How To Avoid A Heart Attack: Putting It All Together

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Cardiovascular disease (eg, myocardial infarction, ischemic stroke) is the leading cause of death in patients who have metabolic syndrome and diabetes mellitus. By effectively treating the whole patient, however, the risk of death from cardiovascular disease can be reduced or prevented. The author describes clinical approaches for achieving this goal. He reviews information that is useful to know about patients regarding modifiable and potentially modifiable risk factors for cardiovascular disease, including hypertension, hyperlipidemia, smoking, activity levels, dietary habits, obesity, carotid artery stenosis, and atrial fibrillation. He also notes the importance of evaluating patients for relevant psychosocial factors such as depression. Finally, the author analyzes treatment options for patients, including effective medications, dietary modification, and exercise—emphasizing the use of pedometers—as well as participation by patients in weight-control support groups.

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Physicians measure success in preventive cardiology by the heart attacks they eliminate, the strokes they avoid, and the lives they save. This presentation, adherent to the osteopathic philosophy of treating the whole patient, provides physicians with the information needed to reduce their patients’ cardiovascular risk.

Partnering with patients, through a comprehensive, evidence-based program of preventive cardiology, physicians will reduce their patients’ risk of strokes, kidney failure, and heart attacks. Atherosclerotic vascular disease is a largely preventable condition. When physicians accurately diagnose, and effectively treat patients for all their cardiovascular risk factors, they avert many cardiac events and save numerous lives.

The Framingham Heart Study1 established the primary focus of cardiovascular disease (CVD) prevention to be the identification of high low-density lipoprotein cholesterol (LDL-C) levels and hypertension and treatment of patients with these risk factors. During the past five decades, the lion’s share of research grants focused on these two modifiable risk factors. In turn, such funded research produced numerous evidence-based medicines proven to favorably enhance patients’ survival.

Cardiovascular disease preventive medicine has undergone a paradigm shift because physicians now recognize that future treatments will be successful only if they address the growing epidemic of diabetes and metabolic syndrome that is fueled by the worldwide explosion of obesity. Physicians’ success will be measured in their ability to diagnose and target the so-called atherogenic dyslipidemia (high-density lipoprotein [HDL-C] levels [<50 mg/dL in women, <40 mg/dL in men] coupled with high triglyceride concentrations [>150 mg/dL].

The most effective way to initiate a preventive cardiac program is to identify the repeatedly occurring risk factors that promote atherosclerosis and then institute the best therapy to dramatically reduce those factors.

The first thing physicians must understand if they are to help patients successfully avoid a major cardiovascular event is that CVD does not exist in a vacuum. Therefore, they should question patients about their having a finite, easily identifiable set of risks factors that increases their risk of a major cardiac event. The INTERHEART study data2...
identified potentially modifiable risk factors. The biggest challenge facing the preventive strategy is to identify those evidence-based markers so that they may be successfully minimized or eliminated.

During the last 50 years, the Framingham Risk Score (FRS) has stood the test of time as a starting point to identify and modify those human patterns that eventually lead to a cardiovascular event. The FRS is a good start, but it truly identifies only about 78% of the patients at risk. The INTERHEART study looked at the world’s burden of CVD from a slightly different perspective; namely, globally, cross-culturally, cross-racially, and cross-sexually. It identified nine risk factors (Figure 1) that are consistently associated with the increased probability of a patient’s having a myocardial infarction (MI).

The goal of preventive medicine is that physicians successfully identify (diagnose) and modify (treat patients for) each and every one of these risk factors. Achieving this goal may well substantially reduce the number of cardiovascular events.

Abnormal Lipid Levels

The most valuable starting point with regard to cholesterol is to obtain an accurate lipid profile. While the INTERHEART study used apolipoprotein A and apolipoprotein B, a more practical and readily available approach in the United States is to request measurement of direct low-density lipoprotein cholesterol (LDL-C), nonfasting triglyceride concentration (ideally 2 to 4 hours after a meal), high-density lipoprotein cholesterol (HDL-C), and finally lipoprotein A.

Data from the Justification for the Use of Statins in Prevention and Intervention Trial Evaluating Rosuvastatin (JUPITER) reported by Ridker et al\(^3\) should prompt physicians to begin to consider including measurement of high-sensitivity C-reactive protein (hs-CRP), the inflammatory marker sometimes referred to as “cardio CRP” in their orders for those laboratory blood tests that are vital to making the best clinical decisions. Ridker and colleagues’ study showed that hs-CRP is an independent risk factor that may predict future cardiovascular events.

The hs-CRP level may influence which patients to treat, as well as the level of LDL-C necessary for maximally lowering the incidence of clinical events. The JUPITER study established hs-CRP as a target that can be successfully reduced through the use of a statin, which in the JUPITER trial resulted in a 45% reduction in cardiovascular events.

Ongoing research efforts to favorably influence the HDL-C molecule include a variety of agents as well as a procedure called plasmapheresis. The ongoing Atherosclerosis Intervention in Metabolic Syndrome with Low HDL-High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study\(^4\) is a multicenter, randomized, double-blind, parallel-group, controlled clinical study designed to evaluate whether the drug combination of extended-release niacin plus simvastatin is superior to simvastatin alone, at comparable levels of on-treatment LDL-C, for delaying the time to a first major cardiovascular event. In the next few years, the data regarding lopropitant (an agent to block the niacin flushing receptor) may allow offering niacin to patients who were previously niacin intolerant.

With the publication of the Stop Atherosclerosis in Native Diabetics Study (SANDS)\(^5\) and the recent decision of the US Food and Drug Administration (FDA) to declare ezetimibe safe, physicians can begin to see the possible beneficial effects of combination therapy using statins and cholesterol absorption inhibitors (ezetimibe). Using carotid intimal medial thickness (CIMT) as the clinical measurement parameter, SANDS is the first study to clearly demonstrate the favorable effects of combination therapy in patients with diabetes. While any therapy to reduce LDL-C levels should remain primarily statin based, the role of add-on therapy and combination therapy is an exciting area of research. Physicians can only expect to solve the problem of major cardiovascular events by undertaking a global approach.

Accurate measurement of three simple lipid components can simplify diagnosis and treatment of all patients physicians are likely to encounter.

- **Low-Density Lipoprotein Cholesterol**—The LDL-C level is most effectively controlled with statins. The addition of the cholesterol absorption inhibitor ezetimibe may be a useful adjunct, especially in patients with diabetes. Resins and dietary alterations may also contribute to success. The goal of secondary prevention is to attain an LDL-C (direct) in the range of 68 mg/dL to 72 mg/dL. According to the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial,\(^6\) this is the blood level that seems to correspond to complete arrest of atherosclerotic disease progression.

In the Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID),\(^7\) achieving an LDL-C level in the range of 60 mg/dL (with perhaps a 15% increase in the HDL-C level) may actually allow for regression of plaque.

- **High-Density Lipoprotein Cholesterol**—Niacin, available as a food supplement or in a prescription-strength form, is the most potent agent available for increasing the HDL-C level. Presently, there is no therapeutic alternative to the flush-associated form of niacin. There-

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**Figure 1. Potentially modifiable risk factors identified by the INTERHEART study that increase a person’s probability of having a heart attack.** Source: Yusuf S, et al; INTERHEART Study Investigators. Lancet. 2004;364:937-952.

**Risk Factors**

- Apolipoprotein A/apolipoprotein B cholesterol (odds ratio 3.25)
- Cigarette smoking (odds ratio 2.87)
- Hypertension (odds ratio 1.91)
- Diabetes mellitus (odds ratio 2.37)
- Abdominal obesity (odds ratio 1.62)
- Psychosocial (odds ratio 2.67)
- Exercise (odds ratio .86)
- Eat fruits and vegetables (odds ratio 0.70)
- Alcohol consumption (odds ratio 0.91)
fore, initiating niacin therapy may be challenging; however, devoting time to patient instruction and education can help accomplish successful initiation in more than 80% of patients. Smoking cessation, exercise, and a weight reduction program can augment niacin’s effectiveness in increasing HDL-C levels.

- **Triglycerides**—To reduce clinical cardiovascular events, triglyceride concentrations are most effectively managed with fish oils (omega-3 fatty acids). The active ingredients of fish oil are eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA). These active ingredients have a dual level of therapeutic effectiveness. The level of these agents necessary to lower the risk of sudden cardiac death is 1000 mg of EPA plus DHA. A combined level of at least 4000 mg of EPA plus DHA (without any other cholesterol-lowering agents) is necessary to effectively lower triglyceride concentrations. Current levels of 875 mg EPA plus DHA is the only FDA-approved, pharmacologic-grade fish oil supplement.

The most potent food supplement fish oil combination (GNC’s triple-strength fish oil) has 900 mg of EPA plus DHA. This food additive has the advantage of being readily available both locally as well as on the Internet.

**Cigarette Smoking**

Tobacco abuse or cigarette smoking remains a worldwide problem. The data from a recent Norwegian case-controlled study reported at the European Society of Cardiology meeting should help physicians convince patients of the danger of cigarette smoke. In a study population of 1784 consecutive patients presenting with an initial MI, the average age among men was 63.9 years for current smokers, 74.7 years for ex-smokers, and 72.2 years for nonsmokers. In women, the age difference was far greater; the first MI occurred at age 66.2 years in current smokers, 74.4 years in ex-smokers, and 80.7 years in nonsmokers. Women who smoked have their first MI 14.5 years prematurely, while men who smoked had the first MI 8.3 years earlier than nonsmokers.

On July 1, 2003, the city of Pueblo, Colo, passed a municipal smoking-free ordinance. The rate of acute MIs dropped from 257 per 100,000 person-years in the 18 months before the ordinance’s implementation to 152 per 100,000 person-years in the subsequent 36 months. This 41% reduction in the heart attack rate in Pueblo is only part of the data beginning to emerge that raises concern that it is about time, as a society, to consider severely limiting exposure to tobacco smoke, not only as an individual’s decision, but as a significant, modifiable contributor to the overall population’s cardiovascular risk.

New therapeutic agents coupled with aggressive re-education programs are now available to help fight the addiction to tobacco smoking. Clinical data would now support the concept that nothing short of complete elimination (also including exposure to second-hand smoke) should be the goal. Agents that clinical trials have demonstrated to be effective in smoking cessation include bupropion hydrochloride and transdermal nicotine patches used individually or in combination.

Several published clinical studies have demonstrated that varenicline may be the most effective agent to assist in cessation from tobacco abuse. However, physicians need to balance the reported risks of this agent (ie, changes in behavior, agitation, depressed mood, and suicidal thoughts) against the benefits of eliminating tobacco exposure.

When considering prescribing varenicline, it is helpful to institute a policy for the patient to complete the Patient Health Questionnaire 2 (PHQ-2) to screen for depression. One of the reported side effects of varenicline has been depression that has rarely led to suicide. Establishing a baseline psychological profile may be valuable to allow better decisions in approaching patients’ smoking cessation problem. Because depression in itself is a cardiovascular risk factor, an office policy to screen for its presence would seem to be sensible.

**Hypertension**

Management of hypertension affords physicians several opportunities to control cardiovascular risk. Research in hypertension has dramatically expanded awareness that diagnosis and adequate blood pressure control are essential components of any risk-reduction program.

It is the severity of hypertension (either systolic or diastolic), coupled with its duration (time), that results in an increased risk of stroke. The primary benefit of successfully controlling blood pressure has been established to lower the risk of cerebrovascular disease (ie, strokes, transient ischemic attacks) as well as to protect kidneys from deterioration to avoid kidney failure, which can lead to the need for dialysis.

The Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attacks Trial (ALLHAT) documented two important conclusions:

- The patient who has high blood pressure will need, on average, at least three different classes of drugs to control it. Searching for one “magic” blood pressure agent is not likely to be successful, and may add unrealistic expectation on the part of the patient. If that patient also has comorbid diabetes mellitus, achieving optimal control of hypertension will require an average of five different agents.

- The ALLHAT established that it is not scientifically sound to use an α-blocker as the sole antihypertensive agent. Other classes (angiotensin receptor blockers [ARBs], β-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors [ACEIs]) have been shown to have superior effectiveness in preventing damage to the kidneys and cardiovascular system as well as reducing major adverse cardiac events.

A patient’s comorbidities may determine which particular class of antihypertensive medication should be used to initiate therapy. For patients in whom the metabolic syndrome or diabetes has been diagnosed, it would be prudent to use an ACEI or an ARB as part of the mix.

The diagnosis of heart failure should influence physicians to consider the use of a β-blocker such as carvedilol combined with one of the angiotensin active agents.
Spironolactone or epleronone should be considered as the diuretic of first choice in patients with heart failure. Emerging data support the use of spironolactone in patients who have sleep apnea.

**Diabetes Mellitus**
Diabetes mellitus has been identified as a cardiovascular risk equivalent, thus warranting physicians’ close attention to its diagnosis and treatment of patients in whom it has been diagnosed. Use of an ARB or an ACE as first-line antihypertensive therapy in patients with diabetes may provide maximal protection of the kidneys. Screening for microalbuminuria, coupled with optimal hypertension control, can avert deterioration of renal function and help patients divert from the need for renal dialysis.

**Abdominal Obesity**
Abdominal obesity and the metabolic syndrome are emerging as a worldwide epidemic attributable to the global spread and acceptance of the fast food culture. The result has been a frightening propagation of obesity in the United States and a worldwide tendency toward an overweight population. This tendency seems especially prevalent in children and adolescents throughout the world and is aggravated mostly in the emerging nations. This epidemic of obesity has lead to the rapid rise in diabetes, and it threatens to reverse the downward trend in the incidence of CVD deaths and to even eliminate the impressive gains medicine has gained in prevention of CVD during the past 40 years.

Diet and exercise are always important elements in treatment to help prevent MI in at-risk patients. Questions about diet and exercise that can be used in a 3-minute lifestyle interview of patients can be found at http://circ.ahajournals.org/cgi/content/full/113/22/2657.

The key to successful dietary management is to keep the diet prescription simple for the patient (**Figure 2**). The impact of even a small weight loss on risk factors is significant. A 5% weight loss reduces the glycosylated hemoglobin (HbA1c) level, lowers blood pressure and the total cholesterol level, and boosts the HDL-C level. In addition, a 5% to 10% weight loss will lower the triglyceride concentration. **Figure 3** offers some dietary tips for managing lipid levels.

Patients with abdominal obesity often present with one or more additional cardiovascular risk factors and prevention will be successful only when management strategy addresses all of them. Abdominal obesity is associated with other risk factors, but it is also an independent risk factor because adipocytes are metabolically active endocrine organs, not simply inert fat storage molecules.

Abdominal obesity increases the risk of type 2 diabetes and coronary artery disease. It is difficult, if not almost impossible, to institute a successful weight loss program in the setting of sleep apnea. It is therefore important to inquire about signs and symptoms of sleep apnea not only of the patient, but also, if possible, of the spouse or the significant other for an accurate assessment concerning the presence of apneic episodes.

“Meal replacement” is a safe, drug-free, and effective method for treating patients for obesity. A meal replacement is any prepackaged food product such as a shake, pudding, entrees, or snack bar that is portion controlled, calorie controlled, and high nutrition. These products replace an entire meal or snack with the goal of reducing calorie intake and enabling weight loss. Meal replacements have been used in several major trials sponsored by the National Institutes of Health, including: the Diabetes Prevention Program (DPP), Action for Diabetes in Health (Look AHEAD), and the Reach out to enhance Wellness in Older Survivors (RENEW).

Examples of pre-prepared meals include Lean Cuisine (Nestle USA, Wilkes-Barre, Pa), Smart Balance (Smart Balance Inc, Paramus, NJ), and Weight Watchers (Weight Watchers International Inc, New York, NY). These packaged meal-replacement foods are readily available to patients. Health Management Resources (HMR) is a company that not only offers shelf-stable packaged food that patients can buy on-site (www.hmrprogram.com) but also provides weight-loss management program services.

The American Dietetic Association Evidence Analysis library cites eight randomized trials in which patients who replaced one to three meals lost 2.5 kg to 3.0 kg more that those who followed a traditional low-calorie diet. This difference represents about a 7% additional weight reduction, or about double the weight loss realized in traditional plans. A meal replacement, coupled with an exercise program, has the additional potential to actually save money. In a recent study of 118 patients, each of which lost more than 100 pounds, a cost savings of $100/month per patient was traced to a 66% discontinuation of medications used to treat them for comorbidities. Patients who continued to replace at least one meal maintained an average 30 kg weight loss for 5 years.

Data reported by HMR show that over 2 years, a population of 1000 patients had an average weight loss of 43 pounds (www.hmrprogram.com). Laboratory studies showed a 14% reduction in the total cholesterol to HDL-C ratio, a 25% reduction in triglyceride concentrations, and a 10% drop in fasting blood glucose levels. In addition, HMR data also showed that systolic blood pressure dropped an average of 8 mm Hg, and diastolic blood pressure was lowered by an average of 6 mm Hg. One out of 5 patients (21%) was able
to eliminate at least one antihypertensive medication.37

Psychosocial Factors
As many as 20% of the population with cardiovascular risk factors may have depression.38 Early diagnosis and treatment is essential because depression is associated with increased major cardiac events. The American Heart Association (AHA) partnered with the American Psychiatric Association to release a science advisory including recommendations for screening, referral, and treatment of depressed patients with coronary heart disease (CHD).38

The AHA Science Advisory Panel recommends the use of the PHQ-2 to screen for the presence of depressive symptoms.39 This screening tool was developed by the MacArthur Initiative on Depression and Primary Care (www.depression-primary care.org). If patients’ responses are affirmative that they are “feeling down, depressed or hopeless” during the past 2 weeks, “more than half the days,” or “nearly every day,” then a full Patient Health Questionnaire (PHQ-9) should be administered. The PHQ-9 can be used to determine provisional diagnosis of depression, which, in turn, may prompt physicians to consider treatment options that may include antidepressants, referral, or psychotherapy singly or in combination.

Exercise
Exercise has a favorable influence on nearly every cardiovascular risk factor. A useful practice tool is to encourage patients to buy a pedometer as well as keep a diary to document their commitment to the exercise program following the AHA guidelines recommendation of at least 10,000 steps a day.39

If the pedometer’s price represents an obstacle, physicians might consider having their practices purchase a few pedometers. Then, whenever cost becomes a deterrent to their use, physicians can provide these patients with one of the office pedometers. The office should require a credit card imprint and inform these patients that they will be charged for the pedometer only if they fail to return it. This practice tool represents a strong motivational technique that enhances both patient compliance and success in reducing cardiovascular risk.

Eating Fruits and Vegetables
Dietary interventions may hold the key to a simple rational approach to start the process of preventive cardiology. Every mother encouraged her children to “eat your vegetables.” It has now been established that mother truly knew best. Recent data indicate that the two most valuable diets are the Dietary Approaches to Stop Hypertension (DASH) for hypertension and the Mediterranean diet for hyperlipidemia.40-43

Alcohol Consumption
The ingestion of 3 ounces to 5 ounces of alcohol a week rounds out the recommendations from the INTERHEART study.2 The study questionnaire inquired only about total alcohol consumption. Data now available advance our understanding of alcohol’s mechanism of action and direct our recommendation to use alcohol in its most effective form.

Researchers from Italy’s Catholic University have reported that levels of omega-3 fatty acids are increased in the blood and plasma membranes of moderate alcohol drinkers.44 The results of the IMMIDIET study further showed that omega-3 fatty acid levels were higher in wine drinkers than in consumers of beer or spirits, suggesting a possible association between wine components other than alcohol and omega-3 fatty acids. Although alcohol represents a small contribution and may not be appropriate for all patients, it does contribute to the reduction of cardiovascular risk.44

What Physicians Should Not Be Doing—Beyond the INTERHEART Study
The Physicians Health Study II,45 a randomized, double-blind, placebo-controlled, 2×2×2×2 factorial design recently reported its results after 8 years of follow-up. The conclusion of the study is that in a population of 14,641 male physicians, 400 IU of vitamin E taken every day, 500 mg of vitamin C, and a multivitamin taken every day had no effect on cardiovascular events when compared with placebo.

The only major cardiovascular event (MI, death, stroke death, ischemic stroke, CVD death, congestive heart failure, angina, revascularization, and total mortality) that showed an unfavorable increase in the vitamin E group was hemorrhagic stroke (HR=1.74; 95% CI,
1.04-2.91). This study established that vitamin E, vitamin C, and a multivitamin have no place in a comprehensive CVD prevention strategy.46

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)47 reiterates the concept that while screening for homocysteine (Hcy) may reveal some increased cardiovascular risk, the treatment of patients for elevated Hcy levels with folic acid and vitamin B12 did not reduce any major vascular events in the 12,064 post-MI patients recruited to participate.

Despite a 28% reduction in Hcy levels, there was no significant reduction in major cardiovascular events.47 This finding reenforces the previous conclusion of the Norwegian Vitamin Trial (NORVIT),48 which demonstrated a similar lack of effectiveness of vitamins B6, B12, and folic acid to reduce cardiovascular events.

Although screening for Hcy levels may influence initiation of therapy for cardiovascular risk, the use of vitamins B6, B12, and folic acid has no role to play in the plan for reducing major cardiovascular events.

Comment

The knowledge that physicians acquire through the evidence-based medicine documented in this article should be combined with an enthusiastic willingness to institute the techniques discussed. Adherence to the program described here ensures a bright future for preventive cardiology.

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