Secondary Prevention of Atherosclerotic Cardiovascular Disease– Adult – Inpatient/Ambulatory Clinical Practice Guideline

Table of Contents

EXECUTIVE SUMMARY ........................................................................................................... 2
SCOPE ......................................................................................................................................... 3
METHODOLOGY .......................................................................................................................... 4
INTRODUCTION .......................................................................................................................... 5
RECOMMENDATIONS ................................................................................................................ 6
   Tobacco 2-11 .......................................................................................................................... 6
   Blood Pressure Control 4,6,8,11 ......................................................................................... 6
   Treatment of Blood Lipids 12 ............................................................................................. 7
   Physical Activity 2,11,13,14 ............................................................................................... 11
   Weight Management 14,15 ................................................................................................. 12
   Type 2 Diabetes Mellitus Management 2,3,11,15,16 ....................................................... 13
   Antiplatelet agents/Anticoagulants 2-6,9-11,16-19 ............................................................... 14
   Renin-angiotensin-aldosterone system blockers 2,3,6-11,13,17 .......................................... 17
   Beta Blockers 2,6-10,17 ........................................................................................................ 17
   Influenza Vaccination 2,6,7,9,11,17 ................................................................................... 18
   Depression 2,6,7,9,11 .......................................................................................................... 18
   Cardiac Rehabilitation 2,4-7,10,11 .................................................................................... 18

APPENDIX A ............................................................................................................................... 20
REFERENCES ............................................................................................................................. 22

Note: Active Table of Contents -- Click to follow link

Release Date: 1/26/2015

Next Review Date: 9/1/2017
Executive Summary

Guideline Overview
The present CPG work group has extensively revised that document to reflect interim advances in science and policy. The following documents were reviewed, their content considered and when appropriate are referenced in this document. With rare exception, the recommendations in this CPG replicate without modification recommendations from the sources listed below.

1. 2013 ACC/AHA Report on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease in Adults
2. 2011 AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update
3. 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease
4. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention
5. 2011 ACCF-AHA Guideline for Coronary Artery Bypass Surgery
6. 2012 ACC, AHA, Stable Ischemic Heart Disease Guideline
7. 2013 ACCF, AHA Guideline for the Management of Heart Failure
8. 2013 Clinical Practice Guidelines for the Management of Hypertension in the Community: A statement by the American Society of Hypertension and the International Society of Hypertension
9. 2014 Joint National Committee (JNC8) Evidence-Based Guideline for the Management of High Blood Pressure in Adults
10. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk
11. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults
12. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction
13. 2014 AHA,ACC,HRS Guideline for the Management of Patients With Atrial Fibrillation
15. 2014 AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic
17. ACCF/ACG/AHA 2008 Expert Consensus on Reducing the Gastrointestinal Risk of Antiplatelet Therapy

Key Practice Recommendations
1. Cessation of all tobacco products.
2. Maintain blood pressure within goal levels.
3. High-intensity statin therapy.
4. Engage in physical activity.
5. Maintain a healthy weight.
6. Properly manage risk factors related to Diabetes in coordination with the patient’s primary care provider.
7. Utilize antiplatelet/anticoagulant therapy as necessary to reduce risk.
8. Use Renin-Angiotensin-Aldosterone System Blockers as indicated per condition.
9. Utilize Beta Blockers for patients at risk of or with a history of coronary events such as MI.
10. Patients with cardiovascular disease should receive an annual influenza vaccination.
11. Patients with cardiovascular disease should be screened for symptoms of depression.
12. Cardiac rehabilitation is appropriate for patients with the following conditions: acute myocardial infarction, coronary artery bypass surgery, percutaneous coronary angioplasty or coronary stenting, stable angina, congestive heart failure (EF ≤35% with AHA Class II-III symptoms), heart transplantation or valve replacement/repair.

Scope

Disease/Condition(s):
- Clinically apparent atherosclerotic cardiovascular disease (ASCVD) including but not limited to clinically apparent coronary artery disease (CAD).
- As used in the remainder of this document the term “clinical ASCVD”, includes acute coronary syndromes, history of myocardial infarction, stable or unstable angina, prior coronary or other arterial revascularization, prior carotid endarterectomy, symptomatic peripheral arterial disease, stroke or TIA presumed to be of atherosclerotic origin.
- In general, this document does not address management of asymptomatic preclinical ASCVD detected by imaging or other methods.

Clinical Specialty:
Cardiovascular Medicine, Cardiovascular Surgery, Family Medicine, Internal Medicine, Neurology, Neurosurgery, Vascular Surgery

Intended Users:
Physicians, Nurse Practitioners, Physician Assistants

CPG objective(s):
To provide core recommendations proven to reduce the incidence of major adverse cardiovascular events for the care of patients with clinically apparent CAD and other forms of clinical ASCVD. Our goal is to deliver the fruits of a mature and rich body of basic and clinical research to each patient with ASCVD at every encounter.

Target Population:
Adult patients (18 years or older) with clinical CAD or other forms of clinical ASCVD.

Interventions and Practices Considered:
1. High-intensity statin therapy.
2. Lifestyle management including weight management, physical activity and diabetes control.
Methodology

Methods Used to Collect/Select the Evidence:
The workgroup reviewed previously published guideline recommendations, and conducted electronic searches to develop the content.

Methods Used to Formulate the Recommendations:
Recommendations made are largely based on major practice guidelines from the National Institutes of Health and updated ACCF/AHA practice guidelines, as well as on results from recent clinical trials. The development of the present guideline involved a process of partial adaption of other guideline statements, reports, supplemental literature searches, as well as a consensus of expert opinion based on current knowledge and clinical experience.

Methods Used to Assess the Quality and Strength of the Evidence and Recommendations:
Classification of recommendations and level of evidence are expressed in ACCF/AHA format (see rating scheme below).

Rating Scheme for the Strength of the Evidence and Recommendations:
A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) rating scheme developed by the American Heart Association and American College of Cardiology (Appendix A) was used to assess the quality and strength of the recommendations. Recommendations adopted from other external guidelines such as the American Diabetes Association maintained the evidence grades provided in the Standards of Medical Care in Diabetes – 2014 guideline (Appendix A).

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. In the tables that follow the abbreviation “LOE” stands for the term “level of evidence”.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.
Introduction

As documented by the following figures from “Trends in Hospitalizations and Outcomes for Acute Cardiovascular Disease and Stroke: 1999-2011,” (Figure 1) very large reductions in death, hospitalization, procedures and costs of care are being achieved by the bench to bedside translation of the scientific knowledge that successfully prevents ASCVD. This guideline is intended to identify the actions we can take to provide current best practices for the secondary prevention of CAD and other forms of clinical ASCVD.¹

Figure 1. A. Maps of trends in observed rates (per 100,000 person-years) of hospitalization for myocardial infarction (top panel) and unstable angina (bottom panel) conditions (1999 to 2011) at the county level. In 1999, the myocardial infarction hospitalization rate varied from lowest counties (green, 0-534) to highest counties (red, 1607-1793) and the unstable angina hospitalization rate varied from lowest counties (green, 0-12) to highest counties (red, 795-1843). For Puerto Rico, the mean (SD) hospitalization rates declined from 9 (7.7) in 1999 to 5 (5.3) in 2011 and from 24 (1.4) in 1999 to 16 (8.0) in 2011 for unstable angina. B. Maps of trends in observed rates (per 100,000 person-years) of hospitalization for heart failure (top panel) and ischemic stroke (bottom panel) conditions (1999 to 2011) at the county level. In 1999, the heart failure hospitalization rate varied from lowest counties (green, 0-860) to highest counties (red, 2884-3259) and the unstable angina hospitalization rate varied from lowest counties (green, 0-682) to highest counties (red, 1830-2059). For Puerto Rico, the mean (SD) hospitalization rates declined for heart failure from 11 (6.2) in 1999 to 2 (1.2) in 2011 and from 11 (6.5) in 1999 to 2 (2.8) in 2011 for ischemic stroke.
Recommendations

Tobacco

**Goals**
- Complete smoking cessation following the recommendations outlined in the Tobacco Cessation – Pediatric/Adult – Inpatient/Ambulatory Guideline.
- No use of tobacco in any form.
- No exposure to environmental tobacco smoke.

**Recommendations**
1. Patients should be asked about tobacco use status at every office visit (Class I, LOE: B)
2. Every tobacco user should be advised at every visit to quit. (Class I, LOE: A)
3. The tobacco user's willingness to quit should be assessed at every visit. (Class I, LOE: C)
4. Patients should be assisted by counseling and by development of a plan for quitting that may include pharmacotherapy and/or referral to a smoking cessation program. (Class I, LOE: A)
5. Arrangement for follow up is recommended. (Class I, LOE: C)
6. All patients should be advised at every office visit to avoid exposure to environmental tobacco smoke at work, home, and public places. (Class I LOE: B)

Blood Pressure Control

**Goals**

<table>
<thead>
<tr>
<th>Goal (mmHg)</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 150/90</td>
<td>&gt; 80 years old and uncomplicated hypertension (including those with known ASCVD)</td>
</tr>
<tr>
<td>&lt; 140/90</td>
<td>&gt; 80 years old and diabetes mellitus or chronic kidney disease</td>
</tr>
<tr>
<td>&lt; 140/90</td>
<td>&lt; 80 years old and uncomplicated hypertension (including those with known ASCVD)</td>
</tr>
<tr>
<td>&lt; 130/80</td>
<td>Chronic kidney disease and proteinuria OR chronic kidney disease and diabetes mellitus OR left ventricular ejection fraction (LVEF) &lt; 40%</td>
</tr>
</tbody>
</table>

Reference the Hypertension – Adult – Inpatient/Ambulatory Guideline for further recommendations
**Recommendations**

1. All patients should be counseled regarding the need for lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, whole grains, and low-fat dairy products. *(Class I, LOE: B)*

2. Patients with blood pressure above goal should be treated, as tolerated, with blood pressure medication, treating initially with carvedilol and/or ACE inhibitors, with addition of other drugs as needed to achieve goal blood pressure. *(Class I, LOE: A)*

---

**Treatment of Blood Lipids**

**Goals**

- Routine use of high-intensity statin therapy for all appropriate patients with clinical ASCVD regardless of baseline cholesterol or LDL-C levels.
- Ongoing monitoring for adherence and safety.
- Appropriate adjustment of statin dosing in patient subgroups:
  1) at increased risk of toxicity
  2) for whom benefit is less
     (see recommendations below)
- Awareness that nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD. However, they may be useful in selected patients (such as those with statin intolerance or residual LDL-C elevations after appropriate statin therapy).

**Recommendations**

1. A fasting baseline lipid profile in all patients should be established. *(Class I, LOE: B)*

2. Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiating statin therapy. *(Class I, LOE: B)* It is not recommended to check baseline Creatine Kinase levels.

3. Routine monitoring of transaminases is not necessary in otherwise healthy patients, but should be considered in individuals with a history of liver disease, on other medications that can cause liver injury (e.g. niacin, fibrates, and other medications), or in individuals otherwise at risk for liver injury. *(Class 2a, LOE: C)*

4. For hospitalized patients statin therapy should be initiated on admission. *(Class I, LOE: B)*
5. Lifestyle modifications including daily physical activity and weight management are strongly recommended for all patients. (Class I, LOE: B)

6. Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), trans fatty acids (to <1% of total calories), and cholesterol (to <200 mg/d) as well as increased intake of fiber (10-25 gm per day) and stanols/sterols (2 gm per day). (Class I, LOE: B)

7. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical ASCVD, unless contraindicated regardless of baseline cholesterol or LDL-C levels. (Class I, LOE: A)

8. The large reductions in cardiovascular events and mortality from statins outweigh the known very small risk of developing or exacerbating underlying diabetes mellitus. (Class 1:LOE:C)

9. High, moderate and low intensities of statin therapy that have been evaluated in randomized clinical trials are listed in the table below.

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;30%</td>
</tr>
<tr>
<td><em><em>Atorvastatin (40</em>)-80 mg</em>* Rosuvastatin 20 (40) mg</td>
<td>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20-40 mg** Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg</td>
<td>Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

Specific statins and doses are noted in **bold** that were evaluated in RCTs included in CQ1, CQ2 and the CTT 2010 meta-analysis included in CQ3. All of these RCTs demonstrated a reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

*Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL

**Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyosis.

bid indicates twice daily; FDA, Food and Drug Administration; IDEAL, Incremental Decrease through Aggressive Lipid Lowering study; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials

10. For individuals with clinical ASCVD, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statins should be used as the second option if tolerated. (Class I, LOE: A)
11. Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
   • > 75 years of age
   • History of previous statin intolerance or muscle disorders.
   • Multiple or serious comorbidities, including advanced stages of heart failure, maintenance hemodialysis, impaired renal or hepatic function.
   • Concomitant use of drugs affecting statin metabolism, including fibrates, niacin, amiodarone, colchicine, cyclosporine.
   • History of hemorrhagic stroke
   • Asian ancestry
   • Treatment for HIV
   • History of solid organ transplantation
   • Pregnancy (statins contraindicated) 
   (Class I, LOE: B, Class IIa, LOE C)

12. For individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. (Class IIa, LOE: B)

13. It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring:
   • High-intensity statin therapy generally results in an average LDL–C reduction of ≥50% from the untreated baseline
   • Moderate-intensity statin therapy generally results in an average LDL–C reduction of 30 to <50% from the untreated baseline
   • LDL–C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. (Class IIa, LOE: B)

14. Decreasing the statin dose may be considered when 2 consecutive values of LDL–C levels are <40 mg/dL and/or Total Cholesterol is <100 mg/dL. (Class IIb, LOE: C)

15. Addition of nonstatin cholesterol-lowering drugs (niacin, bile acid resins, and ezetimibe) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects for individuals:
   . with ASCVD receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response,
   . or those who are statin intolerant.
   These patients may benefit from consultation in Preventive Cardiology Clinic. (Class IIb, LOE: B)

16. Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4 to 12 weeks after initiation or dose adjustment, and every 3 to 12 months thereafter. (Class I, LOE: A)

17. The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. (Class I, LOE: B)
18. In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed:
   • Reinforce medication adherence.
   • Reinforce adherence to intensive lifestyle changes.
   • Exclude secondary causes of hyperlipidemia listed in the table below.  
   (Class I, LOE: A)

<table>
<thead>
<tr>
<th>Secondary Causes of Hyperlipidemia Most Commonly Encountered in Clinical Practice</th>
<th>Elevated LDL-C</th>
<th>Elevated Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Saturated or trans fats, weight gain, anorexia</td>
<td>Weight gain, very low-fat diets, high intake of refined carbohydrates, excessive alcohol intake</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diuretics, cyclosporine, glucocorticoids, amiodarone</td>
<td>Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, ranolaxifene, tamoxifen, beta blockers (not carvedilol), thiazides</td>
</tr>
<tr>
<td>Diseases</td>
<td>Biliary obstruction, nephrotic syndrome</td>
<td>Nephrotic syndrome, chronic renal failure, lipodystrophies</td>
</tr>
<tr>
<td>Disorders and altered states of metabolism</td>
<td>Hypothyroidism, obesity, pregnancy</td>
<td>Diabetes (poorly controlled), hypothyroidism, obesity; pregnancy</td>
</tr>
</tbody>
</table>

19. Individuals with LDL-C ≥190 mg/dL or triglycerides ≥500 mg/dL should be evaluated for secondary causes of hyperlipidemia.  (Class I, LOE: B)
20. If triglycerides are ≥500 mg, triglyceride-lowering is the primary goal of therapy to prevent pancreatitis initial therapy with a fibrate, niacin, or fish oil should be considered instead of a statin.
21. Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effects.  (Class IIb, LOE: C)
22. Consider stopping fibrate therapy if triglycerides normalize after appropriate lifestyle interventions and treatment of secondary causes.  (LOE: C)
23. Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyosis.  (Class III, LOE: B)
24. Routine monitoring of transaminases is not necessary in otherwise healthy patients, but should be considered in individuals with a history of liver disease, on other medications that can cause liver injury (e.g. niacin, fibrates, and other medications), or in individuals otherwise at risk for liver injury.  (Class Ila, LOE: C)
Physical Activity 2,11,13,14

Goals
- At least 30 minutes, 7 days per week (minimum 5 days per week)

Recommendations
1. For all patients, the clinician should encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, household work). (Class I, LOE: B)
2. For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription. (Class I, LOE: B)*
3. The clinician should counsel patients to report and be evaluated for symptoms related to exercise. (Class I, LOE: C)
4. It is reasonable for the clinician to recommend complementary resistance training at least 2 days per week. (Class Ila, LOE: C)
5. For patients with intermittent claudication a program of supervised exercise training is recommended as an initial treatment modality. It should consist of a minimum of 30 to 45 minutes per session, at least 3 times per week, and for a minimum of 12 weeks. (Class 1, LOE: A)
Weight Management

Goals

- Height, Weight, and Waist Circumference should be measured. Patient reported values should be verified by measurement whenever this data is recorded.
- Body mass index between 18.5 and 24.9 kg/m²
- Recommended waist circumference thresholds for abdominal obesity by ethnicity and gender are:

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>≤35 inches (≤90 cm)</td>
<td>≤31.5 inches (≤80 cm),</td>
</tr>
<tr>
<td>Middle East, Mediterranean</td>
<td>≤37 inches (≤94 cm),</td>
<td>≤31.5 inches (≤80 cm),</td>
</tr>
<tr>
<td>Sub-Saharan African</td>
<td>≤37 inches (≤94 cm),</td>
<td>≤31.5 inches (≤80 cm),</td>
</tr>
<tr>
<td>Ethic Central and South American</td>
<td>≤35 inches (≤90 cm)</td>
<td>≤31.5 inches (≤80 cm)</td>
</tr>
<tr>
<td>All Others</td>
<td>&lt;40 inches (&lt;102 cm)</td>
<td>&lt;35 inches (&lt;89 cm),</td>
</tr>
</tbody>
</table>

Reference the Body Mass Index (BMI) Screening and Follow-Up – Adult – Ambulatory/Primary Care Guideline for further recommendations

Recommendations

1. Body mass index and/or waist circumference should be assessed at every visit. (Class I LOE C)
2. Use the current cutpoints for overweight (BMI 25.0–29.9 kg/m²) and obesity (BMI ≥30 kg/m²) to identify adults who may be at elevated risk for recurrent major adverse CV events and the current cutpoints for obesity (BMI ≥30 kg/m²) to identify adults who may be at elevated risk of mortality from all causes. (Class I, LOE B)
3. Advise overweight and obese adults that the greater the BMI, or the greater the waist circumference, the greater the risk of CVD, type 2 diabetes, and all-cause mortality. (Class I, LOE B, Class IIa, LOE B)
4. Counsel overweight and obese adults with ASCVD that lifestyle changes that produce even modest, sustained weight loss of 3%–5% produce clinically meaningful health benefits, and greater weight losses produce greater benefits. (Class I, LOE A)
5. Prescribe a diet to achieve reduced calorie intake for obese or overweight individuals and preferably refer to a nutritional professional. (Class I, LOE A)

6. Any one of the following methods can be used to reduce food and calorie intake:
   - Prescribe 1200–1500 kcal/d for women and 1500–1800 kcal/d for men
   - Prescribe a 500-kcal/d or 750-kcal/d energy deficit; or
   - Prescribe one of the evidence-based diets that restricts certain food types (such as high-carbohydrate foods, low-fiber foods, or high-fat foods) in order to create an energy deficit by reduced food intake. (Class I, LOE A)

7. Advise overweight and obese individuals who would benefit from weight loss to participate for ≥6 months in a comprehensive lifestyle program that assists participants in adhering to a lower-calorie diet and in increasing physical activity through the use of behavioral strategies. (Class I, LOE A)

8. Advise adults with a BMI ≥40 kg/m² or BMI ≥35 kg/m² with obesity-related comorbid conditions who
   - are motivated to lose weight
   - and who have not responded to behavioral treatment with or without pharmacotherapy

   with sufficient weight loss to achieve targeted health outcome goals that bariatric surgery may be an appropriate option to improve health and offer referral to an experienced bariatric surgeon for consultation and evaluation. (Class IIa, LOE A)

---

**Type 2 Diabetes Mellitus Management**

**Recommendations**

*(Note: Recommendations below are for prevention of cardiovascular complications)*

Reference the Diabetes – Pediatric/Adult – Inpatient/Ambulatory Guideline for further recommendations

1. Care for diabetes should be coordinated with the patient’s primary care professional and/or endocrinologist. *(Class I, LOE: C)*

2. Lifestyle modifications including daily physical activity, weight management, blood pressure control, and lipid management are recommended for all patients with ASCVD, especially those with diabetes. *(Class I, LOE: B)*

3. Metformin is an effective first-line pharmacotherapy and can be useful if not contraindicated. *(Class IIa, LOE: A)*

4. It is reasonable to individualize the intensity of blood sugar–lowering interventions based on the individual patient’s risk of hypoglycemia during treatment. *(Class IIa, LOE: C)*

5. Initiation of pharmacotherapy interventions to achieve target HbA1c may be reasonable. *(Class IIb, LOE: A)*

6. A target HbA1c of <7% may be considered. *(Class IIb, LOE: C)*

7. Less stringent HbA1c goals may be considered for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or
macrovascular complications, or extensive comorbidities, or those in whom the goal is difficult to attain despite intensive therapeutic interventions. *(Class IIb, LOE: C)*

### Antiplatelet agents/Anticoagulants 2-6,9-11,16-19

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aspirin (non-enteric-coated, chewable) is recommended in all ASCVD patients without contraindications and should be continued indefinitely. In most cases the appropriate dose is 81 mg daily. <em>(Class I, LOE: A)</em></td>
</tr>
<tr>
<td>2. Enteric-coated or buffered preparations do not reduce the risk of bleeding. For patients at risk of GI bleeding gastroprotection should be prescribed. Many patients who are prescribed low-dose enteric coated aspirin for secondary prevention have persistent uninhibited platelet cyclooxygenase activity. For these reasons non-enteric-coated, chewable aspirin is preferred. <em>(Class I, LOE: B)</em></td>
</tr>
<tr>
<td>3. Clopidogrel 75 mg daily is recommended as an alternative for all patients with clinically apparent ASCVD who are intolerant of or allergic to aspirin. <em>(Class I, LOE: B)</em></td>
</tr>
</tbody>
</table>

#### Coronary Artery Disease and Coronary Stents

<table>
<thead>
<tr>
<th>4. In addition to aspirin, for patients presenting with an acute coronary syndrome or those who receive a drug-eluting coronary stent, P2Y12 inhibitor therapy should be given for at least 12 months <em>(Class I).</em> Options include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clopidogrel: 75 mg daily <em>(LOE: B)</em> or</td>
</tr>
<tr>
<td>• Prasugrel: 10 mg daily <em>(LOE: B)</em> or</td>
</tr>
<tr>
<td>• Ticagrelor: 90 mg twice daily <em>(LOE: B)</em></td>
</tr>
<tr>
<td>5. It is reasonable to use ticagrelor in preference to clopidogrel for P2Y12 inhibitor initial treatment and maintenance therapy in patients with acute coronary syndromes. <em>(Class IIa, LOE: B)</em></td>
</tr>
<tr>
<td>6. It is reasonable to choose prasugrel over clopidogrel for P2Y12 inhibitor initial treatment and maintenance therapy in patients with acute coronary syndromes who undergo PCI who are not at high risk of bleeding complications (i.e. &lt;75 y/o and &gt; 60 kg bwt.) <em>(Class IIa, LOE: B)</em></td>
</tr>
<tr>
<td>7. Prasugrel should not be administered to patients with a prior history of stroke or transient ischemic attack. <em>(Class III, LOE: B)</em></td>
</tr>
<tr>
<td>8. In patients receiving a bare metal stent outside the setting of an acute coronary syndrome, clopidogrel or another P2Y12 antagonist, in addition to aspirin, should be given for a minimum of 1 month and ideally up to 12 months. <em>(Class I, LOE: B)</em></td>
</tr>
<tr>
<td>9. Continuation of dual antiplatelet therapy beyond 12 months may be considered in patients undergoing stent implantation. <em>(Class IIb, LOE: C)</em></td>
</tr>
<tr>
<td>10. If the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of P2Y12 inhibitor therapy after stent implantation, earlier discontinuation (e.g., &lt;12 months) of P2Y12 inhibitor therapy is reasonable.</td>
</tr>
</tbody>
</table>
(Class IIa, LOE: C)

**Coronary Artery Disease and Coronary Bypass Surgery**

11. Assessment of the risk of bleeding and ischemia is recommended when making the decision of CABG surgery (whether with aspirin or DAPT). (Class I, LOE: C)

12. In nearly all patients underdoing CABG surgery, aspirin should be continued without interruption up until the time of surgery. (Class I, LOE: C)

13. In patients with increased bleeding risk and in those who refuse blood transfusion, cessation of aspirin 3-5 days before surgery is recommended based on individualized assessment of ischemia and bleeding risks. (Class I, LOE: C)

14. In patients on P2Y12 inhibitors who need CABG, it is recommended to postpone surgery for 5 days after interruption of ticagrelor or clopidogrel, and 7 days for prasugrel, unless the patient is at high risk of ischemic events.

15. For patients undergoing coronary artery bypass grafting, chewable ASA 75–162 mg/day should be restarted within the first 24 h and preferably within 6 h after CABG surgery and maintained lifelong. (Class I, LOE: B)

16. After CABG, in case of aspirin intolerance or contraindication, a loading dose of clopidogrel 300 mg as soon as bleeding is controlled followed by 75 mg/day is recommended and should be continued lifelong. (Class I, LOE: C)

17. For patients who undergo CABG within 1 year of ACS, resumption of P2Y12 inhibitor early after surgery should be considered as soon as bleeding is controlled. (Class IIa, LOE: B)

18. Early after CABG a 300 mg clopidogrel loading dose, as soon as bleeding is controlled, followed by a 75 mg clopidogrel maintenance dose in addition to aspirin is recommended in stable CAD patients with coronary stent in non-grafted territories for the duration intended following stent implantation. (Class I, LOE: C)

19. Dual antiplatelet therapy with aspirin and clopidogrel may be considered to be (re-) started after CABG surgery for stable CAD patients as soon as considered safe. (Class IIb, LOE: C)

**Peripheral Arterial Disease**

20. For patients with symptomatic atherosclerotic peripheral artery disease of the lower extremity or a history of lower extremity revascularization, antiplatelet therapy should be administered. (*Class I, LOE A)

21. Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other oral anticoagulants to treat patients with atherosclerosis (Class I, LOE: A)

22. In the absence of any other proven indication for warfarin, its addition to antiplatelet therapy to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD is of no benefit and is potentially harmful due to increased risk of major bleeding. (Class III, LOE: B)

**Ischemic Stroke and TIA**

23. For patients with noncardioembolic ischemic stroke or TIA, treatment with aspirin alone (50–325 mg daily) (Class I, LOE A), clopidogrel alone (75 mg daily) (Class IIa, LOE: B), or the combination of aspirin plus extended-release
dipyridamole (25 mg and 200 mg twice daily, respectively) should be started and continued. (Class I, LOE: B)

24. The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for 2 to 3 years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA. (Class III, LOE: A)

**Combined Use of Oral Anticoagulants and Antiplatelet Agents**

25. In the setting of ischemic stroke or TIA, atrial fibrillation and stable CAD with no recent coronary revascularization the usefulness of adding antiplatelet therapy to warfarin therapy is uncertain. Because prior studies with warfarin demonstrated that warfarin is at least as effective as antiplatelet therapy for prevention of recurrent MI, the use of warfarin alone may be sufficient to reduce the risk of both cardiovascular and cerebrovascular events and should be considered. (Class 2b, LOE:C).

26. In the setting of ischemic stroke or TIA and atrial fibrillation the combination of oral anticoagulation (ie, warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement (Class 2b, LOE C);

27. When there are compelling indications for oral anticoagulant therapy (such as atrial fibrillation, prosthetic heart valve, left ventricular thrombus, or concomitant venous thromboembolic disease) as well as compelling indications for antiplatelet therapy, oral anticoagulant therapy should be added to and not replace antiplatelet therapy. (Class I, LOE: A)

28. For patients requiring warfarin and antiplatelet therapy, warfarin should be administered to achieve the recommended INR for the specific condition (Class I, LOE: B)

**Mitigating the Risk of Combined Oral Anticoagulants and Antiplatelet Therapy**

29. Targeting warfarin therapy to a lower international normalized ratio (INR) (e.g., 2.0 to 2.5) may be reasonable in patients also managed with aspirin and a P2Y12 inhibitor. (Class Iib, LOE: C)

30. Use of oral anticoagulants in conjunction with antiplatelet therapy is associated with an increase in the risk of major bleeding and should be monitored closely. (Class I, LOE A)

31. Following coronary revascularization procedures in patients for whom oral anticoagulant therapy is indicated, it may be reasonable to use clopidogrel concurrently with oral anticoagulants, but without aspirin. (Class Iib, LOE: B)

32. The duration of triple antithrombotic therapy with an oral anticoagulant, aspirin, and a P2Y12 receptor inhibitor in patients should be minimized to the extent possible to limit the risk of bleeding. (Class I, LOE: C)

33. Proton pump inhibitors should be prescribed in patients with a history of gastrointestinal bleeding who require triple antithrombotic therapy with an oral anticoagulant, aspirin, and a P2Y12 receptor inhibitor. (Class I, LOE: C)

34. Proton pump inhibitor use is reasonable in patients without a known history of gastrointestinal bleeding who require triple antithrombotic therapy with an oral
Renin-angiotensin-aldosterone system blockers 2,3,6-11,13,17

**Recommendations**

1. ACE inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction ≤40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated. *(Class I, LOE: A)*
2. It is reasonable to use ACE inhibitors in all other patients with coronary artery and/or peripheral arterial disease. *(Class IIa, LOE: B)*
3. The use of renin-angiotensin system blockers in patients following stroke or TIA presumed to be of atherosclerotic origin, for the purpose of reducing cardiovascular risk, when other indications such as hypertension are lacking, has not been studied and is not routinely recommended. *(LOE: C)*
4. The use of ARBs is recommended in patients who have heart failure or who have had a myocardial infarction with left ventricular ejection fraction ≤40% and who are ACE-inhibitor intolerant. *(Class I, LOE: A)*
5. It is reasonable to use ARBs in other patients who are ACE-inhibitor intolerant. *(Class IIa, LOE: B)*
6. Use of aldosterone blockade in post–myocardial infarction patients is recommended when they meet all of the following criteria:
   - are already receiving therapeutic doses of an ACE inhibitor and a β-blocker,
   - have a left ventricular ejection fraction ≤40%,
   - have either diabetes or heart failure and
   - are without significant renal dysfunction or hyperkalemia (creatinine <2.5 mg/dL and potassium <5.0 mEq/L) *(Class I, LOE: A)*
7. Prior to heart surgery using cardiopulmonary bypass the safety of the preoperative administration of ACE inhibitors or ARBs in patients on chronic therapy is uncertain *(Class 2b, LOE: B)*. In patients for whom heart surgery using cardiopulmonary bypass is planned, consider stopping ACE inhibitors and ARBs 48 hours before surgery, especially those with controlled hypertension and without heart failure and a reduced ejection fraction.

Beta Blockers 2,6-10,17

**Recommendations**

1. Beta Blocker therapy should be used in all patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and heart failure unless contraindicated. *(Use should be limited to carvedilol, metoprolol succinate, or
bisoprolol, which have been shown to reduce mortality.) *(Class I, LOE: A)*

2. In all patients with a recent or remote history of MI or acute coronary syndrome and reduced EF, evidence-based beta blockers should be used to reduce mortality *(Class I, LOE: B)*

3. Beta Blocker therapy should be started in all patients with normal left ventricular function with an acute coronary syndrome, particularly those with acute myocardial infarction. *(Class I, LOE: B)*

### Influenza Vaccination 2,6,7,9,11,17

#### Recommendations

1. Patients with cardiovascular disease should have an annual influenza vaccination *(Class I, LOE: B)*

### Depression 2,6,7,9,11

#### Recommendations

For recommendations related to screening and treatment refer to the Depression Guideline

1. For patients with recent coronary artery bypass graft surgery or myocardial infarction, it is reasonable to screen for depression if patients have access to case management, in collaboration with their primary care professional and a mental health specialist. *(Class IIa, LOE:B)*

2. Treatment of depression has not been shown to improve cardiovascular disease outcomes but may be reasonable for its other clinical benefits. *(Class IIb, LOE:C)*

### Cardiac Rehabilitation 2,4-7,10,11

#### Recommendations

1. All eligible patients with any acute coronary syndrome or whose status is immediately post coronary artery bypass surgery or post-PCI should be referred to a comprehensive outpatient cardiovascular rehabilitation program either prior to hospital discharge or during the first follow-up office visit. *(Class I, LOE: A)*

2. All eligible outpatients with the diagnosis of chronic stable angina *(Class I, LOE: B)*, and/or peripheral arterial disease *(Class I, LOE: A)* within the past year should be referred to a comprehensive outpatient cardiovascular rehabilitation program.

3. A home-based cardiac rehabilitation program can be substituted for a supervised, center-based program for low-risk patients. *(Class I, LOE: A)*

4. A comprehensive exercise-based outpatient cardiac rehabilitation program can be safe and beneficial for clinically stable outpatients with a history of heart
Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
Appendix A

ACC/AHA Evidence Grading Scheme:

SIZE OF TREATMENT EFFECT

CLASS I
Benefit >>> Risk
Procedure/Treatment SHOULD be performed/administered

CLASS IIa
Benefit >> Risk
Additional studies with focused objectives needed; it is reasonable to perform procedure/administer treatment

CLASS IIb
Benefit > Risk
Additional studies with broad objectives needed; additional registry data would be helpful; procedure/treatment MAY BE CONSIDERED

CLASS III

- No Benefit
- Harmful

- Greater conflicting evidence from multiple randomized trials or meta-analyses
- Sufficient evidence from multiple randomized trials or meta-analyses
- Recommendation’s usefulness/effectiveness less well established

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Sufficient evidence from multiple randomized trials or meta-analyses

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Evidence from single randomized trial or nonrandomized studies

- Recommendation that procedure or treatment is not useful/effective
- Only diverging expert opinion, case studies, or standard of care
- Recommendation’s usefulness/effectiveness less well established

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Only diverging expert opinion, case studies, or standard of care
- Recommendation’s usefulness/effectiveness less well established

- Recommendation that procedure or treatment is not useful/effective and may be harmful
- Only diverging expert opinion, case studies, or standard of care
- Recommendation’s usefulness/effectiveness less well established

Suggested phrases for writing recommendations

should
is recommended

is indicated
is useful/effective/beneficial

may/might be considered
is probably recommended

- Is reasonable can be useful/effective/beneficial
- is not indicated
- is not useful/effective/beneficial

Comparative effectiveness phrases*:

<table>
<thead>
<tr>
<th>Strategy A</th>
<th>Strategy B</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment</td>
<td>is recommended/indicated in preference to treatment B</td>
</tr>
<tr>
<td>is probably recommended/indicated in preference to treatment B</td>
<td>It is reasonable to choose treatment A over treatment B</td>
</tr>
</tbody>
</table>

COR III: No Benefit
potential harm

COR III: Harmful
excess morbidity/mortality

level of certainty (precision) of treatment effect

LEVEL A
Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses

LEVEL B
Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies

LEVEL C
Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care
## ADA Evidence Rating Scheme

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Clear evidence from well-conducted, generalizable RCTs that are adequately powered, including:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Evidence from a well-conducted multicenter trial</td>
</tr>
<tr>
<td></td>
<td>- Evidence from a meta-analysis that incorporated quality ratings in the analysis</td>
</tr>
<tr>
<td></td>
<td>Compelling non-experimental evidence, i.e., “all or none” rule developed by the Center for Evidence-Based Medicine at the University of Oxford</td>
</tr>
<tr>
<td></td>
<td>Supportive evidence from well-conducted RCTs that are adequately powered, including:</td>
</tr>
<tr>
<td></td>
<td>- Evidence from a well-conducted trial at one or more institutions</td>
</tr>
<tr>
<td></td>
<td>- Evidence from a meta-analysis that incorporated quality ratings in the analysis</td>
</tr>
</tbody>
</table>

| **B** Supportive evidence from well-conducted cohort studies |  |
| | - Evidence from a well-conducted prospective cohort study or registry |
| | - Evidence from a well-conducted meta-analysis of cohort studies |
| | Supportive evidence from a well-conducted case-control study |

| **C** Supportive evidence from poorly controlled or uncontrolled studies |  |
| | - Evidence from randomized clinical trials with one or more major of three or more minor methodological flaws that could invalidate the results |
| | - Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) |
| | - Evidence from case series or case reports |
| | Conflicting evidence with the weight of evidence supporting the recommendation |

| **E** Expert consensus or clinical experience |  |
References


