Evaluating, Managing, and Treating Statin Intolerance

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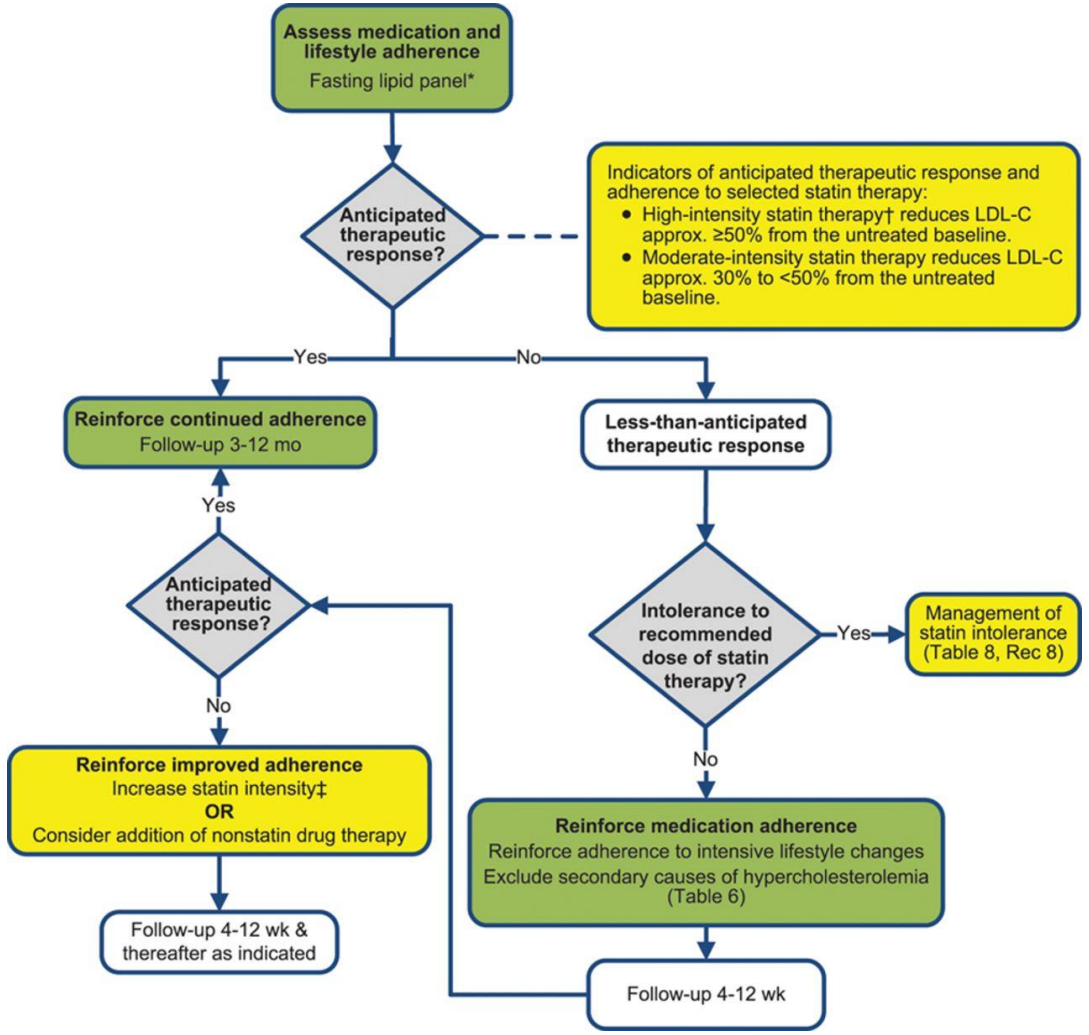
Evaluating for Statin Intolerance

Helping Cardiovascular Professionals
Learn. Advance. Heal.

Statin Therapy: Monitoring Therapeutic Response and Adherence.



The management of statin intolerance

Neil J. Stone et al. Circulation. 2014;129:S1-S45

American Heart Association.

Current Guidelines Suggestions
1st Assess and Evaluate for:

- Less anticipated therapeutic response due to:
  - poor adherence
  - Myalgias
  - hair loss
  - malaise,
  - GI upset
- Individuals intolerant of the recommended intensity of statin therapy should use the maximally tolerated intensity of statin.
  - Establish the symptoms are statin related by a statin re-challenge.
  - Rule out secondary causes of statin intolerance.

Stone et al. JACC 2013 ACC/AHA Blood Cholesterol Guideline (Table 3)

Statin Safety Recommendations.

2013 ACC/AHA Recommendations

- Refer to Table 8 in your briefing materials (pictured to the right)
- Obtain a history of muscle symptoms.
- Unexplained severe pain, discontinue and evaluate CK, UA for myoglobinuria for rhabdomyolysis.
- For mild to moderate musculoskeletal pain, re-challenge statin.
- If causal relationship with previous statin, use low dose different statin.
- Evaluate patient for other secondary causes.

Stone et al. ACC/AHA 2013 Blood Cholesterol Guidelines

Factors that Increase the Risk of Statin-Induced Myopathy

Patient Characteristics

- Increased age
- Female
- Renal insufficiency
- Hepatic dysfunction
- Hypothyroidism
- Diet- grapefruit and other juices potentiate statin
- Polypharmacy
- Rheumatologic disorders

Statin Properties

- High systemic exposure
- Lipophilicity
- High bioavailability
- Limited protein binding
- Potential for drug-drug interactions metabolized by the CYP pathways (especially CYP 450 3A4)

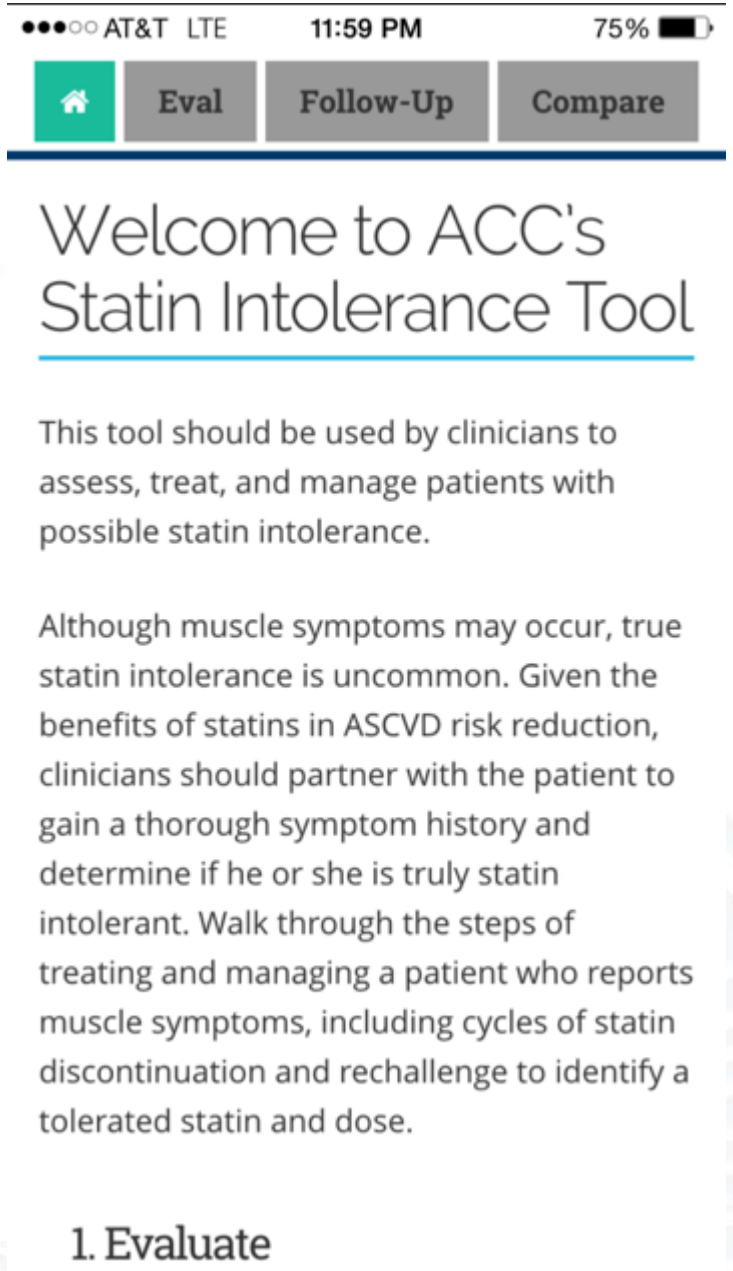
Rosenson. Am J Med. 2004; 116:408-416.
Stone et al. ACC/AHA 2013 Blood Cholesterol Guidelines

Clinical Evaluation of Statin Myopathies

- History:
  - Obtain h/o MSK complaints prior to statin initiation
  - Focus on timing of symptoms in relation to statin initiation/titration
  - Unusual physical activity or concurrent illness
  - Diet (daily grapefruit consumption)
  - Clues to suggest other causes of myopathy
    - Hypothyroidism
    - Vitamin D deficiency
    - Autoimmune disease
    - Neuromuscular disease
    - Systemic illness

- Medications
  - Drugs that inhibit cytochrome P450 3A4 (clarithromycin, HIV meds, voriconazole, etc)
  - Fibrates
  - Independently cause myopathy (steroids, cyclosporine, etc)

- Physical exam
  - Proximal LE weakness



Review of Statins

- There are 7 Statins Available
  - Atorvastatin
  - Fluvastatin
  - Lovastatin
  - Pitavastatin
  - Pravastatin
  - Rosuvastatin
  - Simvastatin

CYP450 Isoenzymes Known to Oxidize Clinically Used Drugs

- CYP2C9
  - alprenolol, diclofenac, fluconazole, **fluvastatin**, hexobarbital N-desmethyldiazepan, tolbutamide, warfarin
- CYP3A4
  - amlodipine, amiodorone, **atorvastatin**, clarithromycin, cyclosporine A, diltiazem, erythromycin, ketoconazole, itraconazole, **lovastatin**, mibefradil, midazolam, nefazodone, nifedipine, protease inhibitors, quinidine, sildefanil, **simvastatin** (including combos), terbinafine, verapamil, warfarin

Rosuvastatin: CYP2C19 and biliary excretion

Pravastatin: Sulphation, biliary excretion, urinary excretion

Pitavastatin: CYP2C8, CYP2C9 and lactonization and biliary excretion

Modified from Brower et al., In: Evans W.E. (Ed). Applied Pharmacokinetics. Principles of the Therapeutic Drug Monitoring, 3rd ed., 1992
2015 updated by Dr. Rhonda Cooper Dehoff

Safety Considerations with Dosing Statins

- Use reduced dosages of drugs when prescribing statins in the same CYP450 pathway.
  - Increased risk of toxicity
  - Increased risk of myopathy
  - Increased risk of rhabdomyolysis

Clinical Pearl….

- If a patient is achy on Simvastatin, they may also be achy on Atorvastatin as it uses the same CYP3A4.
- Try a Statin with a different CYP450 pathway such as Rosuvastatin, Fluvastatin, Pitavastatin and select based on your LDL reduction goal (If we still use goals???).

Lipid Clinic Treatment Strategies

- Avoid drug- drug Interactions
- Select a drug with less utilization of the CYP pathway
- Alternate Statin Dosing (Monday, Thursday dosing for 1 month add one day per week as tolerated).
- Daily Low Dose Statin
- Use Hydrophilic Statins (**pravastatin**, **rosuvastatin**, and **fluvastatin)**
- Plant Sterols 5-10% reduction
- Soluble Fiber
- Mediterranean Eating- PUFAs
- Less data- Vitamin D, Co Q 10

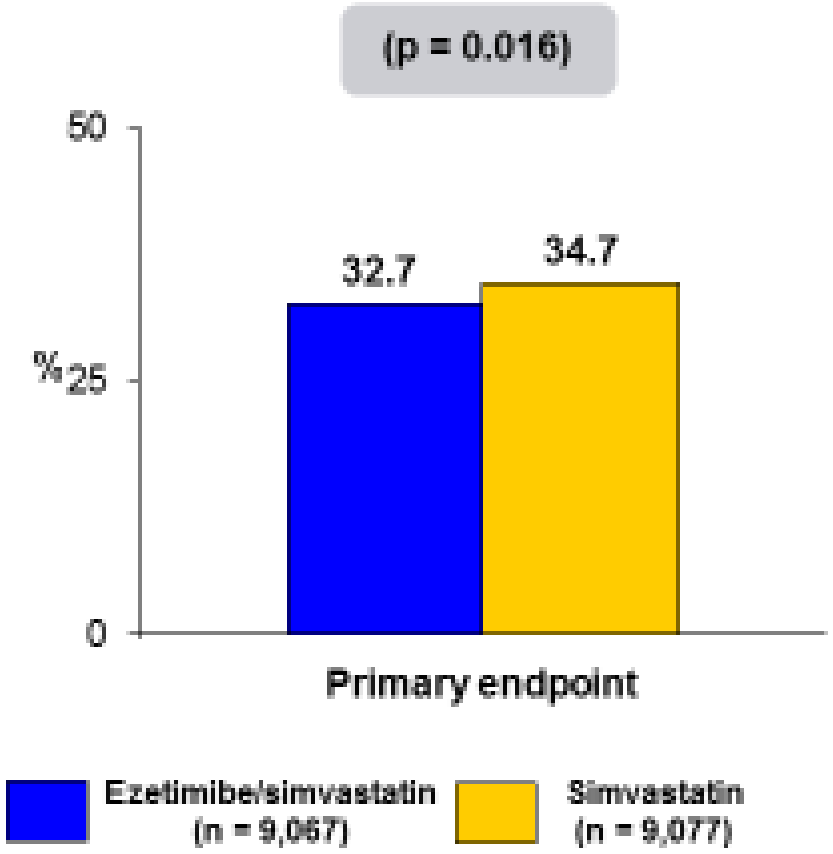
What if your patient is still not medically optimized?

Before considering alternate statin therapies,

- Reiterate adherence to lifestyle and statin therapy
- For patients who are completely statin intolerant, may consider the addition of a non-statin cholesterol-lowering therapy (remember there are 7 to try).
- Add on therapy

IMPROVE-IT

Trial design: Patients with recent ACS were randomized in a 1:1 fashion to either ezetimibe 10 mg/simvastatin 40 mg or simvastatin 40 mg. They were followed for 6 years.



Results

- Primary endpoint (CV death/MI/UA/coronary revasc./stroke/moderate/severe bleeding) for ezetimibe/simvastatin vs. simvastatin: 32.7% vs. 34.7%, HR = 0.94, 95% CI 0.89-0.99; p = 0.016
- MI: 13.1% vs. 14.8%, p = 0.002; stroke: 4.2% vs. 4.8%, p = 0.05; CVD/MI/stroke: 20.4% vs. 22.2%, p = 0.003
- Median LDL follow-up average: 53.7 vs. 69.5 mg/dl

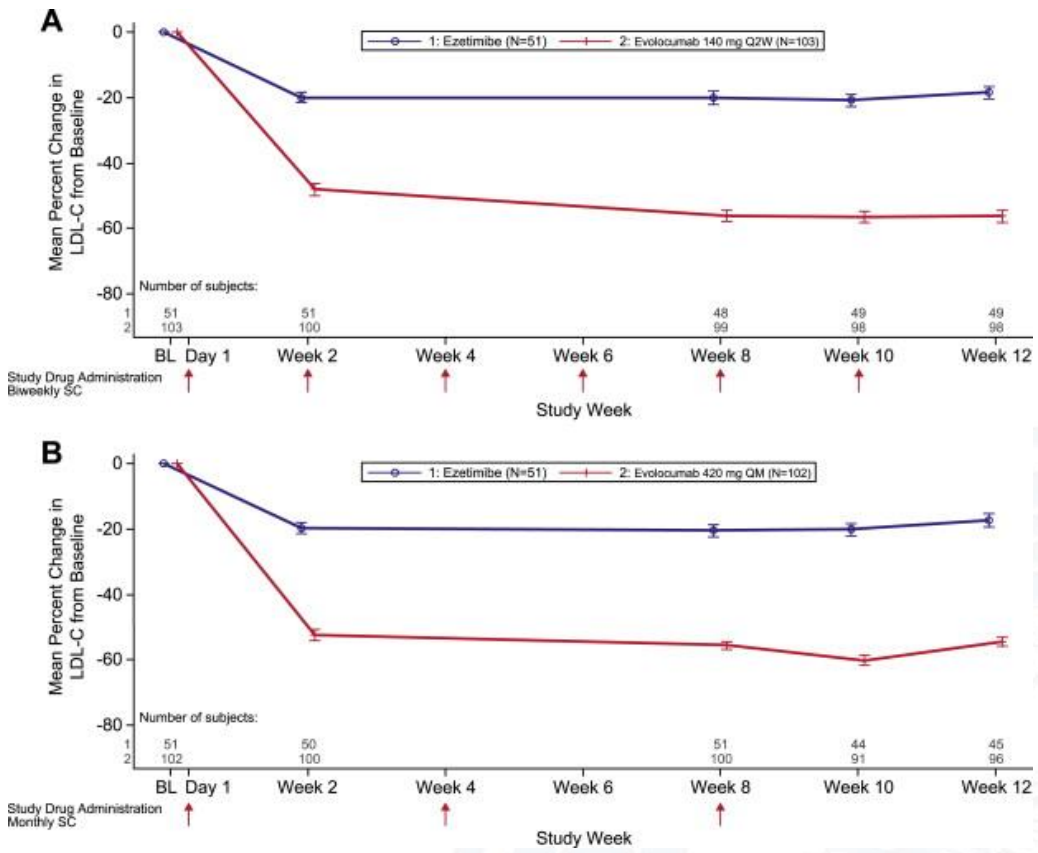
Conclusions

- In patients with high-risk ACS, ezetimibe 10 mg/simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing adverse CV events
- This is the first study powered for clinical outcomes to show a benefit with a nonstatin agent
- Reaffirms the "lower is better" hypothesis with LDL-C

Presented by Dr. Christopher Cannon at AHA 2014

Safety and efficacy of PCSK9 inhibitors in patients with statin intolerance

PCSK9 Inhibitor effectively lowers LDL-C in patients with statin intolerance : GAUSS-2 randomized, placebo-controlled Phase 3 clinical trial of evolocumab

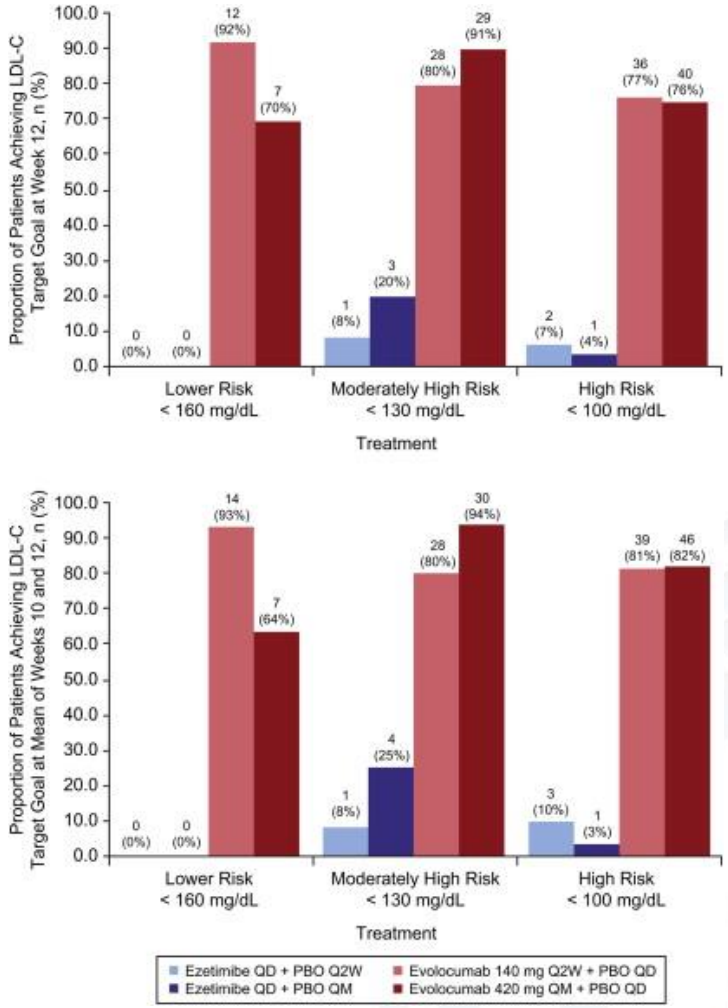


Mean Percent Change in LDL-C from Baseline to Week 12 in Patients Who Received Evolocumab

- Patients who received evolocumab
  - (A) every 2 weeks
  - (B) monthly.

JACC.2014;63:2541–2548

Evolocumab effectively lowers LDL-C in patients with statin intolerance : GAUSS-2 randomized, placebo-controlled Phase 3 clinical trial of evolocumab



Percentage of Patients Achieving Low-Density Lipoprotein Cholesterol Goal at Week 12 and at Mean of Weeks 10 and 12 Stratified by National Cholesterol Education Program Risk Category Rates based on patients with observed values and LDL-C above target ...

JACC. 2014;63:2541–2548

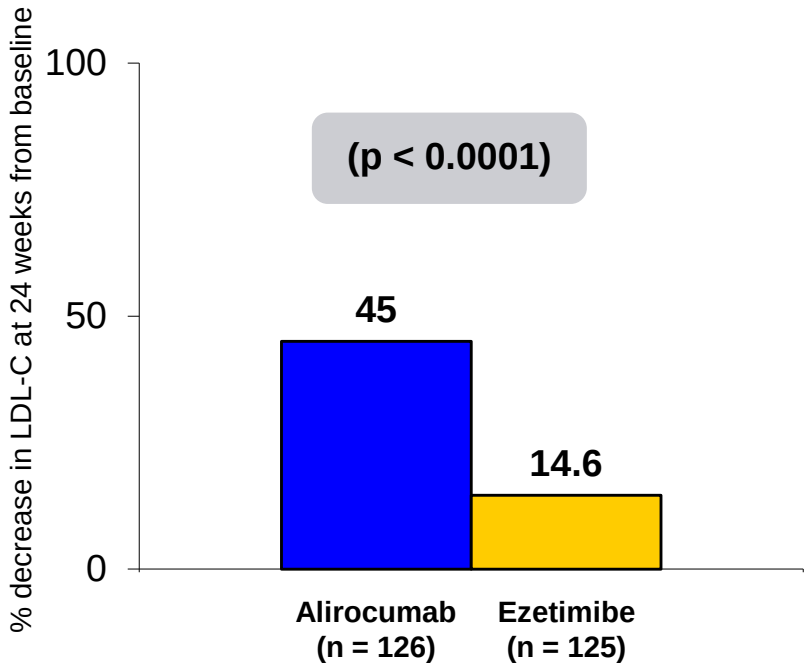
GAUSS-2: Adverse events on placebo, ezetimibe, evolocumab

Event	Ezetimibe			Evolocumab		
	QD + PBO Q2W (n = 51)	QD + PBO QM (n = 51)	All (N = 102)	140 mg Q2W + PBO QD (n = 103)	420 mg QM + PBO QD (n = 102)	All (N = 205)
Treatment emergent						
Any	35 (69)	39 (77)	74 (73)	63 (61)	72 (71)	135 (66)
Serious	1 (2)	3 (6)	4 (4)*	5 (5)	1 (1)	6 (3)†
Leading to discontinuation of investigational product	4 (8)	9 (18)	13 (13)	6 (6)	11 (11)	17 (8)
Deaths	0	0	0	0	0	0
Common treatment emergent‡						
Headache	3 (6)	6 (12)	9 (9)	4 (4)	12 (12)	16 (8)
Myalgia	7 (14)	11 (22)	18 (18)	7 (7)	9 (9)	16 (8)
Pain in extremity	0	1 (2)	1 (1)	2 (2)	12 (12)	14 (7)
Muscle spasms	3 (6)	1 (2)	4 (4)	5 (5)	8 (8)	13 (6)
Fatigue	4 (8)	6 (12)	10 (10)	3.(3)	6 (6)	9 (4)
Nausea	2 (4)	5 (10)	7 (7)	3 (3)	6 (6)	9 (4)
Nasopharyngitis	3 (6)	0	3 (3)	5 (5)	2 (2)	7 (3)
Diarrhea	3 (6)	4 (8)	7 (7)	3 (3)	2 (2)	5 (2)
Injection site erythema	0	3 (6)	3 (3)	2 (2)	2 (2)	4 (2)
Paraesthesia	1 (2)	4 (8)	5 (5)	0	2 (2)	2 (1)
Influenza	3 (6)	0	3 (3)	1 (1)	0	1 (<1)
Pruritus	1 (2)	3 (6)	4 (4)	0	0	0
Abnormal laboratory tests						
CK >5 × ULN	3 (6)	0	3 (3)	0	2 (2)	2 (1)
CK >10 × ULN	1 (2)	0	1 (1)	0	0	0
ALT or AST >3 × ULN	0	0	0	0	0	0
Muscle-related SMQ	8 (16)	15 (29)	23 (23)	13 (13)	12 (12)	25 (12)
Myositis	0	0	0	0	1 (1)	1 (<1)
Myalgia	7 (14)	11 (22)	18 (18)	7 (7)	9 (9)	16 (8)
Musculoskeletal pain	1 (2)	2 (4)	3 (3)	1 (1)	2 (2)	3 (2)
Muscular weakness	0	1 (2)	1 (1)	2 (2)	0	2 (1)
Increased plasma creatinine	0	0	0	2 (2)	0	2 (1)
Blood CK increased	0	1 (2)	1 (1)	2 (2)	0	2 (1)
Potential injection site reactions§	1 (2)	7 (14)	8 (8)	3 (3)	3 (3)	6 (3)‖
Anti-evolocumab antibodies						
Binding	NA	NA	NA	0	0¶	0
Neutralizing	NA	NA	NA	0	0¶	0
Neurocognitive adverse events#	0	0	0	0	0	0

JACC.2014;63:2541–2548

ODYSSEY ALTERNATIVE

Trial design: Patients with statin intolerance were randomized in a 2:2:1 fashion to either self-administered alirocumab 75 mg SC Q2W, ezetimibe 10 mg daily, or atorvastatin 20 mg daily and followed for 24 weeks.



Results

- % decrease in LDL-C levels at 24 weeks from baseline for alirocumab vs. ezetimibe:
  - 45% vs. 14.6%, difference 30.4%, p < 0.0001
- Absolute ↓ in LDL from baseline:
  - 84 vs. 33 mg/dl
- LDL-C <100 mg/dl:
  - 61% vs. 10%, p < 0.0001
- Muscle-related side effects:
  - 32.5% vs. 41.1%, p = 0.096

Conclusions

- Alirocumab is superior to ezetimibe in lowering LDL-C levels and achieving target levels in statin-intolerant patients, with a lower risk of muscle-related side effects
- Trial adds to the growing body of literature with PCSK9 inhibitors

Moriarty PM at AHA Scientific Sessions. Chicago, IL 2014. LBCT.02

ODYSSEY ALTERNATIVE

	Alirocumab	Ezetimibe	Atorvastatin
Treatment emergent adverse event (%)	82.5	80.6	85.7
Serious adverse events (%)	9.5	8.1	11.1
Adverse events leading to discontinuation (%)	18.3	25.0	25.4
Skeletal muscle related adverse event (%)	32.5	41.1	46.0
Skeletal muscle related adverse event leading to discontinuation (%)	15.9	20.2	22.2

Moriarty PM at AHA Scientific Sessions. Chicago, IL 2014. LBCT.02

Final Thoughts

- Statin therapy is the gold standard for the management of the patient with ASCVD.
- There are several studies published on alternative dosing regimens however they are mainly small and observational but seem to be effective in the clinical setting.
- PCSK9 inhibitors are an exciting new therapy that may potentially become an addition/ alternative to statin therapy in patients who otherwise do not tolerate adequate statin dosing.

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Thank you