
# STATINS AND MUSCLE DISEASES

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**Department of Neurosciences,**

**University of Messina, Italy**

# DISCLOSURES

In the last two years, Prof. A. Toscano has received from Genzyme-Sanofi, some reimbursements for teaching courses and for the participation to the meetings of global Pompe advisory board.

# Causes of HyperCKemia/Rhabdomyolysis

Muscular damage:

Traumas, burning

Excessive muscular exercise:

- Jogging
- Seizures
- Delirium tremens
- Asthmatic state

Muscle Dystrophies

- DMD/BMD
- Limb-girdle dystrophies

Metabolic Myopathies

- Lipid storage myopathies
- Muscle Glycogenoses
- Mitochondrial disorders

Malignant hypertermia

Inflammatory myopathies

- Polymyositis
- Dermatomyositis

Systemic metabolic disorders

- HypoKaliemia
- Hyponatriemia
- Tireotoxicosis

Iatrogenic disorders

- Statins
- Salicylates
- Anfotericin B
- Tricyclics, neuroleptics
- Steroids
- Lithium
- Antihistamines

Thermal alterations

- Hypotermia
- Hypertermia (“Heat stroke”)

Toxic disorders

- Ethanol
- Heroin
- Carbon monoxide
- Snakes venom
- Coturnism (quail meat)

Infective disorders

- Viral agents
- Bacterial agents
- Fungal agents

# Iatrogenic myopathies

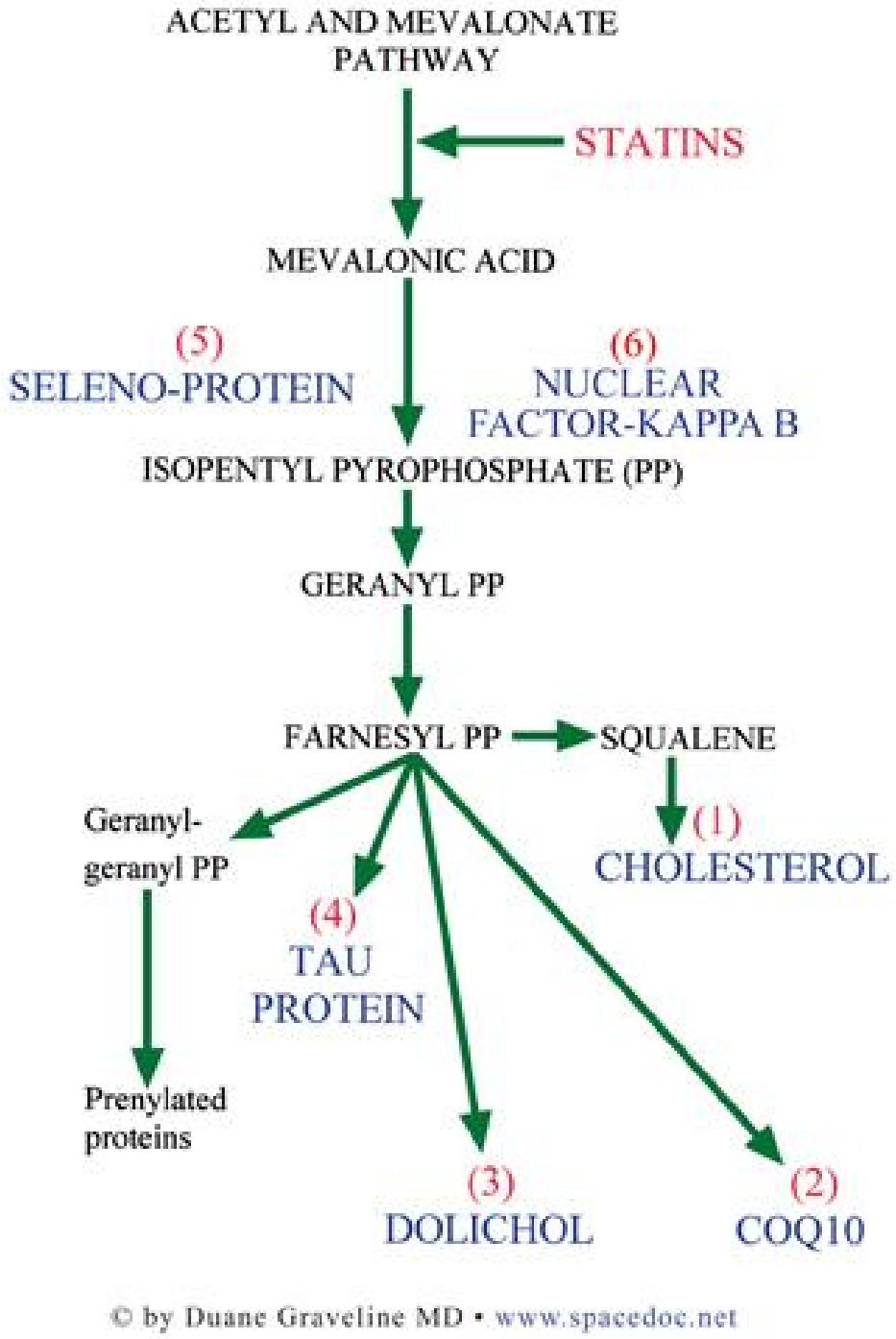
- Necrotizing myopathy and rhabdomyolysis (statins, fibrates, ?-aminocaproic acid, alcohol)
- Mitochondrial myopathy (zidovudine, clevudine, statins)
- Lysosomal/autophagic myopathy and neuromyopathy (chloroquine, hydroxychloroquine, amiodarone, perhexiline)
- Microtubular myopathy and neuromyopathy (colchicine, vincristine)
- Myofibrillar myopathy (emetine, acute quadriplegic myopathy)
- Myopathy with type 2 fiber atrophy (glucocorticoids)
- Inflammatory myopathies (statins, interferon-?, D-penicillamine)

Mastaglia FL- Needham M Curr Neurol Neurosci Rep, 2012

• The 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors, i.e. statins, are the most effective drugs for **prevention and treatment of hypercholesterolaemia and coronary artery disease**

• They are generally well tolerated but recurrent side effects as rhabdomyolysis, myopathy and polyneuropathy have been described (0.1-2%)

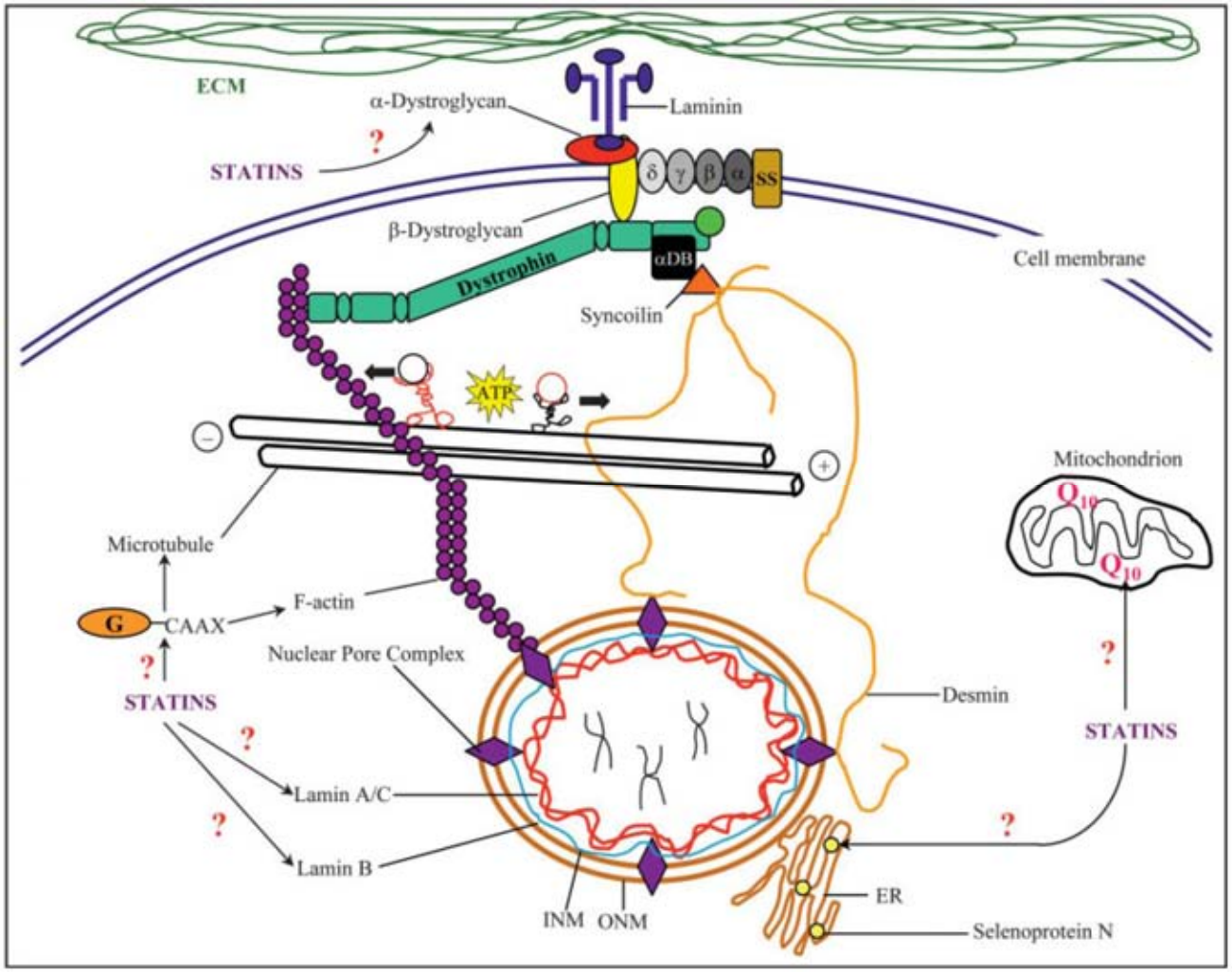
• In some reports, serum levels of coenzyme Q10 (CoQ10-ubiquinone) have been found significantly reduced in asymptomatic subjects treated with statins, supporting the hypothesis of their inhibitory effect on CoQ10 synthesis



*Muscle Nerve* **31:** 572–580, 2005

# MOLECULAR CLUES INTO THE PATHOGENESIS OF STATIN-MEDIATED MUSCLE TOXICITY

STEVEN K. BAKER, MSc, MD



**The biosynthetic pathways of the isoprenoids and cholesterol.**

- **Statins (S) selectively impair the rate-limiting enzyme, -hydroxy--methylglutaryl coenzyme A, which suppresses cholesterol synthesis.**

- Isoprenoids (farnesyl pyrophosphate e geranil pyrophosphate)are secondarily reduced.

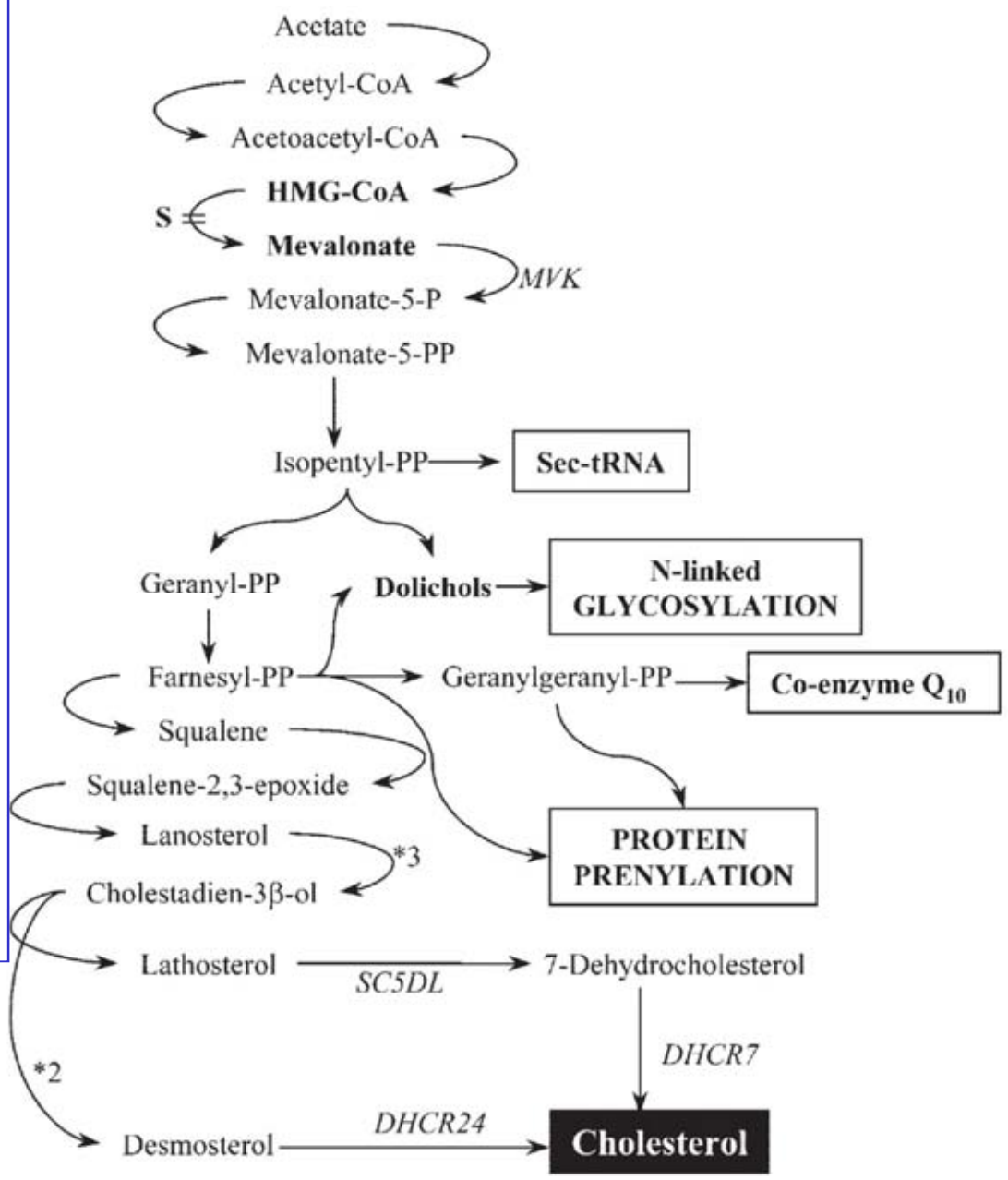
This leads to an impairment of multiple pathways:

1) selenocysteine tRNA isopentenylation,

2) dolichol-mediated *N*-linked glycosylation,

3) protein prenylation

4) **coenzyme Q10 tail synthesis, which may influence antioxidant and respiratory chain capacities within the cell.**

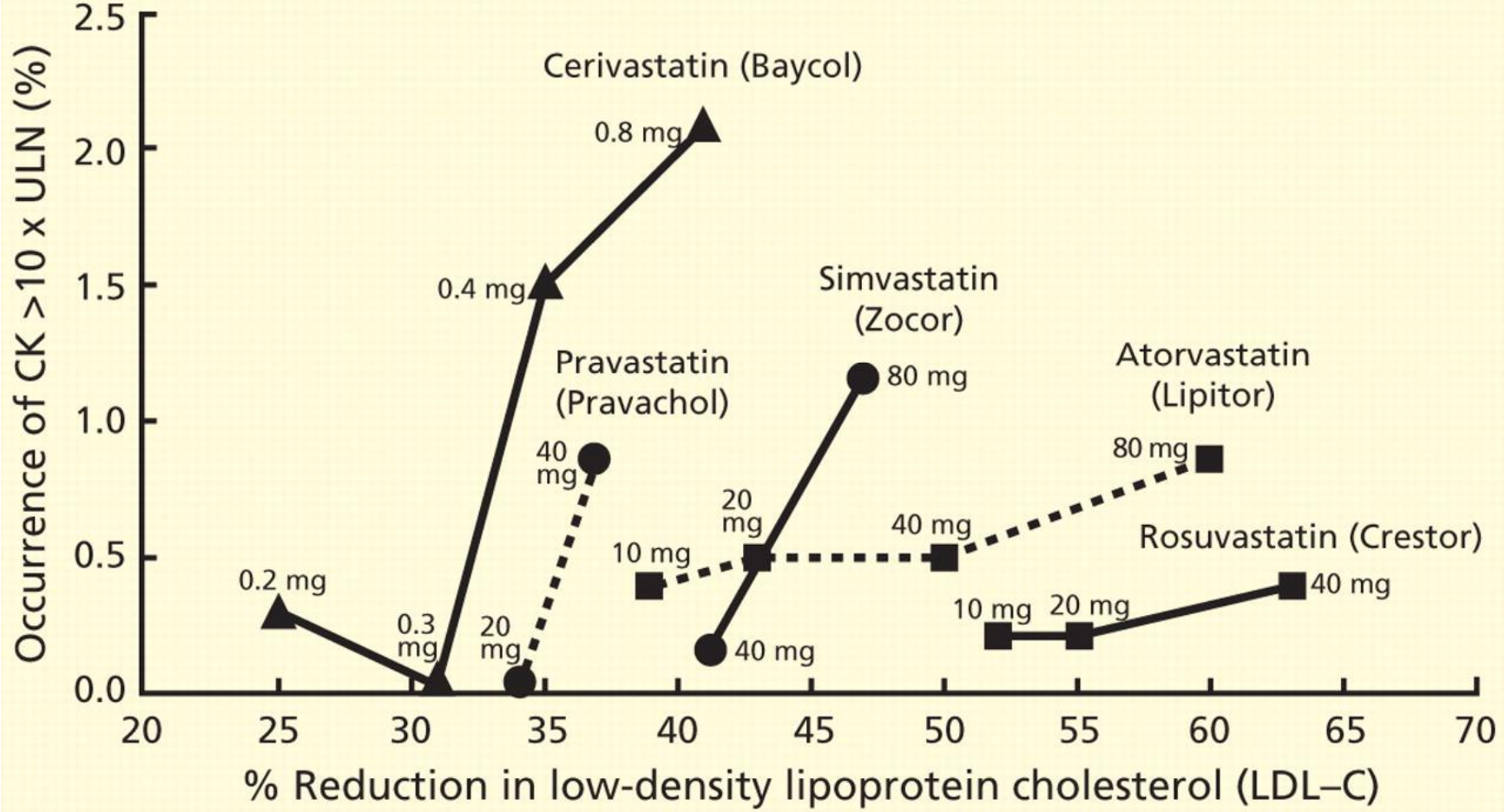


## Table 1. Pharmacologic Characteristics of Statins

| Drug | Dose (mg) | CYP450 Pathway | Bioavailability (%) | Absorption (%) | Lipophilicity | Half-life (h) |
|---|---|---|---|---|---|---|
| Atorvastatin | 10-80 | CYP2C9 (<10%) | 12 | 30 | Yes | 15-30 |
| Fluvastatin | 20-80 | CYP2C9, CYP3A4 (minor) | 19-29 | 98 | Yes | 0.5-2.3 |
| Lovastatin | 10-80 | CYP3A4 | <5 | 30 | Yes | 2.9 |
| Pitavastatin | 1-4 | Glucuronidation, CYP2C9 (minor), CYP3A4 (minor) | 51 | 50 | Yes | 8-12 |
| Pravastatin | 40-80 | None | 18 | 24 | No | 1.3-2.8 |
| Rosuvastatin | 5-40 | CYP2C (<10%), CYP2C19 (minor) | 20 | Rapid | No | 15-30 |
| Simvastatin | 5-80 | CYP3A4, CYP3A5 | <5 | 60-80 | Yes | 2-3 |

*Source: References 6, 9, 20-26.*

# LDL-C reduction and creatine kinase (CK) elevation

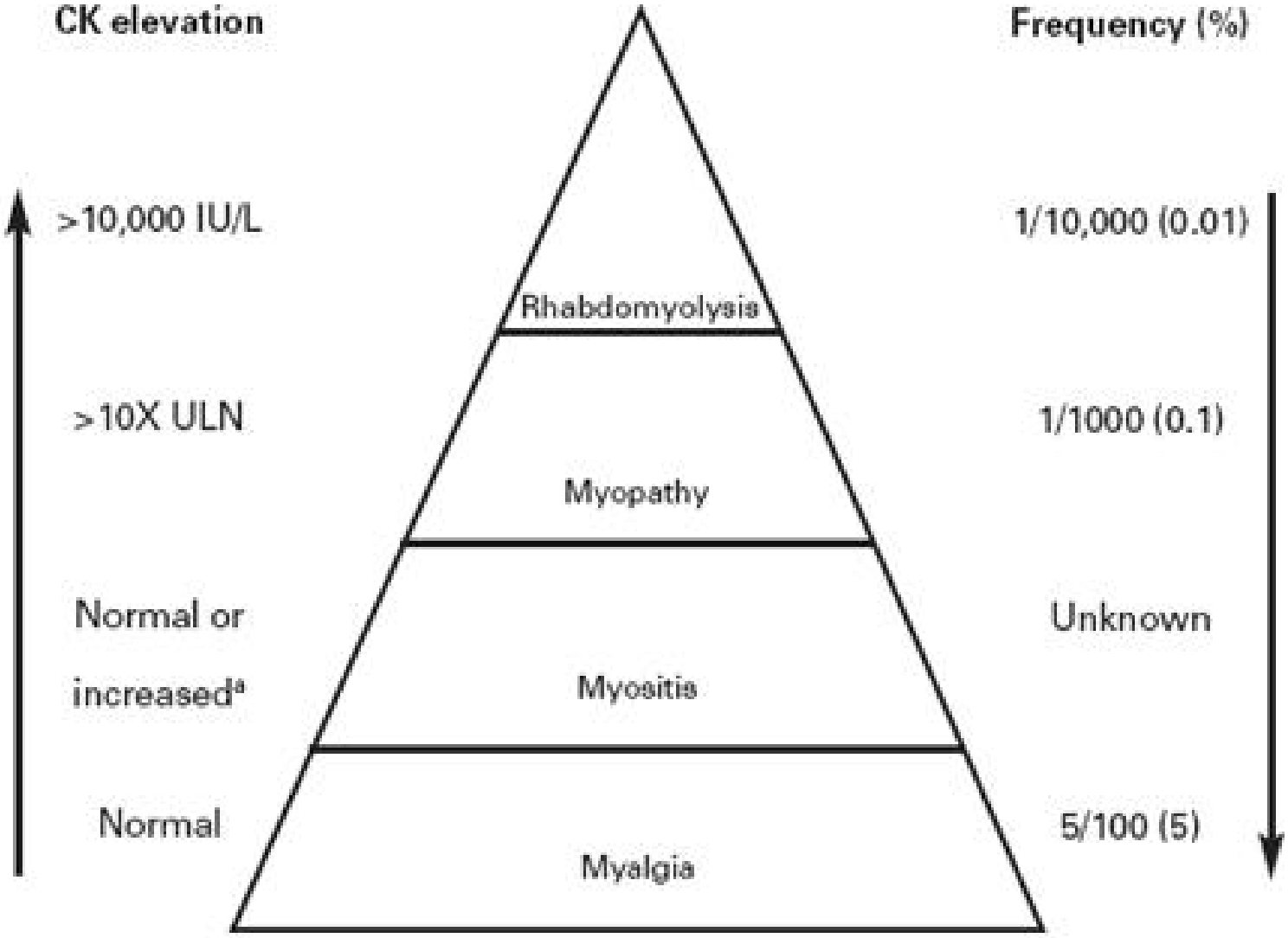


# Diagnostic work up

- History
- Clinical evaluation
- Laboratory investigations
- Neurophysiological studies
- Muscle/Nerve biopsies
- Drug withdrawal

# Statins-induced neuromuscular disorders

- **Myalgias**
- ***HyperCKemia***
- ***Acute Rhabdomyo*lysis**
- **Immune-mediated myopathies**
- **Unmasking of myopathies**
- **Myasthenia gravis**
- **Mitochondrial myopathy**
- **Peripheral neuropathy**


CK elevation
Frequency (%)
>10,000 IU/L
1/10,000 (0.01)
Rhabdomyolysis
>10X ULN
1/1000 (0.1)
Myopathy
Normal or
increased[a]
Unknown
Myositis
Normal
5/100 (5)
Myalgia

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# Necrotizing Myopathy

•Statins have been associated with a variety of inflammatory myopathies i.e., polymyositis, dermatomyositis and necrotizing myopathy

•Anti-HMGCR Abs may play a role in the pathophysiology of the disease.

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

## Statins as a possible cause of inflammatory and necrotizing myopathies

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*Muscle and Nerve 2013*

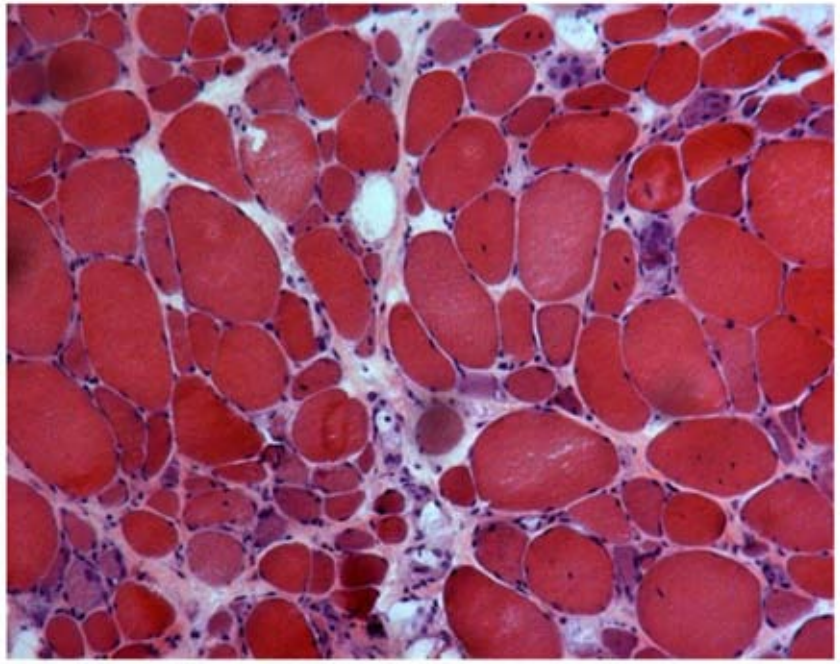
INVITED REVIEW

# STATIN-ASSOCIATED AUTOIMMUNE MYOPATHY AND ANTI-HMGCR AUTOANTIBODIES

PAYAM MOHASSEL, MD[1] and ANDREW L. MAMMEN, MD, PhD[1,2]

**Statin myotoxicity is usually self-limited**, some patients can develop an **autoimmune myopathy** characterized by:

- progressive weakness,
- muscle enzyme elevations,
- a necrotizing myopathy on muscle biopsy
- **autoantibodies that recognize (HMGCR),** the pharmacologic target of statins.



- Anti-HMGCR antibodies are not found in subjects with self-limited statin intolerance.
- Testing for these antibodies may help differentiate self-limited statin myopathy, which recover after statin discontinuation, from progressive statin-associated autoimmune myopathy which typically require immunosuppressive therapy.

# STATINS AND MYASTHENIA

*Muscle Nerve* **38:** 1101–1107, 2008

## STATINS MAY AGGRAVATE MYASTHENIA GRAVIS

SHIN J. OH, MD, ROHIT DHALL, MD, ANGELA YOUNG, MD, MARLA B. MORGAN, MD,
LIANG LU, MD, and GWENDOLYN C. CLAUSSEN, MD

- 170 patients with MG during a 2.5-year period, 54 used statins
- 6/54 reported a worsening of MG symptoms within 8 weeks after receiving statins
- 2/6 the worsening was associated with a confirmed increase in serum acetylcholine receptor antibody concentration
- patients with MG should be informed about the possibility of MG exacerbation, and the statins should be withdrawn if this occurs

- Statins can aggravate myasthenia gravis but the risk is not well quantified, and these compounds are not completely contraindicated in myasthenia.

# Statins-induced neuromuscular disorders

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- **Acute Rhabdomyolysis**
- **Immune-mediated myopathies**
- **Unmasking of myopathies**
- **Myasthenia gravis**
- **Mitochondrial myopathy**
- **Peripheral neuropathy**

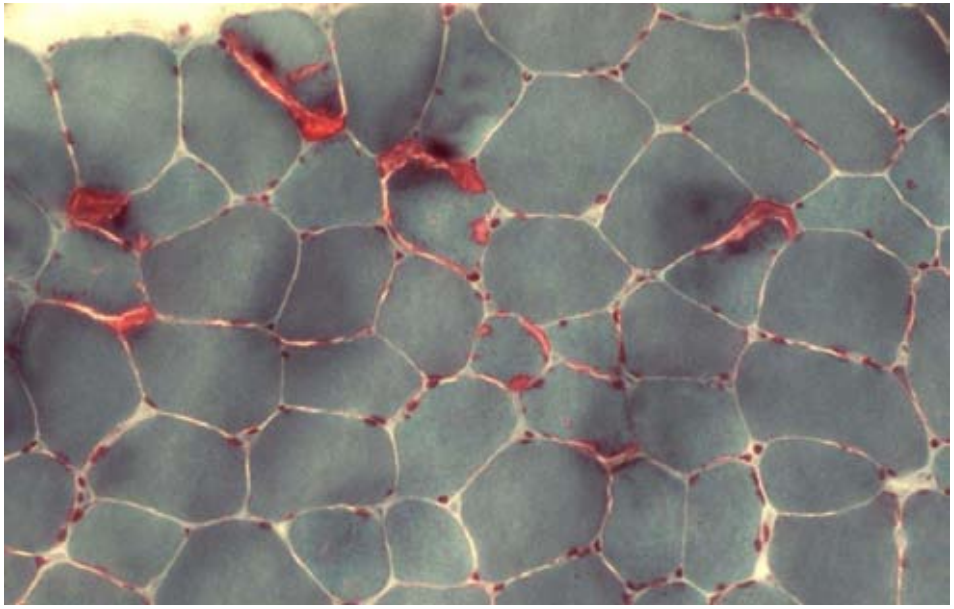
# Case report

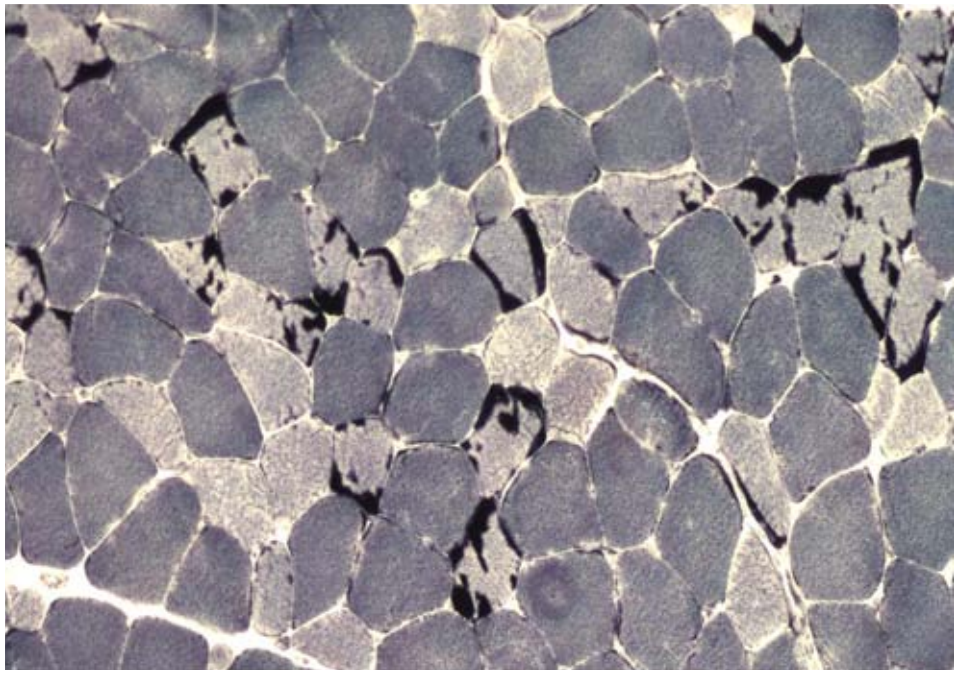
65-year-old man

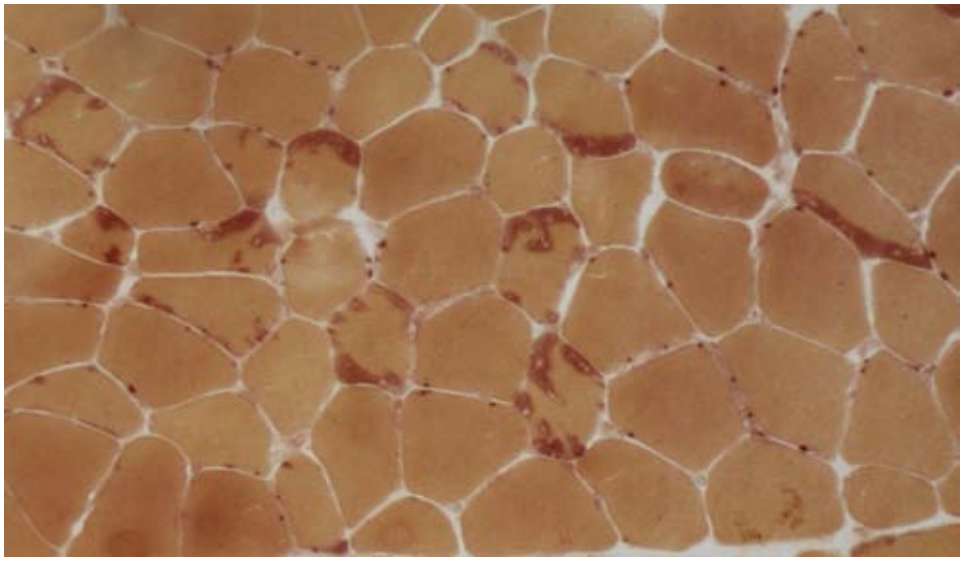
He suffered from hypertension and hypercholesterolemia and had been on statin therapy for the past 20 years. Since two yrs complained of exercise intolerance, myalgias and premature fatigue, but did not describe discoloration of the urine. There was no family history of similar problems.

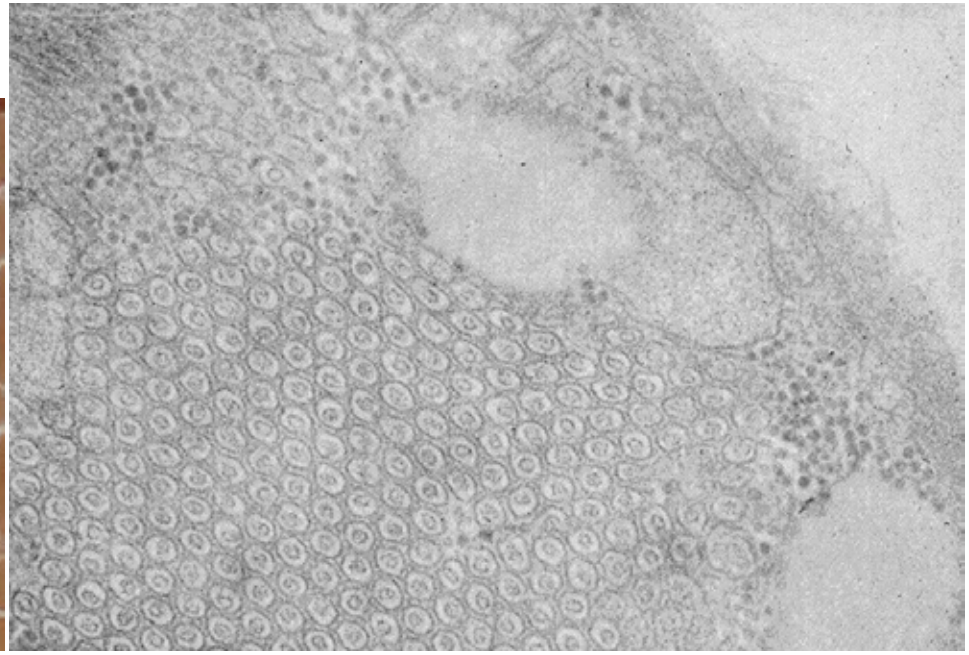
Serum CK was chronically elevated (recently as high as 1,112 IU/L; normal, <200).

Electromyography showed a myogenic pattern



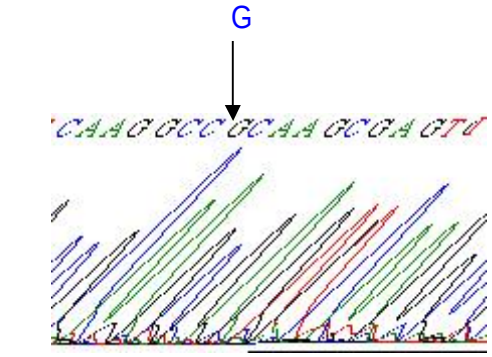






PGAM activity: 5% residual activity (0.12 nmol/min/mg prot; v.n. 2.6±0.43)

## Genetic analysis PGAM gene




Paziente

del 532 G

The deletion determines an anticipated frameshift in exon 2, causing formation of a preamture stop codon

# Statins-induced neuromuscular disorders

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- **Myasthenia gravis**
- **Mitochondrial myopathy**
- **Peripheral neuropathy**

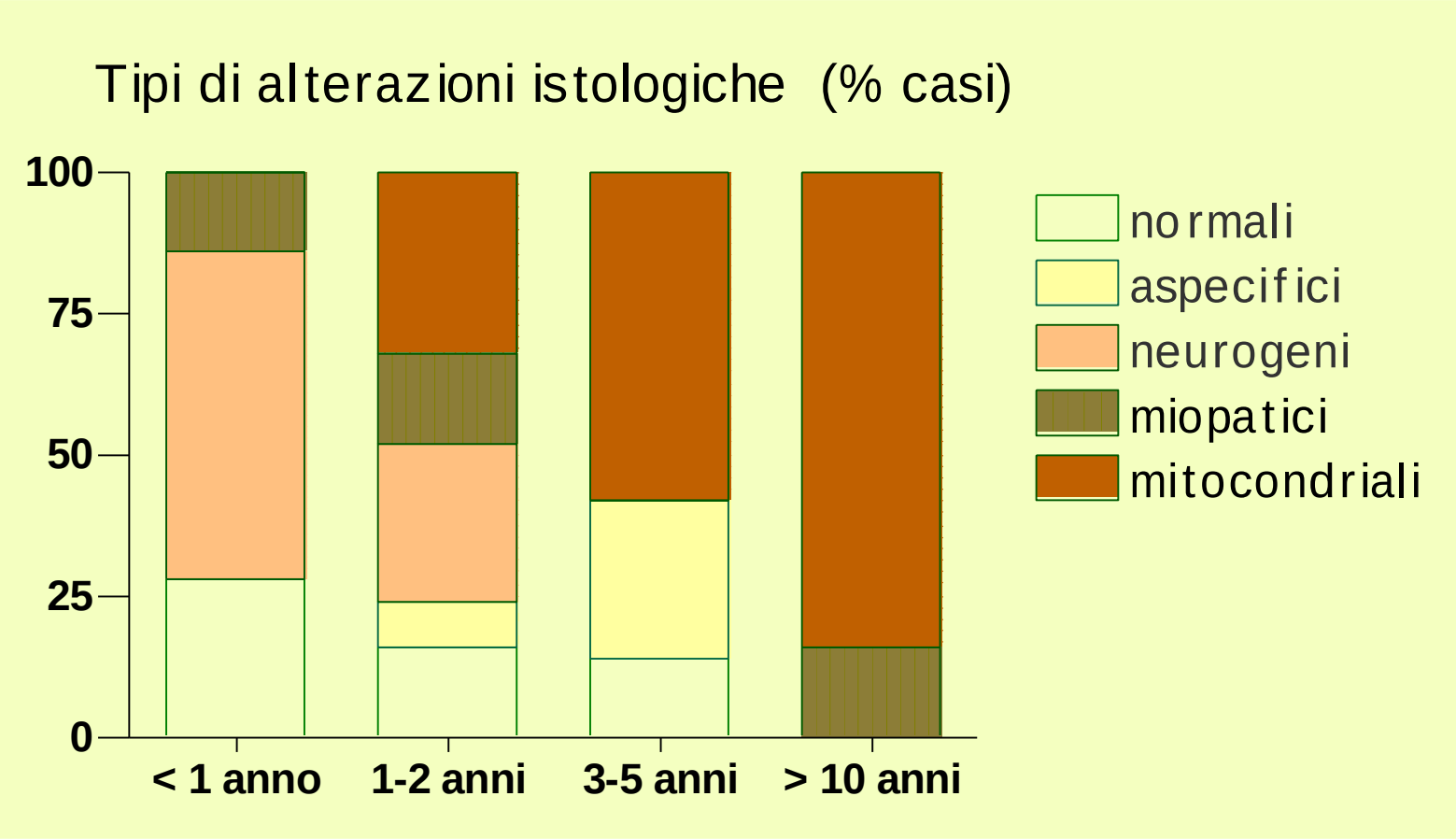
# Materials and methods

- 53 patients, 27 females, 26 males; age ranged from 45 to 75 years in statin therapy for a variable time
- Statin used: pravastatin atorvastatin, slight prevalence of simvastatin
- Elegible clinical criteria: myalgias, muscle cramps, fasciculations, easy fatigability, and weakness; occasional asymptomatic elevated serum CK levels lasting at least three months after drug withdrawal.
- No therapy with amiodarone, colchicine, or other potentially myotoxic drugs was noted
- Family history was unremarkable in all patients.
- Muscle biopsy was performed in 32 individuals.

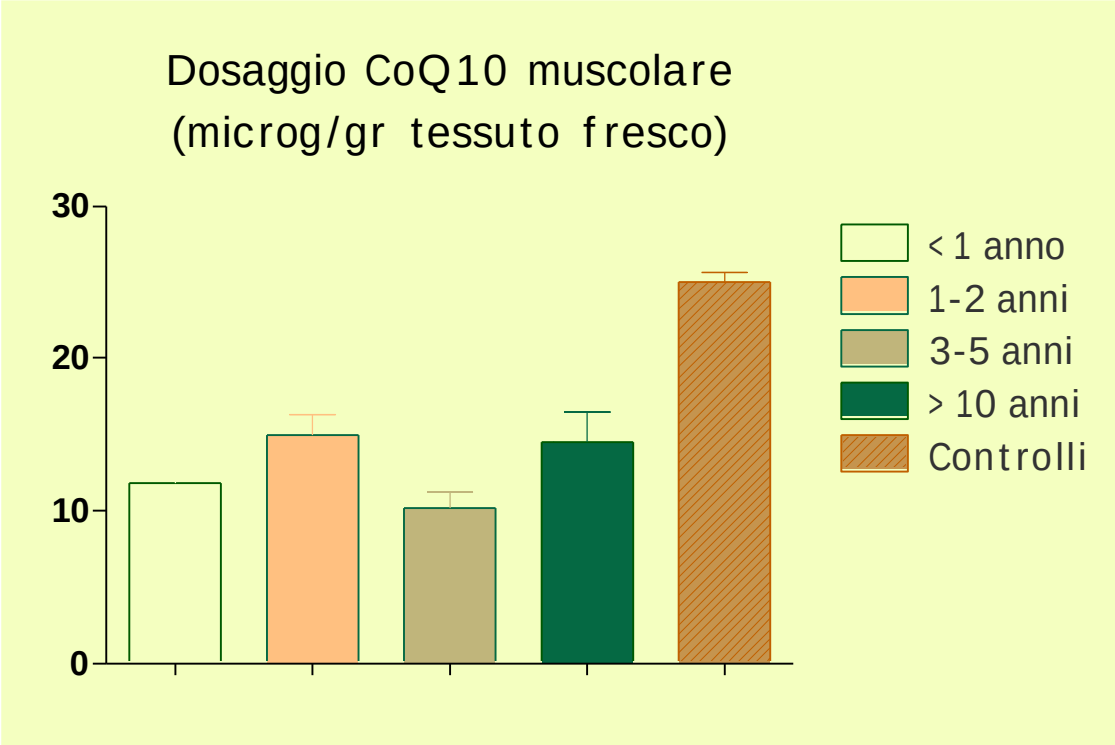
**Toscano A., Mongini T et al., unpublished data**

| | Clinical features | Range of serum CK (n.v. <140 U/l) |
|---|---|---|
| Group 1 | 1 normal, 4 cramps/myalgias, 2 proximal weakness | 140-1500 |
| Group 2 | 9 cramps/ myalgias, 3 proximal weakness | 82-950 |
| Group 3 | 2 normal, 1 cramps/myalgias, 4 proximal weakness | 200-3200 |
| Group 4 | 1 cramps/myalgias, 5 proximal weakness | 46-500 |

# Muscle histology



# Muscle CoQ10 levels




## Alternative lipid-lowering drug

**Chinese red rice depletes muscle coenzyme Q10 and maintains muscle damage after discontinuation of statin treatment**

Vercelli L, Mongini T, Olivero N, Rodolico C, Musumeci O, Palmucci L.

J Am Geriatr Soc. 2006; 54 : 718-20.

# Peripheral neuropathies: main clinical features

Motor/sensory - neuropathy

Distal axonopathy

(most common type)

Mononeuropathy

Multifocal neuropathy

Demyelinating neuropathy

- Hyporeflexia
- Paresthesias
- Muscle weakness/wasting

# Factors that increase the risk of Statins-induced Myopathies

**Patient characteristics**

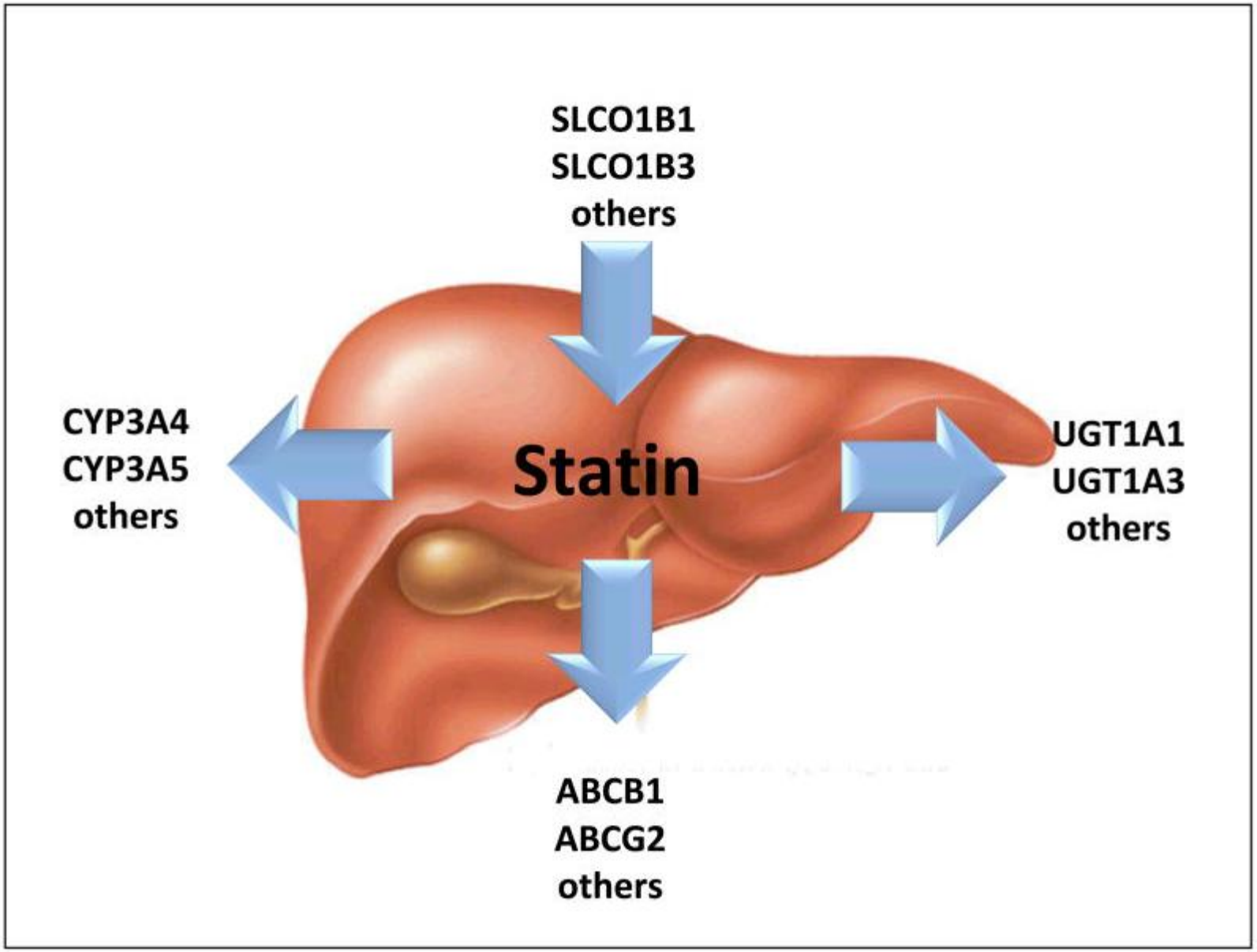
- Increased age
- Female
- Renal insufficiency
- Hepatic dysfunction
- Hypothyroidism
- Diet (grapefruit juice)
- Perioperative periods

**Statin properties**

- Higher doses
- Lipophilicity
- High bioavailability
- Limited protein binding
- CYP 450 3A4 metabolism
- Polypharmacy (nicotinic acid, fibrate, alcohol)

**Genetic predisposition**

- ***SLCO1B1 gene polymorphisms (mainly with simvastatin/atorvastatin)***
- ***5-HT receptor gene polymorphisms***
- ***CYP system (CYP2D6, CYP2C8), UTG1, ABCB1 gene mutations***
- ***COQ2 gene mutations***


SLCO1B1
SLCO1B3
others
CYP3A4
CYP3A5
others
Statin
UGT1A1
UGT1A3
others
ABCB1
ABCG2
others

# Management of Statin Induced Myopathy

***Muscle weakness, tenderness or pain***

**Check the Following:**
Creatine kinase (CK) level
List of medications to rule out any interactions
TSH level
Any recent history of excessive exercise or trauma

**Tolerable symptoms**

No or mild increase of CK level less than 5 times the upper limit of normal

→ Continue the same treatment
Consider reducing the dose of statin

**Tolerable symptoms**
**BUT**
Increase of CK level more than 5 times the upper limit of normal
**OR**
Rhabdomyolysis

→ Discontinue statin
Manage rhabdomylosis if present

**Intolerable symptoms**

→ Discontinue statin
Regardless of the CK level

**Resume statin after resolution of symptoms**
Administration of a lower dose statin
Alternation in the dosing
Twice weekly dosing with longer half lives statins
Different type of statin

***Recurrence of symptoms?***

Use multiple statin at multiple dose

***Recurrence of symptoms?***

Use other lipid lowering drugs

*Adapted from Jacobson TA: Toward "pain-free" statin prescribing: clinical algorithm for diagnosis and management of myalgia*

# Conclusions

• The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, i.e. statins, are the most effective drugs for **prevention and treatment of hypercholesterolaemia and coronary artery disease**

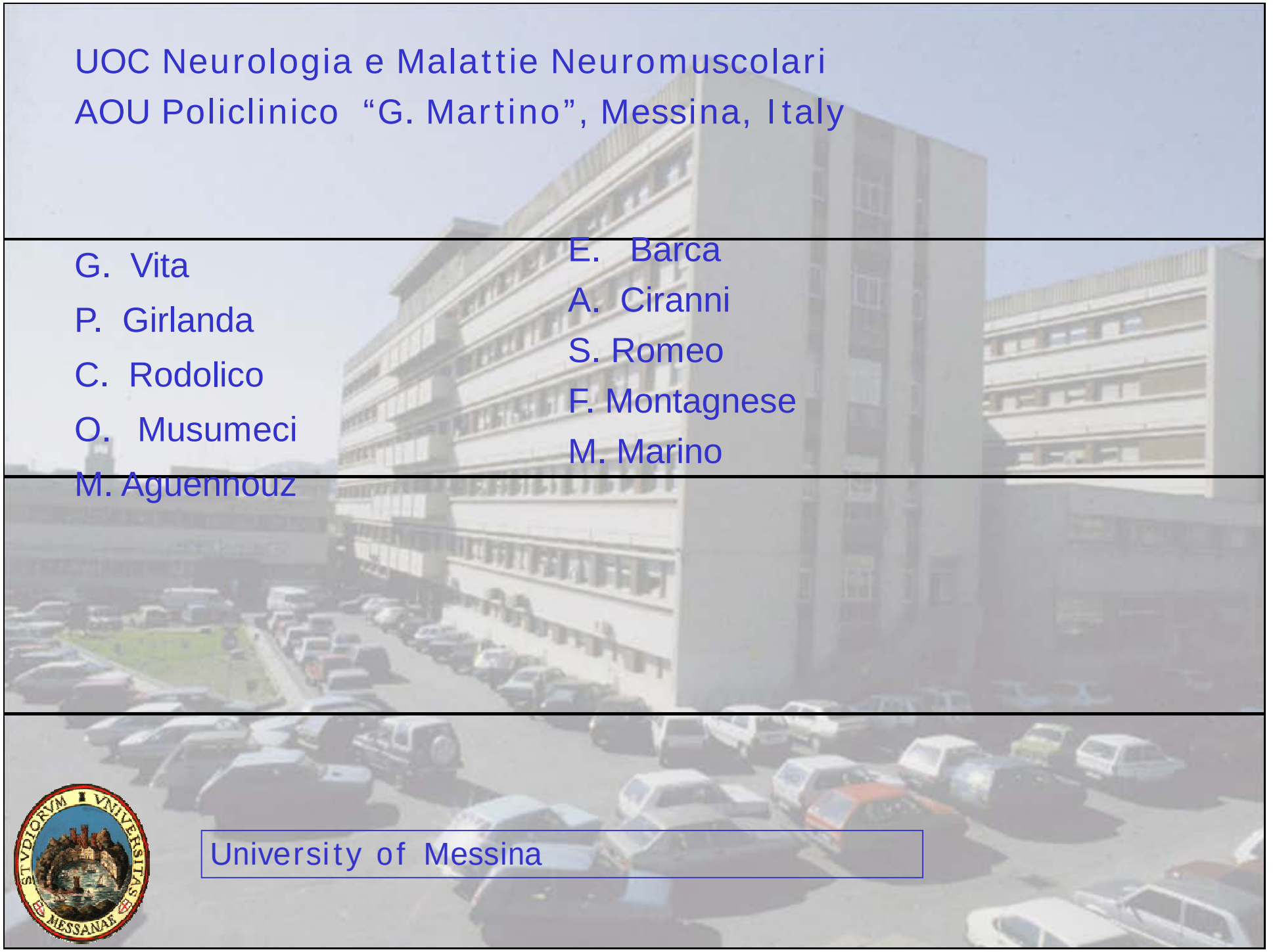
• They are generally well tolerated but recurrent side effects as rhabdomyolysis, myopathies and polyneuropathies have been often described (0.1-2%)

• The pathophysiology of statin myopathy is still not completely understood

• Some genetic variants of SLCO1B1 or other genes may affect statins hepatic uptake and increase the incidence of myalgias/ rhabdomyolysis

• Statins administration may reveal previously asymptomatic muscle disorders (Mc Ardle, CPT II deficiency, myasthenia,others)

• In patients with persistent myopathy, despite statin withdrawal, it is necessary to deeply investigate possible alternative causes of myopathies

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# *Collaborations*

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- Prof. C. Desnuelle, France
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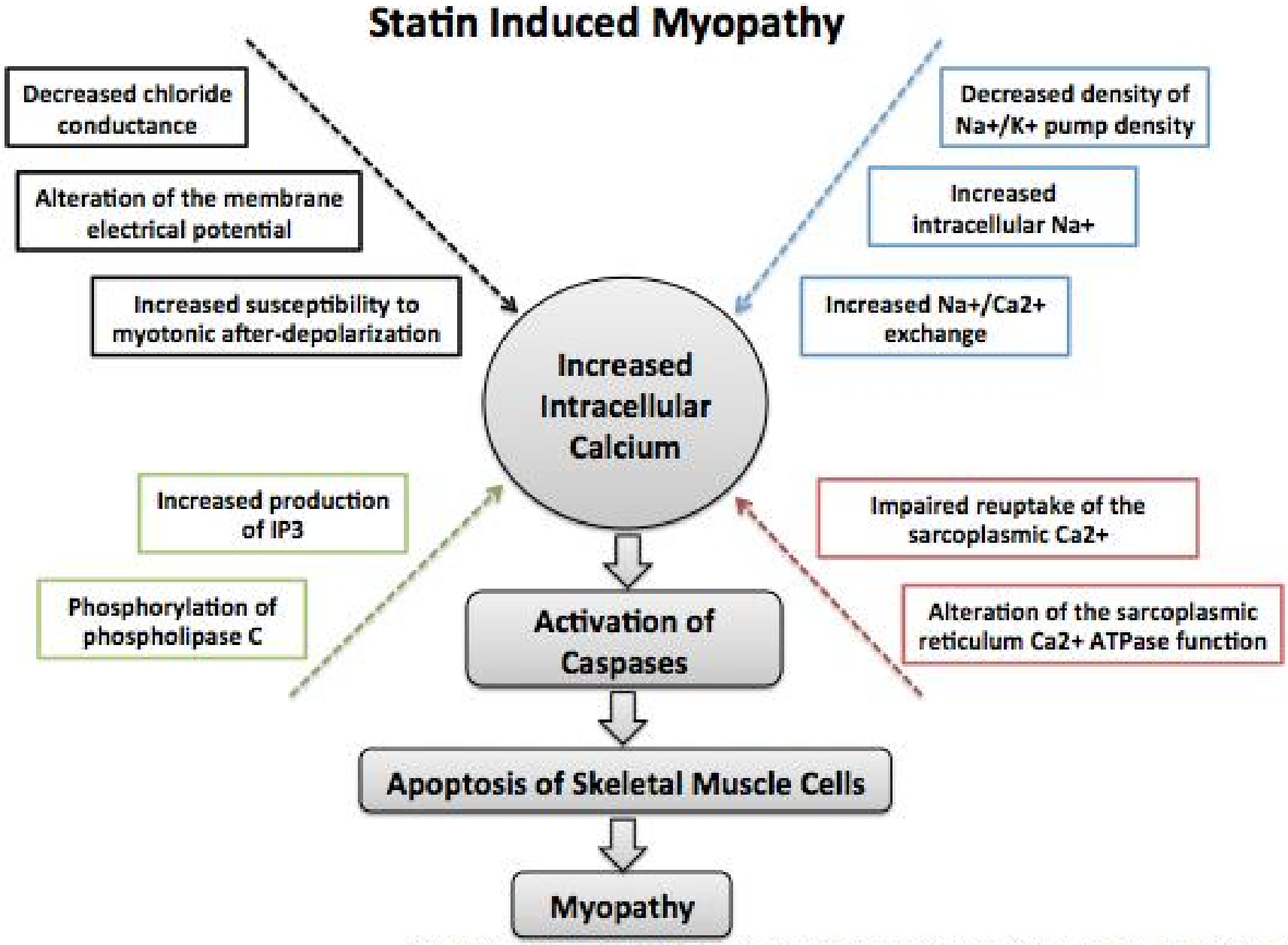


*Adapted from Statin Myopathies: Pathophysiological and Clinical Perspectives. Steven K. Baker et al*