Disclosures

- Relevant Financial Disclosures
  - License for anti-HMGCR antibody test
  - Served on medical advisory board
    - Biogen
    - aTyr
- Non-FDA Approved uses
  - Few treatments for myositis are FDA-approved

Andrew Mammen, MD, PhD

Statin Myopathies

Andrew Mammen, M.D., Ph.D.
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Known Myotoxins

ε-aminocaproic acid
Amiodarone
Apamin
AZT
Barium
Chlorophenoxy
Chloroquine
Ciguatoxin
Clofibrate
Colchicine
Corticosteroids
Crotamine
Crotoxin
Cyclosporine
20,25-Diazacholesterol
Emetine
Ethanol
Fibrates
Germanium
Gold
Gossypol
Interferon-α
Ipecac
Isotretinoin
Lithium
Mojave toxin
Penicillamine
Pentaborane
Procainamide
Propofol
Statins
Taipoxin
TNF-α
Toxic oil
L-tryptophan
Valproate
Vecuronium bromide
Vinca alkaloids
Zidovudine

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Statins

- Millions and millions of Americans treated
- Reduce cardiovascular end-points by 30%
- In trials, muscle complaints rarely different between placebo and statin groups
- Post-market surveillance*
  - 2-11% myalgias
  - 0.5% muscle sx with increased CK levels
  - 0.1% rhabdomyolysis

* With statin therapy alone

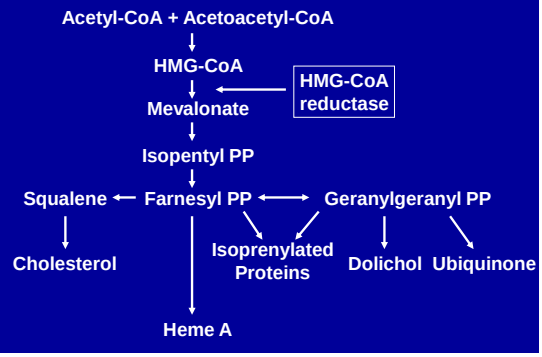
Features of Statin Myopathy

- Duration of therapy before symptom onset*
  - Median 6.3 months (1 wk to 4 yrs)
- Self limited
  - Median duration of myalgia after cessation of statin = 2.3 months (1 wk to 14 months)

*Hansen et al., Arch Intern Med 2005

Proposed Mechanisms of Statin Myopathy

Cholesterol Synthesis



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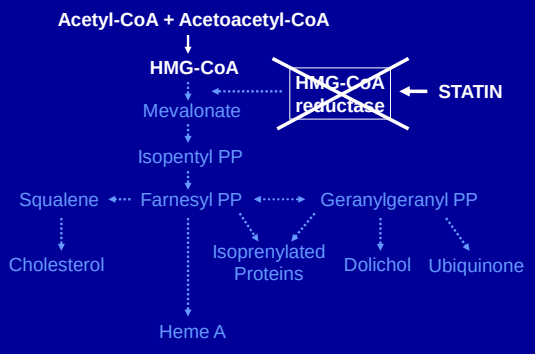
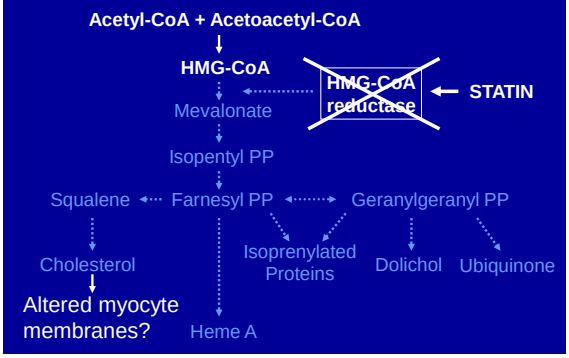
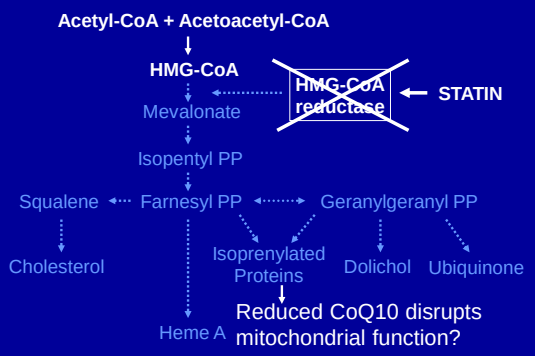


Statin Toxicity Mechanism 1



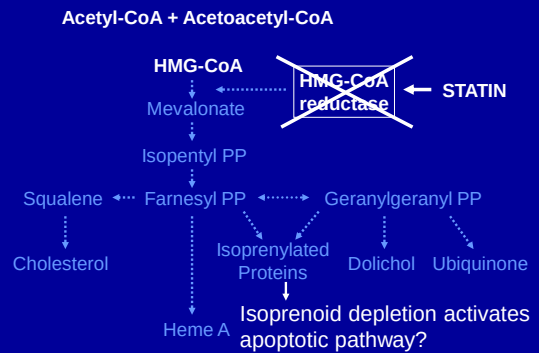
Statin Toxicity Mechanism 2



Preventing Statin Myopathy: Coenyzyme Q10 supplementation?

- CoQ10 depletion may contribute to statin myopathy
- No convincing evidence to support efficacy in preventing/treating statin myopathy
- Some recommend trial of 200 mg/day CoQ10 prior to statin rechallenge and during course of therapy

Statin Toxicity Mechanism 3



Factors that increase risk of statin-associated myopathy

- Dose (of simvastatin)
  - 0.02% at 20 mg/day
  - 0.07% at 40 mg/day
  - 0.3% at 80 mg/day
- Patient characteristics
  - Elderly
  - Kidney disease
  - Heavy alcohol use
  - Hypothyroidism
  - Biliary tract obstruction
  - Underlying muscle disease

Pharmacokinetics: Statins are not created equal…

- CYP3A4 metabolism (more myotoxic)
  - Lovastatin
  - Simvastatin
  - Atorvastatin
- No CYP3A4 metabolism (less myotoxic)
  - Pravastatin
  - Fluvastatin
  - Rosuvastatin

Drugs Metabolized by or Inhibiting CYP3A4*

- Antimicrobial
  - Clarithromycin
  - Clotrimazole
  - Erythromycin
  - HIV protease inhibitors
  - Ketaconazole
  - Rifampin
- Cardiovascular
  - Amiodarone
  - Amlodipine
  - Digitoxin
  - Diltiazem
  - Fibrates
  - Nifedipine
- CNS
  - Alprazolam
  - Carbamazepine
  - Fluoxetine
  - Imipramine
  - Setraline
- Other
  - Cimetidine
  - Cyclosporine
  - Grepefruit juice
  - Omeprazole
  - Tacrolimus
  - Troglitazone
  - Sildenafil

*not a complete list

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*not a complete list

HIV protease inhibitors and statin pharmacokinetics

- Randomized, open-label, HIV-, 56 subjects
- Ritonovir + Saquinavir
  - + simvastatin = 3059% increased statin conc.
  - + atorvastatin = 79% increased statin conc.
  - + pravastatin = 50% decreased statin conc.

Fichtenbaum et al., AIDS 2002 16:569

Other Drug Interactions

- Amiodarone
  - 80 mg/day simvastatin + amiodarone = 6% risk of myopathy
- Fibrates
  - Fibrate + statin = 10 fold-increased risk of rhabdomyolsis (pravastatin may be safest)
- Cyclosporine
  - Lovasatin/simvastatin + Cys = ~20% risk of myopathy
  - Only pravastatin approved for use with Cys

Genetic predisposition to statin myopathy

- The SEARCH Collaborative Group (NEJM 2008:789)
- 12,064 patients who had an MI
- Simvastatin: 80 mg/d (6031 pts) vs 20 mg/d (6032 pts)
- Definite myopathy (sx + CK > 10x nl)
  - **49** on 80 mg/d
  - **2** on 20 mg/d
- Incipient myopathy (CK > 3X nl & > 5x baseline)
  - **49** on 80 mg/d
  - **6** on 20 mg/d

Genomewide association study

- 96 participants in whom myopathy developed on 80 mg/day simvastatin
- 96 matched controls with no myopathy on 80/mg day simvastatin
- Single-nucleotide polymorphism (SNP) analysis performed using DNA from 85 cases and 90 controls

A single SNP has a strong association with statin myopathy

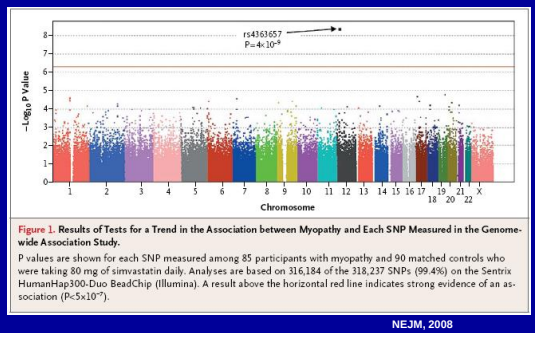


Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

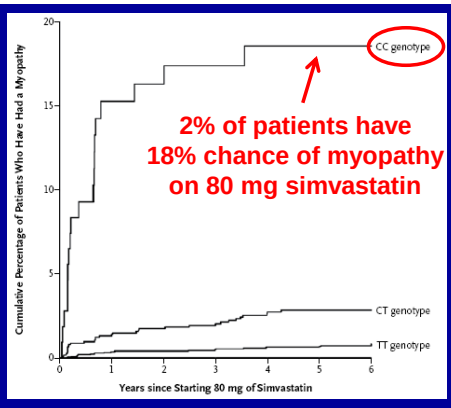
P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association ($P<5\times10^{-7}$).

NEJM, 2008

From SNP to pathophysiology…

- The identified SNP is within the gene coding for organic anion-transporting polypeptide OATP1B1
- OATP1B1 has been shown to regulate the hepatic uptake of statins
- The identified SNP distinguishes between those who have the "C" and "T" allele
- Statin blood concentrations are higher in those with the "C" allele
- Odds ratios for *SLCO1B1* "C" allele
  - **Heterozygotes 4.4**
  - **Homozygotes 17.4**

NEJM, 2008

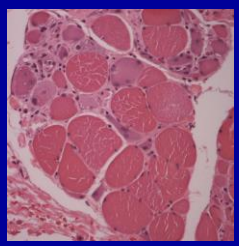


NEJM, 2008

A Case

- 71 year-old gentleman with HTN, Type 2 DM, and hypercholesterolemia
- Three years earlier: started on a statin
- December: antibiotics for bronchitis; myalgias
- January: myalgias and leg weakness
- February 1: arms weak; stopped statin
- March 24: using cane; CK 8,800
- April 16: using wheelchair; hoarse voice
  - EMG: irritable myopathy
  - Exam:
    - Neck flexors 4/5, arm abductors 4-/5, hip flexors 2/5
    - No rash

Muscle biopsy shows a necrotizing myopathy

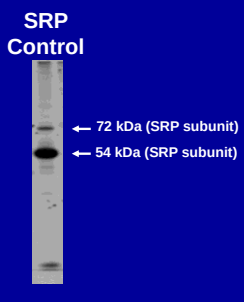


Degeneration and regeneration with no inflammation

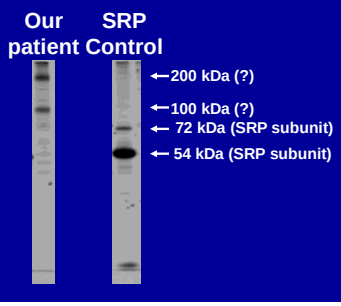
- **Autoimmune**
  - **Anti-SRP immune-mediated necrotizing myopathy**
- **Paraneoplastic myopathy**
- **Muscular dystrophy**
- **Toxic myopathy**
  - **Self-limited statin myopathy**

Testing for autoantibodies

1. **Grow HeLa cells**
2. **Radioactively label cell proteins**
3. **Make cell lysates**
4. **Use patient sera to immunoprecipitate proteins from radioactively labeled HeLa cell lysates**
5. **Run immunoprecipitated protein on a gel**
6. **Expose gel to film**



Autoantibody screening: negative for anti-SRP, but other proteins recognized by sera



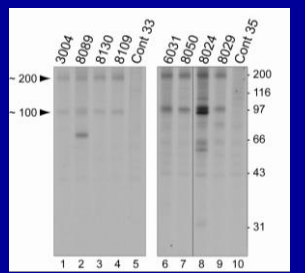
Are there other autoantibodies associated with necrotizing myopathy?

- **225 patients with available muscle biopsy and serum (not our entire cohort)**
- **38 (17%) with necrotizing myopathy on biopsy**
- **12/38 necrotizing myopathy patients had defined disease**
  - **6 anti-SRP**
  - **4 anti-synthetase**
  - **1 profound hypothyroidism**
  - **1 dysferlinopathy (LGMD)**

Christopher-Stine et al., A&R 2010

Serum from idiopathic necrotizing myopathy cases immunoprecipitates 200 and 100 kDa proteins from S^{35}-labeled HeLa cells

- **Sera from 16/26 (62%) remaining patients immunoprecipitated a pair of proteins at 100 and 200 kDa**
- **Only 1/187 (0.5%) patients without prominent necrosis had this immuno-specificity**
- **Anti-200/100 is highly specific for necrotizing myopathy and is found in ~7% of our patients**



Christopher-Stine et al., A&R 2010

Increased statin use in anti-200/100 subjects

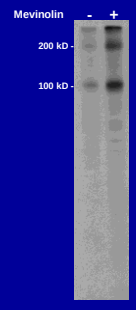
Phenotype	Frequency of Statin Use	Mean age of patient population
Anti-200/100 (age > or = 50)	10/12 (83.3%)	64.4 +/- 9.2
DM (age > or = 50)	4/16 (25%)*	61.0 +/- 8.3
PM (age > or = 50)	7/19 (36.8%)*	60.4 +/- 7.6
IBM (age > or = 50)	10/30 (33.3%)*	68.4 +/- 9.2

** Indicates age significantly different from the anti-200/100 group by use of t-test

* Indicates proportions significantly different from the anti-200/100 group by use of chi2-test

Christopher-Stine et al., A&R 2010

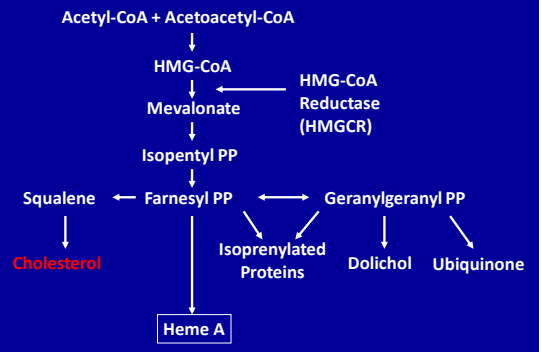
An important clue in identifying the autoantigens: statin treatment up-regulates their expression



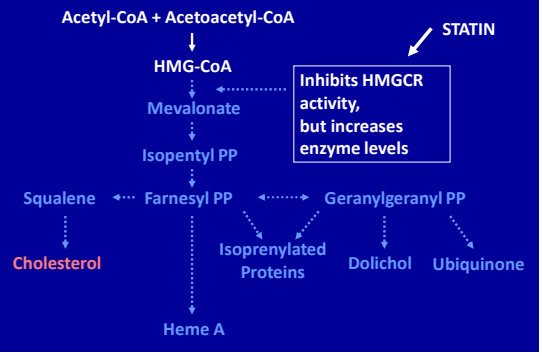
With and without 10 uM mevinolin for 24 hours prior to labeling

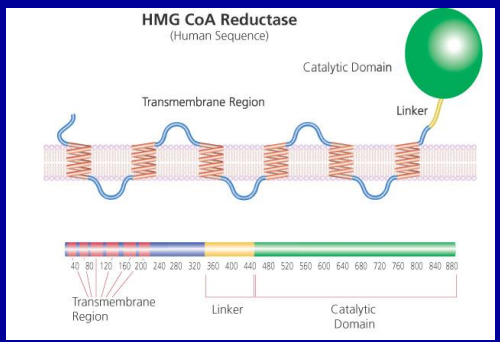
Mammen et al., A&R 2011

Cholesterol Synthesis

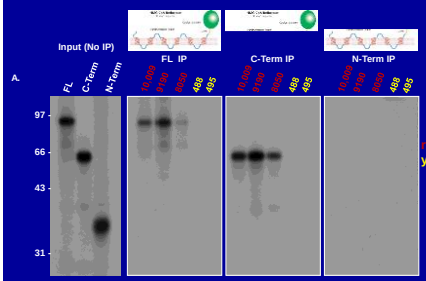


Cholesterol Synthesis





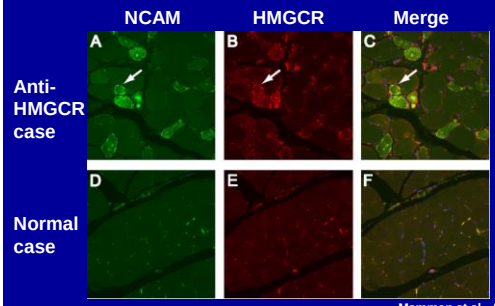
HMGCR protein is immunoprecipitated by serum from patients with statin-associated autoimmune myopathy



red = anti-200/100 serum
yellow = control serum

Mammen et al., A&R 2011

Regenerating muscle fibers express high levels of HMGCR



Mammen et al., A&R 2011

Clinical Features of anti-HMGCR myopathy patients

- Myopathy triggered by statins (70%)
- Progresses despite discontinuing statins
- Requires immunosuppressive therapy to treat (more to follow…)
- No clear gender bias
- 100% proximally weak
- 75% with myalgias
- Maximum CK ~10,000

Christopher-Stine et al., A&R 2010

Features of statin use in anti-HMGCR patients

- Duration of use before onset of muscle symptoms: 31.3 +/- 27.4 months (range 0-84 months)
- Statin used: variable

Anti-HMGCR antibodies are specific for those with autoimmune myopathy

- Not present in any of 1966 participants of community-based ARIC cohort
  - 763 current statin users
  - 322 former statin users
  - 881 statin-naïve subjects
- Not present in 51 patients with self-limited statin intolerance

Mammen et al., AC&R 2012

Anti-HMGCR myopathy: response to therapy

- 12 statin-exposed and 5 statin-unexposed anti-HMGCR positive subjects (each with 5+ visits)
- Analyzed trends over five visits (26 +/- 12 months)
- Treatment of statin-exposed
  - Prednisone + 2 other agents (58%)
  - Prednisone + 1 other agent (25%)
  - Prednisone only (8%)
  - Agent other than prednisone only (8%)
- Treatment of statin-unexposed
  - Prednisone + 2 other agents (60%)
  - Prednisone + 1 other agent (40%)

Werner et al., A&R, 2012

Only Statin-Exposed Subjects Improve with Treatment

Table 5. Clinical features of anti-HMGCR subjects at visits #1 and #5.

All anti-HMGCR subjects	visit #1	visit #5	p-value
Anti-HMGCR titer (NAU) (n=17)	1.17 (0.46)	0.88 (0.42)	*0.003**
Serum CK level (IU/L) (n=15)	4291 (3216)	2031 (4404)	0.100
Arm abduction strength (n=14)	15.79 (4.87)	18.07 (4.51)	0.166
Hip flexion strength (n=13)	11.08 (6.38)	16.00 (5.99)	0.122
Statin-exposed anti-HMGCR subjects			
Anti-HMGCR titer (NAU) (n=12)	1.16 (0.47)	0.79 (0.32)	*0.003**
Serum CK level (IU/L) (n=10)	3870 (1727)	950 (1912)	*0.006**
Arm abduction strength (n=10)	15.50 (5.56)	19.20 (1.40)	*0.039**
Hip flexion strength (n=9)	10.56 (6.29)	18.00 (1.73)	*0.009**
Statin-naive anti-HMGCR subjects			
Anti-HMGCR titer (NAU) (n=5)	1.31 (0.48)	1.15 (0.67)	0.403
Serum CK level (IU/L) (n=5)	5134 (5308)	4194 (7133)	0.811
Arm abduction strength (n=4)	16.50 (3.00)	15.25 (8.22)	0.754
Hip flexion strength (n=4)	12.25 (7.41)	11.5 (9.81)	0.934

Werner et al., A&R 2012

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Werner et al., A&R 2012

Are there immunogenetic risk factors for developing anti-HMGCR antibodies?

HLA Typing of anti-HMGCR subjects vs. controls

- HLA-DR11 in Caucasians
  - 14/20 (70%) anti-HMGCR subjects
  - 89/487 (18%) controls
  - $p=1.2 \times 10^{-6}$
- HLA-DR11 in African Americans
  - 7/8 (88%) anti-HMGCR subjects
  - 35/167 (21%) controls
  - p=0.0002

Mammen et al., AC&R 2012

DRB1*11:01 is strongly associated with anti-HMGCR

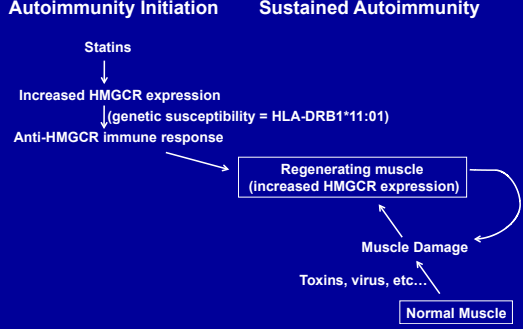
- Fine mapping: 95% DRB1*11:01
- Odds ratios for DRB1*11:01 in subjects vs. controls
  - Caucasians: 24.5 ($p = 3.2 \times 10^{-10}$)
  - African Americans: 56.5 ($p = 3.1 \times 10^{-6}$)
- A very strong link between an HLA allele and an autoimmune disease

Mammen et al., AC&R 2012

Conclusions

- Anti-HMGCR antibodies are found in those with immune-mediated necrotizing myopathy and not in those with self-limited statin intolerance
- Statins may trigger this autoimmune process, possibly by increasing expression of HMGCR
- HLA-DRB1*11:01 is a risk factor for developing anti-HMGCR antibodies
- Statin-exposed subjects respond well to immunosuppressive therapy

HMGCR autoimmunity: a model



A practical approach to patients with suspected statin-associated muscle symptoms

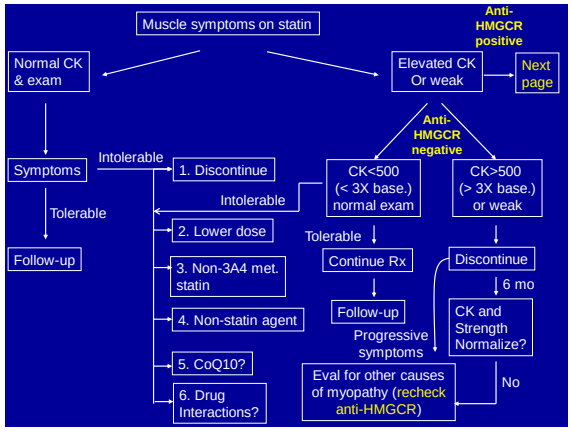
CK Monitoring

- Routine monitoring of CK *after* initiation not recommended
- AHA/NHLBI Statin Advisory Panel recommends measuring CK *prior* to therapy
- NLA Muscle Expert Panel does not
- Why do I recommend checking a baseline CK prior to initiating statin treatment…?

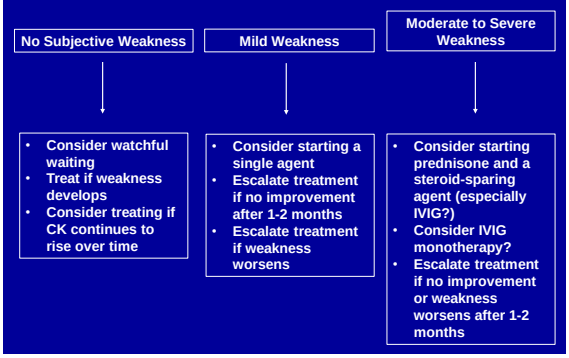
Normal Serum CK Distribution

	Median	97th percentile
All subjects	111	460
Women	95	349
Men	143	616
White	88	286
Women	72	201
Men	110	322
South Asian	104	382
Women	87	313
Men	143	641
Black	149	627
Women	124	414
Men	213	801

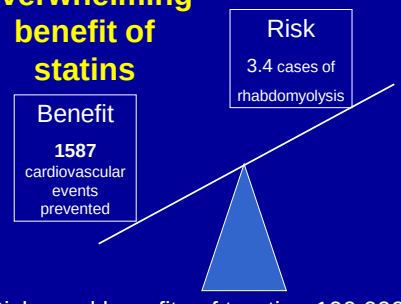
From Brewster, 2007



Anti-HMGCR Positive



Overwhelming benefit of statins



Risks and benefits of treating 100,000 patients with statin for 1 year

Adapted from Harper and Jacobson, Current Op in Lip;2007, 18:401

Acknowledgements

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Case #1

- 65 year-old Caucasian man s/p MI
- On simvastatin 80 mg/d for 6 weeks
- Develops mild myalgias
- CK = 1200
- Meds: no other myotoxins

- Baseline CK = 125
- Discontinue statin
- Wait for CK to normalize
- Consider low dose pravastatin or fluvastatin qod
- With close monitoring, increase dose as tolerated

Case #2

- 65 year-old AA man s/p MI
- On simvastatin 80 mg/d for 6 weeks
- Develops mild myalgias
- CK = 1000
- Meds: no other myotoxins

- Baseline CK = 600
- Continue statin
- Follow-up CKs and monitor for worsening symptoms

Case #3

- 65 year-old Caucasian woman s/p MI
- On simvastatin 80 mg/d for 6 weeks
- Develops mild myalgias
- CK = 600
- Meds: no other myotoxins

- Baseline CK = 105
- Discontinue statin
- Wait for CK to normalize…but it doesn't…and patient begins to develop weakness…

Case #3

- Neuromuscular consult
  - EMG: irritable myopathy
  - Thigh MRI: muscle edema
  - Muscle biopsy 4 months after stopping statin shows necrotizing myopathy
  - Positive anti-HMGCR antibodies
  - Consider immunosuppression