Statin intolerance in clinical practice

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Zeist

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Case

Meet Mrs D, a patient with a history of myocardial infarction

- 68-year-old woman
- Myocardial infarction in 2009
- Hypertensive since 1995
  - BP: 145/90 mm/Hg
- Non-smoker
- BMI: 19.4 kg/m^2

BMI, body mass index; BP, blood pressure.

Medical history

- Hypertensive since 1995
- Myocardial infarction in 2009
  - Hypercholesterolaemia known
- Percutaneous transluminal coronary angioplasty and stent in 2009
- Statin intolerant since 2011[1]

Statin intolerance: what is it?

Discontinuation due to Statin-Associated Side Effects

- **Observational studies:**
  - **Most frequent: statin-attributed muscle symptoms (SAMS)**
  - Gastro-intestinal discomfort
  - Fatigue
  - Peripheral neuropathy
  - Insomnia
  - Neurocognitive symptoms

Carter AA et al. *BMJ*. 2013;346:f2610;
Mancini GB et al. *Can J Cardiol*. 2013;29(12):1553-68;
Richardson K et al. *Ann Intern Med*. 2013 Nov 19;159(10):688-97

Classification of Muscle symptoms/myotoxicity

Table 1. Statin-related myotoxicity phenotype classification

SRM classification	Phenotype	Incidence	Definition
SRM0	CK elevation <4× the upper limit of normal	1.5–26%	No muscle symptoms
SRM1	Myalgia, tolerable	190/100 000 patient-years; 0.3–33%	Muscle symptoms without CK elevation
SRM2	Myalgia, intolerable	0.2–2/1000	Muscle symptoms, CK <4× ULN, complete resolution on dechallenge
SRM3	Myopathy	5/100 000 patient-years	CK elevation >4× ULN, <10× ULN ± muscle symptoms, complete resolution on dechallenge
SRM4	Severe myopathy	0.11%	CK elevation >10× ULN, <50× ULN, muscle symptoms, complete resolution on dechallenge
SRM5	Rhabdomyolysis	0.1–8.4/100 000 patient-years	CK elevation >10× ULN with evidence of renal impairment + muscle symptoms or CK >50× ULN
SRM6	Autoimmune-mediated necrotizing myositis	~2/million per year	HMGCR antibodies, HMGCR expression in muscle biopsy, incomplete resolution on dechallenge

SRM, statin-related myotoxicity. Reproduced with permission from [5▪▪].

Alfirevic A, Clin Pharm Ther 2014.
Preiss D. Curr Op Lipidol 2015

Assessing Statin-Associated Muscle Symptoms (SAMS)

- Usually symmetrical and proximal
- Affect large muscle groups (thighs, buttocks, calves and back muscles)
- Usually occur early (within 4-6 weeks) of starting statin ; but can occur after many years of treatment.
- May occur with an increase in statin dose, initiation of an interacting drug, or increase in physical activity
- May appear more rapidly if patient is re-challenged with a statin

Stroes ES et al. Eur Heart J 2015 ;36:1012-1022

Risk Factors for Statin Induced Myopathy Patient Characteristics

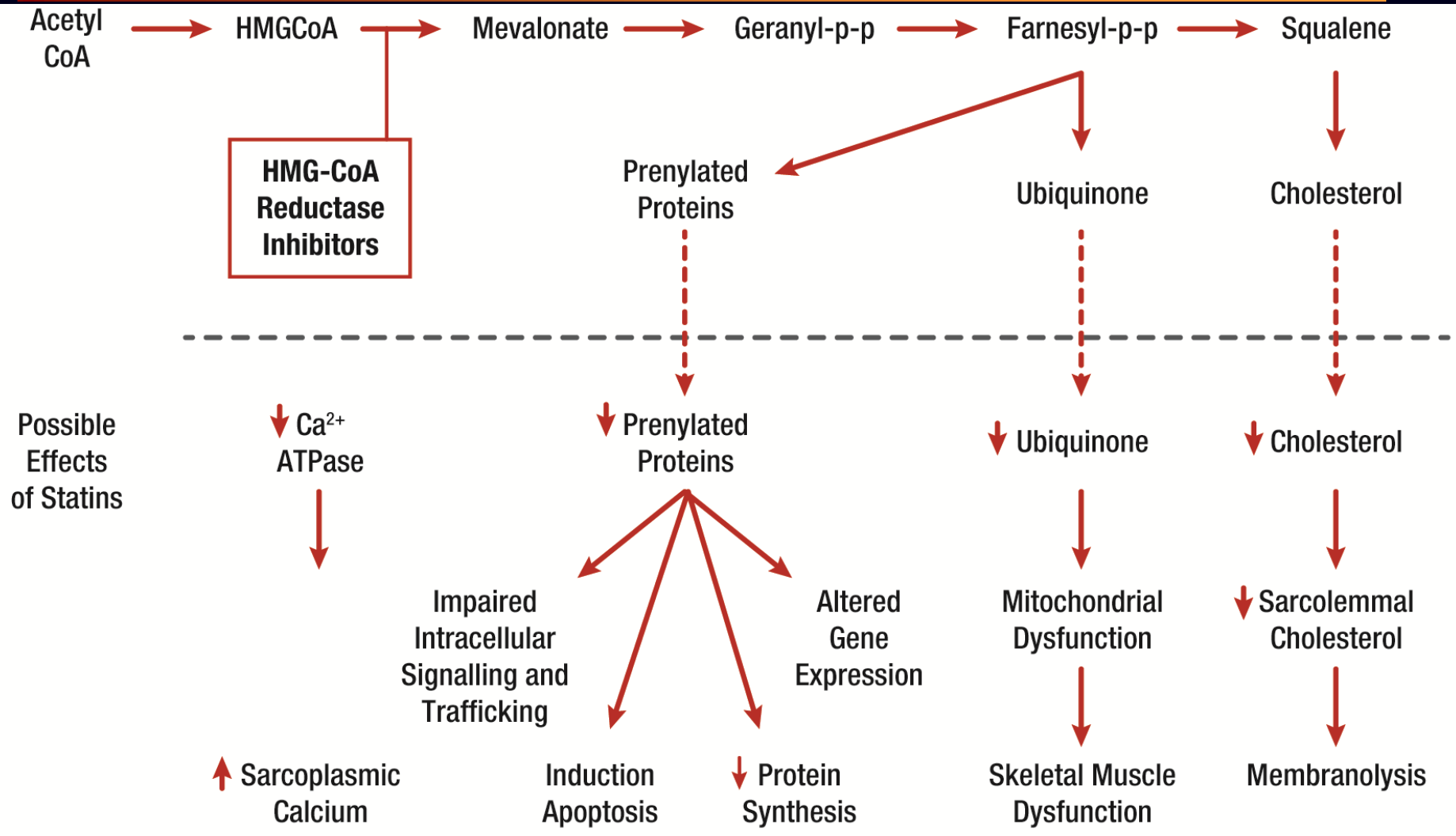
- ***Statin***
  - *Dose of statin++*
  - *Type of statin (?)*
- ***Demographics***
  - Older Age,
  - Female gender
  - Asian race
- **Drug-drug and grape-fruit interaction**
- ***Genetic Predisposition***
- *Comorbidities*
  - Hypothyroidism
  - Systemic disease
  - Alcoholism / drugs
  - Major surgery
  - Myopathy
    - Hereditary (PYGM, CTP II, AMPD)
    - Acquired

Consider factors that influence statin pharmacokinetics

- Pre-existing risk factors and co-morbidities
- High-dose statin therapy
- Polypharmacy
- Drug-drug interactions (eg gemfibrozil, macrolides, azole antifungal agents, protease inhibitors and immunosuppressive drugs, inhibitors of CYP450 isoenzymes, OATP 1B1, or P-gp)
- Pharmacogenetics

Stroes ES et al. Eur Heart J 2015 ;36:1012-1022

Effects potentially involved in statin-related muscle injury/symptoms



Stroes ES et al. Eur Heart J 2015 ;36:1012-1022; adapted from Needham M et al. Neuromuscul Disord. 2014;24(1):4-15

Question 1

What is the prevalence of SAMS in observational studies?

a. < 2% of subjects using statins experience SAMS

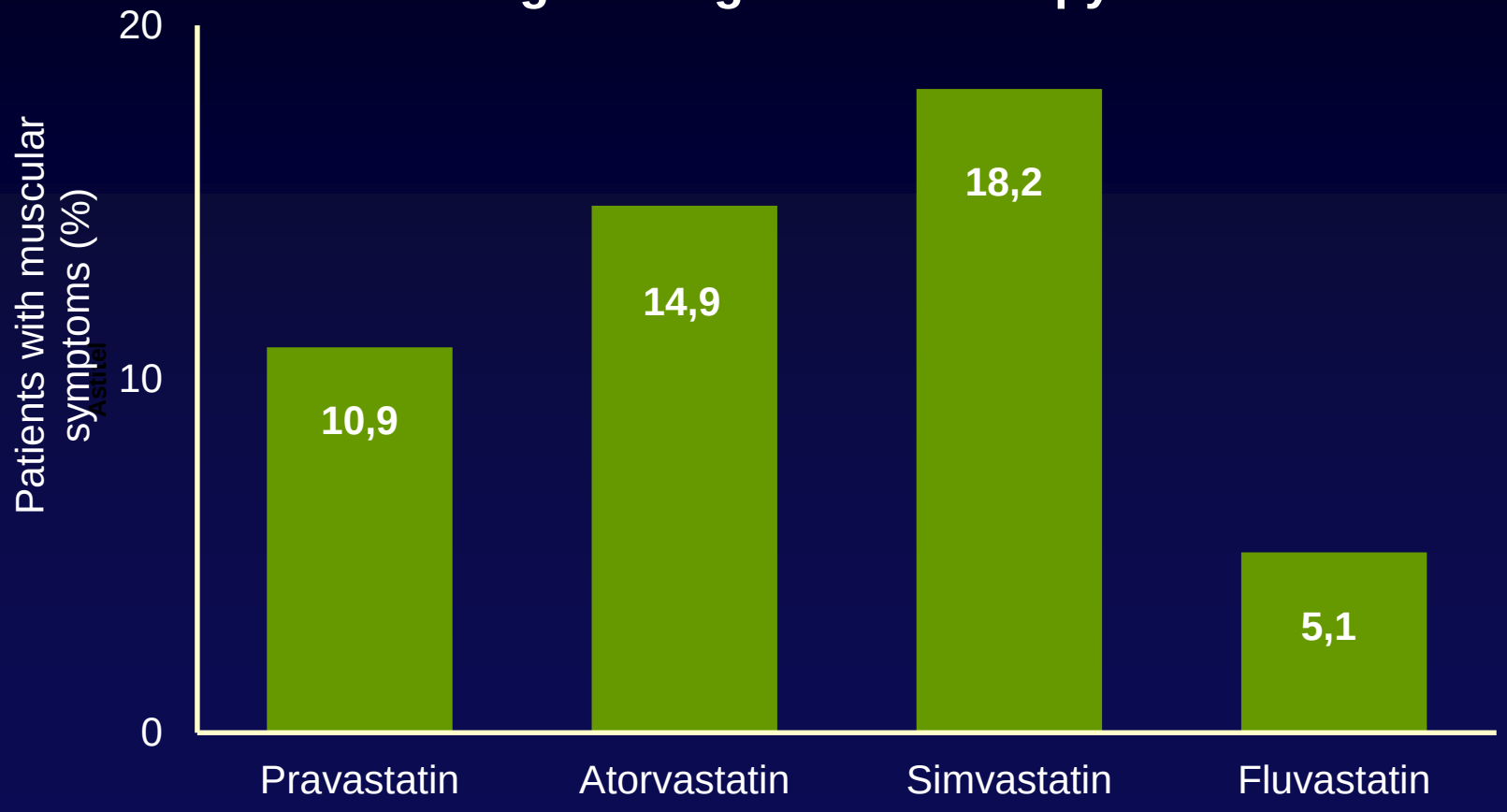
b. 2-10% of subjects using statins experience SAMS

c. 10-20% of subjects using high-dose statins experience SAMS

d. Since there is no difference in SAMS between statin vs placebo, the only correct answer should be: 0%

Muscle symptoms associated with statins are common in observational studies

PRIMO: 7924 patients with hyperlipidaemia receiving high-dosage statin therapy



Bruckert E, et al. Cardiovasc Drugs Ther 2005;19:403–414.

The USAGE survey

Cross-sectional, self-administered Internet-based survey of 10,138 U.S. adults (September to October 2011)

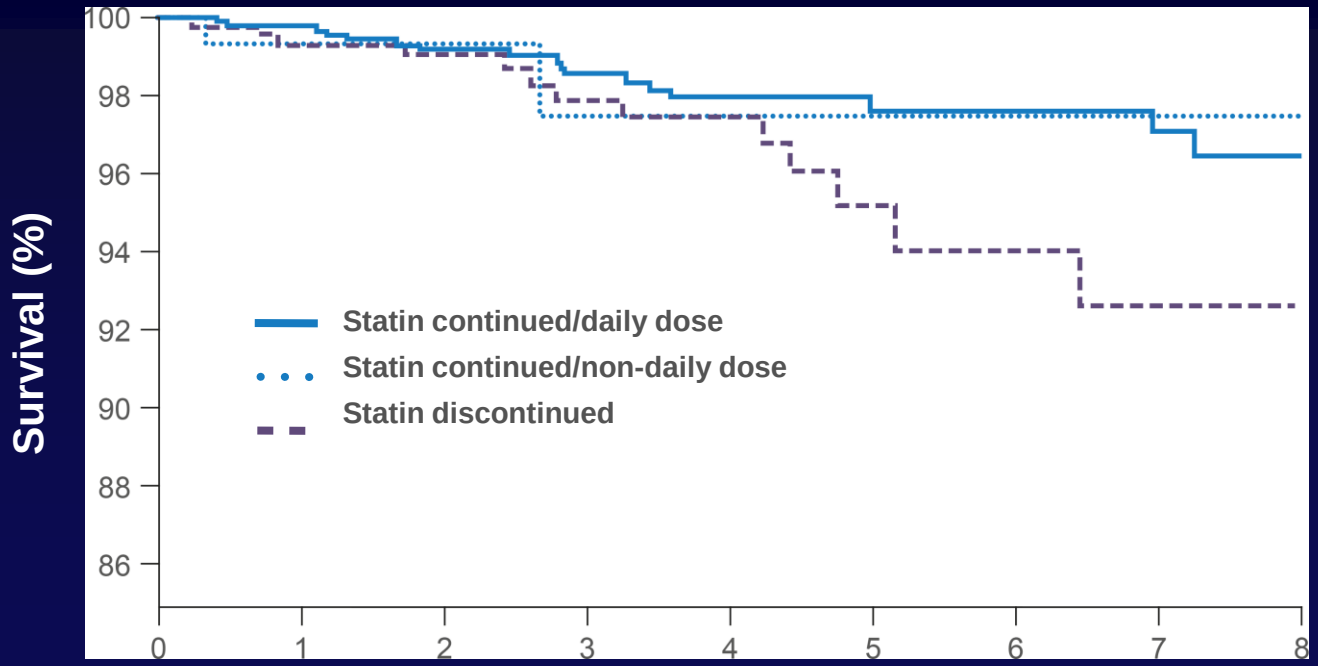
Table 2 Baseline characteristics according to adherence groups in the USAGE survey, 2011

Characteristic	Former statin users	Current statin users			
	Discontinuers	Non-adherent switchers	Adherent switchers	Adherent nonswitchers	*P* value
No. of participants	1,220	161	3,743	4,628	
Age, mean, y	59.4	59.0	62.4	60.4	<.0001
<55, %	29.8	29.8	40.7	40.5	<.0001
>55, %	70.2	70.2	59.3	59.5	<.0001
Sex, %					
Male	32.5	34.2	40.7	40.5	<.0001
Female	67.5	65.8	59.3	59.5	<.0001
Satisfaction with current or most recent statin, %	27.2	59.0	83.7	87.1	<.0001
Muscular side effects while taking statin, %	60.3	51.6	32.9	16.5	<.0001
Out-of-pocket costs have a large influence on taking current statin, %	27.8	44.1	31.0	25.2	<.0001
Satisfied with physicians' explanation of treatments, %	65.3	65.2	85.2	83.0	<.0001
Besides one's physician, use the internet to learn about statins, %	41.3	34.8	31.5	25.9	<.0001
Internet medical resource as the most used information source, %	48.4	48.5	39.3	36.6	<.0001

Wei MY et al J Clin Lipidol Aug 2013

Statin discontinuation leads to reduced survival

- Side effects are the most common reason patients discontinue statins[1]
- Survival is reduced in patients who discontinue, even compared to those on non-daily statin doses[2]



1. Cohen et al. J Clin Lipidol 2012;6:208-15.
2. Mampuya et al. Am Heart J 2013;166:597–603.

The elephant in the room: Real-life data versus RCTs

Evaluation of SAMS

- **RCTs**
- **Spontaneous reports**
- **Real-life studies**

Type of RCTs

- **RCTs with clinical endpoints**
- **Meta-analysis in subgroups**
- **Long term follow-up of RCTs**
- **Statin studies in intolerant patients**
- **Statin naïve pts focused on SAMS**
- **Statin intolerant pts with PCSK9ab**

Type of real-life studies*

- **Databases**
- **Population surveys**
- **Patient chart reviews**
- **Registries**
- **Observational data**
- **Pragmatic trials**

*Saturnin S et al. Pulm Pharmacol & Therapeutics 2014

Statin intolerance is much less common than suggested by observational data

Trial details[1]					Myalgia[1]	
Trial	Total No.	Agent	Dose mg	Duration yr	Statin	Placebo
4S	4,444	Simvastatin	20–40	5.4	3.7%	3.2%
WOSCOPS	6,595	Pravastatin	40	4.9	3.5%	3.7%
PROSPER	5,804			3.2	1.2%	1.1%
CARDS	2,838	Atorvastatin	10	3.9	4.0%	4.8%
ASPEN	2,410			4.0	3.0%	1.6%
SPARCL	4,731		80	4.9	5.5%	6.0%
JUPITER	17,802	Rosuvastatin	20	1.9	7.9%	6.9%

No imbalance

1. Newman CB, et al. JAMA 2015;313:1011–2.

However, selection?

Factors influencing participation in clinical trials

Doctor factors	
Logistic difficulties	Unaware of trials open for accrual
	Lack of time
	Lack of resources eg data management
	Financial constraints
	Type of practice (public *versus* private)
	Difficulty with ethics requirements
	Identification of eligible patients
Personal difficulties	Effect on doctor–patient relationship
	Discomfort with randomisation
	Difficulty with informed consent procedures
	Preference for a particular treatment
	Overall too difficult (too much time and effort)
	Lack of acknowledgment
	Opinion of referring doctor
Patient factors	Demographics such as age, education
	Faith/trust in the doctor
	Preference for a particular treatment
	Concerns about treatment toxicity
	Dislike of randomisation, experimentation
	Loss of control
	Practical issues such as inconvenience
	Access to free medical care
Trial factors	Poorly designed or complex trial protocols
	Presence of a no treatment arm
	Large difference between treatment arms, e.g., surgery *versus* radiotherapy
	Toxic therapy being tested
	Standard therapy arm not considered standard therapy
	Eligibility requirements too narrow
	Irrelevant or unimportant trial question

The percentage of real life patients fullfilling exclusion/inclusion criteria and sharing similar characteristics as those who participate in RCTs may be as low as 5%

Elis PM et al Annals of Oncology 2000

Question 2

How big is the impact of expected side effects in unblinded studies?

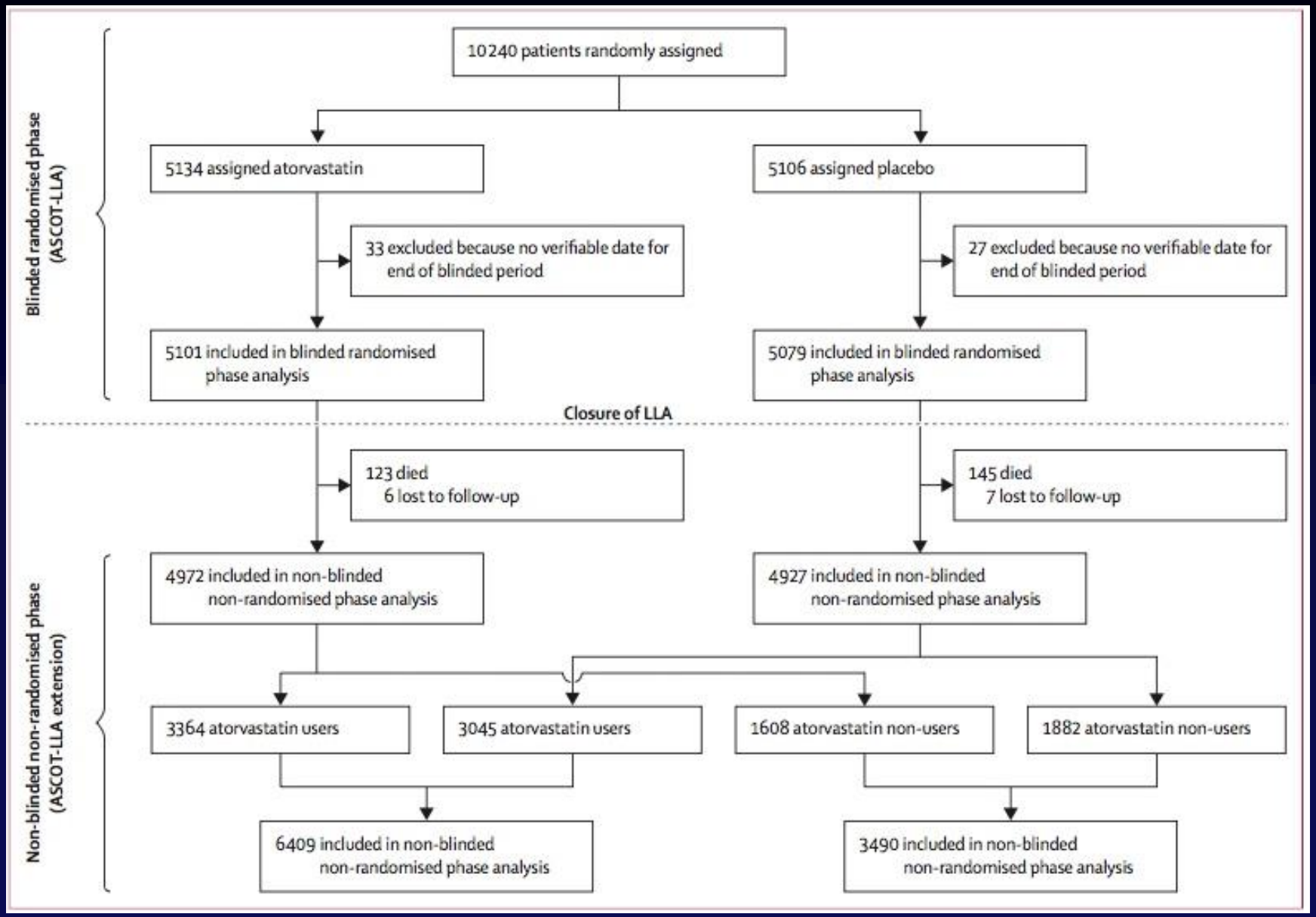
a. insignificant

b. If the doctor provides neutral data, not very impactful

c. If Media coverage is significant, it can be quite impactful

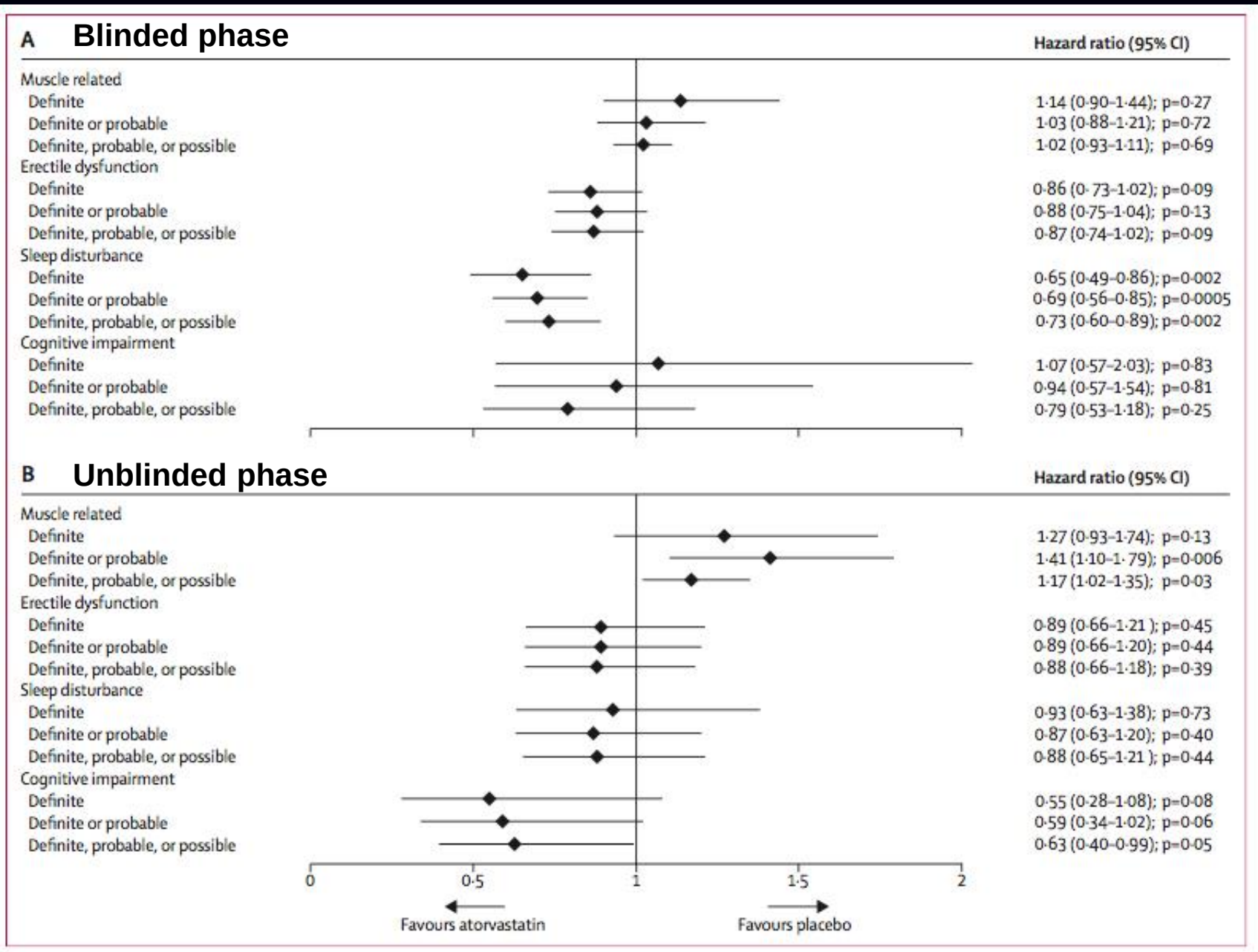
d. If Media coverage and doctor's alert are prominent, the impact can be highly significant

Incidence of SAMS in ‘open-label’ setting



Gupta, Lancet 2017

the NOCEBO effect



Gupta, Lancet 2017

The widespread media coverage that has arisen from claims that statin therapy causes side-effects in up to one fifth of patients,[5,29] and the failure to correct such misleading claims rapidly and fully, has led to patients at high risk of major vascular events with established cardiovascular disease stopping their statin therapy.[30,31] Such reductions in statin use have been estimated to result in thousands of fatal and disabling heart attacks and strokes, which would otherwise have been avoided. Seldom in the history of modern therapeutics have the substantial proven benefits of a treatment been compromised to such an extent by serious misrepresentations of the evidence for its safety. We hope that the demonstration in the ASCOT-LLA of not only the absence of adverse effects of statin therapy on muscle-related and other AEs, but also the effect of ascertainment bias in non-blinding studies (which have been the basis of many of the misleading claims), will help to counter the adverse effect on public health of exaggerated claims about statin side-effects.

 Gupta, Lancet 2017

Why the High incidence in observational studies? Non-statin experience

A big Telecom company decided to put 3 large Antennas in a small town near Paris (Saint Cloud)

- Two days after up to 100 of the residents suffered similar side effects: vertigo, headache and nausea

- The problem was covered by famous newspapers including the « Le Parisien »

- On the Front page the papers described details of this story:

« Le calvaire des habitants de Saint Cloud »

Difficulty to deal with side effect: an example distinct from the statin field

Five days later, The company indicated that the antennas have never been activated!

Real-life data versus RCTs

From estimation of SAMS in RCTs		To Real life studies
Definition unclear	GAUSS 54% had symptoms on placebo but not atorva or on both placebo and atorva	Definition unclear
Selected patients		Nocebo effect
Under-reporting		
Frequency approx. < 1%	Estimated <<5% of patients with SAMS	Frequency approx. 10%

Case - continued

Current lipid profile

- TC: 309 mg/dL (8.01 mmol/L)
- LDL-C: 193 md/dL (5.00 mmol/L)
- HDL-C: 101 mg/dL (2.59 mmol/L)
- TG: 80 mg/dL (0.93 mmol/L)
- Apo B: 2.1 g/L

Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

What next?

The patient is at very high risk of a cardiovascular event because she has a history of cardiovascular disease and is statin intolerant

- She is above the recommended LDL-C target of 70 mg/dL (1.8 mmol/L)[2]
- She is compliant with lifestyle recommendations, such as diet and exercise

LDL-C, low-density lipoprotein cholesterol.

Question 3

What should be the next steps in this high-risk patient?

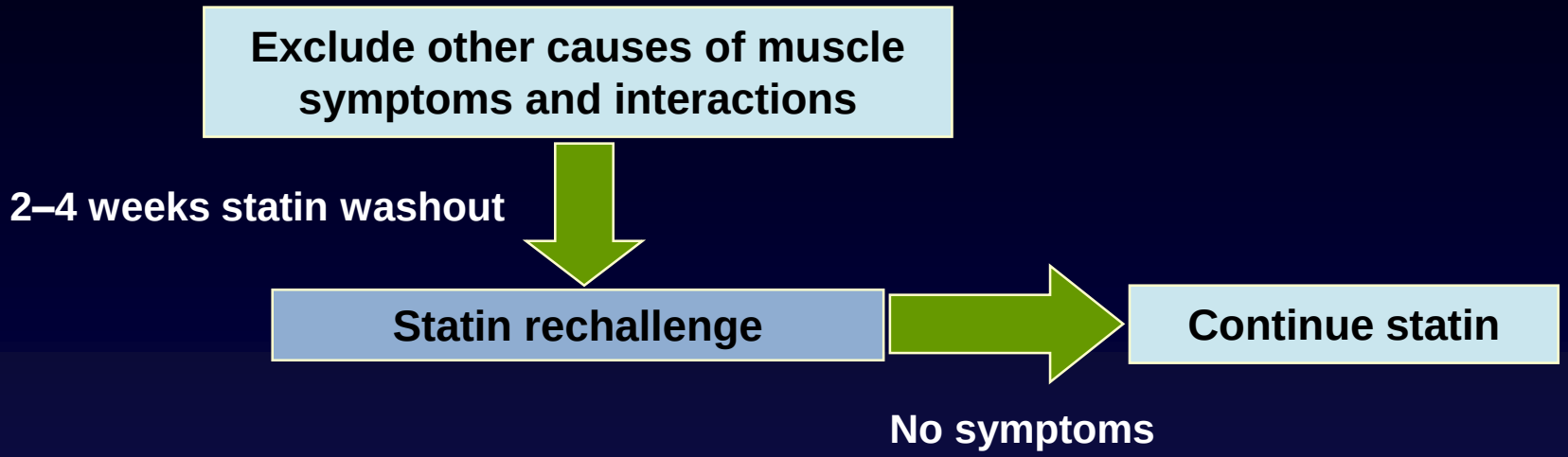
a. Rechallenge with other statin, and consider alternate day dosing

b. Add ezetimibe for further LDLc lowering

c. Consider PCSK9-antibody treatment if far from LDLc goal

d. All of the above, in sequential order

Algorithm for treating patients with statin-associated muscle symptoms



Stroes ES, et al. Eur Heart J 2015;36(17):1012–22.

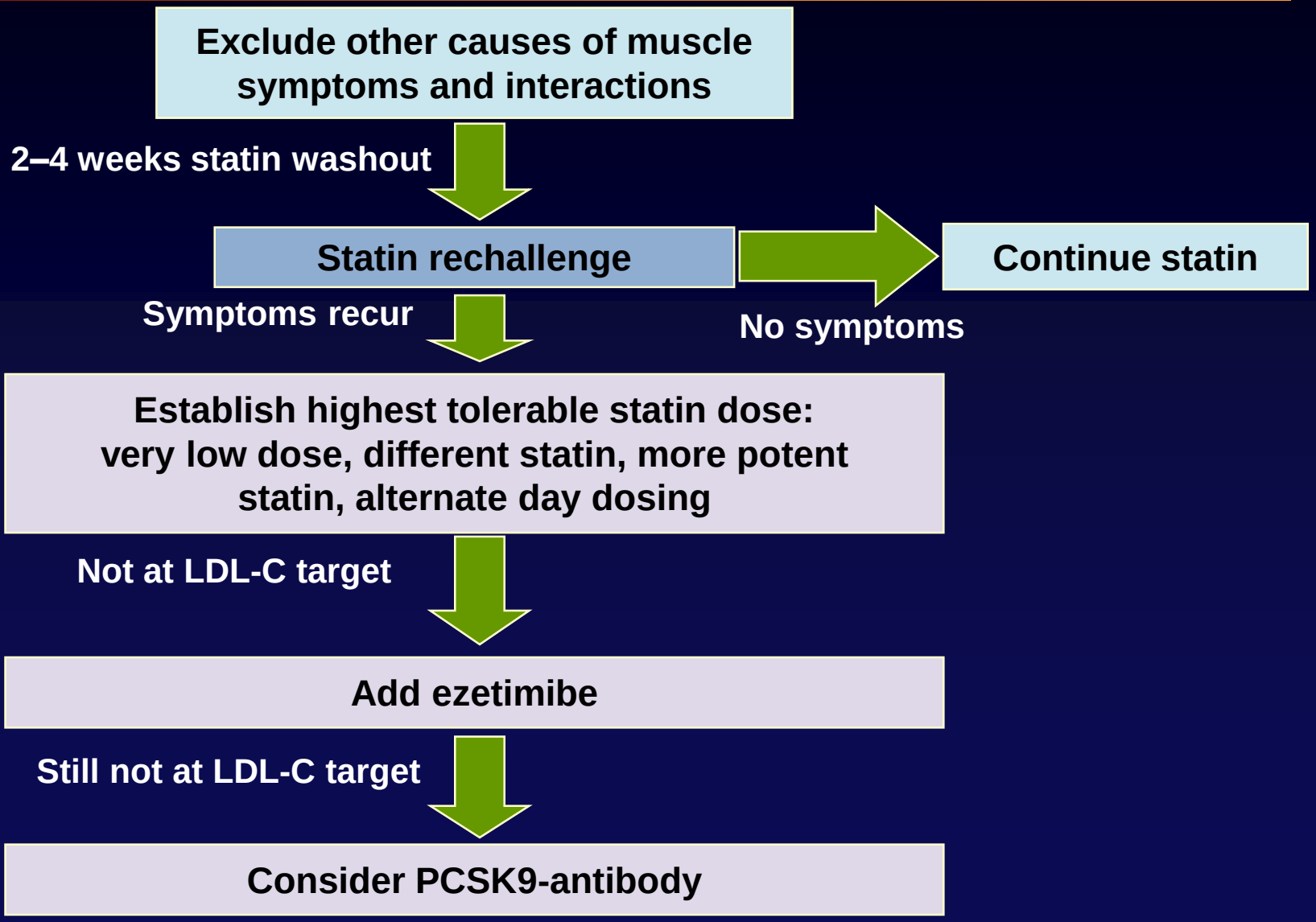
Rechallenge the patient

Most patients rechallenged can tolerate statins long-term

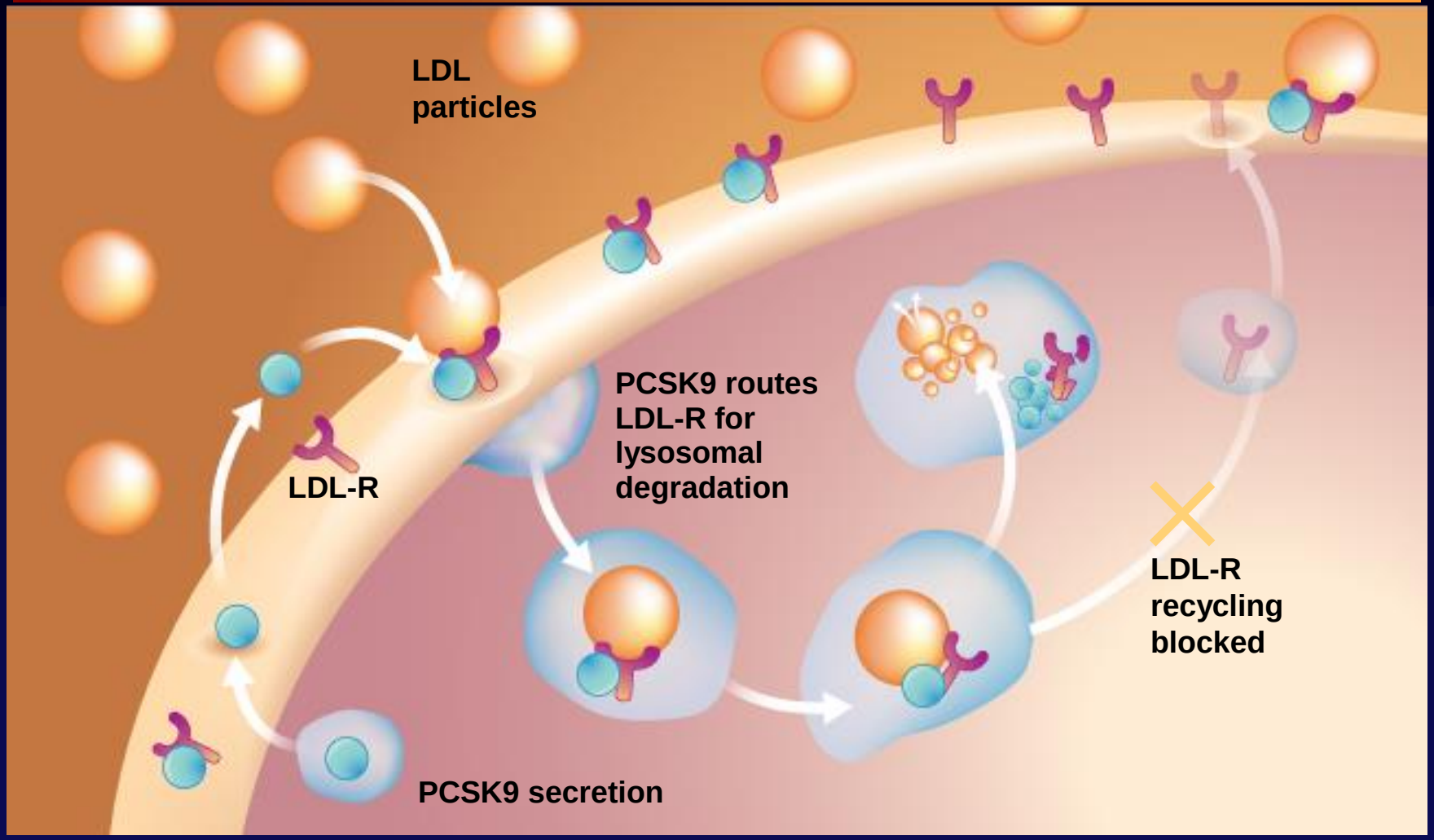
- Retrospective cohort study in 107,835 patients
- 18,778 (17.4%) patients had statin-related events. Statins were discontinued at least temporarily by 11,124 of these patients
- On re-challenge:
  - ✓ 92.2% were still on a statin >12 months later
  - ✓ 47.6% were on the same statin to which they had the statin-related adverse event

Zhang H et al. Ann Intern Med 2013;159:75-6

What do the trials suggest in ‘statin intolerance’ ?

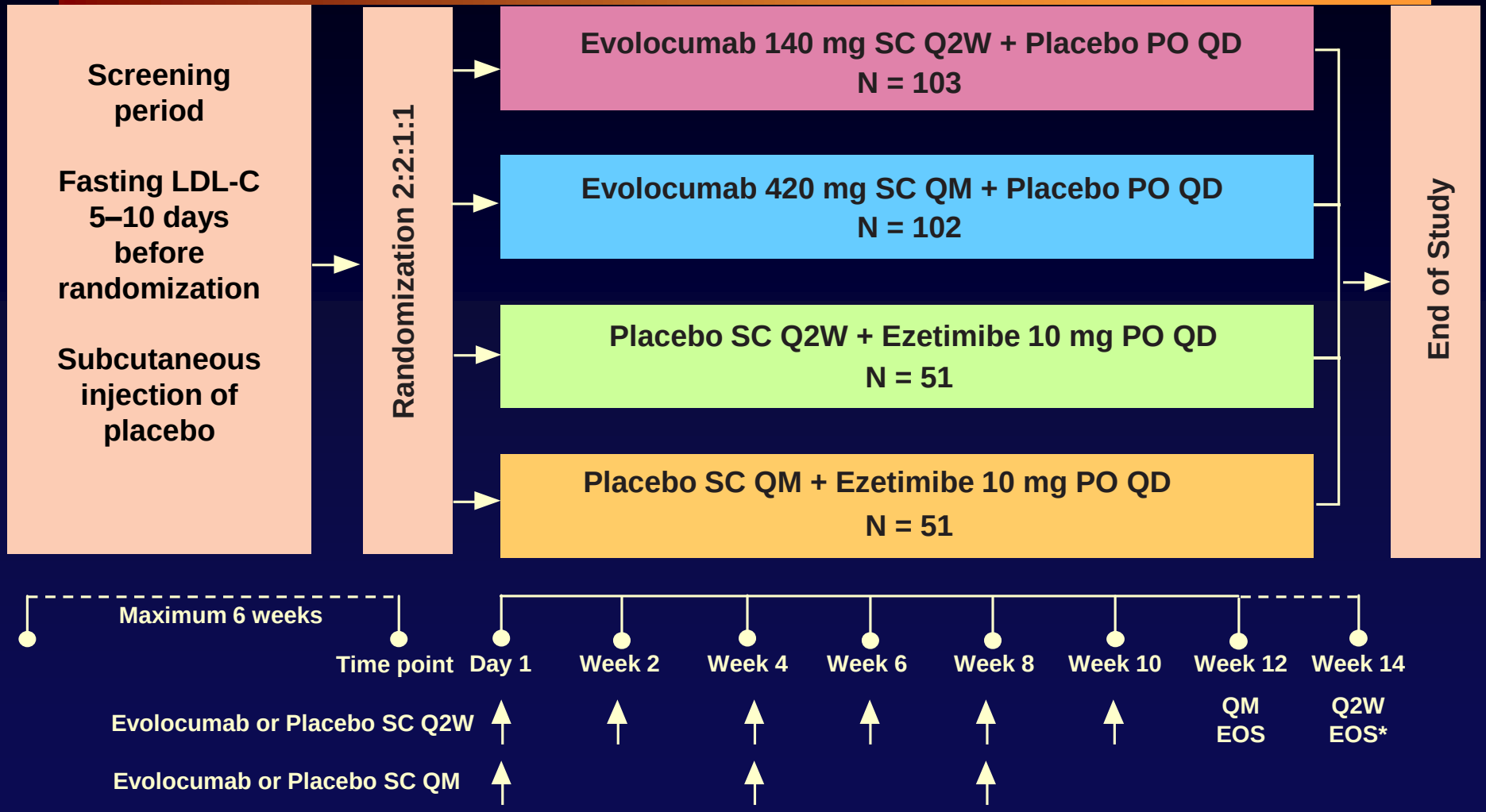


PCSK9 reduces LDLR recycling, thereby increasing plasma LDL-C



Horton et al. J Lipid Res 2009;50:S172–S177.

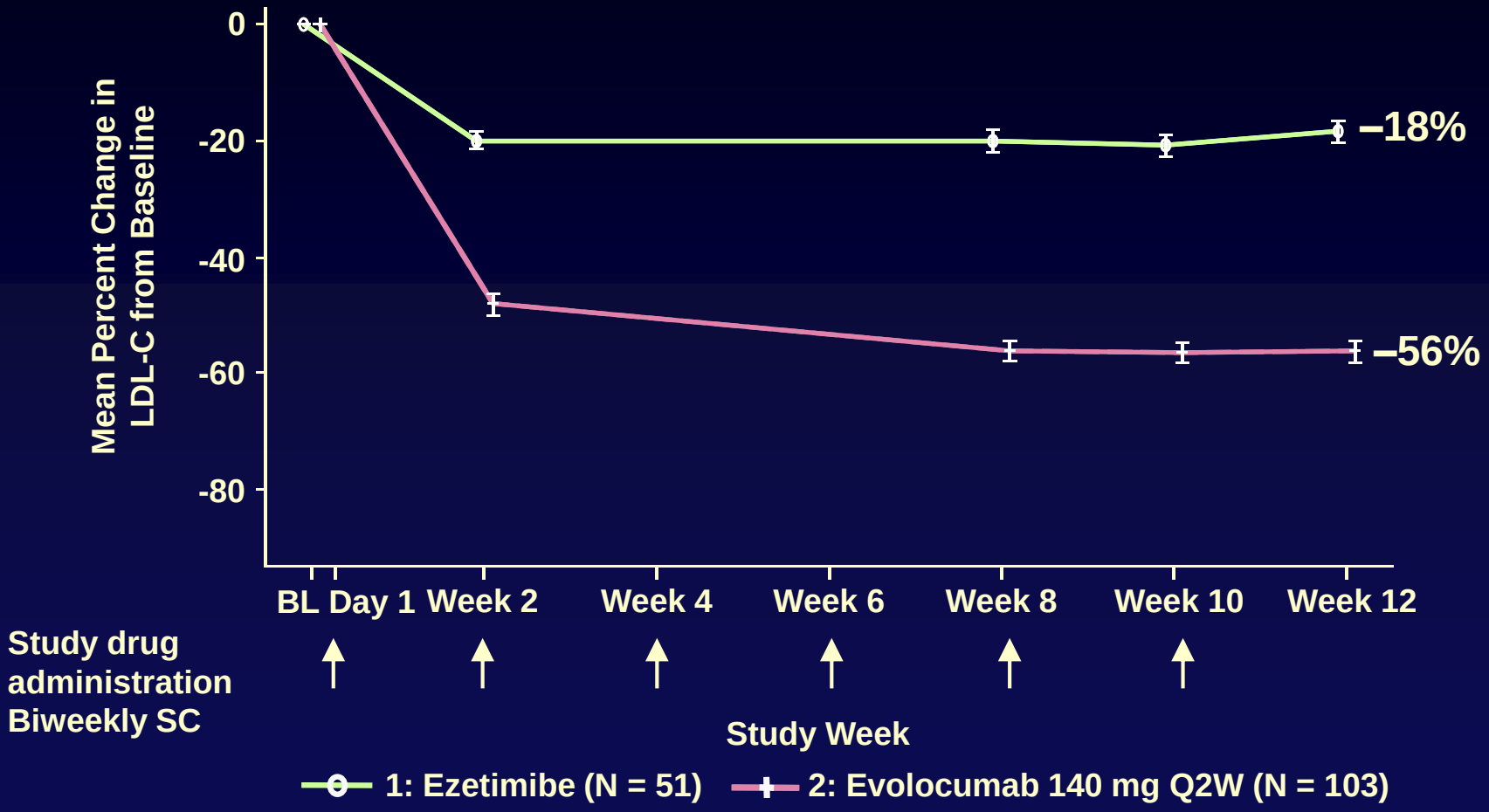
GAUSS-2 Study Design



*Phone call for AEs, SAEs. AEs, adverse events; EOS, end of study; LDL-C, low-density lipoprotein cholesterol; SAEs, serious adverse events; SC, subcutaneous; PO, oral; Q2W, every 2 weeks (biweekly); QM, monthly

GAUSS-2: Evolocumab

Primary Endpoint *Biweekly* Dose

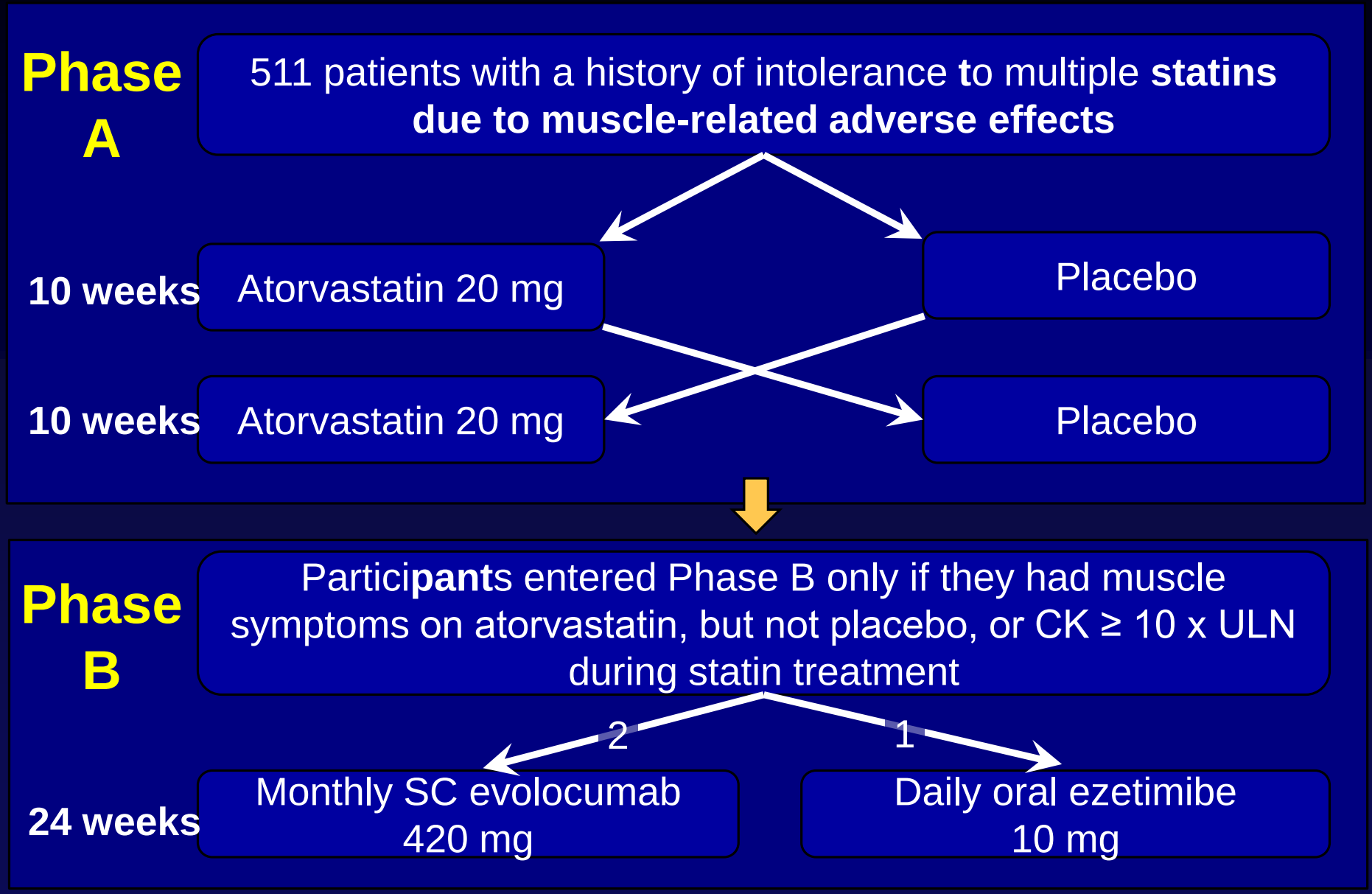


BL, baseline. Vertical lines represent the standard error around the mean. Plot is based on observed data
with no imputation for missing values. *P* value is multiplicity adjusted.

GAUSS-2: Safety and Tolerability

Adverse Events (AEs), n(%)	Ezetimibe (N = 102)	Evolocumab (N = 205)
Treatment-emergent AEs	74 (73)	135 (66)
Common treatment-emergent AEs (≥5% of patients in either treatment arm)		
Headache	9 (9)	16 (8)
Myalgia	**18 (18)**	**16 (8)**
Extremity pain	1 (1)	14 (7)
Muscle spasms	4 (4)	13 (6)
Fatigue	10 (10)	9 (4)
Nausea	7 (7)	9 (4)
Diarrhea	7 (7)	5 (2)
Paresthesia	5 (5)	2 (1)
Serious AEs	4 (4)	6 (3)
AEs leading to study drug discontinuation	13 (13)	17 (8)
Deaths	0	0
Potential injection site reactions*	8 (8)	6 (3)
Muscle-related SMQ†	23 (23)	25 (12)
Neurocognitive AEs††	0	0
Anti-evolocumab antibodies‡	n.a.	0

GAUSS-3: two double-blind phases



Nissen SE, et al. JAMA 2016;315:1580–90.

Question 4

What percentage of patients is ‘expected’ to proceed to phase B, in case SAMS is a ‘purely psychological’ phenomenon?

a. 0%: none of the patients will ‘guess’ correctly 2 times in a row

b. 25%: chance of ‘guessing’ correct two times in a row = 25%

c. The fact that ~20% of Alirocumab users (ODYSSEY Alternative) stopped due to intolerable SAMS shows that these patients will always experience side effects: <10% will pass through phase A

d. I don’t know

Phase A: study drug discontinuation events

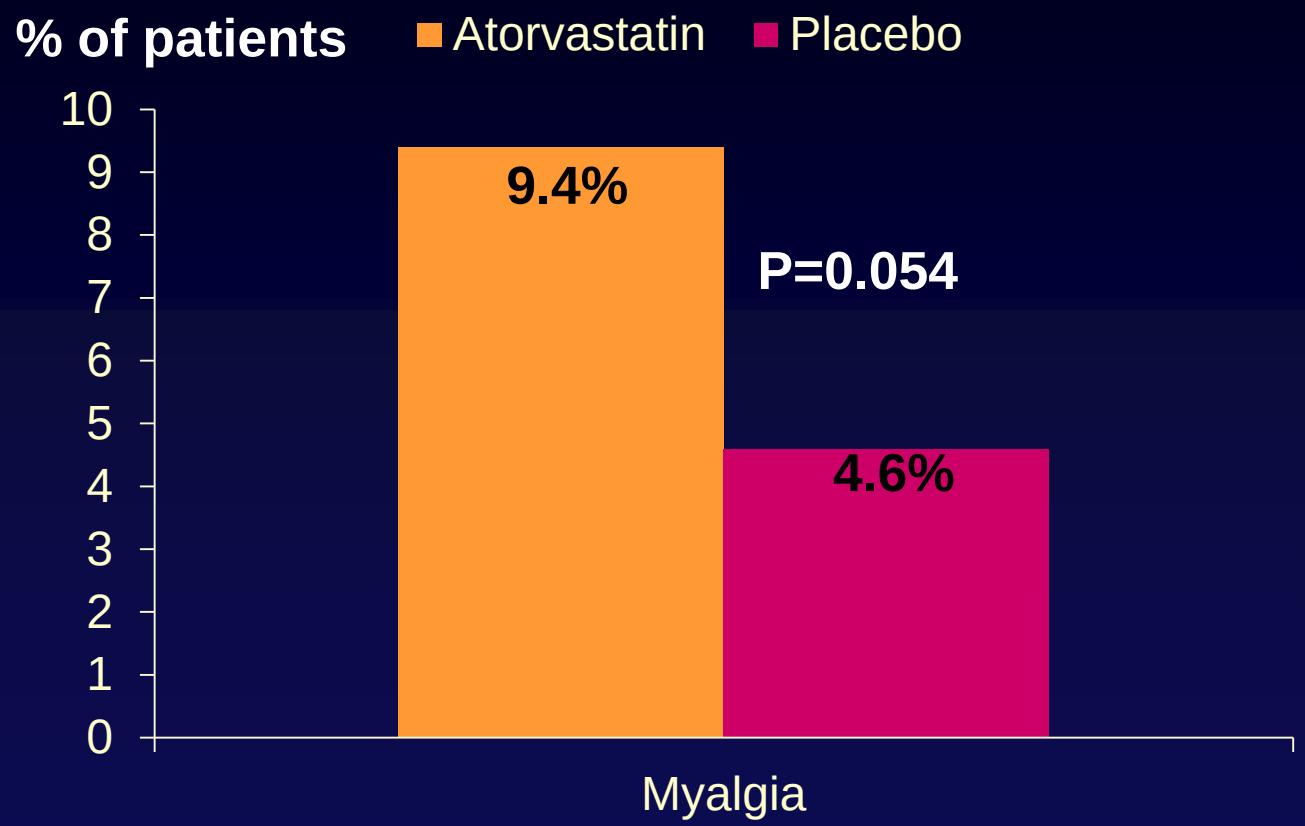
Intolerable muscle symptoms	N=491
On atorvastatin, but not placebo	209 (42.6%)*
On placebo, but not atorvastatin	130 (26.5%)
On both placebo and atorvastatin	48 (9.8%)
No symptoms on either treatment	85 (17.3%)
Did not complete Phase A	*20/511*

Bypassed Phase A due to CK elevation ≥ 10 x ULN	19 (3.9%)*

218 of these 228 patients proceeded to Phase B

Nissen SE, et al. JAMA 2016;315:1580–90.

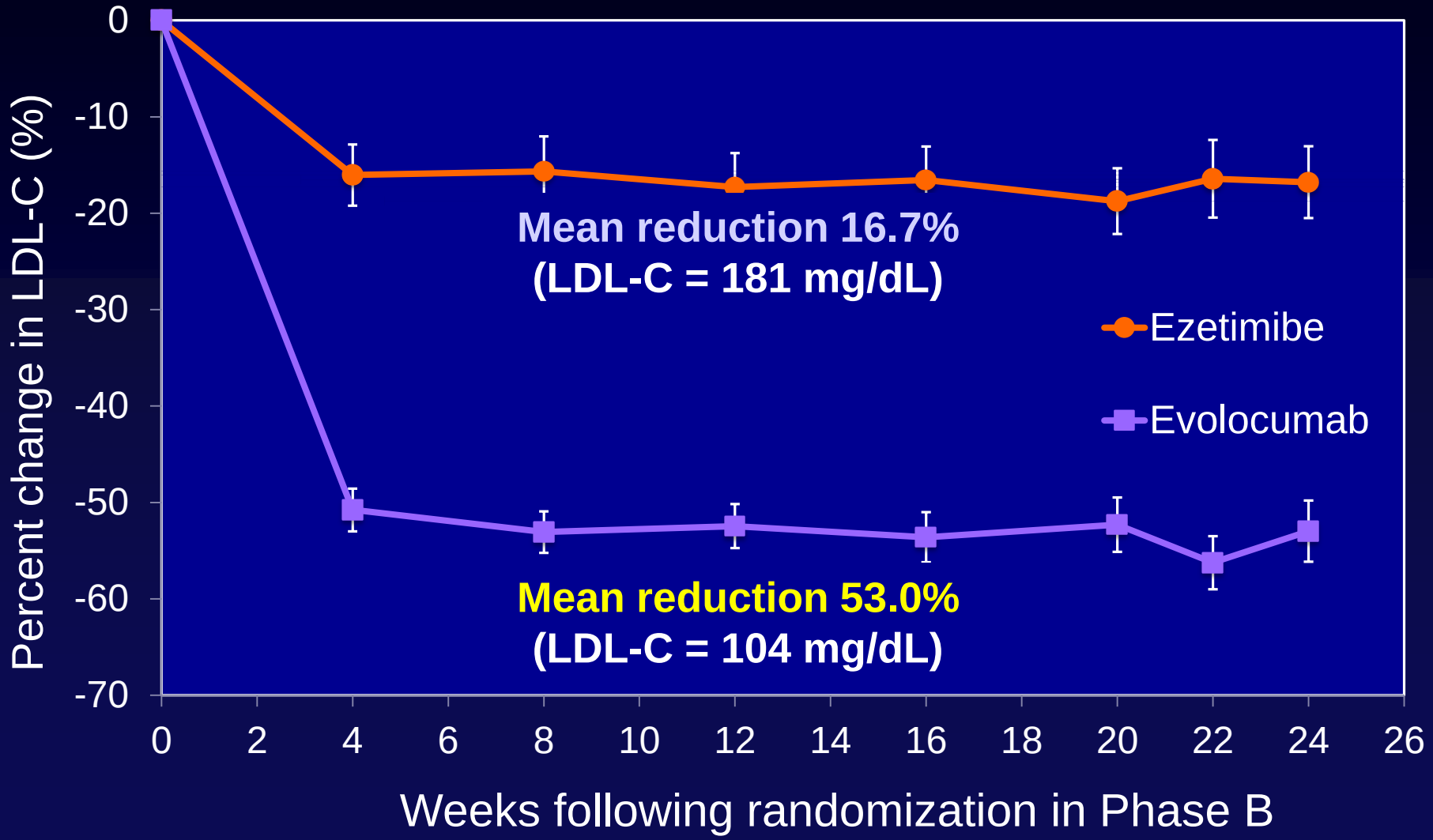
STOMP: Frequency of SAMS



Assessment made before and after atorvastatin 80 mg or placebo , administered for 6 months to 420 healthy, statin-naive subjects.

Parker BA et al. Circulation 2013; 127:96-103

LDL-C values over time during Phase B



Nissen SE, et al. JAMA 2016;315:1580–90.

Phase B: adverse effects and drug discontinuations

	Ezetimibe (n=73)	Evolocumab (n=145)
Total muscle-related events	21 (28.8%)	30 (20.7%)
Myalgia, muscle pain or weakness	17 (23.3%)	25(17.2%)
Investigator reported CK Increase	1 (1.4%)	4 (2.8%)
Discontinuation of treatment for any reason		
Discontinuation of oral treatment	14 (19.2%)	23 (15.9%)
Discontinued SC drug treatment	4 (5.5%)	7 (4.8%)
Discontinuation of treatment for muscle symptoms		
Discontinued oral drug treatment	5 (6.8%)	11 (7.6%)
Discontinued SC drug treatment	0 (0%)	1 (0.7%)

Nissen SE, et al. JAMA 2016;315:1580–90.

Case continued

Treatment outcomes

- TC: 209 mg/dL (5.39 mmol/L)
- LDL-C: 96.7 mg/dL (2.57 mmol/L)
- HDL-C: 100.5 mg/dL (2.52 mmol/L)
- TG: 62 mg/dL (0.67 mmol/L)

- PCSK9 inhibitor treatment was well tolerated with no side effects reported

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; TC, total cholesterol; TG, triglycerides.

Wat wordt vergoed bij patienten die statines niet tolereren?
Evolocumab / Alirocumab

Patiënten met hypercholesterolemie én voldoende hoog risico, niet op streefwaarde* ondanks:

Maximaal verdraagbare statine én ezetimibe

Primaire Preventie (LDL-c > 2,5 mmol/l)	Secundaire Preventie (LDL-c > 1,8 mmol/l)			
HeFH / HoFH	HeFH / HoFH & CVE	Statine Intolerantie** & CVE	CVE & recidief event	DM type II & CVE

PCSK9-antistoffen

* Overeenkomstig de richtlijnen die in Nederland door de desbetreffende beroepsgroepen zijn aanvaard.
**statine-geassocieerde spierpijn voor tenminste 3 verschillende statines vastgesteld volgens het stroomschema en criteria beschreven door EAS/ESC consensus (European Heart Journal 2015; 36: 1012-1022).
Bij homozygote familiaire hypercholesterolemie wordt een aanvangsdosis van 420 mg eenmaal per maand aanbevolen; na 12 weken kan de dosisfrequentie indien nodig worden opgebouwd naar 420 mg per 2 weken.

CardioVasculaire Events:
- (N)STE-ACS
- PCI
- CABG
- CVA (ischemisch) / TIA
- PAD
- overig

Casus

Uitdagingen van triple therapie

- Patiënt van 69 jaar met FH en status na 2x MI
  behandeld met simvastatine 40 mg en ezetimibe 10 mg

- Spierpijn van atorvastatine en rosuvastatine

- Lipiden:
  - Totaal cholesterol 5.7, HDL 1.1, LDL 4.1

Casus

Uitdagingen van triple therapie

- Gestart met evolocumab met streefwaarde LDL <1.8 mmol/l met continueren simva/ezetrol

- Lipiden (4 weken, 12 weken en 9 maanden na start):
  - Totaal cholesterol 3.1, HDL 1.3, LDL 1.4
  - Totaal cholesterol 4.4, HDL 1.0, LDL 3.1
  - Totaal cholesterol 3.2, HDL 1.3, LDL 1.5

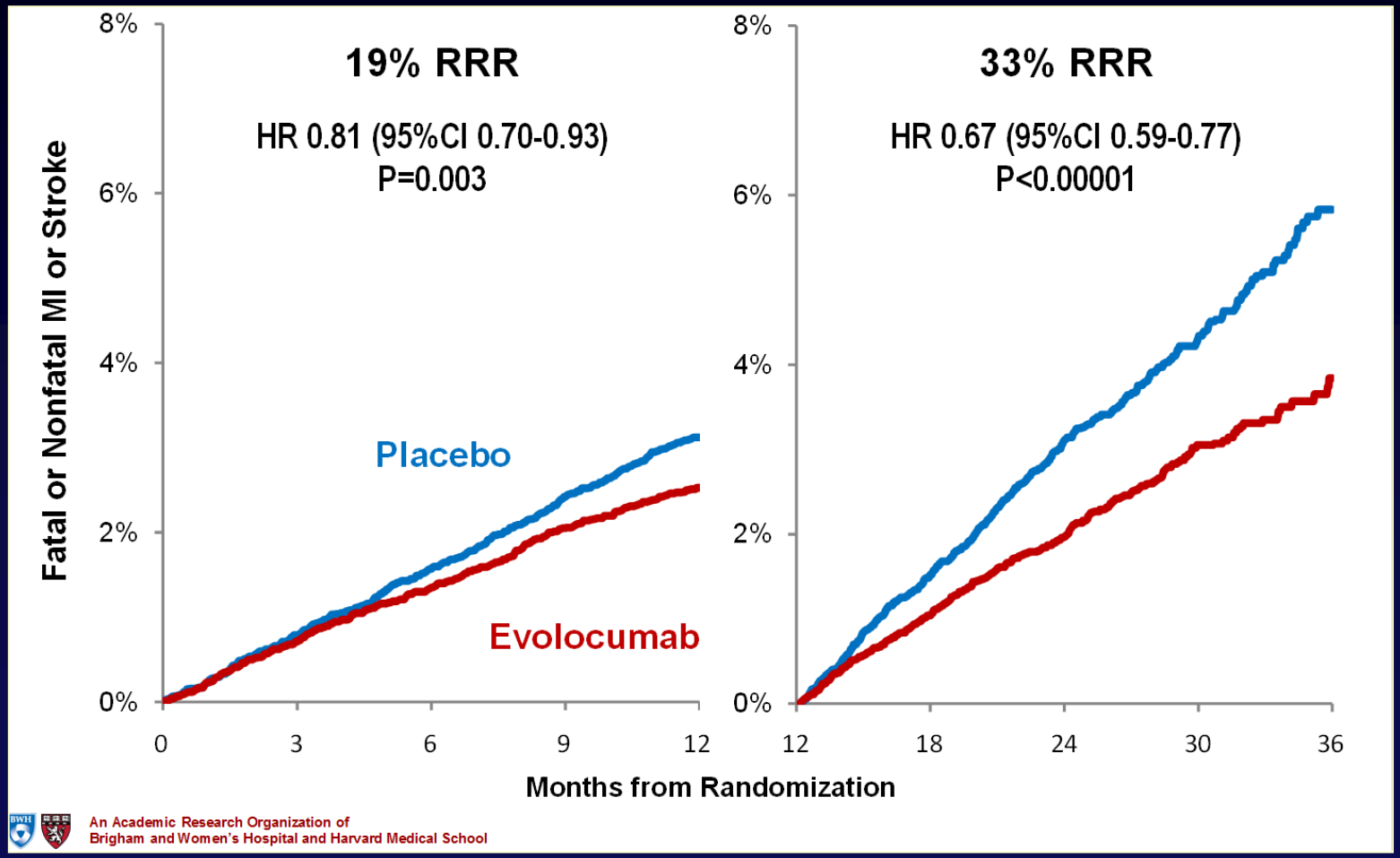
De kenmerken van de ‘Ideale’ aanpak

- **Adequate en krachtige voorlichting:**
  Statines: Groot gezondheidsvoordeel en aangetoond veilig
- **Work-up samen met patient**:
  - *Tijd nemen: herhaalde uitleg benefit/risk*
  - *Staken statine: verdwijnen/verbeteren symptomen?*
  - *Re-challenge: ≥ 3x, lagere dosis, alternate-day, etc*
- **In selecte restgroep die geen statine ‘verdraagt’:**
  - *(zeer) hoog risico? Post-event, FH, verhoogd LDL*
  - *Ezetrol gedoseerd*

  → overwegen PCSK9-therapie

FOURIER landmark analysis

CV Death, MI or Stroke



Sabatine MS – N Engl J Med 2017