

Update on PCSK9 inhibitors and Statin Intolerance

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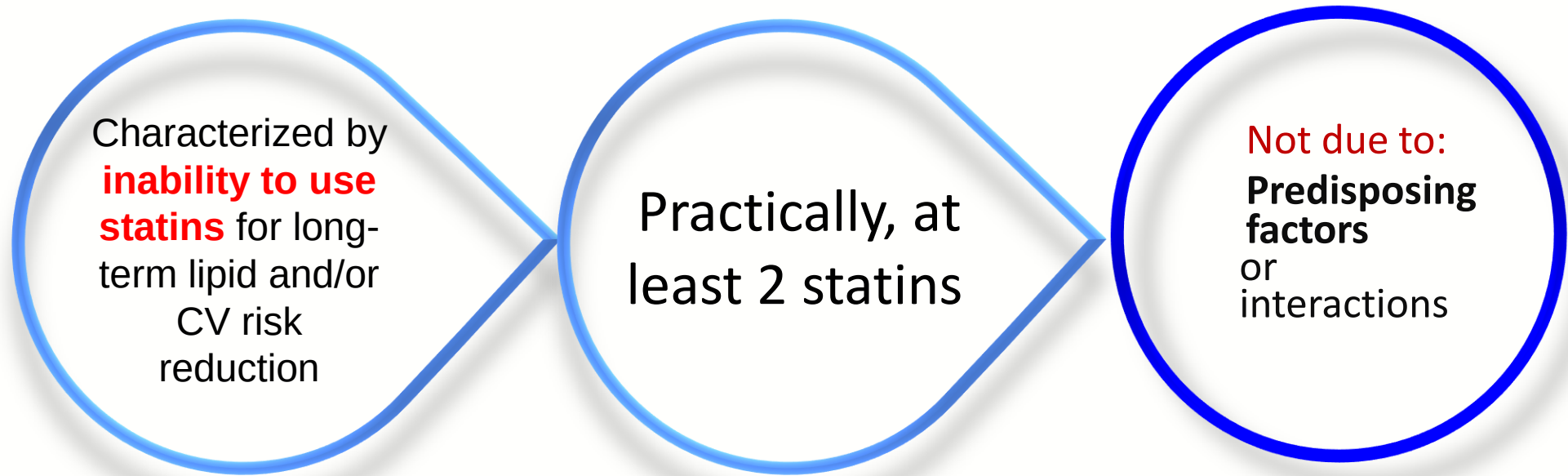
Fujairah Hospital, UAE



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Definition of Statin Intolerance (SI):

A Clinical Syndrome (ie there is no specific test yet) that



Due to:

- Significant or alarming symptoms (most commonly muscle pain and/or fatigue)
- AND/OR
- Biomarker abnormalities attributed temporally and unequivocally to statin use
 - As generally determined by re-challenge



Definition of Statin Associated Muscle Symptoms:

Consensus group	Definition
EAS Consensus Panel	Clinical diagnostic definition--taking into account the nature of the muscle symptoms, the elevation in CK levels and their temporal association with statin initiation, discontinuation, and rechallenge
Statin Muscle Safety Task Force	Definition is based on symptoms plus the magnitude of elevation in CK
Trial	Definition
ODYSSEY ALTERNATIVE Alirocumab	Intolerance to 2 statins , including one at the lowest approved starting dose (Included a placebo run-in and statin rechallenge arm)
GAUSS-2 Evolocumab	Intolerance to 2 statins , defined as inability to tolerate any dose or increase the dose above the smallest tablet strength because of intolerable muscle-related side effects
GAUSS-3 Evolocumab	Intolerance to 3 statins or 2 statins (one of which was atorvastatin 10 mg/day) or with a history of marked CK elevation accompanied by muscle symptoms while on a statin



Definition of Statin Associated Muscle Symptoms:

Consensus group

Definition

2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapy

...unacceptable muscle-related symptoms that resolve with **discontinuation** of therapy and occur with **rechallenge**

- on at least 2 to 3 statins, preferably
- ones that use different metabolic pathways
- and have different lipophilicity,
- and 1 of which is prescribed at the lowest approved dose.

evolocumab

while on a statin



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Patterns of Statin Muscle Intolerance (EAS Consensus Panel):

Muscle Symptoms + Normal
CK

- Myalgia, may be related to Statin SAMS

Muscle Symptoms + CK $\leq$
10x ULN

- Statin Associated Muscle Symptoms (SAMS)

Muscle Symptoms + CK $\geq$
10X ULN

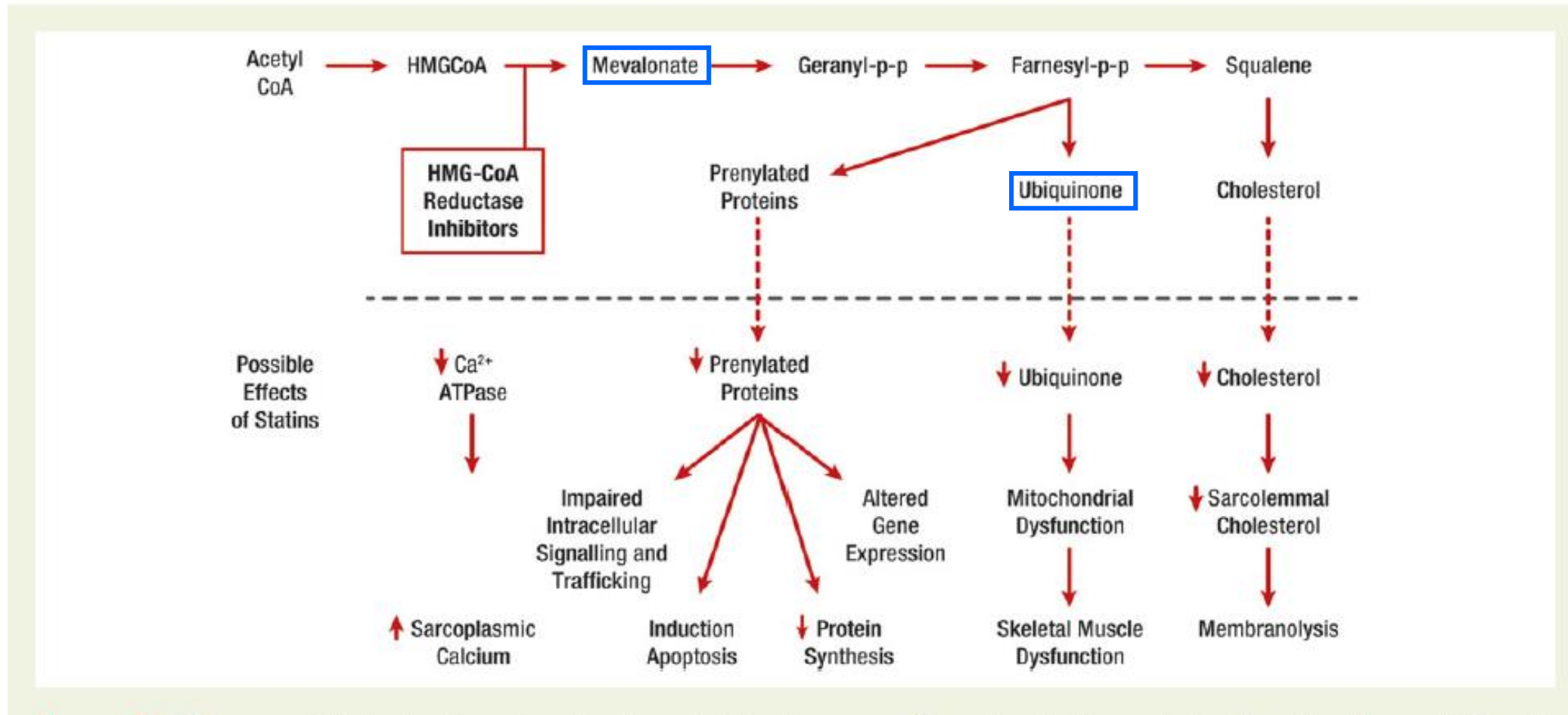
- Myositis/myopathy

Myonecrosis + CK elevation
 $\geq 40x$

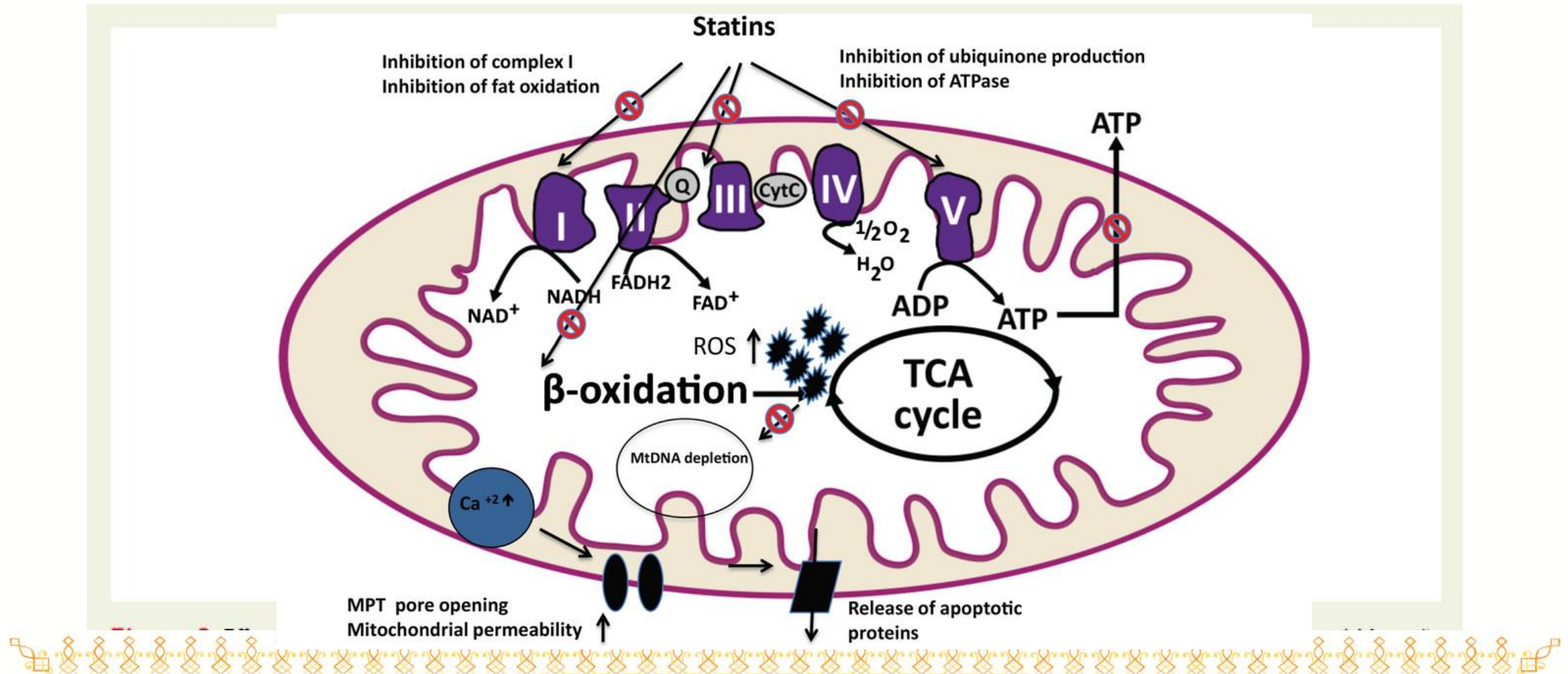
- +/-Myoglobinuria, Rhabdomyolysis



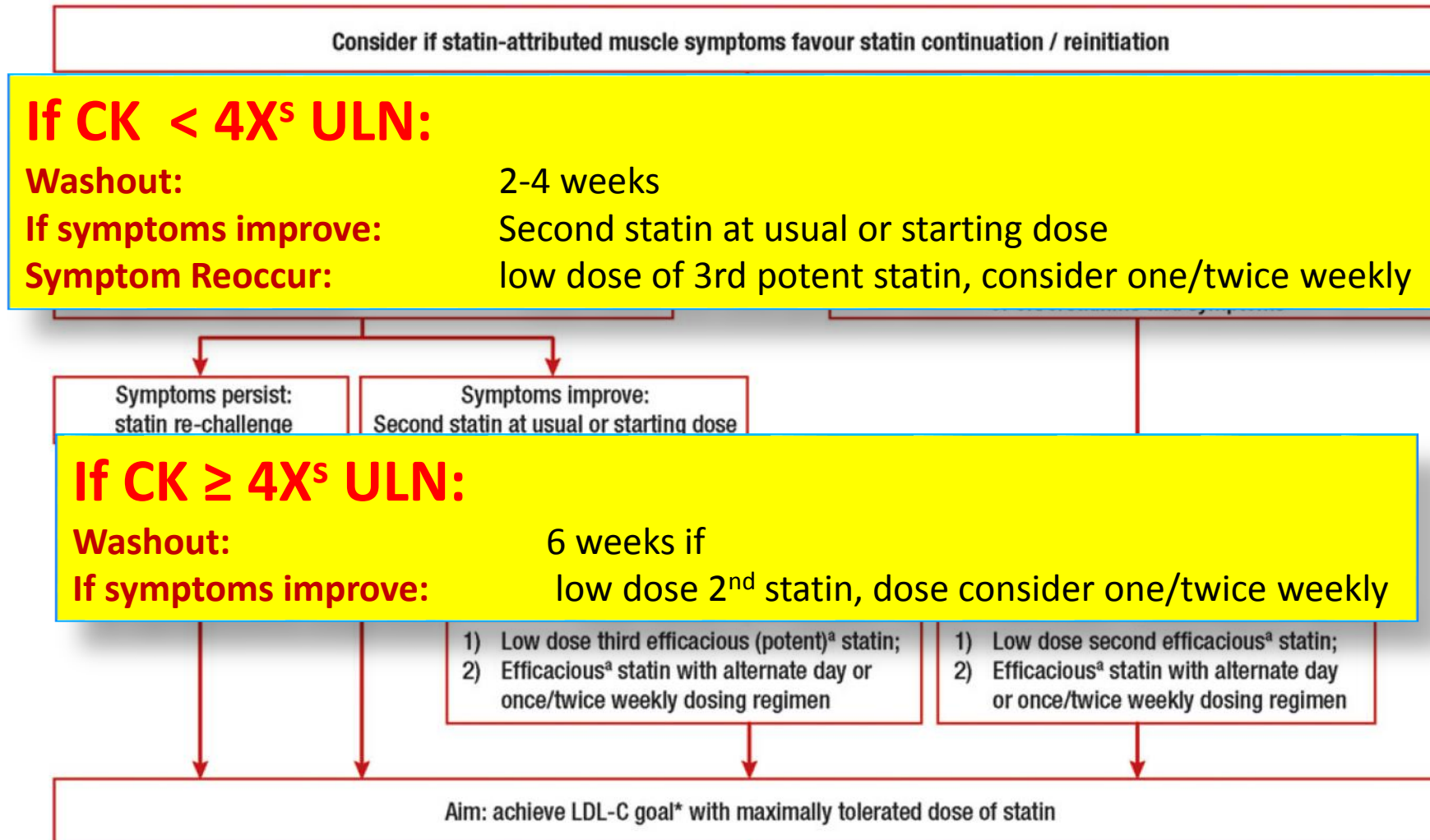
Effects potentially involved in statin related muscle symptoms



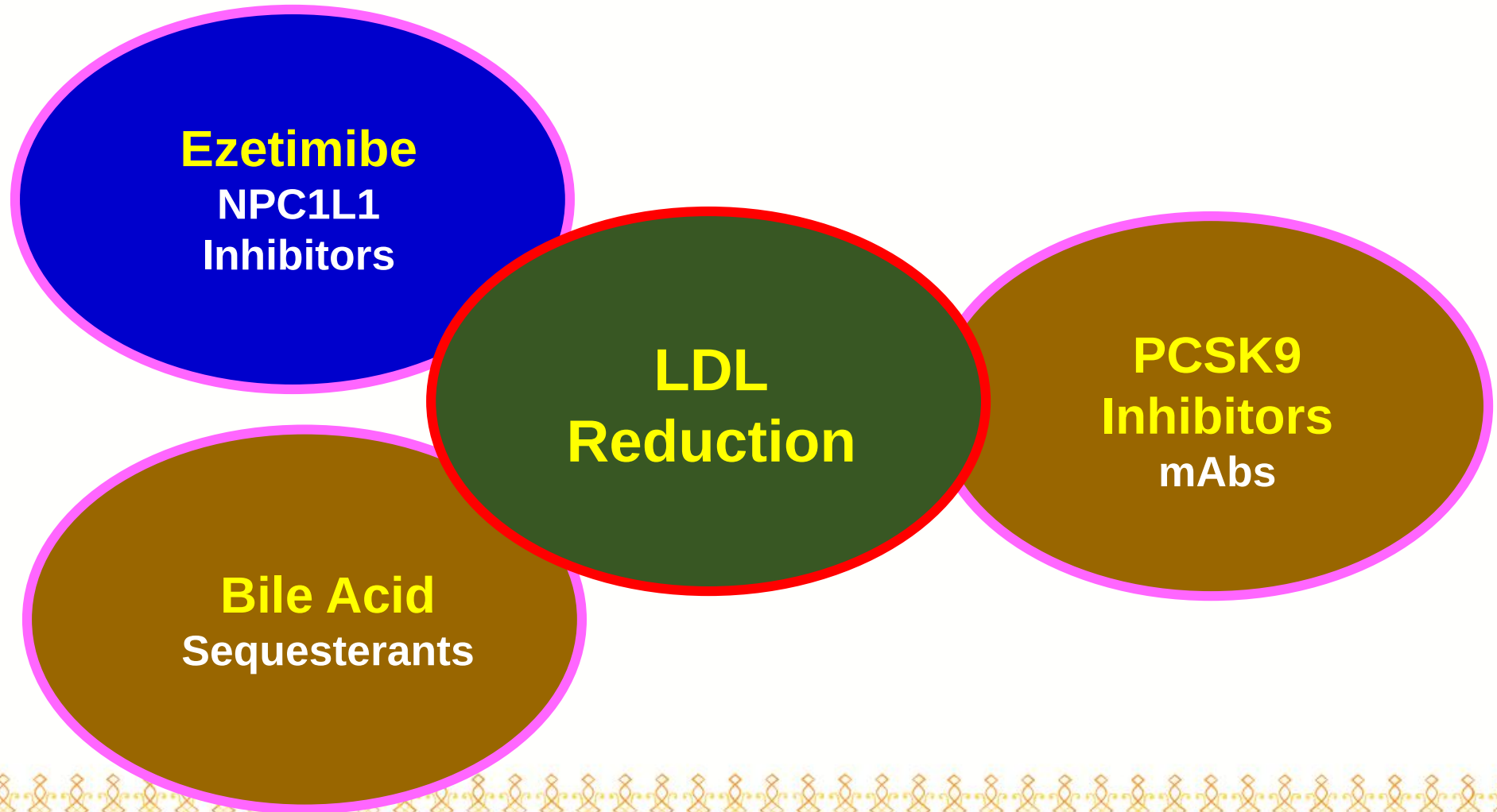
Effects potentially involved in statin related muscle symptoms



Therapeutic flow-chart for management of patients with SAMS by the EAS Consensus Panel :



What “Options” we have for Statin Intolerance ?

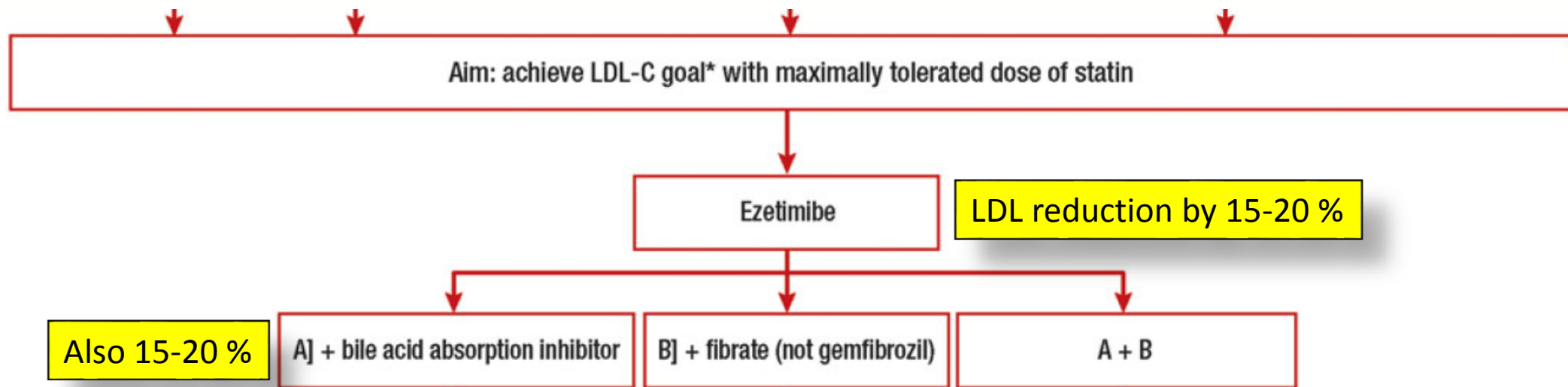


ESC Lipids 2016 and EAS Consensus Document:

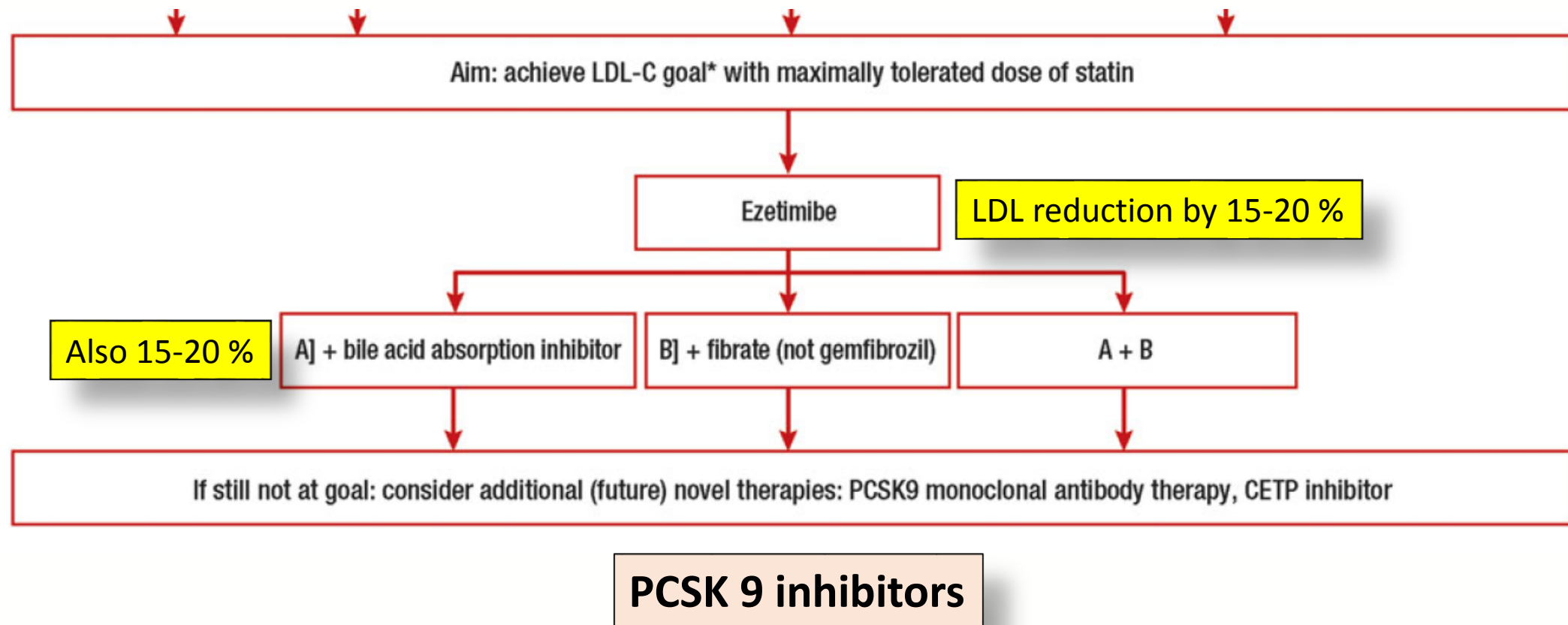


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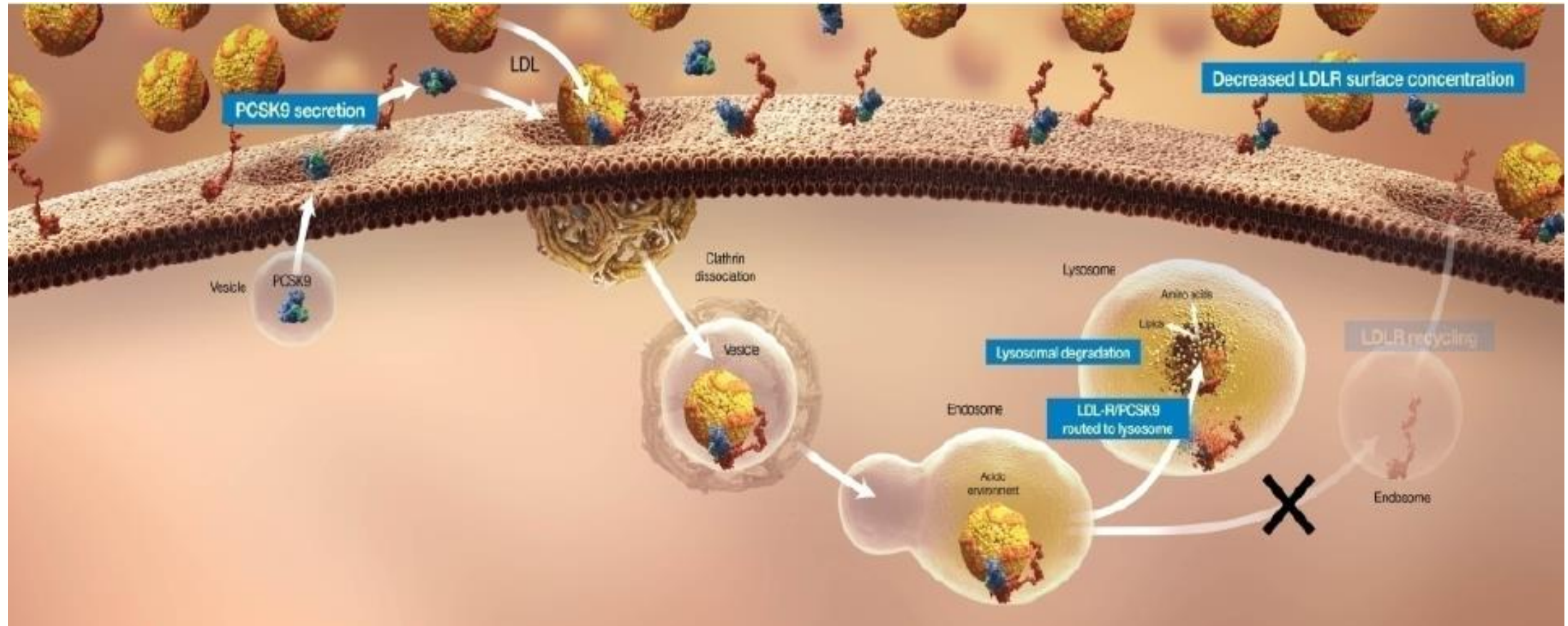
ESC Lipids 2016 and EAS Consensus Document:



ESC Lipids 2016 and EAS Consensus Document:



PCSK9 Regulates the Surface Expression of LDL-Rs by Targeting Them for Lysosomal Degradation



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Horton JD, et al. *J Lipid Res.* 2009;50:S172-S177.
Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

FDA Approved Indications for Anti-PCSK9 Monoclonal Antibodies (Diet + Max. Tolerated Statin Therapy for Additional LDL-C Lowering)

	Clinical ASCVD*	Heterozygous FH	Homozygous FH
Evolocumab	+	+	+
Alirocumab	+	+	-

*Clinical ASCVD includes acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.



Should PCSK9 Inhibitors be Used in Statin Intolerant Patients?

It depends on whom you ask

- “Patients” and “Providers”
- Pharmaceutical Companies
- Payers and Insurance
- Professional Organizations (NLA, ACC, AHA, ECS and EAS)



Evolocumab

- GUASS 1(2012): effect of Evolocumab versus placebo in statin-intolerant patients
- GUASS 2 (2014): **Evolocumab in Patients With Statin Intolerance**
- GUASS 3 (JAMA 2016): **Evolocumab Superior to Ezetimibe in Patients With Muscle-Related Statin Intolerance**

Alirocumab

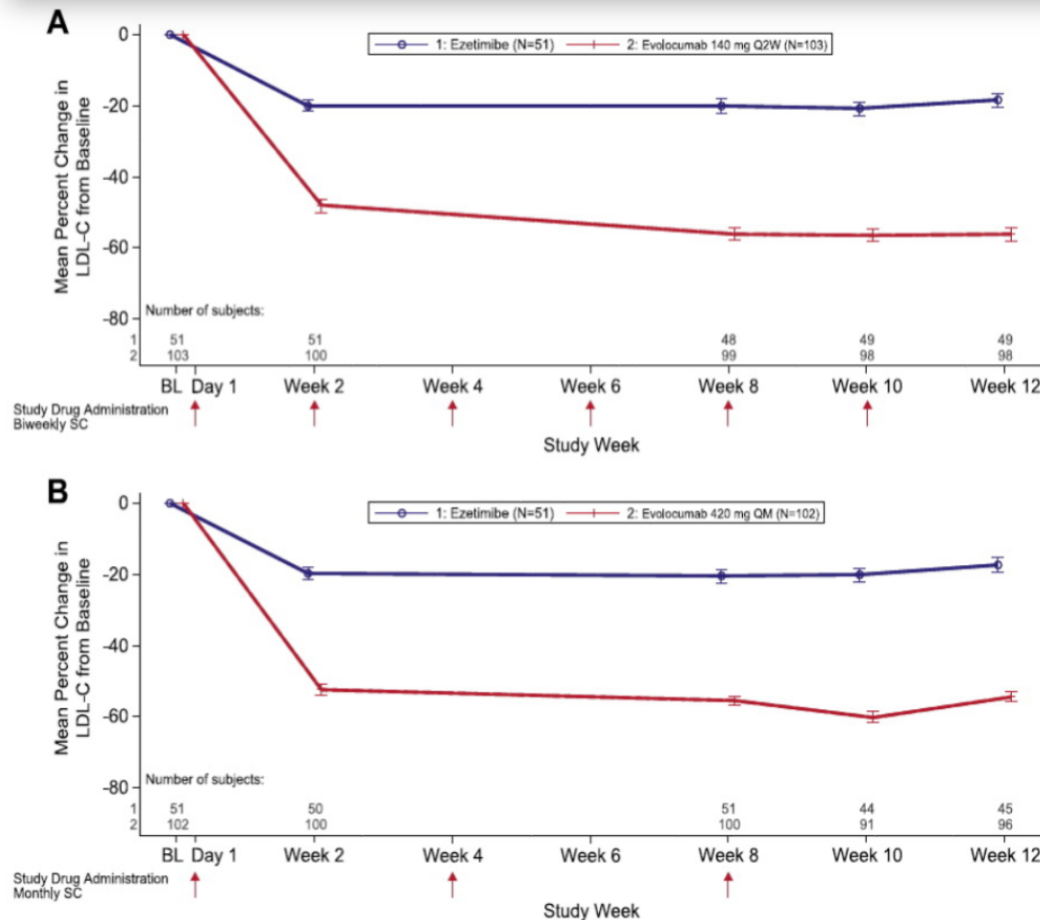
- ODYSSEY ALTERNATIVE



Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients With Statin Intolerance



The GAUSS-2 Randomized, Placebo-Controlled Phase 3 Clinical Trial of Evolocumab



Cohort of 300 patients
SI to at least 2 statins
randomized to Ezetimibe vs SC evolocumab

- LDL C decrease by around 55%
- absolute 38% more than ezetimibe
- 70-90% of the patients were at the LDL target goal

Mean Percent Change in Low-Density Lipoprotein Cholesterol Concentration from Baseline to Week 12 in Patients Who Received Evolocumab

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Efficacy and Tolerability of **Evolocumab vs. Ezetimibe** in Patients with Muscle-Related Statin Intolerance

The **GAUSS-3** Randomized Clinical Trial

Nissen SE, et al [published online ahead of print April 3, 2016]

Steven E. Nissen, MD¹; Erik Stroes, MD, PhD²; Ricardo E. Dent-Acosta, MD³; Robert S. Rosenson, MD⁴; Sam J. Lehman, MBBS, PhD⁵; Naveed Sattar, MD, PhD⁶; David Preiss, MD^{7,8}; Eric Bruckert, MD⁹; Richard Češka, MD^{10,11}; Norman Lopor, MD¹²; Christie M. Ballantyne, MD¹³; Ioanna Gouni-Berthold, MD¹⁴; Mary Elliott, MS³; Danielle M. Brennan, MS¹; Scott M. Wasserman, MD³; Ransi Somaratne, MD, MBA³; Rob Scott, MD³; Evan A. Stein, MD, PhD¹⁵

¹Cleveland Clinic, Cleveland, Ohio ;²University of Amsterdam Faculty of Medicine, Amsterdam, the Netherlands ;³Amgen Inc, Thousand Oaks, California ;⁴School of Medicine at Mount Sinai, New York, New York ;⁵Flinders University, Bedford Park, SA, Australia ;⁶University of Glasgow, Glasgow, United Kingdom ;⁷Clinical Trial Service Unit, University of Oxford, Oxford, United Kingdom ;⁸Epidemiological Services Unit, University of Oxford, Oxford, United Kingdom ;⁹University Hospital of Paris 6, Paris, France ;¹⁰Charles University in Prague, Prague, Czech Republic ;¹¹General University Hospital in Prague, Prague, Czech Republic ;¹²David Geffen School of Medicine at the University of California, Los Angeles ;¹³Baylor College of Medicine, Houston, Texas ;¹⁴Center for Endocrinology, Diabetes and Preventive Medicine, University of Cologne, Cologne, Germany ;¹⁵Metabolic and Atherosclerosis Research Center, Cincinnati, Ohio

GAUSS-3 = **G**oal **A**chievement after **U**tilizing an anti-PCSK9 antibody in **S**tatins Intolerant **S**ubjects-3



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Efficacy and Tolerability of **Evolocumab vs. Ezetimibe** in Patients with Muscle-Related Statin Intolerance

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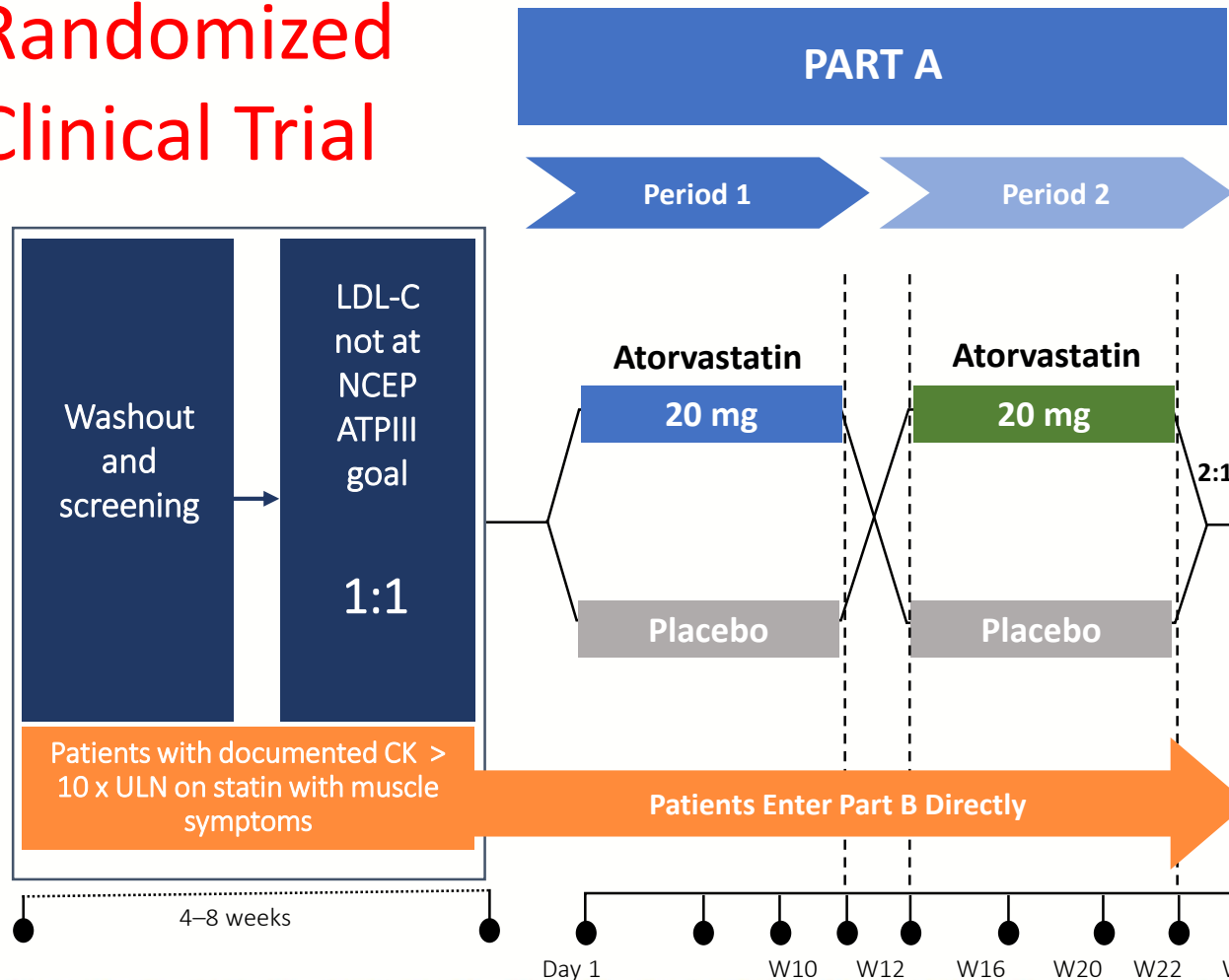
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Patients with history of statin intolerance defined as:

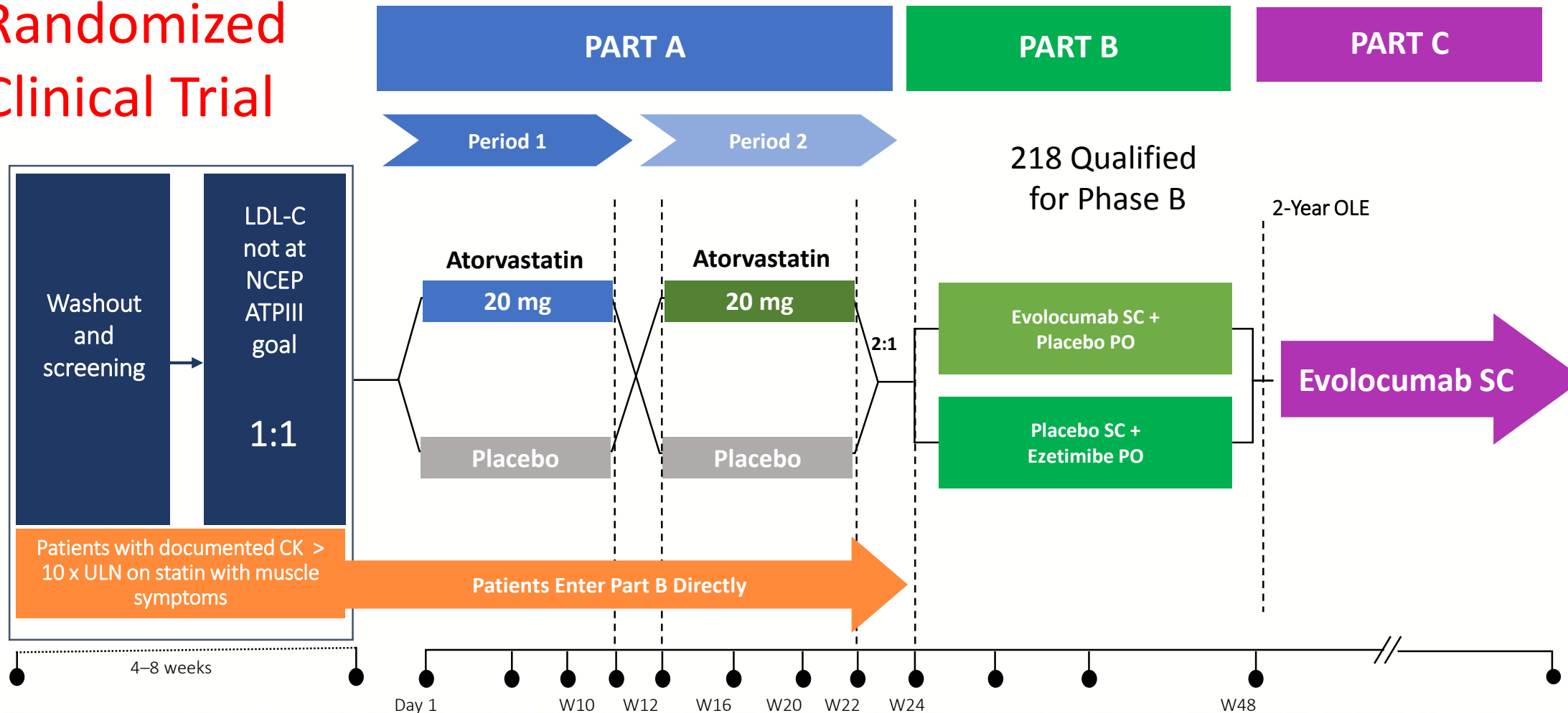
- inability to tolerate atorvastatin 10 mg QD and any other statin at any dose OR
- inability to tolerate ≥ 3 statins[†] OR
- documented history of CK elevation $>10 \times$ ULN with muscle symptoms while on statins



The GAUSS-3 Randomized Clinical Trial

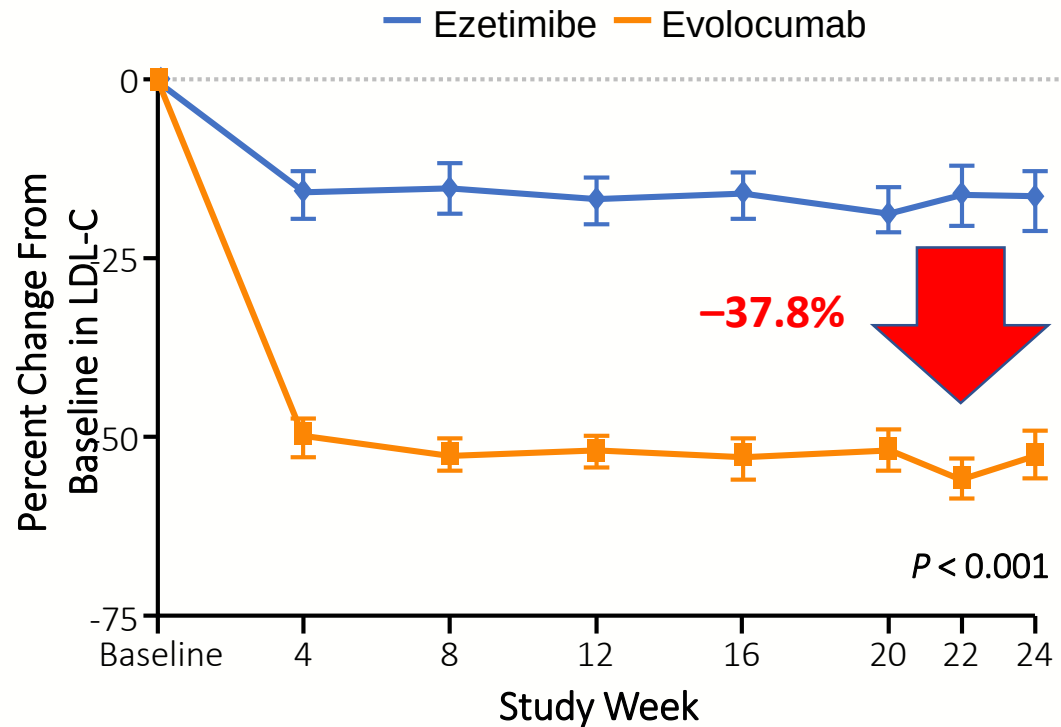


The GAUSS-3 Randomized Clinical Trial



- 26.5% of patients had myalgias associated with placebo but not with statin
- only 43% had a true intolerance to statins.

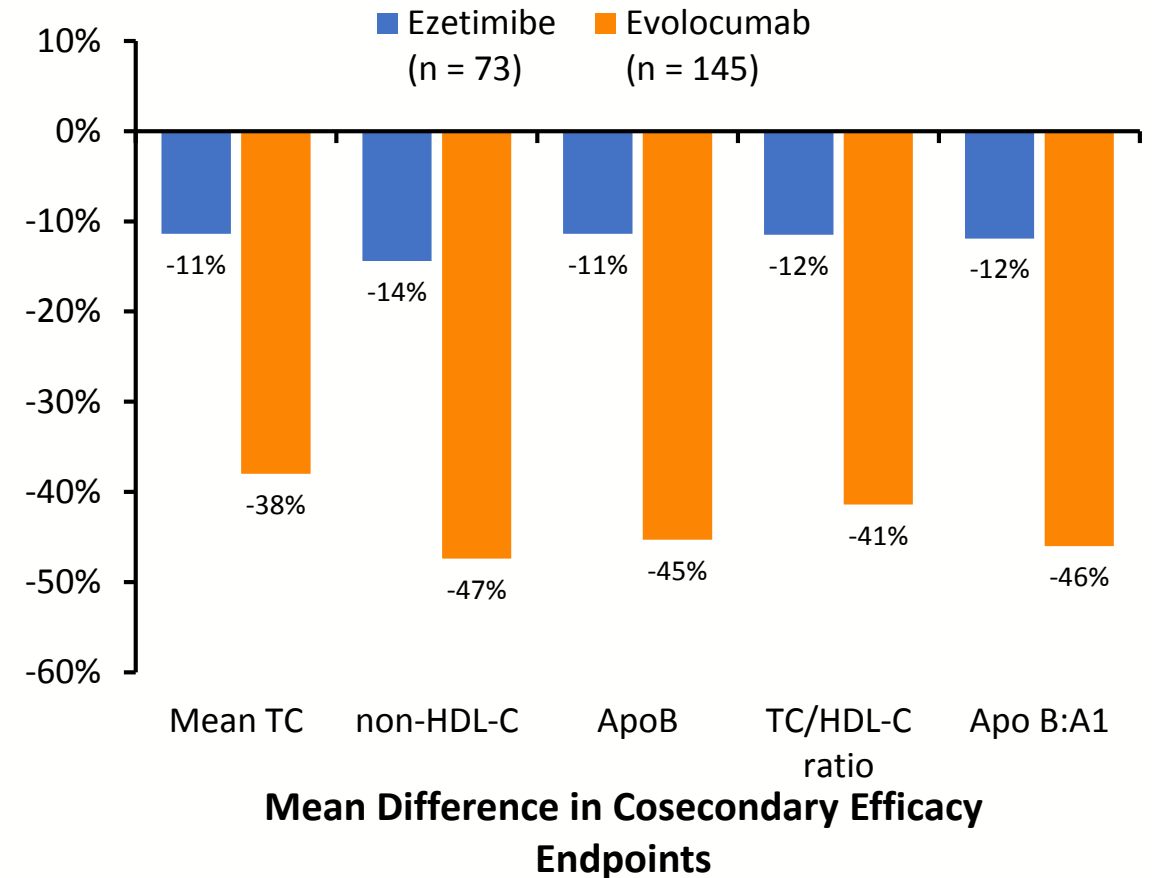
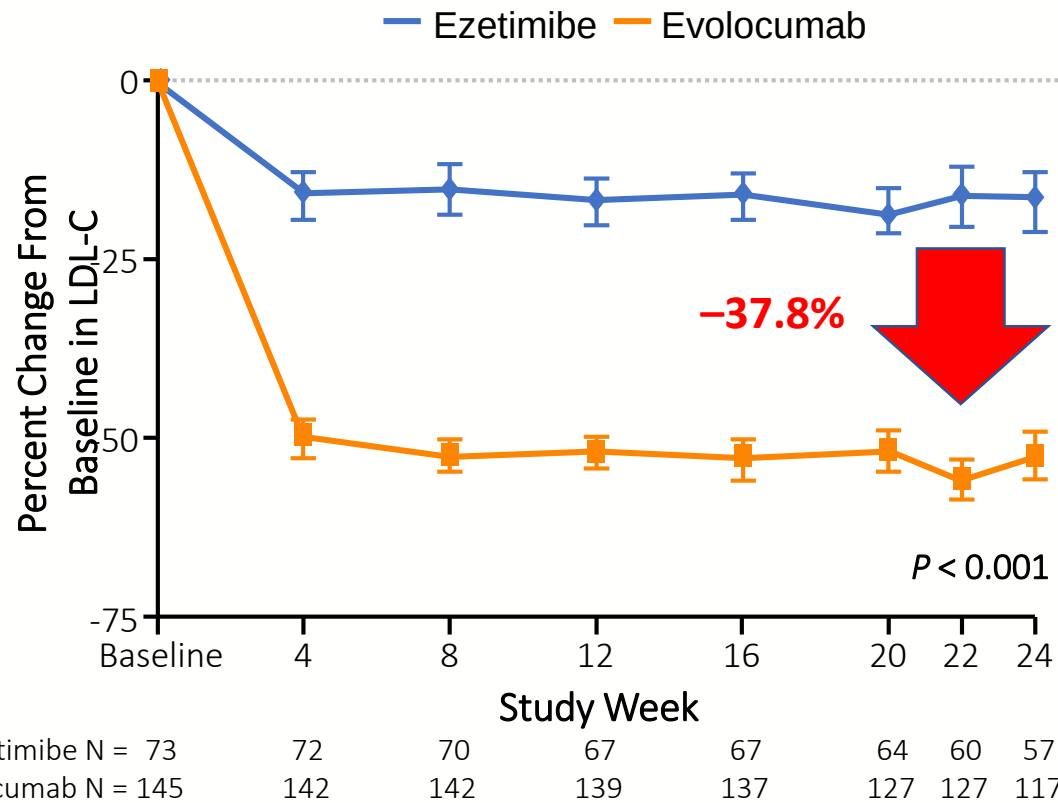
GAUSS-3: Phase B: Percent Change in LDL-C Level & lipid parameters



Ezetimibe N = 73 72 70 67 67 64 60 57
Evolocumab N = 145 142 142 139 137 127 127 117

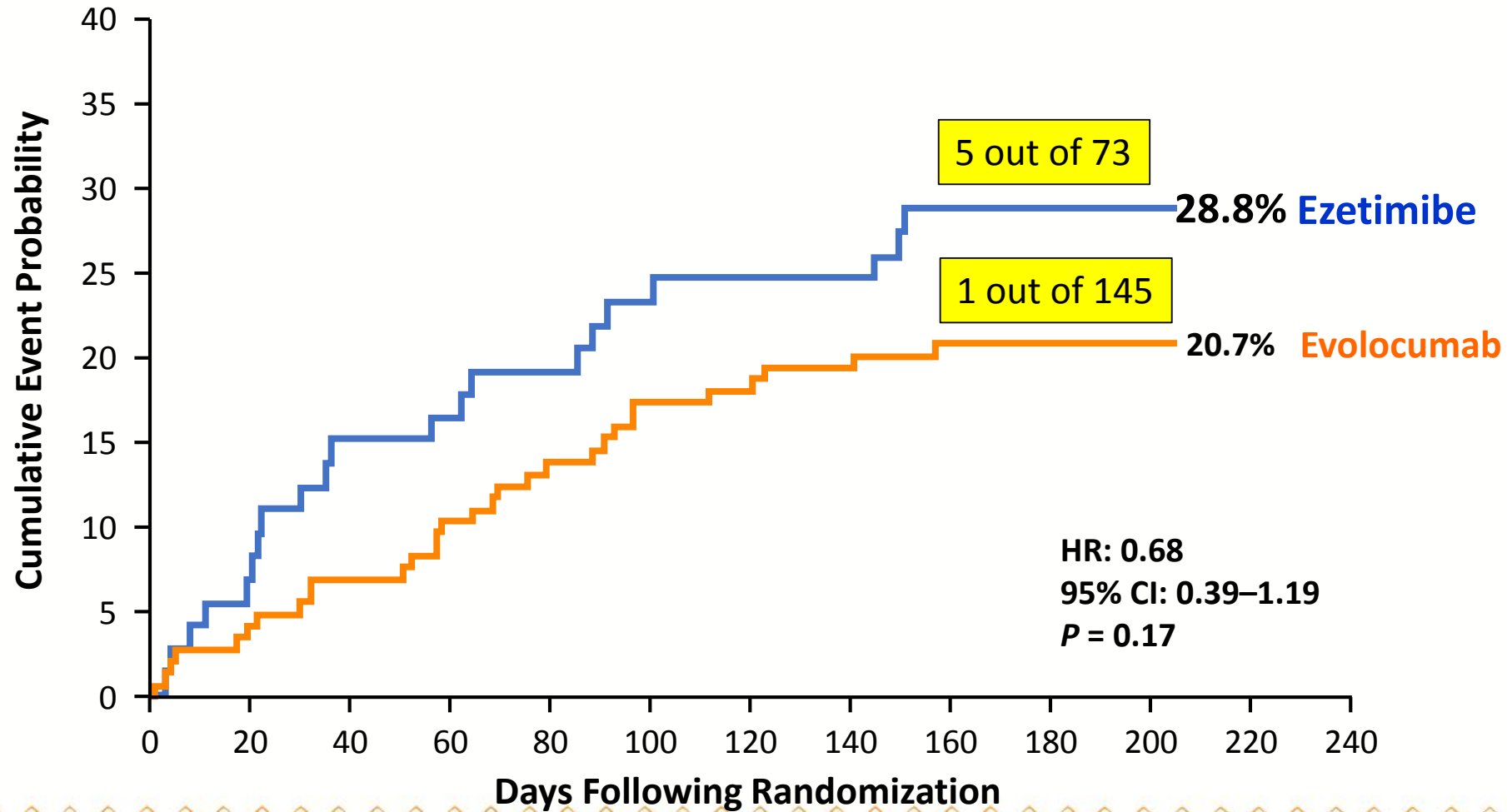


GAUSS-3: Phase B: Percent Change in LDL-C Level & lipid parameters



GAUSS-3:

Phase B: Time to First Occurrence of a Muscle-related AE



GAUSS 3 Conclusions:

- the use of evolocumab compared with ezetimibe resulted in a **significantly greater reduction in LDL-C** and other atherogenic lipoproteins after 24 weeks.
- Both ezetimibe and evolocumab were **well tolerated** during the trial, with 5 out of 73 ezetimibe patients (6.8%) and 1 out of 145 evolocumab patient (0.7%) discontinuing active treatment due to muscle-related adverse events.
- However, 11 evolocumab-treated patients (7.6%) discontinued oral placebo for muscle symptoms.



ODYSSEY ALTERNATIVE:

Efficacy and safety of alirocumab versus ezetimibe, in patients with statin intolerance defined by placebo run-in and statin rechallenge arm

Patrick M. Moriarty¹, Paul D. Thompson², Christopher P. Cannon³, John R. Guyton⁴, Jean Bergeron⁵, Franklin J. Zieve⁶, Eric Bruckert⁷,
Terry A. Jacobson⁸, Marie T. Baccara-Dinet⁹, Jian Zhao¹⁰, Yunling Du¹⁰,
Robert Pordy¹¹, Daniel Gipe¹¹

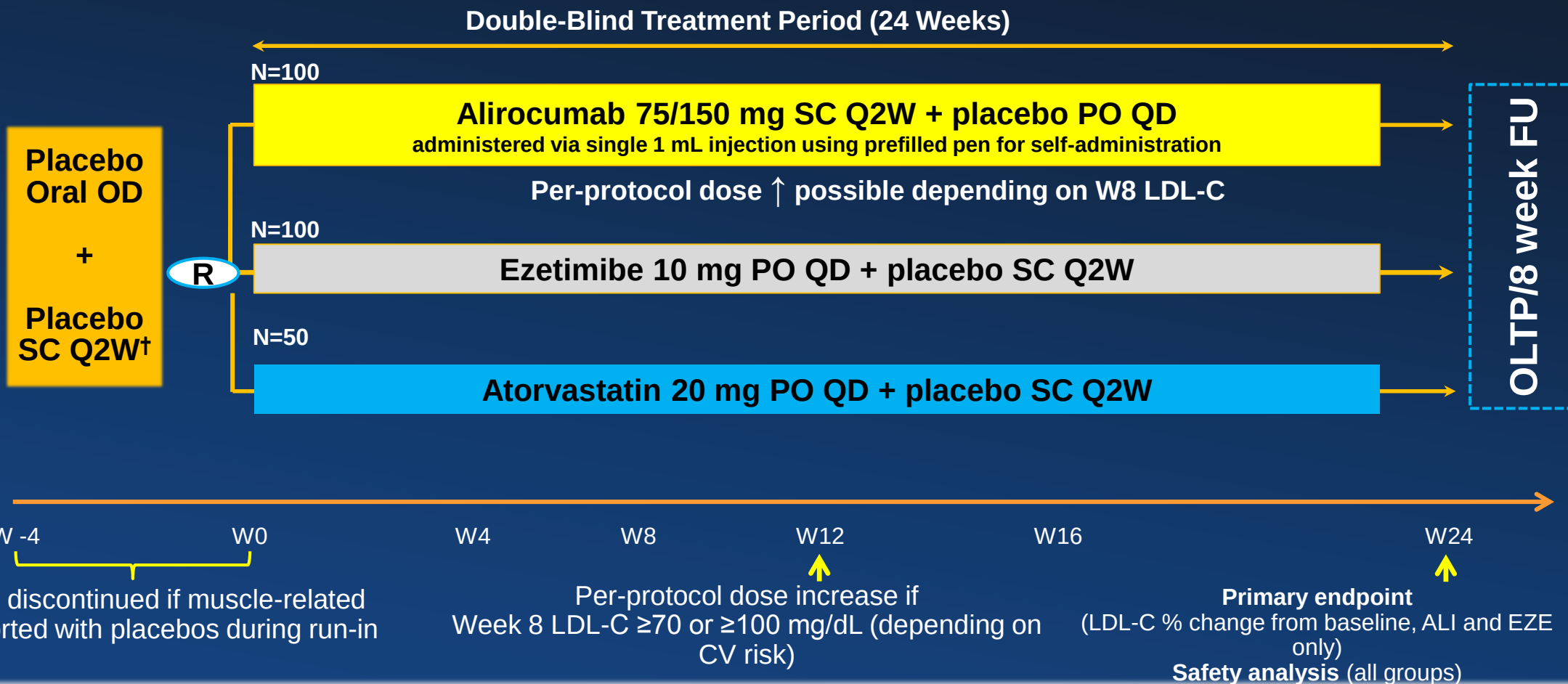
¹Department of Internal Medicine, Division of Clinical Pharmacology, University of Kansas Medical Center, Kansas City, KS, USA;

²Hartford Hospital, Hartford, CT, USA; ³Harvard Clinical Research Institute, Boston, MA, USA; ⁴Duke University Medical Center, Durham, NC, USA; ⁵Clinique des Maladies Lipidiques de Québec Inc., Québec, Canada; ⁶McGuire VA Medical Center, Richmond, VA, USA;

⁷Hôpitalier Pitié-Salpêtrière, Paris, France; ⁸Emory University, Atlanta, GA, USA; ⁹Sanofi, Montpellier, France; ¹⁰Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA; ¹¹Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

ODYSSEY ALTERNATIVE Study Design

Statin intolerant patients*
(by medical history) with LDL-C ≥ 70 mg/dL (very-high CV risk) or ≥ 100 mg/dL (moderate/high risk)



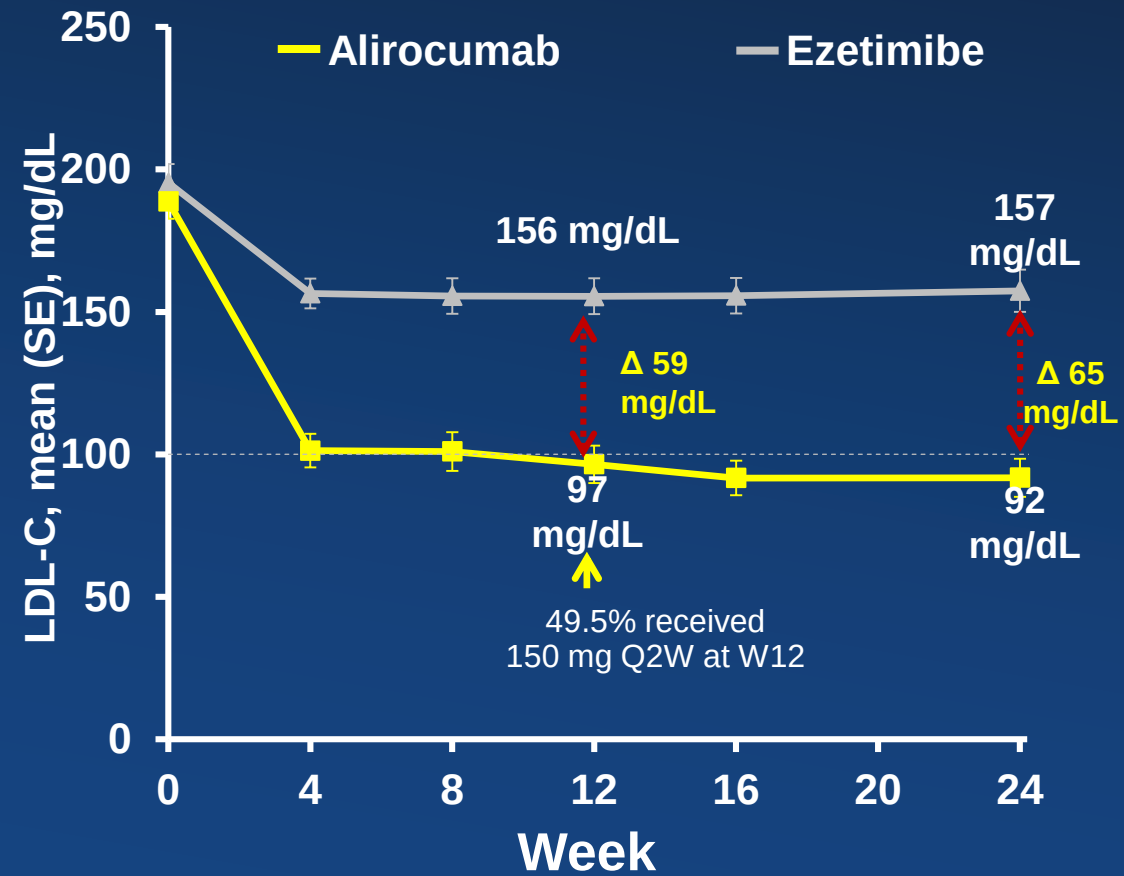
*Unable to tolerate at least two different statins, including one at the lowest dose, due to muscle-related symptoms

†4-week single-blind placebo run-in follows 2-week washout of statins, ezetimibe and red yeast rice.

OLTP: Alirocumab open-label treatment period; W, Week.

Alirocumab Maintained LDL-C Reductions Week 4–24

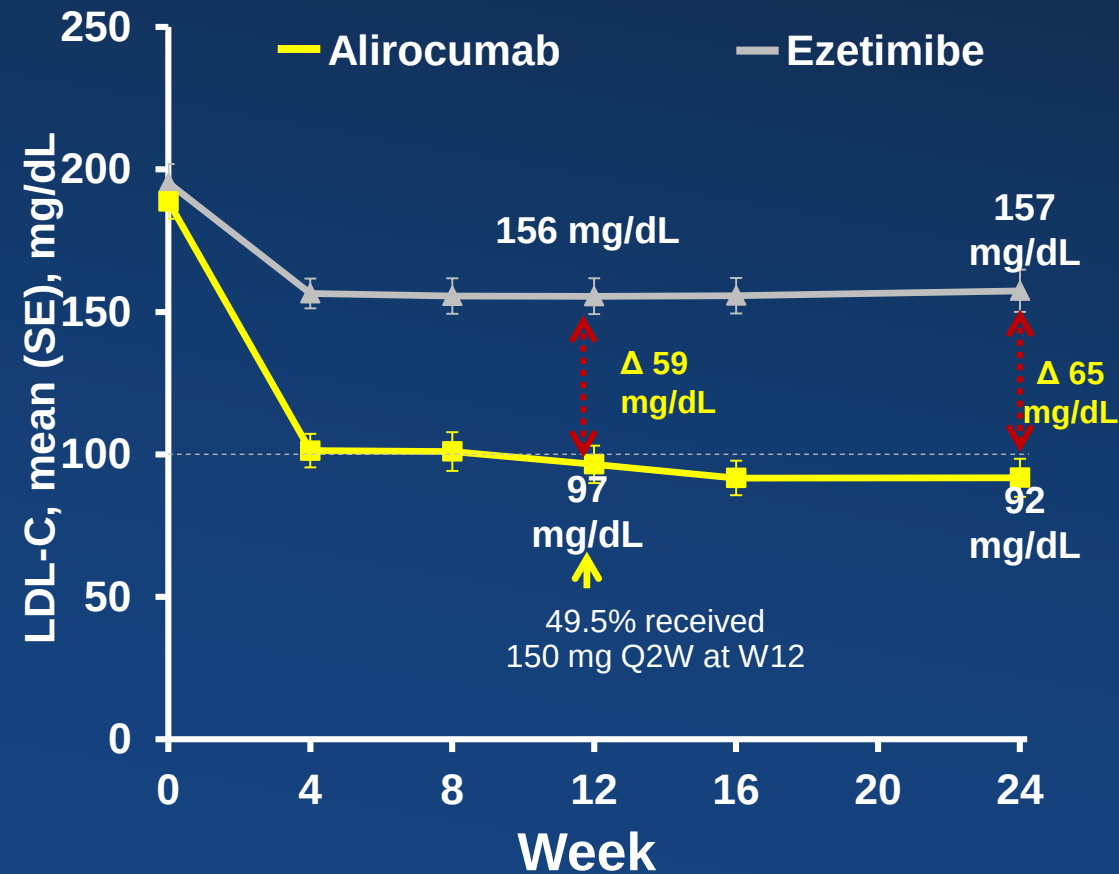
time – on-treatment analysis
(modified ITT – observed data only)



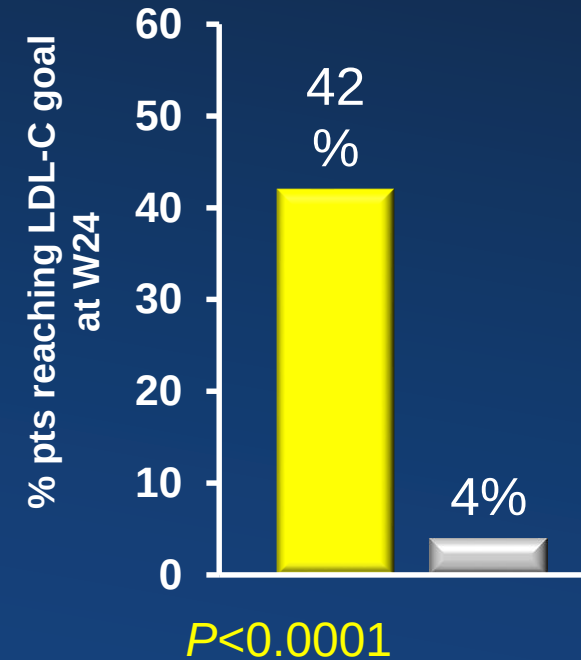
Alirocumab Maintained LDL-C Reductions Week 4–24

Significantly More SI Patients Achieved Target
LDL-C <70 or <100 mg/dL (depending on CV
risk) with Alirocumab vs Ezetimibe

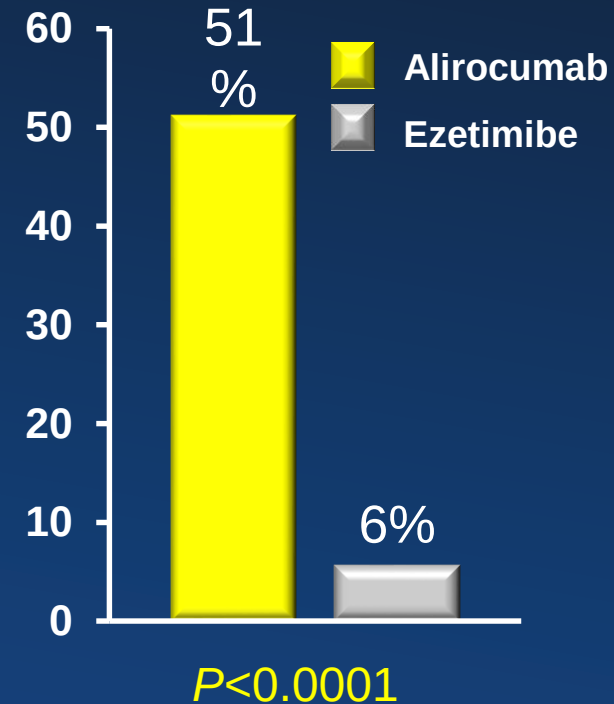
time – on-treatment analysis
(modified ITT – observed data only)



ITT

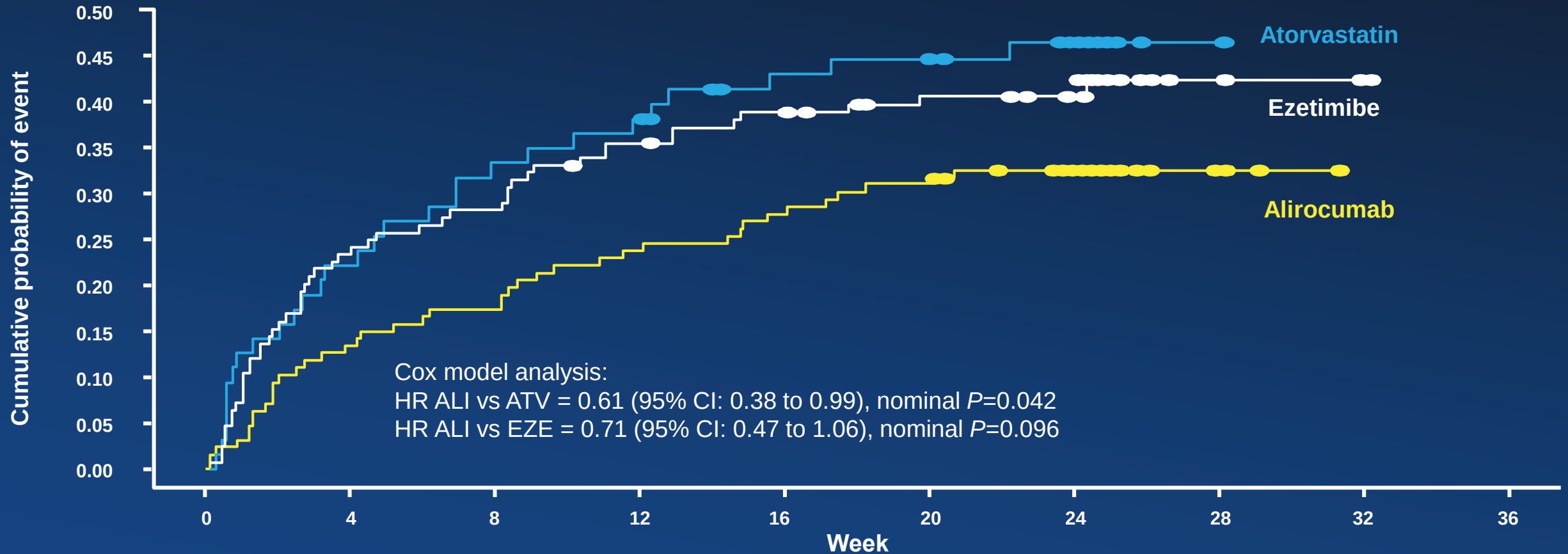


On-treatment



Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event†



†Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.
ALI, alirocumab; ATV, atorvastatin, EZE, ezetimibe.

**So PCSK9i work in Statin Intolerance,
But do we have outcome data ?**

**No outcome trials with PCSK9 inhibitors
in population with statin Intolerance**

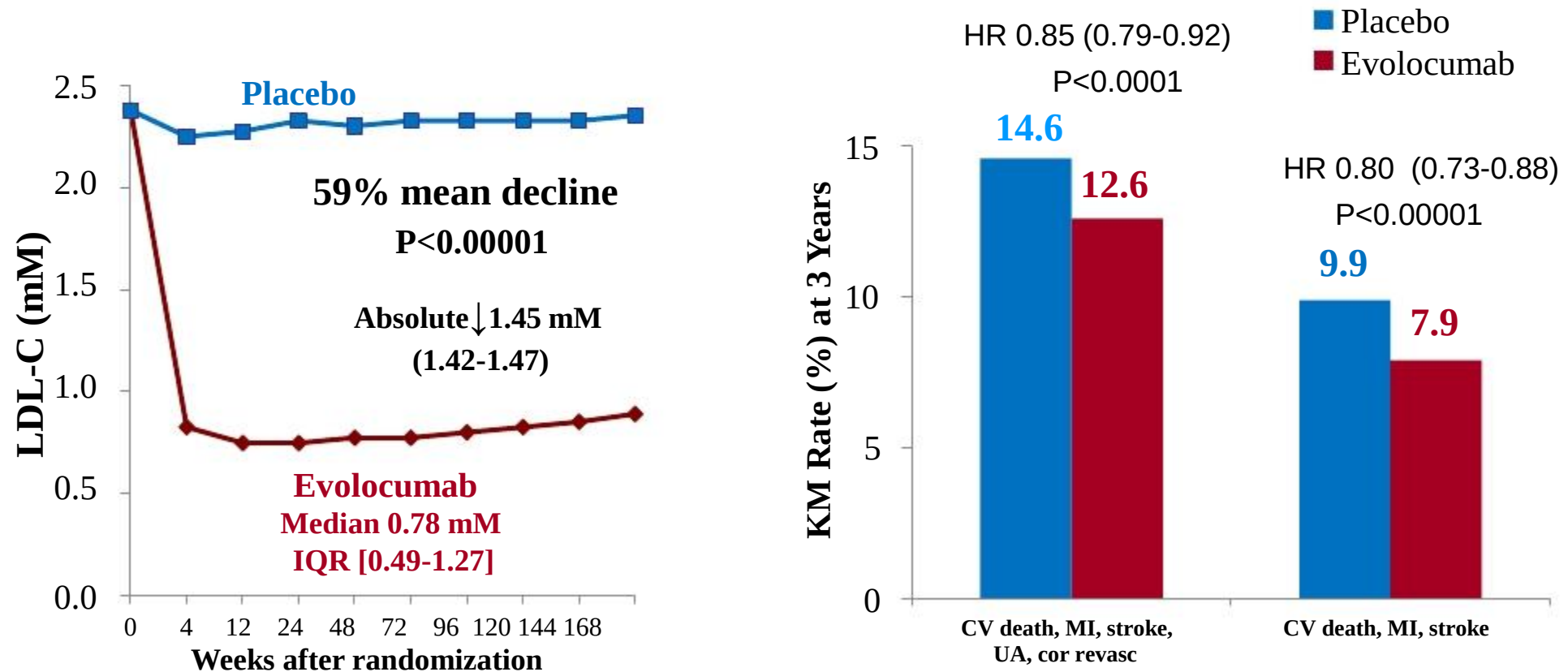




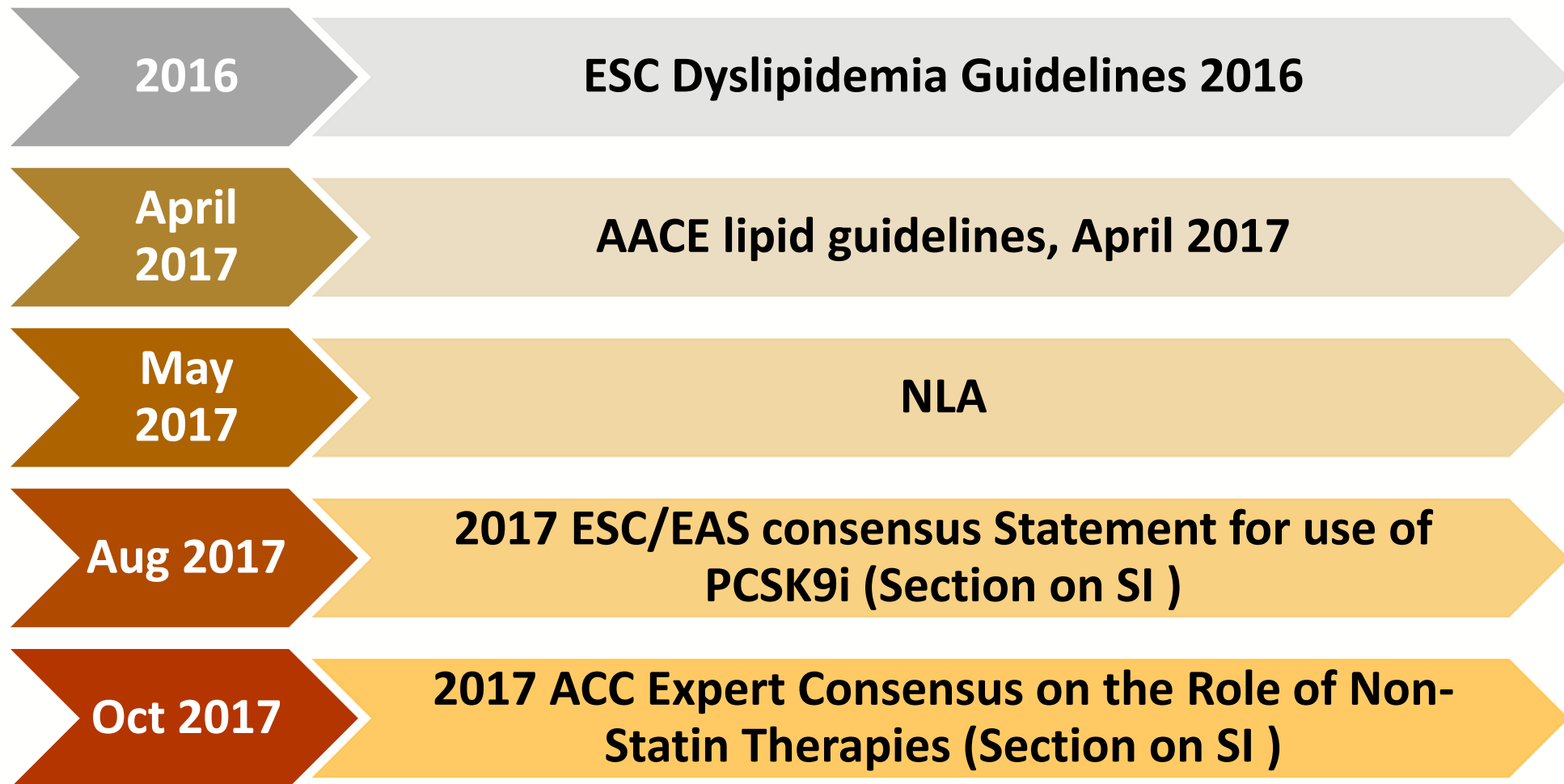
Summary of FOURIER



- ↓ LDL-C by 59% (from 2.4 -> 0.8 [0.5, 1.2] mM)
- ↓ CV outcomes in patients already on statin therapy
- Evolocumab was safe and well-tolerated



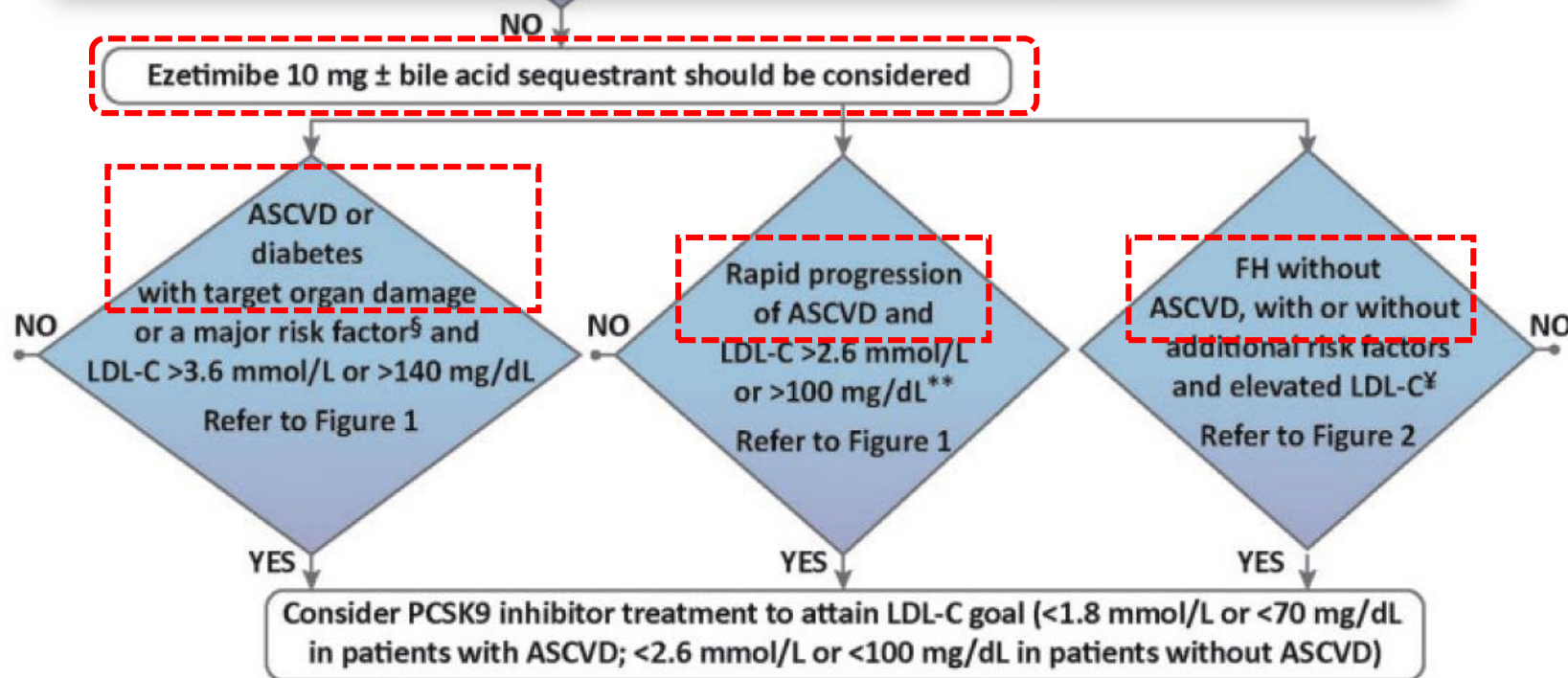
Guidelines on the Use of PCSK9i in Statin Intolerance



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ESC/EAS Task Force Consensus on PCSK9i: Population with SAMS:

Not at LDL-C Goal--- With ASCVD < 70(1.8) or without ASCVD < 100 (2.6)



Conclusions:

- Despite our best efforts, there will a population **who will have Statin Intolerance (full or partial)** which will not allow to reach LDL-C goals
- Use **non-statins such as Ezetimibe and BAS** may help as adjuncts if needed to achieve lipid targets
- **PCSK9 inhibitors** are reasonable options in high risk patients and shown to reduce LDL by 50-60 % in SI patients
- The data from the **long term outcomes and safety studies** in this subset will better inform the true value of PCSK9i therapy





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