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Updates on Evidence-based Statin Re-challenge Guidelines

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Objectives

1. Summaries of Evidence-based Clinical Trials Involving Statins
2. The Statin Re-challenge Guidelines
3. The Centers for Medicare & Medicaid Services (CMS) Quality Star Measure Programs
   - SPC (Statin Therapy for Patients with Cardiovascular Disease)
   - SUPD (Statin Use in Persons with Diabetes)
     - Results from our Provider Phone Call Outreach Program

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1. Summaries of Evidence-based Clinical Trials Involving Statins

Article 1: Very low levels of atherogenic lipoproteins and risk of cardiovascular events; a meta-analysis of statin trials

- **Objective:** to evaluate the reductions in low-density lipoprotein cholesterol (LDL-C) associated with statin therapy and CVD risk.
- **Methods:** meta-analysis of 38,153 individual patient data from 8 randomized controlled statin trials in which LDL levels were determined in all study participants at baseline and at 1-year follow-up.
- **Major findings:** it was observed that a 38.7-mg/dL (1-mmol/L) reduction of LDL-C levels is accompanied by a 21% reduction in ASCVD risk (HR 0.79; 95% CI 0.66-0.94).

Article 2: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials

- **Objective:** to assess the safety and efficacy of more intensive lowering of LDL cholesterol with statin therapy
- **Methods:** meta-analyses of individual participant data from randomized trials involving at least 1000 participants and at least 2 years' treatment duration of more versus less intensive statin regimens (5 trials; 39,612 individuals) and of statin versus control (21 trials; 129,526 individuals).
- **Major findings:** Further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularization, and of ischemic stroke, with each 1.0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth (22%) (RR 0.78; 95% CI 0.76-0.80).
  - There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2-3 mmol/L would reduce risk by about 40-50%.

Article 3: Primary prevention of major cardiovascular and cerebrovascular events with statins in diabetic patients: a meta-analysis

- **Objective:** to assess the efficacy of statins in the primary prevention of the first-time occurrence of a major cardiovascular or cerebrovascular event in diabetic patients.
- **Methods:** a systematic search for trial reports was conducted in PubMed, EMBASE, The Cochrane library and clinicaltrials.gov for the years 1966-2011.
  - Four high-quality, randomized, double-blinded clinical trials (with a total of 10,187 participants) comparing a statin with placebo for the primary prevention of major cardiovascular and cerebrovascular events in diabetic patients were selected.
  - Only large studies with a minimum of 500 diabetic participants followed-up for at least 2 years were included. Endpoints were major cardiovascular and cerebrovascular events.
- **Major findings:** Treatment with statins in the primary prevention of major cardiovascular and cerebrovascular events in diabetic patients resulted in:
  - a significant relative risk (RR) reduction in the first-time occurrence of
    - major cardiovascular or cerebrovascular events (RR 0.75; 95% CI 0.67-0.85),
    - fatal/non-fatal stroke (RR 0.69; 95% CI 0.51-0.92), and
    - fatal/non-fatal myocardial infarction (RR 0.70; 95% CI 0.54-0.90).

Article 4: Low vitamin D does not predict statin associated muscle symptoms but is associated with transient increases in muscle damage and pain

- **Objective:** to examine the influence of baseline and change in Low vitamin D in patients with verified statin-associated muscle symptoms (SAMS).
- **Methods:** researchers randomized 120 patients with rigorously verified prior statin-related muscle complaints to 8 weeks of simvastatin at 20 mg/day and placebo in a double-blind crossover trial.
- **Major findings:**
  - 36% (43/120) of patients experienced muscle pain on simvastatin, but not while on placebo
  - 29% (35/120) had pain on placebo, but not on simvastatin
  - 17.5% (21/120) had pain on both simvastatin and placebo
  - 17.5% (21/120) didn't have pain on either
  - Vitamin D levels before and after statin therapy and placebo were not different in patients with and without confirmed SAMS (all $p>0.45$).

Article 5: Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation

- **Objective:** to assess whether vitamin D supplementation (vitamin D2: 50,000-100,000 units/week) to normalize serum vitamin D would allow successful rechallenge therapy with statins.
- **Methods:** prospective study of 146 patients with intolerable muscle symptoms on two or more statins, all of whom had a serum vitamin D below 32 ng/mL.
  - They were placed on long-term vitamin D2 at 50,000-100,000 units per week and rechallenged with a statin.
- **Major findings:** At 2 years of follow-up while still on supplemental vitamin D ($p<0.0001$):
  - 91% (75/82) of patients had a normal serum vitamin D,
  - 95% (78/82) of these previously statin-intolerant patients were on statin therapy without muscle complaints.

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Article 6: Adverse events associated with statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomized double-blind placebo-controlled trial and its non-randomized non-blind extension phase.

- **Objective:** to evaluate statin therapy adverse events (AEs)
- **Methods:** 10,240 patients aged 40-79 years with HTN & at least three other CV risk factors
  - were randomly assigned to atorvastatin 10 mg daily or matching placebo in a randomized **double-blind** placebo-controlled trial.
    - The rate of reporting of definite or probable muscle-related AEs was similar among patients randomly assigned atorvastatin or placebo:
    - 298 vs 283; HR 1.03 [95% CL 0.88-1.21].
  - In a subsequent non-randomized non-blind extension phase, all patients were offered atorvastatin 10 mg daily **open label**.
    - The rate of reporting of definite or probable muscle-related AEs were reported at a higher rate by statin users than by those who were not:
    - 161 vs 124; HR 1.41 [95% CL 1.10-1.79].
- **Major findings:** The analyses illustrate the so-called nocebo effect, with an excess rate of muscle-related AE reports only when patients and their doctors were aware that statin therapy was being used and not when its use was blinded.
  - These results will help assure both physicians and patients that most AEs associated with statins are not causally related to use of the drug and should help counter the adverse effect on public health of exaggerated claims about statin-related side-effects.

Article 7: Management Strategies for Statin-Associated Muscle Symptoms: How Useful Is Same-Statin Rechallenge?

- **Objective:** to evaluate the tolerability, percent change in low-density lipoprotein cholesterol (LDL-C), and proportion of patients achieving their LDL-C targets among 3 common management strategies: same-statin rechallenge, switching to a different statin (statin switch), and use of nonstatin medications only.
- **Methods:** performed a retrospective analysis of 118 patients referred to a tertiary care center for management of SAMS, defined as development of muscle-related symptoms with 2 or more statins.
- **Major findings:** After a median follow-up of 17 months, most (n = 79; 67%) patients were able to tolerate a statin.
  - Tolerability was similar among the 3 treatment strategies (71% same-statin rechallenge vs 53% statin switch vs 57% for nonstatin therapy only; P = 0.11).
  - Those in the same-statin rechallenge and statin switch groups achieved greater LDL-C reductions compared with those who only tolerated nonstatins (**-38.8** ± 3.4% vs **-36.4** ± 2.9% vs **-17.3** ± 4.5%; P = 0.0007).
  - A greater proportion of patients in the same-statin rechallenge group achieved their target LDL-C compared with those in the nonstatin therapy only group (**50%** vs **15%**; OR 6.8; 95% CI, 1.5-40.7; P = 0.04).

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Article 8: Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients--the PRIMO study.

- **Objective:** to characterize the rate of occurrence, onset, nature and impact of mild to moderate muscular symptoms with high-dosage HMG-CoA reductase inhibitor (statin) therapy in general practice.
- **Methods:** survey was an observational study of muscular symptoms in an unselected population of 7924 hyperlipidemic patients receiving high-dosage statin therapy in a usual care, outpatient setting in France.
  - Information on patient demographics, treatment history and muscular symptoms was obtained by questionnaires.
- **Major findings:** Overall, muscular symptoms were reported by 832 patients (10.5%), with a median time of onset of 1 month following initiation of statin therapy.
  - Pravastatin and Fluvastatin XL treatments were associated with lower numerical rate of occurrence of muscular symptoms (10.9% and 5.1%) compared to Simvastatin and Atorvastatin treatments (18.2% and 14.9%).
  - Odds ratio calculations for the risk of muscular symptoms, using high-dosage pravastatin as the reference, show that both high-dosage atorvastatin and simvastatin treatment were associated with a significantly higher (OR 1.28, P=0.035 and OR 1.78, P<0.0001 respectively) rate of occurrence of muscular symptoms compared with pravastatin.
  - Fluvastatin XL treatment was associated with a significantly lower (OR 0.33, P<0.0001) risk of muscular symptoms compared with pravastatin.

Article 9: Efficacy of rosuvastatin (5 mg and 10 mg) twice a week in patients intolerant to daily statins.

- **Objective:** to evaluate the efficacy of rosuvastatin twice weekly in patients intolerant to daily statins
- **Methods:** 40 patients intolerant to daily statins were given rosuvastatin twice weekly alone or added to other lipid-lowering medications
- **Major findings:** The patients had decreased total cholesterol by 19%, low-density lipoprotein cholesterol by 26%, and triglycerides by 14% ($p<0.01$)
  - High-density lipoprotein cholesterol did not change.
  - 80% of patients tolerated taking twice-weekly rosuvatatin
    - Eight of the 40 patients (20%) discontinued twice-weekly rosuvastatin treatment because of muscle-related symptoms, during an average of 8 weeks of treatment.
  - In conclusion, rosuvastatin twice weekly reduced total cholesterol, low-density lipoprotein cholesterol, and triglycerides and was well tolerated, but determining long-term tolerability and outcome effectiveness requires more prolonged treatment and analysis.

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2. The Statin Re-challenge Guidelines by the American College of Cardiology (ACC)

Statin Intolerance App

https://www.acc.org/StatinIntoleranceApp

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Background

1. Both the American Diabetes Association (ADA) and the American College of Cardiology (ACC) guidelines recommend statin therapy for patients with diabetes and/or ASCVD to manage high cholesterol.

2. Unfortunately, many patients who could benefit from statin therapy stop taking their mediation because they experience muscle pain and inflammation.

3. Per the ACC, less than 5% of patients who experience statin associated muscle symptoms (SAMS) will have a true statin intolerance.

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ACC's Statin Intolerance Tool

1. Evaluate
   a. Evaluate the possible intolerance to patient's current statin prescription.

2. Follow-up
   b. Follow steps to treat and managed possible statin-related muscle symptoms.

3. Drug Compare
   c. Compare statin characteristics and drug interactions to determine the best cholesterol-lowering therapy.

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1) Evaluate

- Muscle symptom severity
  - Creatine Kinase (CK) Level
- Rhabdomyolysis
  - Creatinine
  - Urinalysis (particularly myoglobin)
- Risk Factors/Secondary Causes
  - Thyroid panel (particularly TSH)
  - Hepatic panel (particularly ALT)
  - Electrolyte panel
  - Renal panel
  - ERS (erythrocyte sedimentation rate)
  - Vitamin D 25-OH level

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Rhabdomyolysis Assessment

Clear Data

Is your patient's CK above 5x the ULN?

Yes	No	Don't Know

More information about CK Levels.

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CK Level Information

1. Standard CK ranges may vary by lab
   a. Mayo Clinic defines standard CK levels as
      i. Males 18+ : 52-336 U/L
      ii. Females 18+: 38-176 U/L

2. Severe CK elevation, with possible indication for rhabdomyolysis, may be considered to be > 5x ULN
   a. Using Mayo ranges, > 5x ULN =
      i. Male: CK > 1680 U/L
      ii. Female: CK > 880 U/L

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CK Level Information

3. Some CK elevation above standard levels is characteristic in patients with any of the following criteria:
   - physical exertion (It is best to wait 48 hours to after acute heavy exercise before taking any CK measurement.)
   - ethnicity (blacks and particularly black insulin users-DM)
   - alcoholism
   - illicit drugs (amphetamine or cocaine)
   - atypical antipsychotics
   - hypothyroidism
   - metabolic or inflammatory myopathies
   - neuropathy or radiculopathy
   - seizures
   - trauma
   - idiopathic causes

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Muscle Symptoms

Type, Severity, and Secondary Causes

Symptom Type

Select the group that best describes the symptoms. *

Muscle ache, Weakness, Soreness, Stiffness, Cramping, Tenderness, or General Fatigue

Any from this group: Possible intolerance

Tingling, Twitching, Shooting Pain, Nocturnal Cramps, or Joint Pain

Any from this group: Unlikely intolerance

Symptom Area

Select One *

Bilateral

Muscle symptoms are generalized (e.g., neck and shoulder pain, lower extremity pain)

Bilateral: Possible intolerance

Unilateral

Muscle symptoms are isolated (e.g., knee or shoulder ache)

Unilateral: Unlikely intolerance

Select patient's indicated symptom severity.

Severe/Intolerable	Mild/Moderate/Tolerable

Or use worksheet to assess severity.

When did muscle symptoms start?

Select | Select

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Factors that increase risk for statin symptoms

1. Patient Characteristics
   - Low BMI
   - Excessive grapefruit juice consumption (> 1.2 liters per day)
   - Drug abuse (cocaine, amphetamine, heroin)
   - Dehydration or decrease in daily fluid intake
   - Frailty
   - High alcohol consumption
   - Heavy exercise/physical exertion
   - Personal or immediate family history of statin intolerance
2. Medical History
   - Unexplained ALT elevations ≥3 times ULN
   - Hepatic dysfunction
   - Renal insufficiency
   - Multiple or serious comorbidities

Non-statin causes for muscle symptoms

1. Medical History
   - Multiple or serious comorbidities
   - Heavy exercise/Physical exertion
   - Seizures
   - Vitamin D deficiency
   - Multi-organ disease
   - Elevated ESR (erythrocyte sedimentation rate)
   - Previous muscle disorder history
   - Trauma
   - Electrolytic abnormalities
   - Hypothyroidism
   - Post-op state, especially surgery with high metabolic demands

Non-statin causes for muscle symptoms

2. Medical Conditions

- Primary Muscle Diseases
  - Muscular Dystrophy
  - Polymyosytis
  - Steroid myopathy
  - Polymyalgia rheumatica
  - Rhabdomyolysis
- Rheumatological Disorders
  - Arthritis
  - Systemic Lupus
  - Fibromyalgia
  - Tendonitis or joint disorder
- Additional Disorders
  - Diabetes
  - Addison's disease
  - Hypoparathyroidism
  - Viral illness
  - Adrenal insufficiency/Cushing Syndrome
  - Anemia
  - Peripheral arterial disease

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Secondary Considerations

1. **Determine if patient has done anything recently outside their normal routine that may cause muscle pain. (e.g., moved furniture, started a new medication, changed their eating habits)**
2. **Use the worksheets below to determine any medical history that may also be contributing to symptoms.**

Factors that increase risk for statin symptoms
(e.g., substance abuse, comorbidities)

Evaluate | Skip

Non-statin causes for muscle symptoms
(e.g., primary muscle diseases, rheumatological disorders)

Evaluate | Skip

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Current Statin and Drug Interactions

Current Statin *

Select

Dose *

Select

Frequency

Select

Time of Day

Select

When did the patient start the statin?

Month

Select

Year

Select

Has the patient had muscle pain while taking a previous statin?

Yes | No

Use worksheet to determine interacting medications

(e.g., fenofibrates, strong CYP3A4 inhibitors)

Evaluate | Skip

Statin and Drug Interactions

- Amiodarone
- Amlodipine
- Atazanavir plus ritonavir
- Boceprevir
- Clarithromycin
- Cobicistat-containing products
- Colchicine
- Cyclosporine
- Danazol
- Darunavir plus ritonavir
- Diltiazem
- Dronedarone
- Erythromycin
- Fibrate/Fibric acid
- Fluconazole
- Fosamprenavir plus ritonavir
- Fosamprenavir
- Gemfibrozil
- Itraconazole
- Ketoconazole
- Lomitapide
- Lopinavir plus ritonavir
- Nefazodone
- Nelfinavir
- Niacin ≥ 1 g/day
- Posaconazole
- Ranolazine
- Rifampin
- Saquinavir plus ritonavir
- Telaprevir
- Telithromycin
- Tipranavir plus ritonavir
- Verapamil
- Voriconazole
- Warfarin and other coumarin anticoagulants

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2) Follow-up process

1. Labs have been returned
2. Patient was taken off original statin
3. Patient has been rechallenged with original statin
4. Considering starting patient on alternative statin
5. Muscle symptoms returned on alternative statin

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Follow-up process – Labs have been returned

1. Has a non-statin cause for muscle symptoms been identified?

Yes	No
Next steps: • Treat identified cause of muscle symptoms. • If CK is elevated above 5x ULN, check for rhabdomyolysis by evaluating creatinine and performing urinalysis for myoglobinuria.	Next steps: • If CK is elevated above 5x ULN, check for rhabdomyolysis by evaluating creatinine and performing urinalysis for myoglobinuria.

Continuing Statin Therapy
• If no rhabdomyolysis, continue statin therapy at original dose once issue has been resolved.
• Or, may consider an alternate statin if patient prefers.
	Continuing Statin Therapy
	• If no rhabdomyolysis:
	  • If patient is still taking a statin, consider temporarily suspending the statin and follow up to see if symptoms resolve.
	  • If patient was already taken off original statin, follow up to see if symptoms have resolved.

Follow-up process – Patient was taken off original statin

2. Did muscle symptoms resolve after statin discontinuation?

Yes	No
Next steps: • Establish statin adverse effects causation by restarting patient on a same or lower dose of the statin taken at time of muscle complaint. • Or, if patient prefers, consider starting a low dose of a different statin. If low dose is tolerated, gradually increase the dose as tolerated.	Next steps: • Investigate any possible non-statin causes for symptoms. Use this app's "Evaluate" tab for help. • Do not restart statin until symptoms resolve.
Next Follow-up: • Follow up with patient to assess whether muscle symptoms return.	Things to consider: • In some cases, symptoms can take up to two months to resolve.

Follow-up process – Patient has been rechallenged with original statin

3. Did muscle symptoms return after rechallenge?

Yes	No
Next steps: • Stop original statin. • Wait for muscle symptoms to resolve again.	Next steps: • Continue with current statin prescription.
Next Follow-up: • Once symptoms have resolved, start a low dose of a different statin. • If low dose of a statin is tolerated, gradually increase the dose as tolerated. • Reevaluate if muscle symptoms return.	~~

Follow-up process – Considering starting patient on alternative statin

4. Does patient currently have muscle symptoms?

Yes	No
Wait until symptoms resolve before taking next steps. Next steps: • Start a low dose of a different statin. • If low dose of a statin is tolerated, gradually increase the dose as tolerated. • Reevaluate if muscle symptoms return.	Next steps: • Start a low dose of a different statin. • If low dose of a statin is tolerated, gradually increase the dose as tolerated. • Reevaluate if muscle symptoms return.
Things to consider: • Intolerance to one or more statins does not necessarily indicate intolerance to all statins. • Consider characteristics of each statin such as metabolism, lipophilicity, drug interactions, etc. when prescribing.	

Follow-up process – Muscle symptoms returned after starting an alternate statin

5. Did muscle symptoms resolve after statin discontinuation?

Yes	No
Next steps: • Treat identified cause of muscle symptoms. • Continue current statin therapy prescription once issue has been resolved. • Or, you may consider an alternate statin type or dose if patient prefers.	Next steps: • Consider the patient's ASCVD risk and cardiovascular health history, benefits of statin therapy and risk of removal, and patient preferences.
	Continuing Statin Therapy: • Proceed with one of the following as appropriate: A. Continue with current statin prescription B. Try an alternative statin: Discontinue current statin. Wait for symptoms to resolve. Try patient on a low dose of an alternative statin. If low dose is tolerated, gradually increase dose as tolerated. • If muscle symptoms have occurred on two or more statins, and symptoms outweigh risk and benefit, you may consider discussing alternate treatment methods with the patient.

3) Statin Drug Comparison

When developing a dosing strategy:

1. Compare different statin characteristics, especially lipophilicity and metabolism.
2. Consider patient characteristics (e.g. age, family history of statin intolerance, renal function, liver disease).

Atorvastatin (Lipitor®)

Low Intensity Dose	~~
Moderate Intensity Dose	10-20 mg
High Intensity Dose	40-80 mg
Half-life (h)	14 (Mean plasma elimination) 20-30 (inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites)
Lipophilic?	Yes
Optimal Frequency	Any time of day/evening - Food not required
Pregnancy Category X	Yes
Primary Metabolism	CYP3A4

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Fluvastatin (Lescol®)

Low Intensity Dose	20-40 mg
Moderate Intensity Dose	40 mg
High Intensity Dose	~~
Half-life (h)	3
Lipophilic?	No
Optimal Frequency	Evening/bedtime – Food not required
Pregnancy Category X	Yes
Primary Metabolism	(75%) CYP2C9; (5%) CYP2C8; and 20% CYP3A4

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Fluvastatin XL (Lescol XL®)

Low Intensity Dose	~~
Moderate Intensity Dose	80 mg
High Intensity Dose	~~
Half-life (h)	9
Lipophilic?	No
Optimal Frequency	Any time of day/evening - Food not required
Pregnancy Category X	Yes
Primary Metabolism	(75%) CYP2C9; (5%) CYP2C8; and 20% CYP3A4

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Lovastatin (Mevacor®)

Low Intensity Dose	20 mg
Moderate Intensity Dose	40 mg
High Intensity Dose	~~
Half-life (h)	1.1 to 1.7
Lipophilic?	Yes
Optimal Frequency	Evening/bedtime - Food required except for Altoprev extended-release formulation
Pregnancy Category X	Yes
Primary Metabolism	CYP3A4

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Pitavastatin (Livalo®)

Low Intensity Dose	1 mg
Moderate Intensity Dose	2 to 4 mg
High Intensity Dose	~~
Half-life (h)	12
Lipophilic?	Yes
Optimal Frequency	Any time of day/evening - Food not required
Pregnancy Category X	Yes
Primary Metabolism	Minimal CYP2C9 and CYP2C8

Pravastatin (Pravachol®)

Low Intensity Dose	10 to 20 mg
Moderate Intensity Dose	40 to 80 mg
High Intensity Dose	~~
Half-life (h)	1.8
Lipophilic?	No
Optimal Frequency	Any time of day/evening - Food not required
Pregnancy Category X	Yes
Primary Metabolism	Minimal CYP450 metabolism

Rosuvastatin (Crestor®)

Low Intensity Dose	~~
Moderate Intensity Dose	5 to 10 mg
High Intensity Dose	20 to 40 mg
Half-life (h)	19
Lipophilic?	No
Optimal Frequency	Any time of day/evening - Food not required
Pregnancy Category X	Yes
Primary Metabolism	Minimal CYP2C9

Simvastatin (Zocor®)

Low Intensity Dose	10 mg
Moderate Intensity Dose	20 to 40 mg
High Intensity Dose	80 mg *(Initiation at 80mg daily or increase of up to 80mg daily may cause harm.)*
Half-life (h)	1.9
Lipophilic?	Yes
Optimal Frequency	Evening/bedtime - Food not required
Pregnancy Category X	Yes
Primary Metabolism	CYP3A4

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Dose Intensity of Statins

Statin	Low Intensity	Moderate Intensity	High Intensity
LDL-C lowering	< 30%	30% to 49%	≥ 50%
Atorvastatin (Lipitor®)	~~	10 to 20 mg	40 to 80 mg
Fluvastatin (Lescol®)	20 to 40 mg	40 mg BID	~~
Fluvastatin XL (Lescol XL®)	~~	80 mg	~~
Lovastatin (Mevacor®)	20 mg	40 mg	~~
Pitavastatin (Livalo®)	1 mg	2 to 4 mg	~~
Pravastatin (Pravachol®)	10 to 20 mg	40 to 80 mg	~~
Rosuvastatin (Crestor®)	~~	5 to 10 mg	20 to 40 mg
Simvastatin (Zocor®)	10 mg	20 to 40 mg	*80 mg*

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Optimal Frequency of Statins

Statin	Optimal Frequency
Atorvastatin (Lipitor®)	Any time of day/evening - Food not required
Fluvastatin (Lescol®)	**Evening/bedtime** - Food not required
Fluvastatin XL (Lescol XL®)	Any time of day/evening - Food not required
Lovastatin (Mevacor®)	**Evening/bedtime** - **Food required** except for Altoprev extended-release formulation
Pitavastatin (Livalo®)	Any time of day/evening - Food not required
Pravastatin (Pravachol®)	Any time of day/evening - Food not required
Rosuvastatin (Crestor®)	Any time of day/evening - Food not required
Simvastatin (Zocor®)	**Evening/bedtime** - Food not required

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Comparison of Statins

Statin	Half Life (h)	More Lipophilic?	Primary Metabolism
Atorvastatin (Lipitor®)	14 , 20 to 30	Yes	CYP3A4
Fluvastatin (Lescol®)	3	**No**	(75%) CYP2C9; (5%) CYP2C8; and 20% CYP3A4
Fluvastatin XL (Lescol XL®)	9	**No**	(75%) CYP2C9; (5%) CYP2C8; and 20% CYP3A4
Lovastatin (Mevacor®)	1.1 to 1.7	Yes	CYP3A4
Pitavastatin (Livalo®)	12	Yes	**Minimal CYP2C9 and CYP2C8**
Pravastatin (Pravachol®)	1.8	**No**	**Minimal CYP450 metabolism**
Rosuvastatin (Crestor®)	19	**No**	**Minimal CYP2C9**
Simvastatin (Zocor®)	1.9	Yes	CYP3A4

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ACC 2018 Updated Guidelines on Safety & Statin-Associated Side Effects

1. A clinician–patient risk discussion is recommended before initiation of statin therapy
   a. review net clinical benefit,
   b. weigh the potential for ASCVD risk reduction against the potential for statin-associated side effects,
   c. review potential statin–drug interactions/safety,
   d. emphasize that side effects can be addressed successfully.

2. In patients with statin-associated muscle symptoms (SAMS),
   a. a thorough assessment of symptoms is recommended,
   b. in addition to an evaluation for non-statin causes and predisposing factors.

3. In patients with indication for statin therapy,
   a. identification of potential predisposing factors for statin-associated side effects,
   b. including new onset diabetes mellitus and SAMS,
   c. is recommended before initiation of treatment.

ACC 2018 Updated Guidelines on Safety & Statin-Associated Side Effects

4. In patients with statin-associated side effects that are not severe,
    a. it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by
    b. modified dosing regimen,
    c. an alternate statin, or
    d. in combination with nonstatin therapy.

5. In patients with increased diabetes mellitus risk or new-onset diabetes mellitus,
    a. it is recommended to continue statin therapy,
    b. with added emphasis on adherence,
    c. net clinical benefit, and
    d. the core principles of regular moderate-intensity physical activity,
    e. maintaining a healthy dietary pattern, and
    f. sustaining modest weight loss.

ACC 2018 Updated Guidelines on Safety & Statin-Associated Side Effects

6. In patients treated with statins, it is recommended
   a. to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms,
   b. objective muscle weakness, and
   c. to measure liver transaminases (aspartate aminotransferase, alanine aminotransferase)
   d. as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity.

7. In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated,
   a. it is reasonable to use statins after obtaining baseline measurements and
   b. determining a schedule of monitoring and safety checks.

8. In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge,
   a. it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit.

ACC 2018 Updated Guidelines on Safety & Statin-Associated Side Effects

9. Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS.

10. In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.

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3. The Centers for Medicare & Medicaid Services (CMS) Quality Star Measure Programs

SPC
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SPC (Statin Therapy for Patients with Cardiovascular Disease)

GOALS

- Increase rating in the CMS Five-Star Quality Rating System (CMS Part C measure and HEDIS measure).
- Encourage the use of a moderate to high intensity statin in males 21 -75 years of age and females 40 – 75 years of age with cardiovascular disease.

COMMUNICATIONS

- Outreach: Physicians are sent a letter encouraging the prescribing of a statin. Response is requested and tracked.
- Outreach: Members are mailed a letter encouraging use of a statin.
- Outreach for Low-Dose Statin: Physicians are faxed a letter and followed up by a phone call to increase the dose of the statin to moderate to high intensity of members currently on low dose statins.

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American Heart Association & American College of Cardiology

Guidelines on the Management of Blood Cholesterol
Updated November 2018

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.
2. In patients with clinical **ASCVD**, reduce low-density lipoprotein cholesterol (LDL-C) with **high intensity statin** therapy or **maximally tolerated statin** therapy.
3. In very high-risk ASCVD, use a LDL-C threshold of **70** mg/dL (1.8 mmol/L) to consider **addition of nonstatins to statin** therapy.
4. In patients with severe primary hypercholesterolemia (LDL-C level ≥**190** mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin **high-intensity statin** therapy without calculating 10-year ASCVD risk.
5. Assess **adherence** and **percentage response** to LDL-C–lowering medications and **lifestyle changes** with repeat lipid measurement **4 to 12 weeks** after statin initiation or dose adjustment, repeated every **3 to 12 months** as needed.

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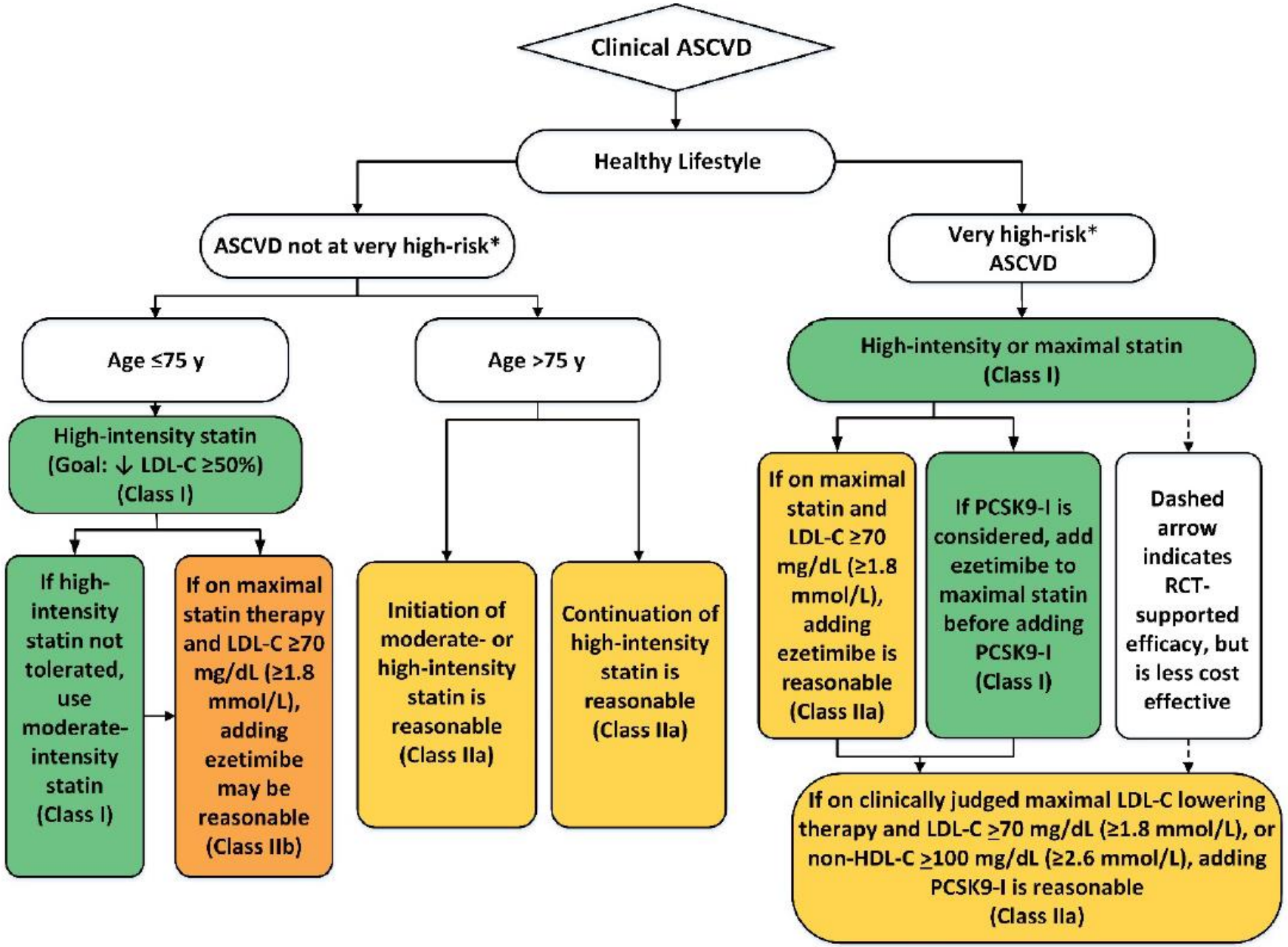
Figure 1. Secondary Prevention in Patients With Clinical ASCVD



SPC (Statin Therapy for Patients with Cardiovascular Disease)

INTERVENTIONS

Faxed out letters to Physician Offices

Mailed out letters to Members

Letters	H0351 (AZ)	H9287 (AZ)	H0562 (CA)	H3561 (CA)	H5439 (OR)	H6815 (OR)	H3237 (CA MMP)	6241 (CA Comm)	Total
No Statin Launch Date: 10/25/18	102	7	539	67	3	107	28	24	877
Low Dose Launch Date: 10/25/18	31	4	202	33	No Data	41	13	4	328

SPC (Statin Therapy for Patients with Cardiovascular Disease)

INTERVENTIONS (11/6/18 to 12/19/18)

Physician Office Responses from Fax Back Forms	Number of responses
Corrected MD	65
Member already on mod/high intensity statin	2
Member Cancelled	8
Wrong MD	2

Physician Office Responses from Fax Back Forms	Number of responses
Call busy	4
Invalid phone number	7
Left voicemail	52
Ring, no answer	3
Spoke with office staff	147
Spoke with physician	5
Other	78

Physician Office Interventions	Number of responses
Claim for higher dose statin on RxClaim	3
MD refused to make any changes	12
MD states no changes needed d/t normal CHOL	3
MD states pt had muscle aches on higher dose statin	3
MD to evaluate	52
MD will prescribe a higher dose statin	9
Refax letter	35
Transferred call to the pharmacist	1
Other	179

SPC (Statin Therapy for Patients with Cardiovascular Disease)

OUTCOMES

For the total members identified from the 10/25/18 launch date intervention, about **7.1%** (104/1,475) of the members now have a paid **moderate or high dose statin** claim by the end of 2018.

- No Statin: 7.4% (81/1091)
- Low Dose Statin: 5.9% (23/384)

Health Plans	H5590 (AZ)	H0351 (AZ)	H9287 (AZ)	H0562 (CA)	H3561 (CA)	H5439 (OR)	H6815 (OR)	H2174 (OR)	H3237 (CA MMP)	6241 (CA Comm)	Total
Percentage of members with verified paid moderate or high dose Statin claim in Caremark through 12/31/18	N/A	4.2% (6/143)	18.2% (2/11)	6.5% (50/768)	10% (10/100)	4.3% (8/186)	8.4% (14/167)	N/A	8.9% (4/45)	18.2% (10/55)	7.1% (104/1,475)

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SPC (Statin Therapy for Patients with Cardiovascular Disease)

Contract	CMS RY 2019 Cut-points	RY 2019 (MY2017) Final RATE**	RY 2019 (MY2017) Final Stars **	RY 2020 (MY2018) YTD RATE**	RY 2020 (MY2018) Stars Estimate**
H0351 HNAZ HMO	1 star: < 70% 2 Star: ≥ 70% to < 76% 3 Star: ≥ 76% to < 81% 4 Star: ≥ 81% to < 85% 5 Star: ≥ 85%	73%	2	74%	2
H9287 HN AZ HMO2		80%	3	79%	3
H0562 HNCA HMO		74%	2	75%	2
H3561 HNCA HMO2		79%	3	78%	3
H5439 HNOR PPO		76%	3	75%	2
H6815 HNOR HMO		81%	4	80%	3

**Based on Centene Medicare and MMP Dashboard – December 2018

SUPD (Statin Use in Persons with Diabetes)

GOALS

- Increase rating in the CMS Five-Star Quality Rating System.
- Encourage the use of a statin in diabetic members.

COMMUNICATIONS

- Outreach: Physicians receive a letter followed by a follow up phone call.
- Outreach: Members receive a letter that includes suggestion to consider a statin and resources for more information.
- Outreach for Statin Re-challenge: Members who physicians said refused to take a statin in the past are followed up with a phone call.

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American Heart Association & American College of Cardiology

Guidelines on the Management of Blood Cholesterol
Updated November 2018

1. In all individuals, emphasize a **heart-healthy lifestyle** across the life course.
2. In patients **40 to 75 years** of age with **diabetes mellitus** and LDL-C ≥**70** mg/dL (≥1.8 mmol/L), start **moderate-intensity statin** therapy without calculating 10-year ASCVD risk.
3. In adults **40 to 75 years** of age **without diabetes mellitus** and with LDL-C levels ≥**70** mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥**7.5%**, start a **moderate-intensity statin** if a discussion of treatment options favors statin therapy.
4. In adults **40 to 75** years of age **without diabetes mellitus** and 10-year risk of **7.5% to 19.9%** (intermediate risk), risk-enhancing factors **favor initiation of statin** therapy.

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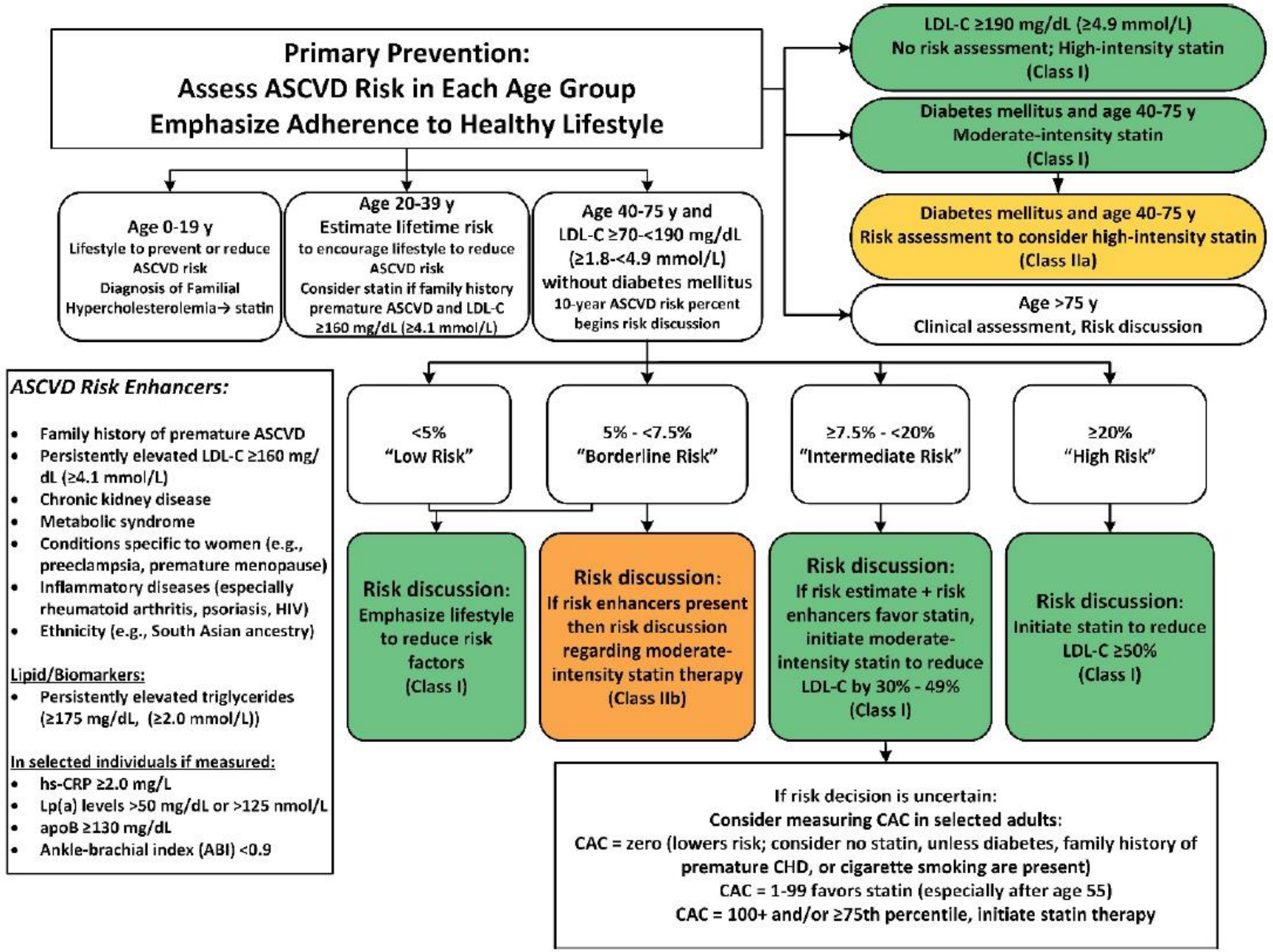
Figure 2. Primary Prevention



SUPD (Statin Use in Persons with Diabetes)

INTERVENTIONS

Faxed out letters to Physician Offices

Mailed out letters to Members

Letters	H5590 (AZ)	H0351 (AZ)	H928 7 (AZ)	H0562 (CA)	H3561 (CA)	H5439 (OR)	H6815 (OR)	H2174 (OR)	H3237 (CA MMP)	6241 (CA Comm)	Total
Launch date: 6/26/2018	29	553	87	3053	763	774	986	79	No data	No data	6324
Launch date: 10/30/2018	20	473	88	2956	587	667	844	62	282	3394	9373

SUPD (Statin Use in Persons with Diabetes)

Statin Re-Challenge

Out of the 663 patients in the statin re-challenge program, 209 (**31.5%**) patients filled a statin after the physician office phone call outreach. (Data results from 11/19/18).

Physician Letters	H5590 (AZ)	H0351 (AZ)	H928 7 (AZ)	H0562 (CA)	H3561 (CA)	H5439 (OR)	H6815 (OR)	H2174 (OR)	H3237 (CA MMP)	6241 (CA Comm)	Total
Launch date: 9/10/2018 Thru: 10/10/2018	N/A	N/A	N/A	347	91	95	130	N/A	N/A	N/A	663

SUPD (Statin Use in Persons with Diabetes)

INTERVENTIONS (10/31/18 to 12/21/18)

Physician Office Responses from Fax Back Forms	Number of responses
Already on Statin	21
Already on ACE/ARB	624
Already on Aspirin	0
Already on ACE/ARB & Aspirin	7
Already on Statin & ACE/ARB	23
Already on Statin & Aspirin	0
Already on Statin, ACE/ARB, & Aspirin	0
Member Cancelled	2
Wrong MD	5
Corrected MD	90

SUPD (Statin Use in Persons with Diabetes)

INTERVENTIONS (10/31/18 to 12/21/18)

Physician Office Initial Call Status	Number of responses
Invalid Phone Number	14
Left Voicemail	265
Disconnected	3
Spoke with Office Staff	1084
Declined Conversation	1
Missing Phone Number	31
Ring, no answer/busy	59
Spoke to Physician	14
Other	109

Physician Office Interventions	Number of responses
Refaxed Letter	169
Refaxed Letter (Updated fax#)	75
Not PCP	20
Transferred Call to Pharmacist	2
MD to evaluate	443
MD will prescribe	21
MD states pt on statin	20
MD refused to make changes	55
MD states no changes d/t normal CHOL	5
MD states pt had muscle aches	29
MD states pt refuses	88
Claims for Statin in RxClaim	50
Claims for ACE/ARB in RxClaim	574
Claims for Aspirin in RxClaim	0

SUPD (Statin Use in Persons with Diabetes)

OUTCOMES

For the total members identified from the 6/26/18 and 10/30/18 launch date intervention, about **17.9%** (2,106/11,769) of the members now have a paid **statin** claim by the end of 2018.

Health Plans	H5590 (AZ)	H0351 (AZ)	H9287 (AZ)	H0562 (CA)	H3561 (CA)	H5439 (OR)	H681 5 (OR)	H2174 (OR)	H3237 (CA MMP)	6241 (CA Comm)	Total
Percentage of members with verified paid Statin claim in Caremark through 12/31/18	15.8% (6/38)	18.1% (119/658)	16.7% (19/114)	25.3% (922/3644)	27.9% (249/893)	16.4% (150/917)	20.4% (229/ 1123)	27.2% (25/92)	8.5% (25/294)	9.1% (362/3996)	17.9% (2,106/ 11,769)

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SUPD (Statin Use in Persons with Diabetes)

Metric	Potential Cut-points Inovalon predicted	MA-PD Avg (2018)	Current Rate (thru 12/31/18)	***Estimated Stars (≥ avg.)*** 2019 (thru 12/31/18)	***Estimated Stars (≥ 2019)*** 2019 (thru 12/31/18)
D17: Statin Use in Persons with Diabetes**	4 star ≥ 80% 5 star: ≥ 85%	81%	79% HNAZ HMO H0351 78% HNAZ HMO2 H9287 83% HNCA HMO H0562 84% HNCA HMO2 H3561 75% HNOR PPO H5439 80% HNOR HMO H6815	★★★ HNAZ ★★★ HNAZ HMO2 ★★★★HNCA HMO ★★★★ HNCA HMO2 ★★★ HNOR PPO ★★★★ HNOR HMO	★★★ HNAZ ★★★ HNAZ HMO2 ★★★★★ HNCA HMO ★★★★★ HNCA HMO2 ★★★ HNOR PPO ★★★★ HNOR HMO

**Based on Centene Medicare and MMP Dashboard – December 2018

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Thank you for your time!

Questions?

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