

# Secondary Prevention of Coronary Artery Disease

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## Summary

### **Disclaimer**

The Permanente Medical Group (TPMG) Clinical Practice Guidelines (and those developed with CMI) have been developed to assist clinicians by providing an analytical framework for the evaluation and treatment of selected common problems encountered in patients. These guidelines are not intended to establish a protocol for all patients with a particular condition. While the guidelines provide one approach to evaluating a problem, clinical conditions may vary significantly from individual to individual. Therefore, the clinician must exercise independent professional judgment and make decisions based upon the situation presented. While great care has been taken to assure the accuracy of the information presented, the reader is advised that TPMG cannot be responsible for continued currency of the information, for any errors or omissions in these guidelines, or for any consequences arising from their use.

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## **Angiotensin -Converting Enzyme (ACE) Inhibitor Therapy**

For most patients with Coronary Artery Disease (CAD),\* Angiotensin-Converting Enzyme (ACE) Inhibitor therapy is recommended for long term use, \*\* unless contraindicated.

\* For CAD patients with documented preserved left ventricular function, excellent blood pressure control, no diabetes, and no chronic kidney disease (CKD), ACE-inhibition therapy is optional. (In the PEACE Trial<sup>1</sup>, patients with stable coronary artery disease and preserved left ventricular systolic function had no benefit on the composite endpoint of cardiovascular death, MI, and coronary revascularization with the addition of an ACE-inhibitor to standard medical therapy.)

\*\* For patients on concomitant aspirin, low-dose aspirin is recommended.

Evidence-based

## **Angiotensin II Receptor Blocker (ARB) Therapy**

- A. Angiotensin II Receptor Blocker (ARB) therapy is recommended for the following patients with CAD who are intolerant to ACE Inhibitors:
- Patients with CAD and diabetes with hypertension and/or microalbuminuria (or albuminuria)
  - Patients with CAD and left ventricular systolic dysfunction (LVSD)
- B. For patients who are intolerant to ACE Inhibitors, with CAD and hypertension (without either LVSD or diabetes), ARB therapy is an option equal to other antihypertensive medications.
- C. For all other patients with CAD who are intolerant to ACE Inhibitors, there is insufficient evidence to recommend for or against ARB therapy.

A: Consensus-based

B, C: Evidence-based

## **ACE Inhibitor + Aspirin**

For all patients with CAD taking low-dose aspirin, ACE Inhibitor therapy may be safely recommended for long term use.

Evidence-based

## **ACE Inhibitor + ARB Therapy**

- A. For CAD patients, the routine addition of ARB therapy to ACE Inhibitor therapy is not recommended.
- B. If ARBs are added to ACE Inhibitors it should be done for clinical reasons, such as uncontrolled hypertension or insufficient vasodilation.
- C. This recommendation applies whether or not a patient is treated with a beta blocker.

A, B, C: Consensus-based

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<sup>1</sup> PEACE Trial Investigators (2004) Angiotensin-Converting–Enzyme Inhibition in Stable Coronary Artery Disease, *New England Journal of Medicine* 351:2058-2068

## **Antiplatelet Therapy - Aspirin**

- A. For all patients with CAD, daily aspirin (81 to 162 mg) is recommended indefinitely, unless there is clear contraindication such as active bleeding, major coagulopathy, or true aspirin allergy.
- B. For patients with congestive heart failure, low-dose aspirin, no more than 81 mg, is recommended.

**NOTE:** The lowest dose commercially available ASA in the United States is 81 mg.

- A: Evidence-based
- B: Consensus-based

## **Antiplatelet Therapy - Clopidogrel Use in Stable Patients**

- A. In stable CAD patients who tolerate aspirin well (and who are not post-procedure), clopidogrel is not recommended as either a substitute for or in addition to aspirin.
- B. In stable CAD patients with contraindications to aspirin, clopidogrel is recommended as the antiplatelet of choice.

A, B: Consensus-based

## **Antiplatelet Therapy - Post-Procedure**

- A. Following coronary artery bare metal stent placement, clopidogrel 75 mg daily plus aspirin 325 mg daily is recommended to be given for at least four weeks.
- B. Following coronary artery drug-eluting stent placement, clopidogrel 75 mg plus aspirin 325 mg is recommended to be given for at least three months after sirolimus stent, and 6 months after paclitaxel stent, and up to one year post-procedure to reduce the risk of thrombotic events.
- C. If there is presence of a rash after clopidogrel use, patients may be switched to ticlopidine.

- A: Evidence-based
- B, C: Consensus-based

## **Beta Blocker Therapy**

Beta blocker therapy is recommended for CAD patients unless contraindicated; specifically:

- A. For post-MI patients non-intrinsic sympathomimetic activity (non-ISA) beta blocker therapy is recommended.
- B. For post-MI patients non-ISA beta blocker therapy is recommended to be initiated within hours after MI and continued long term.
- C. For CAD patients with unstable angina, long term non-ISA beta blocker therapy is recommended.

- D. For CAD patients with chronic stable angina, long term non-ISA beta blocker therapy is recommended for treatment of symptoms.
- E. For CAD patients with silent ischemia, non-ISA beta blocker therapy is recommended.
- F. For patients with CAD, beta blocker therapy is recommended peri-operatively for vascular surgery or noncardiac surgery with general anesthesia.
- G. For patients at risk for CAD, \* beta blocker therapy is recommended peri-operatively for vascular surgery.

\* At risk for CAD is defined as having at least two of the following cardiac risk factors: age  $\geq$  65 years, hypertension, current smoking, serum cholesterol  $\geq$  240 mg/dL (6.2 mmol/L), diabetes mellitus.

**NOTE:** Drugs without ISA are atenolol, betaxolol, bisoprolol, carvedilol, labetalol, nadolol, metoprolol, propranolol, and timolol. Drugs with ISA are acebutolol, and pindolol..

A, D, F, G: Evidence-based

B, C, E: Consensus-based

### **CAD + Mild to Moderate Reversible Airway Disease or Chronic Obstructive Pulmonary Disease (COPD) - Beta Blocker Therapy**

- A. For CAD patients with concomitant mild to moderate reversible airway disease or chronic obstructive pulmonary disease (COPD) cardioselective beta blockers are recommended.
- B. Discuss the risks and benefits of treatment with the patient and instruct the patient to report any increase in airway symptoms.
- C. Initiating beta blocker therapy is NOT recommended:
  - For patients with severe airway disease requiring frequent hospitalization or intubation
  - During acute exacerbation of airway disease
  - When airway disease is unstable or poorly controlled

A: Evidence-based

B, C: Consensus-based

### **CAD + Heart Failure - Beta Blocker Therapy**

- A. For CAD patients with either left ventricular systolic dysfunction (LVSD) (NYHA Class II-IV) or asymptomatic LVSD (NYHA Class I), beta blockers are strongly recommended.
- B. For CAD patients with left ventricular systolic dysfunction carvedilol, metoprolol extended release, or bisoprolol is the recommended choice of beta blocker therapy.

C. Metoprolol tartrate (short-acting formulation) titrated to maximum tolerated dosage, is an acceptable but less well-established alternative to carvedilol, metoprolol CR/XL, or bisoprolol.

A, B: Evidence-based

C: Consensus-based

## **Lipid Management in the Secondary Prevention of CAD**

Excerpted from the Interregional Clinical Practice Guidelines, Dyslipidemia Management in Adults; Secondary Prevention.

### **Secondary Prevention and CAD Risk Equivalents**

- Lifestyle modifications are recommended in ALL secondary prevention and CAD Risk Equivalent people (see “Lifestyle Modification” section).

### **Drug Treatment Strategy**

- Because of its proven effectiveness in event reduction, safety and cost, generic simvastatin is the preferred first-line statin.
- Treatment with statins is recommended for all adults with established atherosclerosis, even if baseline LDL-C is < 100 mg/dL (based on evidence of benefit from the Heart Protection Study).
- Use statins as first-line therapy at doses calculated to bring LDL-C levels to < 100 mg/dL. In people with acute coronary syndrome (ACS), an LDL-C goal of < 70 mg/dL may be appropriate.
- When the LDL-C goal is achieved, reassess LDL-C annually to ensure that the patient remains at goal; it is optional to repeat the lipid panel in three to six months.
- A more aggressive LDL-C goal of < 70 mg/dL is now an option.

Recent statin trials have demonstrated improved outcomes in people whose LDL-C was lowered well below 100 mg/dL. Only people with ACS have been shown to have improved outcomes when the LDL-C was lowered below 70 mg/dL (PROVE-IT TIMI 22 trial). Three other trials have shown improved outcomes in a variety of people with CAD when the LDL-C was lowered below 80 mg/dL (MIRACL, AVERT, REVERSAL).

When to intensify treatment in people with an LDL-C < 100 mg/dL should be a shared decision with the patient, taking into consideration factors such as overall CVD risk, triglyceride status, HDL-C, non-HDL cholesterol, medication tolerance, cost, and patient preference.

### **Lipid Management at the Acute Atherosclerotic Event**

- Obtain a lipid panel and initiate lipid-lowering therapy as soon as possible after hospital admission. Ensure that people receive a prescription for statin medication at discharge.
- Repeat the lipid panel two months after hospital discharge.

Evidence-based

End Excerpt

## CAD Medication Dosing Table

### LIPID LOWERING AGENTS (Goal: LDL-C less than 100 mg/dL)

STATINS		
	Starting daily dose	Baseline LDL-C
lovastatin	40 mg daily with dinner	≤ 140
simvastatin	40 mg daily at bedtime 80 mg daily at bedtime	141 - 170 > 170
ezetimibe/simvastatin	10/80 mg once daily	For patients not at goal with 80 mg simvastatin
FIBRATES Consider adding fibrates and/or niacin to statins if TG 200 - 400 mg/dL		
	Initial Dose	Maximum Dose
gemfibrozil	600 mg BID before meals	600 mg BID before meals
fenofibrate tablets	54 mg – 160 mg daily with food	160 mg daily with food

### BILE ACID SEQUESTRANTS - Daily amounts, divided into 2 - 4 doses daily

	STEP I	STEP II	STEP III	STEP IV
colestipol powder				(max daily dose)
tablets	1 scoop = 5 gm 2 tablets = 2 gm	2 scoops = 10 gm 4 tablets = 4 gm	3 scoops = 15 gm 8 tablets = 8 gm	6 scoops = 30 gm 16 tablets = 16 gm
cholestyramine	1 scoop = 4 gm	2 scoops = 8 gm	3 scoops = 12 gm	6 scoops = 24 gm

### NIACIN IMMEDIATE-RELEASE TABS - Daily amounts, divided into 3 doses with or after meals

Total Daily Dose	STEP I 1000 mg	STEP II 2000 mg*	STEP III 3000 mg*	*If not tolerated, cut to max tolerated dose or D/C

Careful dosage titration for niacin is required to promote tolerance and adherence to therapy. Aspirin (162-325 mg) 30 minutes before niacin dose can minimize flushing/itching. Taking immediate-release niacin with meals may also mitigate flushing.

### ANTI-PLATELET AND ANTI-THROMBOTIC AGENTS

aspirin	81- 325 mg daily
clopidogrel	75 mg daily
ticlopidine	250 mg twice daily with food
warfarin	Dosing based on target INR per anticoagulation protocols

### BETA-BLOCKER

	Initial Dose	Maximum Dose
atenolol → if EF > 40	25 mg daily	100 mg daily
metoprolol tartrate	12.5 mg twice daily	100 mg twice daily
bisoprolol *	2.5 mg daily	20 mg daily
metoprolol-Extended release *	25 mg daily	200 mg daily
carvedilol *	3.125 mg twice daily	25 - 50 mg twice daily
* recommended if EF < 40		

### ACE INHIBITORS

lisinopril	5 - 10 mg daily	40 mg daily
captopril*	12.5 - 25 mg twice daily	150 mg TID
*take on an empty stomach (1 hour AC) for best absorption		

### AT-1 RECEPTOR ANTAGONISTS

losartan	25 mg daily	100 mg daily
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### DHP - CALCIUM CHANNEL BLOCKERS

felodipine-Extended release	2.5 - 5 mg daily	20 mg daily
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### NITRATES - a daily 14-hour nitrate-free interval is necessary to minimize nitrate tolerance

isosorbide dinitrate	10 mg TID	80 mg TID
nitroglycerin transdermal	0.2 mg/hr daily	0.8mg/hr daily
nitroglycerin-Extended release	2.5 mg TID	26 mg QID
isosorbide mononitrate	30 mg daily	240 mg daily

## **Lipid Treatment Thresholds, Medication Starting Doses and Lipid Goal Additional Dosing Instructions**

- If baseline serum creatinine > 1.5 mg/dL, start with half the recommended statin dose.
- All people taking statins should be warned about the risk and symptoms of rhabdomyolysis. Risk is increased in medically complicated people, the very elderly, people with compromised renal function, and interacting drugs. In these settings, lower statin doses and increased monitoring are recommended.

## **Lifestyle Modification – Diet and Dietary Supplement Therapy in the Secondary Prevention of CAD**

### **Diet Therapy**

For all patients with CAD a diet rich in fruits, vegetables, legumes, nuts, whole grains, and n-3- (omega-3) polyunsaturated fat is recommended.

### **Dietary Fat Modification**

For all patients with CAD consuming a usual Western diet the following modifications in dietary fat are recommended:

- Increase intake of n-3 (omega-3) polyunsaturated fatty acids to a level of ~ 1 g /day from a variety of sources (flaxseed, canola, and soybean oils, nuts, fish, and fish oil supplements).\*
- Replace saturated fatty acids with polyunsaturated and monounsaturated fatty acids.
- Reduce or eliminate intake of trans-fatty acids.

\* To limit the bioaccumulation of methylmercury, polychlorinated biphenols (PCBs), dioxins, and other environmental contaminants, intake of certain fish (e.g., swordfish, tuna, and farmed salmon) is recommended not to exceed two servings per week.

Consensus-based

## **Dietary Supplement Therapy**

- A. For patients with CAD, supplemental vitamins C, E and beta carotene are not recommended for prevention of cardiovascular mortality or subsequent coronary events.
- B. For CAD patients who are current or former smokers, supplemental beta carotene is not recommended due to a small but significant excess in all cause mortality reported in this group.
- C. For patients with CAD supplemental folic acid, vitamin B6, and vitamin B12 are not recommended.

A, B: Evidence-based

C: Evidence-based (D)\*

\*Please note that only recommendations approved since the adoption in 2006 of evidence grading will use letters (A, B, C, etc.) to specify the grade of the evidence. Recommendations approved prior to 2006 will not include a letter grade following the statement “evidence-based.”