Secondary Prevention of Ischemic Heart Disease and Stroke Guideline Team

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Secondary Prevention of Ischemic Heart Disease and Stroke in Adults

Patient population: Adults with ischemic vascular disease (IVD), including:

- Ischemic heart disease (IHD) – both angina (stable or unstable) and myocardial infarction (ST segment elevation [STEMI] and non-ST segment elevation [NSTEMI])
- Ischemic stroke and transient ischemic attack (TIA), both referred to as "stroke" in this document.

Other types of IVD (e.g., peripheral vascular disease, ischemic bowel disease) are not addressed.

Objectives: Improve secondary prevention of IVD by assembling in one location core recommendations for the actions that should be taken or considered.

Key points:

Secondary prevention. Patients with IHD or stroke should receive intensive secondary prevention interventions, which offer large absolute risk reductions for subsequent events and mortality *[IA]**. Table 1 summarizes secondary prevention recommendations for the main and modifiable risk factors listed below for patients with coronary and other vascular disease. Less common risk factors for IVD are not addressed in this guideline.

Lifestyle with Medication	Medication	Lifestyle
Blood pressure control	Antiplatelet agents and anticoagulants	Physical activity
Tobacco treatment	β blockers in IHD	Weight management
Lipid management	Renin-angiotensin-aldosterone system blockers in IHD	Nutrition
Diabetes management	Pain control (NSAID caution)	Supplements
Depression screening	Immunizations	**Surgery**
		Carotid endarterectomy or stenting for symptomatic lesions

* **Strength of recommendation:**
I= generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

Levels of evidence for the most significant recommendations
A = randomized controlled trials; B = controlled trials, no randomization; C = observational trials; D = opinion of expert panel

Clinical Background

Clinical Problem

Burden of disease. Cardiovascular disease is the leading cause of death in the United States. IHD accounts for 113 deaths per 100,000 population annually and cerebrovascular disease accounted for 39 deaths per 100,000, most of which are ischemic stroke (2010).

Although the prevalence of IHD is declining somewhat, its prevalence is still 6% in the general population (2010). The prevalence of cerebrovascular disease among individuals age 18 years and older is 2.6% (2010).

The impact on U.S. society and community is enormous. Costs associated with coronary artery disease (CAD) alone were $109 billion in 2010. Stroke is the leading cause of disability.

Risk factors. Adjusted population attributable fractions for cardiovascular disease (CVD) mortality include:

- 40.6% for high blood pressure
- 13.7% for smoking
- 13.2% for poor diet
- 11.9% for insufficient physical activity
- 8.8% for abnormal glucose levels

These risk factors are prevalent in the US population (with and without IVD) despite the progress in medicine. For example, among Americans 18 and above (2011):

- 21% of men and 17% of women are cigarette smokers (2011).

(Text continues on page 6.)

Table 1. Recommendations for Secondary Prevention of IVD

Lifestyle with Medication	
Blood Pressure Control	Blood pressure (BP) goal: • If no relevant comorbidities: <140/90 mm Hg in patients with IHD *[IA].* • Lowering BP in a stroke patient is recommended *[1A]*, although acutely lowering blood pressure after stroke is not recommended. • In patients with lacunar stroke, a systolic blood pressure of less than 130 should be targeted *[IA].* In patients with other types of stroke the target blood pressure is not clear, but experts generally recommended a systolic blood pressure of less than 140. • If diabetes mellitus: SBP < 140*[IA]*, DBP<90, with some evidence for <80. • If CKD with urine albumin excretion > 30mg/24 hours, suggest < 130/80 *[IIA].* For patients not at target: • Initiate lifestyle modifications: weight control, appropriate physical activity, alcohol moderation, sodium reduction, and healthy diet *[IA].* If further BP lowering needed: • Add medications based on patient characteristics and as tolerated. For patients with: – IHD – treat initially with beta blockers and/or angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptors blockers [ARB] in case of ACE intolerance), with addition of other BP drugs such as thiazide diuretics or calcium blockers as needed to achieve goal blood pressure *[IA].* – Stroke – beta blockers are NOT recommended unless another indication for beta blockade exists, as they seem to lower blood pressure without decreasing stroke risk *[IIIA].*
Tobacco Treatment	Goal: Complete cessation. Ask all patients about tobacco use. Tobacco use status should be documented in the medical record and re-assessed at every patient encounter *[IA]*. Advise all tobacco users seriously to consider making a quit attempt using a clear and personalized message *[IA]*. Advice as brief as three minutes is effective *[IA].* Assess all tobacco users' willingness to make a quit attempt. If not ready to quit, offer motivational intervention using the 5 "R's" – relevance, risks, rewards, roadblocks, repetition *[IA].* Assist those ready to make a quit attempt Refer patients interested in quitting within 30 days to a Tobacco Treatment specialist or other appropriate tobacco treatment program *[IA].* Alternatively healthcare providers can directly provide the following treatment: • Set a quit date. Quit date adherence is a strong predictor of long-term success. • Give advice on quitting and provide supplementary materials. • Prescribe pharmacologic therapy as appropriate. Nicotine replacement therapies, bupropion hydrochloride, and varenicline have been proven effective. Arrange follow-up either with phone call or office visit *[IA].* Subsequent visits: • Prevent relapse by congratulating successes and reinforcing reasons for quitting. • Assess any difficulties with pharmacologic therapy.
Lipid Management	Full lipid panel (total cholesterol, LDL-C, HDL-C, and triglycerides): Obtain for all patients *[IA].* Lifestyle modification: recommend regular exercise if no contraindication, assess and strongly recommend lowering caloric intake from saturated fat to <7%, and recommend lowering the percentage of calories from trans fats *[IA].* Secondary causes of lipid disorders: assess for and optimize if identified. Statin (if no contraindication): • If ≤ 75 years old with IVD, recommend high-intensity statin therapy (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) in order to lower LDLC by 50% or greater of baseline *[IA].* • If > 75 years old with IVD, recommend moderate-intensity statin therapy (see text) *[IC].* Other/additional medications. Consider in patients who are completely statin intolerant or are not able to tolerate the recommended statin intensity.

Diabetes Management	Glycemic control: • Type 1 diabetes: Tight glycemic control (HbA1c <7%) *[IA]* • Type 2 diabetes: – Glycemic control prevents microvascular complication, but benefit has not been proven for secondary prevention of macrovascular complications. – The American Diabetes Association in general recommends an A1c goal of <7% *[IIB];* however a less stringent goal of < 8% is reasonable in patients with advanced macrovascular complications or high risk for hypoglycemia *[IIB].* Blood pressure goal: SBP ≤ 140 mm Hg *[IB]*. DBP < 90 per JNC 8 Panel, possibly better if <80 per American Diabetes Association. Statin therapy: at least use moderate-intensity statin therapy if no contraindication. (See "statin" in Lipid Management section above for further details.) Tobacco use: Check status at every encounter and at minimum annually. Recommend nonsmoking, educate, encourage cessation *[IC].*
Depression Screening	Screen for depression: is reasonable in patients with IVD. Treat depression or refer when indicated *[IIB].* Initial screening for patients with IHD can be performed by use of the standard PHQ-2 depression screening tool: During the past month, have you been bothered by: • Little interest or pleasure in doing things? • Feeling down, depressed or hopeless? If the patient responds "yes" to either question, move to the more detailed PHQ-9.
Medication	
Antiplatelet agents & anticoagulants	For established IHD: antiplatelet. Prescribe aspirin at a dose of 81mg daily *[IA]*. In patients intolerant to aspirin, prescribe clopidogrel at a dose of 75 mg daily (or ticlopidine after consulting with cardiology) indefinitely *[IA]*. For recent acute coronary syndromes treated medically without angioplasty: antiplatelet. In addition to aspirin, add clopidogrel at a dose of 75 mg daily for at least 1 month *[IA]* and ideally up to 1 year post-event. Following coronary stent placement: antiplatelet. Prescribe aspirin at a dose of 81mg as above *[IA].* The duration of therapy of additional antiplatelet is usually determined by the cardiologist. If stent for acute coronary syndrome: Whether bare-metal stent (BMS) or drug eluting stent (DES), prescribe a P2Y12 inhibitor for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg bid *[IA].* Specific instructions and cautions regarding each P2Y12 are included in the text. If stent for non-acute coronary syndrome: • If a DES, prescribe clopidogrel 75 mg daily for 12 months *[IA].* • If a BMS, prescribe clopidogrel 75 mg daily for a minimum of 1 month and ideally up to 12 months. In patients at increased risk for bleeding, consider 2 weeks of therapy *[IA].* Following non-cardioembolic stroke: • Antiplatelets are recommended over anticoagulation because of similar benefit and less bleeding risk. Acceptable options for secondary prevention of non-cardioembolic stroke are: aspirin 50-325mg daily, aspirin 25mg plus extended-release dipyridamole 200mg twice daily, and clopidogrel 75mg daily *[IA].* Individual patient factors should guide the choice of agent. • Not recommended: combination of aspirin and clopidogrel for long term prevention of stroke. In general, this combination increases the risk of hemorrhage compared to a single antiplatelet agent *[IIIA].* • If already on an antiplatelet agent (when a stroke occurs): No evidence exists for the effectiveness of changing the dose or switching to a different antiplatelet agent *[IIID].* • Patients who undergo carotid stenting should be on dual antiplatelet therapy before, and for a minimum of 30 days after the procedure *[IB].* Duration should be determined by the interventionist. In patients with persistent or paroxysmal non-valvular atrial fibrillation: an anticoagulant is generally recommended over an antiplatelet.

	• Anticoagulants: Warfarin (target INR 2-3) *[IA],* dabigatran *[IA]*, rivaroxaban *[IIA]*, and apixaban *[IA]* are indicated to prevent recurrent stroke. For patients unsuitable for anticoagulation, aspirin 325 mg, although less effective, is the preferred antiplatelet alternative *[IIB]*. Apixaban is more effective alternative to aspirin in patients who are unsuitable for warfarin without significantly increasing the bleeding risk. – If severe renal failure: do NOT use dabigatran, rivaroxaban, or apixaban (CrCl < 15mL/min for dabigatran and rivaroxaban, CrCl < 25mL/min for apixaban) *[IIID]*. – If impaired renal function: exercise caution and adjust doses when using apixaban, dabigatran, or rivaroxaban *[ID]*. • When considering or using dabigatran, rivaroxaban, or apixaban: – Consider checking renal function every six months as the anticoagulant effects of these agents can be potentiated by worsening renal function *[IID]*. – Use care in prescribing these agents because of the potential for adverse events because clinicians have less experience with them than warfarin or aspirin *[IID]*. – Be aware that there are no FDA approved reversal agents currently available • Management of an antiplatelet agent for patients with a concomitant indication for anticoagulation. In patients with stroke or stable IHD (without ACS, PCI, or CABG in the past year) who require anticoagulation with warfarin, there is no need for an additional antiplatelet agent *[IIA]*. The efficacy of stopping an antiplatelet agent in a patient on a new oral anticoagulant is unclear. • Consider adding PPI (proton pump inhibitor) to lower the risk of GI bleeding in patients taking an anticoagulant or antiplatelet. See text for details.
β blockers in IHD	Beneficial: Start and continue oral β blocker therapy indefinitely (unless contraindicated) in all patients who either have had a STEMI *[IA]* or have unstable angina (UA)/NSTEMI with left ventricular (LV) dysfunction *[IB]*. Reasonable: Prescribe β blockers for low-risk patients (i.e., normal LV function, revascularized, no high-risk features) recovering from UA/NSTEMI in the absence of absolute contraindications *[IIB]*.
Renin-angiotensin-aldosterone system blockers in IHD	ACE inhibitors (ACEI): prescribe unless contraindicated in all patients with IHD who also have hypertension, diabetes mellitus, LV ejection fraction 40% or less, or chronic kidney disease. *[IA]*. ACEI is an appropriate choice for other patients with IHD *[IIB]*. Angiotensin receptor blockers (ARB): prescribe to the above patients if they are intolerant of, ACEI. *[IA]* Aldosterone blockade: prescribe for patients who are post-myocardial infarction and are: • receiving maximum therapeutic doses of an ACE inhibitor (or ARB) and beta blocker, and • have a left ventricular ejection fraction <40%, and • have either diabetes or symptomatic heart failure, and • have estimated creatinine clearance > 30 ml/min and do not have hyperkalemia (potassium is < 5.0 mEq/L).
NSAID for Pain Control	At admission for acute coronary syndrome: discontinue all cyclooxygenase-2 (COX-2) inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs), EXCEPT aspirin as above *[ID]*. NSAIDs increase IHD events and alternative should be sought. In patients with IHD requiring analgesia: a stepped-care approach to treatment should be used *[ID]* (see text).
Immunizations	Influenza vaccination: annually (inactivated, injectable) *[IB]*. Pneumococcal vaccination (polysaccharide vaccine): initially when diagnosed with IVD and if initial vaccination occurred before age 65 years, revaccination after age 65 and 5 years have passed since initial vaccination *[IB]*.

Lifestyle	
Physical Activity	Assess risk associated with exercise (e.g., need for cardiopulmonary monitoring) using a physical activity history and/or exercise test to guide the exercise recommendation *[IB]*. Encourage: • Moderate intensity aerobic activity for at least 30 minutes daily, at least 5 days per week, supplemented by an increase in daily lifestyle activities *[IIB]*. • Resistance training 2 days per week *[IID]*. For those with recent acute coronary syndromes or recent revascularization: Recommend medically supervised cardiac rehabilitation programs *[IA]*.
Weight Management	Each visit: Assess body mass index (BMI) and encourage weight maintenance/reduction through an appropriate balance of physical activity, nutrition/caloric intake, and formal behavioral programs when indicated to achieve and maintain a BMI between 18.5 and 24.9 kg/m^2 *[IC]*. For patients > 65 years, a BMI of < 22 kg/m^2 may be below normal and a BMI of 25-30 kg/m^2 may be acceptable *[IID]*. Initiate treatment for non-elderly patient: If overweight (BMI 25–29) or obese (BMI ≥ 30), initiate lifestyle change through diet and exercise *[IC]*. Weight loss goals: Initial goal of weight loss strategy should be to reduce body weight 5-10% from baseline over a span of 6 months. With success further weight loss can be attempted if indicated through further assessment *[ID]*.
Nutrition	Promote: • Consuming a variety of nutritious foods: – Fruits, vegetables, legumes, nuts, soy products, low-fat dairy products, whole grain breads, and lean meat. – Baked or broiled fish at least twice per week. – Oils and margarines low in saturated fats and trans fat and high in omega-3 fat, such as canola, soybean, walnut, and flaxseed oils including those fortified with stanols and sterols. Monosaturated fats like olive oil are preferred over saturated fats. – Less than 2 grams of sodium per day, especially if there is comorbid HTN. • Avoiding: – High calorie foods including sugar, sugar-sweetened beverages, and candy. – Foods high in saturated and trans fats, such as red meat, whole milk products, and pastries (saturated fats < 7% daily calories, trans fatty acids < 1% daily calories, cholesterol < 200 mg per day). • Limiting: – Eating out and fast food – Alcohol to no more than 2 drinks per day (men) or 1 drink per day (women). Complete abstinence if alcohol contraindicated or history of alcohol abuse. • Addressing environmental and family factors associated with eating, including creating a healthful eating environment that is responsive to hunger and fullness cues.
Surgery	
Symptomatic Carotid Artery Disease	Carotid endarterectomy: • Recommended for patients with a non-disabling stroke or TIA within 6 months and 70-99% ipsilateral stenosis when the perioperative rate of major adverse events is < 6% *[IA]*. • Consider for patients with a non-disabling stroke or TIA within 6 months and 50-69% ipsilateral stenosis, based on individual patient factors when the perioperative rate of major adverse events is less than 6% *[IIA]*. • Perform carotid endartectectomy as early as judged possible after the stroke or TIA, when risk of another stroke is highest. This benefit of surgery decrease with time *[IIB]*. Carotid stenting: An alternative to carotid endarterectomy when patients at high risk for surgery or in specific circumstances (e.g. high carotid bifurcation, extensive radiation induced stenosis, prior carotid intervention). The perioperative morbidity and mortality of carotid stenting should be less than 6% *[IIA]*. Other therapies: All patients with carotid disease after stroke should be on optimal medical therapy and have appropriate lifestyle modifications, whether or not an intervention is performed *[IA]*.

Table 2. Supplements: Benefit in Reducing Cardiovascular Risk

Probably beneficial:
- Omega-3 supplements 1-2 g per day if insufficient intake from fish *[II C]*

Possibly beneficial:
- Stanol / sterol ester margarines (2 g per day) *[II D]*
- Soluble fiber such as oat bran, psyllium, guar, and pectin (5 to 20 g per day) *[II D]*
- Soy foods and soy protein (equivalent to 25 g of soy protein daily) *[II D]*
- Tea containing flavonoids, e.g., black tea, green tea, and some herbal tea (1-2 cups) *[II D]*
- Magnesium to recommended dietary intake (men 420 mg, women 320 mg) *[II D]*

Not recommended:
- Vitamin C, vitamin E, and beta-carotene supplementation in patients with stable IHD *[III A]*
- Treatment of elevated homocysteine with folate or vitamins B6 and B12 in patients with stable IHD *[III A]*
- Garlic, coenzyme Q10, selenium and chromium *[III D]*
- Chelating therapy *[III D]*

Not recommended and possibly harmful:
- Estrogen therapy in post-menopausal women with stable IHD and or history of TIA or stroke *[III A]*
- Testosterone in men with IVD *[III B]*
- Levels exceeding the upper tolerable limits for vitamins C (2,000 mg/day) and E (1,000 mg/day); and beta-carotene
- Ephedra, oleander, or other herbal/ botanicals with well-defined contraindications to cardiovascular drug and or CVD conditions

Among Americans over 20 years old (2010):
- Two-thirds are overweight or obese
- Two-thirds do not regularly engage in aerobic exercise
- One-third have hypertension (only half have controlled blood pressure)
- 14% have high serum cholesterol (>240)
- 8% have diabetes mellitus

Need for improved secondary prevention. Individuals with IHD and other vascular disease are at appreciably higher risk for subsequent vascular events and mortality. For these patients several treatments and lifestyle changes addressed in this guideline have demonstrated large absolute risk reductions.

Although effective secondary prevention is available, a number of studies have shown that secondary prevention does not occur for many patients and that only some aspects of secondary prevention are performed for many other patients. A more comprehensive approach is needed for secondary prevention of IVD.

Approach

An initial step to increasing the secondary prevention of IHD and stroke (again referring to ischemic stroke and TIA) is to assemble in one place the most important recommendations for this care. For convenience, preventive care activities for underlying conditions have been grouped into those typically requiring lifestyle changes with medication (Lifestyle with Medication), those requiring medication only (Medication), those requiring lifestyle changes only (Lifestyle), and those requiring surgery (Surgery).

The overview of secondary prevention recommendations was assembled from existing guidelines. The University of Michigan Health System (UMHS) has already developed guidelines addressing many of the components of secondary prevention (i.e., tobacco cessation, hypertension, lipid management, diabetes mellitus, obesity [physical activity, weight management, nutrition], and immunizations). The review began with the UMHS guidelines and the national guidelines referenced in them. The review expanded to other relevant guidelines of the American College of Cardiology (ACC), the American Heart Association (AHA), and the American Stroke Association (ASA). Then evidence from relevant guidelines referenced in those guidelines and other relevant national guidelines known to the authors were added. The search focused on guidelines published from January 2000 through July 2008 to produce the 2009 version of this guideline. This 2014 update included similar searches for evidence in more current guidelines over the period from August 2008 through December 2013. The section of this guideline on "Related National Guidelines" lists twenty current national guidelines on which this overview is based.

The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. Conclusions were based on prospective randomized controlled trials if available, to the exclusion of other data; if randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given

link in the problem formulation, expert opinion was used to estimate effect size.

Recommendations for Secondary Prevention

The major recommendations are summarized in Table 1. The recommendations generally closely parallel the relevant national and UMHS guidelines. Discrepancies between national and UMHS guidelines are noted in the text and reflect new data and controversies in the most recent guidelines. Additionally, recommendations concerning supplements are summarized in Table 2.

Further information regarding each of the recommendation categories is presented in the following sections. The sources for each recommendation category are listed at the end of this guideline. The focused UMHS guidelines present more detail and can be accessed by hyperlink from this guideline.

Blood Pressure Control

Blood pressure goal. BP goal is generally < 140/90 mm Hg for stable IHD. For individuals above 80 years old, controlling blood pressure to < 150/90 was effective in lowering the risk of stroke in the Hypertension in the Very Elderly Trial (HYVET) study. Although the latter was a primary prevention study and may not be generalizable to secondary prevention

Until recently expert opinion had been that lower systolic blood pressure reduced cardiovascular morbidity and mortality in patients with diabetes or end organ damage. However recent trials have demonstrated that strict systolic blood pressure control provides little benefit over usual blood pressure control. Current recommendations are:

- If diabetes, < 140/90 per JNC 8 Panel, although a possible benefit might occur with lowering further to < 140/80 according to the American Diabetes Association
- If chronic kidney disease, 140/90 is reasonable based on best evidence.
- If chronic kidney disease associated with urine albumin excretion > 30 mg/24 hours, the Kidney Disease Improving Global Outcomes (KDIGO) CKD Workgroup suggests a blood pressure < 130/80.

Hypertension is the most prevalent treatable risk factor for stroke. While a normal blood pressure has been defined by JNC 8 Panel as less than 120/80, most expert opinions recommend targeting treatment to reach systolic blood pressure target of consistently less than 140 mm Hg for stroke prevention.

A recent study found a trend toward fewer strokes when patients with lacunar stroke achieved a systolic blood pressure of less than 130. The generalizability of this finding to patients with other types of stroke is unclear.

Lifestyle modification. All patients should be counseled regarding the need for lifestyle modification: weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on consumption of fresh fruits, vegetables, poultry, fish, legume and low fat dairy products.

Physical activity: In order to reduce blood pressure, patients should be advised to engage in moderate intensity aerobic physical activity 3-4 times a week for on average 40 minutes each time.

Medication. Patients with IHD and blood pressure ≥140/90 mm Hg should be treated, as tolerated, with blood pressure medication.

The specific medications used for treatment of high blood pressure in IHD should be based on specific patient characteristics starting with ACE inhibitors (or ARBs in case of ACEI intolerance) and/or beta blockers, with addition of other drugs, such as thiazide diuretics or calcium blockers, if needed to achieve blood pressure goal.

The optimal drug regimen to lower blood pressure after stroke is unknown. Beta blockers are not recommended for blood pressure lowering after stroke, unless there is another indication for beta blockade, as they seem to lower blood pressure without decreasing stroke risk. Acute blood pressure lowering after stroke is not recommended. In the ALLHAT trial, African American patients had more strokes using ACEI compared to CCB. Therefore, the JNC8 does not recommend ACEI as first line therapy for hypertension treatment in African Americans. However, this is more pertinent to primary prevention. For stroke secondary prevention, the focus of this guideline, we recommend ACEI (or ARBs), CCB, or thiazide diuretic as first line therapy. In African Americans, the ACEI is based on expert opinion given the lack of secondary prevention trials among African Americans.

Specific blood pressure agents can be chosen based on the presence of other indication such as favoring the use of ACEI or ARBs in case of chronic kidney disease. For indications for individual drug classes in specific vascular diseases, see UMHS Essential Hypertension Guideline.

Tobacco Treatment

Recommendations in this guideline follow those of the Public Health Service (updated in 2008) and the University of Michigan Health System (UMHS) Tobacco Treatment Guideline.

General approach.

Ask about tobacco use, assess user's readiness to quit and document status in the medical record *[IA]*. A clinical screening system prompting clinicians increases the rate of physicians remembering to ask.

Advising tobacco users to seriously consider making a quit attempt increases the rate of tobacco cessation *[IA]*. Even three-minute physician interventions meaningfully increase rates of abstinence. Give key advice on successful quitting including abstinence and dealing with other tobacco users in the household. Provide supplementary educational materials that can come from the UMHS Patient Education materials, or consider providing the National Cancer Institute pamphlet "Cleaning the Air".

Assess user's willingness to quit *[IA]* is an appropriate predecessor to assisting them with developing a quit plan. If not yet ready to quit, offer motivational intervention using the 5 "R's" – relevance, risks, rewards, roadblocks, repetition.

Assist those ready to make a quit attempt. Refer patients interested in quitting to a Tobacco Treatment Specialist or other appropriate tobacco treatment program *[IA].* This should happen within 30 days. Alternatively, health care providers can directly provide treatment. Tobacco users report that advice from a clinician is an important motivator to quit.

Consider referral to intensive counseling (multi-session, group or individual). While brief intervention increases long-term quit rates, a strong dose response relationship exists between the intensity of person-to-person contact and successful outcomes *[A]*. Barriers to quitting tobacco use exist and should be identified during the initial assessment. They include severe withdrawal during previous attempts, presence of other tobacco users in the home or workplace, heavier tobacco use, low socioeconomic status, menthol cigarette, stressful life circumstances, psychiatric co-morbidities, multiple quit attempts, concern of weight gain, and low motivation.

- Encourage pharmacologic therapies as appropriate (transdermal nicotine patch, nicotine lozenge, nicotine gum, nicotine nasal spray, nicotine inhaler, bupropion, varenicline, nortriptyline, or clonidine). Pharmacological therapy should be recommended to all patients except in the presence of specific contraindications. Nortriptyline and clonidine are the two non-FDA approved agents with potential benefit in quitting tobacco use.
- Provide supplemental educational materials.

Arrange follow-up. Schedule follow-up, preferably during the first week after the quit date. Actions to consider during follow-up will depend on whether the patient is abstinent, or using tobacco and can be found in the UMHS Tobacco Treatment guideline (2012).

Combining counseling and pharmacologic therapy. The combination of counseling and medication is more effective than either alone.

Counseling. Counseling sessions by a variety of clinician types are successful. More intensive interventions are more successful – a target of four or more intervention sessions is reasonable.

Pharmacologic therapy. Pharmacologic interventions should be considered *[IA].*

- Bupropion and nicotine supplementation (gum, patch, inhaler, or nasal spray) are proven to be effective in assisting patients in tobacco cessation.
- Varenicline is also proven to be effective in assisting patients to quit smoking. The FDA issued alerts regarding serious neuropsychiatric symptoms occurring in patients taking varenicline, lower seizure threshold in patients with history of seizures, and increased intoxicating effects of alcohol. However, it still continues to be considered first line therapy. Clinicians should elicit information on their patients' psychiatric history and monitor them for changes in mood or behavior on therapy.

Use nicotine supplementation with caution in patients with IHD. Nicotine transdermal formulations are contraindicated in patients with arrhythmias, worsening angina, severe angina, and within 2 weeks of myocardial infarction; however the use of a short acting nicotine supplement is reasonable during these first two week post MI such as nicotine lozenge.

Lipid Management

Lipid profile. Obtain a baseline screening lipid profile (TC, LDL-C, HDL-C, and TG). Ideally this should be obtained when the patient is fasting for a more accurate evaluation of potential dyslipidemias, including hypertriglyceridemia. However, if patient convenience or compliance is an issue, a non-fasting lipid profile is adequate. While non-fasting LDL-C is less accurate than fasting LDL-C, non-fasting values are sufficient for monitoring general statin compliance. If lipids are obtained non-fasting and are abnormal (i.e. TC >200 mg/dL, HDL-C <40 mg/dL, or triglycerides >500 mg/dL), consider obtaining a follow up fasting lipid panel to better evaluate for dyslipidemias.

LDL-C is typically measured indirectly in a lipid panel. The indirect measure is less accurate if triglycerides (TG) > 400 mg/dL, so most laboratories also perform a direct LDL-C if TG > 400 mg/dL. At the University of Michigan, the lab automatically measures the direct LDL-C when TG > 400 mg/dL or if the order was non-fasting. If a local laboratory does not measure LDL-C directly when non-fasting TG > 400 mg/dL, obtain a fasting lipid panel.

If a secondary cause of lipid disorders is suspected, perform appropriate work up and optimize treatment.

Lifestyle modification. Lifestyle changes can improve lipid levels. Strongly recommended for all IVD patients are optimizing diet and physical activity. Optimizing diet includes limiting unhealthy fats (aiming for saturated fat intake of no more than 5 - 6% of total calories and reducing the percent of calories from trans fatty acids, preferably to <

1% of calories) and eating primarily plant-based foods (e.g., vegetables, fruits, whole grains, legumes, and nuts), low-fat dairy products, poultry, fish, and non-tropical vegetable oils.

Physical activity. Toward reducing LDL, patients should be advised to engage in moderate intensity aerobic physical activity 3-4 times a week for on average 40 minutes each.

Statins. For years, it was recommended to lower LDL-C to less than 100 mg/dL. The framework for lipid management has changed simply to prescribing statins based on the patient's risk for atherosclerotic disease.

Consistent with the ACC/AHA 2013 guidelines for lipid management, for IVD patients ≤ 75 years of age prescribe high-intensity statin therapy (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) in the absence of contraindication or documented adverse effects. High-intensity statin therapy reduces the LCL-C by 50% or more. For patients 75 or older with IVD, based on expert opinion, the ACC/AHA guideline recommends continuing statin therapy when present or to initiate moderate-intensity statin therapy after considering the patient's individual characteristics and preferences. Moderate-intensity statin therapy reduces LDL-C by 30% to 50% and includes atorvastatin 10-20 mg, rosuvastatin 5-10 mg, pitavastatin 10-20 mg, simvastatin 20-40 mg, lovastatin 40-80 mg. pravastatin 10-80 mg, and fluvastatin 80 mg.

Monitoring of statin therapy should take place every 3-12 months as clinically indicated (e.g., monitor statin adherence, manage statin intolerance). An annual lipid profile is recommended to check on statin adherence and to provide an opportunity to reinforce lifestyle modifications - the cornerstone of athlerosclerotic cardiovascular disease (ASCVD) risk reduction.

Secondary prevention trials demonstrate a reduction in IHD and total mortality via lipid control. Patients who experience a larger reduction in LDL-C will benefit from a larger relative risk reduction. Statins may increase the risk of hemorrhagic stroke, but this risk is offset by their benefits in preventing ischemic events.

Statin intolerance. If an IVD patient is unable to tolerate a high potency statin, consider lowering the dose or changing to a lower potency statin. If other statins are still not tolerated, consider a trial of twice weekly, or every other day atorvastatin or rosuvastatin.

If a patient does not achieve the target LCL-C reduction while on statin or due to statin intolerance, other medication to consider includes the addition of a bile acid sequestrant (e.g. cholestyramine), although GI side effects may result in poor patient tolerability. Bile acid sequestrants (resins) are relatively contraindicated in patients with triglycerides ≥ 200 mg/dL. Although these medications probably lower the LDL, their IVD preventive benefit is questionable.

See the UMHS clinical guideline Screening and Management of Lipids for more information

Diabetes Mellitus Management

Diabetes mellitus itself is a coronary artery disease equivalent. Those patients who have an ischemic event should receive intensive secondary prevention interventions. These interventions offer large absolute risk reductions for subsequent events and mortality *[IA].*

Lifestyle modifications. Encouraging physical activity and a healthy diet are also very important.

Glycemic control. Starting pharmacotherapy in order to attain the target hemoglobin A1c is reasonable *[IIA].* Rosiglitazone should not be started in patients with stable IHD *[IIID].*

Tight glycemic control for the prevention of coronary artery disease is critically important in Type 1 diabetes.

The ADA recommends A1c <7% in most type 2 diabetic patients in order to lower the risk of microvascular complications. However, a less stringent A1c goal (probably <8%) is reasonable for patients with advanced macrovascular complications or high risk for hypoglycemia *[IIB]*. Glycemic control has not been shown to be important in the secondary prevention of macrovascular complications of Type 2 diabetes. For patients with long standing type 2 diabetes and either established CVD or have multiple CVD risk factors, there is no reduction of CVD outcome with intensive glycemic control as shown in three large trials (ACCORD, ADVANCE, and VADT). Moreover, the ACCORD and ADVANCE studies have raised concerns about the potential for increasing adverse cardiovascular outcomes with tight control.

An A1c goal of <7% is reasonable in those with a short duration of diabetes and long life expectancy *[IIC].*

For diabetics with stroke or TIA, the American Stroke Association recommends following existing guidelines (such as those above) for glycemic control *[IB].*

Blood pressure. For diabetic patients both the ADA and the JNC 8 Panel agree on lowering SBP to <140. A lower SBP level of <130 might be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden *[IID].*

For DBP, the JNC 8 Panel recommends a DBP target of < 90 mmHg, while the ADA recommends a target of < 80 mmHg. The recommendations reflect views of conflicting evidence, with one large randomized controlled trial showing no benefit for DBP below 90 mmHg and another showing a benefit below 80 mmHg.

The ADA recommends either an ACE inhibitor or ARB for hypertensive patients who have diabetes, primarily to

prevent nephropathy. See Hypertension section for further details.

For patients with stroke or TIA, the American Stroke Association recommends existing BP targets (such as those above) in patients with diabetes *[IB].*

Lipids. Diabetic patients with known IVD and age ≤ 75 years should be on a high-intensity statin unless a statin is contraindicated. For those age >75 years, a moderate-intensity statin is recommended. Please also see section on lipids.

Tobacco use. Counseling on tobacco cessation is highly recommended. This may include also enrollment in formal tobacco cessation programs and use of alternative nicotine delivery systems or pharmacologic therapies (see tobacco section).

Antiplatelet agents. Aspirin is recommended in patients with diabetes who have CVD *[IA]*. Clopidogrel is recommended as an alternative therapy in aspirin-intolerant patients or an adjunctive therapy in the first year after an acute coronary syndrome.

See the UMHS guideline Management of Type 2 Diabetes Mellitus for more information.

Depression Screening

It is reasonable to screen and treat patients with IVD for depression *[IIB]* as well as educating those patients on common symptoms of stress and depression *[IID].*

Depression is present in approximately 20% of patients with angiographic evidence of CAD and those recovering from MI. Major depressive disorder may occur in half of stroke survivors and has been associated with impaired recovery and worsened mortality. Depression is independently associated with worse survival of patients with CVD. Depression contributes to atherogenesis probably via behavioral and biological effects. Untreated depression could adversely affect preventive activities (e.g., tobacco cessation, medication adherence, physical activity, weight management, and nutrition modification).

Treating comorbid depression can improve patients' wellbeing overall and adherence to therapy. Data are lacking concerning the impact of depression therapy in reducing mortality in patients with IVD.

The screening and treatment methods for IHD are similar to those for the general patient population and are described in the UMHS Depression Guideline. The PHQ2 is quick screening test that can be easily administered in the office setting by asking:

During the past two weeks, have you been bothered by:
- Little interest or pleasure in doing things?
- Feeling down, depressed or hopeless?

The optimal screen for depression in stroke patients is not clear, though use of the PHQ2 is reasonable. Treatment of depression in stroke patients is similar to the general population.

If PHQ2 screen was positive, recommend to proceed with PHQ9. See the UMHS Depression guideline for more information about screening, diagnosis, and treatment.

Antiplatelet and Anticoagulant Therapy

Table 1 summarizes the key recommendations.

For established IHD: antiplatelet. In patients with established IHD:

- If not on aspirin, it should be prescribed at a dose of 81-mg daily *[IA]*.
- If have a coronary event on aspirin 81mg or less daily, expert opinion suggests aspirin dose of 325mg daily or the addition of clopidogrel. This is an area of controversy.
- If intolerant to aspirin, Clopidogrel at a dose of 75 mg daily (or ticlopidine after consulting with a cardiologist) should be considered indefinitely *[IA].*

For acute coronary syndromes treated medically (no angioplasty): antiplatelet. In patients with recent acute coronary syndromes who are treated with medical therapy, the addition of clopidogrel to aspirin at a dose of 75 mg daily is recommended for at least one month *[IA]* and ideally up to 1 year post-event *[IA].*

For post-stent antiplatelet therapy: antiplatelet. Appropriate use of dual antiplatelet therapy is critical in the early period after stent placement and varies depending upon whether a bare-metal or drug-eluting stent was used, as well as whether the stent was placed in the setting of an acute coronary syndrome. The choice and duration of antiplatelet therapy is often decided by cardiology.

In general, aspirin should be used at a dose of 81mg.

Acute coronary syndrome (ACS). In patients receiving a stent for ACS (BMS or DES), a P2Y12 inhibitor should be given for at least 12 months in addition to aspirin 81 mg. Options include clopidogrel 75 mg daily; and two newer agents: prasugrel 10 mg daily or ticagrelor 90 mg twice daily *[IA].*

Prasugrel was compared with clopidogrel in patients with ACS in TRITON-TIMI 38. In contrast to clopidogrel, prasugrel leads to more stable platelet inhibition and fewer major adverse cardiac events, but at the expense of higher rates of major bleeding. Note that:
- Prasugrel is contraindicated in patients with a prior history of stroke or transient ischemic attack. Patients weighing < 60 kg have an increased risk of bleeding on the 10 mg daily maintenance dose and the package

insert suggests lowering to 5 mg daily in this group of patients.
- Prasugrel is not recommended in patients older than 75 years of age except in those patients with diabetes or prior history of MI.
- Prasugrel has not been studied in patients undergoing elective PCI.

Ticagrelor differs from prasugrel and clopidogrel in that it is not a thienopyridine. Additionally, it reversibly binds the P2Y12 receptor and does not require metabolic conversion to an active metabolite. Ticagrelor was compared with clopidogrel in patients with ACS in PLATO and was associated with a decrease in cardiovascular events and all-cause mortality. However, there was a greater incidence of major bleeding compared with clopidogrel in patients not undergoing CABG. Note that:
- Ticagrelor is associated with higher rates of transient dyspnea and bradycardia.
- Maintenance doses of aspirin greater than 100 mg reduce the effectiveness of ticagrelor and should be avoided.
- Given that ticagrelor is a twice-daily medicine and a reversible inhibitor, patient compliance is an especially important consideration.
- Similar to prasugrel, ticagrelor has not been studied in elective PCI.

Non-acute coronary syndrome. For patients receiving:

- A bare-metal stent, in addition to aspirin, clopidogrel should be given at a dose of 75 mg daily for at least 4 weeks, but ideally up to 1 year (unless the patient is at an increased risk of bleeding; then clopidogrel should be given for a minimum of 2 weeks) *[IB].*
- A drug-eluting stent, in addition to aspirin, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at a high risk of bleeding *[IB].* If clopidogrel requires discontinuation within 1 year of drug-eluting stent placement, consultation with interventional cardiology may be helpful to assess whether technical or angiographic factors place the patients at very-high risk for late stent thrombosis necessitating additional measures *[IID].*

Continuation of clopidogrel beyond 1 year may be considered in patients at low-risk for bleeding and high-risk for late stent thrombosis *[IID].* Prasugrel and ticagrelor have not been studied in this setting (non-acute coronary syndrome).

Balloon angioplasty for coronary artery disease. Even after PCI without stent placement, aspirin at a dose of 81 mg daily should be used indefinitely and clopidogrel should be used at a dose of 75 mg daily for at least 2 weeks and ideally up to 1 year.

After non-cardioembolic ischemic stroke: antiplatelet. These patients benefit from antiplatelet therapy.

Being on any antiplatelet agent is more important than the specific drug. Agents commonly used for secondary stroke prevention include aspirin (50-325 mg), clopidogrel (75 mg), and the combination of aspirin and extended release dipyridamole (ASA-ERDP). The absolute difference in effect sizes in terms of secondary stroke prevention between the agents is modest. All of the antiplatelet agents increase the risk of bleeding, but this risk is generally outweighed by their benefits in preventing ischemic vascular events. The choice of agent depends on individual patient factors.

When considering antiplatelet agents, note that:
- Doses of aspirin higher than 325 mg daily are associated with an increased risk of side effects without clear evidence of benefit.
- The combination of aspirin and clopidogrel increases the risk of bleeding without reducing the risk of stroke, therefore, the long-term use of dual antiplatelet therapy cannot be recommended for non-cardioembolic stroke.
- No data suggest that changing antiplatelet agents after an ischemic stroke has a benefit in terms of stroke prevention.

Exception to dual antiplatelet use in non cardioembolic stroke. Preliminary data suggests that short-term dual antiplatelet therapy may be effective after TIA or minor stroke, but research studies are ongoing.

After a carotid stent, patients should be on dual antiplatelet therapy (aspirin plus clopidogrel) for at least 30 days. The duration of dual antiplatelet therapy should be determined by the proceduralist who placed the stent.

Anticoagulation not recommended. Anticoagulation is not recommended for secondary stroke prevention unless the stroke was caused by a cardiac embolus. Anticoagulation with warfarin or one of the three new anticoagulants increases the risk of bleeding without reducing the risk of ischemic events in patients with stroke due to cardioemboli.

Other antiplatelet therapy considerations. Also consider the following when prescribing antiplatelet therapy.

PPIs and antiplatelet therapy. Antiplatelet therapy reduces risk of cardiovascular events, but increases risk for gastrointestinal (GI) tract bleeding. PPIs may reduce gastrointestinal tract bleeding. Adding a PPI to antiplatelet therapy is cost-effective for individuals at increased risk for GI bleeding, but is not cost-effective in patients with average bleeding risk.

- Prescribe a PPI for patients on dual antiplatelet therapy who have a prior history of GI bleeding.

- Prophylactic PPI use is reasonable in patients on dual antiplatelet therapy who are at increased risk of GI bleeding (e.g., advanced age, concomitant use of warfarin, steroids, NSAIDs, history of H pylori infection).
- Consider adding PPI to lower the risk of GI bleeding in patients taking an anticoagulant or antiplatelet

A PPI other than omeprazole may be preferred based on pharmacokinetics, but no supporting clinical data exist. Pharmacokinetic evidence indicates that omeprazole interferes with clopidogrel metabolism. However, no data support a clinical interaction (COGENT trial).

Clopidogrel genetic testing. Patients with decreased CYP2C19 function metabolize clopidogrel poorly and thereby have a diminished ability to convert clopidogrel to its active metabolite. Genetic tests are available to identify these polymorphisms; however, the evidence base is insufficient to recommend routine genetic testing. A potential role for testing may exist in select circumstances at the discretion of the individual physician.

Platelet function testing. At the present time, the evidence base is insufficient to recommend routine platelet function testing. In patients who are treated with clopidogrel and are found to have high platelet reactivity, alternative agents such as prasugrel or ticagrelor may be considered.

Anticoagulation for stroke prevention in non-valvular persistent and paroxysmal atrial fibrillation. Atrial fibrillation causes about 20% of all ischemic strokes. The risk of stroke due to atrial fibrillation varies depending on co-morbidities, but the most significant predictor of risk is prior stroke or TIA. In general, patients who have had a prior stroke or TIA and have atrial fibrillation should be anticoagulated. Anticoagulation is the most efficacious way to reduce the risk of stroke in patients with atrial fibrillation. Warfarin reduces risk of stroke by two-thirds. In contrast, aspirin reduces risk of stroke by one-fifth.

Anticoagulation with any agent is not recommended immediately after an acute stroke due to the risk of hemorrhagic transformation. The optimal time to start an anticoagulant after an acute stroke is not known, but decisions should be made based on the type of anticoagulant, size of the infarct, and other patient specific factors.

Warfarin. For many years, warfarin was the primary anticoagulant used to prevent stroke in patients with atrial fibrillation. Studies have shown that patients taking warfarin reduce their risk of stroke by about two-thirds compared to controls. The International Normalized Ratio (INR) goal for patients with atrial fibrillation taking warfarin for stroke prevention is 2-3.

Some important points regarding warfarin use include:

- Difficulty maintaining INR. Some patients have difficulty maintaining an INR in the therapeutic range—a lower INR increases the risk of stroke and systemic embolism, while a higher INR increases the risk of hemorrhage.
- Underutilized. Warfarin has been underutilized because of concerns about monitoring requirements as well as food and drug interactions.
- Difficulty predicting bleeding risk. While scores that predict risk of bleeding on warfarin have been published, they generally perform poorly and most do not incorporate the increased bleeding risk conferred by combining warfarin with one or more antiplatelet agents.

Newer anticoagulants. Recently, new oral anticoagulants have been approved by the FDA that do not have warfarin's limitations: apixaban and rivaroxaban (Xa inhibitors) and dabigatran (a thrombin inhibitor). These agents do not require monitoring of the intensity of anticoagulation and have fewer drug interactions than warfarin.

Important information regarding the newer anticoagulants includes:

- Little data to differentiate. The data available to assist in choosing between the new oral anticoagulants are limited as no comparative effectiveness studies have been done. The choice of agent depends on clinical judgment and individual level patient factors.
- Contraindicated with renal failure. The new oral anticoagulants are contraindicated for patients with renal failure and caution should be used in patients with renal impairment. While dose adjustments can be made to account for impaired renal function, these lower doses have not been well studied. As worsening renal function can potentiate the anticoagulant effects of the new agents, kidney function should be monitored bi-yearly for patients taking these drugs.
- Fewer bleeding events, but no reversal agent. In the trials, patients taking the new oral anticoagulants had fewer bleeding events than those on warfarin. However, when patients do have a significant bleeding event on the new agents, no reversal agent has been approved for use.
- Most benefit: when INR control is poor with warfarin. In trials, dabigatran, rivaroxaban, and apixaban showed the most benefit in patients with poorer INR control. For patients with atrial fibrillation, currently taking warfarin with good INR control, the benefit of changing from warfarin to a new agent is unknown.

If unsuitable for anticoagulation therapy. For patients unsuitable for anticoagulation therapy due to poor INR control, adverse events, poor patient adherence, drug or diet interactions, or patient refusal, aspirin 325 mg, is the preferred antiplatelet alternative although it is less effective.

In patients with atrial fibrillation, aspirin reduces the risk of stroke by about 1/5 when compared with placebo.

The combination of aspirin and clopidogrel is not as effective as anticoagulation at reducing the risk of stroke and systemic embolus but is more effective than aspirin alone, however, dual antiplatelet therapy is associated with a higher risk of bleeding than aspirin alone.

A recent study found that apixaban, one of the new anticoagulants as mentioned above, is more effective than aspirin in patients who were unsuitable to warfarin in terms of lowering stroke risk in patients with atrial fibrillation without significantly increasing the bleeding risk.

Stopping antiplatelet if on anticoagulant. In patients who require anticoagulation with warfarin, an antiplatelet agent can be stopped in those with either stroke or stable IHD and had no acute coronary syndrome, PCI, or CABG in the past 12 months *[IIA]*. In these patients an antiplatelet agent provides little additional benefit and increases risk of bleeding. Consider consulting with cardiology before stopping the antiplatelet, especially regarding patients who may have higher risk for IHD recurrence.

For patients who are on a newer oral anticoagulant rather than warfarin, no data are available concerning the effect of discontinuing an antiplatelet agent. Bleeding risks are likely higher when aspirin or other antiplatelet agents are used with the newer oral anticoagulants.

"Triple" antiplatelet and anticoagulant therapy. Patients considered for dual anti-platelets as well as anti-coagulants usually have had acute coronary syndrome in the last twelve months and also have an indication for anti-coagulation. The patient's cardiologist should typically be involved in decisions regarding "triple therapy."

In general, long-term therapy with warfarin should be prescribed only for those patients with established indications for anticoagulation, such as atrial fibrillation, left ventricular thrombus or mechanical heart valves even when they are on dual antiplatelet therapy. There are limited data on the safety of "triple therapy" with aspirin, clopidogrel and warfarin, leading to significant concerns about the risk of bleeding. In this setting, therapies should be individualized and strong consideration should be made for low-dose aspirin (81 mg daily) and close monitoring of anticoagulation with an INR goal of between 2.0 and 2.5.

The use of clopidogrel and warfarin without aspirin appears to be associated with a reduction in bleeding complications with no increase in the rate of thrombotic events compared to triple therapy. This reduction was suggested in data from the WOEST trial, a randomized clinical trial examining the use of clopidogrel without aspirin following cardiac PCI in patients required to take warfarin. However, these data have yet to be incorporated into ACCF/AHA/SCAI guidelines. In patients who are at high risk of adverse events on triple therapy, consideration of aspirin discontinuation could be given following discussion and at the discretion of the patient's cardiologist.

Beta Blockers after IHD

STEMI. The ACC 2013 recommends starting oral beta blockers in the first 24 hours and continuing indefinitely in patients with STEMI who do not have a contraindication (signs of acute heart failure, evidence of a low output state, increased risk for cardiogenic shock or other contraindication to beta blocker therapy) indefinitely *[IA].*

Unstable angina or NSTEMI. In patients recovering from unstable angina or NSTEMI, beta blockers are indicated for all patients unless contraindicated. Therapy should be initiated within a few days of the event and continued indefinitely *[IB].*

- Patients recovering from unstable angina or NSTEMI with moderate or severe LV failure should receive β blocker therapy with a gradual titration scheme *[IB].*
- In low-risk patients (i.e., normal LV function, revascularized, no high -risk features), it is reasonable to prescribe beta-blockers to patients recovering from unstable angina or NSTEMI in the absence of absolute contraindications *[IIB].*

When ejection fraction is <40%, the ACC recommends carvedilol, metoprolol succinate, or bisoprolol since they have been shown to reduce risk of death

In the *acute* setting, the routine use of IV beta blockers for all patients is not recommended, as it may be harmful to administer them to those with contraindications to beta blockade, signs of heart failure or low output state, or other risk factors for cardiogenic shock. These risk factors include age greater than 70, SBP less than 120 mmHg, heart rate greater than 110 or less than 60, or increased time since onset of symptoms *[IIIA].* IV beta blockers may be used to treat concomitant hypertension in patients without any contraindications *[IIB].* If beta blockers are used, the preferred method is oral administration.

Renin-Angiotensin-Aldosterone System Blockers in IHD

ACE inhibitors. If no contraindication, ACE inhibitors are:

- Recommended for all patients with IHD who also have hypertension, diabetes mellitus, LV ejection fraction 40% or less, or chronic kidney disease. ACEI probably has a more positive effect on those with STEMI than on those with Non-ST elevation myocardial infarction (NT-SEMI).
- Reasonable for all other patient with IHD.

Angiotensin-receptor blockers (ARBs). ARBs are indicated for patients who should receive ACEI, but intolerant to ACEI.

Aldosterone blockade. Aldosterone blockade is recommended in patients who have all of the following:

- Already receiving therapeutic doses of an ACE inhibitor and beta blocker
- Left ventricular ejection fraction <40%
- Ether diabetes or symptomatic heart failure.
- Creatinine clearance >30 ml/min (no significant renal dysfunction)
- Potassium < 5.0 mEq/L (no hyperkalemia)

Begin therapy within 30 days of discharge, as a mortality benefit is seen within 30 days.

Serum potassium should be monitored closely during treatment. Although uncommon, life-threatening hyperkalemia can occur due to the combination of aldosterone inhibition, reduced aldosterone secretion associated with ACE inhibitor therapy, and a progressive decline in renal perfusion due to heart failure. Elderly patients with renal insufficiency are at greatest risk.

NSAIDs Use For Pain Control

The selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) and other nonselective NSAIDs have been associated with increased cardiovascular risk. The risk of cardiovascular events is proportional to COX-2 selectivity. With the exception of aspirin, all NSAIDS and COX-2 inhibitors should be discontinued immediately at the time of an acute coronary syndrome presentation.

In patients with IHD requiring analgesia: Non-pharmacologic approaches such as physical therapy, heat or cold application, or the use of orthotic devices should be attempted first. If symptoms are not controlled, use a stepwise pharmacologic approach, emphasizing using the lowest effective dose for the shortest possible time. Initial choices include acetaminophen and/or small doses of narcotics.

If these measures are insufficient to control pain or in case of intolerance/allergies to acetaminophen/opiate, a higher dose of aspirin is an option. Expert opinion suggests that it is probably as effective and a safer choice than non-selective NSAIDs. If inadequate pain control, nonselective NSAIDs (e.g. naproxen) may be tried next. The practitioner and patient should understand that pain relief may come at the cost of in increased risk of cardiovascular or cerebrovascular complications. Other side effects such as GI bleed are applicable to aspirin and non-selective NSAID.

Topical NSAID analgesic use has fewer side effects although no data on safety are available regarding their use in patients with IHD.

If an NSAID must be used, available evidence suggests that selective COX-2 inhibitors pose a greater risk than nonselective ones. Only in the event of failure of nonselective NSAID therapy should NSAIDs with some COX-2 selectivity be considered. The COX-2 selective agents are a last resort. The lowest effective dose of any medicine should be used for the shortest possible time.

Immunizations

Influenza vaccine. Annual influenza vaccination is now recommended for all individuals age 6 months and older. Patients with coronary artery disease fall into the high priority category for vaccination as they are at high-risk for influenza-related hospitalization and death per CDC and AHA *[IB]*. Due to antigenic shift and drift in circulating influenza A and B strains, the vaccine is manufactured and administered annually.

An inactivated influenza vaccine administered intramuscularly is recommended. It is contraindicated in patients with severe egg allergy or previous allergy/ anaphylaxis to influenza vaccine, and caution is suggested in patients with previous Guillain-Barre syndrome.

Two alternative vaccines are available. A high-dose (4 times the antigen) inactivated (injectable) vaccine is licensed for use with individuals age ≥ 65 years because their immune responses may be lower than younger individuals. A live attenuated (intranasal) vaccine is licensed for non-pregnant healthy adults < 50 years old as an alternative to inactivated vaccine.

Pneumococcal vaccine. Patients with chronic heart disease are also at elevated risk for pneumococcal infection with related hospitalization and death. The CDC recommends pneumococcal polysaccharide vaccination (PPSV23/ Pneumovax) for patients with heart disease.

If not previously vaccinated due to another indication, individuals with chronic heart disease should be vaccinated when chronic heart disease is diagnosed. A one-time revaccination should occur for individuals ≥ 65 years who received an initial PPSV vaccination at < 65 years and ≥ 5 years have passed since that vaccination.

See the UMHS Adult Immunization Guideline for more information on immunization.

Physical Activity

General recommendations. To guide prescription of increased intensity exercise, assess risk with a physical activity history and/or exercise test *[IB]*. Recommendations should be tailored to the patient's physical status, limitations, and prognosis. An exercise stress test is not required for assessing patients' fitness for low to moderate physical activities.

For IHD, the ACC/AHA recommends 30-60 minutes of moderate intensity aerobic activity at least 5 days per week, supplemented by an increase in daily lifestyle activities such as walking breaks at work, gardening and household

work *[IB].* It is reasonable to encourage resistance training 2 days per week *[IID]*. These recommendations are similar to those of the American College of Sport Medicine. An alternative to the above is 40 minutes of aerobic physical activity for 3 to 4 times week involving moderate-intensity physical activity. This latter physical activity recommendation can lower two major IVD risk factors, LDL cholesterol and blood pressure if these factors were specifically targeted.

Moderate intensity means your breathing and hart rate are noticeably faster, but you can still carry on a conversation (i.e. you can talk, but not sing). Examples include walking more than 3 mph, vacuuming, lawn mowing, bicycling on flat ground, light effort and leisurely swimming.

Medically supervised cardiac rehabilitation program for IHD. While a home-based cardiac rehabilitation program could suffice for low-risk patients *[IA],* medically supervised rehabilitation programs are advised for high-risk patients *[IA].* In particular, all patients with acute coronary syndrome and patients who have just undergone coronary artery bypass surgery or PCI should be referred to a comprehensive outpatient cardiovascular rehabilitation program upon discharge or during their first follow up visit *[IA].*

Patients with disability after stroke probably need a supervised program by a healthcare professional.

Exercise and elderly patients. In general, exercises for elderly patients should include flexibility exercises, muscle strengthening, moderated-intensity aerobic activities and reducing sedentary life style. Balance exercises are recommended for elderly patients with fall risk. The College of Sport Physicians recommends exercise programs to be modified according to an individual's aerobic fitness, health status. For elderly individuals, tailor the exercise prescription to their fitness level and other comorbid conditions.

See the UMHS guideline Obesity Prevention and Management for more information about physical activity and weight management.

Weight Management

Assess BMI (with/without waist circumference) on each visit, and consistently encourage weight maintenance/ reduction through an appropriate balance of physical activity, nutrition/caloric intake and formal behavioral programs when indicated to achieve and maintain a BMI between 18.5 and 24.9 kg/m^2.

Patients age 65 years and older tend to have increased body fat and decreased lean muscle mass. Depending on individual patient factors (e.g., life expectancy, co-morbidities), a BMI of < 22 may be below normal. Also, depending on patient factors, a 25-30 may be acceptable. If so, they would not require a formal behavioral program to lose weight, but should still follow recommendations regarding diet and exercise.

No clinical trials specifically address the effects of weight loss on cardiovascular event rates in patients with IHD. Recommend weight reduction if overweight (BMI 25.00–29.99) or obese (BMI ≥ 30.00) for non-elderly patients. Also, consider treatment strategies for metabolic syndrome as indicated.

Initial goal of weight loss strategy should be to reduce body weight 5-10% from baseline over a span of 6 months. Depending on the BMI, this corresponds to an average energy deficit of approximately 400 – 1000 kcal per day, resulting in a weight loss rate of 1 to 2 pounds per week. Individualized targets for reduced calorie intake can be calculated by dietitians or estimated using free online "weight loss calorie calculators."

Subsequent weight loss strategy will depend upon the initial amount of weight loss.

See the UMHS guideline Obesity Prevention and Management for more information.

Nutrition

In general, good nutrition is promoted by eating a variety of nutritious foods, eliminating or reducing less nutritious foods, and establishing an environment that promotes healthy eating.

Eat a variety of nutritious foods. Emphasize:

- Fruits and vegetables (at least 4 servings/day)
- Whole grains
- Legumes
- Fat-free or low-fat dairy products
- Lean meats, skinless poultry, fish, beans, soy products, eggs, nuts. Eat baked or broiled fish at least twice per week.
- Choose oils and margarines low in saturated fats such as canola, soybean, walnut, and flaxseed oils, including those fortified with stanols and sterols. Monosaturated fats like olive oil are also preferred over saturated fats.
- Less than 2 grams of sodium per day.

Eliminate or reduce foods with high saturated fat and high in calories and/or low nutrients. These include:

- Foods high in saturated fat, e.g., fatty meats, fried foods. (Limit intake of saturated fats to < 7% of daily calories, trans fatty acids to < 1% of daily calories, and cholesterol to < 200 mg per day.)
- High calorie beverages, e.g., sugar sweetened beverages
- Red meat
- High calorie and low nutrient foods, e.g., sweets and “junk” food

Limit alcohol to 1- 2 drinks per day (men) or 1 drink per day (women) unless alcohol is contraindicated or if patient

has history of alcohol abuse. A "drink" is 4 ounces of wine, 12 ounces of beer, or 1 ounce of spirits.

Limit eating out and when eating out choose nutritious foods.

Establish helpful environmental and family factors. Promote healthy eating by:

- Reducing portions, e.g., use smaller plates
- Schedule food consumption
- Read food labels and select low fat, high fiber, and low sodium foods.

See the UMHS guideline Obesity Prevention and Management for more information about nutrition and weight management.

Supplements

Many patients are interested in herbal supplements and other complementary medical therapies for secondary prevention of heart disease. This is a large, complex area beyond the scope of this guideline. Our highlighted recommendations are in Table 2. Of note, some herbal remedies can have cardiotoxic properties, some may lower serum potassium, and some may interact with cardiovascular drugs.

Symptomatic Carotid Artery Disease

Large artery atherosclerotic disease, including carotid artery disease, is a common cause of ischemic stroke. Options for managing symptomatic carotid disease include medical treatment, carotid endarterectomy plus medical treatment, and carotid artery stenting plus medical treatment. Management of asymptomatic carotid disease is beyond the scope of this guideline.

Carotid endarterectomy (CEA). Pooled data from 3 major trials suggests that patients with greater than 70% stenosis who underwent CEA had 15% less stroke recurrence or death than similar patients with medical treatment alone. In patients with less than 50% stenosis, CEA was not beneficial. For patients with 50-69% stenosis the benefits of CEA are more modest and can be overwhelmed if the surgical complication rate is greater than 6%.

Carotid artery stenting (CAS). CAS with medical management is an alternative to CEA with medical management. The contemporary trials of CAS enrolled a heterogeneous population of both symptomatic and asymptomatic patients making generalizability to patients with a history ischemic stroke difficult. The CREST trial compared CEA with CAS and found that there was no difference between the two treatments with regard to the primary endpoint, a composite of stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization. However, the incidence of stroke was higher in the stenting group compared with the CEA group. Additionally, the CEA group had rated higher quality of life despite a higher incidence of non-Q wave MIs. Older age was associated with a higher rate of neurologic complications with CAS secondary to greater atherosclerotic disease burden in the aortic arch and supra-aortic trunk in these patients. CAS may be a good alternative to CEA in patients at are at low risk of complications from the endovascular procedure, have high surgical risk or in specific circumstances (e.g., high carotid bifurcation, radiation induced stenosis, prior carotid intervention). As in CEA, the perioperative morbidity and mortality of carotid stenting should be less than 6%.

Timing of carotid revascularization. The benefits of carotid revascularization are highest within the first two weeks after a stroke. In patients with smaller strokes and TIAs, surgery can generally be done safely within this timeframe. For patients with larger strokes, there is a risk of hemorrhagic transformation and other complications with early surgery and recommendations must be individualized.

Patient selection for benefit. The benefits of carotid revascularization have been shown in patients with non-disabling strokes and these benefits likely do not apply to patients with significant disability after a stroke. Patient selection for carotid revascularization is important as perioperative risks can negate potential benefits from the procedure. Patients should have at least a two-year life expectancy before the decision is made to proceed with surgery. Men tend to benefit more from revascularization than women. Plaque characteristics, such as ulceration, may increase the risk of stroke. If a decision to perform an intervention is made based only on carotid duplex ultrasonography, an additional diagnostic test (such as a magnetic resonance angiography, computed tomography angiography, or catheter angiography) can be used to further characterize the stenosis and provide information about tandem lesions that may not be visible on ultrasound.

Related National Guidelines

Note:
AANN = American Association of Neuroscience Nurses
AANS = American Association of Neurological Surgeons
AATS = American Association for Thoracic Surgery
ACC = American College of Cardiology
ACCF = American College of Cardiology Foundation
ACIP = Advisory Committee on Immunization Practices
ACP = American College of Physicians
ACR = American College of Radiology
ACSM = American College of Sport Medicine
ADA = American Diabetes Association
AHA = American Heart Association
ASA = American Stroke Association
ASNR = American Society of Neuroradiology
CNS = Congress of Neurological Surgeons
JNC 8 Panel = Eighth Joint National Committee Panel
KDIGO = Kidney Disease: Improving Global Outcomes

PCNA = Preventive Cardiovascular Nurses Association
SAIP = Society of Atherosclerosis Imaging and Prevention
SCAI = Society for Cardiovascular and Angiography Interventions
SIR = Society of Interventional Radiology
SNIS = Society of Neurointerventional Surgery
SVM = Society for Vascular Medicine
STS = Society of Thoracic Surgeons
SVS = Society for Vascular Surgery

ACC/AHA:
- Guideline on the Assessment of Cardiovascular Risk (2013)
- Guideline on Lifestyle Management to Reduce Cardiovascular Risk (2013)
- Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)

ACCF: Integrating complementary medicine into cardiovascular medicine (2005)

ACCF/AHA:
- Focused update incorporated into guidelines for the management of patients with unstable angina/ non-ST-elevation myocardial infarction (2011)
- Guideline for the management of ST-elevation myocardial infarction (2013)
- Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: update (2011)

ACCF/AHA/AATS/PCNA/SCAI/STS: Guideline for the diagnosis and management of patients with stable ischemic heart disease (2012)

ACCF/AHA/SCAI: Guideline for percutaneous coronary intervention (2011)

ACIP: Recommended immunization schedule for adults aged 19 and older (2013)

ACSM: Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise (2011)

ACSM/AHA: Physical activity and public health in older adults (2007)

ADA: Standards of medical care in diabetes (2014)

AHA: Use of nonsteroidal anti-inflammatory drugs (2007)

AHA/ACCF: Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease (2011)

AHA/ASA:
- Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack (2011)
- Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation (2012)

ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS: Guideline on the management of patients with extracranial carotid and vertebral artery disease (2011)

JNC 8 Panel: Guideline for the management of high blood pressure in adults (2013)

KDIGO: Clinical practice guideline for evaluation and management of chronic kidney disease (2013)

Measures of Clinical Performance

The Centers for Medicare & Medicaid Services have several clinical performance measures directly related to secondary prevention of IVD that are part of the clinical quality measures for financial incentives for Meaningful Use of certified Electronic Health Record technology. The outpatient measures include:

IVD: aspirin or another antithrombotic. Percentage of patients ≥ 18 years old who were discharged alive for AMI, CABG, or PTCA in the 12 months prior to the measurement period, or who had an active diagnosis of ischemic vascular disease during the measurement period, and who had documentation of use of aspirin or another antithrombotic during the measurement period.

IVD: LDL. The percent of patients ≥ 18 years old who were discharged alive for AMI, CABG, or PTCA during the prior year or who had a diagnosis of IVD during the measurement year and the year prior to the measurement year and who had a complete lipid profile performed during the measurement year and whose LDL-C was < 100 mg/dL.

CAD: blood pressure. The percent of patients ≥ 18 years old who were discharged alive for AMI, CAGB, or PTCA during the year prior to the measurement year or a diagnosis of IVD during the measurement year and the year prior to the measurement year with most recent BP ≤ 140/90.

CAD: oral antiplatelet therapy. Percent of patients ≥ 18 years old with an active diagnosis of CAD or who have had a cardiac surgery procedure who were prescribed oral antiplatelet therapy.

CAD: lowering LDL. Percent of patients ≥ 18 years old with a diagnosis of CAD or who have a cardiac surgery procedure who were prescribed a lipid-lowering therapy (based on current ACC/AHA guidelines).

CAD: beta-blocker therapy if prior myocardial infarction or left ventricular systolic dysfunction. Percentage of patients ≥ 18 years old with a diagnosis of coronary disease seen within a 12 month period who also have a prior MI or current or prior LVEF < 40% who were prescribed beta-blocker therapy.

CAD: atrial fibrillation and warfarin. Average percentage of time in which patients ≥ 18 years old with atrial fibrillation without valvular heart disease who are on chronic warfarin therapy have International Normalized Ratio text results within the therapeutic range during the measurement period.

Seven additional measures directly related to IVD exist for secondary prevention during inpatient care.

Many additional measures exist for care associated with depression, diabetes, hypertension, immunizations, lipid management, obesity, and tobacco treatment. While patients with IVD often also have one or more of these conditions, the measures apply to patients with the relevant condition, whether or not IVD is present. For information regarding those measures see the UMHS clinical practice guideline for the condition.

Disclosures

University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

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Review and Endorsement

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