Azərbaycan Kardiologiya Cəmiyyəti

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Statin Dözümsüzlüyü. LDL hədəfinə çatıla bilmədikdə nələrə diqqət olunmalıdır?

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29.04.2023

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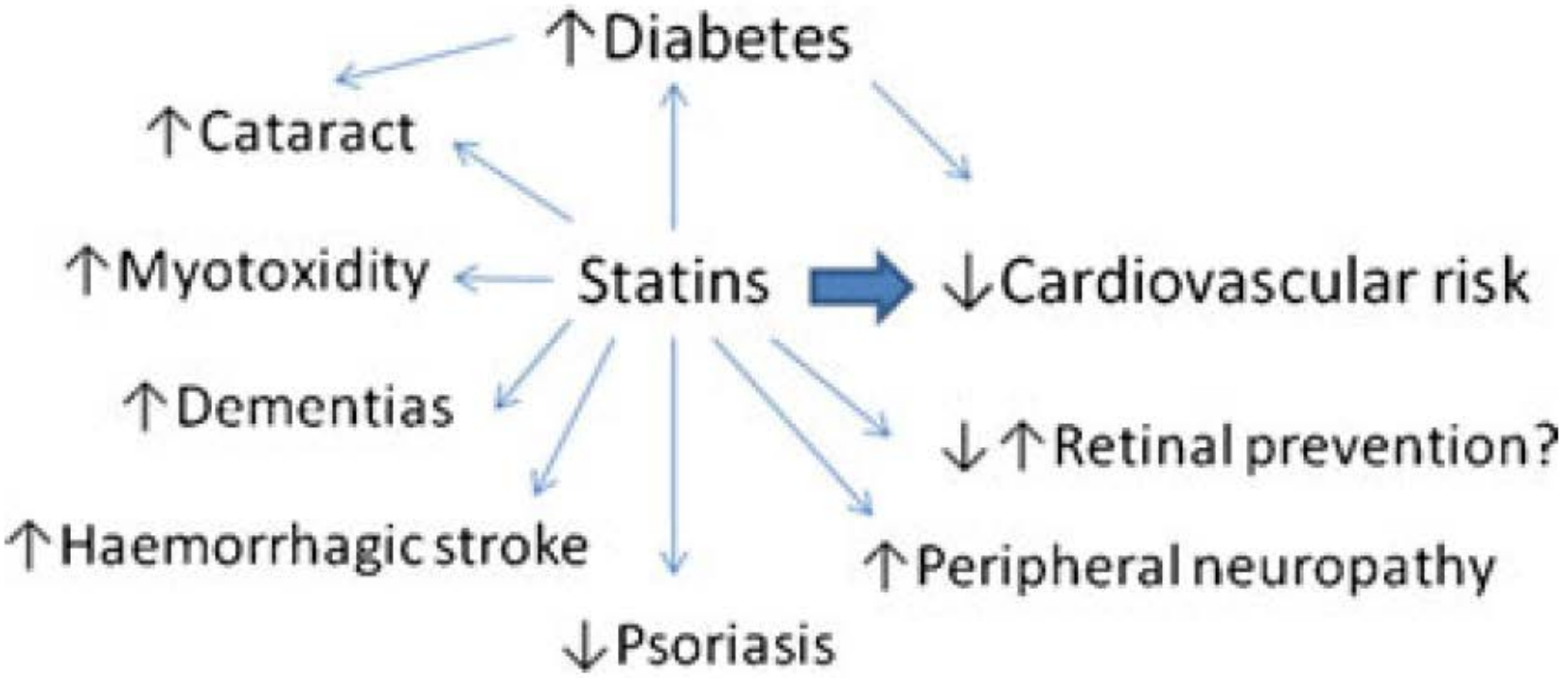

Fig. 1 Wanted and unwanted effects of statin treatment

Statin Resistance,

Statin Intolerance,

Statin Toxicity,

Nonadherence to Statins,

Statin Adverce Effects.

Guidelines

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 111–188
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

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CHOLESTEROL CLINICAL PRACTICE GUIDELINES

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Statin Resistance

- When discussing these guidelines, in none of them the term “statin resistance” is mentioned and the term “statin intolerance” does exist but without any further explanation or data concerning this issue.

Reiner Ž, Resistance and intolerance to statins, *Nutrition, Metabolism and Cardiovascular Diseases* (2014), doi: 10.1016/j.numecd.2014.05.009.

Drug Resistance

- Drug resistance is diminished or failed response of an individual to the intended effectiveness of a drug.

Reiner Ž, Resistance and intolerance to statins, *Nutrition, Metabolism and Cardiovascular Diseases* (2014), doi: 10.1016/j.numecd.2014.05.009.

Statin Resistance

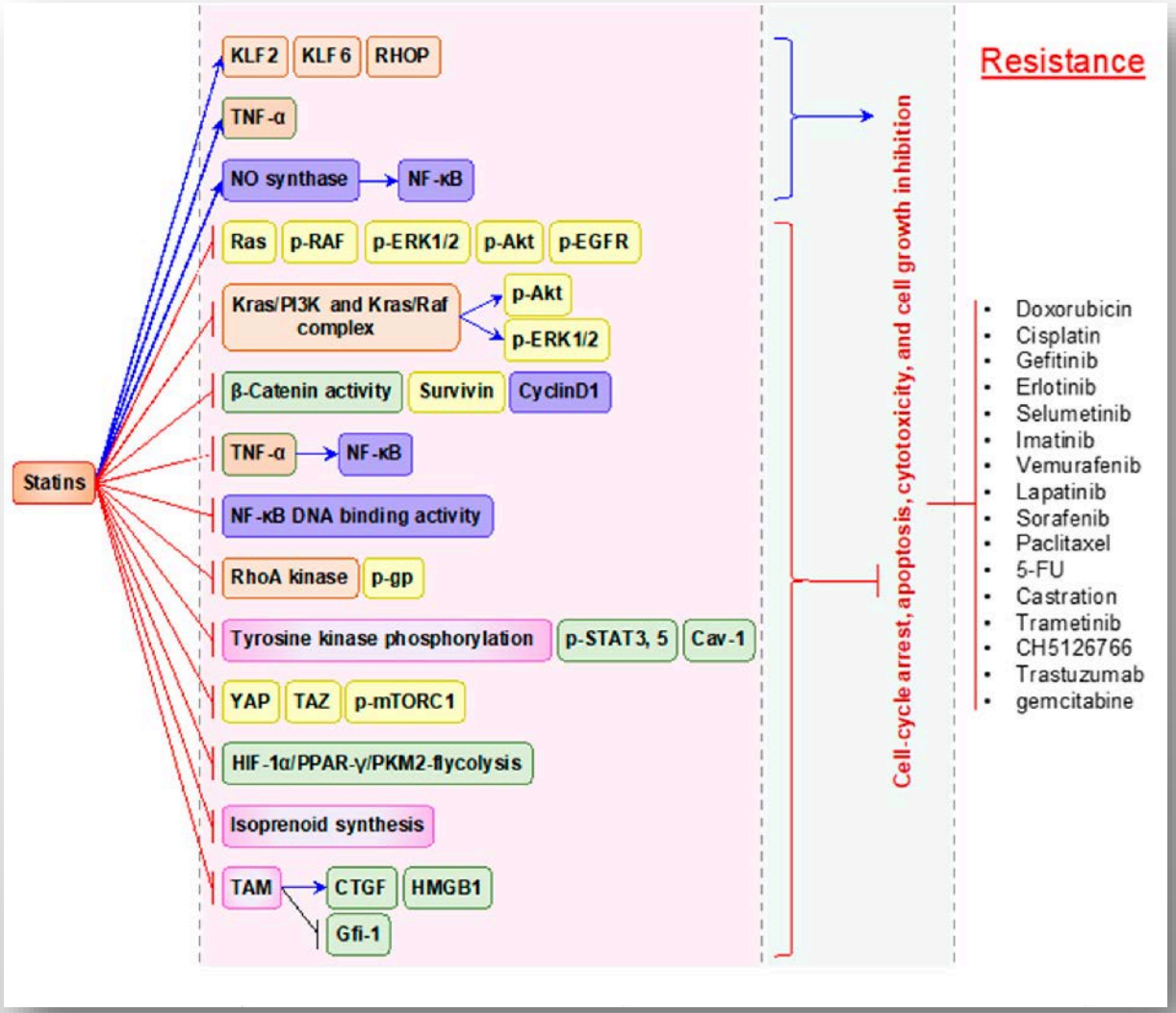
- Patients who fail to reach LDL-C target values despite best available therapy, mostly a highest tolerable dose of a more potent statin, are considered to be statin-resistant.

- It is well known that the reduction of LDL-C in response to statin therapy can vary by as much as 5% to 70% from person to person.

Reiner Ž, Tedeschi-Reiner E. Prevalence and types of persistent dyslipidemia in patients treated with statins. Croat Med J 2013;54:339-45.

Statin Resistance

- Resistance to statins can be related to differences in drug absorption, drug transport, intrahepatic drug metabolism, drug metabolism within other organs, and finally drug excretion mechanisms.

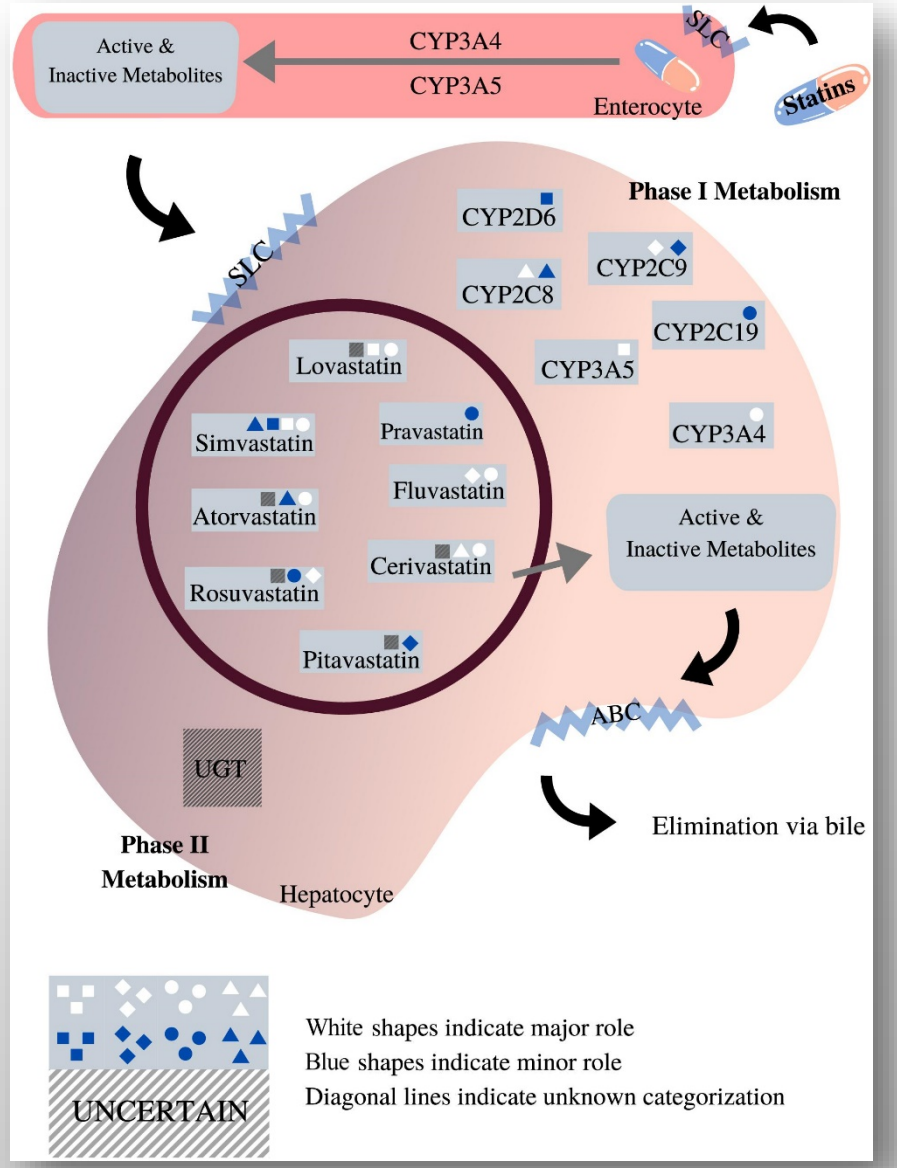


Reiner Ž, Resistance and intolerance to statins, *Nutrition, Metabolism and Cardiovascular Diseases* (2014), doi: 10.1016/j.numecd.2014.05.009.

Impact of genetic factors on **Statin Resistance**

- The resistance to statins has been associated with polymorphisms in the HMG-CoA-R, ABCB1, ABCG2, ABCC1, ABCC2, OATP1B1, OATP2B1, RHOA, NPC1L1, FXR, CYP7A1, ApoE, PCSK9, LDLR, LPA, CETP and TNF-α genes.

- Still not enough evidence to advocate pharmacogenetic testing before initiating therapy



Reiner Ž, Resistance and intolerance to statins, *Nutrition, Metabolism and Cardiovascular Diseases* (2014), doi: 10.1016/j.numecd.2014.05.009.

Impact of genetic factors on **Statin Resistance**

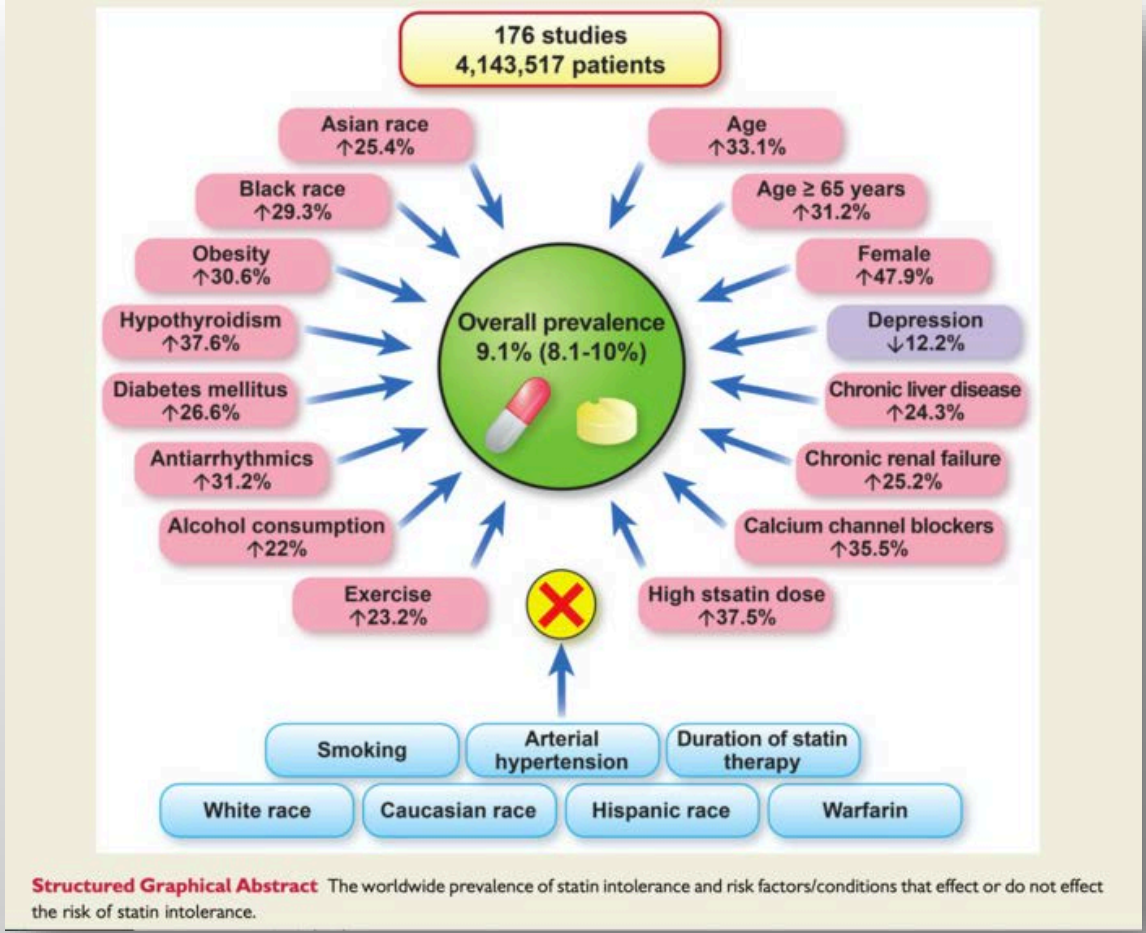
- According to the results of this study, gene variants involved in statin pharmacokinetics only had small effects (less than 1% per allele) on lipid response to statin treatment.

- Results of these studies cannot be translated into the clinical practice yet.

Reiner Ž, Resistance and intolerance to statins, *Nutrition, Metabolism and Cardiovascular Diseases* (2014), doi: 10.1016/j.numecd.2014.05.009.

Possible causes of Statin Resistance

- For example it has been shown that smokers have smaller statin-induced LDL-C decrease compared with non-smokers and that patients with hypertension have smaller decrease than those without hypertension.



Structured Graphical Abstract The worldwide prevalence of statin intolerance and risk factors/conditions that effect or do not effect the risk of statin intolerance.

Simon JA, Lin F, Hulley SB, Blanche PJ, Waters D, Shiboski S, et al. Phenotypic predictors of response to simvastatin therapy among African-Americans and Caucasians: the Cholesterol and Pharmacogenetics (CAP) Study. Am J Cardiol 2006;97:843-50.

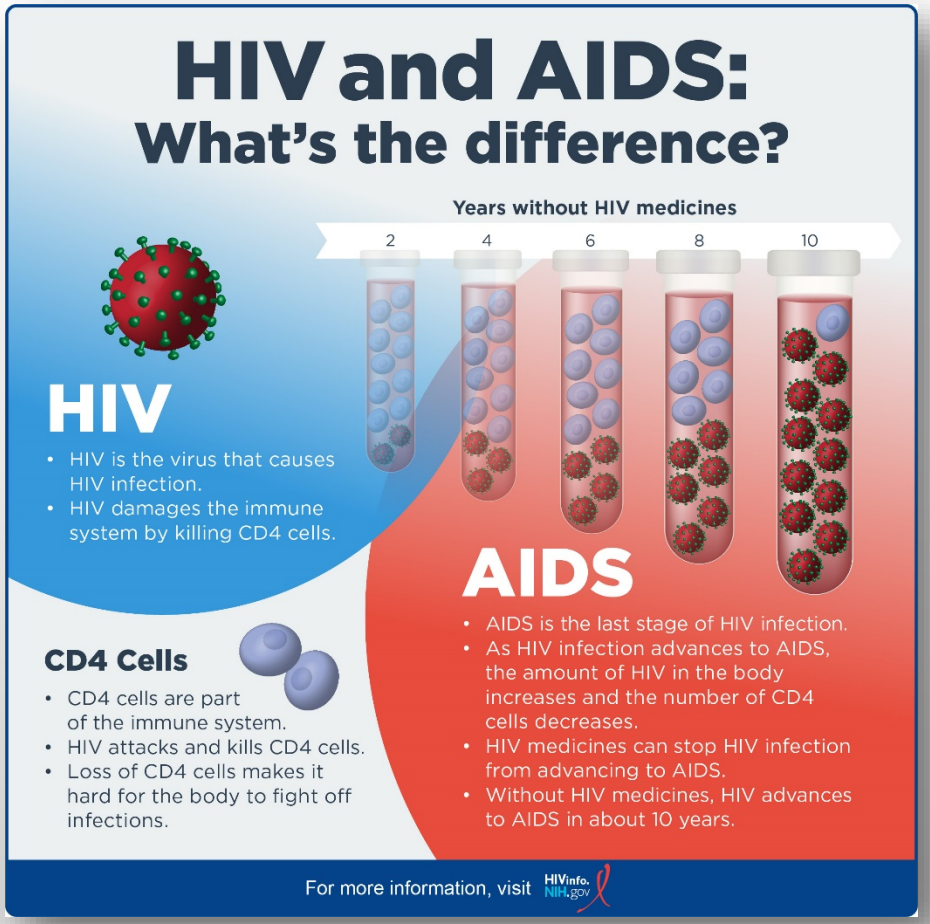
Possible causes of Statin Resistance

- It also seems that inflammation might cause statin resistance.
- It has been shown that inflammatory cytokines, in particular IL-1β cause statin resistance.
- Therefore it has been suggested that in inflammatory states higher concentrations of statin may be required to achieve the appropriate LDL-C lowering.

Chen Y1, Ku H, Zhao L, Wheeler DC, Li LC, Li Q, et al. Inflammatory stress induces statin resistance by disrupting 3-hydroxy-3-methylglutaryl-CoA reductase feedback regulation Arterioscler Thromb Vasc Biol 2014;34:365-76.

Possible causes of Statin Resistance

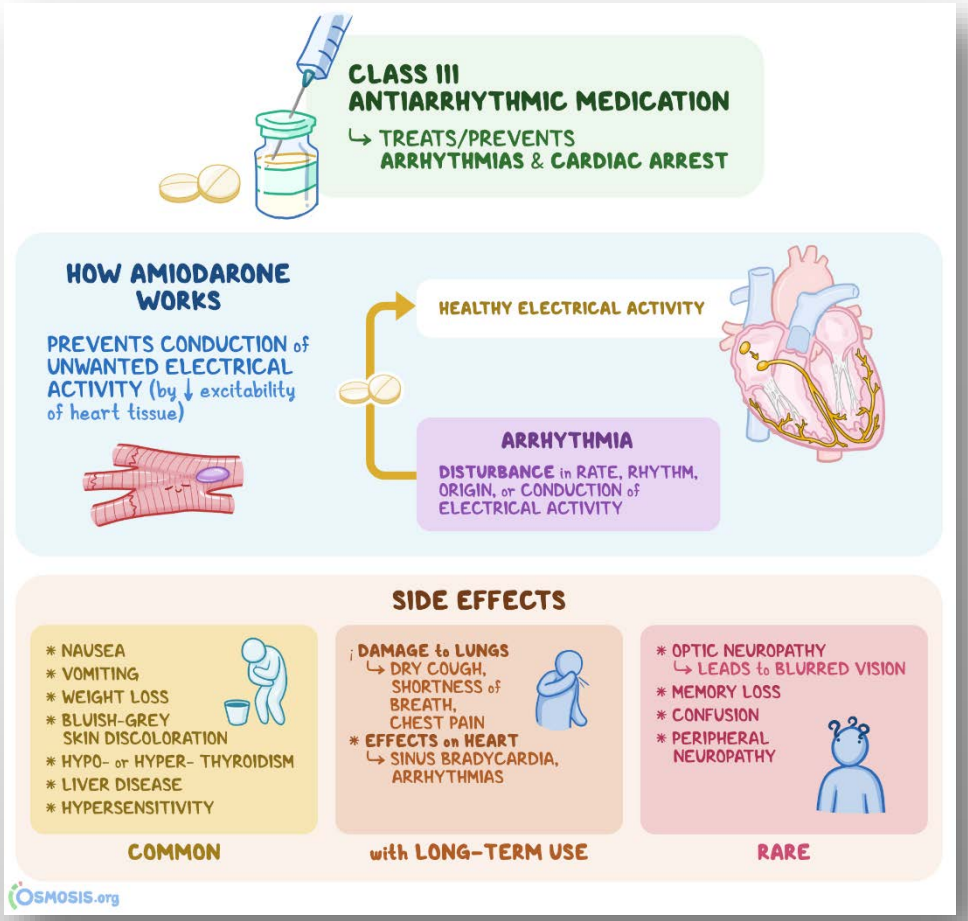
- Some studies have shown statins to be less effective in individuals with HIV infection as compared with HIV-negative individuals.



Boccara F, Simon T, Lacombe K, Cohen A, Laloux B, Bozec E, et al. Influence of pravastatin on carotid artery structure and function in dyslipidemic HIV-infected patients receiving antiretroviral therapy. AIDS 2006;20:2395-8.

Amiodorone

- Both amiodarone and amiodarone-induced hypothyroidism influence the synthesis of LDLR which may explain the lack of statin effect.
- Hypothyroidism is a well-known cause of secondary dyslipidemia characterized by elevated LDL-C levels.
- Administration of amiodarone increases LDLC levels.



Al-Sarraf A, Li M, Frohlich J. Statin resistant dyslipidemia in a patient treated with amiodarone. BMJ Case Rep 2011. pii: bcr0820114620.

Pseudo-resistance / Non-adherence

- In fact, pseudoresistance due to non-adherence or non-persistence is in real life circumstances probably the main cause of insufficient LDL-C response to statin treatment.

- It has been shown that 50% or more of all patients discontinue statins within one year of treatment initiation while after two years 75% of patients who were prescribed a statin for primary prevention and 40% of patients with an acute coronary syndrome were non-adherent.

Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. Ann Pharmacother 2010;44:1410–21.

Non-adherence

- Adherence is better in middle-aged (50-69 years) than the oldest (≥ 70 years) and the younger (< 50 years) patients suggesting a U shaped association.

- It is also better in men, in white, in those with higher income and in those who had a cardiovascular event.

Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. Ann Pharmacother 2010;44:1410–21.

Drug Intolerance

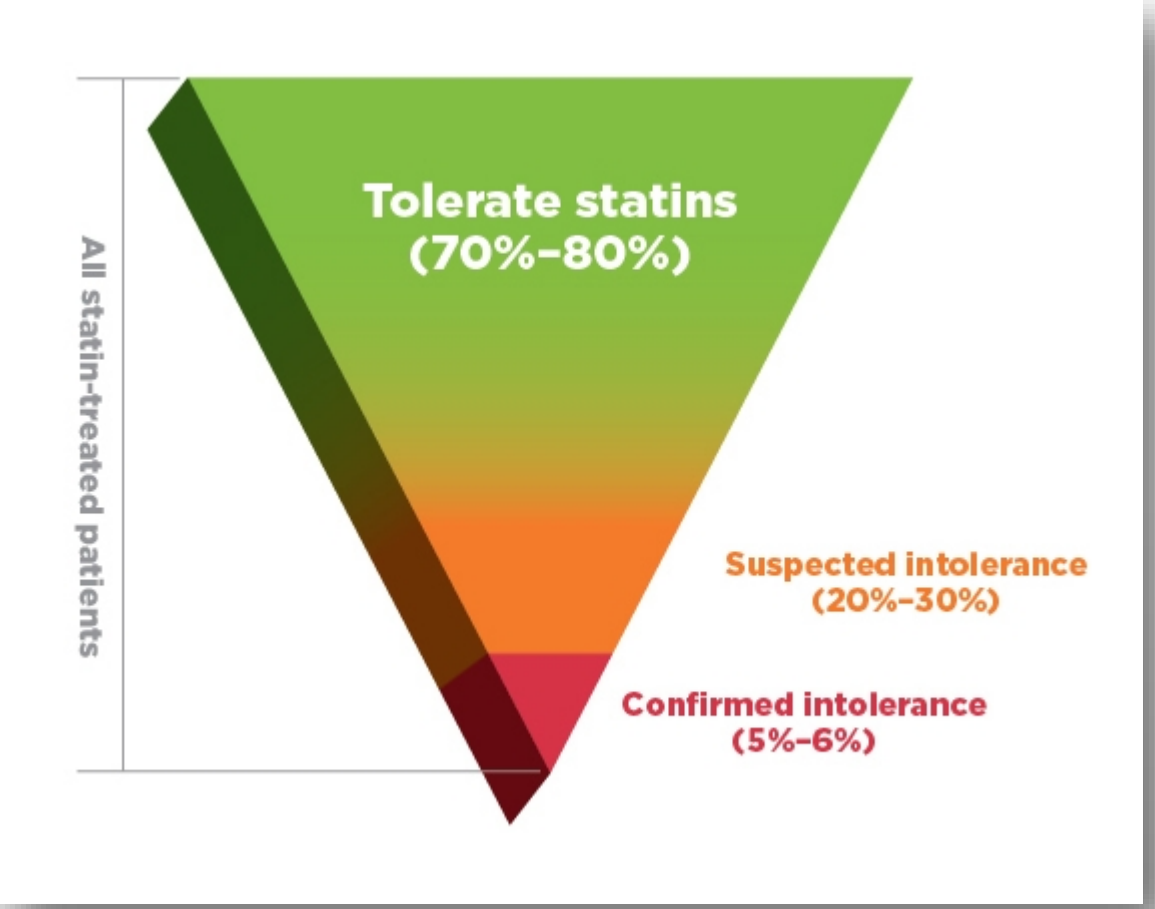
- Progressive diminution of the susceptibility of a patient to the effects of a drug, as a result of continued administration, or excess of adverse effects which prevent the patient from further treatment or using the adequate drug doses.

Reiner Ž, Resistance and intolerance to statins, *Nutrition, Metabolism and Cardiovascular Diseases* (2014), doi: 10.1016/j.numecd.2014.05.009.

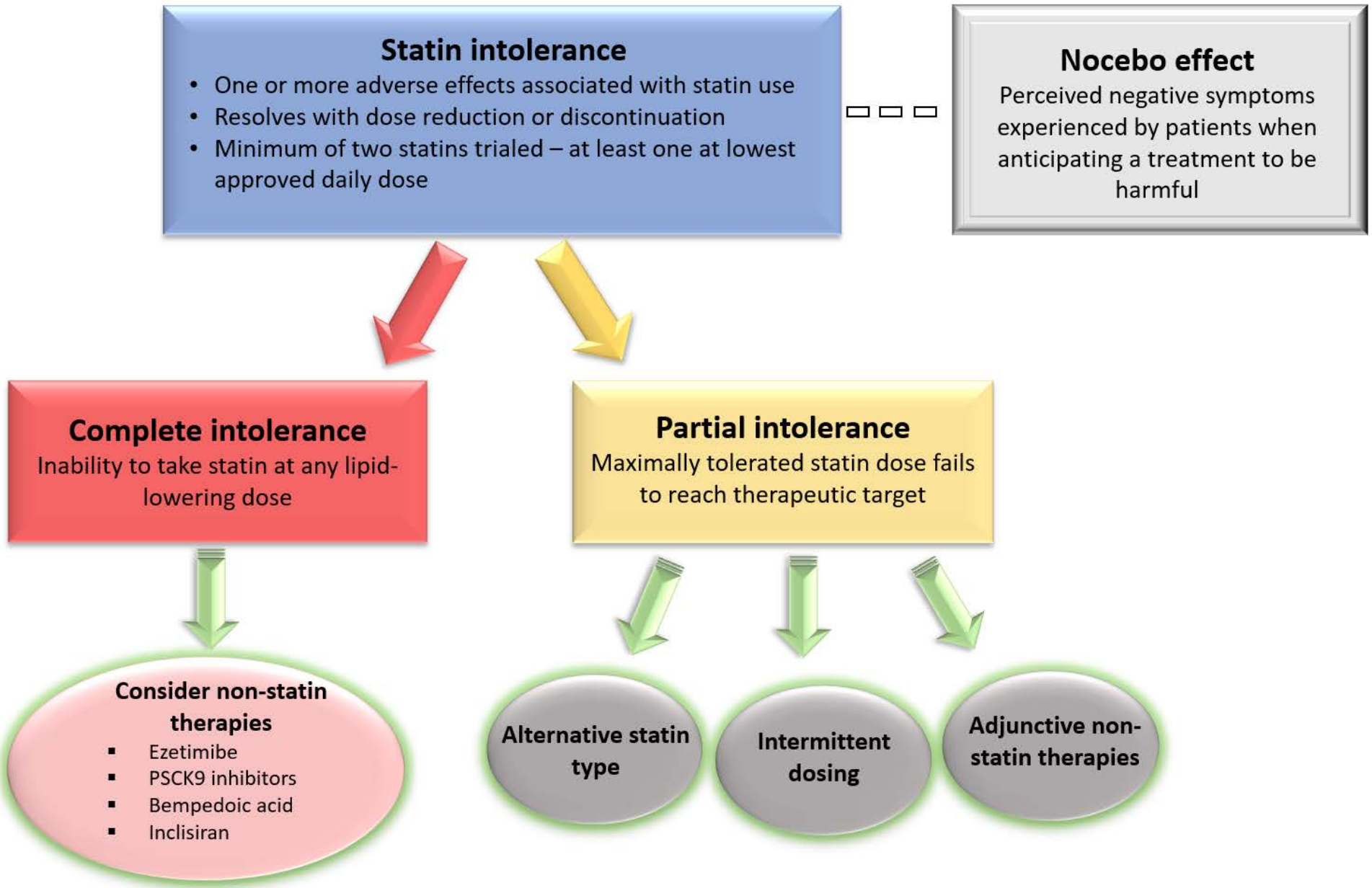
Statin Intolerance

- Inability to tolerate statin at all or to tolerate a full dose having adverse effects, mostly myopathy.

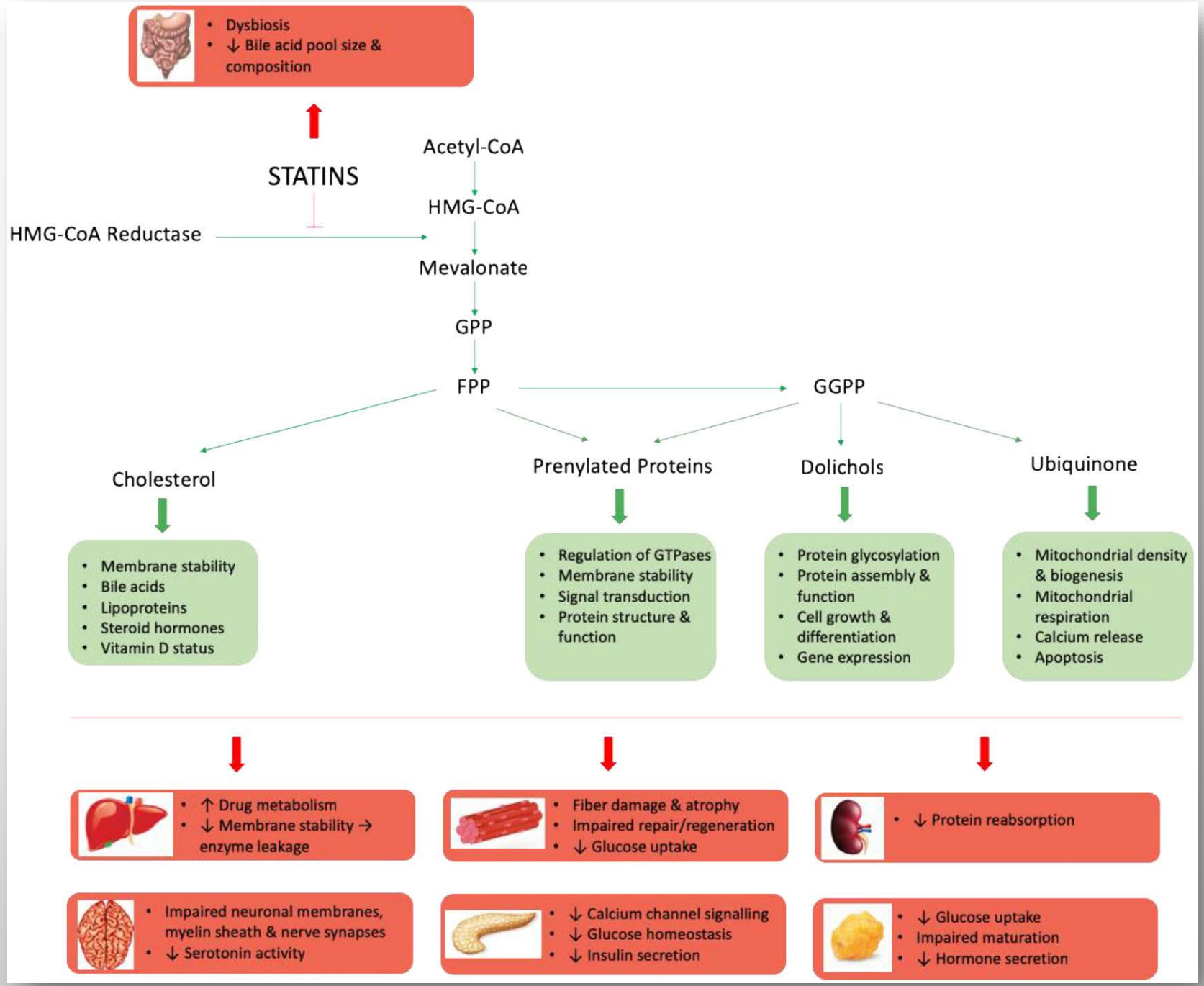
- Inability to tolerate at least two different statins, with one statin assessed at its lowest effective dose.



Banach, M. et al. Statin intolerance — an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch. Med. Sci.* **11**, 1–23 (2015).


Statin intolerance
One or more adverse effects associated with statin use
Resolves with dose reduction or discontinuation
Minimum of two statins trialed – at least one at lowest approved daily dose
Nocebo effect
Perceived negative symptoms experienced by patients when anticipating a treatment to be harmful
Complete intolerance
Inability to take statin at any lipid-lowering dose
Partial intolerance
Maximally tolerated statin dose fails to reach therapeutic target
Consider non-statin therapies
Ezetimibe
PSCK9 inhibitors
Bempedoic acid
Inclisiran
Alternative statin type
Intermittent dosing
Adjunctive non-statin therapies

Mechanisms of Statin Intolerance



Statin-associated Muscle Symptoms (SAMS)

- SAMS are the most commonly reported adverse effects of statins (present in 10–29% of patients taking statin therapy according to observational studies).

- In patients taking statins, the incidence of myopathy with plasma creatine kinase changes >10 times ULN is estimated to be approximately 1 in 1,000, whereas the incidence of rhabdomyolysis is approximately 1 in 10,000.

Cohen, J. D., Brinton, E. A., Ito, M. K. & Jacobson, T. A. Understanding statin use in America and gaps in patient education (USAGE): an internet-based survey of 10,138 current and former statin users. *J. Clin. Lipidol.* **6**, 208–215 (2012).

SAMS

- Symptoms are usually bilateral and affect large muscle groups (thighs, calves, hip flexors or proximal upper extremities).

- Symptoms can occur at rest or shortly after exercise and usually occur within 1 month of initiation of therapy or an increase in dose.

Rosenson, R. S. et al. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J. Clin. Lipidol.* **8**, S58–71 (2014).

SAMS

1. Myalgia or mild hyperCKemia (<5x ULN);

2. Self-limited toxic statin myopathy (CK levels between 10 and 100 ULN); and

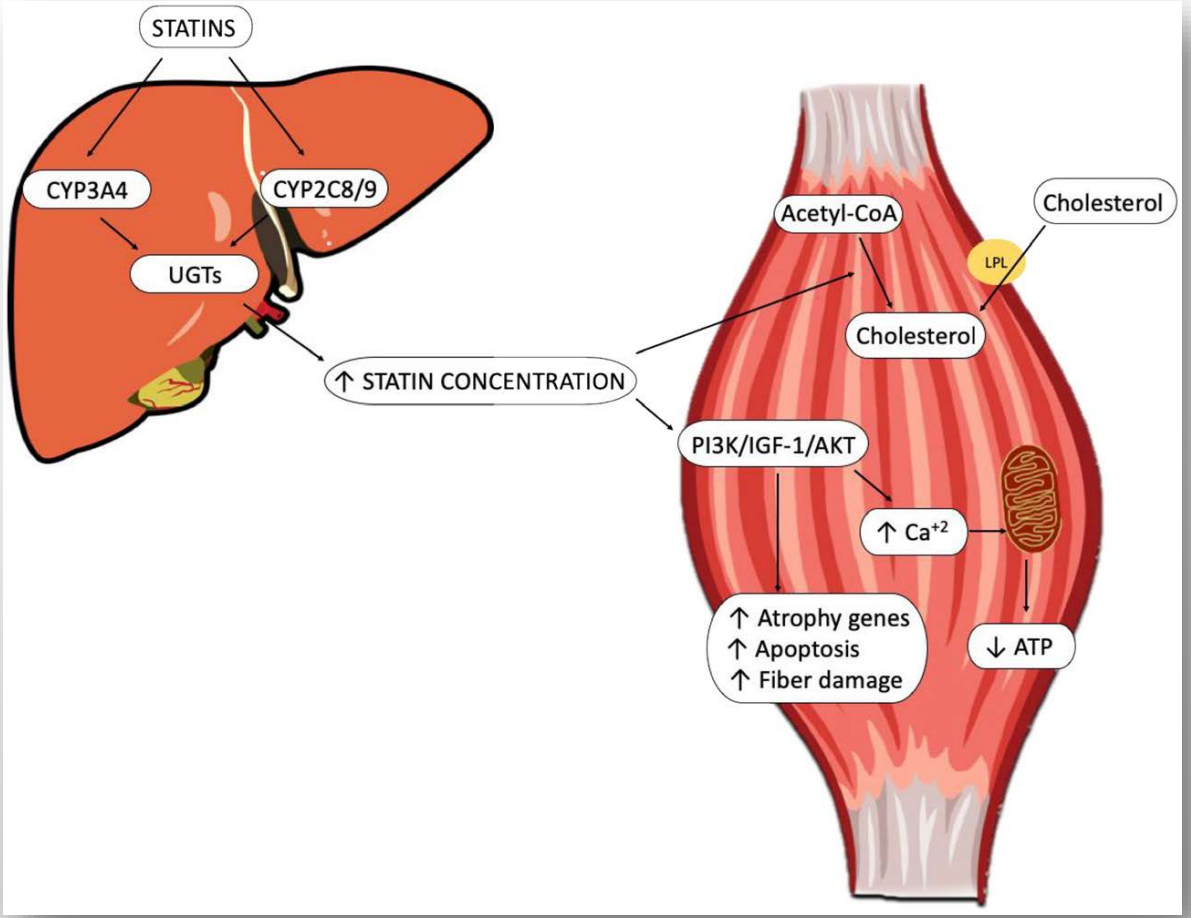
3. Myositis or immune-mediated necrotizing myopathy with HMG-CoA reductase antibodies and CK levels between 10 and 100x ULN

4. Rhabdomyolysis characterized by high CK concentrations (>100-fold the upper limit of normal [ULN]), myoglobinuria, and renal impairment

Mechanism of SAMS

- Alteration in mitochondrial function and cellular energy utilization related to the depletion of coenzyme Q10, which would lead to ATP depletion with augmentation of oxidative stress by the increased production of reactive oxygen species.

- Induction of mitochondria-dependent apoptosis



Stroes, E. S. et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur. Heart J.* **36**, 1012–1022 (2015).

Evaluation

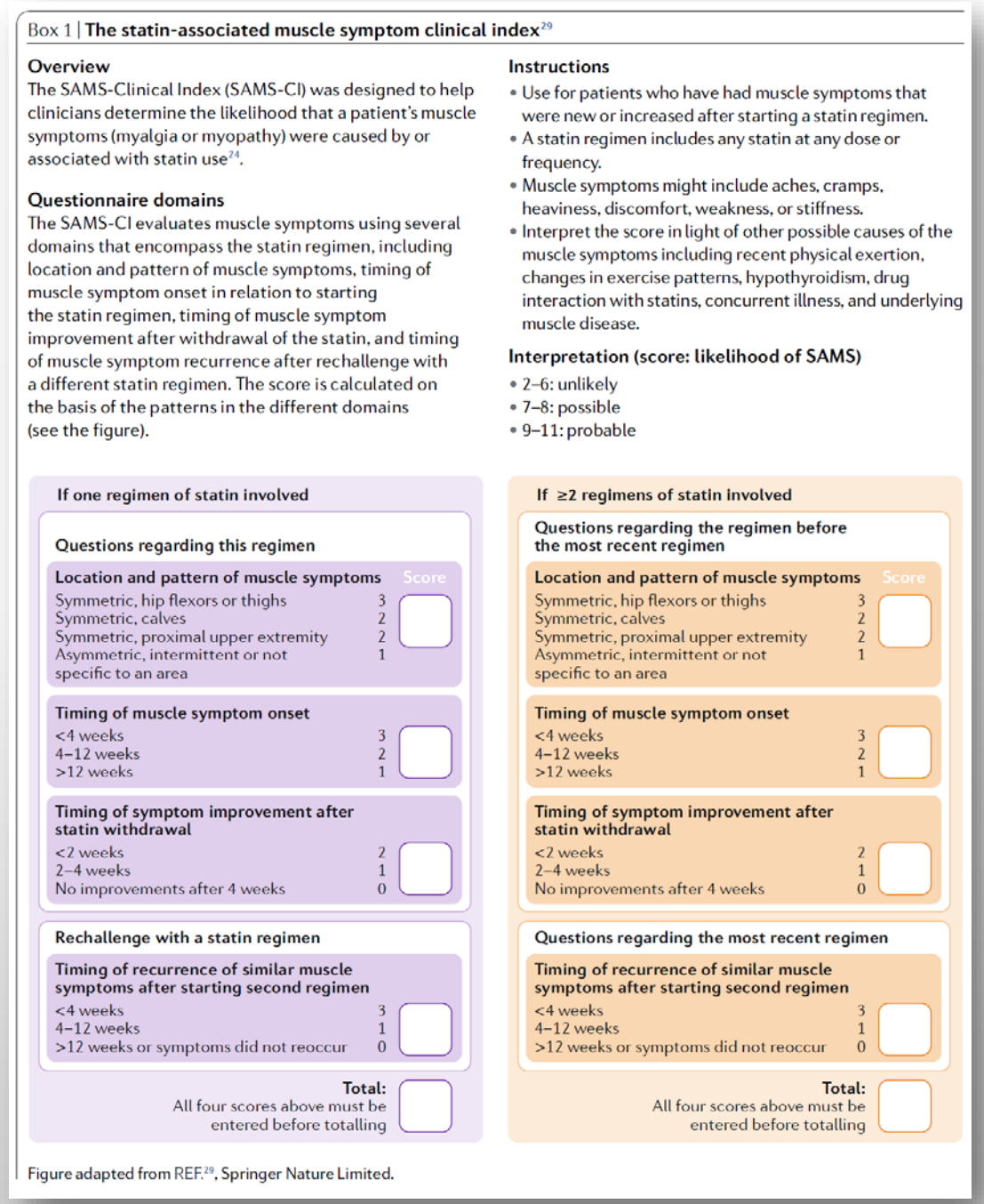
- The next step in evaluating SAMS is statin discontinuation and rechallenge with either a lower dose of the same statin or the use of another statin.
- A washout period of several weeks might be helpful before rechallenge.
- A meta-analysis of 13 RCT studies showed that alternate-day dosing can be as efficacious as daily dosing in lowering LDL-C levels, but its effect on ASCVD outcomes remains unclear.

Awad, K. et al. Efficacy and Safety of alternate-day versus daily dosing of statins: a systematic review and meta-analysis. *Cardiovasc. Drugs Ther.* **31**, 419–431 (2017).

SAMS Clinical İndex

The term myalgia was applied to patients who met all the following criteria:

- new muscle symptoms that were not associated with exercise,
- symptom duration >2 weeks,
- symptom resolution within 2 weeks of statin cessation and
- symptom recurrence within 4 weeks of drug rechallenge.



Box 1 | **The statin-associated muscle symptom clinical index**[29]

Overview
The SAMS-Clinical Index (SAMS-CI) was designed to help clinicians determine the likelihood that a patient's muscle symptoms (myalgia or myopathy) were caused by or associated with statin use[24].

Questionnaire domains
The SAMS-CI evaluates muscle symptoms using several domains that encompass the statin regimen, including location and pattern of muscle symptoms, timing of muscle symptom onset in relation to starting the statin regimen, timing of muscle symptom improvement after withdrawal of the statin, and timing of muscle symptom recurrence after rechallenge with a different statin regimen. The score is calculated on the basis of the patterns in the different domains (see the figure).

Instructions
- Use for patients who have had muscle symptoms that were new or increased after starting a statin regimen.
- A statin regimen includes any statin at any dose or frequency.
- Muscle symptoms might include aches, cramps, heaviness, discomfort, weakness, or stiffness.
- Interpret the score in light of other possible causes of the muscle symptoms including recent physical exertion, changes in exercise patterns, hypothyroidism, drug interaction with statins, concurrent illness, and underlying muscle disease.

Interpretation (score: likelihood of SAMS)
- 2–6: unlikely
- 7–8: possible
- 9–11: probable

If one regimen of statin involved

Questions regarding this regimen

Location and pattern of muscle symptoms		Score
Symmetric, hip flexors or thighs	3	
Symmetric, calves	2	
Symmetric, proximal upper extremity	2	
Asymmetric, intermittent or not specific to an area	1	

Timing of muscle symptom onset	
<4 weeks	3
4–12 weeks	2
>12 weeks	1

Timing of symptom improvement after statin withdrawal	
<2 weeks	2
2–4 weeks	1
No improvements after 4 weeks	0

Rechallenge with a statin regimen

Timing of recurrence of similar muscle symptoms after starting second regimen	
<4 weeks	3
4–12 weeks	1
>12 weeks or symptoms did not reoccur	0

Total: All four scores above must be entered before totalling

If ≥2 regimens of statin involved

Questions regarding the regimen before the most recent regimen

Location and pattern of muscle symptoms		Score
Symmetric, hip flexors or thighs	3	
Symmetric, calves	2	
Symmetric, proximal upper extremity	2	
Asymmetric, intermittent or not specific to an area	1	

Timing of muscle symptom onset	
<4 weeks	3
4–12 weeks	2
>12 weeks	1

Timing of symptom improvement after statin withdrawal	
<2 weeks	2
2–4 weeks	1
No improvements after 4 weeks	0

Questions regarding the most recent regimen

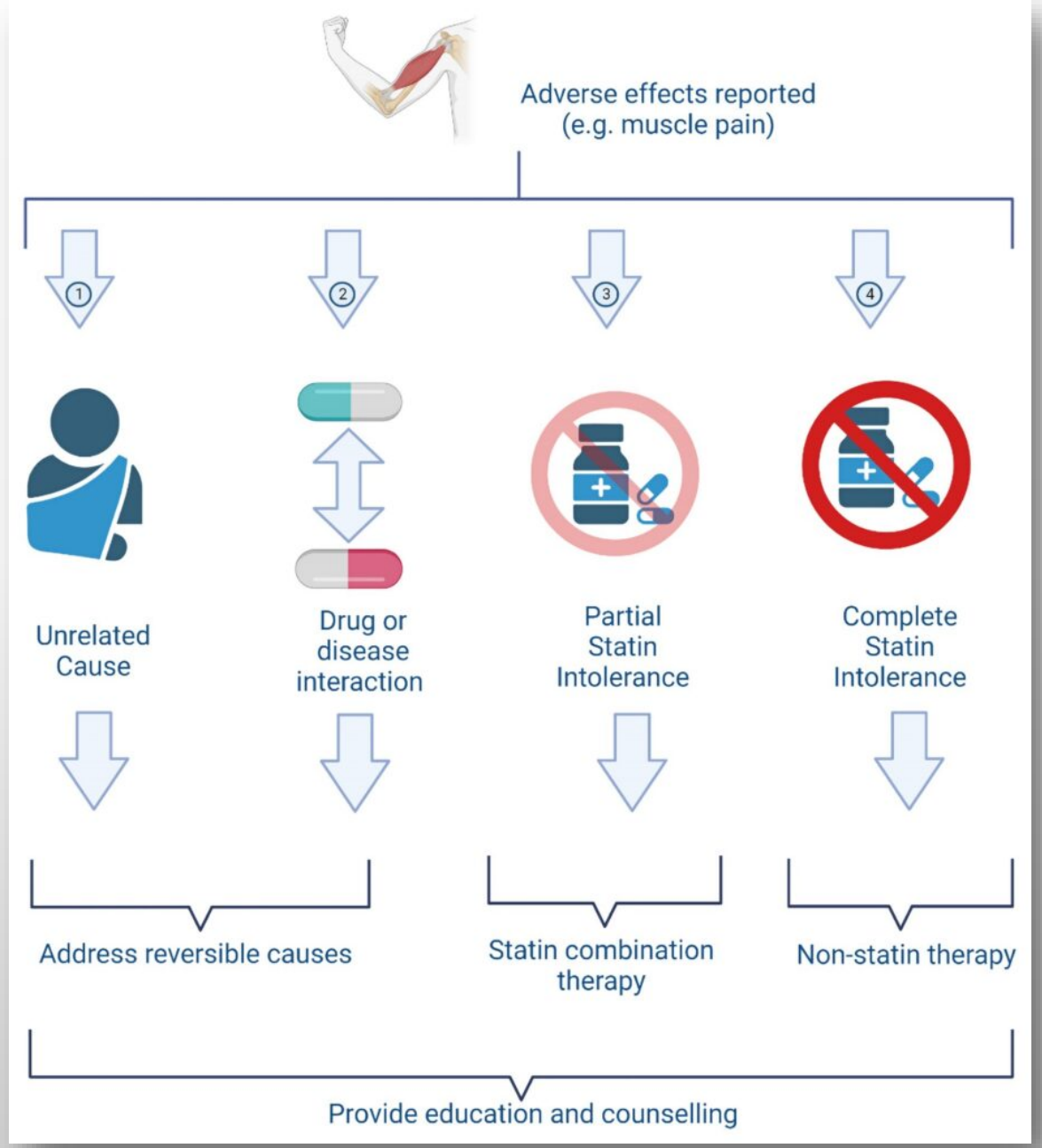
Timing of recurrence of similar muscle symptoms after starting second regimen	
<4 weeks	3
4–12 weeks	1
>12 weeks or symptoms did not reoccur	0

Total: All four scores above must be entered before totalling

Figure adapted from REF.[29], Springer Nature Limited.

SAMS Clinical İndex

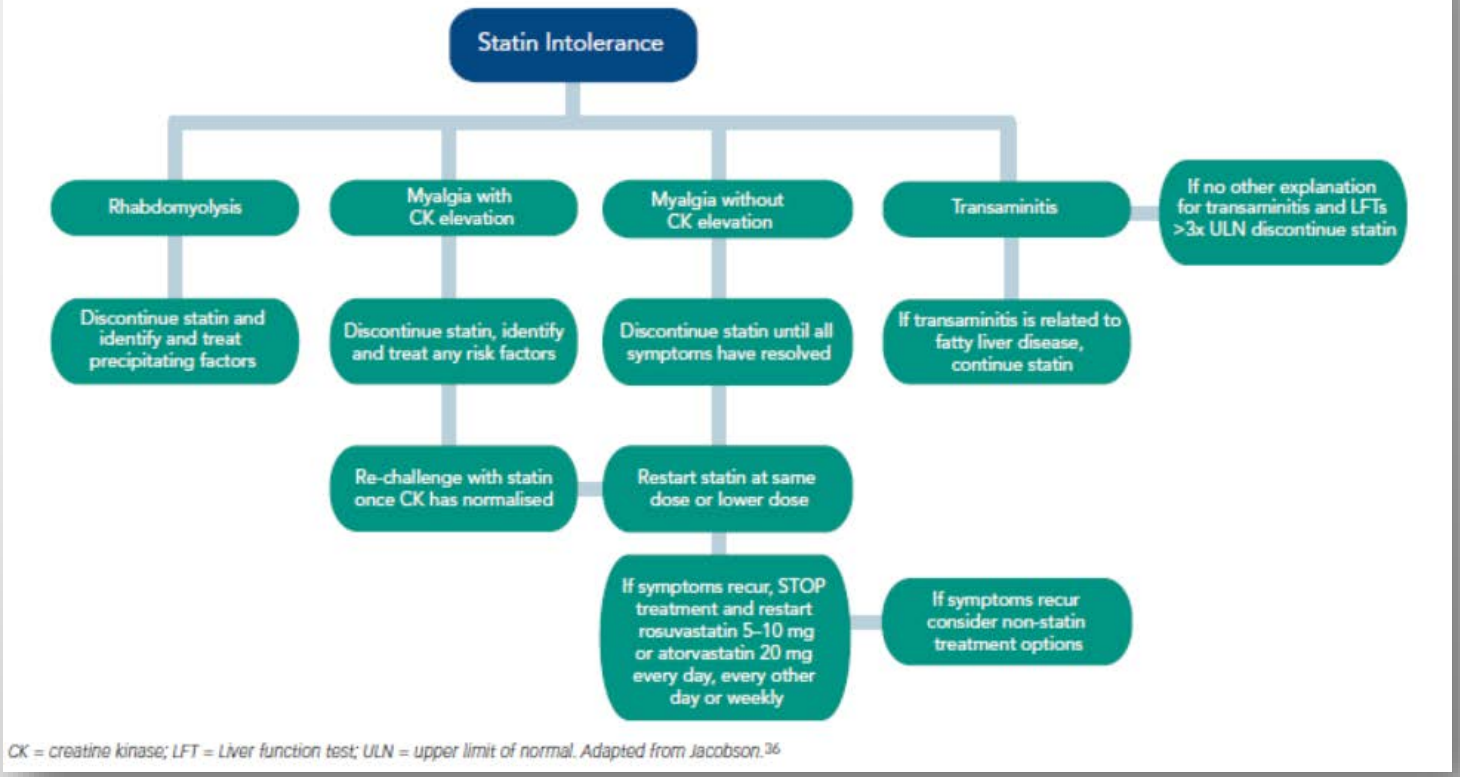
- This tool might also be helpful for clinicians to motivate patients to adhere to statin therapy even in the presence of muscle symptoms.



SAMS

- Although it is well documented that statin-induced myotoxicity is dose-dependent, the risk of myopathy increases particularly if statins are co-administered with other medications which interact to increase plasma statin levels.

Figure 2: Algorithm for Management of Statin Intolerance



CK = creatine kinase; LFT = Liver function test; ULN = upper limit of normal. Adapted from Jacobson.[36]

Mancini GB, Baker S, Bergeron J, Fitchett D, Frohlich J, Genest J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. Can J Cardiol 2011;27:635-62.

Factors which increase SAMS

- High doses and increased serum concentration of statins,
- Use of statin-interacting drugs that inhibit statin catabolism,
- Hypothyroidism,
- Reduced muscle mass,
- Increased physical activity,
- Advanced age,
- Female sex,
- Physical frailty,
- Alcohol use.

Banach, M. et al. Statin intolerance — an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Expert Opin. Drug Saf.* **14**, 935–955 (2015).

Statin Intolerance

- It has to be mentioned that recent clinical experience suggests that most statin intolerant patients if re-challenged with intermittent dosing manage to subsequently tolerate statins.

Mampuya WM, Frid D, Rocco M, Huang J, Brennan DM, Hazen SL, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. Am Heart J 2013;166:597-603.

Nocebo effect

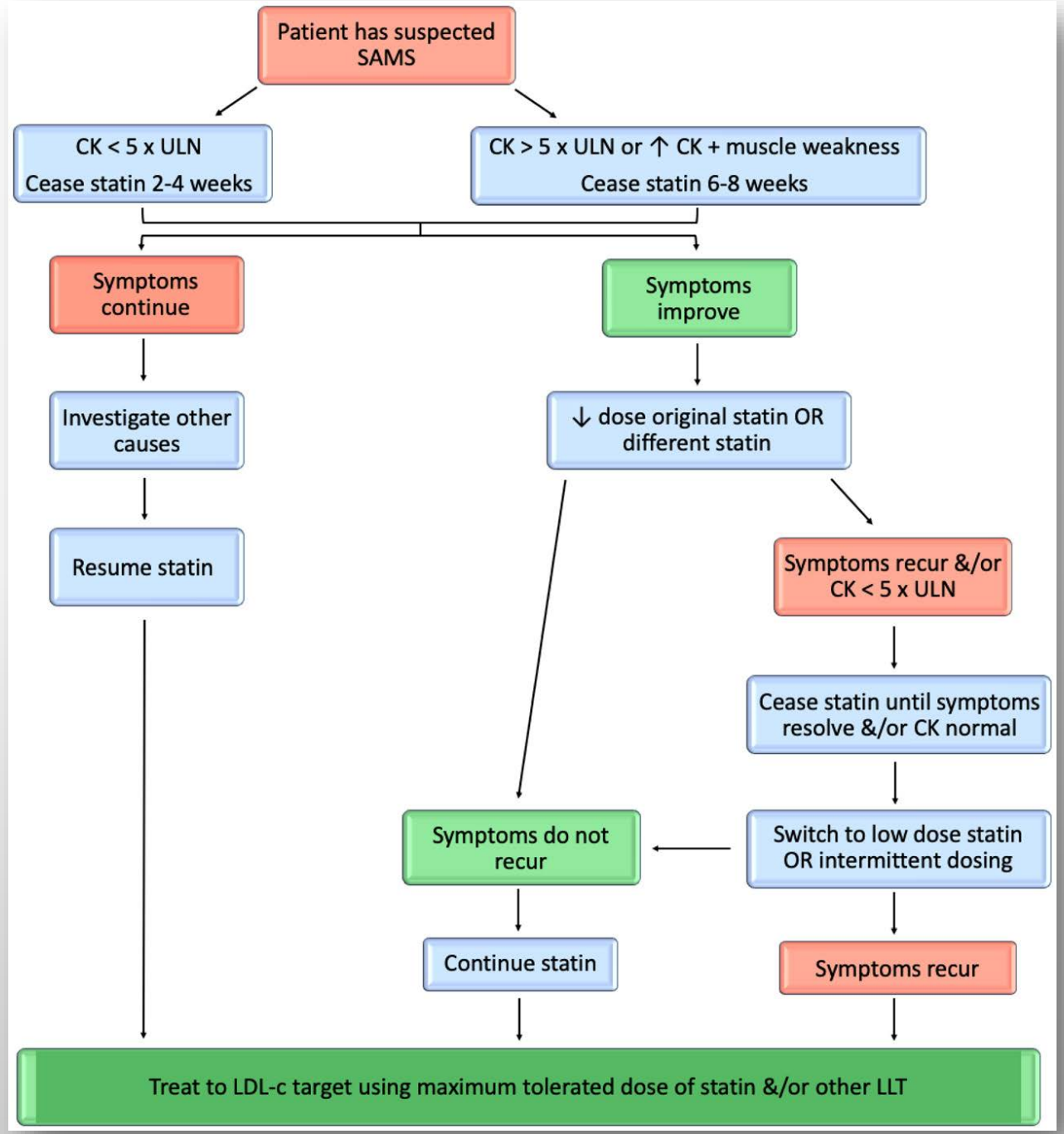
Nocebo effect - effect caused by negative expectations.

- Prevalence of SAMS in observational studies is much higher (10–29%) than the prevalence reported in RCTs (1–2%).

- Blinded/unblinded phases of ASCOT-LLA study.

Adhyaru, B. B. & Jacobson, T. A. Unblinded ASCOT study results do not rule out that muscle symptoms are an adverse effect of statins. *Evid. Based Med.* **22**, 210 (2017).

SAMS management algorithm



Risk of diabetes mellitus

- In 2008, the landmark JUPITER study provided evidence that rosuvastatin (20 mg daily) significantly increased the relative risk of newly diagnosed diabetes by 25% compared with placebo.

- A subsequent analysis of the JUPITER study suggested that the cardiovascular and mortality benefits exceeded the risk of diabetes even in patients at high risk of developing diabetes.

Ridker, P. M. et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.* **359**, 2195–2207 (2008).

Risk of diabetes mellitus

Table 3 | **Incidence of diabetes mellitus in major trials on statin therapy**[49]

Study (year)	Statin therapy	Patients (*n*)	Rate of new-onset diabetes[a]		OR (95% CI)	Refs
			Statin group	Placebo or control group		
ASCOT-LLA (2003)	Atorvastatin 10 mg	7,773	11.9	10.5	1.14 (0.89–1.46)	37
HPS (2003)	Simvastatin 40 mg	14,573	9.2	8.0	1.15 (0.98–1.35)	83
JUPITER (2008)	Rosuvastatin 20 mg	17,802	16.0	12.8	1.26 (1.04–1.51)	48
WOSCOPS (2001)	Pravastatin 40 mg	5,974	5.2	6.5	0.79 (0.58–1.10)	84
LIPID (2003)	Pravastatin 40 mg	6,997	6.0	6.6	0.91 (0.71–1.71)	85
CORONA (2007)	Rosuvastatin 20 mg	3,534	20.9	18.5	1.14 (0.84–1.55)	16
PROSPER (2002)	Pravastatin 40 mg	5,023	20.5	15.8	1.32 (1.03–1.69)	72
MEGA (2006)	Pravastatin 10–20 mg	6,086	10.8	10.1	1.07 (0.86–1.35)	86
AFCAPS/TEXCAPS (1998)	Lovastatin 20–40 mg	6,211	4.5	4.6	0.98 (0.70–1.38)	87
4 S (1994)	Simvastatin 20–40 mg	4,242	17.3	16.8	1.03 (0.84–1.28)	88
ALLHAT (2002)	Pravastatin 40 mg	6,087	16.4	14.4	1.15 (0.95–1.41)	89
GISSI-HF (2008)	Rosuvastatin 10 mg	3,378	34.8	32.1	1.10 (0.89–1.35)	17
GISSI-PREV (2000)	Pravastatin 20 mg	3,460	27.5	30.6	0.89 (0.67–1.20)	90
Meta-analysis[b]	All statins	91,140	12.23	11.25	1.09 (1.02–1.17)	49

[a]Events per 1,000 patient-years. [b]Pooled odds ratio from a meta-analysis of the 13 trials.

Mechanism

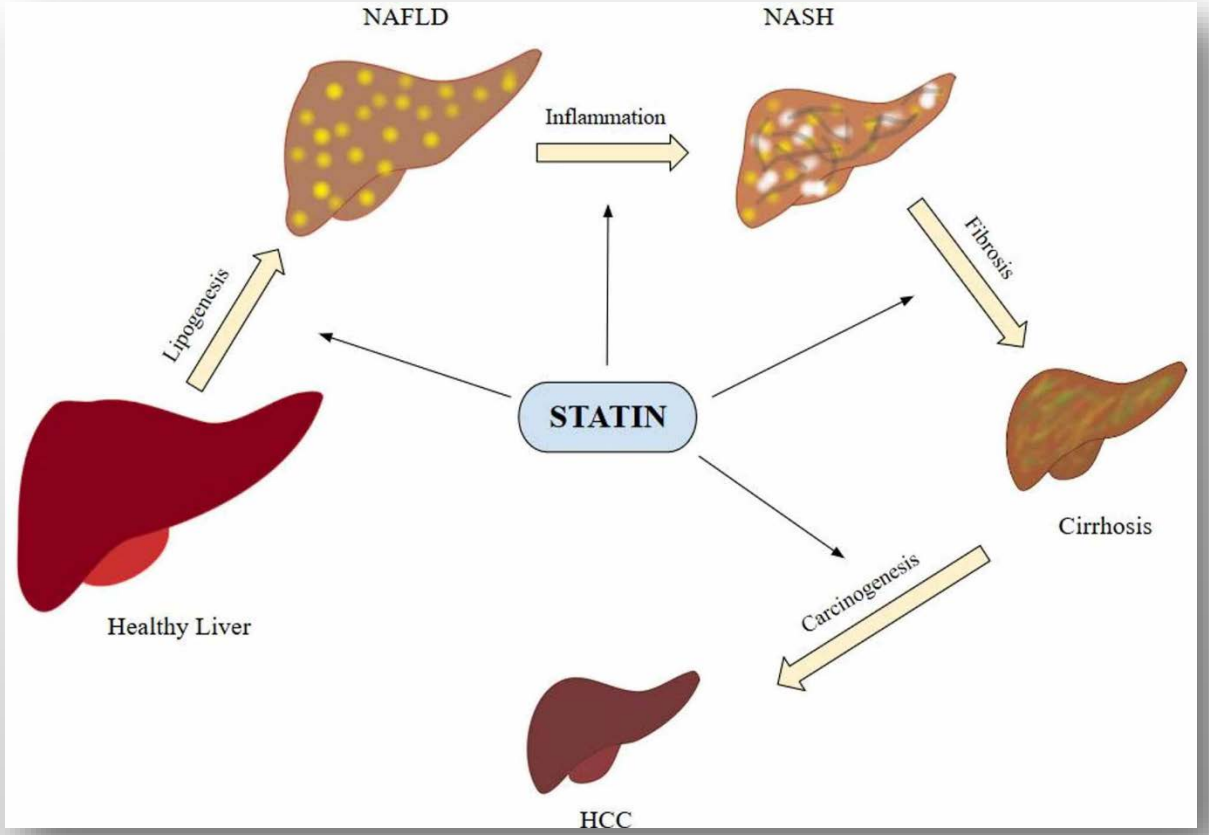
- Statins might interfere with peripheral insulin signalling and pancreatic β-cell function.

- Single nucleotide polymorphisms in the *HMGCR* gene as proxies for 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) inhibition by statins.

Swerdlow, D. I. et al. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet* **385**, 351–361 (2015).

Liver

- Statin use in patients with nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH) is associated with a reduction in transaminase plasma levels, with improvements in steatosis and the liver necroinflammatory grade but no change in the liver fibrosis grade.

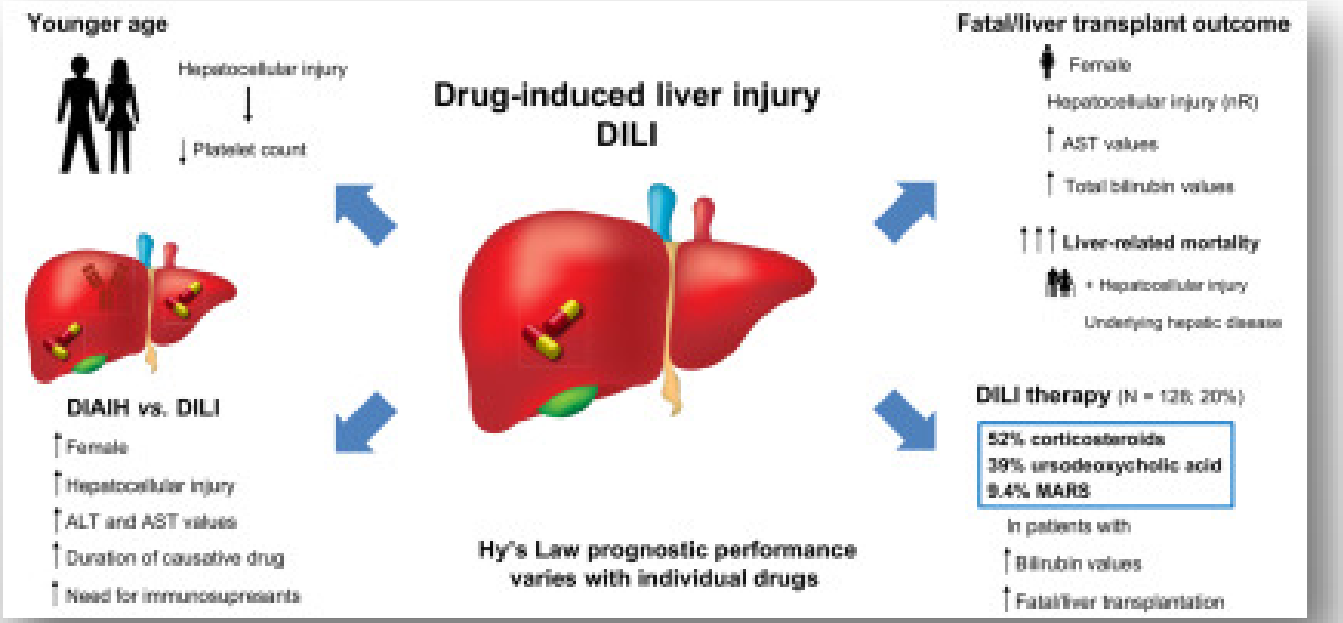


Hyogo, H. et al. Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia. *Metabolism* **57**, 1711–1718 (2008).

Drug-induced liver injury: Hy's Law

3 criteria must be satisfied to suggest drug-induced liver injury:

- elevation in AST or ALT ≥3 times ULN,
- increase in total bilirubin levels >2 times ULN, and
- no other demonstrable cause such as cholestasis, viral hepatitis, pre-existing or acute hepatobiliary disease, or use of another drug that can cause the observed injury.



Bays, H., Cohen, D. E., Chalasani, N. & Harrison, S. A., The National Lipid Association's Statin Safety Task Force. An assessment by the Statin Liver Safety Task Force: 2014 update. *J. Clin. Lipidol.* **8**, S47–S57 (2014).

Algorithm - 1

The algorithm is based on the degree of ALT or AST elevation:

- if ALT or AST elevation is above the ULN but ≤ 3 times the ULN, bilirubin levels should be evaluated;

- if ALT or AST levels are normal and creatine kinase level is normal, the patient likely has nonalcoholic fatty liver disease (NAFLD), and statin therapy can be reasonably continued;

Algorithm - 2

- if the elevation in bilirubin level is indirect and not new and the creatine kinase level is normal, the patient could have underlying Gilbert syndrome or NAFLD, and the statin can be continued;

- a new elevation in bilirubin levels requires further evaluation, and the statin should be stopped until further work-up is completed;

- if the elevation in ALT or AST level is >3 times ULN, a repeated evaluation of ALT or AST levels should be considered, and statin therapy should be held or stopped until further evaluation is completed.

Hepatitis C

- The hepatitis C virus (HCV) and lipid metabolism are interrelated, given that viral replication involves the LDL receptor (LDLR) and enzymes involved in cholesterol biosynthesis.

- Several studies have shown that statin use is linked to improvements in viral response to HCV treatments.

Henderson, L. M., Patel, S., Giordano, T. P., Green, L. & El-Serag, H. B. Statin therapy and serum transaminases among a cohort of HCV-infected veterans. *Dig. Dis. Sci.* **55**, 190–195 (2010).

SNS

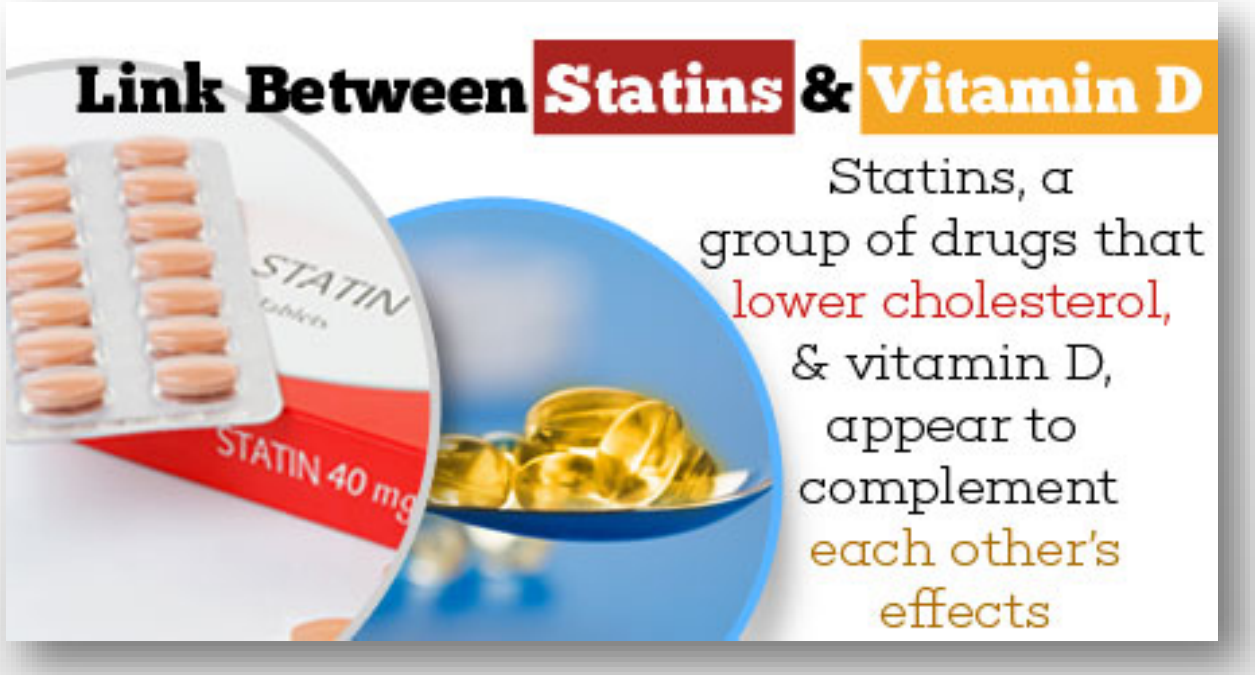
- **Cognitive Dysfunctions**
  - Totality of the evidence, including several meta-analyses of multiple RCTs, does not indicate an association between statin use and cognitive dysfunction.

- **Haemorrhagic stroke**
  - The small additional risk of haemorrhagic stroke is clearly outweighed by the large reductions seen in the risk of ischaemic stroke and major cardiovascular events.

Vitamin D

- It remains debatable whether vitamin D insufficiency leads to statin-induced myalgia or statins contribution to vitamin D deficiency.

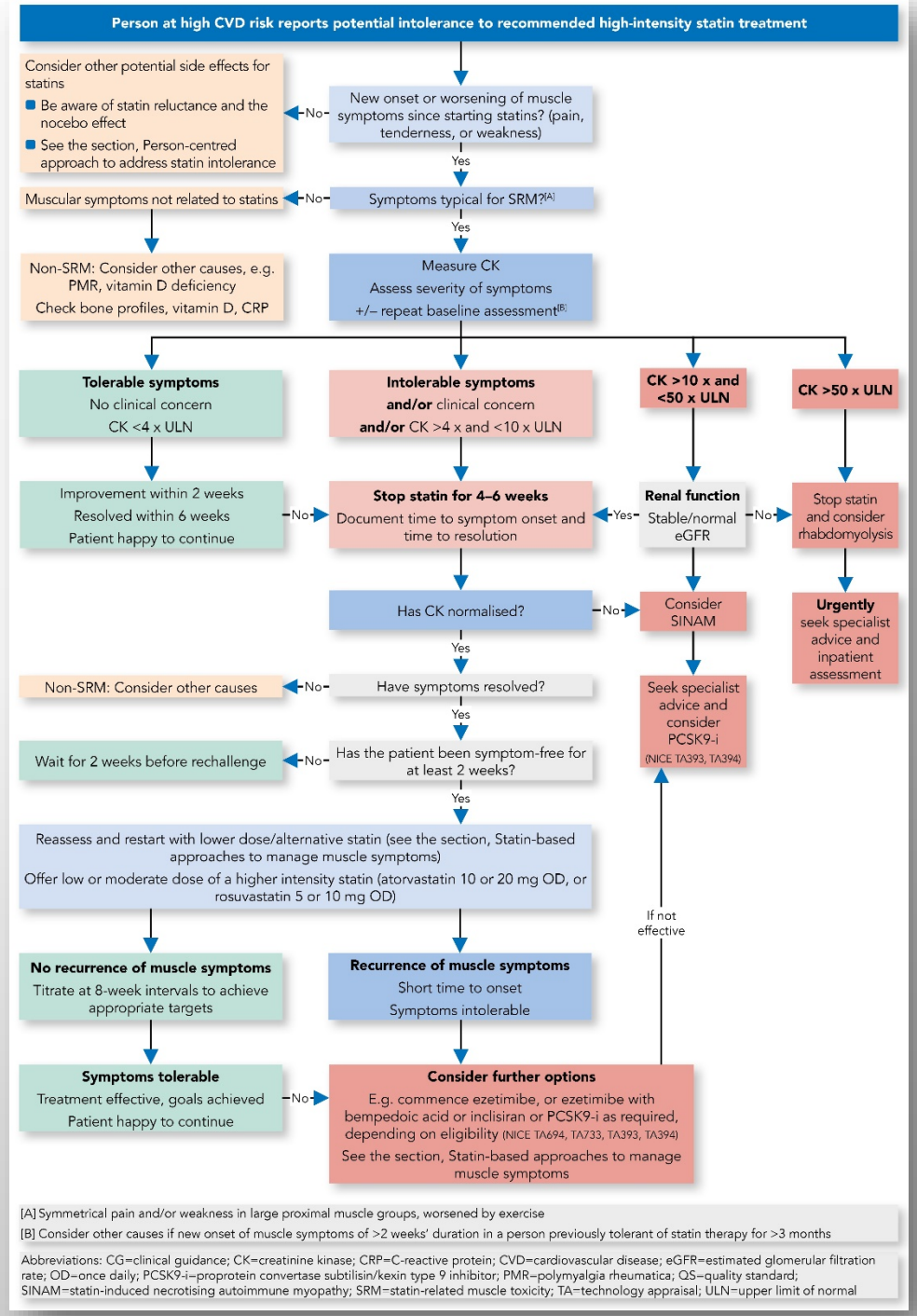
- Normalization of serum vitamin D levels has been shown to facilitate successful statin rechallenge in ≈88% of patients previously intolerant because of SAMS.



Khayznikov M, Hemachrandra K, Pandit R, Kumar A, Wang P, Glueck CJ. Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation. *N Am J Med Sci*. 2015;7:86–93. doi: 10.4103/1947-2714.153919

Table 5. Approaches to Minimizing Adverse Effects of Statins

For the present
1 Reduce the dose of statin, alternate daily dosing of statin, or switch to weaker statin
2 Add ezetimibe, bile acid sequestrants, niacin, fibrates, proprotein convertase subtilisin/kexin 9 antagonists/antibodies
Possible treatments worth considering
1 Supplement with Coenzyme Q10 200 to 400 mg twice daily
2 Supplement with L-carnitine 500 to 1000 mg twice daily
In future
1 Squalene synthase inhibitors?
2 Other new therapies in development



[A] Symmetrical pain and/or weakness in large proximal muscle groups, worsened by exercise

[B] Consider other causes if new onset of muscle symptoms of >2 weeks' duration in a person previously tolerant of statin therapy for >3 months

Abbreviations: CG=clinical guidance; CK=creatinine kinase; CRP=C-reactive protein; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; OD=once daily; PCSK9-i=proprotein convertase subtilisin/kexin type 9 inhibitor; PMR=polymyalgia rheumatica; QS=quality standard; SINAM=statin-induced necrotising autoimmune myopathy; SRM=statin-related muscle toxicity; TA=technology appraisal; ULN=upper limit of normal

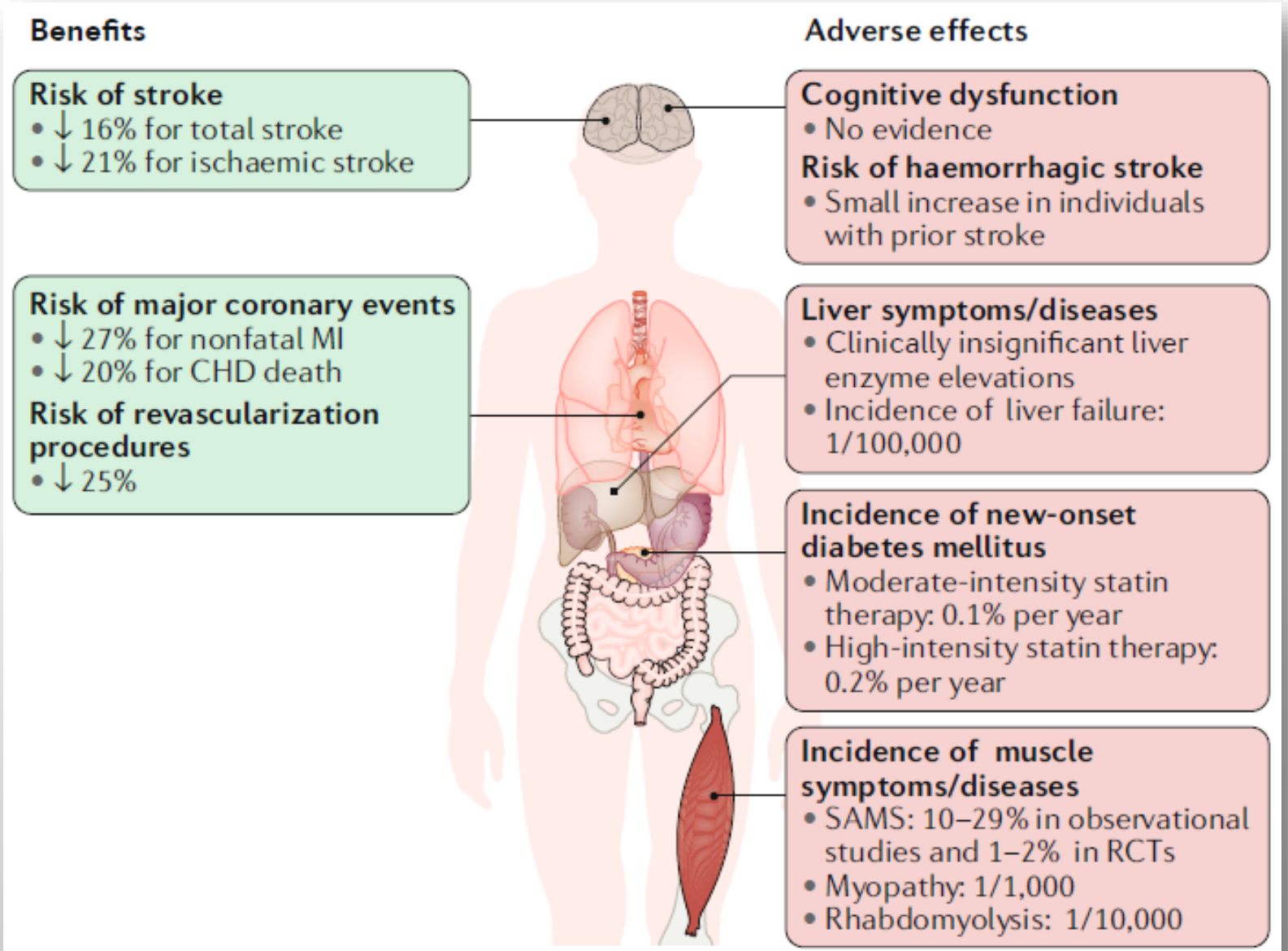
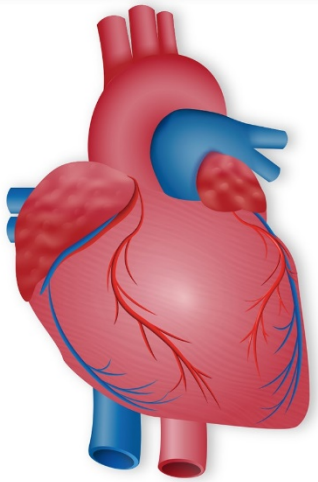


Fig. 1 | **Clinical benefits and potential adverse effects of statin therapy.** The

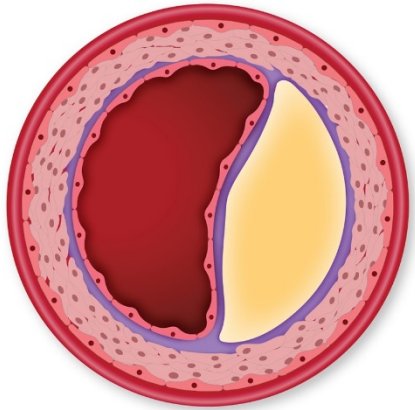
Approach to Statin Intolerance

Discussion and shared decision making with patient

Assess ASCVD risk and share with patient their risk of cardiovascular events and expected risk reduction with statins



35-40% reduction in heart attack, stroke, revascularization or death



Stabilize plaque if LDL-C <70 mg/dl (1.8 mmol/L)

Evaluate for other medical conditions (e.g. hypothyroid, vitamin D deficiency) or drug interactions

If on statin and having muscle or other symptoms: propose a 1-month holiday – AND – a rechallenge to assess for recurrence of those symptoms

Can try non-daily dosing of ultra low dose statin (e.g. rosuvastatin 2.5 mg 3x/week)

If intolerant of all statins – move to non-statins: ezetimibe, PCSK9 inhibitor (or bempedoic acid or bile acid sequestrants)

ESC Guidelines approach

Use maximally tolerated statin +/- ezetimibe +/- PCSK9 inhibitor to titrate to ESC goal based on cardiovascular risk

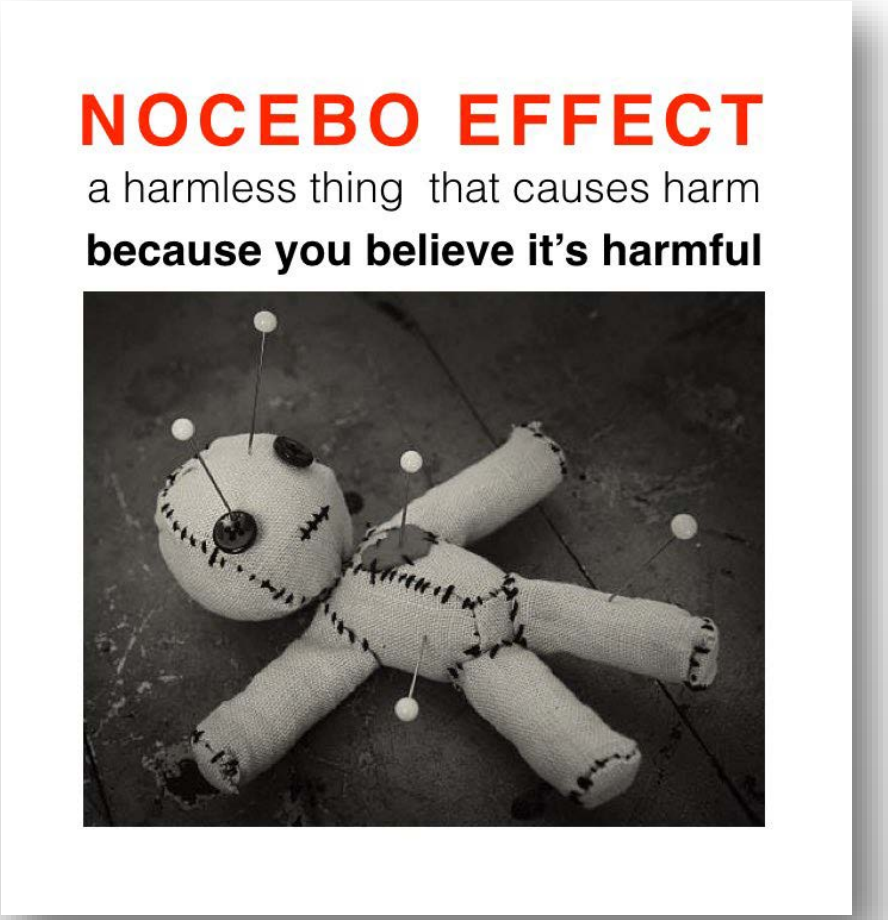
Statin Resistance,

Statin Intolerance,

Statin Toxicity,

Nonadherence to Statins,

Statin Adverce Effects.



Təşəkkür edirəm....