The MIGHTY MEDIC
Global Scientific Society

12th Lipid Club
and Therapeutic Apheresis 2017

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Istituto Salesiano Sacro Cuore

La Scuola di Lipidologia Clinica di MIGHTY MEDIC
Sessione Primaverile

IperLp(a)Lipoproteinemia

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MIGHTY MEDIC
Multidisciplinary International Group for Hemapheresis TherapY and MEtabolic Disturbances Contrast

Luca (♂ 1960)

1988 (age 28) Hodgkin lynphoma (chemotherapy plus radiotherapy)

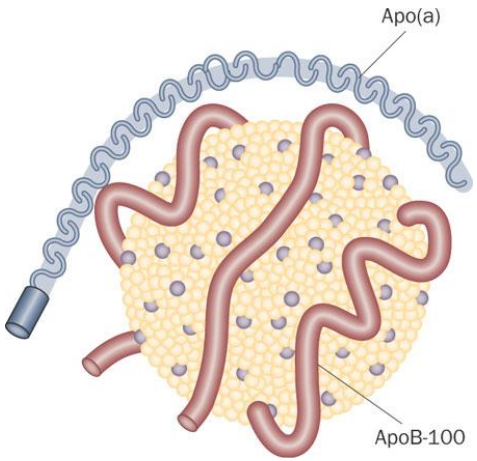
2009 (age 49) myocardial infarction (bivasal CAD; PTCA+stent)

2014 (age 54) RePTCA ; carotid stenosis; diabetes

Former Smoker (2009)

Muscle-related statin intolerance,
- Atorvastatin: CPK >1000 U/L, myalgia (2009)
- Rosuvastatin: CPK ~ 600 U/L , myalgia (2010)

Ezetimibe intolerance (CPK ~ 400 U/L), myalgia (2014)



2014
Lp(a)=106 mg/dl
LDL-C= 160 mg/dl
Fibrinogen=3.1g/L
HbA1c = 6.5%

Physical examination
Body weight 83 kg,
BMI 25.7 kg/m2,
Blood Pressure 120/70 mmHg.

Therapy
Clopidogrel
Ivabradina
Ranolazine
ASA
Omega 3 fatty acid

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Table 5 Risk categories

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10%.
Moderate risk	SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.
Low-risk	SCORE <1%.

Recommendations for lipid control

Recommendations[d,e]	Class[a]	Level[b]	Ref[c]
In patients at VERY HIGH CV risk, an LDL-C goal <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.[f]	I	B	350–353
In patients at HIGH CV risk, an LDL-C goal <2.6 mmol/L (<100 mg/dL), or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) is recommended.	I	B	350–353
In the remaining patients on LDL-C lowering treatment, an LDL-C goal <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	350–353

3a.7.6 Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein to which an additional protein called apolipoprotein(a) is attached. High concentrations of Lp(a) are associated with increased risk of CAD and ischaemic stroke and Mendelian randomization studies support a causal role in CVD for Lp(a). There is no randomized intervention study showing that reducing Lp(a) decreases CVD risk.[362] At present there is no justification for screening the general population for Lp(a), but it may be considered in patients at moderate risk to refine risk evaluation or in subjects with a family history of early CVD.

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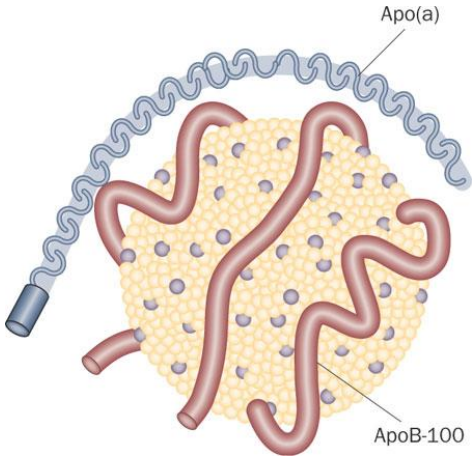


2014

Lp(a)=106 mg/dl

LDL-C= 160 mg/dl

Fibrinogen=3.1g/L

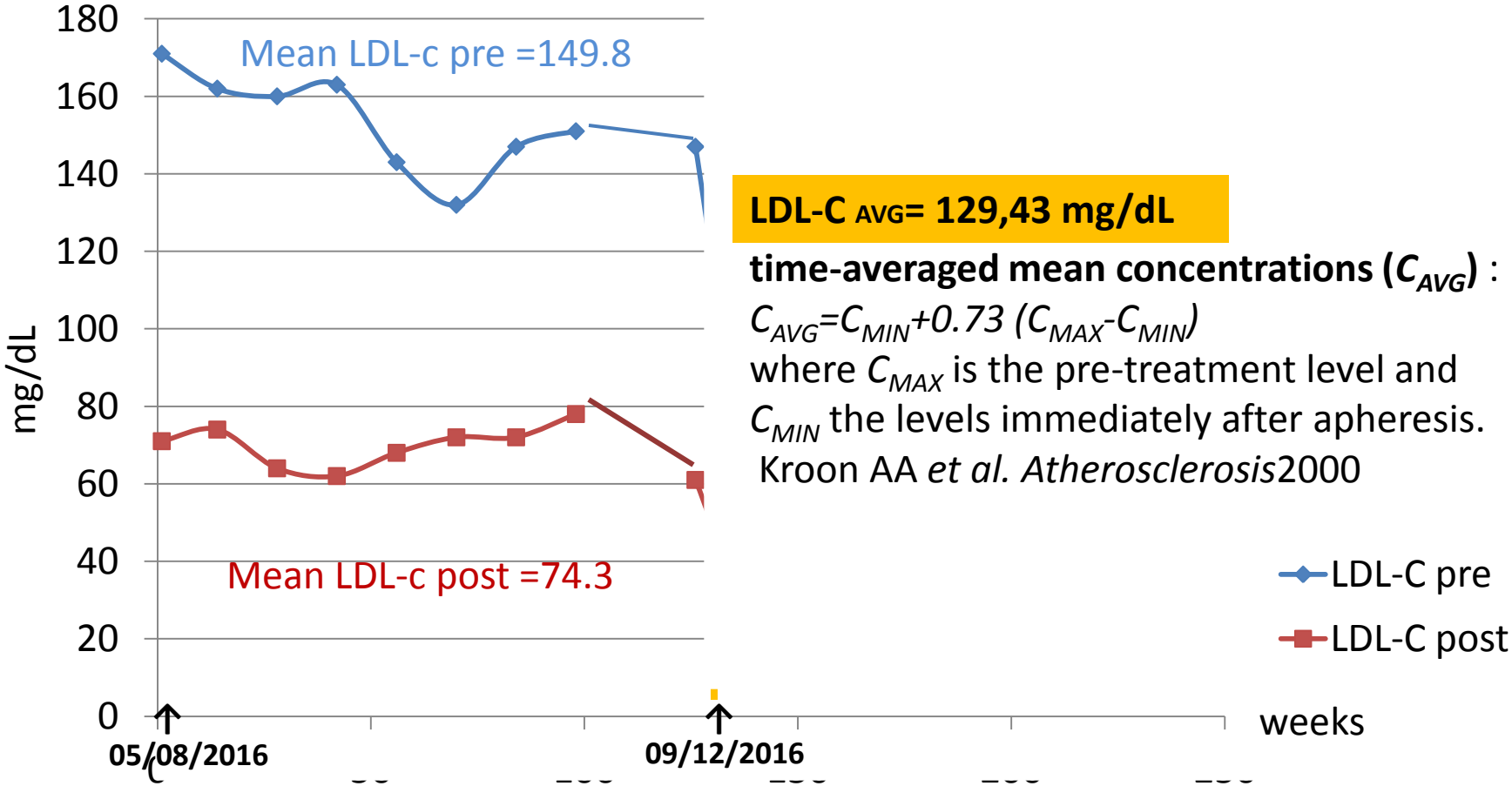
Very High CV Risk

LDL-C Goal < 1.8 mmol/L

(< 70 mg/dL)

Lipoprotein-Apheresis from november 2014

LDL-C plasma values during HELP apheresis treatment Q2W



LDL-C AVG= 129,43 mg/dL

time-averaged mean concentrations (C_{AVG}) :

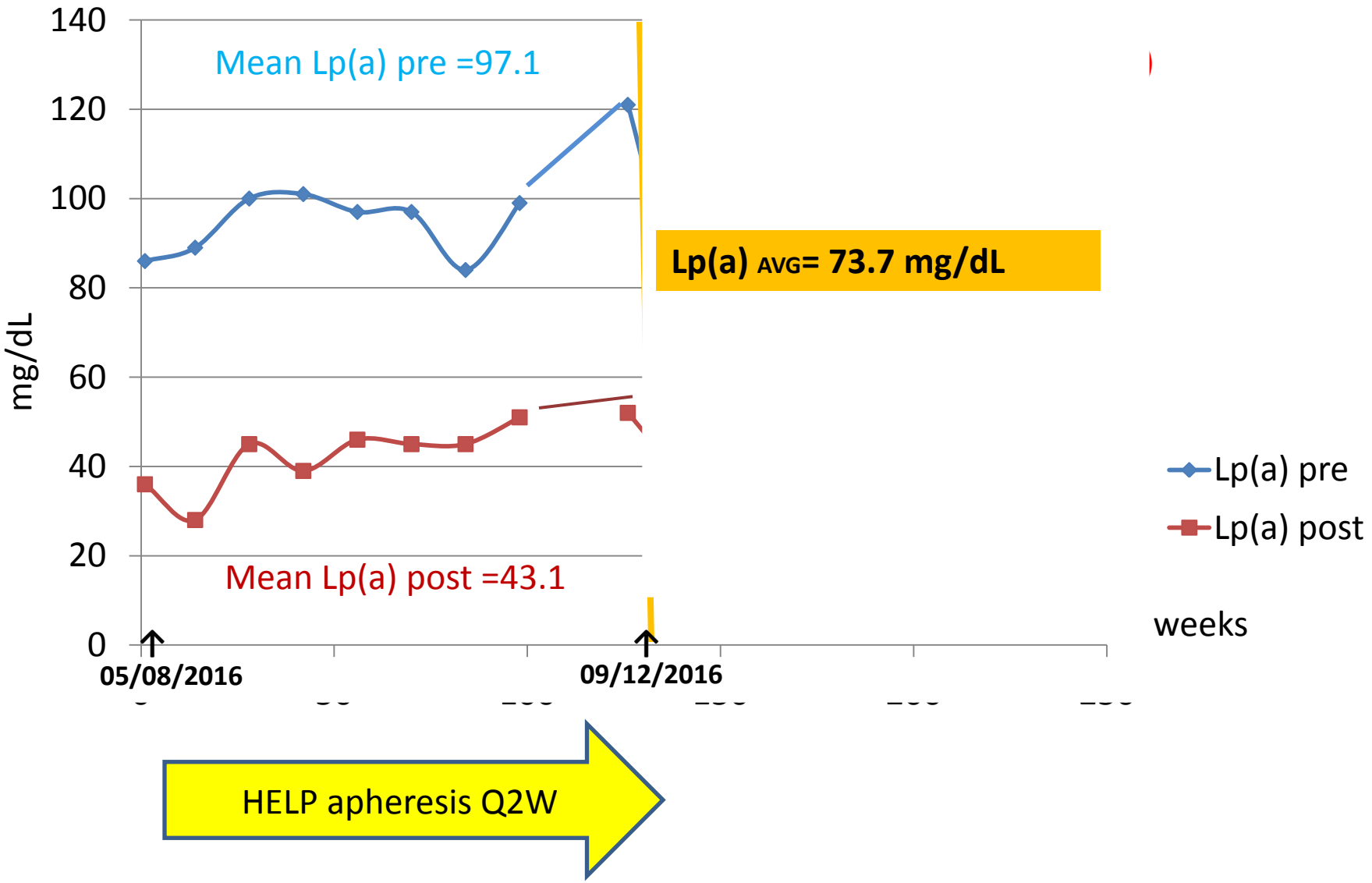
$C_{AVG}=C_{MIN}+0.73\ (C_{MAX}-C_{MIN})$

where C_{MAX} is the pre-treatment level and C_{MIN} the levels immediately after apheresis.

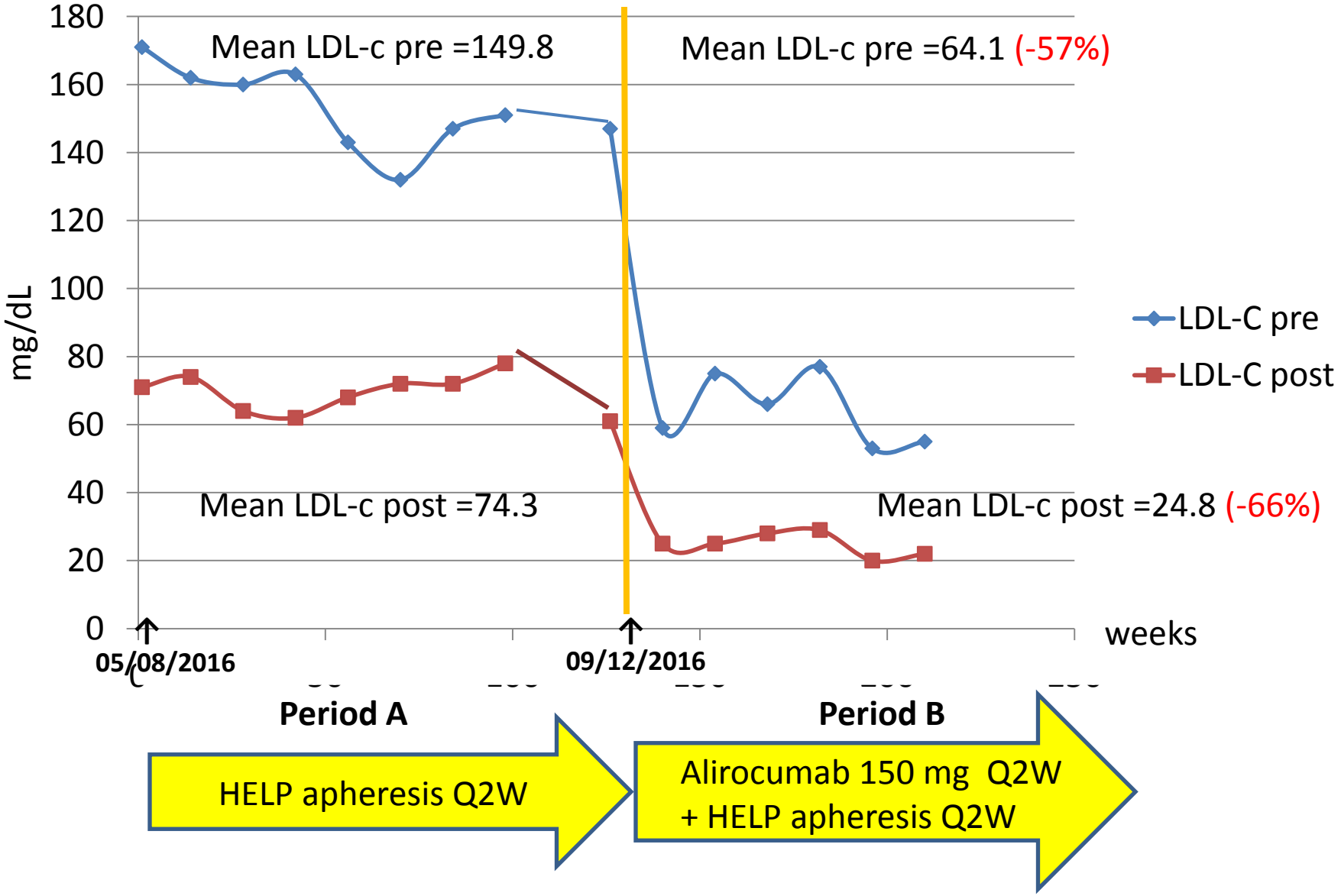
Kroon AA *et al. Atherosclerosis*2000

HELP apheresis Q2W

Lp(a) plasma values during HELP apheresis treatment Q2W



LDL-C plasma values during HELP apheresis treatment Q2W and after starting alirocumab 150 mg every two weeks + HELP apheresis Q2W



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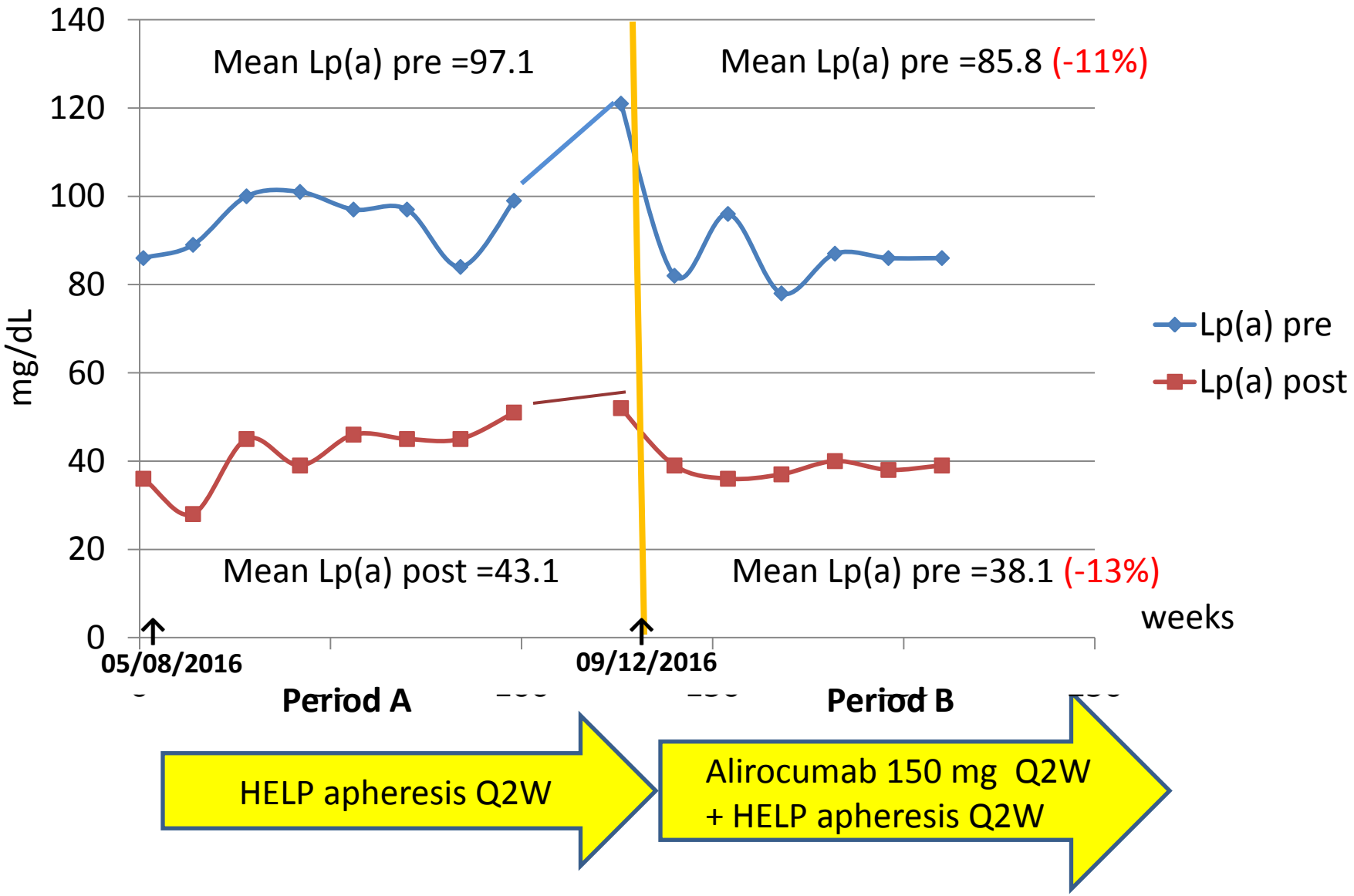
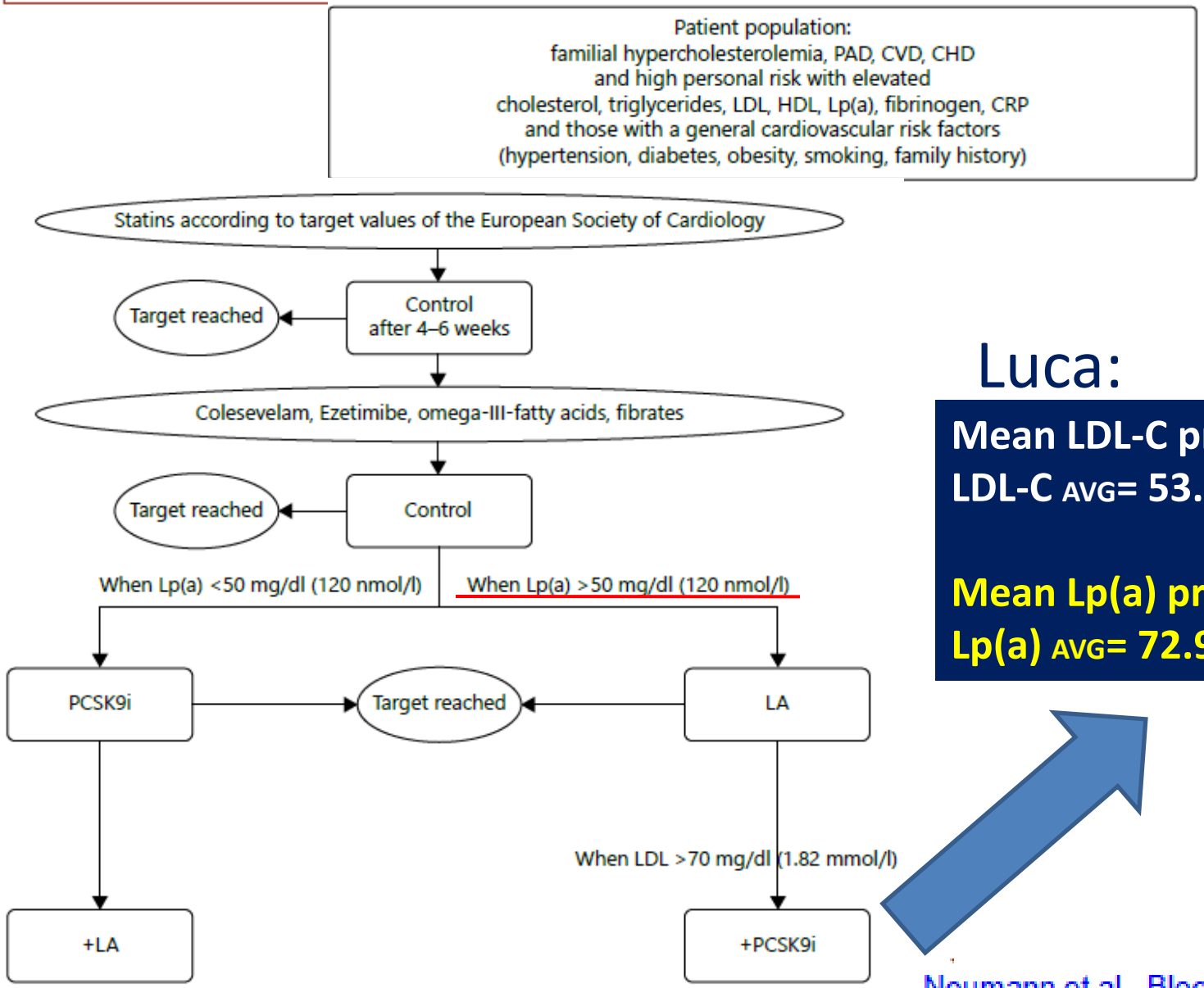


Potential treatment algorithm in relation to the use of PCSK9-AB and LA



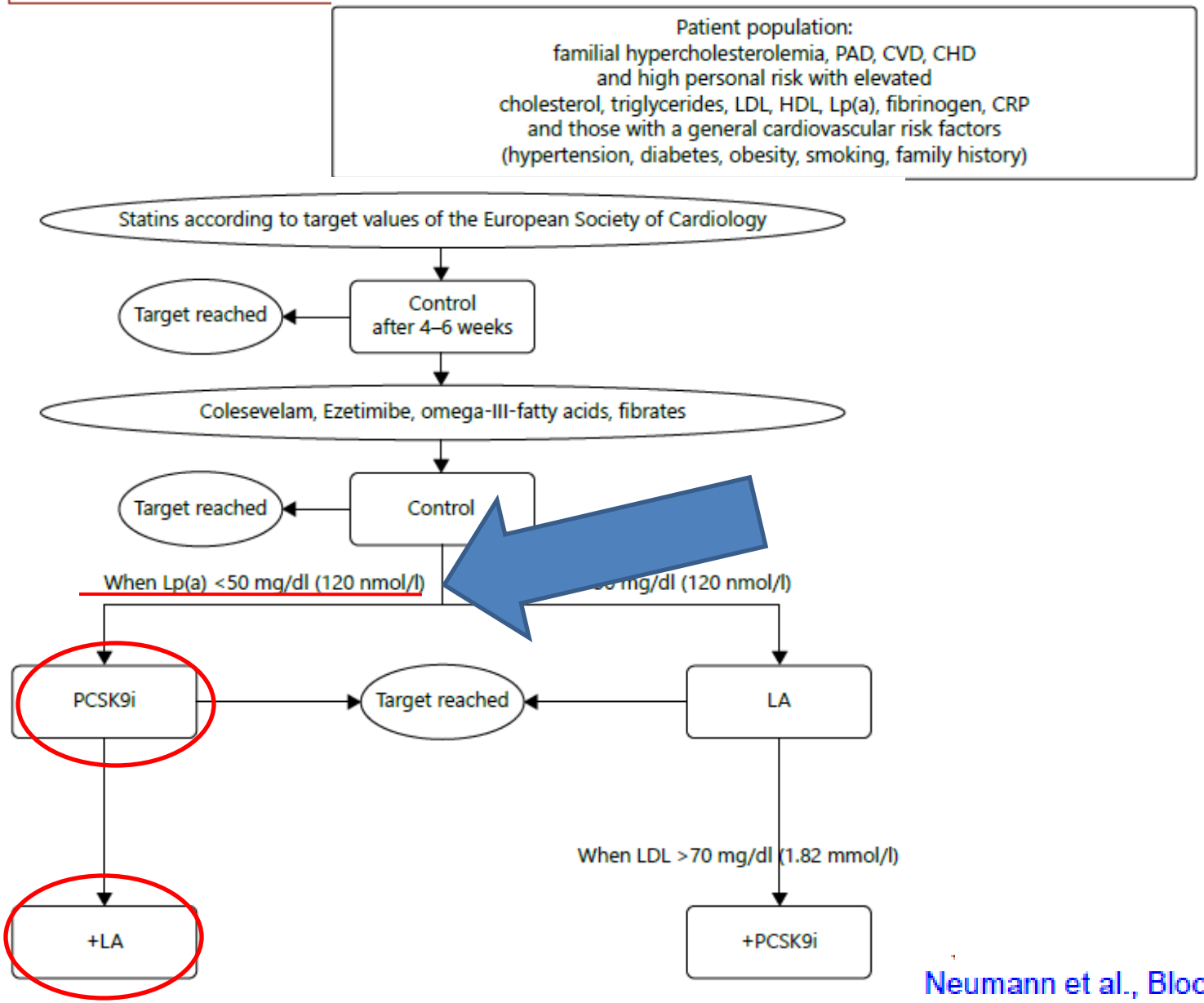
Luca:

Mean LDL-C pre =64.1 mg/dL
LDL-C AVG= 53.5 mg/dL

Mean Lp(a) pre =85.8 mg/dL
Lp(a) AVG= 72.9 mg/dL

Neumann et al., Blood Purif 2016;41:270-276

Potential treatment algorithm in relation to the use of PCSK9-AB and LA



Neumann et al., Blood Purif 2016;41:270-276

Case Report: Marina (1967)

- A 49-years old female patient presented in the Outpatient Lipid Clinic of the Verona University Hospital on May 2015.
- A clinical diagnosis of **Heterozygous Familial Hypercholesterolemia (HeFH)** was made in her adolescence at 17 years of age, according to extant plasma LDL-C concentrations above 300 mg/dL and to a positive family history of hypercholesterolemia and early coronary heart disease (CHD)(father and paternal uncles).
- A genetic test conducted in 2016 revealed a heterozygous mutation (c.1646G>A; p.Gly528Asp) in the exon 11 of the LDL-receptor (LDLR) gene, pathogenic for HeFH.
- In 2000, she was diagnosed as being affected by **Cogan's Syndrome**, a rare rheumatologic autoimmune disorder characterized by corneal and inner ear inflammation.

Lipid-lowering therapy

- **cholestyramine** p.o. bid treatment was promptly started at diagnosis in 1985 and it was continued until 1991.
- from 1991, **pravastatin** 20 mg/die was initiated in place of the bile acid sequestrants and this therapy was continued until 2000 with sporadic interruptions due to disabling muscle pain
- In 2001, the lipid lowering therapy was potentiated by introducing **atorvastatin** 20 mg/die
- In 2002, she experienced acute muscle pain, **rhabdomyolysis** with massive myoglobinuria and concomitant acute renal failure, which required immediate **hospitalization and hemodialysis** (myoglobin=15.98 mg/dL, creatine-kinase> 100.000 U/L, LDH=7,656 U/L, GOT=2469 U/L, GPT=646 U/L).
- After a full clinical and laboratory recovery the patient was switched to an alternative combination therapy with **fluvastatin and ezetimibe:** muscle symptoms and CK elevation reappeared.
- From 2003: nutraceutical treatment with substances characterized by complementary lipid-lowering properties (yeast rice, policosanol and berberine combined with folic acid, astaxanthin and coenzyme Q10)

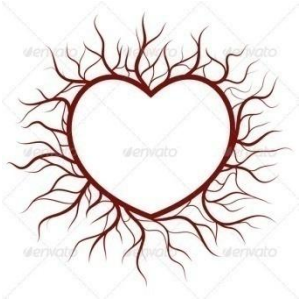
Marina

Physical examination

- Body weight 68 kg, BMI 27,3 kg/m2,
- Blood Pressure 120/84 mmHg.

- No tendinous xanthomatosis
- No arcus corneae

Cardio Vascular assessment



- Atheromatous calcifications in internal and esternal carotid artery
- Multislice CT: Coronary Artery Calcium Agatston Score: 46.9

Marina

Basal lipid profile

- Total cholesterol 522 mg/dl
- **LDL cholesterol 434 mg/dl**
- HDL cholesterol 84 mg/dl
- Triglicerides 120 mg/dl
- Lp(a) 13 mg/dL

therapy

- Nutraceutical treatment
- Systemic corticosteroids (Methylprednisolone)
- Immunosuppressive agents (methotrexate)
- Aspirin

Muscle-related statin and ezetimibe intolerance

December 2015 :
subcutaneous evolocumab 140 mg every 2 weeks

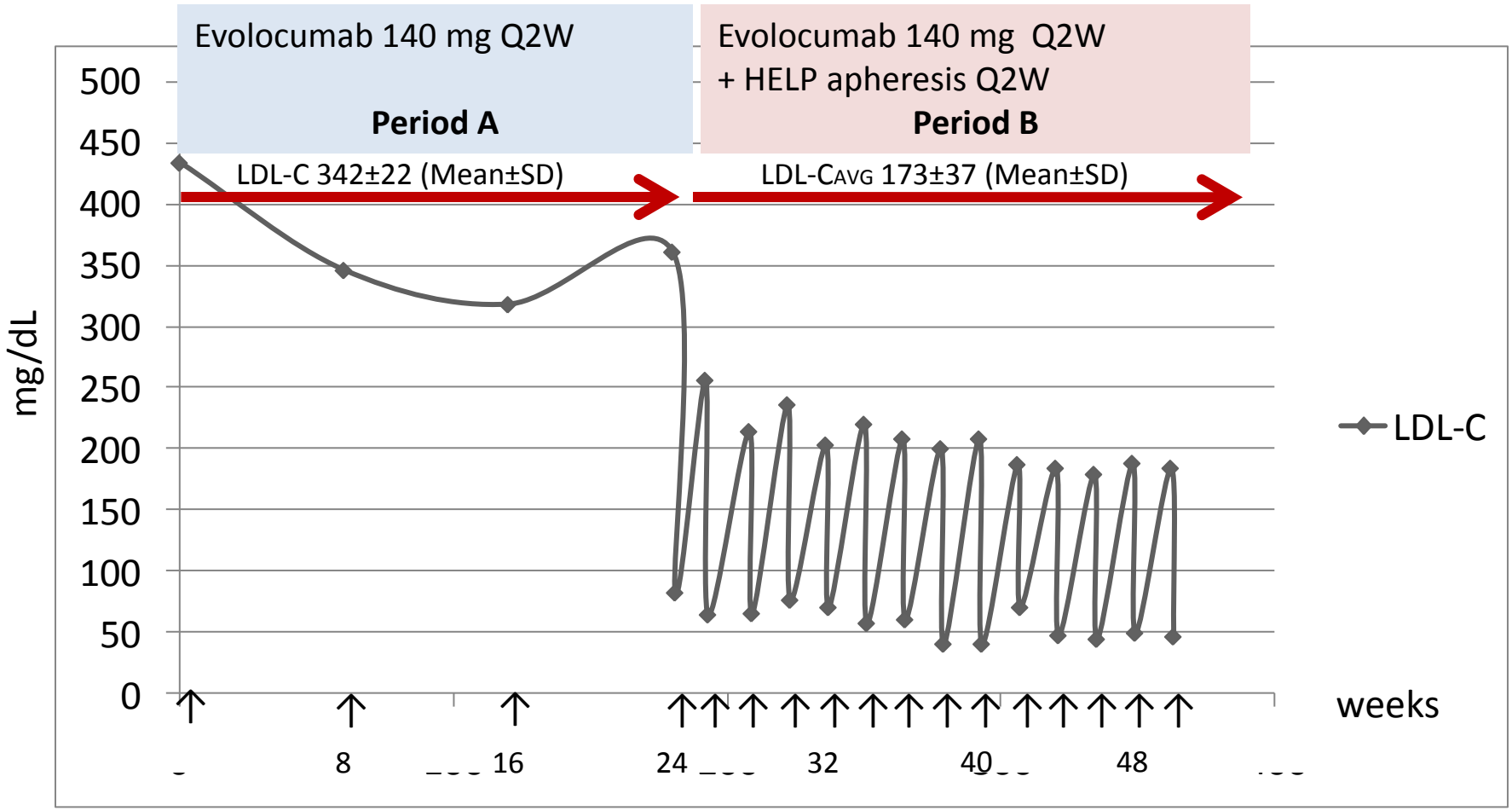
Lipid and liver profile during evolocumab treatment in monotherapy (140 mg every two weeks)

	0	8 weeks	16 weeks	24 weeks
Total-C (mg/dl)	522	468	392	446
HDL- C (mg/dl)	84	81	70	67
LDL-C (mg/dl)	**434**	**346**	**318**	**361**
Tryglicerides (mg/dl)	120	87	88	97
Lp(a) (mg/dl)	13	11	ND	ND
AST (U/L)	25	19	29	13
ALT (U/L)	23	24	36	22
CPK (U/L)	69	59	60	78

ND=Not Determined

From May 2016, a treatment with lipoprotein apheresis was added to the evolocumab therapy

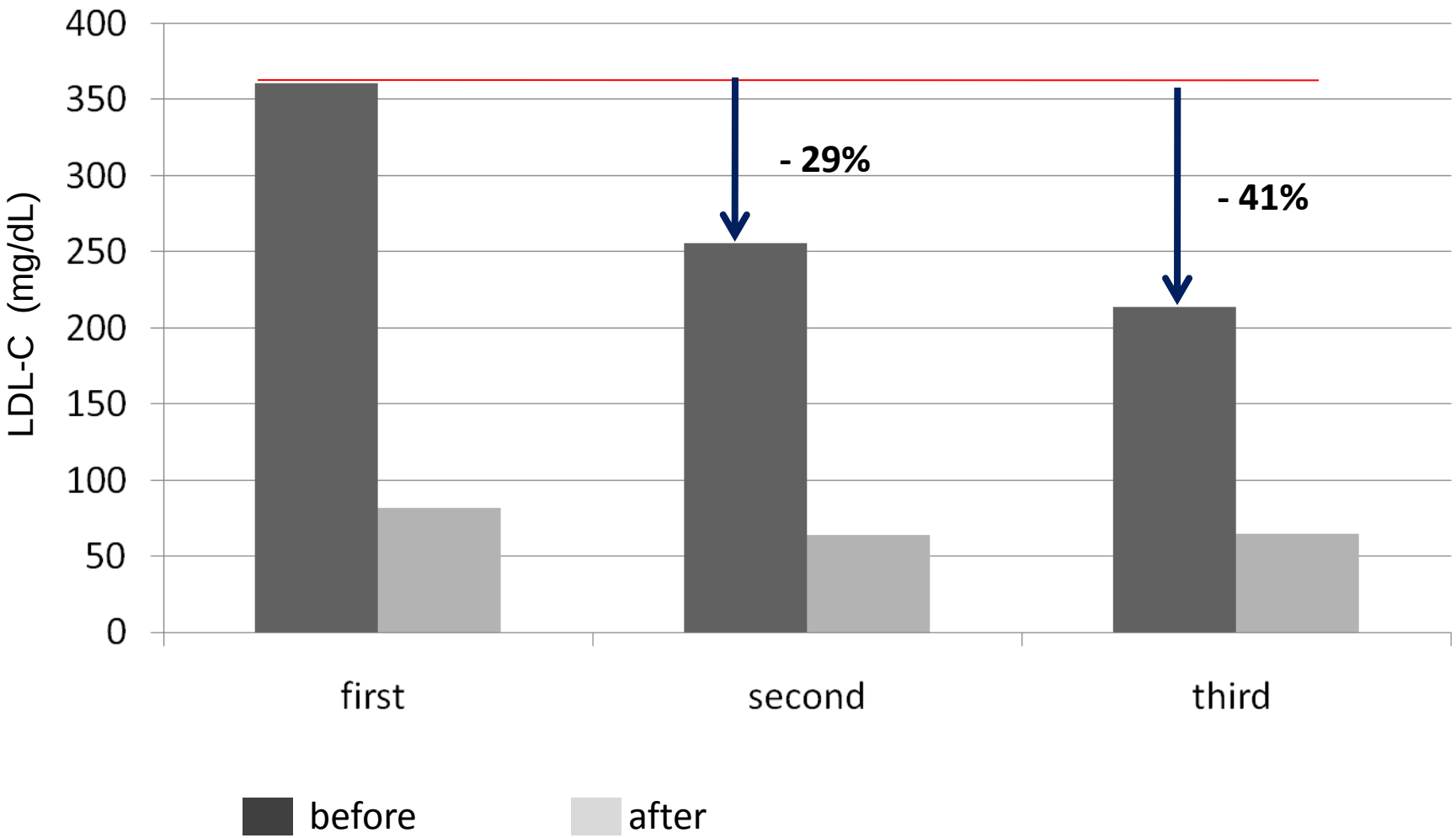
LDL-C plasma values during evolocumab treatment in monotherapy (140 mg QW2) and after starting HELP apheresis (every two weeks). Blood sampling was performed at baseline (0), every 8 weeks for period A, and every two weeks (immediately before and after apheresis) for period B.



Δ% = -21.2%

Δ% = -49.4%

LDL-C plasma values immediately before and after the first, second and third HELP apheresis (every two weeks). After starting HELP apheresis, preapheresis LDL-C plasma values were reduced by 29% and 41%, respectively.



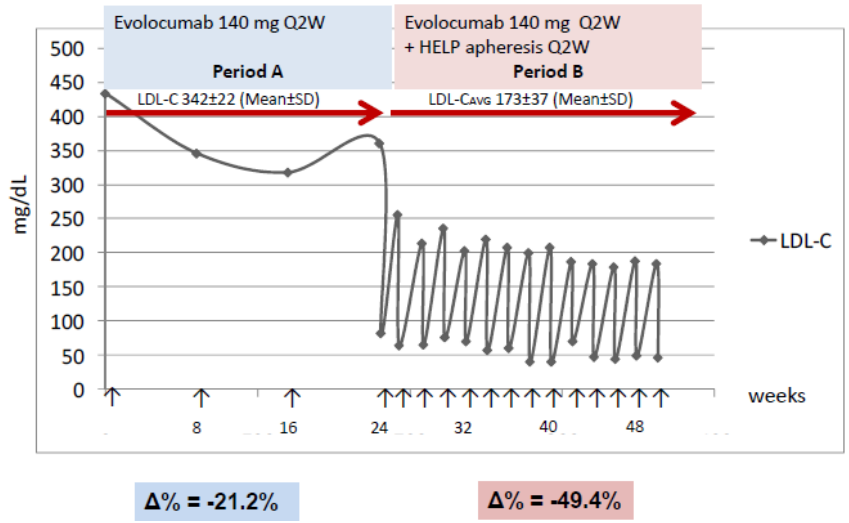
evolocumab therapy + lipoprotein : a synergic effect?

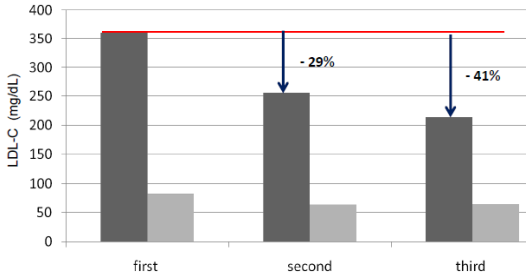
ODYSSEY ALTERNATIVE: 24-week administration of alirocumab obtained a reduction of mean LDL-C levels by **45%** in patients with statin intolerance

GAUSS-3: the mean percent change in LDL-C levels after 24 weeks with evolocumab was -**52.8%** in patients with statin intolerance

MARINA (HeFH and rheumatic disease): evolocumab in 24 weeks reduced LDL-C levels by **21.2%.**

- Pfohl M: in HeFH patients, Lipoprotein Apheresis determined a long-term reductions in pre-treatment LDL-C approximately **30%** after 6 months of therapy
- **MARINA**: pre-apheresis LDL-C levels showed a remarkable reduction of about **41%** after 4 weeks of combination therapy, as compared to the LDL-C obtained during the evolocumab monotherapy





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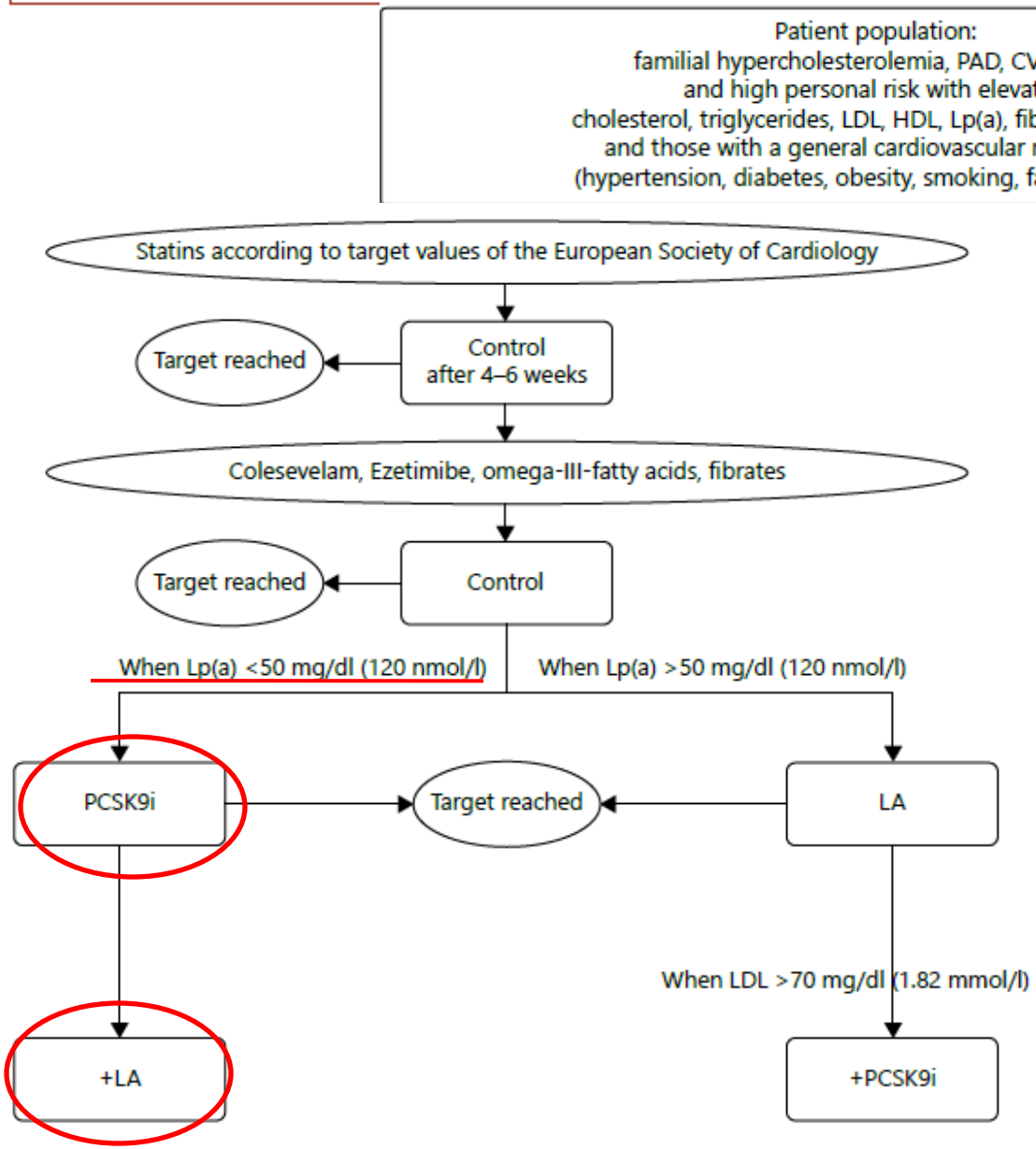

Marina

Period A:

LDL-C 342±22 (Mean±SD)

Period B:

LDL-C_{AVG} =173±37 mg/dL

Neumann et al., Blood Purif 2016;41:270-276

Highlights

- Monoclonal antibody against PCSK9 are approved for the treatment of Hypercholesterolemia in patients with intolerance or inadequate response to statins
- Lipoprotein Apheresis is currently the best treatment option to bring high risk FH patients closer to target LDL levels
- Monoclonal antibody against PCSK9 in association with Lipoprotein Apheresis may have a synergic effect on the resulting lipid levels
- **Lipoprotein Apheresis is currently the most effective and safe treatment available for Lp(a)HLP** .

Thanks for your attention