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Pharmacogenetics of statin-induced myopathies

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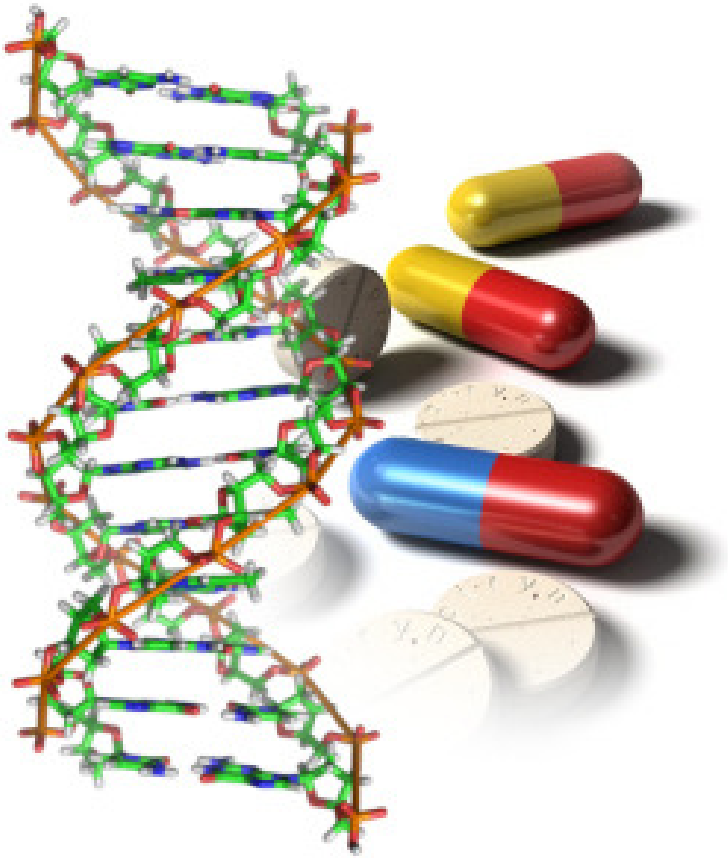

It started with a fungus

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1973: Isolation of Mevastatin (Penicillium)

1978: Isolation of Lovastatin (Aspergillus), Merck

1987: Marketing of Lovastatin

1994: Results from Scandinavian „4S-study“ (Simvastatin): Statins reduce mortality

Statins inhibit cholesterol synthesis

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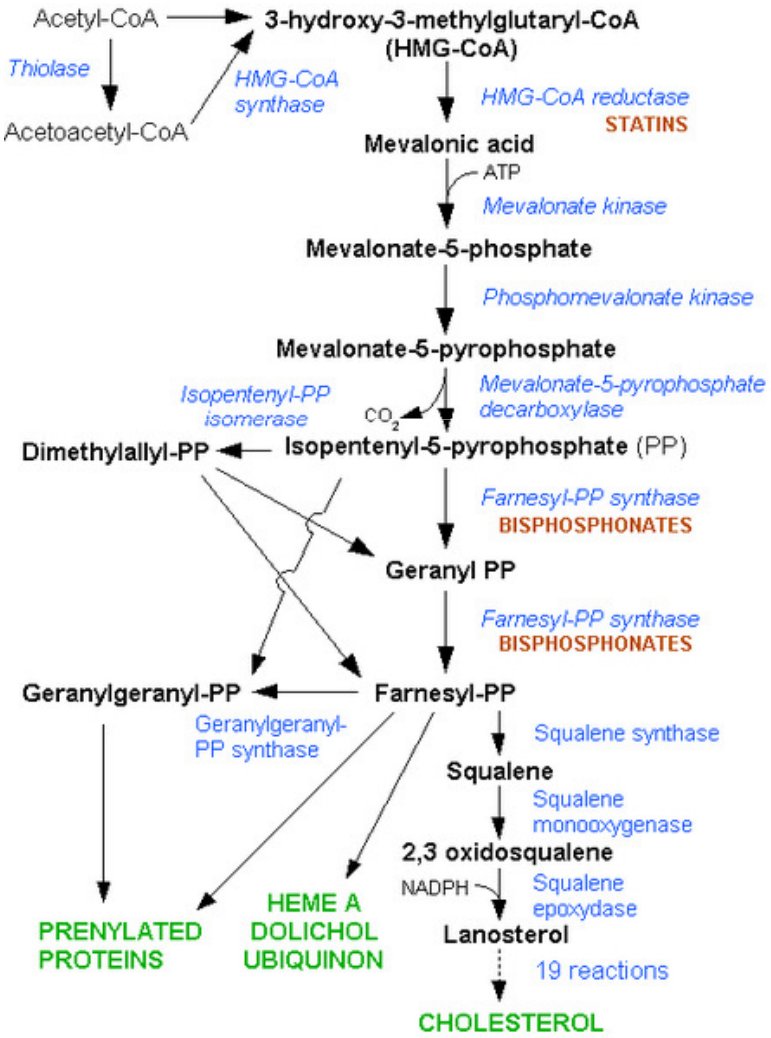

Inhibition of HMG-CoA-Reductase (cholesterol synthesis)

Lovastatin
Simvastatin
Cerivastatin (withdrawn)
Pravastatin
Fluvastatin
Rosuvastatin

Statins act within the liver cell

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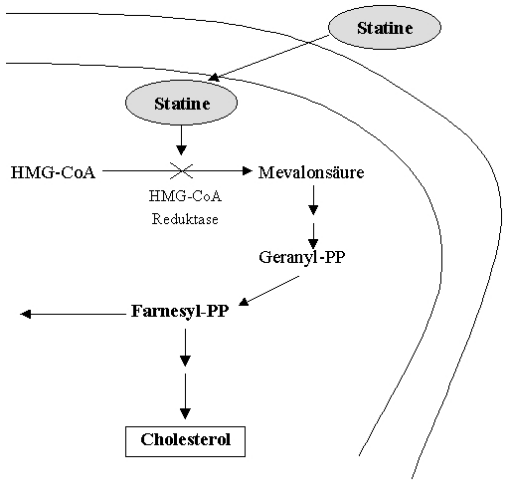
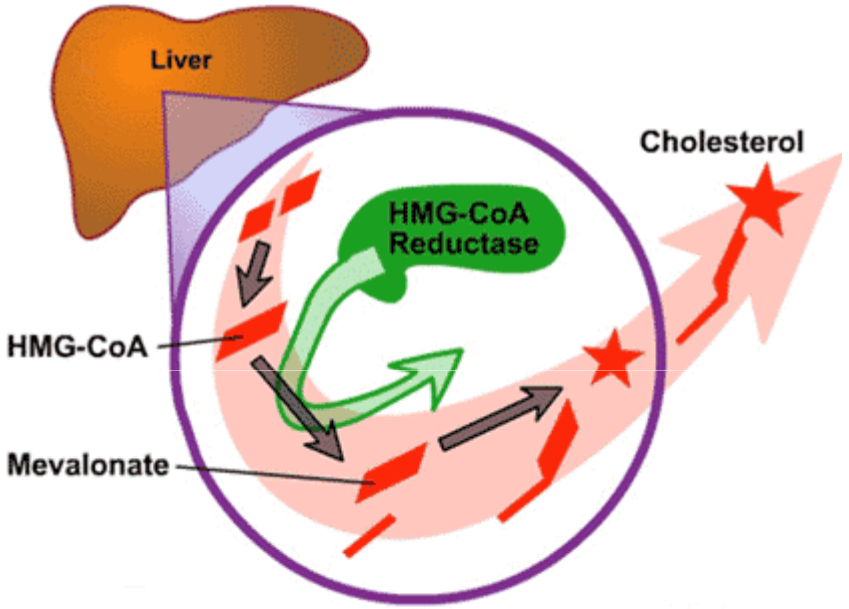
Liver as target organ

Oral administration,
uptake into hepatocyte





Are statins effective and safe?

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Statins are safe

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NNT (number needed to treat)

15 – 19 (High risk patients, secondary preventions)
28 – 32 (Moderate risk patients, secondary prevention)
42 – 119 (Low risk patients, primary prevention)

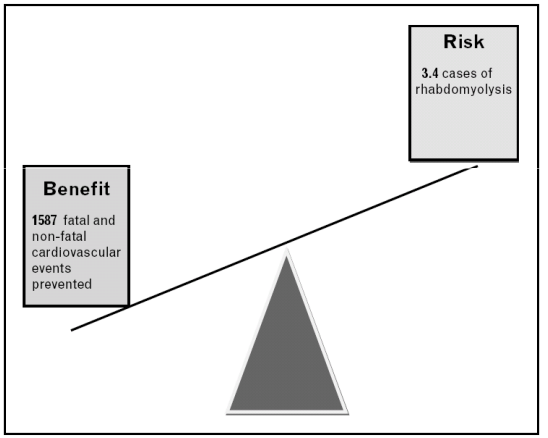
(Fernandez, 2011)

NNK (number needed to kill) © W. Renner

6.600.000

(Thompson, JAMA 2003)

Figure 4 An analysis of risks [8] and benefits [36] of treating 100 000 patients with a stain for 1 year



Statin-induced myopathy: Definitions

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Myopathy: Any disease of muscles

Myalgias: pain in a muscle or group of muscles
~10%

Myositis: muscle symptoms with ↑ CK
(-itis?)
~2.5%

Rhabdomyolysis: > 50 fold ↑ in CK + renal impairment
<0.1%

Statin & myopathy: Clinical trials versus real life

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“Statin induce muscle pain: A common dilemma not reflected in clinical trials”

	Clinical trials:	Clinical routine:
Myalgia:	1% - 5%	5% - 10%

- Pre-exclusion of risk patients in clinical trials (35% of eligible patients!)
- Patients with pain lost to follow-up

Consequences of myalgia?

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Lipid-lowering: Usually life-long therapy

BUT:
Discontinuation of statins:
25% within 6 months
60% within 24 months

Muscle pain affects patient's compliance

"When the body aches, the mind will follow..." (Rossi, J Am Coll Cardiol, 2009)

The search for cause…

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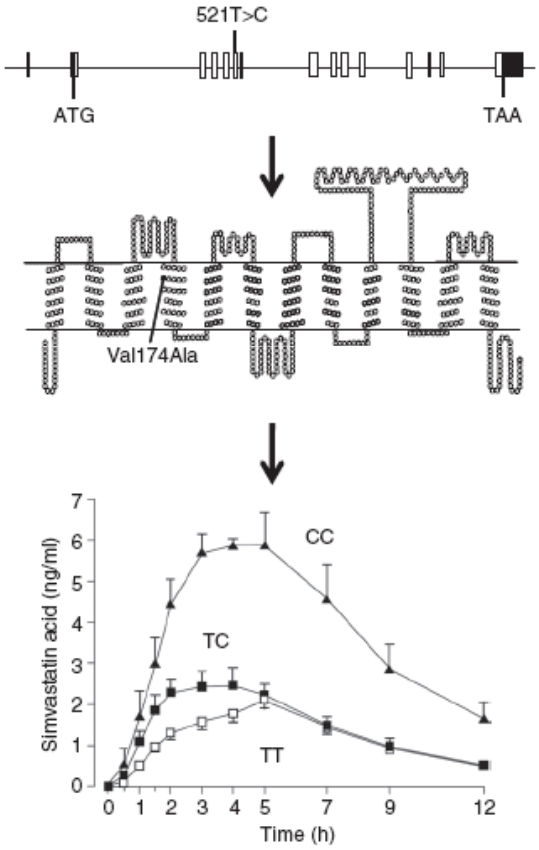
Endogenous risks
Advanced age (> 65 years)
Low body mass index and frailty
Multisystem disease
  Renal dysfunction
  Hepatic dysfunction
Thyroid disorders, especially hypothyroidism
Hypertriglyceridemia
Metabolic muscle diseases:
  Carnitine palmityl transferase II deficiency
  McArdle disease (myophosphorylase deficiency)
  Myoadenylate deaminase deficiency
Family history of muscular symptoms
Personal history of elevated creatine kinase or muscular symptoms

Exogenous risks
Alcohol consumption
Heavy exercise
Surgery with severe metabolic demands
Drugs affecting the cytochrome P450 system:
  Cyclosporine
  Fibrates
  Nicotinic acid
  Nondihydropyridine calcium channel blockers—eg, verapamil (Calan), diltiazem (Cardizem)
  Amiodarone (Cordarone)
  Azole antifungals
  Colchicine
  Digoxin
  Human immunodeficiency virus protease inhibitors
  Warfarin (Coumadin)
Consuming > 1 L of grapefruit juice per day

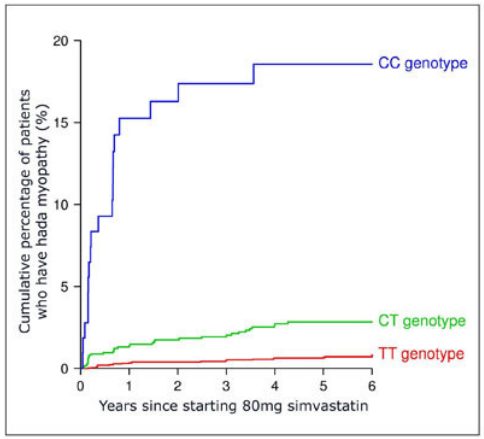
The breakthrough: SLCO1B1



2008: Genome-wide search identifies transporter variant (SLCO1B1): Transporter in hepatocyte membrane

SLCO1B1 V174A (T>C): Reduced statin uptake into hepatocyte, higher statin plasma levels, less effect & more side effect

Heterozygous (28%): 4-fold myopathy risk
Homozygous (2%): 16-fold myopathy risk



Link E. et al., N. Engl. J. Med. 2008

SLCO1B1 and statin types

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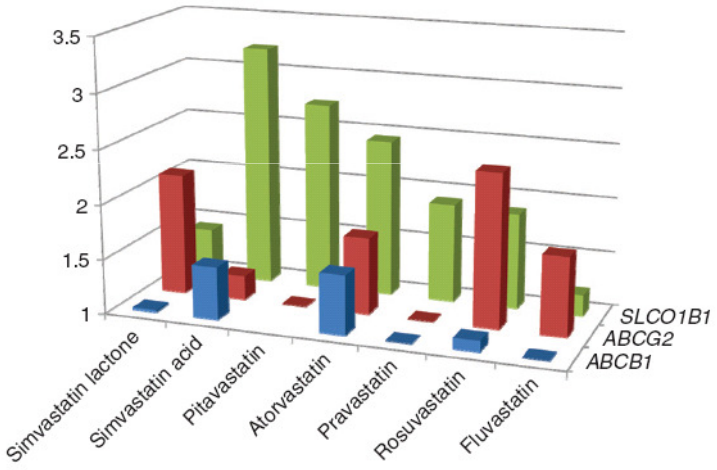
Effect of SLCO1B1 genotype: dependent on statin type and dose



	SLCO1B1 c.521T>C genotype			
	TT	TC	CC	Normal dose range*
Simvastatin	80 mg	40 mg	20 mg	5–80 mg/day
Pitavastatin	4 mg	2 mg	1 mg	1–4 mg/day
Atorvastatin	80 mg	40 mg	20 mg	10–80 mg/day
Pravastatin	80 mg	40 mg	40 mg	10–80 mg/day
Rosuvastatin	40 mg	20 mg	20 mg	5–40 mg/day
Fluvastatin	80 mg	80 mg	80 mg	20–80 mg/day

Figure 3 Recommended maximum statin doses for Caucasian adult patients according to *SLCO1B1* genotype. Statin therapy should be started with the starting dose recommended by the manufacturer or half of the recommended maximum dose, whichever is lower. The dose should be titrated up to the minimum effective dose or the suggested maximum dose on the basis of lipid response and tolerability, and the statin should be changed or discontinued as necessary. Other factors known to affect statin pharmacokinetics or myopathy risk should be taken into account when selecting a statin and its dose for an individual patient (interacting drugs, concomitant diseases, age, etc.). *Based on US Food and Drug Administration–approved maximum doses; lower maximum doses may apply in some countries.

Niemi M, Clin Pharmacol Ther. 2010

Complex decisions

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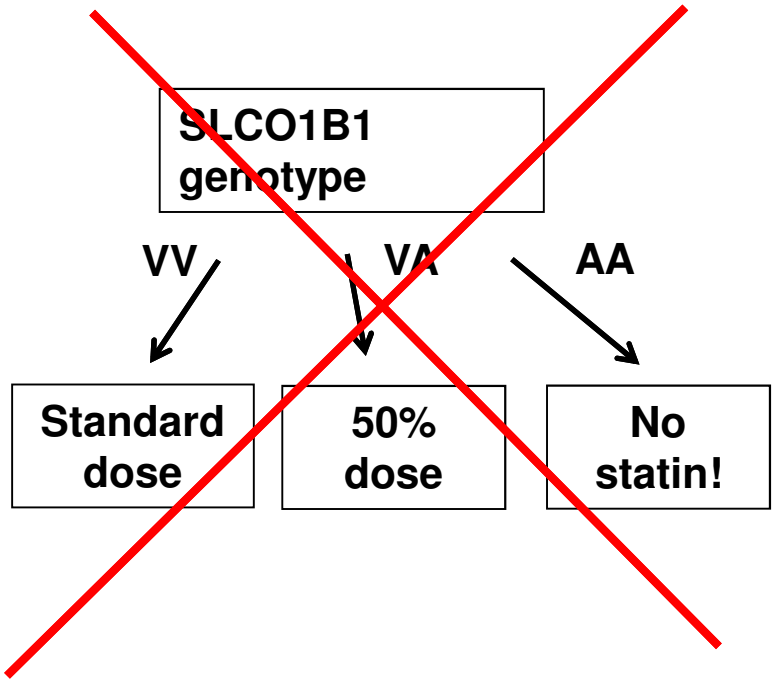

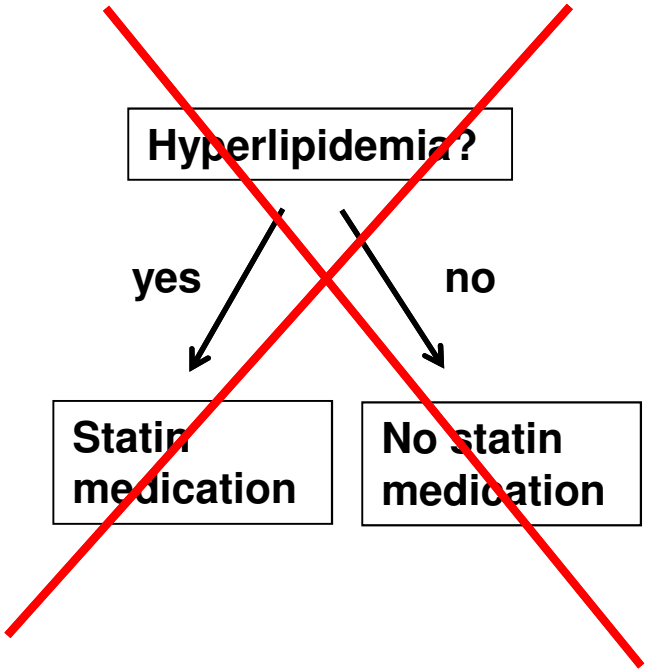

Statin-induced myopathy & SLCO1B1 genotyping

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Patient with statin medication and muscle pain

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Myopathy related to statins? (Differential diagnosis?)
- History of muscle pain
- Physical examination
- Laboratory tests (CK, inflammation markers, SLCO1B1 genotype...)

↓

Evaluation of risk/benefit ratio of current statin medication
- Primary/secondary prevention?
- Coronary risk profile?
- Compliance? Comedication?

↙ ↓ ↓ ↘

Re-define lipid-lowering goals (NNT?)	Decrease statin dose	Switch statin	Statin holidays

Re-defining personal lipid goals

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Guide for estimating benefit from statin therapy: A comparison of statin efficacy trials by patient risk

PATIENT RISK CATEGORY[a]	TRIAL	TYPE OF PREVENTION	FOLLOW-UP (YEARS)	NO. NEEDED TO TREAT[b]
High	4S[47]	Secondary	5.4 (median)	15
	Heart Protection Study[48]	Primary and secondary[c]	5 (mean)	19
	PROVE-IT[49]	Primary and secondary[d]	2 (mean)	26
Moderate	LIPID[50]	Secondary	6.1 (mean)	28
	CARE[51]	Secondary	5 (median)	33
	PROSPER[52]	Primary and secondary[e]	3.2 (mean)	48
Low	WOSCOP[53]	Primary[f]	4.9 (mean)	42
	AFCAPS/TexCAPS[54]	Primary[g]	5.2 (mean)	50
	JUPITER[55]	Primary[g]	1.9 (median)	83
	ASCOT-LLA[56]	Primary[g]	3.3 (median)	91
	MEGA[57]	Primary	5.3 (mean)	119
	ALLHAT-LLT[58]	Primary	4.8 (mean)	NS[h]

(Fernandez, Cleveland Clin J Med 2011)

Risikokategorie	LDL-C-Zielwert
sehr hoch	< 70 mg/dl
hoch	< 100 mg/dl
mittel	< 130 mg/dl***
niedrig	< 160 mg/dl

Statin, Dosierung	LDL-C-Veränderung (%)
Standarddosis	
- Atorvastatin, 10 mg	–37
- Fluvastatin, 80 mg	–33
- Lovastatin, 40 mg	–37
- Pravastatin, 40 mg	–29
- Rosuvastatin, 10 mg	–43
- Simvastatin, 40 mg	–37
Hochdosis	
- Atorvastatin, 80 mg	–55**
- Rosuvastatin, 40 mg	–53**
- Simvastatin, 80 mg	–42**

(Österreichischer Lipidkonsensus 2010)

Switching statins

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	SLCO1B1 c.521T>C genotype			
	TT	TC	CC	Normal dose range*
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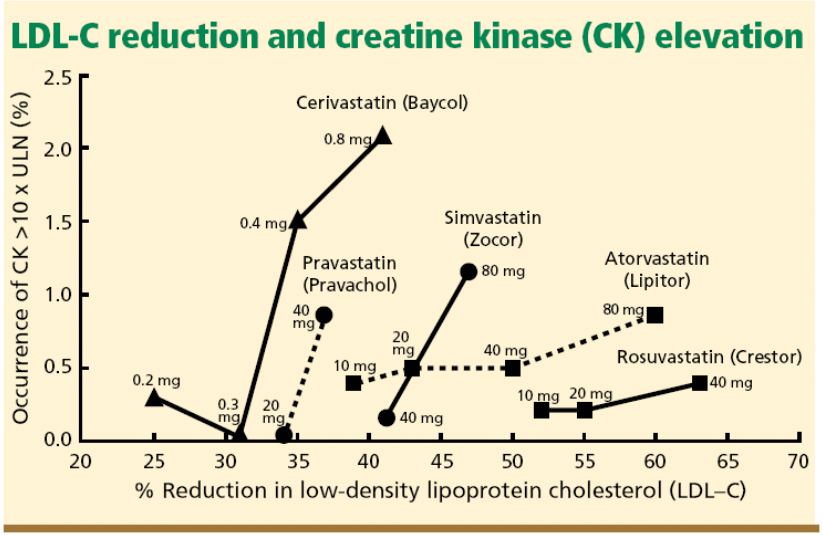

Fernandez 2011

Bioproducts SLCO1B1 Test

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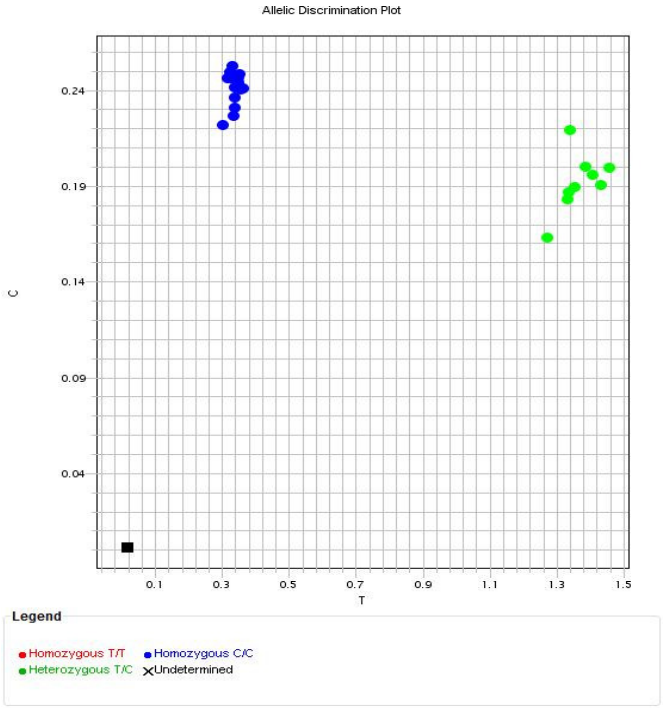
Entwicklung eines kommerziellen Tests zur SLCO1B1 Typisierung.

Bio Products



Summary

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Statins are effective and major adverse events are very rare.

Mild to moderate muscle pain is common statin-side-effect and threatens patient‘s compliance.

SLCO1B1 V174A polymorphism is the strongest genetic risk factor for statin-induce myopathy.

Decisions about stopping / switching / reducing / continuing statin treatment should include SLCO1B1 genotype.

Bioproducts SLCO1B1 test coming soon...