A Primer on Statin Myopathy

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Statins

- Can reduce cardiac morbidity and mortality
- Billion dollar business

  Pfizer (Lipitor) 12.4 billion dollars sales in 2008
- Akira Endo“The indigo dyer wears white trousers”

- 40% of patients who could receive statins do not:
  - Education
  - Expense
  - Side effects - muscles

Case One

- 52 year old female with fibromyalgia is begun on a statin for hyperlipidemia. On her return visit she complains about achiness in her calves. CPK, TSH and EMG are normal. Does she have a statin induced myopathy?

Case Two

- A 38 year old male with polymyositis and hyperlipidemia. He currently is controlled on prednisone and cyclosporine. His most recent CPK is 540 (down from 4200 four months earlier) His strength is good.
- CVD risks are high with family history and smoking.

What do I want to know?

- How does one define statin induced muscle disease?
- How often does it occur?
- Does it differ between drugs, dosage?
- Are there risks factors ?
- What are the proposed pathologic mechanisms?
- Is it treatable?

Epidemiology

- Clinical trials: incidence of statin myopathy in RCT's is about 1.5% to 5.0%

So why do 10-15% patients quit statins and complain so much?


BEWARE
of DOG

How Often Does it it occur?

- Difficult to directly compare the incidence of statin myopathy in clinical trials with real - world clinical practice given the inconsistent definition of myopathy.

A Little Restrictive?

127,391 rest-time statin users in the UK – 2yr F/U

4 cases of myopathy-defined as CPK > than 10 X ULN and muscle symptoms requiring hospitalization (.4/10,000 patient years)

Rodriguez LA, et. al. The Safety of Rosuvstatin in Comparison with other Statins in over 100,000 Statin Users in UK Primary Care. Pharmacy epidemiology Drugs 2008; 17:943– 952

Myopathy vs. Myositis vs. Rhabdomyolysis

"Governing Bodies"

- Food and Drug Administration- FDA
- National Lipid Association-NLA
- American Heart Association – AHA
- American College of Cardiology – ACA
- National Blood Heart and Lung Institute – NBHLI

Myopathy

	Muscle Pain/Weakness	Increase CPK
NLA	Yes	>10 times normal
FDA	No	>10 times normal
ACC*		
NBLHI*		
AHA*		

*General term for any disease of muscle

Myositis

	Muscle Pain/Weakness	Increase CPK
NLA	NA	NA
FDA	NA	NA
ACC	Yes	Elevated
NBHLII	Yes	Elevated
AHA	Yes	Elevated

RHABDOMYOLYSIS

	Muscle Symptoms/Weakness	Elevated CPK	Elevated Creatinine
NLA		Yes > 10 times normal or 10,000 iu	Yes or medical intervention with IV hydration
FDA		> 50 times normal	Yes and end organ damage
ACC	Yes	Yes > 10 times normal	Yes
NBHLI	Yes	Yes > 10 times normal	Yes
AHA	Yes	Yes > 10 times normal	Yes

Consequence of Multiple Definitions

- Difficult to assess effect that statins have on muscle pain/myositis
- Myalgia was not increased - meta-analysis of Rats

  (relative risk [RR] 1.09, 95% CI 0.97-1.23)
- **Does not necessarily mean that statins do not cause myalgia**

- Some patient groups prone to statin-induced muscle disease have been excluded from trials
  - Elevated creatine kinase
  - Elderly
  - Renal insufficiency
  - Hepatic insufficiency
  - Muscle pain

- Most studies show an increase in myalgias of about 10%
- Rhabdomyolysis appears to be rare
- Premier can occur and is often asymptomatic

Are There Differences Between Statins?

Yes and No

Muscular Related Symptoms

No study has researched this head on:

Primo study 2005 -7924 pts – (Prediction of Muscular Risk in Observational Conditions)

- Fluvistatin 5.1%
- Pravistatin 10.9%
- Atorvastatin23.4%
- Simvistatin 18.2%

AERS 1991-2001 Fatal Rhabdomyolysis Prescriptions

Lovastatin 1/5.2 million prescriptions

Pravistatin 1/27.1

Atorvastatin1/23.4

Simvistatin 1/8.4

AERS 2001 – Fatal Rhabdomyolysis Prescriptions

- Compared with cerivastin 1/316,000
- Overall rhabdomyolysis rates .1-.3/1000

A reanalysis of this data also revealed significantly fewer cases of myalgia in those not taking concomitant CY3A4 inhibitors

Differences among Statins

- FDA 2002-2004
  - For Rhabdomyolysis
    - Atorvastatin.27/ million prescriptions
    - Rosuvastatin 2.37/million prescriptions (also highest for myopathy, myositis)

  Remember FDA criteria most restrictive

To Complicate Matters

- Analysis of THIN database in Great Britain.
  - 939,831 patients 1996-2006
  - Myopathy at 12, 26 and 52 weeks
  - Fluvistatin highest at 12 weeks – rate ratio of 33.1
  - Rosuvastatin 9.91 at 26 weeks
  - Pravistatin 29.9 at 52 weeks

Aggressive Therapy

- (PRIMO)7924 patients
- Increased dosage increased risk of muscular symptoms

Bruckert E et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403-14.

Hydrophilic vs. Lipophilic

- Studies suggest hydrophilic (pravastatin) less likely to produce muscular side effects
- Pravastatin has limited penetration into muscle cells but its hepatic extraction ratio is very low

Clinical Features and and Risk Factors

- Thighs, cramping, calves, 25% generalized
- Tendinopathy
- Variable intensity of discomfort
- Time of onset variable
- Often followed unusual heavy exertion

Predisposing Factors of Statin Myopathy

Associated with all statins

Increased statin exposure (e.g. dose, drug interactions, genetic variants or other factors that affect clearance or hepatic uptake)

May unmask a latent underlying inherited or acquired myopathy such as McArdles disease

Risks for Statin Induced Muscle Disorders

- Small size
- Advanced age
- Female
- Alcoholism
- Hypothyroidism
- Grapefruit juice (> 1 qt)
- History of elevated CPK
- Previous statin myopathy
- Excessive physical exertion
- Major surgery or perioperative
- Genetic

Drug Metabolism

- Metabolized by the CYP3A4 pathway
  - Atoravastin, lovastatin, cerivastin
- Metabolized by the CYP2C9 pathway
  - Fluvastatin, rosuvastatin

Fibrates

Gemfibrozil competitively inhibits glucuronidation of statins- the process of removal of the statin metabolites

Fenofibrate undergoes glucuronidation by different pathways suggesting that in combination that this might be safer

Risky Medications

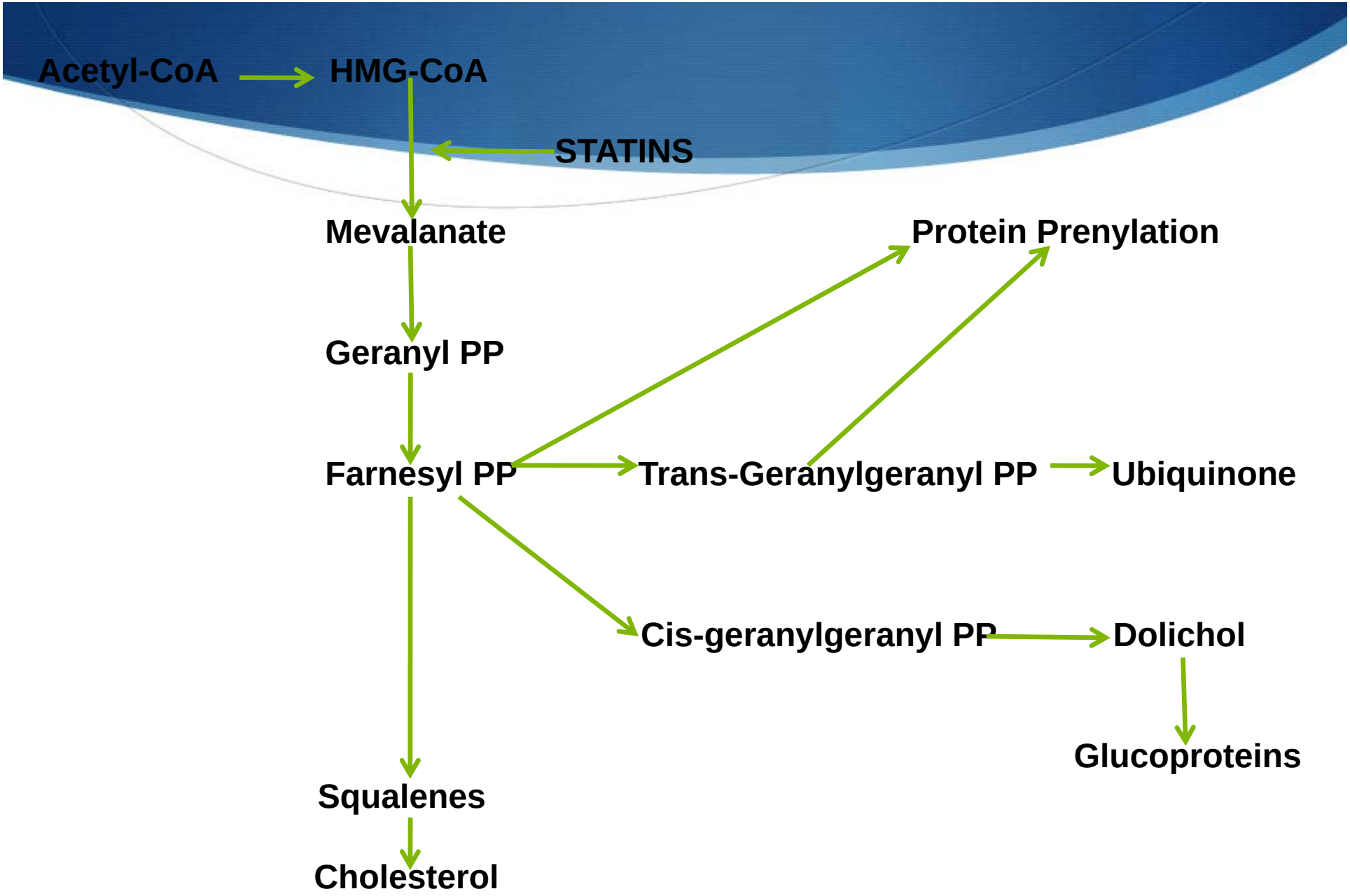
- Fibrates
- Cyclosporine
- Anti fungals
- Macrolide antibiotics
- Fluoxetine
- Amiodarone
- Verapamil
- Nefazadone
- HIV Protease inhibition

Inflammatory Statin Myositis

- Necrotizing myopathy in absence of significant inflammatory disease on biopsy
- Persistent or worsening disease despite stopping statin
- May require biopsy

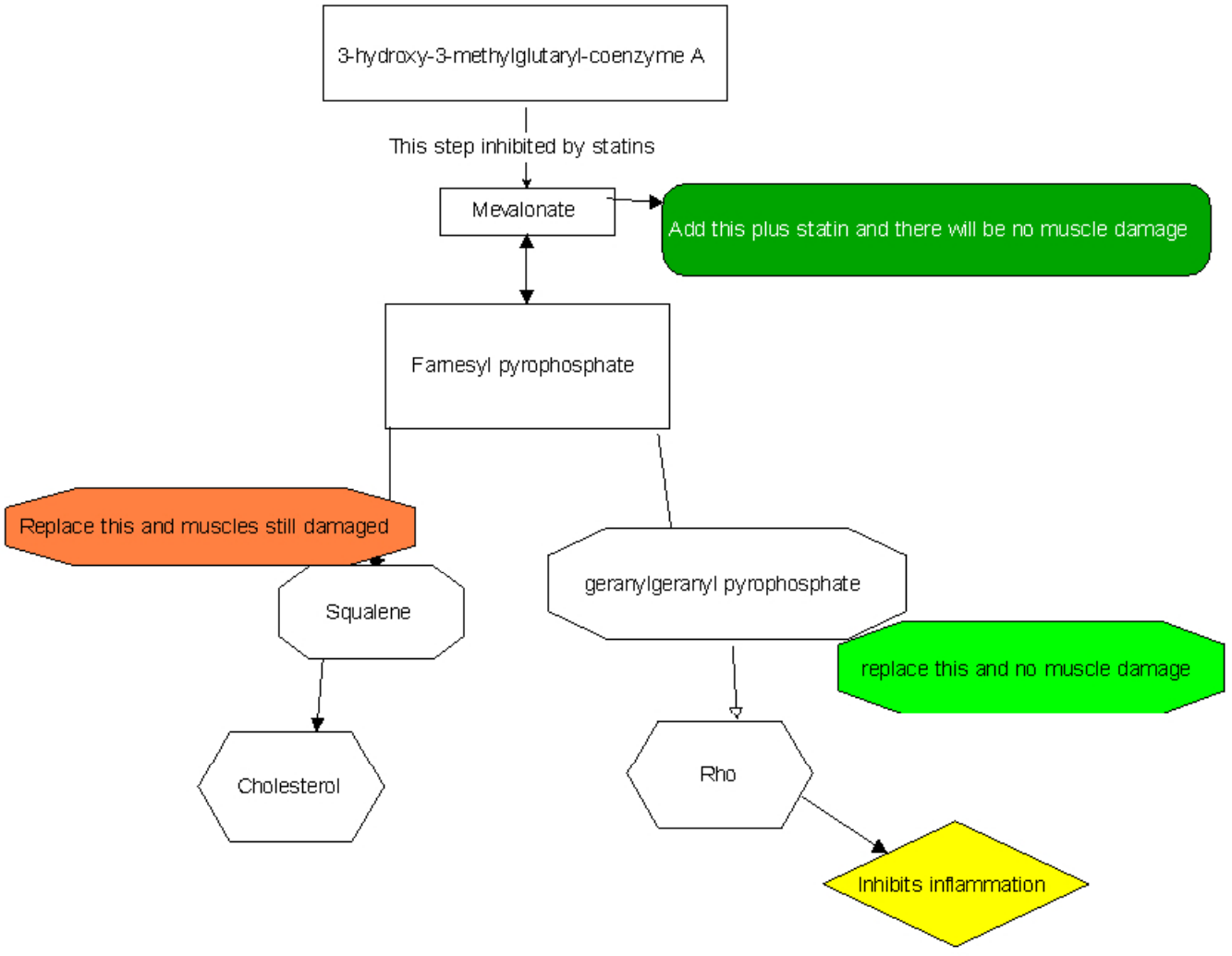
Pathophysiology

- Depletion of myocyte cholesterol
- Depletion of Coenzyme Q-10
- Depletion of isoprenoids
- Genetic


Acetyl-CoA
HMG-CoA
STATINS
Mevalanate
Protein Prenylation
Geranyl PP
Farnesyl PP
Trans-Geranylgeranyl PP
Ubiquinone
Cis-geranylgeranyl PP
Dolichol
Glucoproteins
Squalenes
Cholesterol

Decrease cholesterol

- Cause myocyte membrane instability
- Unlikely:
  - Inhibit squalene synthesis do not get myopathy


3-hydroxy-3-methylglutaryl-coenzyme A
This step inhibited by statins
Mevalonate
Add this plus statin and there will be no muscle damage
Farnesyl pyrophosphate
Replace this and muscles still damaged
Squalene
geranylgeranyl pyrophosphate
replace this and no muscle damage
Cholesterol
Rho
Inhibits inflammation

Co-Enzyme Q-10

Ubidecarenone, and ubiquinone

In all human cells, highest concentrations in the heart, liver, kidney, and pancreas.

Potent antioxidant, a membrane stabilizer, and an integral cofactor in the mitochondrial respiratory chain, regenerates antioxidants vitamin C and E.

Co Enzyme Q -10

- Reduction in CoQ10 leads to mitochondrial respiratory chain dysfunction impairing energy production in skeletal muscle
- Leading to a statin induced myopathy
- Some believe that treatment with CoQ10 may reduce myalgic symptoms and allow patients to remain on statin therapy

Coenzyme Q-10

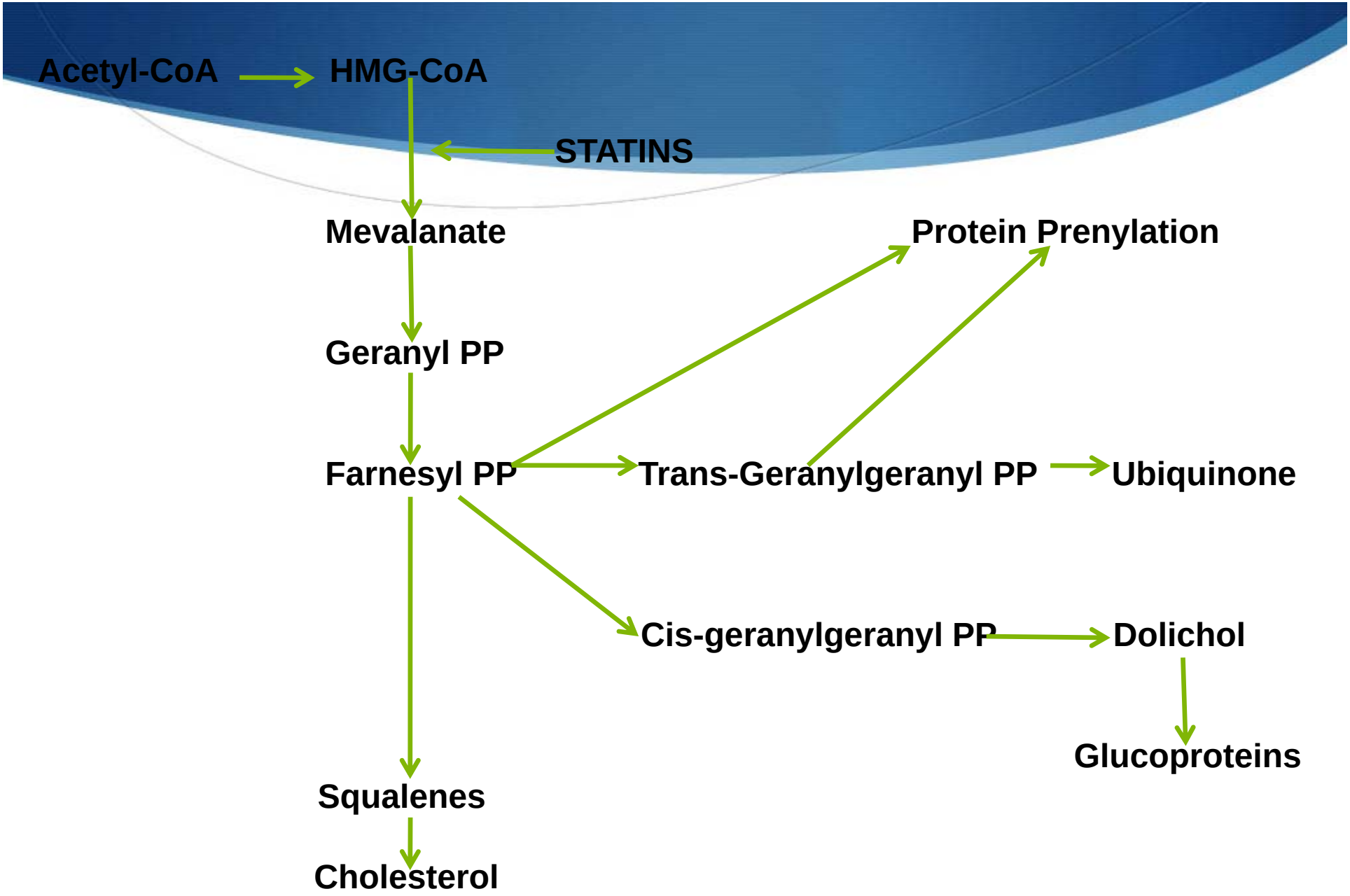
- Primarily transported on LDL particles and adjustments for reduced LDL may account for the reduce plasma level of CoQ-10
- Intramuscular levels correlate imperfectly
- No firm correlation with mitochondrial dysfunction

Clinical Studies of Co Q10

- Caso et al 32 pts with statin myalgia:
  - CoQ-10 or Vit E.
  - Brief Pain Inventory,
  - 30 days Pain lessened by 40% in Co Q 10
- Young et al 44 pts with statin intolerance:
  - CoQ-10 or placebo along with Simvistatin
  - Dose doubling every week to 40mg-
  - Visual analogue score - no difference in score, number taking 40mg or continuing statin

Isoprenoid Depletion

- Pathology reversed by mevalonate or geranylgeraniol
- Absent with squalene inhibition
- Inhibiting FPP and GPP synthetase might enhance toxicity of statins by reducing prenylation of small GTPases (RHO, Ras, Rab)


Acetyl-CoA
HMG-CoA
STATINS
Mevalanate
Protein Prenylation
Geranyl PP
Farnesyl PP
Trans-Geranylgeranyl PP
Ubiquinone
Cis-geranylgeranyl PP
Dolichol
Glucoproteins
Squalenes
Cholesterol

- Small GTPase proteins are prenylated proteins that cycle between GDP and ATP
- If inhibited can lead to apoptosis
- Bisphosphonates inhibit FPP. One study (in vitro) enhanced myocyte apoptosis with statin and bisphosphonates

Genetic

- Single nucleotide polymorphism (SNP) within the gene SLCO1B1
- Codes for the protein OATP1B1, that regulates hepatic uptake of statins (cyclosporine and gemfibrozil)

How to treat

- No consensus among major organizations
  - CPK > 10 x ULN (10,000IU/L) ACC/AHA/NBHLI- stop therapy
  - NLA- stop if symptoms intolerable

Recommendations

- Baseline CPK and Pain scale
- If CPK elevated rule out other causes (hypothyroidism)
- IF CPK less than 5 x ULN – follow closely, discontinue if symptomatic-check CPK weekly until stable or significantly changes
- If CPK > 5 but less than 10 x normal either discontinue or switch drug

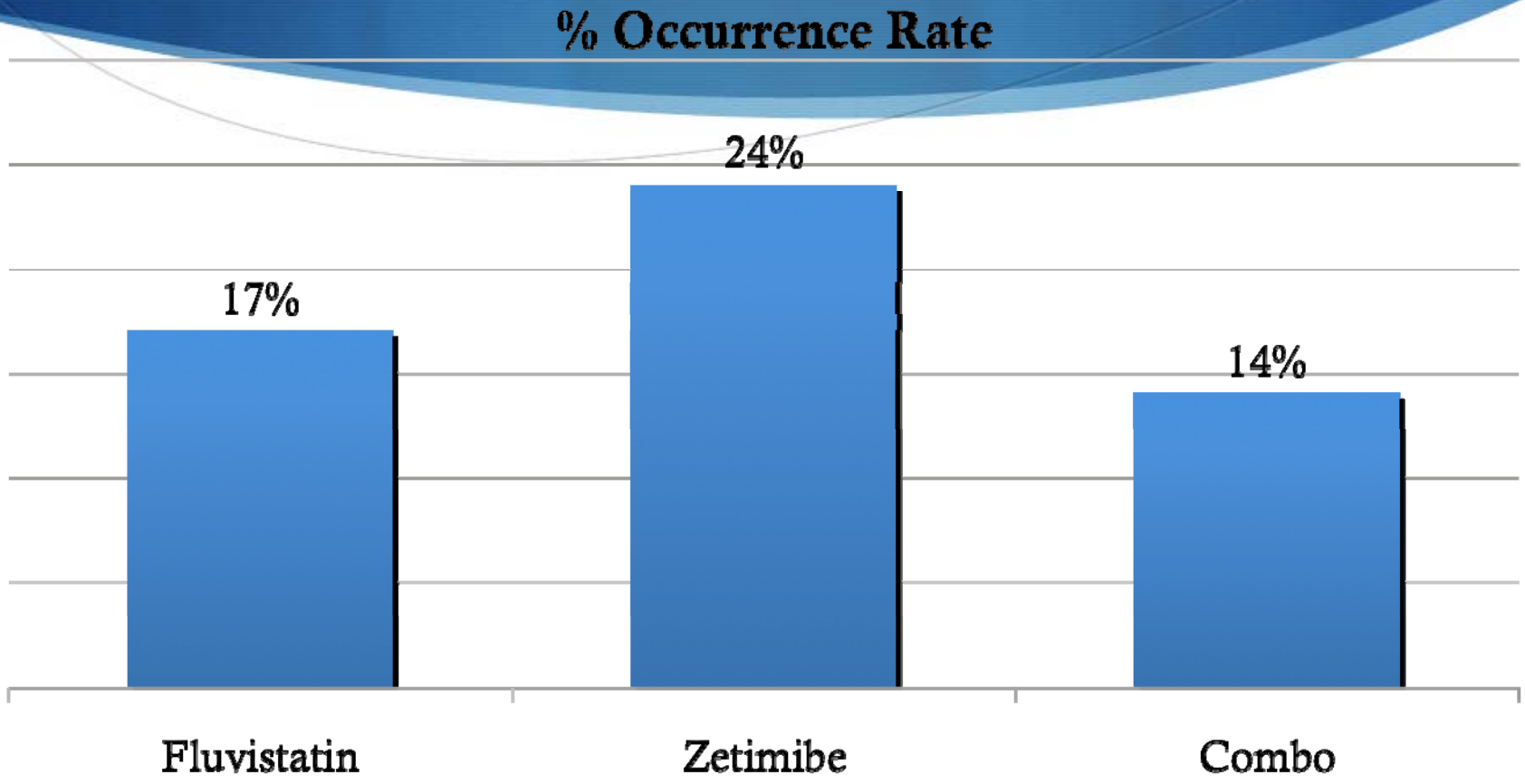
Switching Drugs

- Consider changing to fluvistatin or rosuvastatin
  - PRIMO study showed that patients receiving fluvastatin had fewer myopathy symptoms than did those receiving lovastatin, simvastatin, or atorvastatin.
  - No case of fatal rhabdomyolysis has ever been reported with fluvastatin.

Switching Statins

- Stein et al. 2008 12 week treatment using extended-release fluvastatin, 80 mg/d; ezetimibe 10 mg/d; or the combination:
  - 199 patients
  - Symptomatic with other statins
  - No cases of CPK elevation > than 10 X ULN

Myopathic Symptoms



- Alter dosages i.e. alternate daily dosing:
  - Atorvastatin and
  - Rosuvastatin - metabolized by CYP2C9
- Bile resin binders
- Ezetimibe
- Coenzyme Q-10

Case One

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Case Two

- A 38 year old male with polymyositis presents for evaluation. He currently is moderately controlled on prednisone 10mg daily and cyclosporine. His most recent CPK is 540 (down from 4200 four months earlier) His strength is good.
- CVD risks are high with family history and smoking.

- None are considered “safe”
- Myalgias are not uncommon with statins
- Rhabdomyolysis is still rare
- Risk factors need to be considered in prescribing
- Consider aggravating causes such as the CY3A4 system

- Genetics can play a part- genotyping may be helpful
- Treatment options include switching drugs and alternate dosing regimens
- Mechanism or mechanisms are still unclear

- Golomb and Evans " Statin Adverse Effects: A review of the Literature and Evidence fo a Mitochondrial Mechanism" Am J Cardiovsc Drugs 2008;8(6)n317-418
- Hansten " Possible risks to patients receiving statins combined with other medications" 2003;41;519-520 *J. Am. Coll. Cardiol.*
- Joy and Hegele "Narrative Review: Statin-Related Myopathy" Ann Intern Med. 2009;150:858-868
- Mammen and Amato " Statin myopathy: a review of recent progress: " Curr Opin Rheumatol 22:644–650
- Vaklavass et al "Molecural Basis of Statin Myopathy" Athersclerosis 2009 (202) 18-28

- Rodriguez LA, et. al. The Safety of Rosuvastatin in Comparison with other Statins in over 100,000 Statin Users in UK Primary Care. Pharmaco epidemiol DrugSaf 2008; 17:943– 952
- BackesJM, VeneroCV, GibsonCA, et al. Effectiveness and tolerability of every-other day rosuvastatin dosing in patients with prior statin intolerance. AnnPharmacother 2008; 42:341–346
- Wlodarczyk J, SullivanD, SmithM. Comparisonof benefits and risks of Rosuvastatin versus atorvastatin from a meta-analysis of head-to-head rando- Mized controlled trials. AmJCardiol 2008; 102:1654–1662.


HAPPY
HALLOWEEN