Reviews

A Clinician's Guide to the ABCs of Cardiovascular Disease Prevention: The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease and American College of Cardiology Cardiosource Approach to the Million Hearts Initiative

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ABSTRACT

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death in the United States and worldwide. Fortunately, it is often preventable with early adoption of lifestyle modification, prevention of risk factor onset, and aggressive treatment of existing risk factors. The Million Hearts Initiative is an effort by the Centers for Disease Control that aims to prevent 1 million myocardial infarctions and strokes over the next 5 years. As part of this initiative, we present a simply organized "ABCDE" approach for guiding a consistent comprehensive approach to managing cardiovascular risk in daily clinical practice. ABCDE stands for assessment of risk, antiplatelet therapy, blood pressure management, cholesterol management, cigarette/tobacco cessation, diet and weight management, diabetes prevention and treatment, and exercise, interventions regularly used to reduce cardiovascular (CV) risk. Throughout this article we summarize recommendations related to each topic and reference landmark trials and data that support our approach. We believe that the ABCDE approach will be the core framework for addressing CV risk in our effort to prevent CVD.

Introduction

Atherosclerotic cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States. Fortunately, it is a condition ideally suited for prevention. CVD accounts for more than 2 million heart attacks and strokes in this country alone. It is also caused by risk factors that are readily modified by lifestyle change and inexpensive pharmacotherapy. As identified in the INTERHEART study (A Global Case-Control Study of Risk Factors for Acute Myocardial Infarction), 9 risk factors—smoking, dyslipidemia, diabetes mellitus (DM), hypertension, abdominal obesity, stress, poor diet, physical inactivity, and excess alcohol consumption—were associated with more than 90% of the risk for a first myocardial infarction (MI).[1] Finally, it takes decades to develop. In the wake of an MI or stroke, patients and clinicians alike often lament the presence of longstanding risk factors that may have been overlooked.

Preventive therapy for at-risk individuals remains the best way to avoid its consequences.[2] It is estimated that nearly half the decline in coronary heart disease (CHD) deaths from 1980 to 2000 resulted from population-wide risk factor reduction (44%), whereas another half resulted from medical therapies targeting patients with known or suspected atherosclerosis (47%). In contrast, only 5% of the reduction in deaths was estimated to be due to revascularization in patients with established chronic stable angina.[3]

Because of this, we offer this guide to assist clinician participation in the Million Hearts Initiative, which is an effort by the Centers for Disease Control (CDC) that aims to prevent 1 million MIs and strokes over the next 5 years.[4] We present our recommendations in a simple "ABCDE" approach to the primary prevention of CVD (Table 1).

Assessment of Risk

The first step is to identify and treat individuals with established CHD or a CHD risk equivalent.[5] The latter conditions include individuals with noncoronary atherosclerotic vascular disease (cerebrovascular disease, peripheral artery disease [PAD], or abdominal aortic aneurysms), DM, and chronic kidney disease (stage II or worse).

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Table 1. ABCDE Approach to Assessment and Management of Cardiovascular Risk

A	Assessment of risk
	Antiplatelet therapy
B	Blood pressure
C	Cholesterol
	Cigarette/tobacco cessation
D	Diet and weight management
	Diabetes prevention and treatment
E	Exercise

For those without these conditions, global risk assessment tools can help identify low-, moderate-, and high-risk patients. Primary prevention interventions are then focused on those at moderate to high risk of developing CVD events, which maximizes the benefit of interventions while reducing unnecessary treatment. Periodic risk assessment should be undertaken for adults in the primary care setting, especially in those with cardiovascular (CV) risk factors, which include tobacco use, hypertension, dyslipidemia, increasing age, a family history of premature CHD, obesity, and lack of brisk exercise.[5]

The Framingham Risk Score (FRS) remains the most commonly used global risk assessment tool.[6] It approximates the 10-year risk of an initial MI or CHD-related death by using age, total cholesterol, high-density lipoprotein cholesterol (HDL-C) level, systolic blood pressure (BP), and smoking status. Patients are then stratified into low (<10% 10-year risk), intermediate (10%–20% 10-year risk), or high (>20% 10-year risk) risk groups. It is currently used in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines for dyslipidemia.[7]

Unfortunately, in many situations the traditional FRS falls short. For such individuals, other tools can be used for risk stratification.

Total CVD Risk

The original FRS measures the risk of CHD events, but does not include the risk of other clinically important cardiac events. In response, a more comprehensive FRS was published in 2008 to include the 10-year risk of all CVD events, including CHD but also stroke, PAD, and heart failure (HF).[8] Using 2 separate scoring methods, total CVD risk can be calculated in the office setting based on age, smoking status, BP, and laboratory studies (HDL-C and total cholesterol) or office measurements (body mass index [BMI]).[9] Combining routine height and weight checks with readily available BMI charts can facilitate office BMI measurements. Total CVD risk calculators can identify at-risk patients who may be missed with traditional FRS scoring.

Lifetime Risk

Such an approach is very helpful for communicating risk to middle-aged and even younger patients who are not yet high risk by virtue of age. To address these issues, the Framingham investigators published a risk score to help predict risk of hard CVD events (MI, stroke, or death) over 30 years.[10] Along with traditional risk factors (male sex, age, hypertension, cholesterol, smoking, and diabetes), obesity was identified as an independent predictor of long-term events. Accumulation of risk factors added synergistically to long-term (30-year) risk even when 10-year risk was not particularly high. This is illustrated in the Figure 1, which estimates CVD risk in 25-year-old women with various risk factor profiles. Patients with increased lifetime risk warrant early aggressive lifestyle and risk factor modifications even when 10-year risk would not call for treatment.

Women and Minorities

The traditional FRS also underestimates CHD risk in women and minorities. According to the National Health and Nutrition Examination Survey III data, only 5% of asymptomatic women would be characterized as being at intermediate or high risk using the traditional FRS.[11] However, about 40% of women will have a CV event after the age of 50 years.[12] For women, risk factors such as family history and subclinical inflammation, as assessed by high sensitivity C-reactive protein (hsCRP), can refine risk prediction.[13,14] Another shortcoming of the Framingham Heart Study was its inclusion of a primarily Caucasian population. To that end, studies such as the Multi-Ethnic Study of Atherosclerosis (MESA) are seeking to identify ethnic differences in CVD.[15,16]

Given these limitations, the Reynolds Risk Score (RRS) was developed as an alternative risk assessment tool.[17] Along with traditional risk factors, the RRS takes into account family history of premature CHD as well as hsCRP. Use of the RRS does not fully resolve the limitations of the FRS, but can sometimes reclassify patients into a higher or lower risk group. When applied to 25,000 healthy women from the Women's Health Study, about 40% of women originally classified as low risk were determined to be at higher risk.[17] Pitfalls include the inconsistency of hsCRP measurements and the accuracy of a family history, which depends on careful history taking and accurate patient recall.

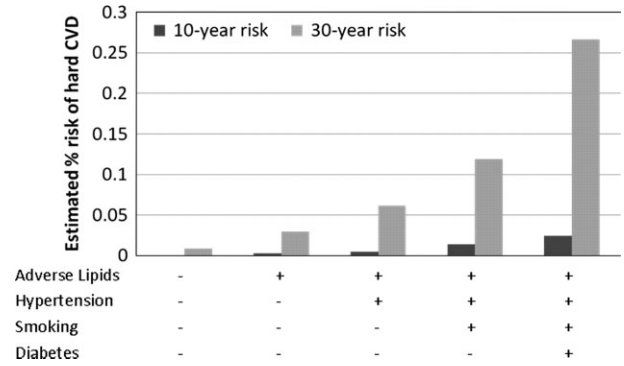

Figure 1. The 10- vs 30-year risk of hard cardiovascular CVD events (myocardial infarction, stroke, death) for 25-year-old women with different risk profiles. No risk factors profile: total cholesterol = 150 mg/dL; high-density lipoprotein (HDL) cholesterol = 60 mg/dL; untreated systolic blood pressure (SBP) = 110 mm Hg; nonsmoker; nondiabetic. Adverse lipids: total cholesterol = 260 mg/dL; HDL cholesterol = 35 mg/dL. Hypertension: SBP = 160 mm Hg, untreated. From Pencina et al.[10]

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Online risk calculators exist for all the aforementioned risk scores can be found in Table 2.

Intermediate Risk Patients

Often, it is unclear how aggressively patients at intermediate risk should be treated. In these situations, assessment for subclinical atherosclerosis can prove useful. Coronary artery calcium (CAC) scoring, as measured by computed tomography, is emerging as the most predictive test of CHD risk in intermediate-risk patients.[18–20] In fact, use of CAC score groups of 0, 1 to 100, and >100 proved predictive of subsequent CV events in low-to-intermediate risk patients (i.e. those meeting inclusion criteria for the JUPITER [Justification for the Use of Statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin] study) and can be used to target subgroups from this population that would be expected to derive the most benefit from statin treatment.[20] In 2010, the American College of Cardiology (ACC)/American Heart Association (AHA) joint guidelines for the assessment of CV risk considered CAC scoring useful for risk stratification in intermediate risk patients (10%–20% 10-year risk) (class IIa recommendation).[21]

Antiplatelet Therapy

Primary Prevention

Aspirin: Substantial evidence supports the use of aspirin in the primary prevention of CVD. The Antithrombotic Trialists' Collaboration was an important meta-analysis that evaluated 95,456 patients from 6 clinical trials.[22] Patients were randomized to aspirin or placebo for 4 to 10 years. Aspirin therapy was associated with a small reduction in serious vascular events (0.51% vs. 0.57% per year; P = 0.0001), but also a slight increase in the rate of major gastrointestinal and extracranial bleeding (0.10% vs 0.07% per year; $P < 0.0001$). Other studies, however, have called into question the value of aspirin in primary prevention.[23–25]

As a result, current guidelines limit the use of low-dose aspirin for primary prevention as follows:

1. Aspirin (81 mg/d) in patients with at least intermediate risk (10-year risk of CHD >10%) (ACC/AHA class I, level A).[26]
2. Aspirin (81 mg/d) in at-risk women 65 years or older (ACC/AHA class IIa, level B).[27]
3. Aspirin (81–162 mg/d) in patients with DM who are older than 40 years with other risk factors (family history of premature CVD, hypertension, smoking, dyslipidemia, or albuminuria) (AHA/American Diabetes Association).[28]

Table 2. Online References for Different Risk Score Calculators

Risk Score	Online Location
Framingham Risk Score[6]	http://www.framinghamheartstudy.org/risk/coronary.html[111]
Total CVD risk[8]	http://www.framinghamheartstudy.org/risk/gencardio.html[112]
Lifetime risk[10]	http://www.framinghamheartstudy.org/risk/cardiovascular30.html[113]
Reynolds Risk Score[17]	http://www.reynoldsriskscore.org[114]

Abbreviations: CVD, cardiovascular disease.

$P2Y_{12}$ Receptor Antagonists: These agents comprise the other major class of antiplatelet agents. Currently, there are no guidelines for using them in primary prevention.

Secondary Prevention

Aspirin: There is clear support for the use of aspirin in the secondary prevention of CVD. The most convincing data come again from the Antithrombotic Trialists' collaboration, in which approximately 17,000 high-risk patients randomized to low-dose aspirin vs placebo were found to have a significant reduction in major vascular events (6.7% vs 8.2% per year), stroke (2.1% vs 2.5%), and coronary events (4.3% vs 5.3%).[29]

For patients who undergo coronary revascularization, aspirin is mandatory. Traditionally, higher doses of aspirin have been used for at least a month after stent placement. However, the recently published Clopidogrel optimal loading dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes (CURRENT OASIS 7) trial showed no significant difference in the primary end point of CV death, MI, or stroke for patients randomized to low-dose aspirin (75–100 mg/d) vs high-dose aspirin (325 mg/d) immediately after a loading dose (aspirin 325 mg once).[30]

$P2Y_{12}$ Receptor Antagonists: Multiple studies demonstrated benefit with clopidogrel either as an alternative to aspirin or in addition to aspirin for the secondary prevention of CV events. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial compared aspirin (325 mg/d) vs clopidogrel (75 mg/d) monotherapy and found clopidogrel was associated with a 9% relative risk reduction in the primary end point of ischemic stroke, MI, or vascular death.[31]

Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin, as compared to aspirin alone, has also been shown to reduce adverse outcomes including death, nonfatal MI, and stroke in patients after both non–ST-elevation acute coronary syndrome as well as ST-elevation MI. This has been shown in several studies, including the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial,[32] the Clopidogrel as Adjunctive Reperfusion Therapy in Thrombolysis in Myocardial Infarction (CLARITY-TIMI 28) trial,[33] and the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT/CCS2).[34] Current guidelines recommend DAPT for at least 12 months in individuals after acute coronary syndrome (ACS) or after drug-eluting stents.[35] However, the optimal duration of DAPT after coronary stenting is still poorly defined. DAPT for as short as 6 months after coronary stenting was recently shown to yield fewer hemorrhagic events without an increased risk of thrombotic events when compared to 24 months of DAPT.[36]

The newer $P2Y_{12}$ receptor antagonists, prasugrel and ticagrelor, afford incremental event reduction when compared to clopidogrel in patients with ACS, but at the cost of increased bleeding. These agents were studied in the Trial to Assess Improvement in Therapeutic Outcomes

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by Optimizing Platelet Inhibition with Prasugrel-TIMI 38 (TRITON-TIMI 38), which included patients undergoing percutaneous coronary intervention (PCI),[37] and the Platelet Inhibition and Patient Outcomes (PLATO) trials, respectively.[38] Prespecified subgroup analysis found that diabetics benefited the most from prasugrel.[39] Prasugrel, however, was associated with a higher rate of significant bleeding, along with less overall benefit in those with prior stroke, age >75 years, or weight below 60 kg. Ticagrelor, on the other hand, was not associated with greater overall rates of TIMI major bleeding or life-threatening bleeds.

For the secondary prevention of ischemic stroke or transient ischemic attack, we recommend either aspirin (81–325 mg/d) or clopidogrel (75 mg/d) alone.[40] Combination therapy may be associated with increased rates of bleeding. For those with symptomatic PAD, it is reasonable to use aspirin (81–325 mg/d) or clopidogrel alone (75 mg/d). There are no data supporting the use of antiplatelet therapy in patients with asymptomatic PAD.[41]

The following is a summary of the guidelines for the use of aspirin and $P2Y_{12}$ receptor antagonists for secondary prevention:

1. Aspirin (81 mg/d) is recommended for all patients following ACS.[42–45]
2. Aspirin (81–325 mg/d) is recommended for all patients following an ischemic stroke.[43,46]
3. Aspirin (81 mg/d) is recommended for all patients with PAD.[47]
4. Clopidogrel may be used as monotherapy in patients who are intolerant of aspirin for the secondary prevention of CV events,[43] stroke,[46] or PAD.[47]
5. A $P2Y_{12}$ receptor antagonist should be used in combination with aspirin for at least 1 year in patients following ACS.[42,43,48]
    A. If no PCI was performed, either clopidogrel or ticagrelor should be used.[42,43]
    B. If PCI was performed, clopidogrel, ticagrelor, or prasugrel may be used.[42,43]
6. A $P2Y_{12}$ receptor antagonist should not be used in patients revascularized by coronary artery bypass graft surgery, unless some other indication exists.[42,43]
7. Clopidogrel should be used in combination with aspirin in patients receiving PCI for stable coronary artery disease, for a time period specific to the type of stent placed, followed thereafter by lifelong aspirin.[35]
    A. If a bare-metal stent was used, clopidogrel should be taken for at least 1 month and ideally 1 year.[35]
    B. If a drug-eluting stent was used, clopidogrel should be taken for at least 1 year.[35]

Blood Pressure

Hypertension is an important risk factor for CHD as well as stroke, atrial fibrillation, HF, left ventricular hypertrophy, renal failure, and dementia. It is partly responsible for 54% of strokes and 47% of ischemic heart disease worldwide, and there is a graded relationship between the degree of hypertension and risk of CV disease.[49] This relationship is so important that prehypertension (systolic BP [SBP] of 120–139 mm Hg or diastolic BP [DBP] of 80–89 mm Hg) is now identified as a marker of increased risk.

Guidelines by the Joint National Committee (JNC 7) support treatment of BP once the SBP is >140 mm Hg or the DBP is >90 mm Hg.[50] Current guidelines suggest a lower target of 130/80 in patients with DM, chronic kidney disease (CKD), or CHD. Further lowering of BP is not recommended. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial found no significant overall benefit in diabetics to targeting a SBP goal of 120 mm Hg as opposed to 140 mm Hg.[51]

Stage I Hypertension: This stage is defined as SBP 140–159 mm Hg or DBP 90–99 mm Hg. For these patients, lifestyle modifications come first, including weight loss, increased physical activity, less consumption of alcohol, reduced dietary sodium, and a diet rich in fruits, vegetables, and fiber. If lifestyle modifications fall short of achieving BP targets, a single agent can be chosen and up-titrated. A thiazide diuretic is the first line for most patients, but other agents can be chosen if compelling indications exist, such as angiotensin converting enzyme inhibitors for those with diabetes or metabolic syndrome and β-blockers for those with coronary disease. The emphasis in JNC 7 is on thiazide diuretics, though amlodipine and other agents are similarly effective first line agents.[52]

Stage II Hypertension: This stage is defined by a SBP of 160 mm Hg or greater, or DBP of 100 mm Hg or greater. Even though initial treatment should include lifestyle intervention, drug therapy is indicated up front, almost always using a 2-drug regimen.

Refractory Hypertension: In the face of refractory hypertension, ensure that proper BP measurements are being made, verify that a diuretic is included in the regimen or evaluate the efficacy of that diuretic (thiazides are less effective in the setting of stage IV-V CKD [glomerular filtration rate < 30 mL/min], and loop diuretics should be used instead),[53] assess and limit sodium and alcohol intake, and withdraw any interfering substances (eg, nonsteroidal anti-inflammatory drugs, illicit drugs, oral contraceptives).[50] Spironolactone can be a helpful agent to add in refractory hypertension. Therapies on the horizon include renal sympathetic denervation, which is an investigational new treatment that may add to the treatment armamentarium for refractory hypertension.[54]

Cholesterol

Cholesterol-containing lipoproteins are central to the pathogenesis of atherosclerosis. Validation of this has come from the demonstration that elevated cholesterol is associated with increased CV risk,[55,56] and lipid-lowering medications can reduce this risk.[57–59]

United States guidelines for the management of cholesterol are defined by the NCEP (ATP III) guidelines.[7,60] Patients are stratified into low (0–1 risk factor), moderate (≥2 risk factors but FRS <10%), moderately high (≥2 risk factors and FRS 10%–20%), and high-risk groups (CHD, CHD risk equivalent, or FRS >20%). Low-density lipoprotein cholesterol (LDL-C) is the primary target of lipid-lowering

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therapy, with the desired goal reflecting the underlying risk (Table 3). For intermediate risk patients, it is reasonable to use hsCRP or CAC scoring to help further risk stratify this group.[20]

Targeting LDL-cholesterol alone is not enough, however, as this tactic misses individuals at risk for CVD. Within the ATP III algorithm, an important secondary goal is the reduction of non–HDL-C (equal to total cholesterol minus HDL-C), which includes cholesterol carried by all atherogenic apolipoprotein-B (apo-B)–containing lipoproteins.[7]

Furthermore, there are other lipid disorders that confer risk above that predicted by LDL-C alone. Atherogenic dyslipidemia refers to the triad of increased concentrations of LDL-C particles, decreased HDL-C particles, and increased triglycerides. It is associated with the metabolic syndrome, insulin resistance, and type 2 DM and confers atherogenic risk independent of LDL-C. It can be assessed by directly measuring apo-B.[61] Another important atherogenic particle is lipoprotein(a), or Lp(a), which is a modified form of LDL-C that confers atherogenic risk independent of LDL-C. Serum Lp(a) levels are primarily genetically determined and can be elevated in the absence of other lipid abnormalities. It can be assessed by directly measuring its serum level; Lp(a) levels above the 80% percentile of the population are independently predictive of CHD.[62] Although statin therapy does not lower Lp(a), further lowering of LDL-C appears to mitigate the added risk associated with high Lp(a).

Both atherogenic dyslipidemia and Lp(a) abnormalities contribute to residual CVD risk in patients with LDL-C at goal. No guidelines exist that utilize apo-B or Lp(a) levels in assessment and treatment. In our practice, however, we often check for elevated apo-B and Lp(a) levels once LDL-C and non–HDL-C goals are met to assess whether lipid-lowering therapy could be intensified. We feel that patients with elevated apo-B and Lp(a) levels comprise an important subset of patients who might benefit from additional statin therapy and lifestyle interventions even after traditional goals are met.

Statins

The hydroxymethylglutaryl-CoA reductase inhibitors are the most widely studied lipid-lowering agents. They should be used as first line agents if therapeutic lifestyle interventions fail. A wealth of accumulated data supports the use of statins in primary prevention in patients with elevated cholesterol levels along with another CHD risk factor.[63–65] More recently, the JUPITER trial showed that patients with more "normal" cholesterol levels also derive benefit from statin treatment.[14]

Statins are essential for the secondary prevention of CHD risk. The Heart Protection Study showed a 13% relative risk reduction in total mortality over a mean of 5.5 years when patients with increased CVD risk were treated with simvastatin 40 mg/d, regardless of baseline LDL-C levels.[66] Multiple secondary prevention trials have demonstrated benefit from the use of statins after an ACS (Myocardial Ischemia Reduction with Acute Cholesterol Lowering [MIRACL], Pravastatin or Atorvastatin Evaluation and Infection Therapy [PROVE IT], "Zocor" phase of the Aggrastat to Zocor [A to Z] Trial)[67–69] as well as in patients with stable CHD (Scandinavian Simvastatin Survival Study [4S], Treating to New Targets [TNT], Incremental Decrease in Endpoints Through Aggressive Lipid Lowering [IDEAL], among others).[70–73] A robust dose-dependent relationship between the degree of LDL-C lowering and reduction of CHD events, independent of baseline patient risk, has been noted across these trials.[74]

The incidence of side effects observed after run-in phases of clinical trials is low, but these include myalgias (1.1%–5.0%), creatine kinase elevation (0.9%), and transaminitis (1.4%), all of which can be exacerbated with concomitant use of gemfibrozil, certain antifungal medications, and certain antibiotics.[75] Some reports have raised concerns for adverse long-term effects on cancer incidence, cognitive function, and DM.[76] Overall, careful evaluation of existing scientific evidence does not support an impact of statins on the incidence of cancer or cognitive decline.[77,78] Regarding the increased risk of DM, a recent study found that the risk was limited to patients already at high risk of developing DM, and in these patients, the benefits of statins still outweighed the risk associated with earlier onset DM.[79]

When statin medications are not tolerated due to mild side effects, a drug holiday for 2 to 4 weeks should be considered, followed by reinitiation with an every other day or twice weekly schedule. Alternatively, a switch to a more hydrophilic statin (eg, pravastatin, rosuvastatin, or fluvastatin XL) may help alleviate side effects.[80] Given the strong evidence for statins, we try 3 different statin medications before labeling a patient as intolerant of statin therapy.

Table 3. NCEP ATP III Risk Categories and Intervention Goals (Adapted from ATP III)

Risk Category	Lifestyle Intervention	Consider Drug Therapy	LDL-C Goal	Non–HDL-C Goal
Low risk	≥160 mg/dL	≥190 mg/dL	<160 mg/dL	<190 mg/dL
Moderate risk	≥130 mg/dL	≥160 mg/dL	<130 mg/dL	<160 mg/dL
Moderately high	≥130 mg/dL	≥130 mg/dL	<130 mg/dL	<160 mg/dL
		100–129: optional	<100: optional	<130: optional
High risk	≥100 mg/dL	≥100 mg/dL	<100 mg/dL	<130 mg/dL
		70–99: optional	<70: optional	<100: optional

Abbreviations: ATP III, Adult Treatment Panel III; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

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Other Lipid-Lowering Agents

Despite the above approach, a small minority of patients remains intolerant of statin therapy. Meanwhile, other patients do not reach goal LDL-C or non–HDL-C levels despite intense statin therapy. For such patients it is reasonable to turn to other agents, such as bile acid sequestrants, fibrates, or niacin, although supporting data are admittedly limited.

Bile acid sequestrants (eg, cholestyramine, colesevelam) lower LDL-C by 15% to 20% and have been shown to reduce CV risk when used as monotherapy.[57,58] Ezetimibe is a cholesterol absorption inhibitor with favorable outcome data when used in combination with statins in patients with CKD.[81] Fibrates alone, such as gemfibrozil or fenofibrate, modestly reduce LDL-C levels and increase HDL-C and have been shown to reduce rates of death and nonfatal MI.[82] For patients with atherogenic dyslipidemia persisting after single-agent statin therapy, addition of fenofibrate can lower non–HDL-C more; furthermore, the ACCORD trial showed a strong trend for benefit for fenofibrate in the subgroup with triglycerides >200 mg/dL and low HDL-C.[83] Niacin is another alternative that effectively decreases LDL-C and triglycerides while increasing HDL-C and has been shown to reduce CV events when used as monotherapy.[84] Disappointing results, however, have been noted in recent studies (ACCORD, Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides [AIM-HIGH], and Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE] trials) evaluating combination therapy with statin and fibrate or niacin.[85–87]

Cigarette/Tobacco Cessation

Tobacco use in all of its forms is proatherogenic and prothrombotic. It is also the leading cause of preventable death in the Western world. A recent study showed that even secondhand smoke is as bad a risk factor as dyslipidemia.[88] A meta-analysis of 20 prospective cohort studies demonstrated a 36% relative reduction in mortality for CHD patients who were able to quit smoking.[89]

On a positive note, there exists a desire for many smokers to quit. The CDC recently reported that 69% of current smokers want to completely stop smoking, and 52% of smokers had attempted to quit in the past year.[90] To help providers broach the subject, the Agency for Healthcare Research and Quality recommends the 5 As, which stand for:

1. Ask all patients about tobacco.
2. Advise patients to quit.
3. Assess willingness to quit.
4. Assist with counseling or pharmacotherapy.
5. Arrange for follow-up within the first week after a quit date.

The most important factor is patient self-motivation. Once present, behavioral support has been shown to be effective. Such interventions include behavioral counseling with physician extenders, telephone resources (eg, 1-800-QUIT-NOW), identifying and altering triggers and lifestyle factors that lead to tobacco use, and enlisting the help of family and friends.

The addition of pharmacotherapy (nicotine replacement therapy [NRT], bupropion [Zyban; GlaxoSmithKline Plc., London, UK], or varenicline [Chantix; Pfizer Inc., New York, NY]) can also be effective. Varenicline seems to be the most effective, with data demonstrating that its use increased the chance of smoking cessation 2- to 3-fold.[91] Its effect is also greater than that of bupropion.[92] For those who cannot tolerate or do not wish to try varenicline, bupropion itself is more effective than placebo.[93] The Cochrane Collaboration also reviewed over 100 studies of NRT and found NRT made smoking cessation attempts 50% to 70% more likely to succeed.[94]

Each pharmacotherapy has important side effects. Varenicline most commonly causes nausea, which usually subsides. Less common side effects include gastrointestinal upset, abnormal dreams, and insomnia. The combination of varenicline and NRT increases the incidence of nausea and headaches. Bupropion can also lower the seizure threshold. Most seriously, the US Food and Drug Administration (FDA) issued a black box warning for both varenicline and bupropion in 2009, detailing the rare but increased incidence of neuropsychiatric side effects, including behavior change, hostility, agitation, depression, and suicidality. Because of this, proper use of these drugs requires well-informed, shared decision making.

Diet and Weight Management

Obesity (BMI $\geq$30 kg/m^2) is a major risk factor for CHD. When it is viscerally deposited, there is an even greater risk of developing CHD, hypertension, impaired glucose tolerance, obstructive sleep apnea (which itself is strongly associated with CHD), and dyslipidemia. This risk increases for men and women with a waist circumference greater than or equal to 40 inches and 35 inches, respectively. Even lower cutoffs should be used in other ethnic populations (eg, Hispanic, Asian, and African descent).[95] Based on this, weight, BMI, and waist circumference should be measured routinely for optimal risk assessment.

Even modest goals to reduce caloric intake can lead to weight reduction. Calorie counting and reducing consumption of high-calorie beverages is helpful. Although many diets have been studied and can be successful, the Mediterranean-style diet yields the most heart healthy benefits.[96] In fact, the Mediterranean diet was recently shown in a large, randomized trial to reduce the incidence of CV events in high-risk patients.[70] Specifically, the diet studied was rich in olive oil, legumes, fish, chicken, nuts, wine, fruits, and vegetables, and low in artificial sugars, commercial sweets, pastries, butter, margarine, and red meat.[70]

There are specific dietary guidelines within ATP III for patients with LDL-C levels above goal.[7] These include limiting saturated fats to <7% of total caloric intake, dietary cholesterol to <200 mg/d, and adding plant sterols (2 g/d) and fiber (10–25 g/d) to the diet. Saturated fats should be limited and trans fats eliminated. Reducing the glycemic load and mean glycemic index of the diet is also important.

For certain patients, bariatric surgery may be considered if the BMI is >40 kg/m^2 or if BMI is >35 kg/m^2 in diabetics. Pharmacotherapeutic options remain limited. The FDA recently approved 2 new medications, Belviq (Arena

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Table 4. American Heart Association Guide to the Primary Prevention of CVD in ABCDE Format

ABCDE Component	Recommendation
Antiplatelet therapy	Aspirin 81 mg/d if >10% 10-year risk; use contraindicated if risk of bleeding outweighs benefit. No role for clopidogrel.
Blood pressure	Lifestyle interventions ± pharmacotherapy. Goal: <140/90 mm Hg, < 130/80 if CKD or DM.
Cholesterol	Lifestyle interventions ± pharmacotherapy (statins 1st line). Goal: see Table 3.
Cigarette/tobacco cessation	Assessment, counseling, pharmacotherapy. Goal: complete tobacco cessation.
Diet and weight management	Heart healthy, Mediterranean-style diet. Goal (primary): BMI 18.5–24.9 kg/m2. Goal (secondary): Waist <40 in (men), <35 in (women).
Diabetes prevention and treatment	Lifestyle interventions, oral hypoglycemic, insulin. Goal (no DM): normal fasting glucose and hemoglobin A1c. Goal (DM): hemoglobin A1c <7%
Exercise	Regular physical activity. Goal: <30 min/d, moderate intensity most days/week

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus.

Table 5. American Heart Association/American College of Cardiology Guidelines for the Secondary Prevention of Cardiovascular Disease in ABCDE Format

ABCDE Component	Recommendation
Antiplatelet therapy	Aspirin 81–162 mg/d indefinitely. Clopidogrel 75 mg/d for 12 months after ACS. Clopidogrel after stent; duration depends on stent type.
Blood pressure	Lifestyle Interventions + pharmacotherapy. Goal: <140/90 mm Hg, <130/80 if CKD or DM. ACEI if LVEF ≤40%, hypertension, CKD, DM. ARB if intolerant to ACEI. Aldosterone-antagonist post-MI if on ACEI, BB, LVEF ≤40%. BB indefinitely if post-MI, ACS, or left ventricular dysfunction unless contraindicated.
Cholesterol	Statin; intensify initial statin before adding second drug. First goal: LDL-C <100 mg/dL (optimal <70). Second goal: non–HDL-C <130 mg/dL (optimal <100).
Cigarette/tobacco cessation	Assessment, counseling, pharmacotherapy. Goal: complete cessation
Diet and weight management	Heart healthy, Mediterranean-style diet. Goal (primary): BMI 18.5–24.9 kg/m2. Goal (secondary): waist <40 in (men), < 35 in (women)
Diabetes prevention and treatment	Lifestyle interventions, oral hypoglycemic, insulin. Goal (no DM): normal fasting glucose and hemoglobin A1c. Goal (DM): hemoglobin A1c <7%
Exercise	Cardiac rehab for patients post-MI. Goal: <30 min/d moderate intensity most days of week
Immunizations	Influenza vaccination

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BB, β-blocker; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; non–HDL-C, non–high-density lipoprotein cholesterol.

Pharmaceuticals, Inc., San Diego, CA) and Qsymia (VIVUS, Inc., Mountain View, CA), but these should only be used in conjunction with sustained diet and exercise plans.[97]

Diabetes Prevention and Treatment

Diabetes and prediabetes are important risk factors for CHD.[98] In 2010, the American Diabetes Association (ADA) added hemoglobin A1c cutoffs to its definitions of DM and pre-DM, which has made it simpler to diagnose both. DM can be diagnosed with a hemoglobin A1c of ≥ 6.5%, whereas those with A1c levels of 5.7% to 6.4% are prediabetic. The ADA recommends screening for any adults who are overweight or obese, or beginning at age 45 years. If tests are normal, they can be repeated every 3 years. Prediabetics should be monitored yearly for the progression to DM.[99]

Identifying pre-DM is helpful because multiple interventions have been shown to reduce the development of DM. The Finnish Diabetes Prevention Study demonstrated that lifestyle interventions in obese patients with impaired fasting glucose helped reduce the incidence of DM by 58%.[100] The Diabetes Prevention Program demonstrated that randomizing high-risk nondiabetics to metformin (850 mg twice daily) or lifestyle modifications significantly reduced the incidence of diabetes when compared to placebo.[101] Thiazolidinediones have also shown benefit, but are falling out of favor given the increased incidence of associated CV events and bladder cancer.[102,103]

If pre-DM is identified, therapy should be aimed at weight loss of 5% to 10% of body weight, increasing physical activity to 150 min/wk of moderate activity, and increasing the consumption of fiber and whole grain carbohydrates. Metformin can be considered for obese, prediabetic individuals younger than 60 years that are at high risk of developing DM (eg, family history of DM or presence of metabolic syndrome).[99]

For those with DM, the ADA recommends treatment to achieve a goal hemoglobin A1c of <7%. More intensive goals should be avoided, as the ACCORD Study Group showed in 2008 that intensive glucose lowering to a goal hemoglobin A1c of 6% as opposed to a goal of 7% resulted in increased mortality.[104]

Exercise

Lack of regular, brisk activity is another important risk factor for CHD.[105] Physical activity has many benefits, including

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weight loss, lipid control, BP improvement, and insulin sensitization. In the United States, however, the combination of increasingly sedentary lifestyles and jobs remain a barrier for many individuals.

There are limited randomized data on the independent effects of exercise on the primary prevention of CVD events. Multiple prospective and retrospective observational studies have shown that increased physical activity and regular exercise are associated with lower rates of CVD.[106,107] Exercise has also been shown to benefit those with established CHD by reducing subsequent CV events and all-cause mortality.[108]

Accordingly, the AHA guidelines recommend 30 or more minutes of moderate-intensity (3–6 metabolic equivalents [METs]) physical activity on at least 5 days per week.[109] Although it can be difficult to encourage patients to adopt new exercise regimens, even simple tools like a pedometer can lead to reliable increases in physical activity. In fact, a systematic review evaluating the use of pedometers demonstrated an increase in average daily steps by 2491 (or approximately 1 mile), an increase in average physical activity by 27%, and a modest decrease in BMI.[110]

Summary

Consistent with the Million Hearts Initiative, we recommend that all patients undergo assessment of CV risk as well as initiation of therapies outlined in the primary and secondary prevention guidelines for CVD (Tables 4 and 5, respectively). We have organized these guidelines in a simple ABCDE approach (Table 1) that that should facilitate the use of these risk-reducing interventions in the office setting.

It is important to note that the field of preventive cardiology is constantly evolving. In fact, new guidelines for the management of blood pressure (JNC 8) and dyslipidemia (ATP IV) are on the near horizon. We offer this current iteration of our ABCDE guide to include the evidence to date and look forward to revising this guide in the future to incorporate emerging evidence and treatment guidelines for the prevention of CVD.

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