Combinazioni a dosi fisse nella terapia delle dislipidemie. Nuovi sviluppi

Prof. Alberto Corsini

Univerisità degli Studi di Milano

Terapia d’associazione

- La terapia di combinazione rappresenta una strategia terapeutica ben consolidata in numerose patologie quali cardiovascolari, infezioni ed in ambito oncologico
- Le aumentate conoscenze sulla fisiopatologia e sulla patogenesi di numerose patologie hanno, a tutti gli effetti, sottolineato l’intelligenza farmacologica di un intervento che prevede l’associazione di principi attivi che possono interessare diversi meccanismi alla base delle patologie stesse
- Lo scopo e’ quello di ottimizzare l’intervento terapeutico sia per un’aumentata efficacia sia per minimizzare le resistenze e gli eventi avversi associati alle alte dosi delle mono-terapie

Management of Dyslipidemia

- 1st line therapy :
  Statins

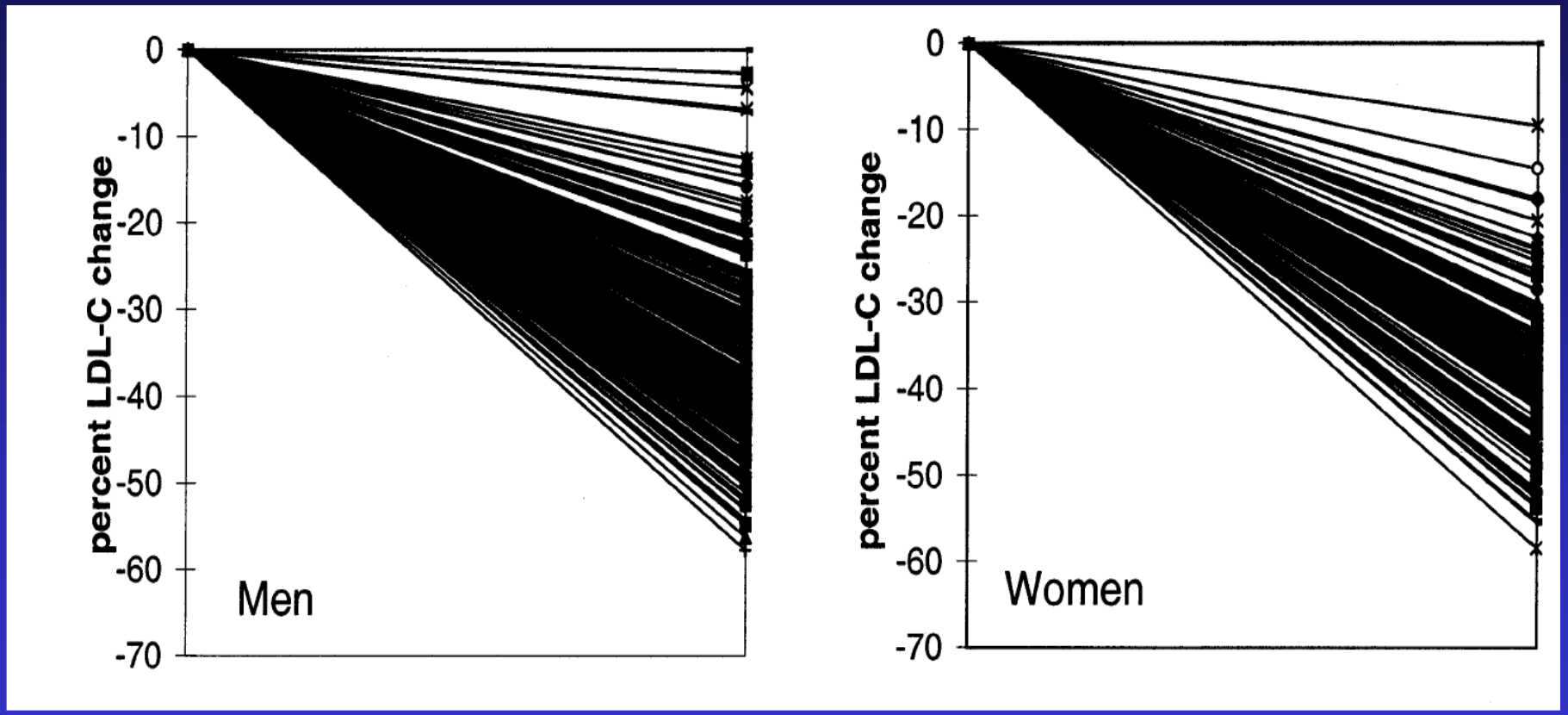
- 2nd line therapy :
  Add-on or combination therapies

Other classes of drugs :

CAI (ezetimibe), BAS, PCSK9 inhibitors

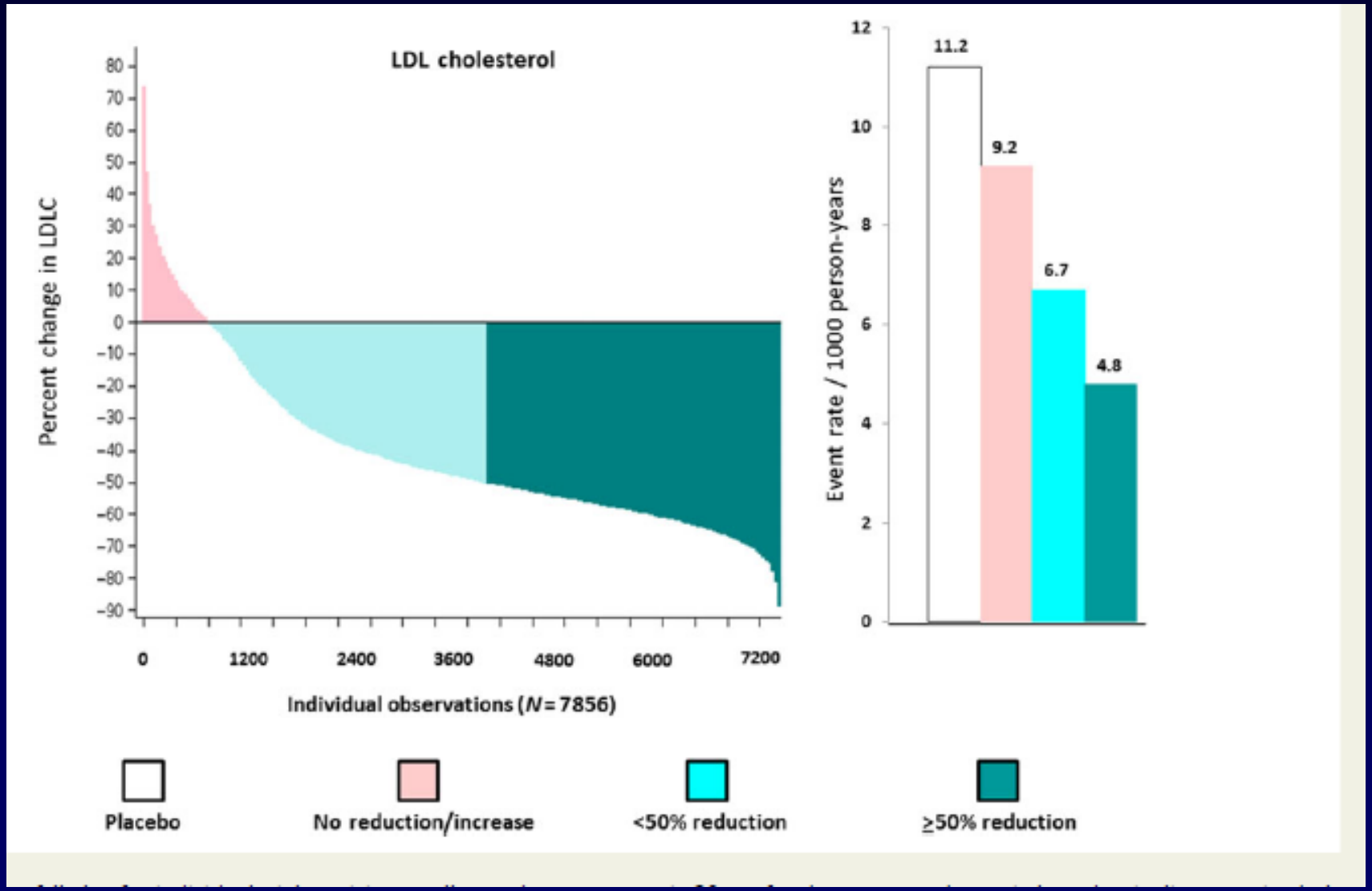
Alberico L. Catapano et al. Eur Heart J 2016;eurheartj.ehw272

Individual LDL-C % Response to Atorvastatin 10mg/day



Pedro-Botet J et al. Atherosclerosis 158 (2001) 183-193

Waterfall plot for participants allocated to rosuvastatin 20 mg for % change in LDL-C and incident event rates in JUPITER trial



Ridker PM et al Eur Heart J. 2016 Feb 24

Lipids in Health and Disease

BioMed Central

Research

Open Access

NPC1L1 haplotype is associated with inter-individual variation in plasma low-density lipoprotein response to ezetimibe

Robert A Hegele*[1,2], Justin Guy[1], Matthew R Ban[1] and Jian Wang[1]

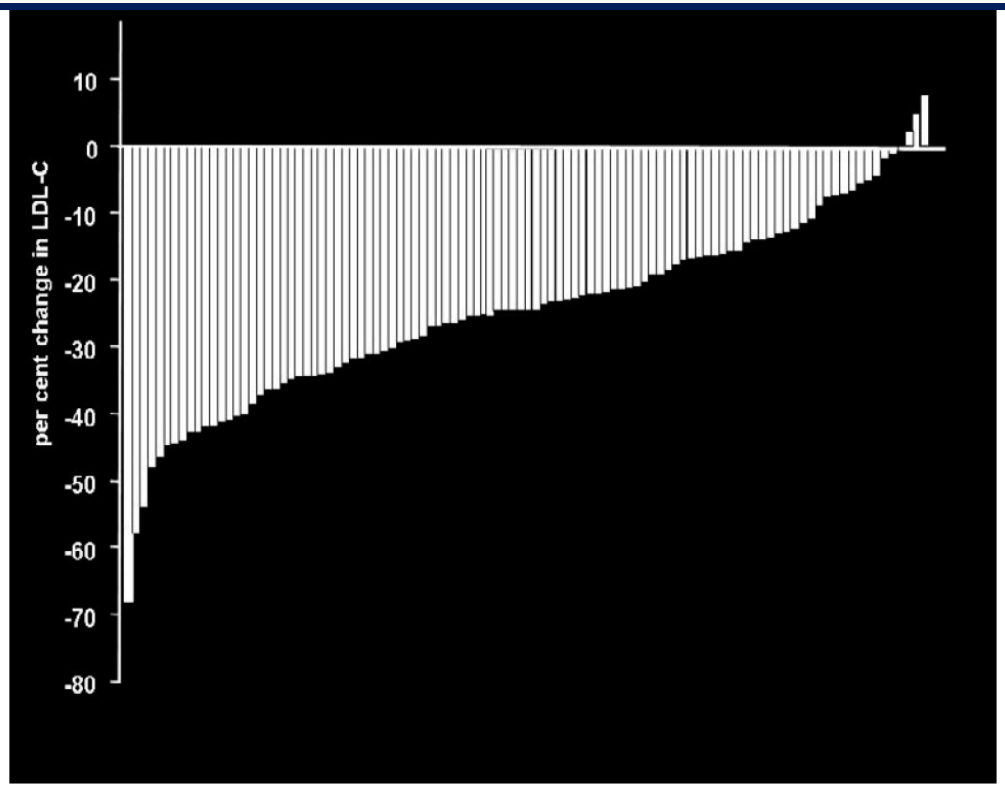


Figure 1
Individual LDL-cholesterol response to ezetimibe 10 mg. Each bar represents the percent change in LDL-cholesterol from baseline for one study subject; these data are arranged in rank order to show the range of responses.

Lipids in Health and Disease 2005, 4:16

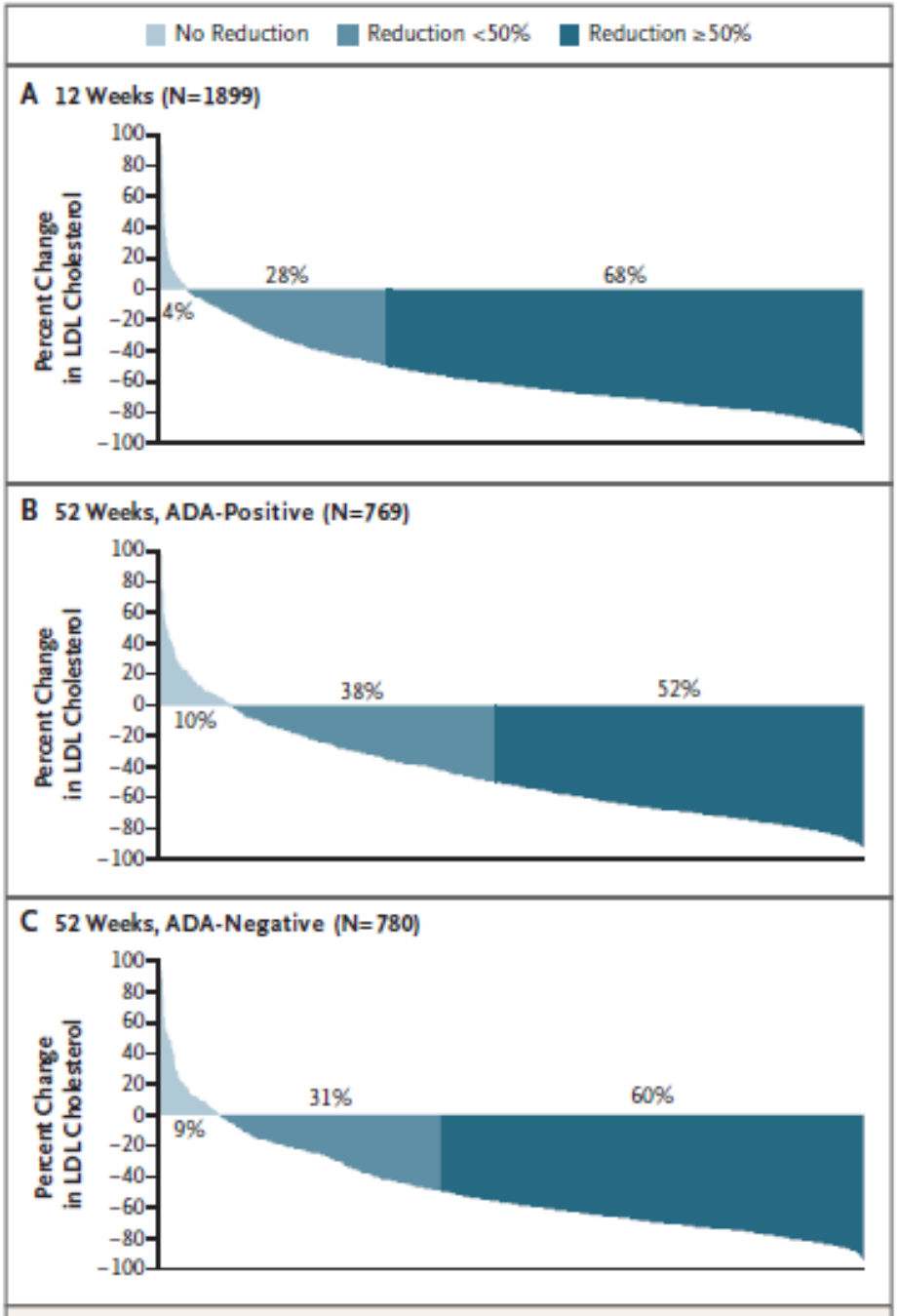
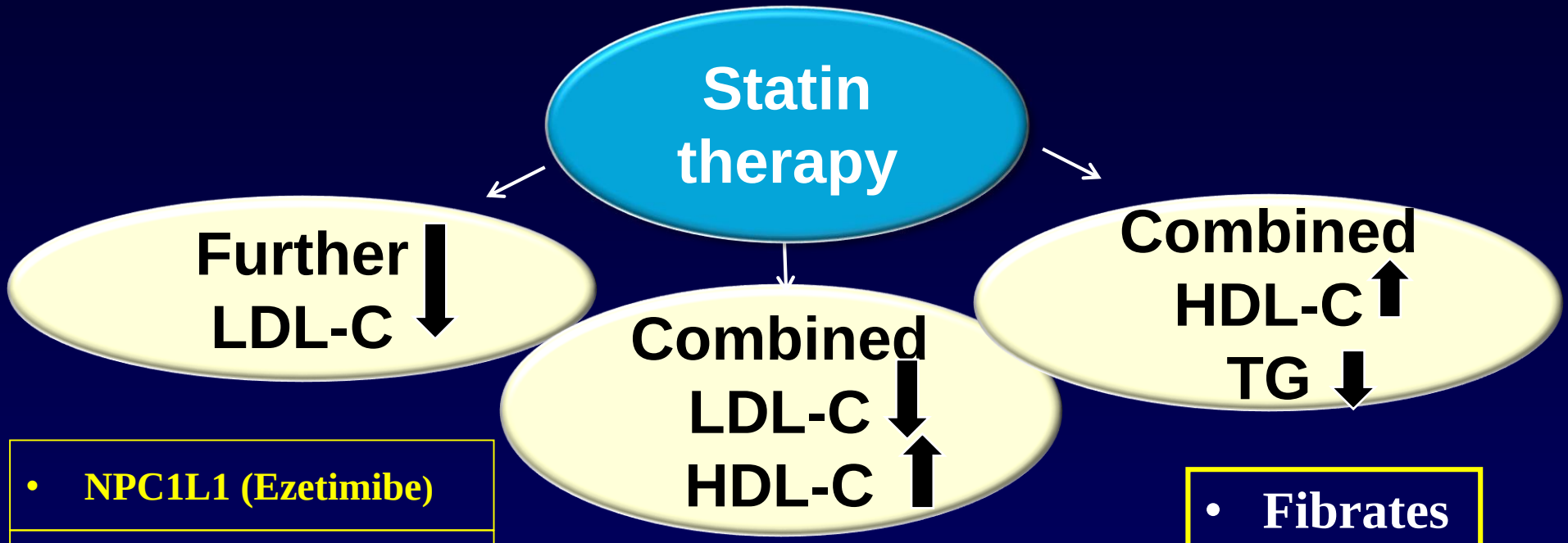


Figure 2. Variability in the Reduction in LDL Cholesterol Levels, According to the Presence or Absence of Antidrug Antibodies (ADAs).

Ridker P et al March 17, 2017, at NEJM.org

Future development of lipid-lowering drugs



- NPC1L1 (Ezetimibe)
- PCSK9 inhibition (Monoclonal Ab*)
- ApoB-100 Antisense oligonucleotides
- Lopitamide

- CETP inhibition (Anacetrapib*, Evacetrapib*)

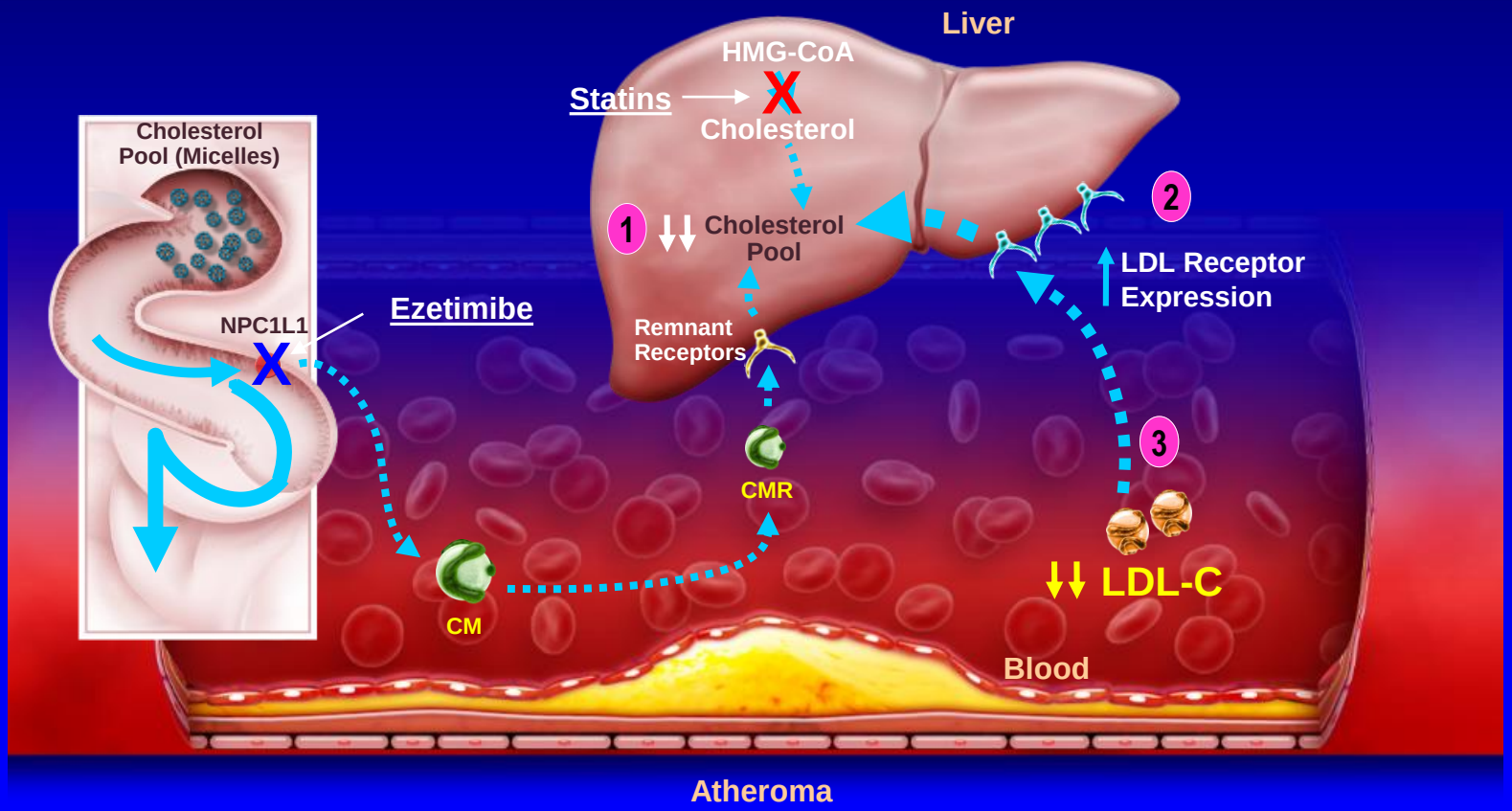
- Fibrates
- ApoCIII Antisense oligonucleotides
- Gene Therapy for LPL deficiency

Modified from Landmesser U Eur Heart J. 2013 ;34(17):1254-7

Ezetimibe and Statins Have Complementary Mechanisms of Action[1]

Together, ezetimibe in combination with a statin provides:

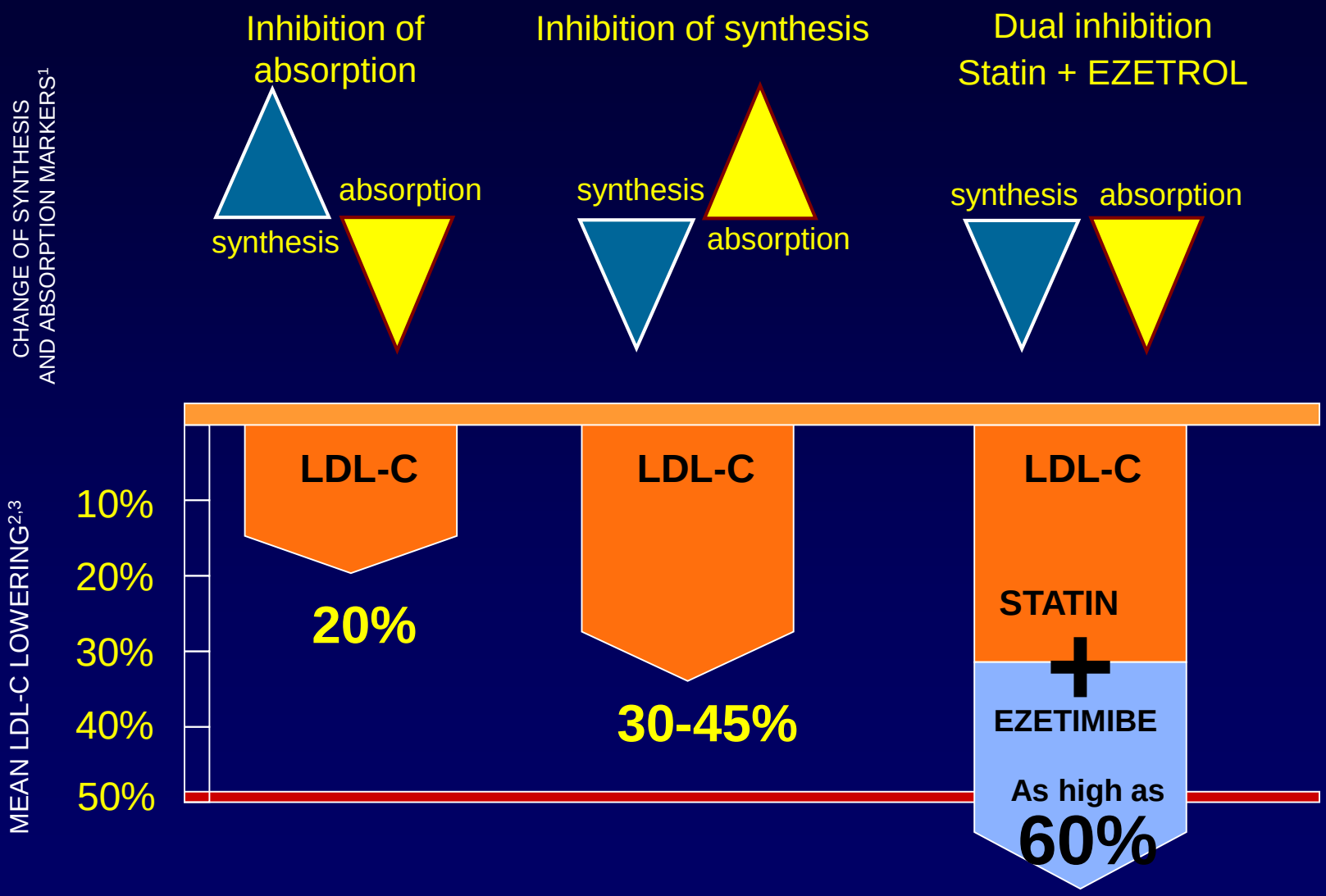
1. Reduction of hepatic cholesterol
2. Increased LDL receptor expression
3. Increased clearance of plasma LDL-C



NPC1L1 = Niemann-Pick C1-like 1; HMG-CoA = 3-hydroxy-3-methylglutaryl acetyl coenzyme A; CMR = chylomicron remnant.

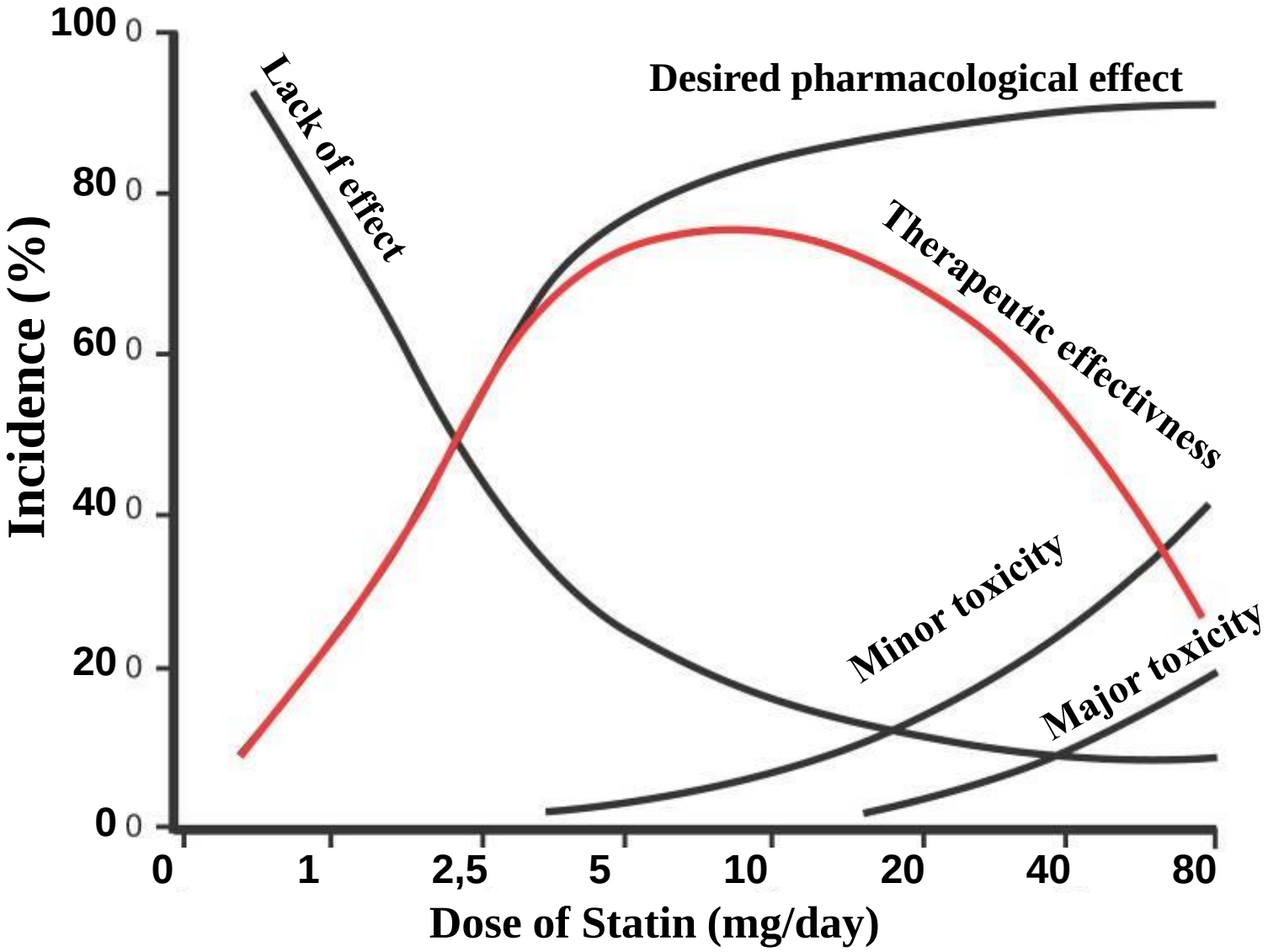
1. Grigore L et al. *Vas Health Risk Manag*. 2008;4:267–278.

As high as 60% LDL-C lowering via dual inhibition



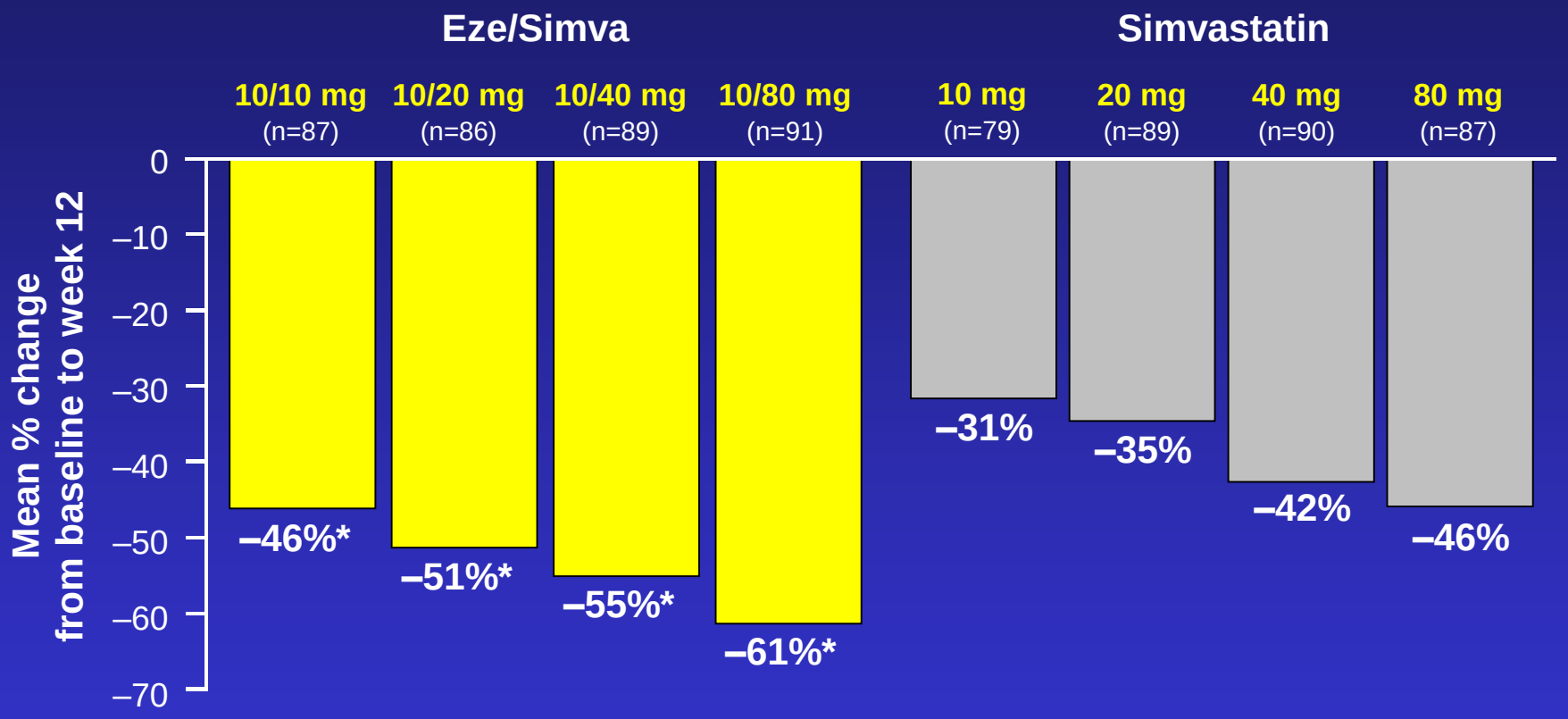
1. Assmann G, et al. *J Am Coll Cardiol* 2004;43(5, Suppl. 2):A445-A446; **2.** Goldberg AC, et al. *Mayo Clin Proc.* 2004 May;79(5):620-9.; **3.** Davidson M et al. J Am Coll Cardiol 2002; 40:2125-34.

Statin: dose-effect relationship



Adapted from Rowland M et al., Clin. Pharmacokin.: Concepts and Applications. 2nd Ed. Philadelphia, Lea & Febiger, 1989

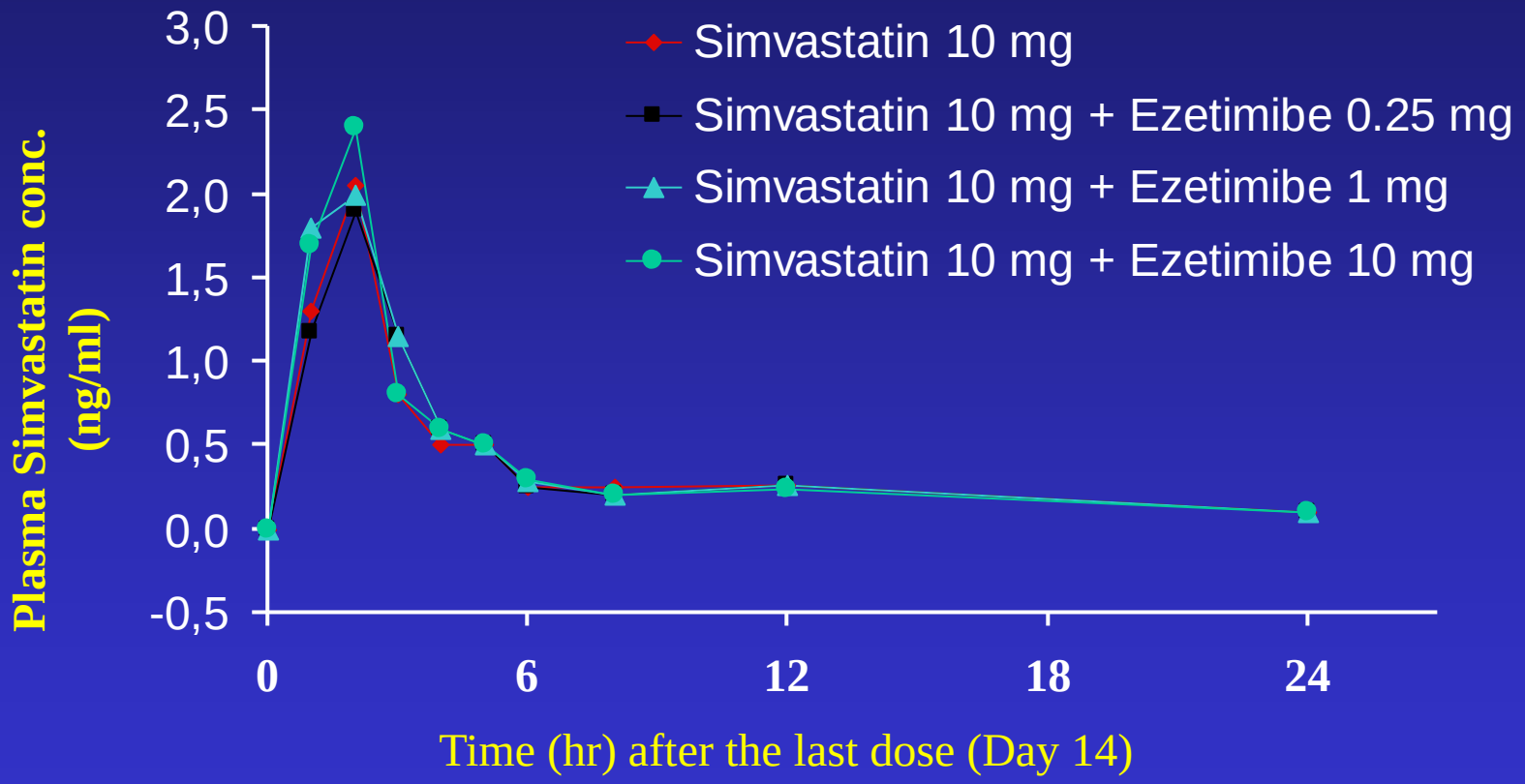
LDL-C Reduction Across the Dose Range



*p<0.001 vs. corresponding dose of simvastatin

Adapted from Goldberg AC et al. Poster presentation at the 53rd ACC, March 7–10, 2004.

Co-administration with Statins



Kosoglou et al. *Atherosclerosis.* 2000;151:135.

There is a negative correlation between the LDL-C response to statins and the response to Ezetimibe

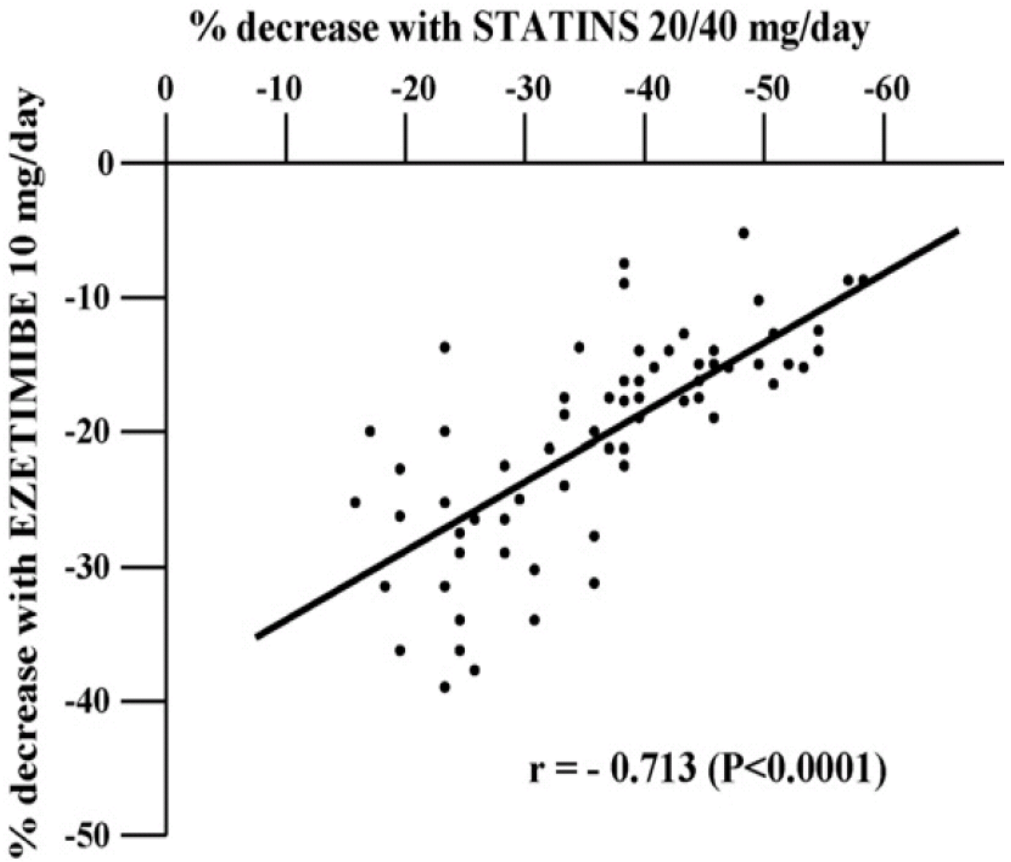
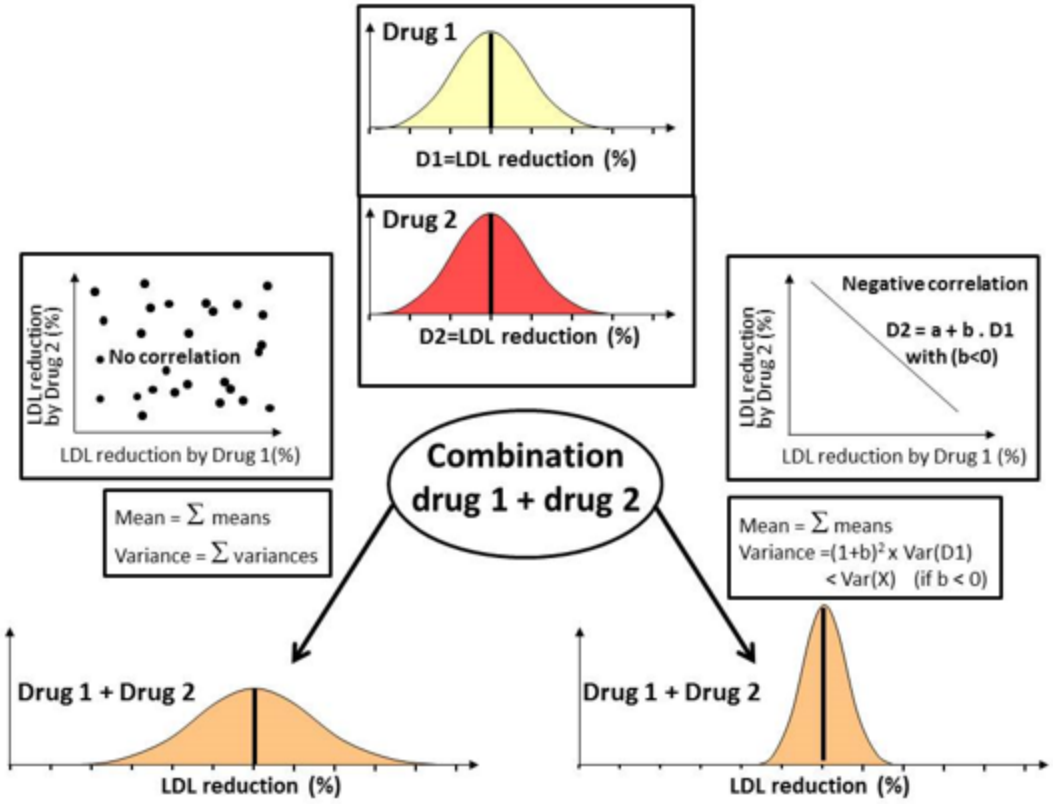


Fig. 2. Pearson's correlation between percent decrease of LDL-C induced by statins and by ezetimibe in genotype confirmed heterozygous FH patients.

Pisciotta L et al. Atherosclerosis 2006

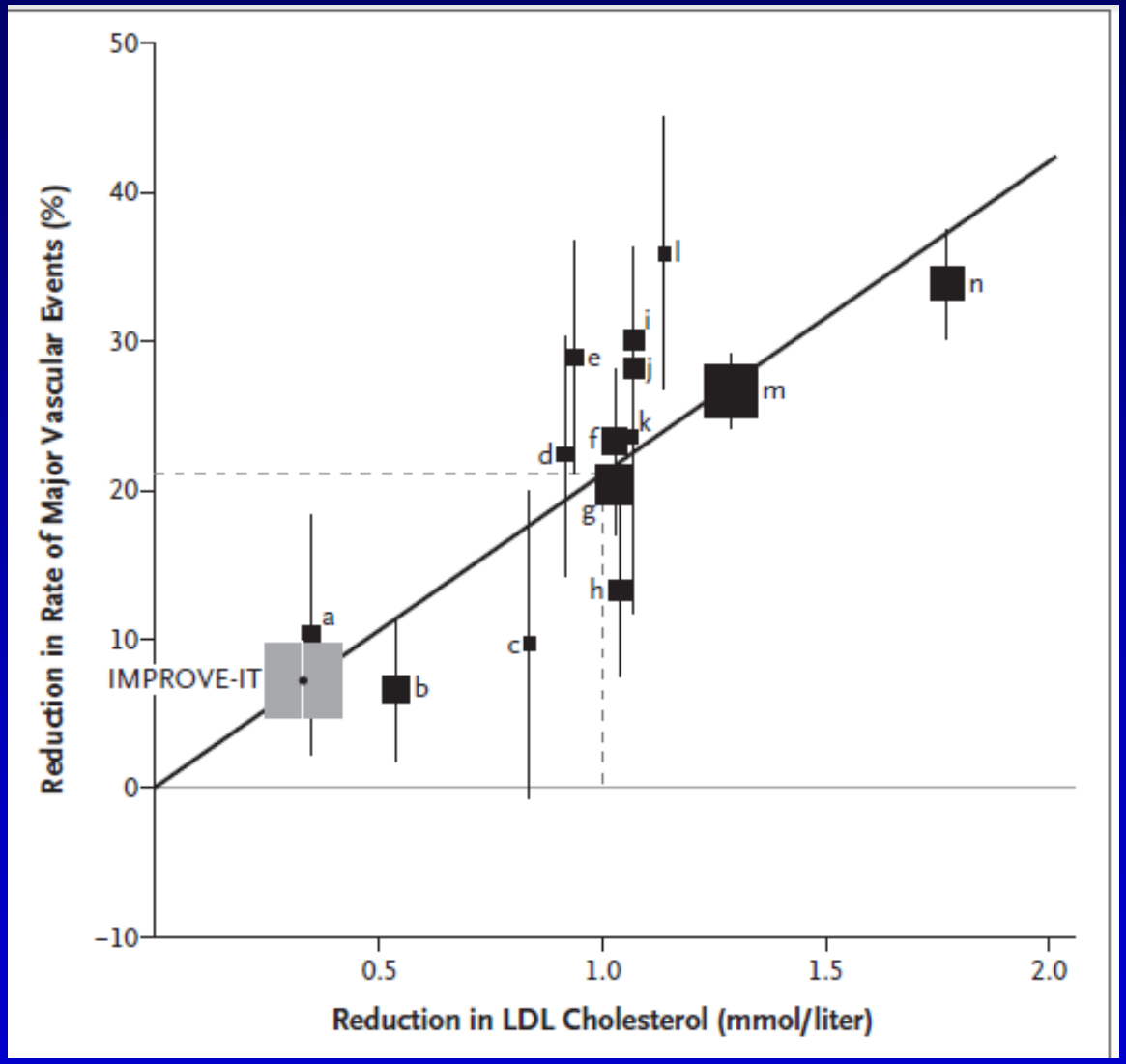
Effect of a negative correlation between the LDL reduction of two drugs on the final variance of LDL reduction induced by the combination of the two drugs

Supplemental Figure 2.



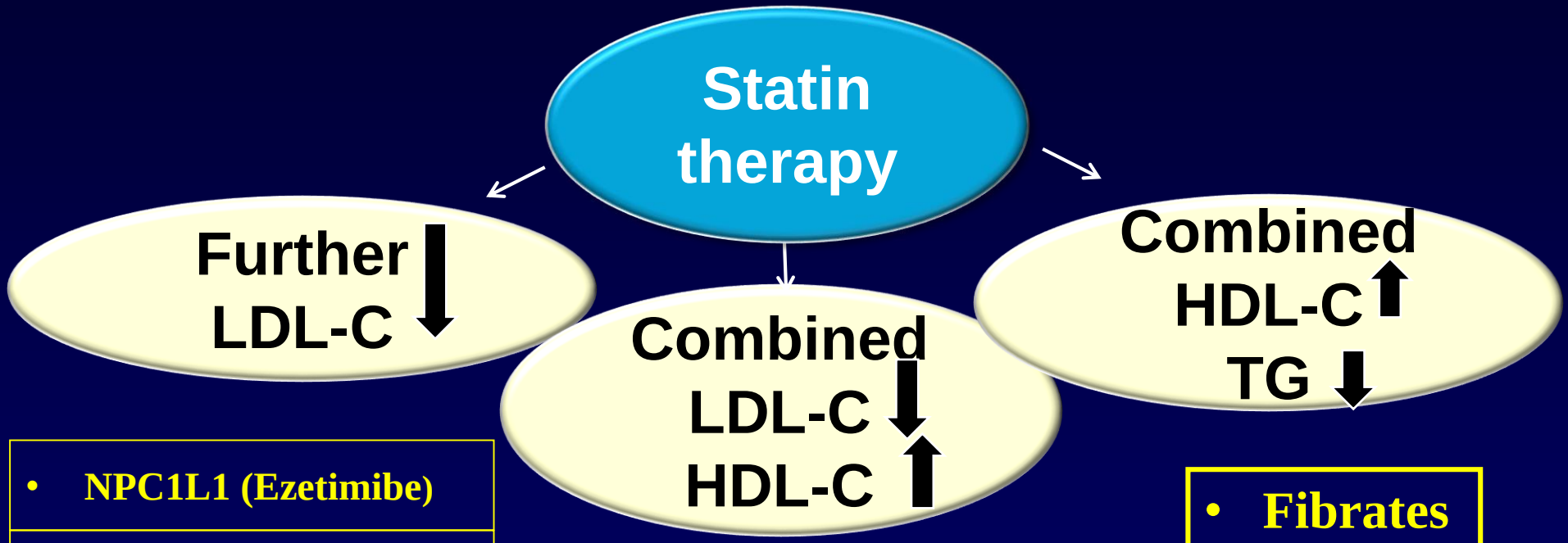
Mathematical demonstration of the effect of a negative correlation between the LDL reduction of two drugs on the final variance of LDL reduction induced by the combination of the two drugs.

Plot of the IMPROVE-IT Trial Data and Statin Trials for Change LDL-C vs Clinical Benefit



Cannon CP et al. N Engl J Med 2015;372:2387-2397

Future development of lipid-lowering drugs



- NPC1L1 (Ezetimibe)
- PCSK9 inhibition (Monoclonal Ab*)
- ApoB-100 Antisense oligonucleotides
- Lopitamide

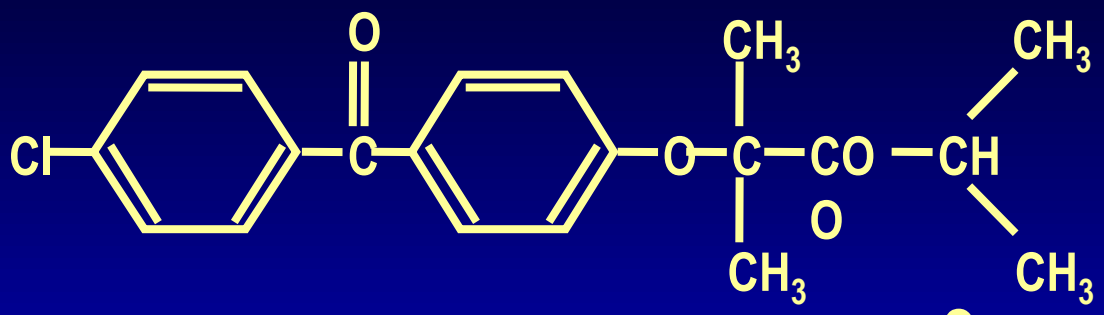
- CETP inhibition (Anacetrapib*, Evacetrapib*)

- Fibrates
- ApoCIII Antisense oligonucleotides
- Gene Therapy for LPL deficiency

Modified from Landmesser U Eur Heart J. 2013 ;34(17):1254-7

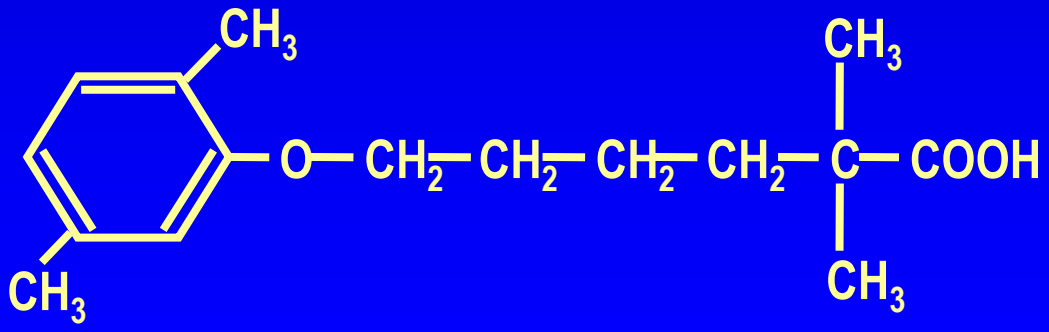
Fibrates

Fenofibrate

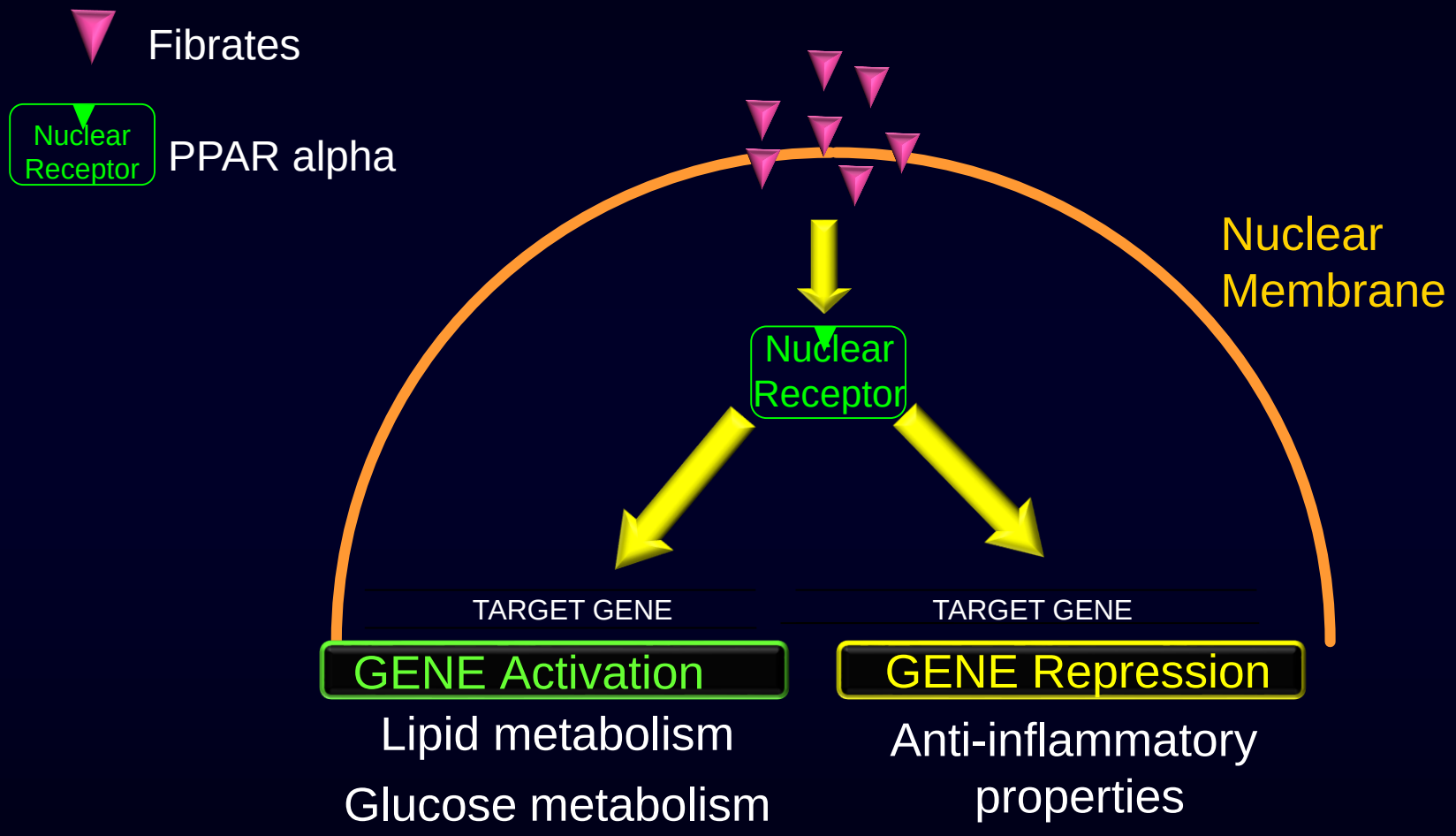


Bezafibrate

Gemfibrozil



Fibrates: Mechanism of Action



PPAR:Peroxisome proliferator-activated receptor

Effects of Fenofibrate on Plasma Lipids Double-Blind, Multicenter Study in Patients with Type IIa or IIb Hyperlipidemia

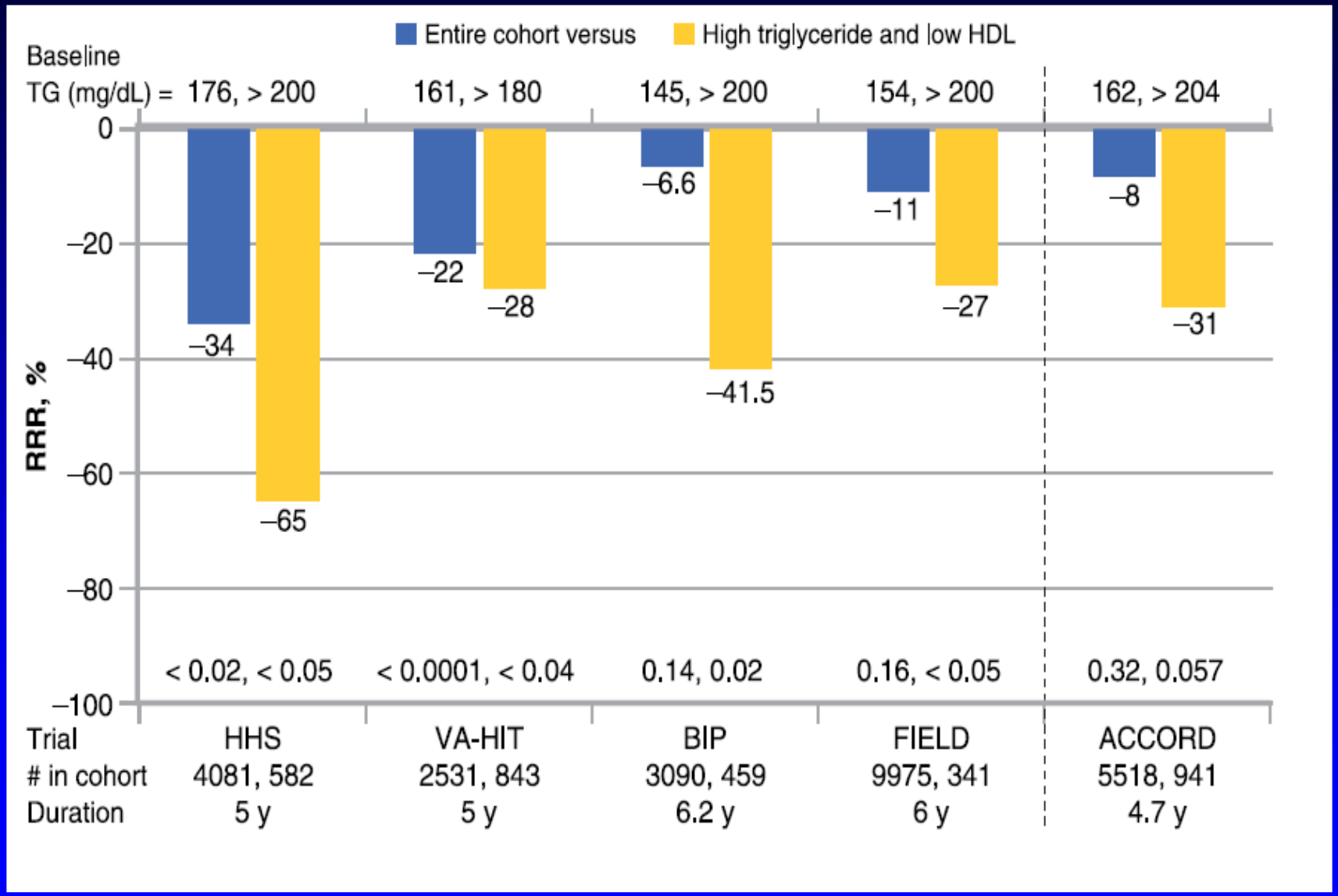
Percentage Changes at Endpoint from Baseline Values after 24 Weeks of Double Blind Study vs Placebo (Plb)

	Type IIa (%)		Type IIb (%)	
	Feno n=92	Plb n=88	Feno n=24	Plb n=22
Total Cholesterol	**-17.5**	**-0.4**	**-15.8**	**+4.6**
LDL Cholesterol	**-20.3**	**+0.4**	**-6.1**	**-0.5**
HDL Cholesterol	**+11.1**	**-1.2**	**+15.3**	**-3.5**
Total Triglycerides	**-37.9**	**-4.2**	**-44.6**	**+22.3**
LDL/HDL Cholesterol	**-27.1**	**-1.9**	**-13.3**	**0.0**
VLDL Cholesterol	**-38.4**	**-2.5**	**-52.7**	**+8.4**

P<0.01 except for LDL-C in Type IIb, where *P*>0.10

Brown WV, et al. Arteriosclerosis. 1986; 6:670-678.

Cardiovascular event risk reduction in large monotherapy fibrate clinical trials



Rosenblit PD Curr Cardiol Rep (2012) 14:112–124

NOTA 13

Approfondimenti e basi teoriche della nota

- La terapia dovrebbe essere intrapresa contemporaneamente alla modifica dello stile di vita nei pazienti a rischio molto alto con livelli di C-LDL >70 mg/dL e in quelli a rischio alto con livelli di LDL-C >100 mg/dL
- L'uso dei farmaci ipolipemizzanti deve essere continuativo
- E' sempre necessario assicurare l'ottimizzazione del dosaggio della statina prima di prendere in considerazione la sua sostituzione o la sua associazione
- Per i pazienti con dislipidemia aterogenica (TG>200 mg/dl, HDL<34 mg/dl) e per quelli con ipertrigliceridemia i farmaci di seconda linea da somministrare in associazione alle statine sono i fibrati. Tra questi, il farmaco di prima scelta è il fenofibrato per la maggiore sicurezza di uso nei pazienti in terapia con statine; la combinazione di statine e gemfibrozil è invece associata ad un aumentato rischio di miopatia

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy), Ian Graham* (Chairperson) (Ireland), Guy De Backer (Belgium), Olov Wiklund (Sweden), M. John Chapman (France), Heinz Drexel (Austria), Arno W. Hoes (The Netherlands), Catriona S. Jennings (UK), Ulf Landmesser (Germany), Terje R. Pedersen (Norway), Željko Reiner (Croatia), Gabriele Riccardi (Italy), Marja-Riita Taskinen (Finland), Lale Tokgozoglu (Turkey), W. M. Monique Verschuren (The Netherlands), Charalambos Vlachopoulos (Greece), David A. Wood (UK), Jose Luis Zamorano (Spain)

Additional Contributor: Marie-Therese Cooney (Ireland)

Document Reviewers: Lina Badimon (CPG Review Coordinator) (Spain), Christian Funck-Brentano (CPG Review Coordinator) (France), Stefan Agewall (Norway), Gonzalo Barón-Esquivias (Spain), Jan Borén (Sweden), Eric Bruckert (France), Alberto Cordero (Spain), Alberto Corsini (Italy), Pantaleo Giannuzzi (Italy),

Table 18 Recommendations for drug treatments of hypertriglyceridaemia

Recommendations	Class [a]	Level [b]	Ref [c]
Drug treatment should be considered in high-risk patients with TG >2.3 mmol/L (200 mg/dL).	IIa	B	261, 262
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	IIb	B	263, 264
In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins.	IIb	C	261–264

NUMBER OF REPORTS OF RHABDOMYOLYSIS FOR FIBRATE/STATIN THERAPIES (1998 to 2002)

Medication	No. Cases Reported*	No. Prescriptions Dispensed†	No. Cases Reported per Million Prescriptions
Fenofibrate			
With cerivastatin	14	100,000	140
With other statins	2	3,419,000	0.58
Fenofibrate total	16	3,519,000	4.5
Gemfibrozil			
With cerivastatin	533	116,000	4,600
With other statins	57	6,641,000	8.6
Gemfibrozil total	590	6,757,000	87

*Food and Drug Administration's Adverse Event Reporting System (January 1, 1998 to March 31, 2002).

†Calculated from data from the National Prescription Audit *Plus* Report, IMS Health (January 1, 1998 to March 31, 2002), and a Verispan, LLC Concomitancy Report (January 1, 1998 to March 31, 2002).

Jones PH et al, Am J Cardiol, 95:120-122, 2005

Pharmacokinetic Interactions Between Statins and Fibrates

Alberto Corsini, PhD, Stefano Bellosta, PhD, and Michael H. Davidson, MD,

Am J Cardiol 2005;96[suppl]:44K–49K

Metabolic Pathways of Statins

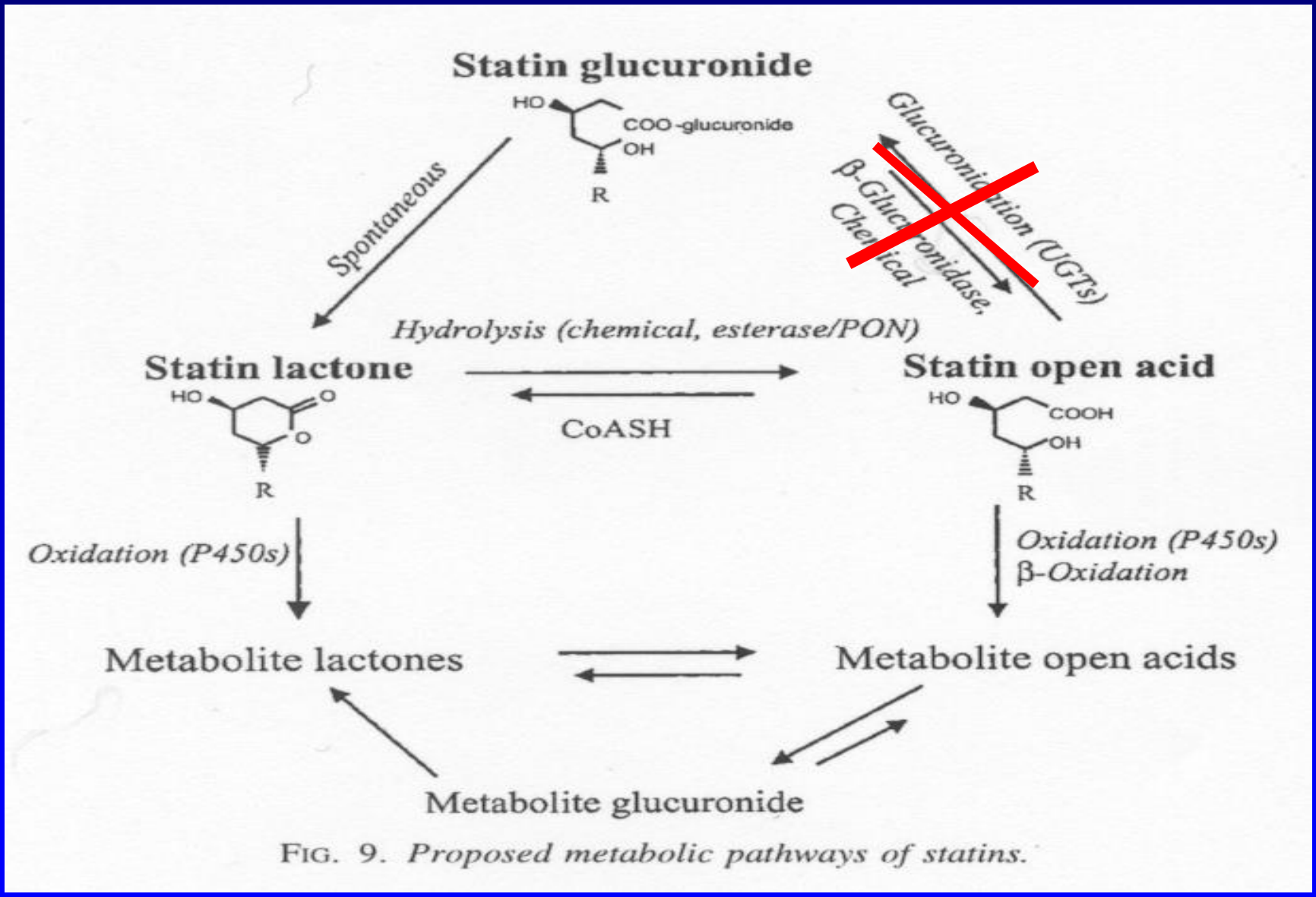
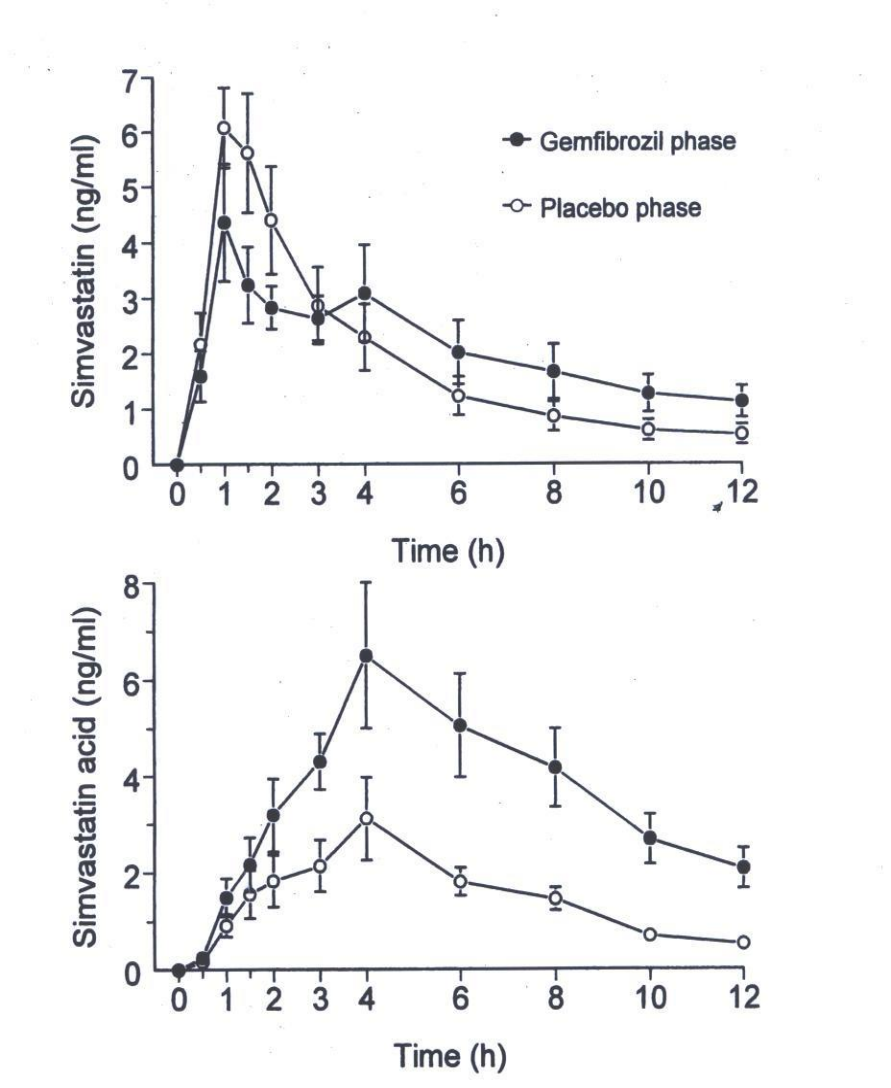


FIG. 9. *Proposed metabolic pathways of statins.*

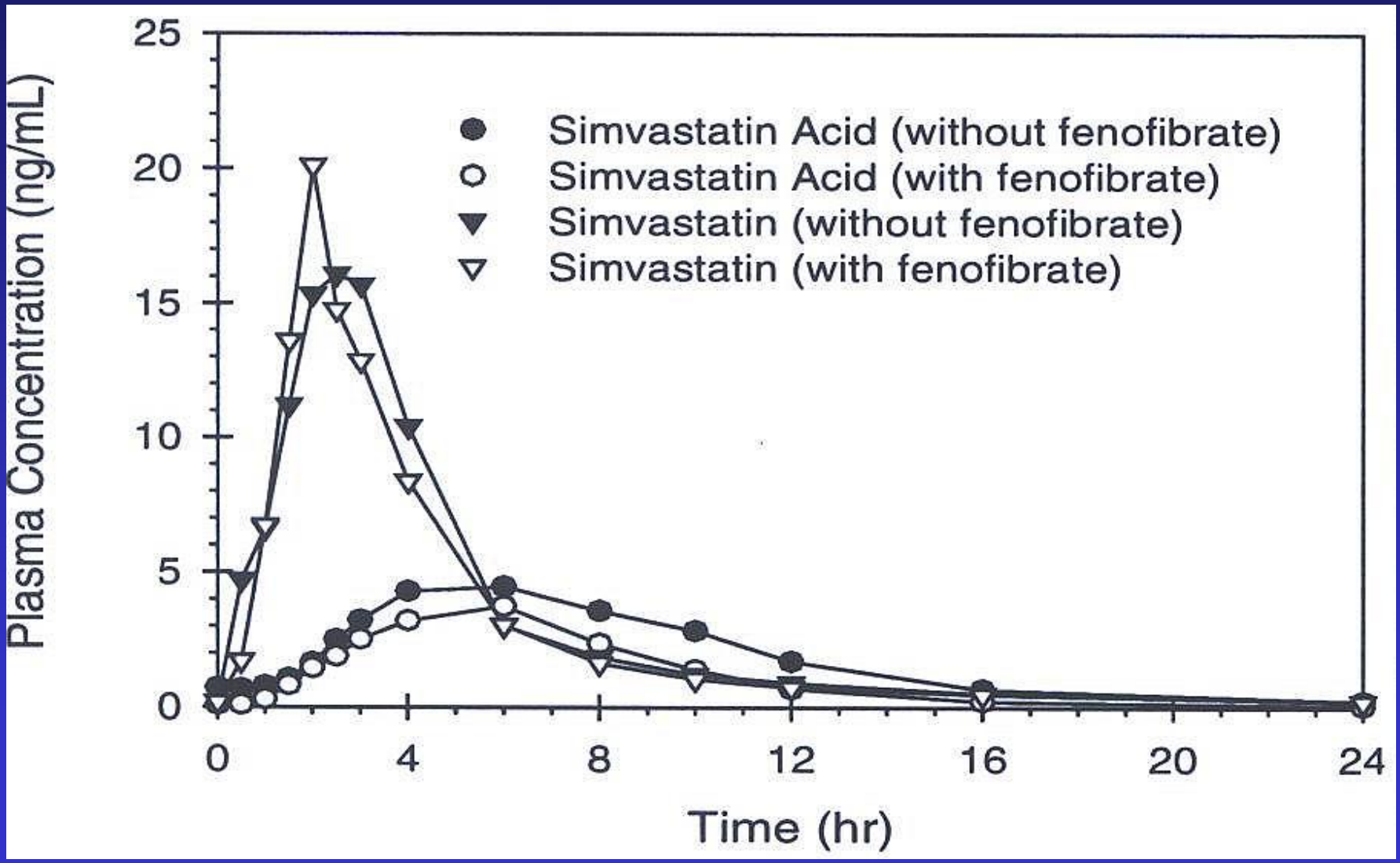
Drug Metabolism and Disposition 2002; Vol 30, N.5:505-512

Plasma concentration of simvastatin and simvastatin acid after oral dose simvastatin following a 3-day pretreatment with gemfibrozil



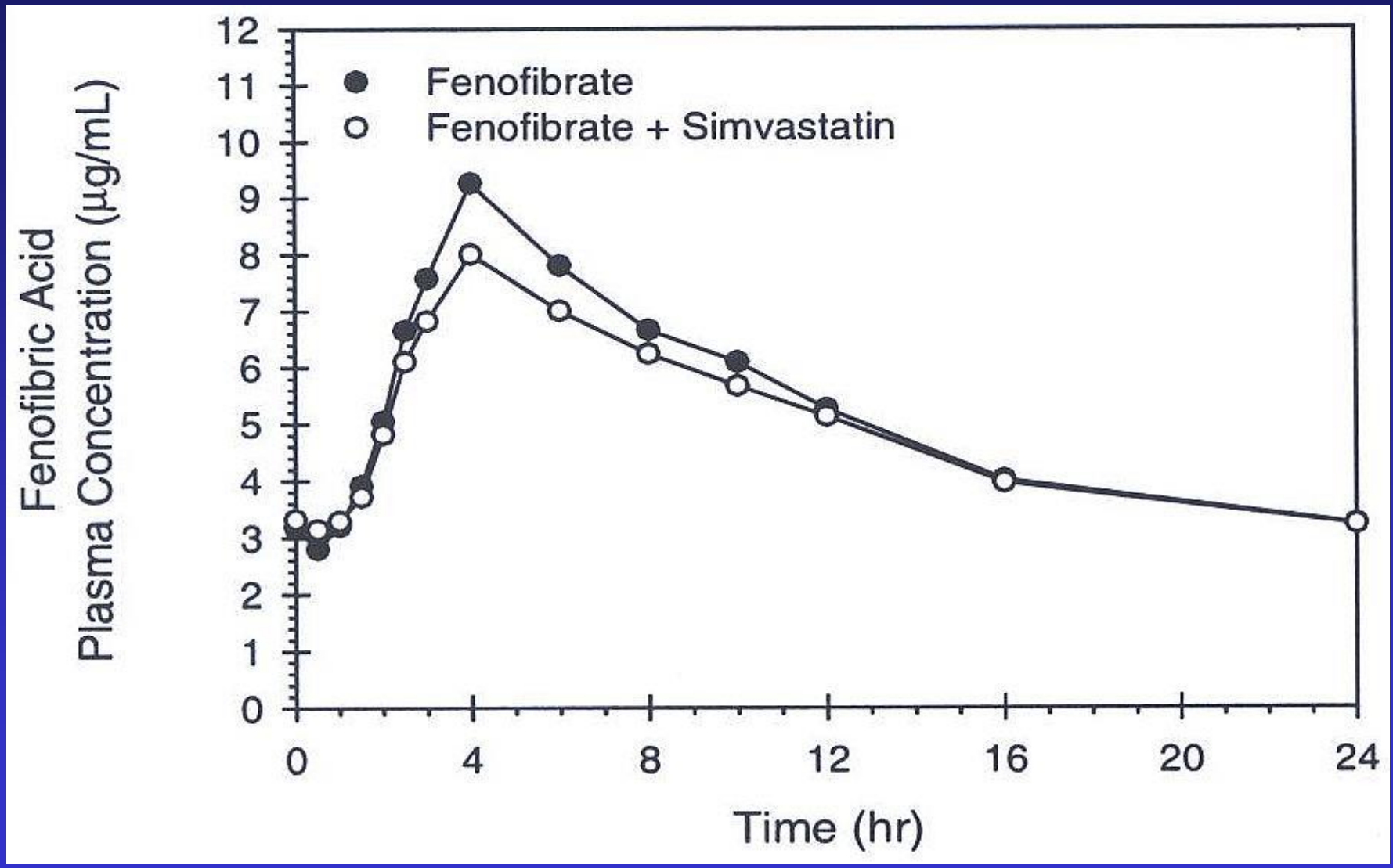
J T Backman et al. Clin Pharmacol Ther 2000:68:122-9

Mean plasma concentration-time profiles of simvastatin and simvastatin acid following multiple oral doses of 80mg simvastatin with or without multiple oral doses of 160mg fenofibrate (n = 12)



A.J. Bergman et al., Journal of Clinical Pharmacology 2004;44:1054-1062

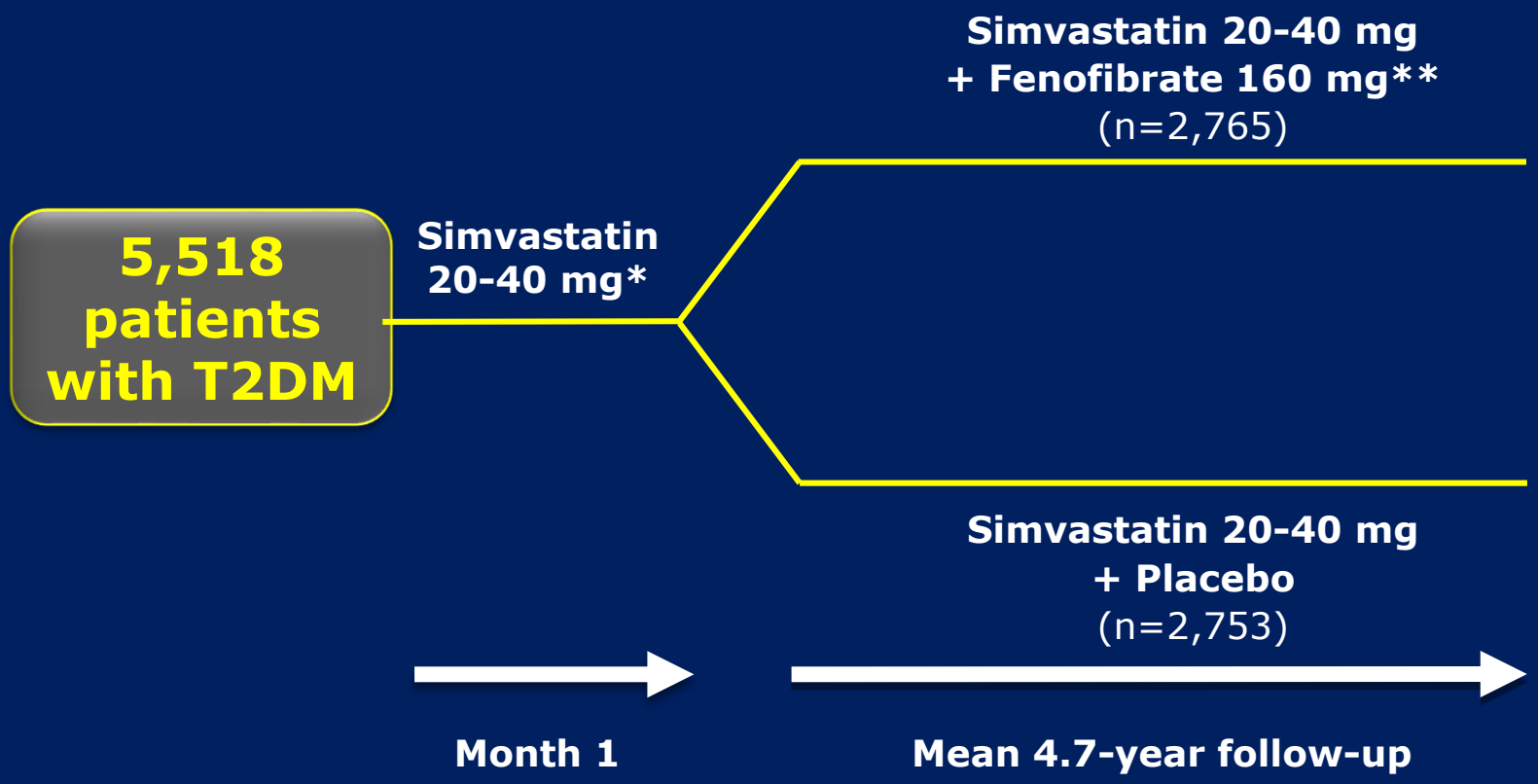
Mean plasma concentration-time profiles of fenofibric acid following multiple oral doses of 160mg fenofibrate with or without multiple oral doses of 80mg simvastatin (n = 12)



A.J. Bergman et al., Journal of Clinical Pharmacology 2004;44:1054-1062

ACCORD Lipid

Evaluating the effects on macrovascular events of fenofibrate/simvastatin combination therapy



*According to patients' LDL-C levels and CVD history

**Bioequivalent to 200 mg micronised and 145 mg nanocrystal. Patients whose eGFR was 30-50 mL/min/1.73 m^2 received a lower dose of fenofibrate, corresponding to 1/3 of the normal daily dose

Ginsberg HN et al. Am J Cardiol 2007;99(12A):56i-67i.
ACCORD Study Group. N Engl J Med. 2010. Epub.

ACCORD Lipid

No difference in serious adverse events between groups during follow-up

Adverse events, no. (%)	Simvastatin + Fenofibrate (N=2765)	Simvastatin + Placebo (N=2753)	*p* value
Out of the ordinary severe muscle aches/pains:			
Regardless of CK	1110 (40%)	1115 (41%)	0.81
Plus CK > 5 X ULN	7 (0.3%)	8 (0.3%)	0.79
Plus CK > 10 X ULN	1 (0.04%)	2 (0.07%)	0.56
Any non-hypoglycemic SAE	54 (2.0%)	43 (1.6%)	0.27
Any myopathy/myositis/ rhabdomyolysis SAE	4 (0.1%)	4 (0.1%)	1.00
Any hepatitis SAE	3 (0.1%)	0 (0.0%)	0.18
Any SAE attributed to lipid meds	27 (1.0%)	19 (0.7%)	0.24

ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

European Heart Journal Advance Access published February 18, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv043

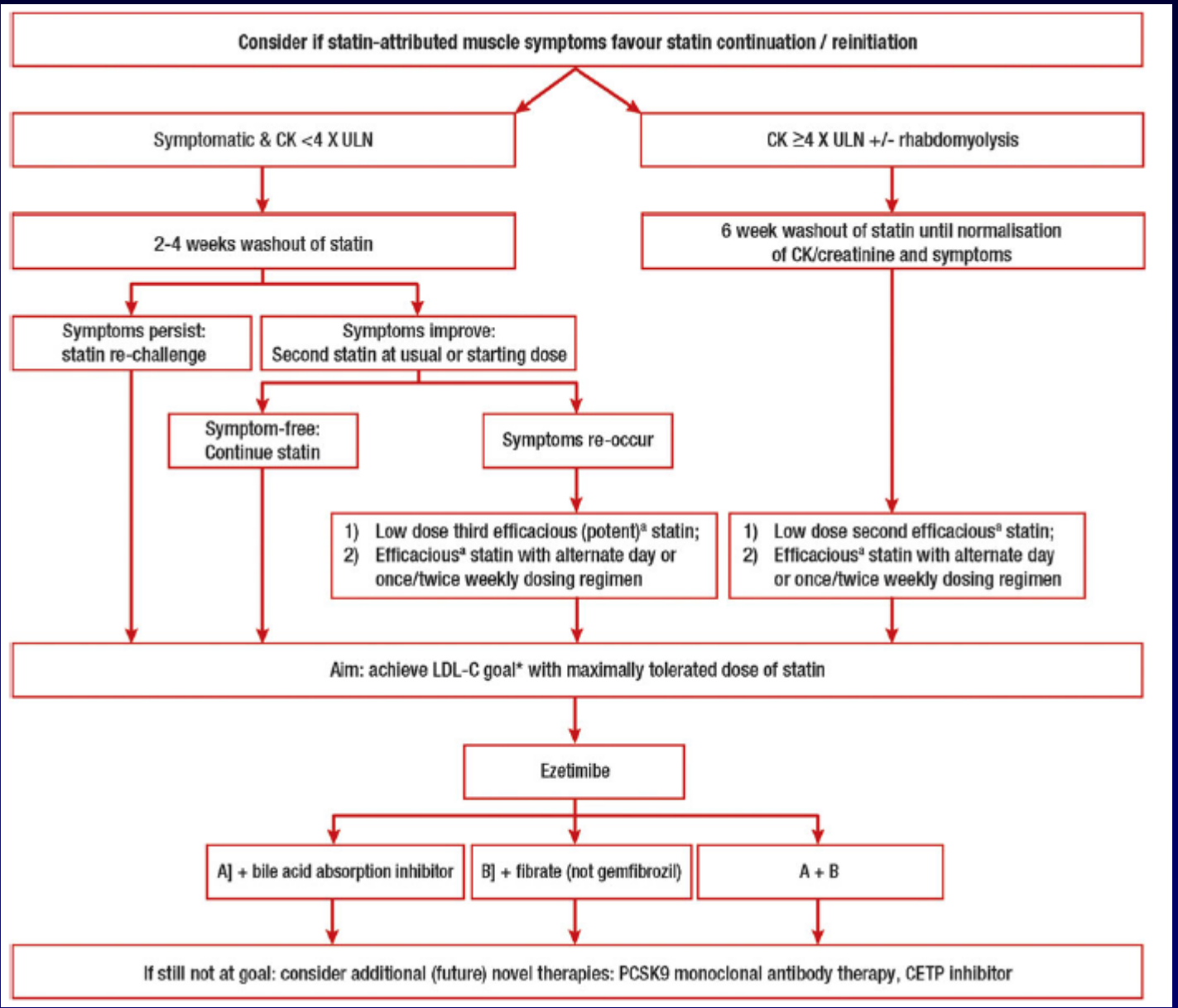
REVIEW

Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

Erik S. Stroes[1*], Paul D. Thompson[2], Alberto Corsini[3], Georgirene D. Vladutiu[4], Frederick J. Raal[5], Kausik K. Ray[6], Michael Roden[7], Evan Stein[8], Lale Tokgözoğlu[9], Børge G. Nordestgaard[10], Eric Bruckert[11], Guy De Backer[12], Ronald M. Krauss[13], Ulrich Laufs[14], Raul D. Santos[15], Robert A. Hegele[16], G. Kees Hovingh[17], Lawrence A. Leiter[18], Francois Mach[19], Winfried März[20], Connie B. Newman[21], Olov Wiklund[22], Terry A. Jacobson[23], Alberico L. Catapano[3], M. John Chapman[24], and Henry N. Ginsberg[25], European Atherosclerosis Society Consensus Panel[†]

Therapeutic flow-chart for management of patients with statin-associated muscle symptoms



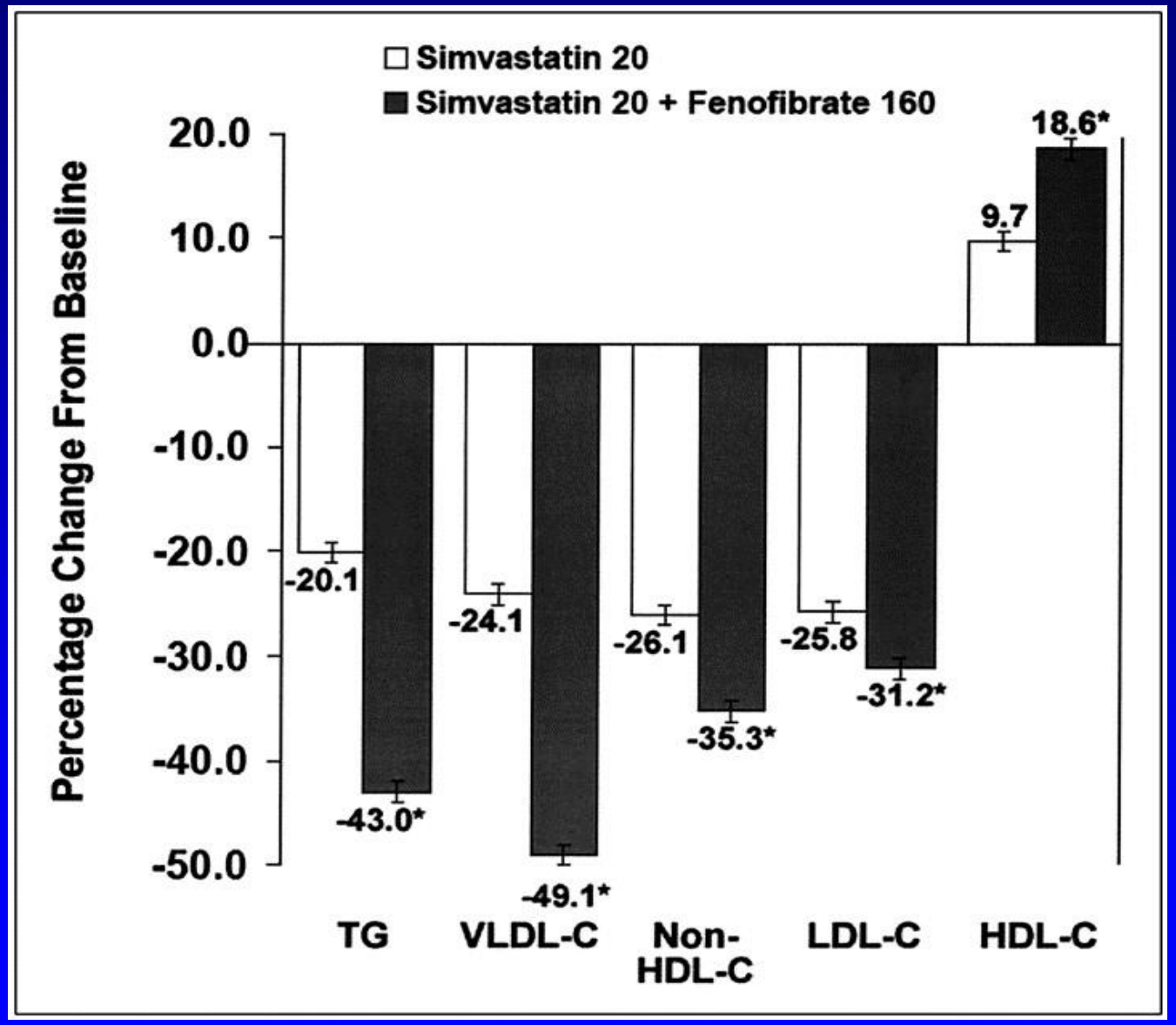
Fenofibrate can lower LDL-C by 15–20% in patients with high baseline levels who do not have concomitant hypertriglyceridaemiaThis fibrate is easy to take, and has shown an excellent safety record in the Accord trial

Eur Heart J. 2015 Feb 18.

EFFECTIVENESS AND TOLERABILITY OF *SIMVASTATIN* PLUS *FENOFIBRATE* FOR COMBINED HYPERLIPIDEMIA (The SAFARI Trial)

S.M. Grundy et al., Am. J. Cardiol., 95: 462-468, 2005

CHANGE FROM BASELINE IN LIPID PARAMETERS



S.M. Grundy et al., Am. J. Cardiol., 95: 462-468, 2005

Il valore delle associazioni precostituite

Guidance for Industry

Codevelopment of Two or More New Investigational Drugs for Use in Combination

Additional copies are available from:
Office of Communications
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Food and Drug Administration
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Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

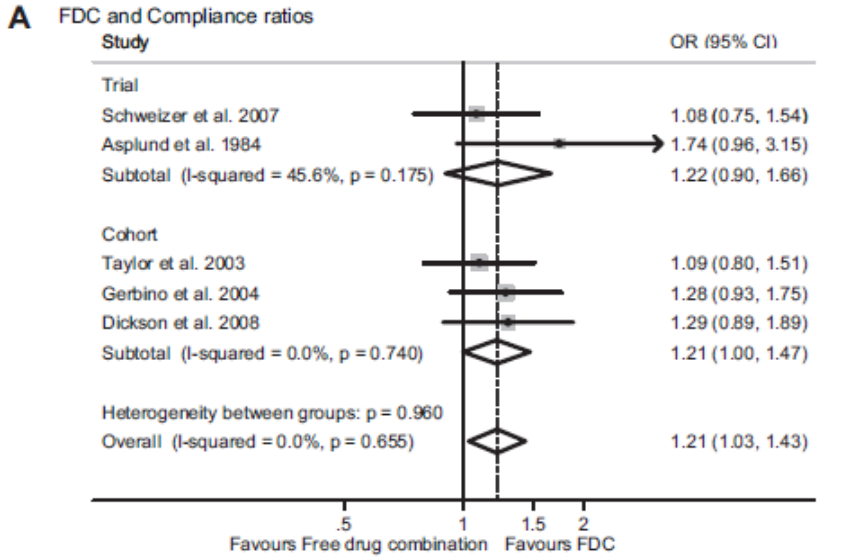
June 2013
Clinical Medical

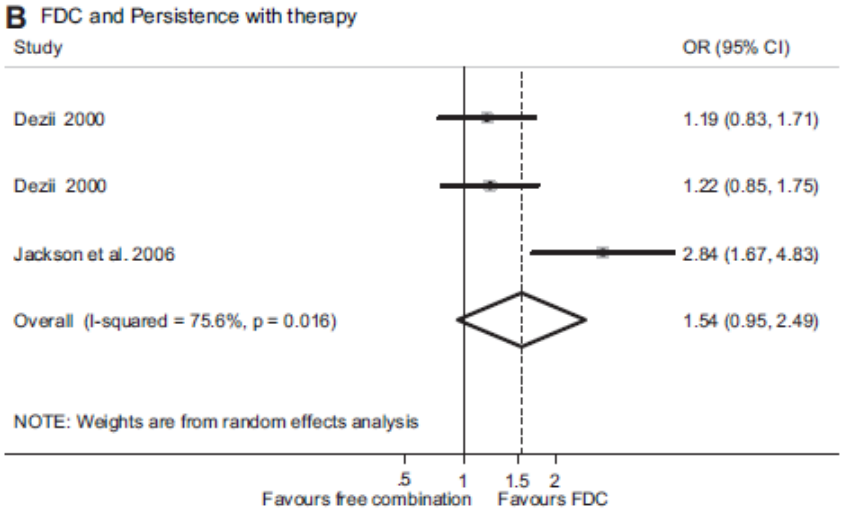
[2] The term *codevelopment* as used in this guidance refers to the concurrent development of two or more new investigational drug products that are intended to be used in combination to treat a disease or condition. A sponsor may elect to codevelop two or more new investigational drug products to be marketed as individual agents intended to be used in combination as a fixed-combination or co-packaged drug.

Compliance, Safety, and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents

A Meta-Analysis

Ajay K. Gupta, Shazia Arshad, Neil R. Poulter





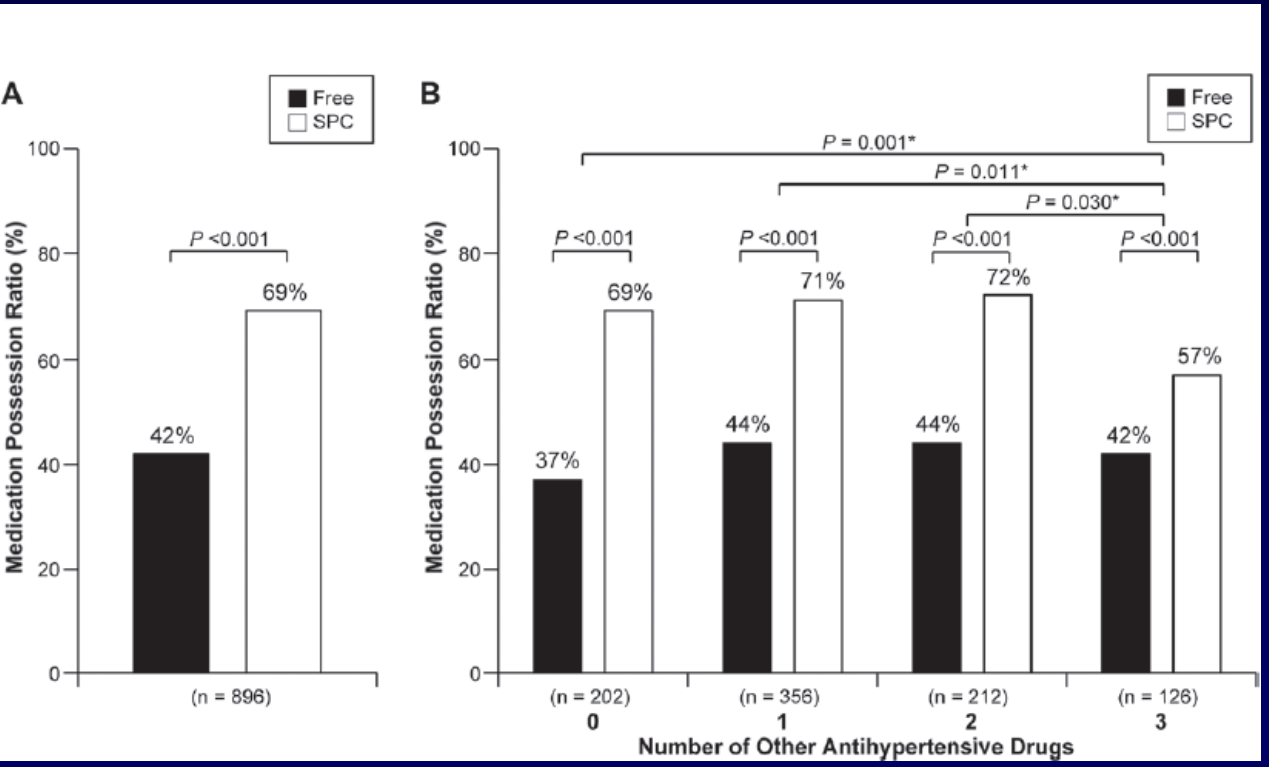
Adesione al trattamento (A) e persistenza nelle terapie combinate (B): effetto della FDC vs le mono-terapie

Hypertension
Journal of the American Heart Association

American Heart Association

Bidirectional Adherence Changes and Associated Factors in Patients Switched From Free Combinations to Equivalent Single-Pill Combinations of Antihypertensive Drugs

Tzung-Dau Wang, Ying-Hsien Chen, Chien-Hua Huang, Wen-Jone Chen and Ming-Fong Chen



Effetto della sostituzione delle mono-terapie a FDC sull'adesione al trattamento nell'intera popolazione (A) e nei pazienti caratterizzati da un numero ulteriore di farmaci anti-ipertensivi utilizzati (B)

Hypertension. published online January 20, 2014;

2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC)

ESH/ESC Task Force for the Management of Arterial Hypertension

Treatment strategies and choice of drugs

Recommendations	Class	Level
Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations with each other.	I	A
Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of OD.	IIa	C
Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk.	IIb	C
The combination of two antagonists of the RAS is not recommended and should be discouraged.	III	A
Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable.	IIa	C
Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension.	IIb	B

ACE, angiotensin-converting enzyme; BP, blood pressure, CV, cardiovascular; OD, organ damage; RAS, renin–angiotensin system.

Mancia G et al. Eur HJ 2013 : 34(28): 2159-219

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/CHMP/308856/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cholib

International non-proprietary name: fenofibrate / simvastatine

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of *Cholib indicated as adjunctive therapy to diet and exercise in high cardiovascular risk adult patients with mixed dyslipidaemia to reduce triglycerides and increase HDL - C levels when LDL - C levels are adequately controlled with the corresponding dose of simvastatin monotherapy,*
is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Bioequivalence studies

In order to bridge the clinical studies that were conducted with the co-administration of fenofibrate (145mg) and simvastatin (20mg or 40mg) to the proposed fixed dose combination, the applicant conducted two bioequivalence studies: one study with the 20 mg simvastatin (S285.1.001) and the other with the 40 mg simvastatin (S285.01.002). The dose of fenofibrate was 145mg. Both studies used the open label, randomised, replicate, 4 period, 2 sequence design with 10 day washout period between studies. The sample size was adequate for both studies (n=150 and n=148 respectively) with 143 and 140 subjects completing all 4 sequences. The main results of these studies are presented in the table below.

Results of bioequivalence studies

Study		**S285.1.001**		**S285.1.002**	
Parameter		***Point Est***	***90% CI***	***Point Est***	***90% CI***
Fenofibric acid					
	AUC_t	0.998	0.987-1.010	1.020	1.008 – 1.032
	C_{max}	0.970	0.954- 0.987	1.032	1.012 – 1.051
Simvastatin					
	AUC_t	1.002	0.959 – 1.048	0.892	0.858 – 0.927
	C_{max}	0.692	0.659 – 0.727	0.939	0.897 – 0.983
Simvastatin acid					
	AUC_t	1.165	1.115 – 1.216	1.082	1.045– 1.120
	C_{max}	1.081	1.029 – 1.134	1.121	1.077– 1.166

Cholib 145 mg/20 mg compresse rivestite con film

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

Una compressa rivestita con film contiene 145 mg di fenofibrato e 20 mg di simvastatina.

4.1 Indicazioni terapeutiche

Cholib è indicato come terapia aggiuntiva alla dieta e all'esercizio fisico in pazienti adulti a elevato rischio cardiovascolare affetti da dislipidemia mista per ridurre i trigliceridi e aumentare i livelli di colesterolo HDL quando i livelli di colesterolo LDL sono adeguatamente controllati con la dose corrispondente di simvastatina in monoterapia.

4.2 Posologia e modo di somministrazione

Prima di prendere in considerazione la terapia a base di Cholib, devono essere adeguatamente trattate le cause secondarie di iperlipidemia, come ad esempio forme non controllate di diabete mellito di tipo 2, ipotiroidismo, sindrome nefrotica, disproteinemia, epatopatia ostruttiva, trattamento farmacologico (quali estrogeni orali) e alcolismo e i pazienti devono essere messi a dieta standard per la riduzione del colesterolo e dei trigliceridi, che deve essere proseguita durante il trattamento.

Posologia
La dose raccomandata è una compressa al giorno. Deve essere evitato il succo di pompelmo (vedere paragrafo 4.5).

Modo di somministrazione
Ogni compressa deve essere deglutita intera con un bicchiere d'acqua. Le compresse non devono essere rotte o masticate e possono essere assunte con o senza cibo (vedere paragrafo 5.2).

Comparison high fat fed (Reg A) versus fasting (Reg C) [study K LF K178P 0206 KH 0302]

HFF versus Fasting				
Parameter n = 44 (PKS)	**Geometric Mean HFF (Regimen A)**	**Geometric Mean Fasting (Regimen C)**	**Point Estimate**	**90% CI**
AUC	124.8	118.5	**1.052**	1.018 – 1.088
AUCt	123.0	116.5	**1.054**	1.020 – 1.090
Cmax	7.82	7.77	**1.007**	0.963 – 1.054
LFF versus Fasting				
AUC	119.8	118.5	**1.012**	0.978 – 1.046
AUCt	118.1	116.5	**1.013**	0.981 – 1.047
Cmax	7.84	7.77	**1.009**	0.964 – 1.055

PKS: pharmacokinetic sample, HFF: high fat fed, LFF: low fat fed

The results of the study alleviate the concerns about the food effect on the micronised formulation of fenofibrate and thus, it is concluded that food has negligible influence on the 145mg fenofibrate tablet. It is assumed that there is no food effect on the fixed combination product. Adequate wording has been included in the SmPC of Cholib.

Comparison of Pharmacokinetic Properties of Fibric Acid Derivatives (Immediate-Acting Forms)

	Bezafibrate	Ciprofibrate	Clofibrate	Fenofibrate	Gemfibrozil
Oral bioavailability (%)	100		100	60	100
Volume of distribution	17L		14.5L	0.89- L/kg	
t½ in healthy volunteers (h)	1.5-3.0	81	15	19-27	1.3
t½ in patients with renal failure (h)	9.2	172	30-110	143	
Protein binding (%)	95	99	96	>99	98
Route of elinimation	Renal (unchanged)	Renal	Renal (metabolites)	Renal (glucuronide)	Renal (glucuronide)

Abbreviation: t½=half-life

David B. Miller and J. David Spence, Clin Pharmacokinet 1998 Feb 34 (2):155-162

Pazienti anziani (≥ 65 anni di età)
Non è necessario un adeguamento della dose. È raccomandata la dose abituale, eccetto nei casi di funzionalità renale ridotta con velocità di filtrazione glomerulare stimata < 60 ml/min/1,73 m^2, in cui Cholib è controindicato (vedere paragrafo 4.3).

Pazienti con danno renale
Cholib è controindicato nei pazienti con insufficienza renale da moderata a grave, la cui velocità di filtrazione glomerulare stimata è < 60 ml/min/1,73 m^2 (vedere paragrafo 4.3).

Funzionalità renale
Cholib è controindicato in presenza di danno renale da moderato a grave (vedere paragrafo 4.3).

Cholib deve essere usato con cautela nei pazienti con insufficienza renale lieve, la cui velocità di filtrazione glomerulare stimata è compresa tra 60 e 89 ml/min/1,73 m^2 (vedere paragrafo 4.2).

Sono stati segnalati aumenti reversibili della creatinina sierica in pazienti trattati con fenofibrato in monoterapia o in associazione con statine. Gli aumenti della creatinina sierica erano generalmente stabili nel tempo, senza evidenza di aumenti continuati dei valori con la terapia a lungo termine, e tendevano a tornare ai livelli basali dopo l'interruzione del trattamento.

Nel corso di studi clinici, il 10% dei pazienti ha manifestato un aumento della creatinina rispetto al basale, maggiore di 30 µmol/l, con l'associazione di fenofibrato e simvastatina rispetto al 4,4% con una statina in monoterapia. Lo 0,3% dei pazienti trattati con la terapia di associazione ha mostrato aumenti clinicamente rilevanti della creatinina fino a valori >200 µmol/l.

Clinical Pharmacokinetics of Statins

Metabolism

Parameter	Atorva	Rosuva	Fluva	Fluva XL	Lova	Prava	Simva
Hepatic extraction (%)	> 70	63	> 68	> 68	> 70	46 - 66	78 - 87
Metabolism	CYP3A4	biliar CYP2C9, 2C19 (minor)	CYP2C9	CYP2C9	CYP3A4	Sulfation	CYP3A4
Systemic metabolites	Active	Active (minor)	Inactive	Inactive	Active	Inactive	Active
Clearance (ml/min)	291.6	805	1131.6	4433	303-1166	945	525
Cl_R ml/min	-	226	-	-	-	>400	-

Adapted from Corsini et al. 1999 Pharmacol Ther 84: 413-428

Sostanze che interagiscono	Raccomandazioni di prescrizione
Potenti inibitori del CYP 3A4: Itraconazolo Ketoconazolo Fluconazolo Posaconazolo Eritromicina Claritromicina Telitromicina Inibitori della proteasi dell'HIV (ad es. nelfinavir) Nefazodone	Controindicate con Cholib
Danazol Ciclosporina	Controindicate con Cholib
Gemfibrozil, altre statine e fibrati	Controindicate con Cholib
Amiodarone Verapamil Diltiazem Amlodipina	Non superare una compressa di Cholib da 145 mg/20 mg al giorno, a meno che il beneficio clinico superi il rischio
Niacina (acido nicotinico) ≥1 g/die	Evitare la somministrazione con Cholib a meno che il beneficio clinico superi il rischio Monitorare i pazienti per individuare la comparsa di segni e sintomi di dolore, dolorabilità o debolezza muscolare
Acido fusidico	I pazienti devono essere mantenuti sotto stretto controllo. Può essere presa in considerazione la sospensione temporanea del trattamento con Cholib.
Succo di pompelmo	Evitare durante il trattamento con Cholib
Antagonisti della vitamina K	Adeguare la dose di questi anticoagulanti orali in funzione del monitoraggio dell'INR
Glitazoni	Monitorare il colesterolo HDL e interrompere uno dei farmaci (glitazone o Cholib) se il valore è eccessivamente basso

Title: A multicenter, double-blind, randomized, active comparator, forced-titration study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 20 or 40 mg simvastatin with 40 mg simvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 20 mg simvastatin alone.

Study identifier	C LF0242780-01 05 01
Design	Multicenter phase III, randomized, double-blind, 2-parallel arm, and comparative study with a 6-week active run-in period

Effect estimate per comparison (ANCOVA with treatment, baseline value, gender and CV risk as covariate)	TG	feno145 + simva20 (LS mean estimate)	-35.26
		simva40 (LS mean estimate)	-11.96
		Treatment comparison LS mean (95%CI)	-26.47 (-29.99, -22.78)
		P-value	<0.001
	LDL-C	feno145 + simva20 (LS mean estimate)	-5.62
		simva40 (LS mean estimate)	-10.37
		Treatment comparison LS mean (95%CI)	4.75 (2.00, 7.51)
		P-value	NA*
	HDL-C	feno145 + simva20 (LS mean estimate)	8.26
		simva40 (LS mean estimate)	2.50
		Treatment comparison LS mean (95%CI)	5.76 (3.88, 7.65)
		P-value	<0.001
	*Non inferiority test with the non-inferiority on percent change in LDL-C being demonstrated if the upper boundary of the 95% CI was smaller than the non-inferiority margin fixed at 4%.		

Title: A multicenter, double-blind, randomized study to compare the efficacy and safety of the combination of 145 mg fenofibrate and 40 mg simvastatin with 40 mg simvastatin monotherapy in patients with mixed dyslipidemia at risk of cardiovascular disease not adequately controlled by 40 mg simvastatin alone

Effect estimate per comparison (ANCOVA with treatment, baseline value, gender and CV risk as covariate)	TG	Feno145 + simva40 (LS mean estimate)	-35.062
		Simva40 (LS mean estimate)	-9.570
		Treatment comparison LS mean (95%CI)	-28.19 (-32.91, -23.13)
		P-value	<0.001
	LDL-C	Feno145 + simva40 (LS mean estimate)	-7.731
		Simva40 (LS mean estimate)	-6.487
		Treatment comparison LS mean (95%CI)	-1.24 (-5.22, 2.73)
		P-value	0.539
	HDL-C	Feno145 + simva40 (LS mean estimate)	7.296
		Simva (LS mean estimate)	0.834
		Treatment comparison LS mean (95%CI)	6.46 (3.83, 9.09)
		P-value	<0.001

ORIGINAL RESEARCH ARTICLE

Cardiovascular Therapeutics

New Fixed-Dose Combinations of Fenofibrate/Simvastatin Therapy Significantly Improve the Lipid Profile of High-Risk Patients with Mixed Dyslipidemia Versus Monotherapies

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Cardiovascular Therapeutics 33 (2015) 329–337

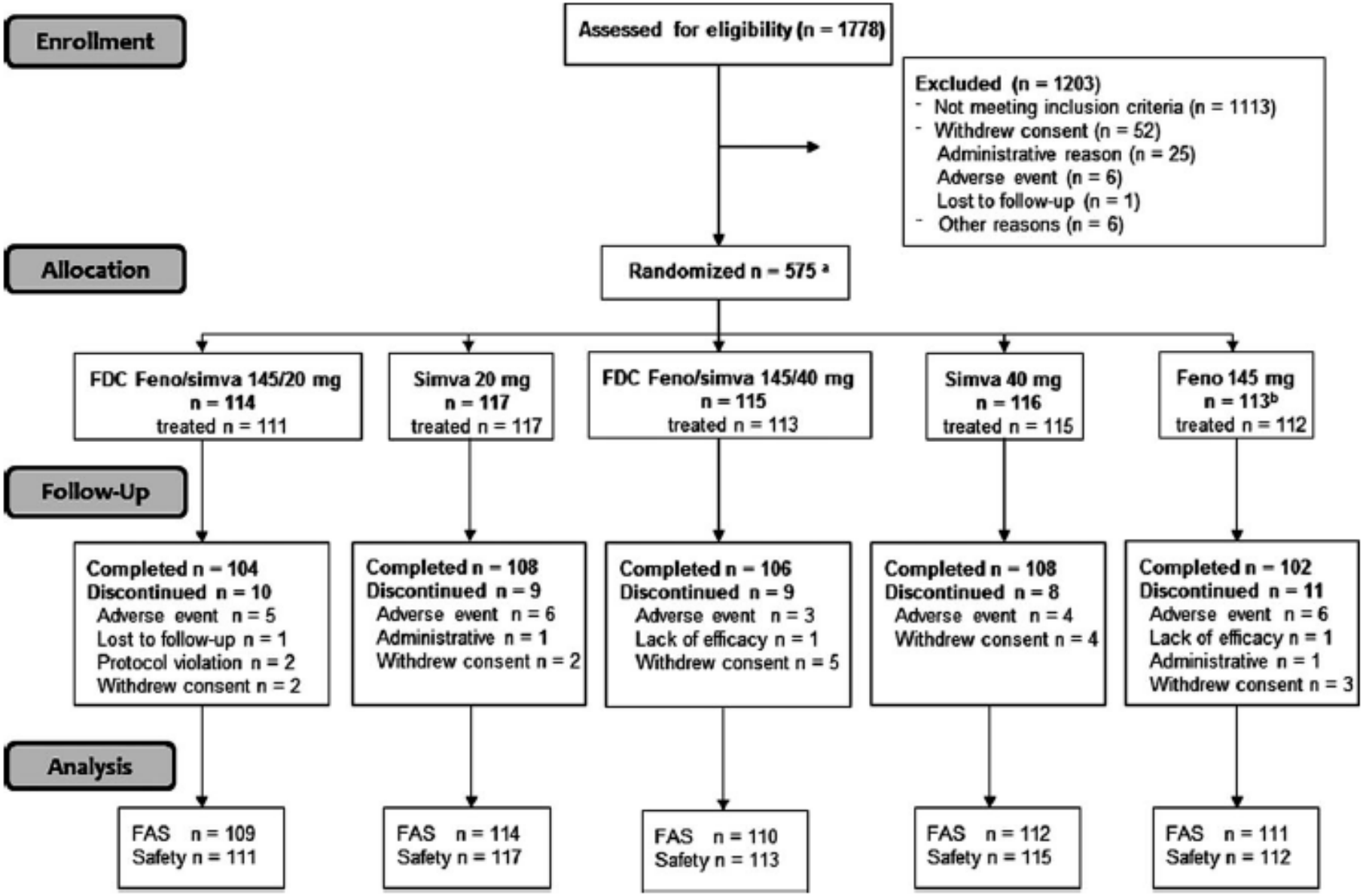
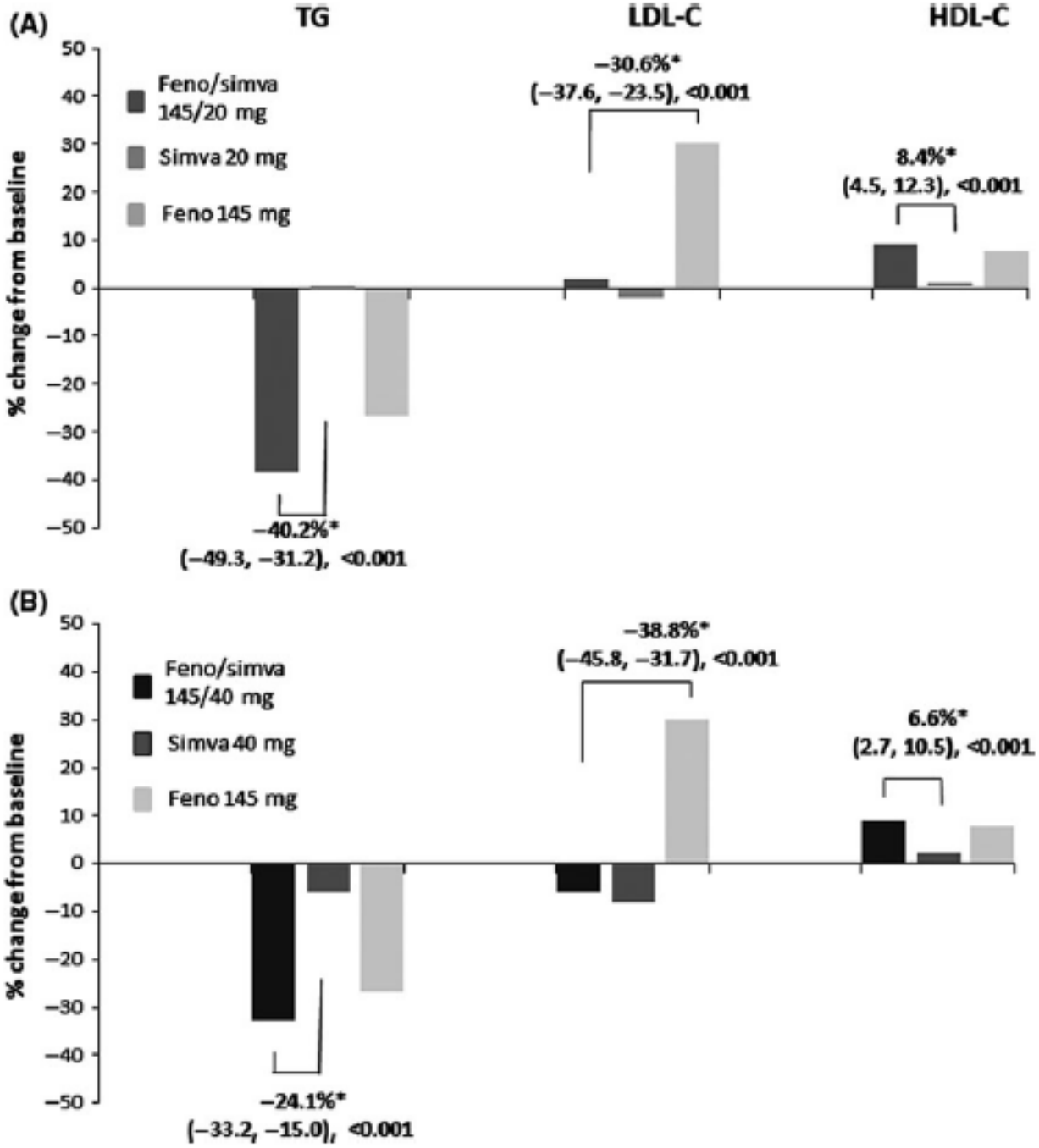


Figure 1 Study Flow Chart Diagram. [a]One randomized patient withdrew consent before taking any study drug medication. [b]Pooled groups from the two study parts. FAS: Full analysis set, FDC: fixed-dose combination, Feno: fenofibrate, feno/simva: fenofibrate/simvastatin, simva: simvastatin.

Table 2 Effect of the FDC fenofibrate/simvastatin on lipids, apolipoproteins and C-reactive protein

	Feno/simva 145/20 mg (N = 109)	Simva 20 mg (N = 114)	Feno/simva 145/40 mg (N = 110)	Simva 40 mg (N = 112)	Feno 145 mg (N = 111)	*P* value[a]
TG (mg/dL)						
Baseline	226 (117/601)	194 (90/592)	208 (110/1103)	216 (122/576)	236 (126/843)	
% changes[b]	−38.5 (−71.3/57.6)	0 (−51.0/254.7)	−32.9 (−83.0/188.4)	−6.1 (−63.6/101.6)	−26.7 (−72.1/108.6)	<0.001[c]
LDL-C (mg/dL)						
Baseline	101 ± 18	100 ± 16	101 ± 17	104 ± 17	105 ± 18	
% changes[b]	1.9 ± 25.4	−2.0 ± 24.8	−6.1 ± 26.2	−8.2 ± 25.8	30.2 ± 35.6	<0.001[d]
HDL-C (mg/dL)						
Baseline	43 ± 10	46 ± 12	46 ± 11	46 ± 12	46 ± 10	
% changes[b]	9.0 ± 16.8	0.3 ± 12.1	8.8 ± 16.5	2.2 ± 12.5	7.6 ± 15.7	<0.001[c]
Non-HDL-C (mg/dL)						
Baseline	133.4 ± 22.8	129.5 ± 20.5	133.8 ± 25.9	135.3 ± 22.4	139.6 ± 24.7	
% changes[b]	−7.9 ± 21.0	0.4 ± 24.7	−13.7 ± 25.9	−8.7 ± 21.7	16.0 ± 28.8	0.003[c]
Total Cholesterol (mg/dL)						
Baseline	176.7 ± 23.2	175.2 ± 22.0	179.8 ± 25.5	181.0 ± 23.2	184.8 ± 25.9	
% changes[b]	−3.9 ± 15.9	0.01 ± 18.3	−8.3 ± 19.3	−6.5 ± 16.6	13.5 ± 20.1	<0.001[d]



Effect of the low dose of FDC feno/simva (A) and high dose of FDC feno/simva (B) on the % change from baseline of TG, LDL-C, and HDL-C after 12 weeks of treatment

Table 3 Adverse events and safety laboratory parameters

	Feno/simva 145/20 mg (N = 111)	Simva 20 mg (N = 117)	Feno/simva 145/40 mg (N = 113)	Simva 40 mg (N = 115)	Feno 145 mg (N = 112)
Adverse events (N (%))					
At least one	30 (27.0)	32 (27.4)	30 (26.5)	30 (26.1)	34 (30.4)
Adverse events occurring in ≥2% of patients					
Diarrhoea	1 (0.9)	2 (1.7)	2 (1.8)	0	5 (4.5)
Nasopharyngitis	1 (0.9)	0	1 (0.9)	3 (2.6)	3 (2.7)
Blood creatine kinase increased	4 (3.6)	0	1 (0.9)	1 (0.9)	1 (0.9)
Gastroenteritis	1 (0.9)	2 (1.7)	0	0	4 (3.6)
Dyspepsia	1 (0.9)	0	0	4 (3.5)	1 (0.9)
Cough	0	3 (2.6)	0	1 (0.9)	1 (0.9)
Serious adverse events	3 (2.7)	3 (2.6)	3 (2.7)	1 (0.9)	3 (2.7)
Adverse events leading to discontinuation	5 (4.5)	6 (5.1)	3 (2.7)	3 (2.6)	6 (5.4)
Death	0	1 (0.9)	1 (0.9)	0	0
Specific adverse events (N (%))					
Myalgia	1 (0.9)	0	1 (0.9)	0	1 (0.9)
Muscle spasms/muscular weakness	2 (1.8)	1 (0.9)	0	0	0
Renal impairment	0	0	1 (0.9)	0	0
Safety Laboratory					
Creatinine levels (μmol/L)					
Baseline	79.4 ± 15.7	79.2 ± 15.5	77.5 ± 15.6	83.2 ± 30.1	80.0 ± 14.3
6 weeks[a]	90.5 ± 22.0	80.2 ± 17.4	87.7 ± 19.8	80.0 ± 17.9	89.3 ± 17.8
12 weeks[a]	89.0 ± 20.0	81.4 ± 18.3	87.5 ± 20.4	79.7 ± 16.0	90.1 ± 17.1
% changes at 12 weeks[a]	12.0 ± 13.5	2.0 ± 12.0	14.9 ± 15.4	−1.9 ± 11.9	15.2 ± 14.8
Creatinine ≥177 μmol/L (N)	1	0	0	0	0
Cystatin C (mg/L)					
Baseline	0.96 ± 0.17	0.95 ± 0.18	0.92 ± 0.17	0.93 ± 0.14	0.95 ± 0.16
6 weeks[b]	1.03 ± 0.21	0.95 ± 0.18	0.96 ± 0.19	0.91 ± 0.14	1.01 ± 0.18
12 weeks[b]	1.02 ± 0.18	0.93 ± 0.18	0.98 ± 0.18	0.92 ± 0.14	1.02 ± 0.17

Combined lipid-lowering therapy

Drug class	LDL-C Decrease (%)	Non-HDL-C Decrease (%)	HDL-C Increase (%)	TG Decrease (%)
Statin	++++	++++	+	++
Ezetimibe	+++	+++	+	+
Feno	+	+	++	++++