European Heart Journal Supplements (2017) **19** (Supplement D), D55–D63
The Heart of the Matter
doi:10.1093/eurheartj/sux020

ANMCO Position Paper: diagnostic–therapeutic pathway in patients with hypercholesterolaemia and statin intolerance

Michele Massimo Gulizia, FACC, FESC (Coordinator)[1]*, Furio Colivicchi, FACC, FESC (Coordinator)[2], Marcello Arca[3], Maurizio Giuseppe Abrignani[4], Gian Piero Perna[5], Gian Francesco Mureddu[6], Federico Nardi, FACC, FESC[7], and Carmine Riccio[8], on behalf of the Italian Association of Hospital Cardiologists (ANMCO)

[1]*Cardiology Department, Ospedale Garibaldi-Nesima, Azienda di Rilievo Nazionale e Alta Specializzazione "Garibaldi", Via Palermo 636, 95122 Catania, Italy*
[2]*Cardiology Department, Presidio Ospedaliero San Filippo Neri, Rome, Italy*
[3]*Atherosclerosis Center, Policlinico Umberto I, Sapienza Università di Roma, Rome, Italy*
[4]*Cardiology Department, Ospedale Civile Sant'Antonio Abate, Erice (Trapani), Italy*
[5]*Cardiology Department, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy*
[6]*Cardiology Department III, A.O. San Giovanni-Addolorata, Rome, Italy*
[7]*Cardiology Department, Ospedale Castelli, Verbania, Italy*
[8]*Cardiology and Cardiac Rehabilitation Unit, A.O. Sant'Anna e San Sebastiano, Caserta, Italy*

***Revised by*: Pasquale Caldarola, Giacomo Chiarandà, Mario Chiatto, Mauro Mennuni, Marino Scherillo, Massimo Uguccioni**

Consensus Document Approval Faculty in Appendix

KEYWORDS
Intolerance;
Diagnostic–therapeutic pathways;
Statins

Statins are a class of drugs used to lower total and low-density lipoprotein (LDL)-cholesterol. Clinical trials performed over the last 25 years have shown that these agents are effective in improving cardiovascular outcomes in several different clinical settings. However, in some cases statin treatment may be associated with significant side effects and adverse reactions. The occurrence of these adverse events during statin therapy may cause discontinuation of treatment, and hence the impossibility of achieving recommended lipid goals. The clinical condition in which patients experience major unacceptable symptoms and/or develop laboratory abnormalities during statin therapy is defined as statin intolerance. This document outlines the diagnostic and therapeutic pathways for the clinical management of patients with hypercholesterolaemia and statin intolerance.

Introduction

Statins are drugs registered for the treatment of hypercholesterolaemia. The clinical effect of these drugs is mainly linked to a reduction of the plasmatic level of total

*Corresponding author. Tel: 095/7598502, Fax 095/7598505; Email: michele.gulizia60@gmail.com

cholesterol and of the low-density lipoprotein (LDL) fraction which has a central role in the genesis of atherosclerotic cardiovascular disease. A reduction in plasmatic lipid levels is obtained by inhibition of hepatic3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the key enzyme in cholesterol biosynthesis. Depletion of hepatic intracellular cholesterol triggers an increase in the expression of surface receptors for plasmatic LDL-cholesterol (LDL-C) which facilitates its removal from the plasma. The result is a reduction in the plasmatic cholesterol level due to reduced synthesis and increased catabolism.[1]

There are differences among statins in terms of pharmacokinetics, metabolism, excretion route, and efficacy in decreasing plasmatic cholesterol. Simvastatin and lovastatin are both given as prodrugs, whereas other statins are taken in the active form. Pravastatin and rosuvastatin are hydrophilic compounds, but other statins are lipophilic. Lipophilic compounds are metabolized in more hydrophilic compounds as the latter are better able to be eliminated via urinary excretion. Instead, hydrophilic statins are eliminated without being metabolized, thus resulting in less inter-drugs interactions. Excluding pravastatin and rosuvastatin, all the other statins are metabolized in the liver by the isoenzymes of cytochrome P450 (*Table 1*).

The introduction of these drugs in clinical practice has radically changed management of patients with high cardiovascular risk, both in primary and secondary prevention. In all clinical studies conducted in the last 25 years, the reduction of cholesterolaemia values obtained by statins has always been linked with a significant reduction in atherosclerotic cardiovascular morbidity.[1,2] The clinical effect of statins seems independent of the molecule used, being instead completely ascribable to the statin's efficacy in reducing LDL-C levels.[1,2] Meta-analysis shows that each 1 mmol/L (40mg/dL) LDL-C reduction, regardless of the statin used, reduces the relative risk of ischemic cardiac events by 25%, the relative risk of all-cause mortality by 10%, and the ictus risk by 17%.[1,2] Being a relative risk reduction, the clinical benefit of statin therapy is independent of single patient characteristics. The probability of adverse cardiovascular events decreases proportionally to the initial risk profile, therefore the higher the initial cardiovascular risk, the more considerable the benefit.

Scientific evidence shows a progressive increase in both prescription and pharmaceutical expense for statins in western countries. In Italy, for example, the statin consumption in 2014 reached a defined daily dose of 66 per 1000 inhabitants per day, which reflects an approximately 4% increase in consumption as compared to the previous year.[3] Data analysis of pharmaceutical expense covered by public insurance shows that statins have an overall cost of 646 million euros for the Italian National Health Service (SSN) with a total cost of about 11 euros per person per year.[3] This cost is quite high considering the lack of patent protection on almost all of these drugs. On the whole, statins account for 3.2% of total SSN pharmaceutical costs.[3]

Safety and tolerability of statin therapy

Statins have proven to be safe in the great majority of patients who use them. However, like all drugs, they are not completely without adverse reactions and side effects. The onset of these negative events is the main reason for insufficient adherence to statin treatment and for the resulting failure to meet therapeutic targets. Statin side effects are linked to four main risk factors.[4-6]

(1) Statin dose: as for all drugs, side effects depend on the dose used and have been observed especially during the so-called 'intensive treatment', when high doses of lipophilic statins are used (atorvastatin and simvastatin).
(2) Exogenous factors: alcohol consumption and excessive physical activity may cause myalgia and an increase in muscle enzyme levels during statin treatment.
(3) Endogenous factors: advanced age, female gender, and low body weight are all conditions that can predispose patients to statin side effects, especially in cases of systemic disease (renal and hepatic dysfunctions, untreated hypothyroidism) and congenital metabolic muscle disease (McArdle disease, carnitinepalmitoyl transferase II deficiency). A complete list of endogenous and exogenous factors associated with statin side effects is reported in *Table 2*.
(4) Drug interaction: 58% of the most severe side effects are linked to an interaction with concomitant drugs and occur mostly in cases where statins

Table 1 Clinical pharmacokinetics of the statins

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Sinvastatin
Dose, mg	10-80	40-80	20-40	20-40	5-40	10-40
LDL-c reduction, %	30-55	25-35	25-35	25-35	35-60	25-40
Optimal time of administration	Any time	Evening	With meals	Evening	Any time	Evening
Absorption	30%	98%	30%	40%	50%	70%
Solubility	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Primary metabolic pathway-cytochromes	CYP3A4	CYP2C9	CYP3A4	CYP3A4-minimal	CYP2C9-minimal	CYP3A4
Metabolites	Active	Inactive	Active	Mainly inactive	No	Active
Renalexcretion	2%	6%	30%	60%	10%	15%
Hepaticexcretion	90%	90%	70%	40%	90%	85%

LDL-C, low-density lipoprotein-cholesterol.

metabolised by cytochrome P450 were used. Therefore, concomitant use of drugs known to interact with statins has to be carefully evaluated. *Table 3* reports the list of interacting drugs.

Muscle-related adverse effects

The most prevalent side effects associated with statin treatment are musculoskeletal complaints referred to in scientific literature as *statin-associated muscle symptoms* (SAMS). Muscle pain can be persistent and symmetrical, typically involving proximal limb muscles and often associated with weakness and stiffness.[4,7,8] Myalgia usually occurs at the beginning of statin treatment (within the first 4 weeks to 6 months of statin exposure), has a widely variable intensity, and, in the majority of cases, occurs without an increased plasmatic level of cytolysis muscle markers, such as creatine kinase (CK).[4,7,8]

A mild increase in CK levels can also be observed in the absence of myalgia. In rare cases 'myopathy or myositis' (the presence of myalgia with a CK elevation typically 10-fold higher than the normal upper limit of normal) or 'rhabdomyolysis' (muscle symptoms associated with a CK level >10 000 U/L or 40-fold higher than the normal upper limit, myoglobinuria, and acute renal failure) can occur.[4,7,8]

Overall diagnosis of statin muscle injury can be challenging in clinical practice. To overcome these difficulties, several criteria for defining myopathy induced by statins have been proposed. The recent European Atherosclerosis Society Consensus Panel[4] avoiding the use of the term 'intolerance', suggests classifying SAMS based on symptoms and the increase of the CK plasmatic level. Based on these criteria several distinct cases can be identified (*Table 4*).

Over the last 25 years, clinical trials have reported a SAMS incidence of approximately 13% in both patients who received statins and in those who received a placebo[9] (*Table 5*). Rhabdomyolysis has seldom been observed, with a rate of 0.03% in patients treated with statins and of 0.02% in patient treated with placebo. Withdrawal of treatment due to muscle problems has been reported in about 0.5% of participants, with a rate of 0.49% in patients treated with statins and of 0.47% in patients treated with a placebo. However, it must be highlighted that in the majority of clinical trials, SAMS are not systematically evaluated and there is a lack of a standard definition for myalgia and myopathy. Furthermore, CK values during treatment are often not adequately collected and reported.[9]

Data gathered from the real world depicts a different scenario than that reported in clinical trial. Based on observational studies, it has been estimated that 25–30% of patients starting statin treatment develop SAMS during follow-up.[10,11] These adverse events lead to treatment discontinuation in the majority of cases.[10] In patients who had significant complaints or considerable CK elevation, the treatment is often withdrawn permanently.[10,11] However, the majority of patients who suspend statin

Table 2 Exogenous and endogenous risk factors for statin side effects

Risk factors	
Anthropometric	Advanced age
	Female sex
	Small body weight
	Asian ethnicity
Concomitant disease	Acute infections
	Hypothyroidism
	Chronic kidney disease
	Liver cirrhosis
	Biliary tree obstruction
	Hepatitis C virus infection
	Vitamin D deficiency
Medical history	Previous evidence of CK elevation
	History of muscle pain
	Neuromuscular disease
	History of statin adverse reactions
Other factors	Drug addiction
	Alcohol abuse
	Strenuous exercise
	Grapefruit juice consumption

CK, creatine kinase.

Table 3 Main drug–statin interactions

Drugs	Statin to use or to avoid
Fibrates (fenofibrate)	Treatment with statins is possible but it is necessary to check CK level because of the myopathy risk
Cyclosporine	Statin use not recommended
Antifungals (azoles)	Statin use not recommended
Macrolide antibiotics	Statin use not recommended
Proteaseinhibitors	Therapy is possible with pravastatin
Amiodarone	Use of simvastatin and lovastatin not recommended
Dronedarone	Use of simvastatin and lovastatin not recommended
Non-dihydropyridine calcium channel blockers	Use of simvastatin not recommended
Ranolazine	Use of simvastatin not recommended

CK, creatine kinase.

Table 4 Definitions of statin-associated muscle symptoms according to the European Atherosclerosis Society EAS Consensus Panel

Symptoms	Biomarkers	Comment
Muscle pain, weakness, cramps	Normal CK	Usually named 'myalgia'—causal relationship with statin treatment not always certain or obvious. Detailed clinical assessment is advisable.
Muscle pain, weakness, cramps	CK>ULN <4× ULN	Muscle symptoms associated with modest CK increase are often ascribable to physical activity. A detailed clinical study (thyroid function check) and cardiovascular risk reassessment are advisable. Statin discontinuation may be indicated.
Muscle pain, weakness, cramps	CK > 4 <10× ULN	Condition associated with higher risk of clinically significant muscle problems. Statin discontinuation is appropriate.
Muscle pain, weakness, cramps	CK > 10× ULN	Indicated as 'myositis' or 'myopathy' by international regulatory agencies. It has an incidence of about 1 per 10 000 per year. Intense proximal muscle pain associated with loss of strength. It is often associated with underlying muscle disease. Statin discontinuation is necessary.
Muscle pain, weakness, cramps	CK > 40× ULN	Referred to as rhabdomyolysis if associated with impairment of kidney function and/or myoglobinuria
Absent	CK >ULN < 4× ULN	CK elevation found incidentally during statin treatment. Useful to assess thyroid function and the possibility of an exercise-related CK elevation.
Absent	CK > 4× ULN	Unclear clinical significance. Repeated checks of CK value end accurate clinical evaluation are necessary.

CK, creatine kinase; ULN, upper limit of the normal range.

Table 5 Incidence of muscle problems associated with statins in clinical studies[9]

Variables	Statin group (%)	Placebo group (%)	*P*-value
Any muscle problems	12.7	12.3	0.06
CK > 5× ULN	0.3	0.1	0.11
CK > 10× ULN	0.2	0.1	0.28
Rhabdomyolysis	0.03	0.02	0.48
Treatment discontinuation because of muscle symptoms	0.49	0.46	0.75

CK, creatine kinase; ULN, upper limit of the normal range.

therapy because of SAMS eventually restart the treatment with a different statin without developing further complications.[10,11] Discrepancy between real world and clinical trial data might be explained, at least in part, by patient selection criteria in clinical trials which often excludes subjects with a concomitant disease potentially predisposing them to statin adverse events. However, rhabdomyolysis incidence in the real world is very low, similar to the 0.01% incidence found in clinical trial.[12]

In closing, several clinical conditions can be associated with muscle problems and biochemical abnormalities similar to those typical of statin myopathy (*Table 2*). Among these conditions are advanced age, severe chronic renal disease, untreated hypothyroidism, vitamin D deficiency and neuromuscular disease.[4-6] Furthermore, unfavourable interaction with several drugs may also be relevant in clinical practice, increasing plasmatic concentration of statins and the risk of adverse reactions[4-6] (*Table 3*).

Abnormalities in hepatic function

Asymptomatic alteration in hepatic function tests (transaminases elevation >3 higher than the normal upper limit) has been found in 0.5–2% of patients treated with statins.[13] These abnormalities are more common in patients who take higher statin doses and usually occur within the first 4–12 weeks of treatment.[14] In most cases, hepatic abnormalities are ascribable to adverse drug–drug interactions rather than to statin toxicity.[14] In clinical practice, detection of a hepatic alteration almost unavoidably leads to statin discontinuation.[15]

Other adverse reactions and side effects

Although SAMS and asymptomatic alterations in hepatic function are the most frequent adverse events during statin treatment, other side effects can be observed with a much lower frequency[5] (*Table 6*).

How to define statin intolerance in clinical practice

During statin treatment, the occurrence of the adverse events previously described might require a dosage change (lowering the dose or reducing the dosage frequency) or treatment discontinuation, either temporarily or permanently. In clinical practice, the term 'statin intolerance' (SI) refers to the occurrence of clinically significant side effects or adverse reactions that cause treatment discontinuation. To date, a consensus on a standardized definition of SI does not exist in Italy. This void has very relevant clinical and normative implications, one of which being the *employment of* new non-statins cholesterol-lowering agents (PCSK-9 inhibitors) which would potentially be useful in case of SI. In general, SI can be defined as a condition in which unacceptable patient symptoms or biochemical

Table 6 Possible side effects associated with statin treatment

Organ/system	Side effects
Respiratory system	Risk of interstitial lung disease increased by about 0.01% Risk of upper respiratory tract infection increased by 1%
Nervous system	Headache increased by 2–17% Dizziness increased by 1–4% Asthenia increased by 1–4%
Endocrine	Increase of the relative risk of diabetes mellitus. One extra case every 255 patients after four years of treatment
Eye	Possible increase of cataract risk
Gastrointestinal tract	Constipation risk increased by 1–5% Dyspepsia risk increased by 1–5%

parameter alterations occur during statin treatment which suggests a significant clinical risk. Both symptoms and biohumoral abnormalities should be reversible and conclusively linked to statin treatment. The occurrence of these events can lead to therapy discontinuation.[16] In the majority of cases, SI is characterized by disabling symptoms perceived as unacceptable by patients which leads to the discontinuation of treatment. Cases in which SI is related to the occurrence of asymptomatic alterations in laboratory parameters are less frequent. Nevertheless, in a non-negligible percentage of cases statins are withdrawn by a physician because of an overstated perception of clinical risk associated with the treatment, even when relevant clinical complications are absent.[15-17] The correct identification of an actual condition of SI is particularly important in order to avoid unnecessary treatment discontinuation. Statin withdrawal can expose at-risk patients to adverse cardiovascular events.[15-17]

The international definitions

In recent years, several scientific and professional associations have aimed to establish a more concrete definition of the clinical condition termed SI. Various definitions have been proposed for this complex phenomenon.[16-19] Of particular interest is the work published on the SI issue by the Canadian Working Group Consensus Conference on Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance in 2013.[18] The Canadian working group proposes defining SI as a clinical syndrome characterized by:

(1) Inability to use statins for reduction of LDL-C and cardiovascular risk because of symptoms or biomarker abnormalities that are temporally linked to starting or increasing dose of treatment. Correlation between symptoms or laboratory alterations and statins can be confirmed by treatment withdrawal and rechallenge.
(2) SI can be either ‘complete’ (intolerance to any statin at any dose) or ‘partial’ (intolerance to some statins at some doses).
(3) Symptoms or laboratory alterations not ascribable to modifiable clinical conditions (such as concomitant disease, drug interactions).

In 2014, the National Lipid Association (NLA) of the USA also presented a document on SI,[19] which proposes identifying SI in light of all symptoms, signs and laboratory abnormalities attributed by the patient or by the physician to statin therapy. Symptoms are perceived by the patient as disabling when they interfere with normal daily activities, leading to a discontinuation or reduction of the treatment dose. In some cases, the decision to discontinue or reduce the treatment dose can be made by a physician due to the occurrence of asymptomatic laboratory abnormalities (increase of CK or transaminases values) suggesting a significant risk of adverse events. The NLA highlights the need for assessing each individual case in depth, taking into account every aspect of physician–patient communication, and supporting a patient-centred approach. The NLA discourages the discontinuation of treatment for a symptomatological framework which is not actually ascribable to a possible statin toxicity. Furthermore, the NLA proposes a pragmatic and actionable definition:

> Statin intolerance is a clinical syndrome characterized by the inability to tolerate at least 2 statins: one statin at the lowest starting daily dose AND another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease). Specifically, the lowest starting statin daily dose is defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, and pitavastatin 2 mg.

Operational summary for clinical practice

In many cases, there may be difficulties in making an accurate diagnosis of SI. A simplified approach focusing on the identification and characterization of this condition can be very useful in clinical management of these cases. A diagnosis of SI should be considered in the presence of muscle symptom characteristics, the occurrence of CK and/or transaminase elevation, and their temporal association with statin use, discontinuation, and rechallenge.

We propose the following definitions:

(1) ‘Muscle statin intolerance’: the patient complains of clinically relevant muscle symptoms, with or

without significant CK increase, which disappear when the treatment is withdrawn and recur after the rechallenge;
(2) 'Hepatic statin intolerance': the patient has a significant transaminase elevation of (>3 fold higher the normal upper limit) that disappears when statins are withdrawn and recurs after the rechallenge;
(3) 'Complete statin intolerance': the adverse reactions occur with all statins at any dose;
(4) 'Partial statin intolerance': the patient can tolerate a reduced dose of any statin.

Diagnostic–therapeutic pathway in patients with muscle statin intolerance

In the event that a patient complains of muscle symptoms during statin treatment, it is necessary to first of all check the CK levels (*Figure 1*). In general, it is always advisable to assess CK values before starting treatment with any statin.

If high CK levels are found (CK values in the rhabdomyolysis range) it is necessary to withhold drug intake, carefully monitor renal function, and, if need be, to arrange hospitalization. When CK values are >4 times higher than the normal upper limit, it is recommended to stop the drug and evaluate the presence of factors that increase myopathy/myalgia risk.[1] More specifically, it is necessary to exclude the presence of hypothyroidism, rheumatic polymyalgia, osteo-articular disease, or recent intense physical activity. If there are not secondary causes, a rechallenge, using the same statin previously used or a different one based on the pharmacokinetic characteristics, is encouraged. In the event that muscle symptoms recur (regardless of whether or not they are associated with CK increase), the presence of an SI can be considered confirmed.

The management of patients with 'confirmed SI' should contemplate:

(1) a further attempt at prescribing another statin, different from that/those initially used (hydrophilic vs lipophilic molecules) and/or with different metabolism (CYP3A4 o CYP2C9), starting with a minimum dosage then increasing the dose until the optimal dose is achieved;
(2) prescription of a low statin dose combined with ezetimibe (intestinal cholesterol absorption inhibitor);
(3) prescription of statins with longer half-life (atorvastatin and rosuvastatin) administered on alternate days or every 2 days at low/minimum dosages;
(4) ezetimibe prescription as monotherapy or combined with nutraceuticals, based on the target of LDL-c reduction.

The sequence of these interventions must take into account the relative efficacy of single options. Indeed, using ezetimibe or nutraceutical allows only a modest LDL-c reduction when compared to statin treatment. In conclusion, an additional possibility is offered by the new non-statin lipid lowering agents, particularly the PCSK9 protein inhibitors. However, to date the cost of these drugs (alirocumab and evolocumab) is not covered by the SSN in Italy.

Diagnostic–therapeutic pathway in patients with hepatic statin intolerance

It should be take into account that an increase of transaminases values <3 times the normal upper limit is not a contraindication to statin therapy (*Figure 2*). Several patients with diabetes, metabolic syndrome, or obesity have transaminases values fluctuating around 1–3 times the normal upper limit values[20] because of a non-alcoholic steatohepatitis. In the case that an increase >3 times the normal value occurs during statin treatment, it is recommended to discontinue the drug. There is not a consensus on when the best time is to recheck transaminases values. In some clinical trials with statins, hepatic function tests were rechecked after 2–3 weeks, and in 70% of these cases the values had normalized. Some authors suggest repeating the tests after 6 weeks.[21]

After verifying the absence of other factors which could be responsible for transaminase increases, a rechallenge should be considered in which the new intake of a statin is prescribed (either the same previously used, or a different one based on pharmacokinetic characteristics). If a transaminase increase reoccurs, different options should be contemplated. Since a greater incidence of hepatic abnormalities occurs when higher statin doses are used, it may be more appropriate to prescribe low doses or non-daily dosing regimens. Transaminase levels should be checked monthly during the first 3–4 months, and then every 3 months thereafter. In addition, the use of statins not metabolized in the liver (rosuvastatin or pravastatin) or non-statin compounds may also be considered.

Conclusions

Currently, statins remain a mainstay of hypercholesterolaemia treatment and it is not ethical to deny this therapy to patients with high or very-high cardiovascular risk (like those with diabetes or documented cardiovascular disease). On the other hand, the use of this 'lifesaving' treatment in cases of SI opposes the basic therapeutic principle of not causing damage (*primum non nocere*). Therefore, it is fundamental to implement unanimous and unambiguous procedures which can guarantee the continuation of an optimal lipid-lowering treatment complying with patient safety needs. The diagnostic–therapeutic pathways proposed in this document represent a summary of the current knowledges and of the best available clinical procedures. In conclusion, it is necessary to point out that the diagnostic–therapeutic pathway of each individual patient with SI must be completely and accurately documented. In particular, the rechallenge procedure must be sufficiently verified and each therapeutic change duly recorded. These precautions can safeguard the maximum appropriateness and ensure transparency in public health care resource allotment, especially in light of the high cost of prospective new non-statin drugs.

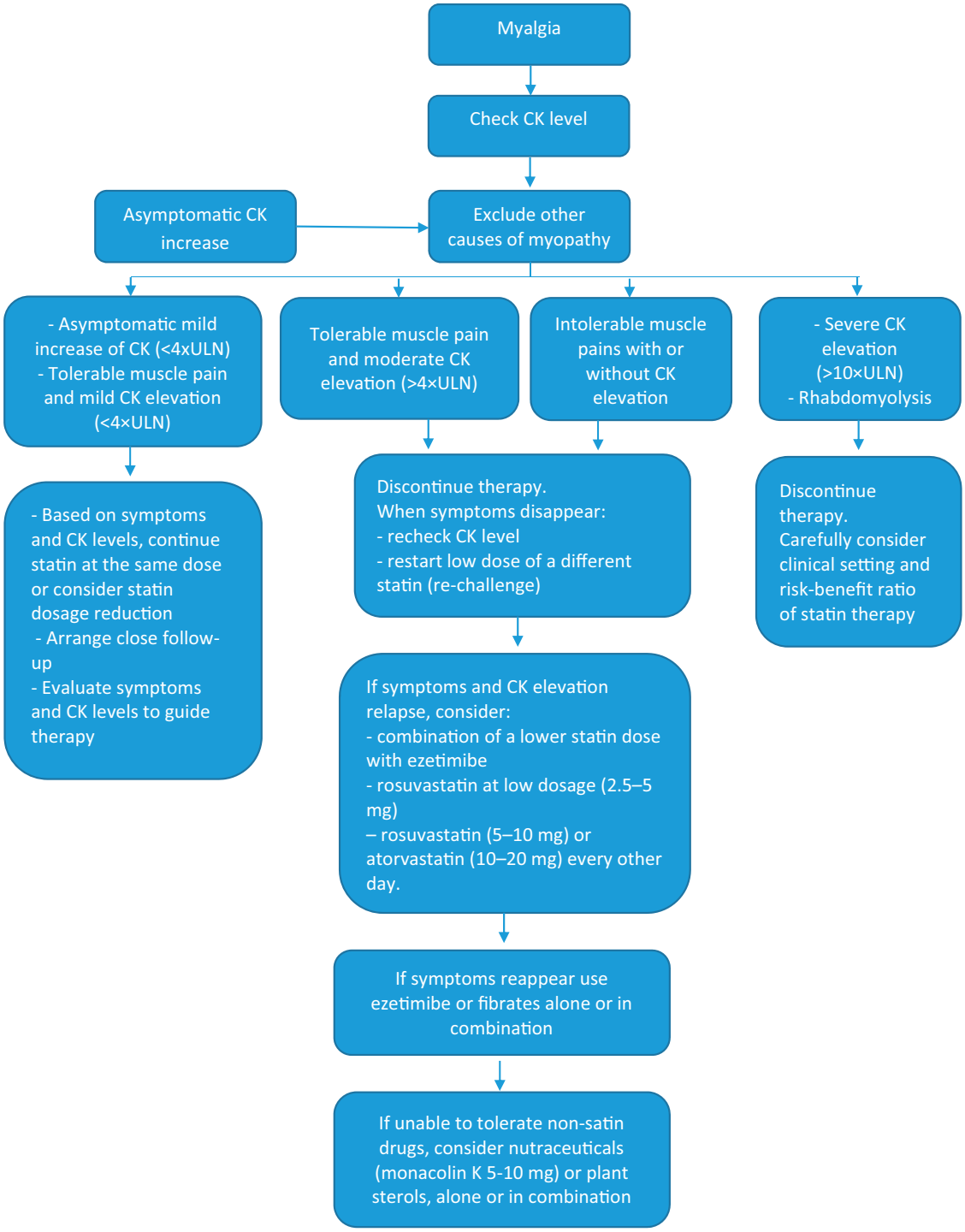

Figure 1 Diagnostic-therapeutic pathway in the patient with muscle statin intolerance. CK, creatine kinase; ULN, upper limit of the normal range.

Consensus Approval Faculty

Alunni Gianfranco, Amico Antonio Francesco, Amodeo Vincenzo, Angeli Fabio, Aspromonte Nadia, Audo Andrea, Azzarito Michele, Battistoni Ilaria, Bianca Innocenzo, Bisceglia Irma, Bongarzoni, Amedeo, Bonvicini Marco, Cacciavillani Luisa, Calculli Giacinto, Capecchi Alessandro, Caporale Roberto, Caretta Giorgio, Carmina, Maria Gabriella, Casazza Franco, Casolo Giancarlo, Cassin, Matteo, Casu Gavino, Cemin Roberto, Chiarella Francesco, Cibinel, Gian Alfonso, Ciccone Marco Matteo, Cicini Maria Paola, Clerico Aldo, D'Agostino Carlo, De Luca Giovanni, De Maria Renata, Del Sindaco Donatella, Di Fusco Stefania Angela, Di Lenarda, Andrea, Di Tano Giuseppe, Egidy Assenza Gabriele, Egman Sabrina, Enea Iolanda, Fattirolli Francesco, Favilli Silvia, Ferraiuolo Giuseppe, Francese

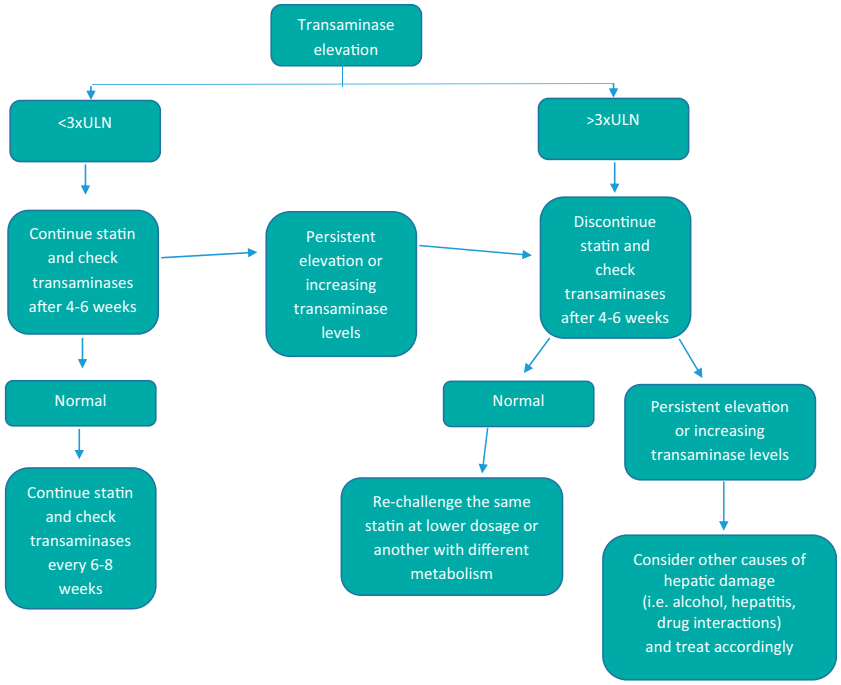

Figure 2 Diagnostic–therapeutic pathway in the patient with hepatic statin intolerance. ULN, upper limit of the normal range.

Giuseppina Maura, Gabrielli Domenico, Geraci Giovanna, Giardina Achille, Greco Cesare, Gregorio Giovanni, Iacoviello Massimo, Khoury Georgette, Ledda Antonietta, Lucà, Fabiana, Lukic Vjerica, Macera Francesca, Marini Marco, Masson, Serge, Maurea Nicola, Mazzanti Marco, Menotti Alberto, Menozzi, Alberto, Mininni Nicola, Moreo Antonella, Moretti Luciano, Mortara Andrea, Mureddu Gian Francesco, Murrone Adriano, Musumeci Giuseppe, Navazio Alessandro, Nicolosi Gian Luigi, Oliva Fabrizio, Parato Vito Maurizio, Parrini Iris, Patanè Leonardo, Pini Daniela, Pino Paolo Giuseppe, Pirelli Salvatore, Procaccini Vincenza, Pugliese Francesco Rocco, Pulignano Giovanni, Radini, Donatella, Rao Carmelo Massimiliano, Roncon Loris, Rossini Roberta, Ruggieri Maria Pia, Rugolotto Matteo, Sanna Fabiola, Sauro Rosario, Severi Silva, Sicuro Marco, Silvestri Paolo, Sisto Francesco, Tarantini Luigi, Urbinati Stefano, Valente Serafina, Vatrano, Marco, Vianello Gabriele, Vinci Eugenio, Zuin Guerrino.

Conflict of interest: none declared.

References

1. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;**37**:2999–3058.
2. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–1681.
3. Gruppo di Lavoro dell'Osservatorio Nazionale sull'Impiego dei Medicinali. L'uso dei farmaci in Italia. Rapporto nazionale anno 2014. Roma, luglio 2015. www.agenziafarmaco.gov.it (15 May 2016).
4. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, Roden M, Stein E, Tokgözoğlu L, Nordestgaard BG, Bruckert E, De Backer G, Krauss RM, Laufs U, Santos RD, Hegele RA, Hovingh GK, Leiter LA, Mach F, März W, Newman CB, Wiklund O, Jacobson TA, Catapano AL, Chapman MJ, Ginsberg N; European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J* 2015;**36**:1012–1022.
5. Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, Aronow WS, Athyros V, Djuric DM, Ezhov MV, Greenfield RS, Hovingh GK, Kostner K, Serban C, Lighezan D, Fras Z, Moriarty PM, Muntner P, Goudev A, Ceska R, Nicholls SJ, Broncel M, Nikolic D, Pella D, Puri R, Rysz J, Wong ND, Bajnok L, Jones SR, Ray KK, Mikhailidis DP. Statin intolerance—an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Expert. *Opin Drug Saf* 2015;**14**:935–955.
6. Arca M, Pigna G. Treating statin-intolerant patients. *Diabetes Metab Syndr Obes* 2011;**4**:155–166.
7. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;**289**:1681–1690.
8. Fernandez G, Spatz ES, Jablecki C, Phillips PS. Statin myopathy: a common dilemma not reflected in clinical trials. *Cleve Clin J Med* 2011;**78**:393–403.
9. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. *Am Heart J* 2014;**168**:6–15.
10. Zhang H, Plutzky J, Skentzos S, Morrison F, Mar P, Shubina M, Turchin A. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med* 2013;**158**:526–534.
11. Newman CB, Tobert JA. Statin Intolerance. Reconciling clinical trials and clinical experience. *JAMA* 2015;**313**:1011–1012.
12. Andrade SE, Graham DJ, Staffa JA, Schech SD, Shatin D, La Grenade L, Goodman MJ, Platt R, Gurwitz JH, Chan KA. Health plan administrative databases can efficiently identify serious myopathy and rhabdomyolysis. *J Clin Epidemiol* 2005;**58**:171–174.
13. de Denus S, Spinler SA, Miller K, Peterson AM. Statins and liver toxicity: a meta-analysis. *Pharmacotherapy* 2004;**24**:584–591.
14. Pastori D, Polimeni L, Baratta F, Pani A, Del Ben M, Angelico F. The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease. *Dig Liver Dis* 2015;**47**:4–11.

15. Colivicchi F, Bassi A, Santini M, Caltagirone C. Discontinuation of statin therapy and clinical outcome after ischemic stroke. *Stroke* 2007;**38**:2652–2657.
16. Stulc T, Ceška R, Gotto AM. Jr., Statin intolerance: the clinician's perspective. *Curr Atheroscler Rep* 2015;**17**:69.
17. Colivicchi F, Tubaro M, Santini M. Clinical implications of switching from intensive to moderate statin therapy after acute coronary syndromes. *Int J Cardiol* 2011;**152**:56–60.
18. Mancini GB, Tashakkor AY, Baker S, Bergeron J, Fitchett D, Frohlich J, Genest J, Gupta M, Hegele RA, Ng DS, Pearson GJ, Pope J. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Working Group Consensus update. *Can J Cardiol* 2013;**29**:1553–1568.
19. Guyton JR, Bays HE, Grundy SM, Jacobson TA; National Lipid Association Statin Intolerance Panel. An assessment by the Statin Intolerance Panel: 2014 update. *J Clin Lipidol* 2014;S72–S81.
20. Argo CK, Loria P, Caldwell SH, Lonardo A. Statins in liver disease: a molehill, an iceberg, or neither? *Hepatology* 2008;**48**:662–669.
21. Anfossi G, Massucco P, Bonomo K, Trovati M. Prescription of statins to dyslipidemic patients affected by liver diseases: a subtle balance between risks and benefits. *Nutr Metab Cardiovasc Dis* 2004;**14**:215–224.