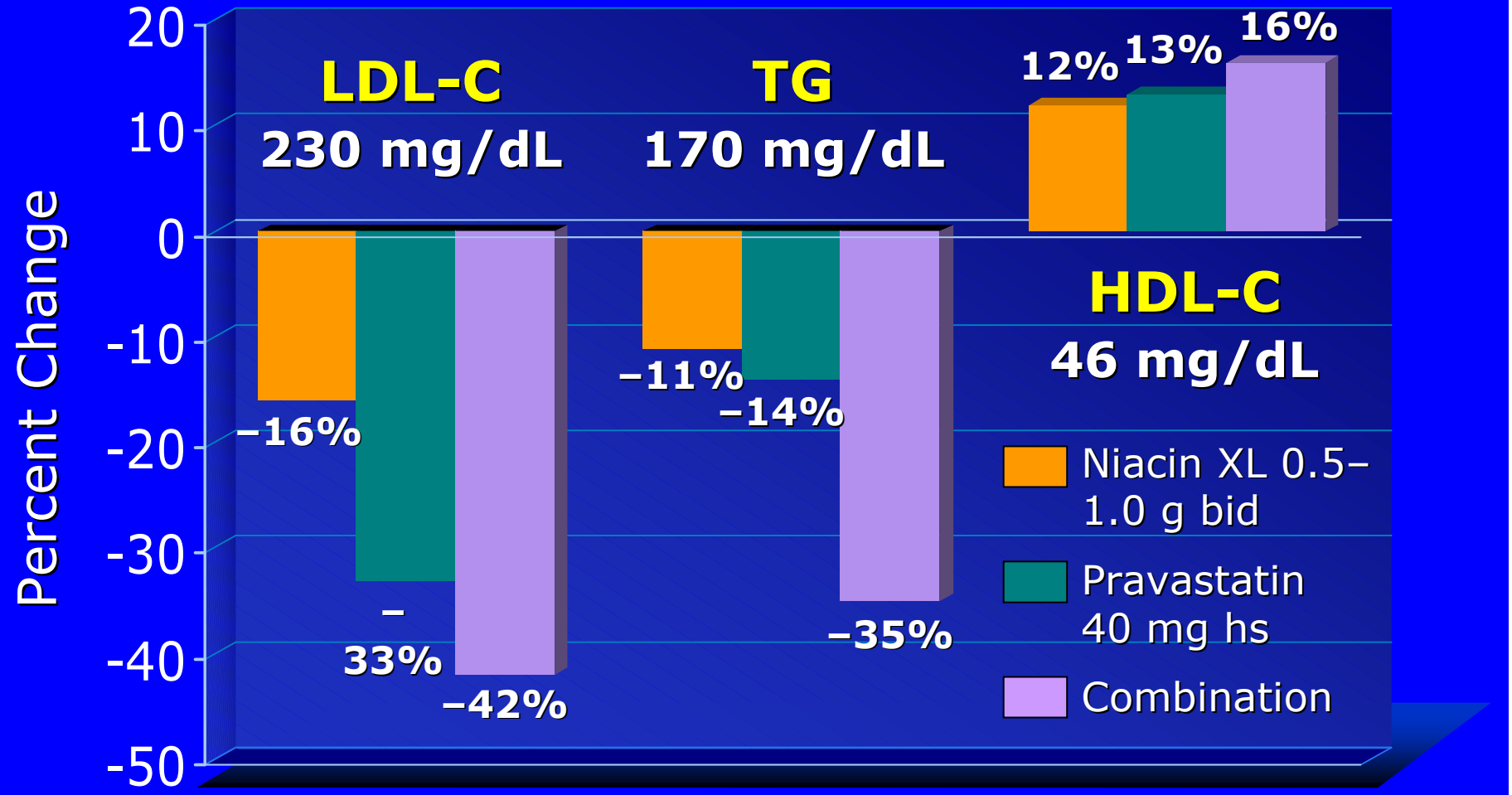
Worz and Bottorff. Pharmacotherapy. 2003;23(5):625–637

Combination Therapy
Statin Plus Niacin



1. Guyton JR, Capuzzi DM. *Am J Cardiol* 1998;82:82U–84U.
2. Jacobson TA et al. *Am J Cardiol* 1994;74:149–154.

Pravastatin and Niacin Alone and Together



Davignon J et al. *Am J Cardiol* 1994;73:339-345.

ADVOCATE: Change From Baseline at 16 wk (%)

	Advicor® 2000/40 mg	Atorvastatin 40 mg	Simvastatin 40 mg
LDL-C	–42	–49*‡	–39
HDL-C	+32*†	+6	+7
TG	–49*	–31*	–19
Lp(a)	–21*†	0	–2

*$P \leq 0.05$ vs simvastatin
†$P \leq 0.05$ vs atorvastatin
‡$P \leq 0.05$ vs Advicor® 2000/40 mg(Niacin ER/lovastatin)

Adapted with permission from Bays HE et al. *Am J Cardiol*. 2003;91:667

Efficacy of Niaspan®: Long-Term Study

Treatment*	Duration	n	Mean Change From Baseline (%)					
			TC	LDL-C	HDL-C	TG	Lp(a)	Apo B
Niaspan® alone	**Baseline**	723	–	–	–	–	–	–
	48 wk	320	–12	–18	+26	–27	–30	–16
	96 wk	225	–13	–20	+28	–28	–40	–17
Niaspan® + Statin†	**48 wk**	120	–27	–36	+28	–33	–36	–30
	96 wk	122	–27	–36	+27	–35	–41	–30
Niaspan® + BAS‡	**48 wk**	25	–11	–19	+25	–6	–21	–17
	96 wk	9	–14	–25	+26	+8	–39	–21

All changes from baseline with Niaspan® alone or + HMG-CoA were statistically significant

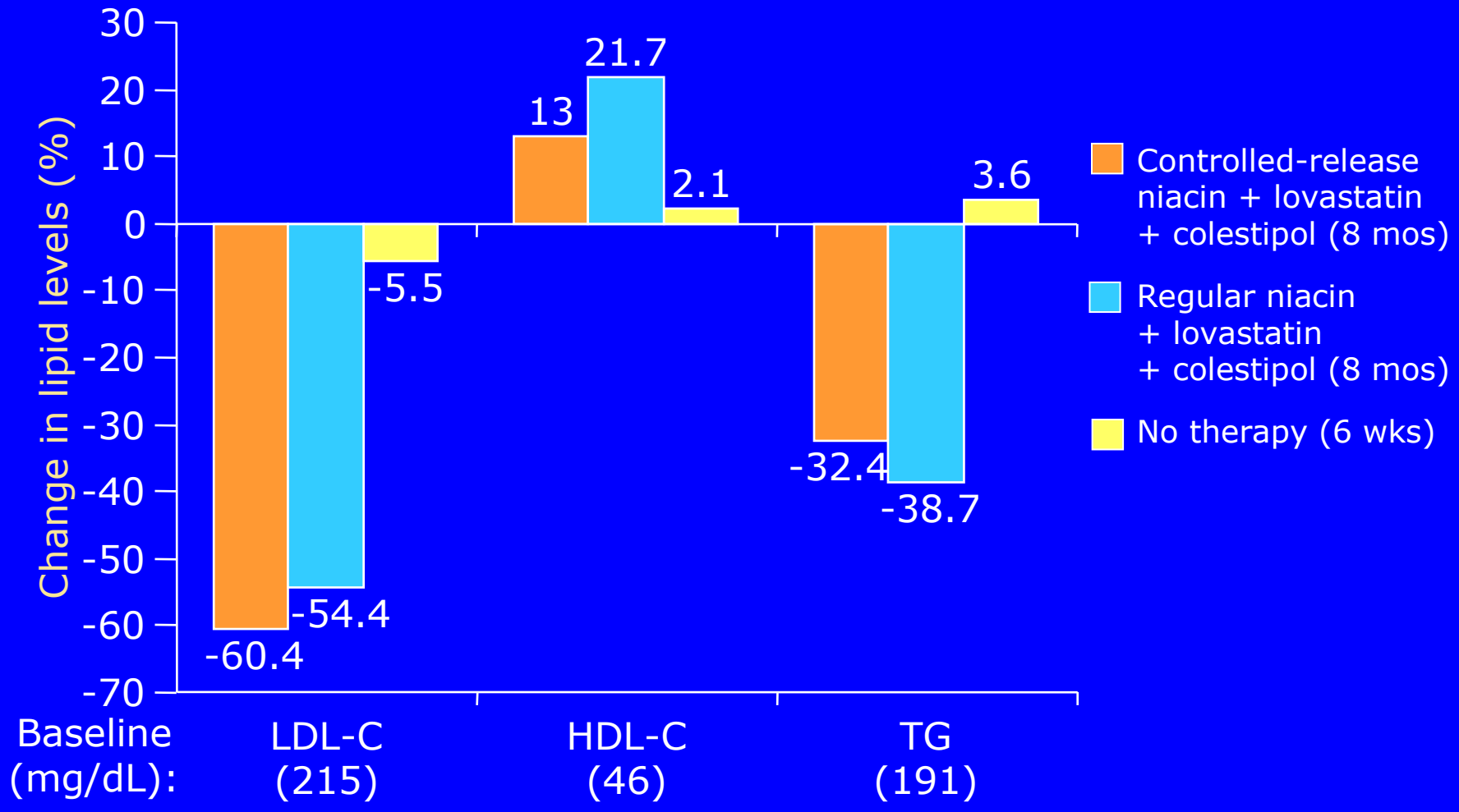
*** Median Niaspan® dose was 2000 mg qhs**

† Mean duration of HMG-CoA combination therapy was ~56 wk

‡ Mean duration of BAS combination therapy was ~34 wk

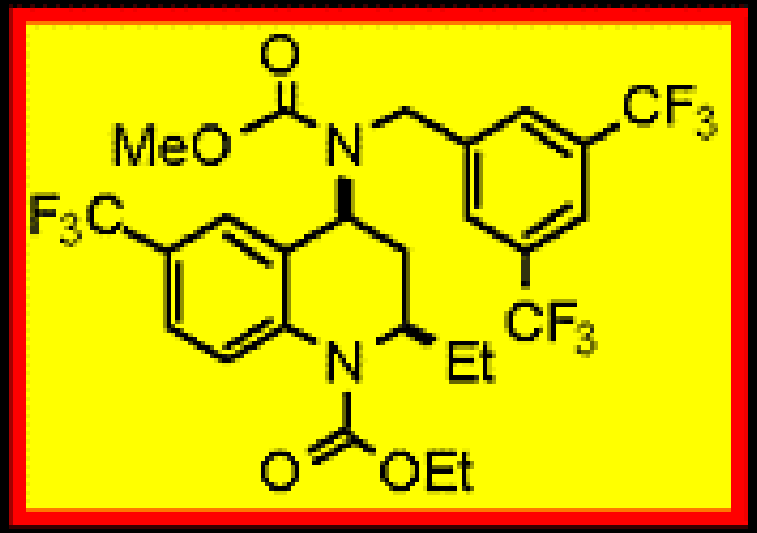
Kos Pharmaceuticals, Inc., data on file, 2003

Combination Therapy
Niacin + Statin + Colestipol



Brown BG et al. *Am J Cardiol* 1997;80:111–115.

Torcetrapib



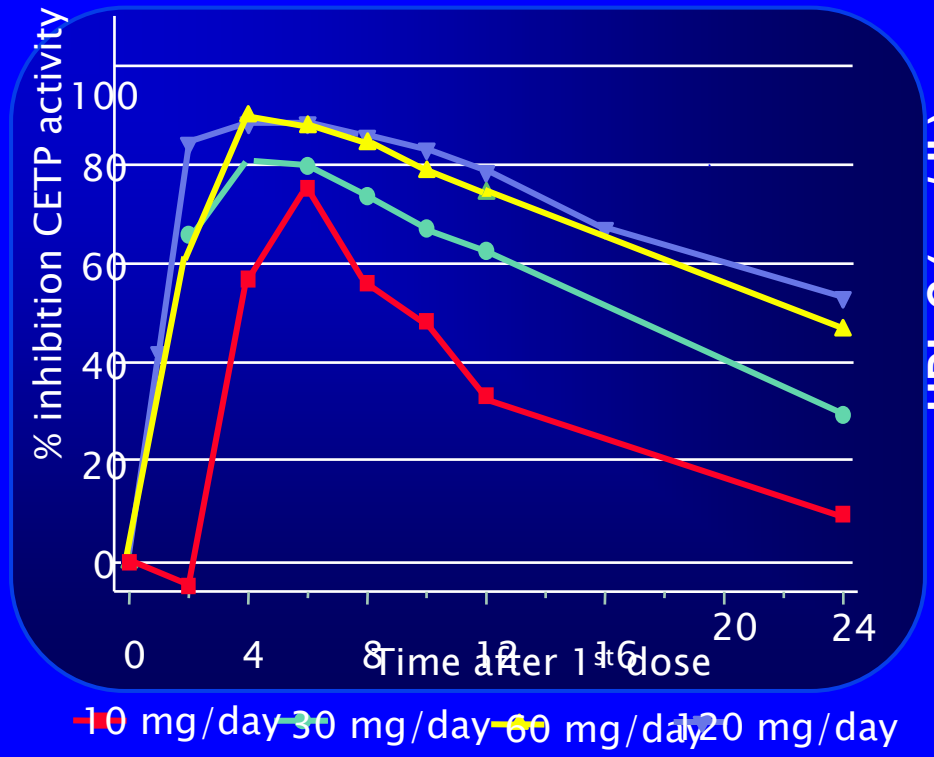
Potent and selective inhibitor of CETP

Linear PK in tested range

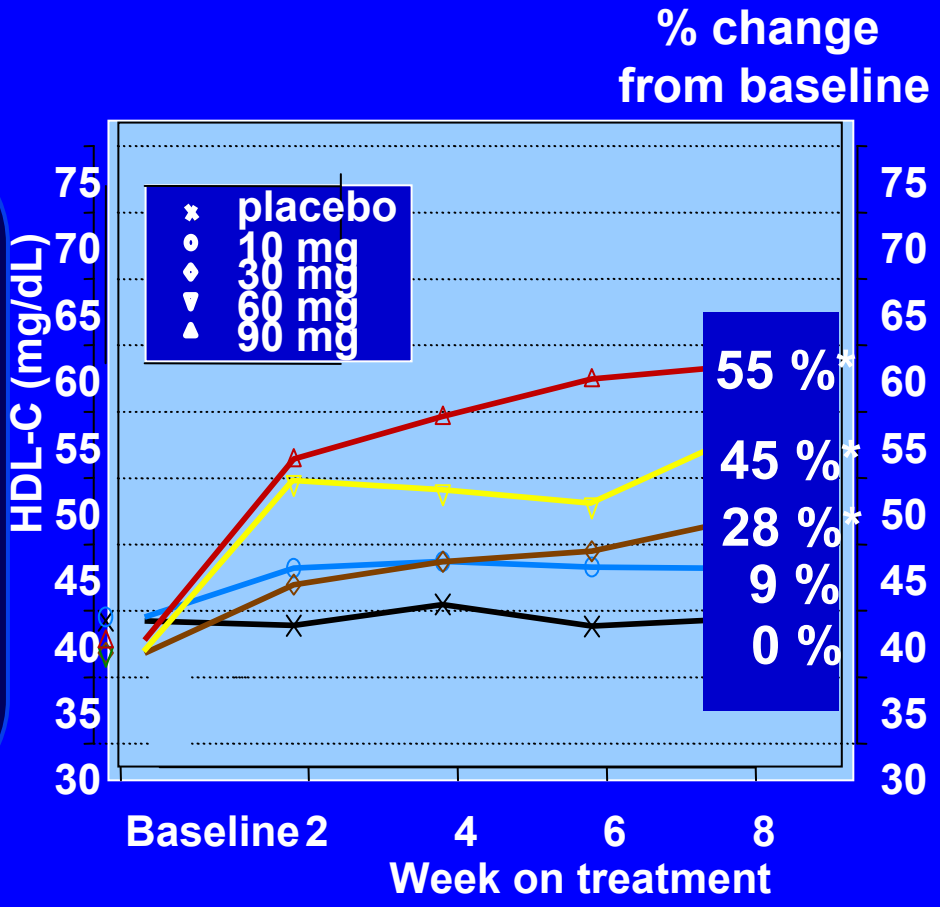
Oral Formulation

Clark et al Arterioscler Thromb Vasc Biol 2004;24:490

Torcetrapib: Dose-dependent CETP Inhibition

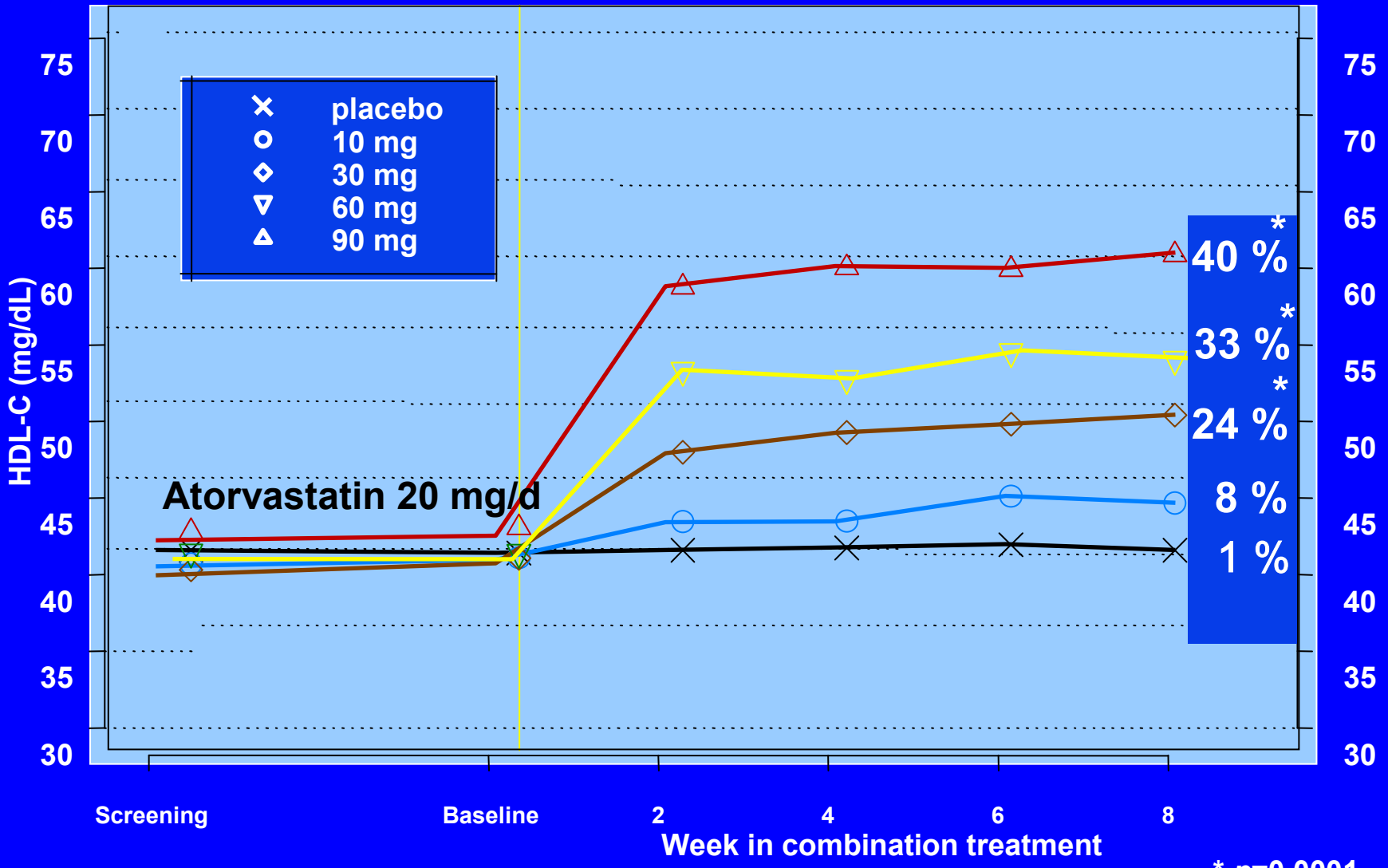


% Change in HDL-C with Torcetrapib

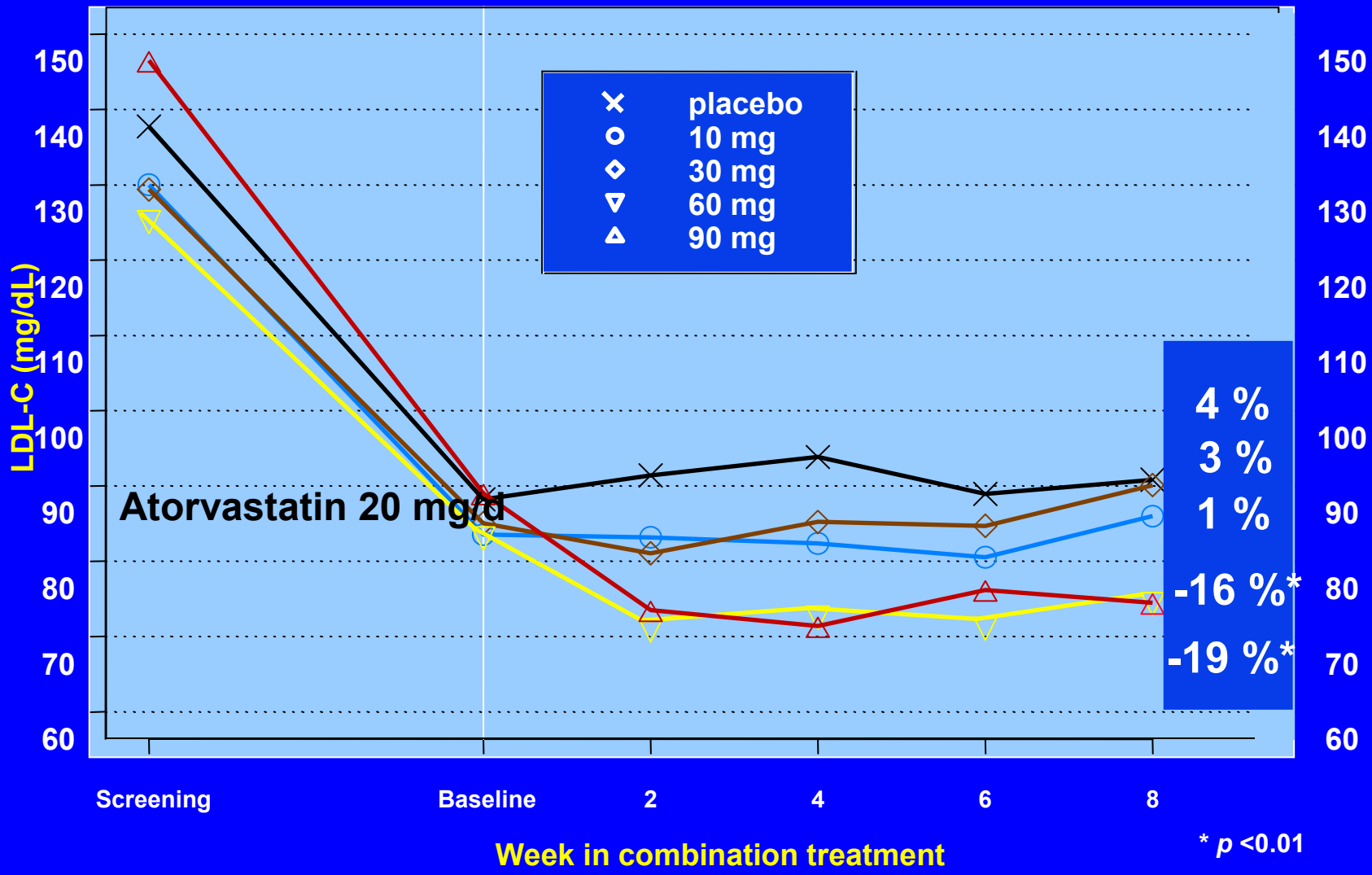


Adapted from Clark et al. *ATVB.* 2004. 24:1-9

% Change in HDL-C with Torcetrapib and Atorvastatin 20 mg/d



% Change in LDL-C with Torcetrapib And Atorvastatin 20 mg/d

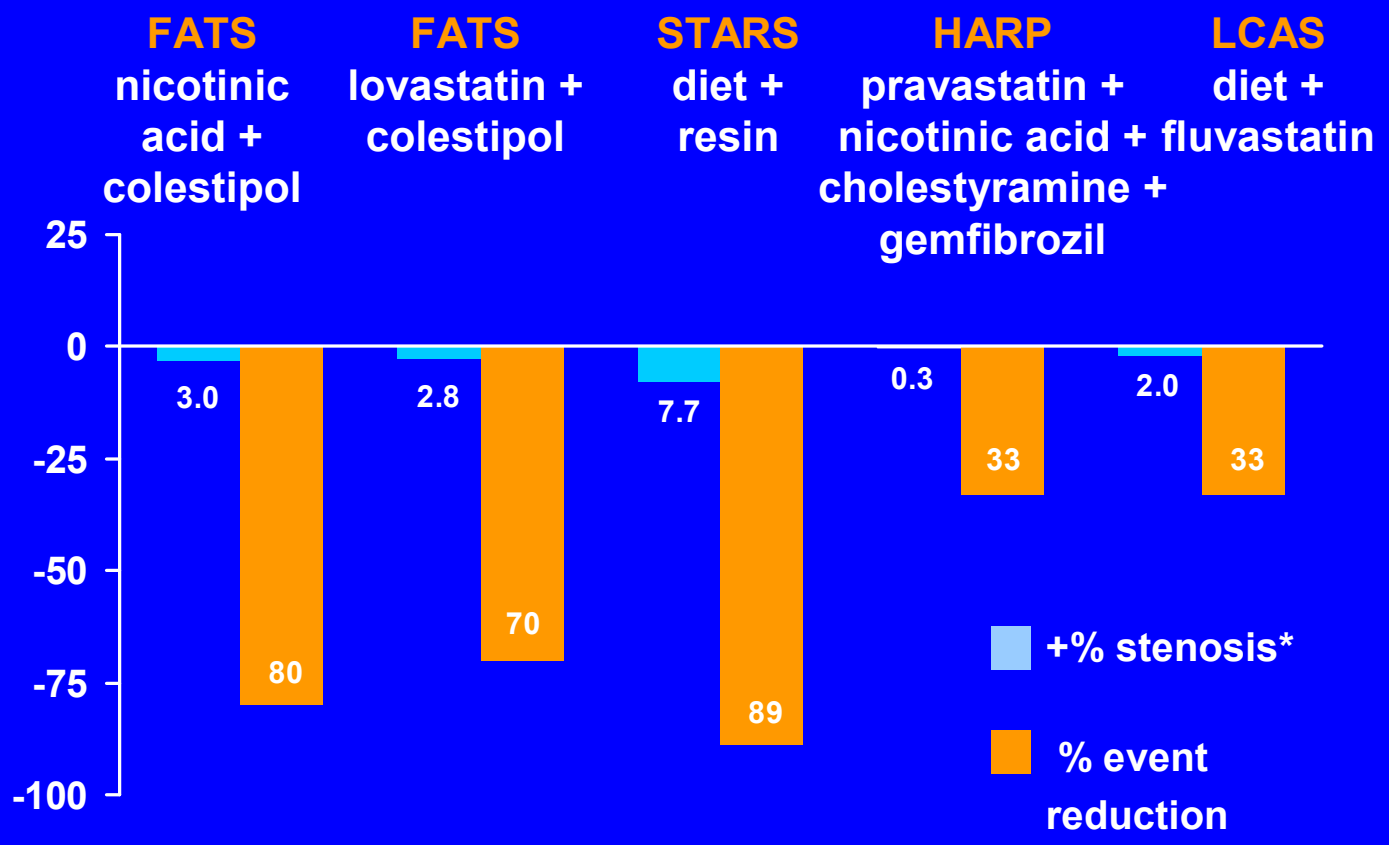


Angiographic Trials of Combination Therapy

- Cholesterol Lowering Atherosclerosis Study (CLAS)[1]
  - Diet and niacin + colestipol (vs diet and placebo)
  - 188 men (aged 40–59 y), post-CABG
  - Nonsmokers or former smokers, nondiabetic, nonhypertensive
  - Total-C at entry: 185–350 mg/dL; drug responsive
- Familial Atherosclerosis Treatment Study (FATS)[2]
  - Lovastatin + colestipol, niacin + colestipol, or conventional therapy
  - 146 men (aged $\leq$ 62 y) with CAD and family history of CAD
  - ApoB $\geq$ 125 mg/dL
  - Average stenosis: 34%

1. Blackenhorn DH et al. *JAMA*. 1987;257:3233–3240
2. Brown G et al. *N Engl J Med.* 1990;323:1289–1298

Event Reduction in Angiographic Plaque Regression Trials



*As defined by the comparison between the change in the treated group *vs* the change in the control.
FATS = Familial Atherosclerosis Treatment Study; STARS = St Thomas' Atherosclerosis Regression Study; HARP = Harvard Atherosclerosis Reversibility Project; LCAS = Lipoprotein and Coronary Atherosclerosis Study.
Brown BG *et al*. *Circulation* 1993;**87**:1781–1791. Herd JA. *Am J Med* 1998;**104**:42S–49S. Sacks FM *et al*. *Lancet* 1994;**344**:1182–1186.

ARBITER 2

- **Objective**
  - Compare effects of niacin ER 1000 mg/d with placebo on carotid intima–media thickness (primary endpoint) over 12 months
- **Study population**
  - Patients with known CHD with good LDL-C on statin therapy
- **Design**
  - Randomized, double-blind, placebo-controlled, single-center, investigator-initiated study
- **Timeline**
  - Enrollment: December 2001 through May 2003
  - Final follow-up: May 2004

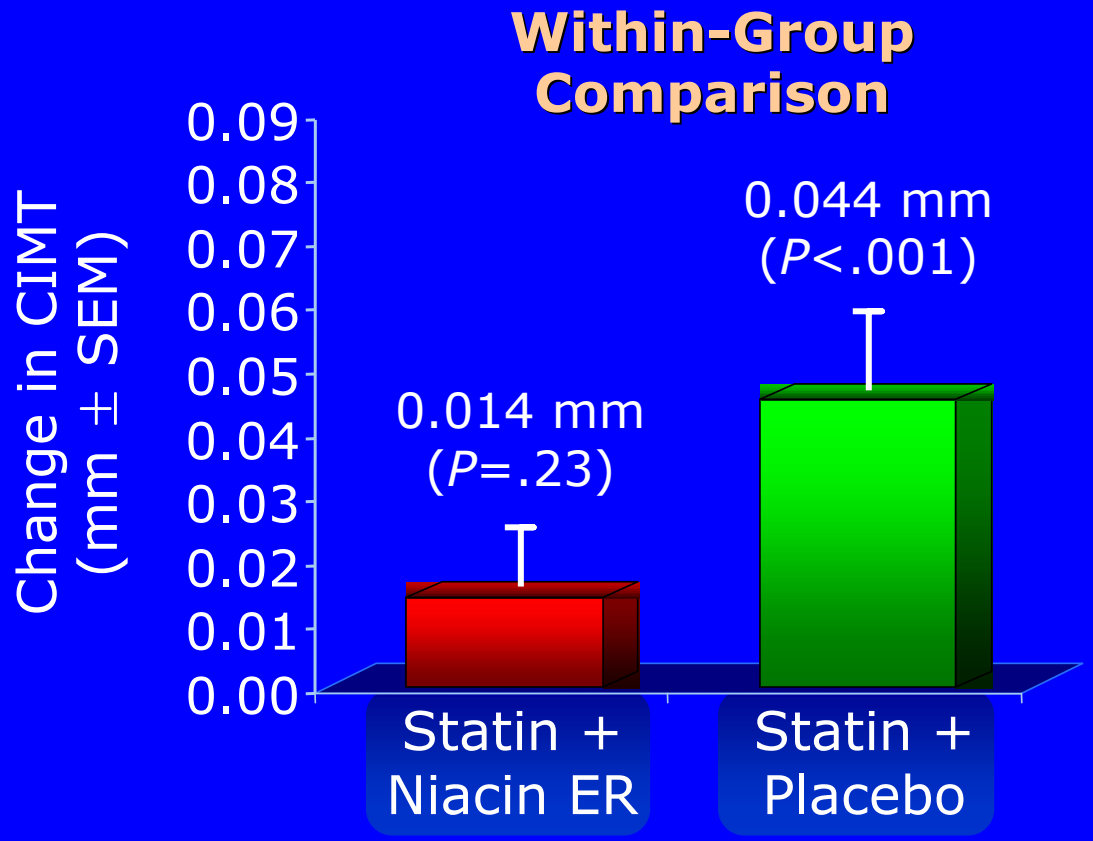
Taylor AJ et al. *Circulation* 2004;110:3512-3517.

ARBITER 2: Lipid and CRP Values

Mean ± SD; mg/dL unless noted	Baseline			12 Months			*P* (baseline vs 12 months)	
	Placebo	Niacin ER	*P*	Placebo	Niacin ER	*P*	Placebo	Niacin ER
n	71	78		71	78			
LDL-C	91 ± 22	87 ± 17	NS	86 ± 20	85 ± 25	NS	NS	NS
HDL-C	40 ± 7	39 ± 7	NS	40 ± 9	47 ± 16	.002	NS	<.001
TG	172 ± 104	154 ± 82	NS	164 ± 83	134 ± 87	.03	NS	.009
Non-HDL-C	121 ± 27	115 ± 26	NS	115 ± 21	107 ± 34	NS	.03	.02
hs-CRP, mg/L	3.0 ± 4.7	3.8 ± 4.3	NS	3.5 ± 4.7	4.0 ± 5.8	NS	NS	NS

Taylor AJ et al. *Circulation* 2004;110:3512-3517.

ARBITER 2: Δ CIMT at 12 Months versus Baseline



Statin + Niacin ER

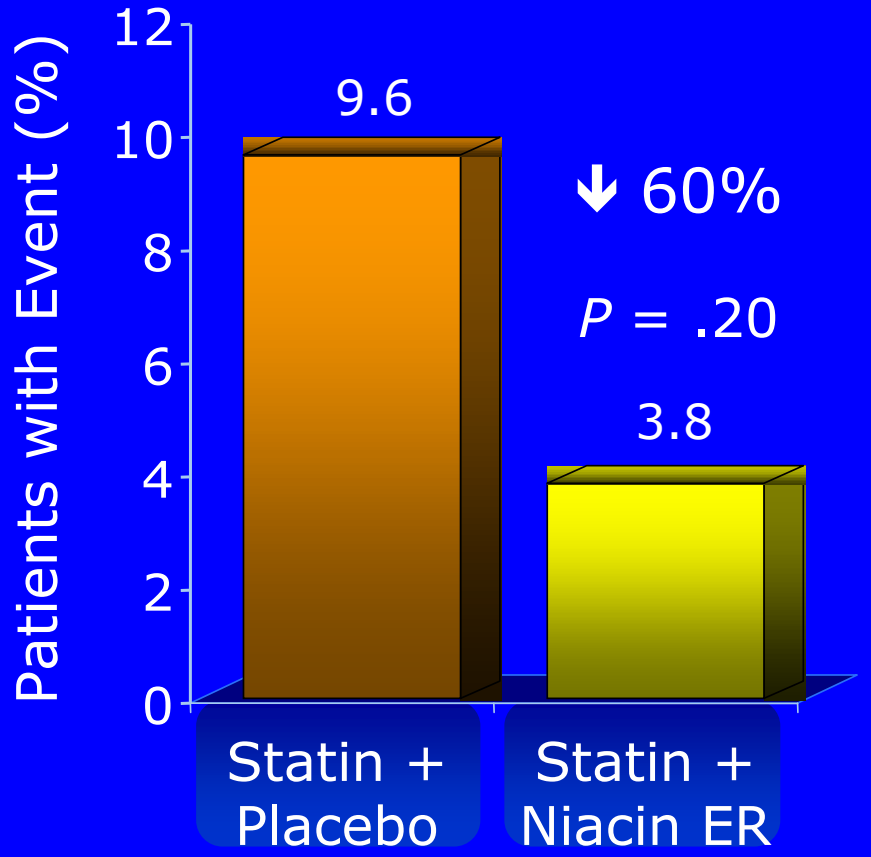
- Safe
- Flushing common, occurred in 2/3 of patients
- Adherence >90%

Between-group comparison: *P*=.08, intent-to-treat analysis of placebo > niacin ER, *P*=.048.

Taylor AJ et al. *Circulation* 2004;110:3512-3517.

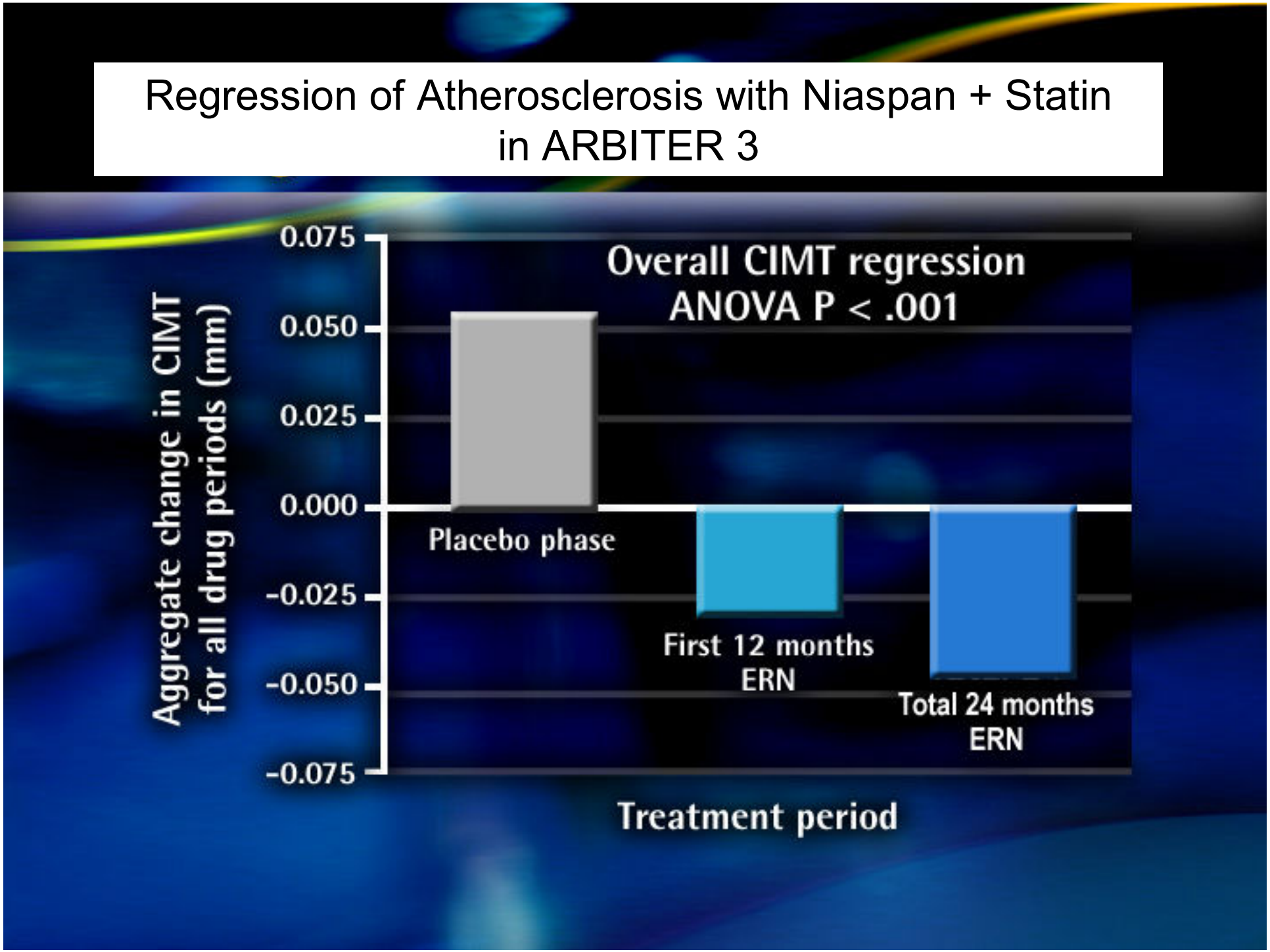
ARBITER 2: Secondary Efficacy Endpoint — Clinical Events

- Composite clinical event endpoint
  - Unstable angina/MI hospitalization
  - Stroke
  - Sudden cardiac death
  - Percutaneous coronary revascularization, CABG, or peripheral revascularization



Taylor AJ et al. *Circulation* 2004;110:3512-3517.

Regression of Atherosclerosis with Niaspan + Statin in ARBITER 3



Statins and fibrates

- Complementary effects on triglyceride concentrations and LDL-C levels
- Effectiveness (especially statin-and-fenofibrate combination) for patients with mixed hyperlipidemia (elevated triglyceride and LDL-C levels)
- Restriction in use of statins and gemfibrozil only in lowest effective doses and only in patients with normal liver and kidney function

Statins and bile acid resins

- As great as a 50% reduction in low-density lipoprotein (LDL-C) or reduction equal to that occurring with a high-dose statin alone
- Favorable side effect profile

Statin and niacin

- Usefulness in patients with mixed hyperlipidemia and patients with elevated cholesterol alone
- Increased chance of myopathy
- Reduced tolerability due to vasodilatory effects of niacin

Cholesterol absorption inhibitors and low-dose statin

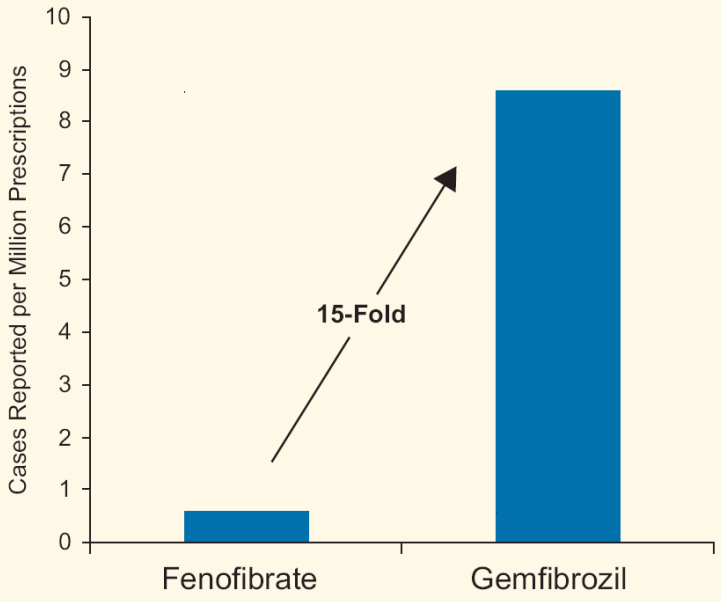
- Reduction in intestinal absorption of both dietary and biliary cholesterol from intestine
- Inhibition of both endogenous and exogenous production of cholesterol
- Possible reduction of plasma LDL-C levels, with subsequent decreased potential for development of CHD

Bile acid resins and nicotinic acids

- Reductions of 32% to 43% in LDL-C
- Increases of 37% to 43% in high-density lipoprotein cholesterol (HDL-C) in patients with coronary heart disease (CHD)

Fibrate and niacin

- Synergistic effects on triglyceride and HDL-C levels
- Usefulness in patients with very high triglyceride concentrations



Statin	Gemfibrozil	Fenofibrate
Atorvastatin	↑ in C_{max} (expected)	No effect
Simvastatin	↑ in C_{max} by 2-fold	No effect
Pravastatin	↑ in C_{max} by 2-fold	No effect
Rosuvastatin	↑ in C_{max} by 2-fold	No effect
Fluvastatin	No effect	No effect
Lovastatin	↑ in C_{max} by 2.8-fold	Not available
Cerivastatin	↑ in C_{max} by 2-fold	No effect

Abbreviations: C_{max}, maximum plasma concentration; ↑, increase.

More cases of rhabdomyolysis are reported with gemfibrozil treatment than with fenofibrate treatment

Statin/Fibrate Combination Therapy Pharmacokinetic Interactions

Jones PH et al. *Am J Cardiol.*2005;95:120-122.
Prueksaritanont Tet al. *Drug Metab Dispos.* 2002;30:1280-1287.

Steps to Minimize the Risk of Muscle Toxicity with Fibrate–Statin Combination Therapy

- Use statin alone for non-HDL-C goals
- Use fish oils or niacin rather than fibrates
- Keep the doses of the statin and fibrate low
- Dose the fibrate in the AM and the statin in the PM
- Avoid (or cautiously use) combo in renal & liver impairment
- Teach the patient to recognize muscle symptoms
- Discontinue therapy if muscle symptoms are present and CK is >10 times the upper limit of normal

Safety Considerations for Combination of Statins with Niacin

- Statins + niacin
  - Potential increased risk of myopathy (low)
  - Potential increased risk of transaminitis
  - Caution in patients with uncontrolled diabetes

Third Report of the National Cholesterol Education Program. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final Report. At: www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf. Accessed June 21, 2004.

Ezetimibe: Laboratory Safety Monitoring

- Laboratory monitoring is not required for ezetimibe monotherapy. When ezetimibe is added in combination with statins, liver enzyme monitoring is recommended at initiation of ezetimibe therapy and then according to statin recommendations.
- Ezetimibe administration is not associated with excess risk for myopathy or rhabdomyolysis. However, myopathy and rhabdomyolysis are known adverse reactions to statins. Therefore, if myalgias occur during combination therapy with ezetimibe and statin, muscle enzyme monitoring may be indicated.

Package insert.
Bays H. *Expert Opin Investig Drugs* 2002;11:1587-1604.

Applying Combination Logic to Lipid Lowering

- **Safer combinations**
  - Statin + bile acid sequestrants for LDLlowering
  - Statin + cholesterol absorption inhibitor for LDL-lowering
  - Statin + fish oil for combined dyslipidemias

- **"Riskier" combinations**
  - Statin+ fibric acid for combined dyslipidemias
  - Statin + niacin + fibric acid for combined dyslipidemia
  - Statin + niacin for combined dyslipidemia

TABLE 3 Clinical Laboratory Protocol for Monitoring Lipid-Lowering Therapy
Admission Lab—Comprehensive Metabolic Panel (CMP)*

Medication	Lab† Needed (Before Start)	Repeat (Initially or Dose Change)	Maintenance Monitoring‡ (If at Goal)
Fibrates	CMP	Lipids, glucose, AST, ALT, and CBC @ 2 mos	Lipids, AST, and ALT every 6 mos; CMP, CBC, and TSH annually
Statins	CMP and CPK	Lipids, AST, and ALT @ 2 mos	Lipids, AST, and ALT @ 3 mos; then every 6 mos; TSH and glucose annually
Niacin Niacin ER	CMP	Lipids, glucose, AST, and ALT, @ 2 mos	Lipids, glucose, AST, and ALT every 3 mos for 1st year; then every 6 mos; TSH annually
Niacin ER/lovastatin combination	CMP and CPK	Lipids, glucose, AST, and ALT @ 2 mos	Lipids, glucose, AST, and ALT @ 3 mos; then every 6 mos. TSH annually
Resins	CMP	Lipids @ 2 mos	Lipids every 6 mos; gucose, AST, ALT and TSH annually
Fish oils	CMP	Lipids and glucose @ 2 mos	Lipids every 6 mos; glucose, AST, ALT, and TSH annually
Niacin with any statin	CMP and CPK	Lipids, glucose, AST, and ALT @ 2 mos	AST and ALT every 3 mos; lipids, glucose every 6 mos; CMP and TSH annually
Niacin with fibrate	CMP and CPK	Lipids, AST, and ALT @ 2 months (if adding fibrate, CBC @ 2 mos)	AST and ALT every 3 mos; lipids, glucose every 6 mos; CMP, CBC, and TSH annually
Fibrate with statin§	CMP and CPK	Lipids, AST, and ALT @ 2 mos (If adding fibrate, CBC @ 2 mos)	Lipids, AST, ALT every 3 mos (include BUN and creatinine, CPK every 6 mos); CMP, CBC, and TSH annually

CMP:*CPK, TSH, lipid profile, Lp(a), and apo-B (to rule out nephrotic syndrome, obstructive liver disease, diabetes, dysproteinemias, & hypothyroidism and assess CAD risks). Brown AS. AJC 2002;90(suppl):44K–49K

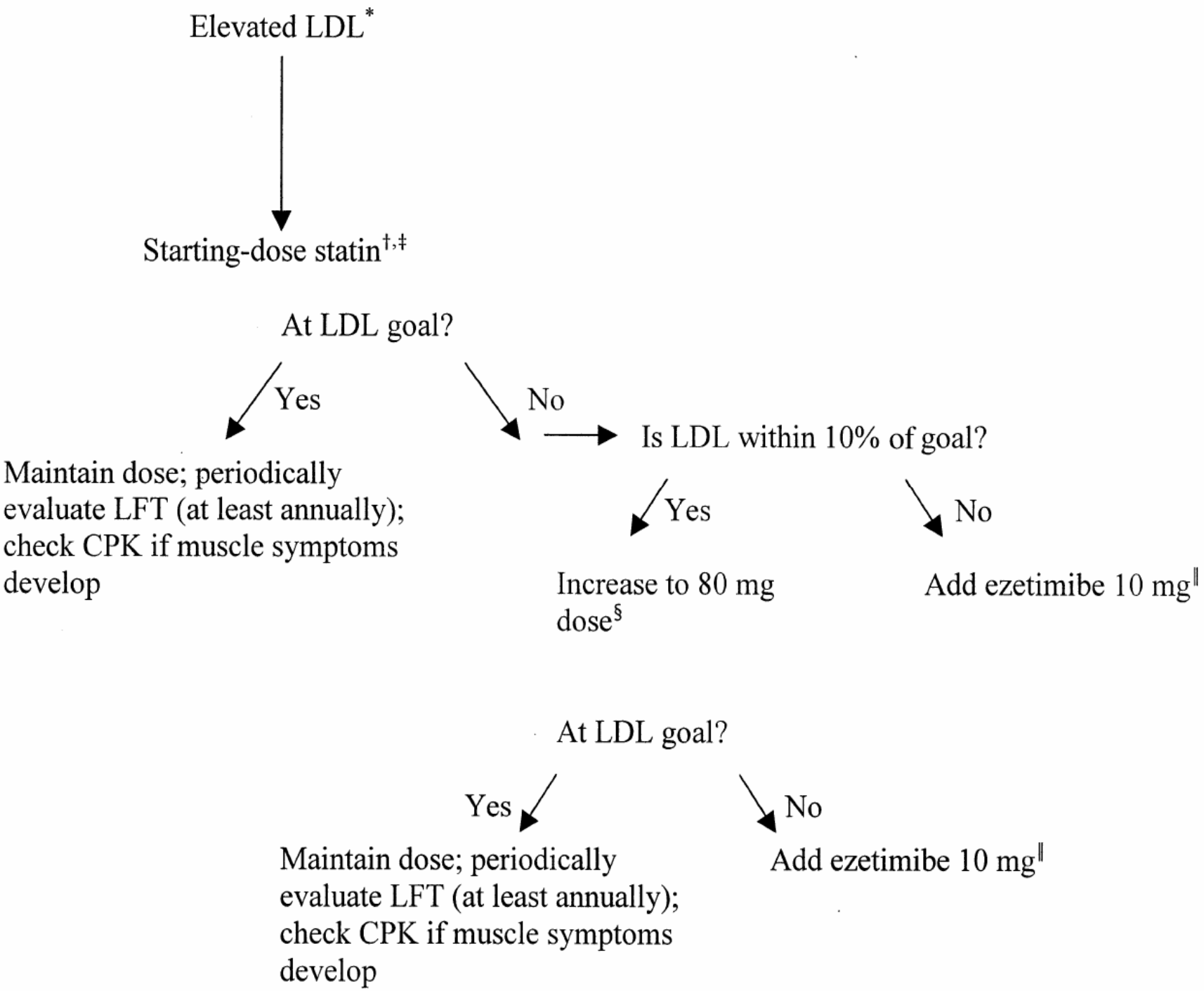
Combination Therapy: Pros and Cons

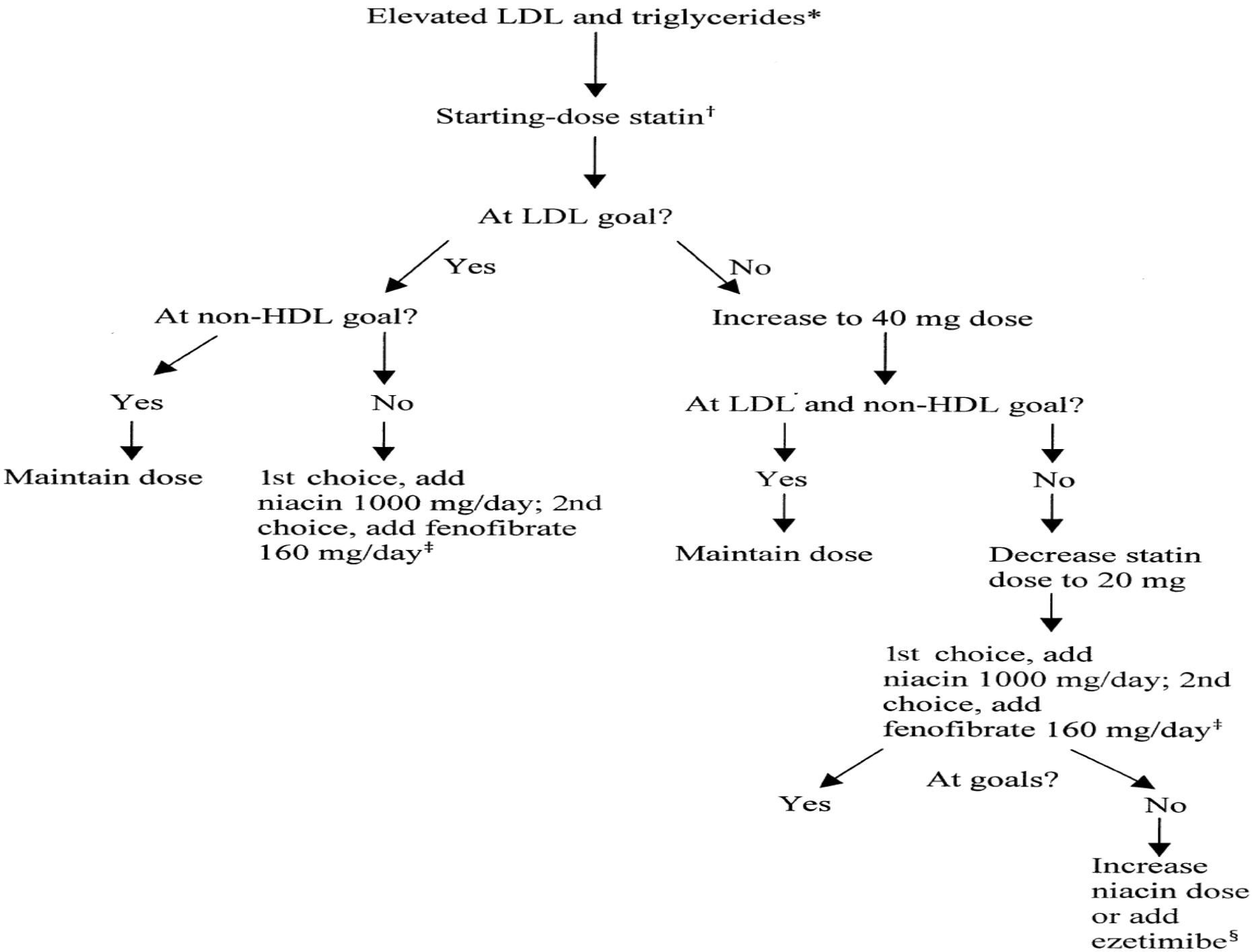
Pros

- ↓LDL-C, ↓TG, ↑HDL-C
- May ↓Lp(a) (niacin)
- ↑LDL particle size
- ↓Fibrinogen (fibrate)
- Angiographic data

Cons

- Increased adverse effects (rhabdomyolysis)
- Drug interactions
- Increased costs
- Lack of outcome studies
- Adherence


Elevated LDL*
Starting-dose statin†,‡
At LDL goal?
Yes
No
Maintain dose; periodically evaluate LFT (at least annually); check CPK if muscle symptoms develop
Is LDL within 10% of goal?
Yes
No
Increase to 80 mg dose§
Add ezetimibe 10 mg‖
At LDL goal?
Yes
No
Maintain dose; periodically evaluate LFT (at least annually); check CPK if muscle symptoms develop
Add ezetimibe 10 mg‖


Elevated LDL and triglycerides*
Starting-dose statin†
At LDL goal?
Yes
No
At non-HDL goal?
Increase to 40 mg dose
Yes
No
At LDL and non-HDL goal?
Maintain dose
1st choice, add niacin 1000 mg/day; 2nd choice, add fenofibrate 160 mg/day‡
Yes
No
Maintain dose
Decrease statin dose to 20 mg
1st choice, add niacin 1000 mg/day; 2nd choice, add fenofibrate 160 mg/day‡
At goals?
Yes
No
Increase niacin dose or add ezetimibe§


감사합니다!