The Failure of Risk Factor Treatment for Chronic Disease

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Large drug trials have attempted to prove that targeting risk factors such as lipid or glucose levels with pharmacologic agents reduces the risk of important chronic disease endpoints such as cardiovascular events, diabetes, and mortality. Despite hundreds of millions of research dollars spent over many decades, aggressive risk factor treatment of the two most important targets—lipids and glucose—has consistently failed to show benefit in primary prevention.

Patients with metabolic syndrome and diabetes have as high a risk of adverse cardiac events as patients who have had a previous myocardial infarction. Therefore, much focus has been placed on aggressive risk factor reduction. However, as the recent data show, we may have been focusing on the wrong targets—lipids, glucose, and blood pressure, rather than insulin resistance and its primary causes, which are the main drivers of cardiovascular disease, diabetes, dementia, cancer, and most chronic disease mortality. A recent 40-year prospective study of 4857 Pima Indian children found that the most important predictor of premature death was insulin resistance, not hyper tension or hyperlipidemia. Those in the highest quartile of glucose intolerance had a 73% increased death rate compared to those in the lowest quartile.

Recent trials from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Groups published in The New England Journal of Medicine have confirmed that we may not only be ineffective in preventing cardiovascular events, diabetes, and mortality but causing harm by aggressively treating risk factors. Lipids, glucose, and blood pressure were all effectively reduced in these trials. But there was no reduction in morbidity and mortality in any of the trials reported, and there were significant side effects. The question is why.

Chronic disease is the result of complex network of biological disturbances driving systemic neuroendocrineimmune dysregulation induced by the effects of diet, levels of stress and physical activity, and exposure to environmental toxins affecting gene expression. Isolating one risk factor, or even separately treating multiple risk factors, will fail until it is done in the context of addressing the upstream drivers of disease. While dyslipidemia, hyperglycemia, and hypertension are risk factors for chronic disease, they are not the cause of chronic disease. Distinguishing between risk factors and causes is necessary for effective primary prevention and treatment of chronic disease. Treatment must focus on the system, not the symptom. Dyslipidemia, hyperglycemia, and hypertension are symptoms of upstream biological causes. They are the smoke, not the fire. Unless medicine refocuses on treating the system rather than symptoms (risk factors) through a comprehensive clinical and social systems approach that addresses diet, exercise, stress management, and treatment of environmental toxic exposures, medicine will fail to stem the impending tsunami of chronic disease.

Despite the elegant simplicity of single-drug treatment with statins or antihyperglycemic agents, they have not fulfilled their promise of primary prevention. Despite the difficulty of behavior change and lifestyle and environmental treatment, they are the only proven model for preventing chronic disease. Risk factor treatment must be replaced with elimination of the drivers, triggers, and causes of chronic disease. Newer tools supporting behavior change with regular feedback and social networks have proven successful and should be widely adopted in policy and medical practice.

Four recent large trials targeting blood pressure, lipids, and glucose, while effective in lowering the risk factors (lower lipids, glucose, blood pressure), failed to show benefit in reducing primary composite endpoints of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. A dramatic paradigm shift is needed in the targets for primary prevention. The era of individual risk factor reduction must now be supplanted by treatment of the etiology of chronic disease through a systems or functional model of diagnosis and treatment.

The ACCORD study was designed to test the effect of intensive treatment of blood glucose, blood pressure, and plasma lipids on cardiovascular outcomes in 10251 patients with type 2 diabetes who were at high risk for cardiovascular disease. The lipid arm of the ACCORD trial studied 5518 patients over 4.7 years and found that adding fenofibrate to simvastatin showed no benefit in primary outcomes despite improvements in HDL and
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but led to more arterial plaque and no fewer cardiac events.13 Other data also challenge the importance of LDL-C as a cardiovascular risk factor. Using statins to lower LDL-C in patients over 69 years old.10 The eNHANCe trial showed that aggressive treatment with two medications (simvastatin and ezetimibe) lowered cholesterol much more than one drug alone but led to more arterial plaque and no fewer cardiac events.15 Other data also challenge the importance of LDL-C as a cardiovascular risk factor. Using statins to lower LDL-C in patients with low high-density lipoprotein cholesterol (HDL-C) without reductions in inflammation (measured by C-reactive protein) showed no benefit.13,14 Yet this study is touted as proof of the effectiveness of statin therapy in primary prevention through lipid lowering. There is no proven benefit for statins in healthy women with dyslipidemia or in anyone over 69 years old.16 The ENHANCE trial showed that aggressive cholesterol treatment with two medications (simvastatin and ezetimibe) lowered cholesterol much more than one drug alone but led to more arterial plaque and no fewer cardiac events.15 Other data also challenge the importance of LDL-C as a cardiovascular risk factor. Using statins to lower LDL-C in patients with low high-density lipoprotein cholesterol (HDL-C) also reveals no benefit.14 An often-ignored data point is that 50% to 75% of people who have myocardial infarction have normal cholesterol.17 The Honolulu Heart Study showed that older patients with lower cholesterol have higher risks of death than those with higher cholesterol.18

While there is benefit to treatment of those with existing disease with statin therapy for secondary prevention, there is no good evidence for primary prevention. For high-risk males younger than 69 years of age, there is some evidence of benefit, but the number needed to treat is 50 to 100 for reduction of one event.1 The absolute risk reduction is from 2% to 3%. Seventy-five percent of statin prescriptions are written for primary prevention at a cost of more than $20 billion per year. However, the 2004 National Cholesterol Education Program guidelines expanded the previous guidelines to recommend that more people take statins (from 13 million to 40 million) and promote statins for primary prevention (or about 75% of the patients taking statins).17 Eight of the nine experts on the panel who developed these guidelines had financial ties to the drug industry. Thirty-four other non–industry-affiliated experts sent a petition to protest the recommendations to the National Institutes of Health, saying the evidence was weak.

If these medications were without side effects, then we might be able to justify the risk, but they cause myopathy10 (even in the absence of pain and elevated creatine phosphokinase), sexual dysfunction, liver and nerve damage, and other problems in 10% to 15% of patients who take them.19 Recent evidence points to the occurrence of not only myositis, rhabdomyolysis, elevation of serum creatine kinase levels, myalgias, muscle weakness, muscle cramps, exercise intolerance, and persistent myalgias from statin therapy but also asymptomatic myopathy, mitochondrial injury, apoptosis, and neuromuscular injury.20

RETHINKING TARGETS FOR TREATMENT

If the evidence indicates that lowering lipids, glucose, or blood pressure—in other words, aggressively reducing cardiovascular or diabetes risk factors—doesn’t produce the desired outcome, namely, less cardiovascular disease, diabetes, and death, we must wonder what the treatment targets should be.

If lipids are implicated in the development of atherosclerosis, then the right question is not, “How low is the LDL target level?” Rather, the right questions are “What causes lipids to become atherogenic, and how do we treat that?” Conventional methods of lipid analysis are outdated because we now understand that atherogenic particles are small, dense HDL and LDL and large very low-density lipoprotein particles.22 Insulin resistance, oxidative stress, and inflammation cause this atherogenic lipid phenotype, and although statins may lower inflammation marginally, they do not have a significant effect on increasing lipid particle size.

What does reduce total and cardiovascular mortality and diabetes are lifestyle changes including a low glycemic load, phytonutrient-rich, plant-based diet that is rich in omega-3 fatty acids and fiber, and exercise that reduces atherogenic lipid particles, oxidative stress, and inflammation. Niacin also can increase lipid particle size and raise HDL-C and reverse atherosclerotic plaque.23 We use the tools we have, not necessarily the right “medicine” for the problem. The right “medicine” for both preventing and treating heart disease is a healthy lifestyle, which works better than medication. Statin use is not without risk, and the benefit is overstated, especially for its major indication—primary prevention. The question then becomes, “What are the true contributors to cardiovascular disease?”

PRIME CONTRIBUTORS TO CARDIOVASCULAR DISEASE

The interaction of genes, lifestyle, and environment determines risk. This dynamic interaction leads to the primary drivers
of cardiovascular disease, including insulin resistance, inflammation, oxidative stress and inflammation, environmental toxins, and stress.

The data show that preventing heart disease has very little to do with simply lowering LDL cholesterol with statins or intensive glucose or blood pressure lowering. Our current thinking about how to treat and prevent heart disease is at best misguided and at worst harmful. We believe we are treating the causes of heart disease by lowering cholesterol, blood pressure, and glucose with medication. But we are treating surrogate risk factors, not causes. The real question is what causes dyslipidemia, hypertension, and dysglycemia in the first place.

The environment influencing gene expression is what determines risk. In other words, the way we eat, how much we exercise, how we deal with stress, and the effects of environmental toxins are the underlying causes of dyslipidemia, hypertension, and dysglycemia. Those factors—not a lack of medication—are what determine the risk of heart disease.

The research clearly shows that changing how we live is a much more powerful intervention for preventing heart disease than any medication. The EPIC (European Prospective Investigation Into Cancer) study published in the Archives of Internal Medicine studied 23,000 people’s adherence to four simple behaviors (not smoking, exercising 3.5 hours a week, eating a healthy diet [fruits, vegetables, beans, whole grains, nuts, seeds, and limited amounts of meat], and maintaining a healthy weight [BMI <30]). In those adhering to these behaviors, 93% of diabetes, 81% of heart attacks, 50% of strokes, and 36% of all cancers were prevented.

The INTERHEART study, published in The Lancet in 2004, followed 30,000 people and found that changing lifestyle could prevent at least 90% of all heart disease.

These studies are among a large evidence base documenting that lifestyle intervention is often more effective in reducing cardiovascular disease, hypertension, heart failure, stroke, cancer, diabetes, and deaths from all causes than almost any other medical intervention. It is because a healthy lifestyle not only reduces risk factors such as high blood pressure, glucose, and cholesterol; our lifestyle and environment influence the fundamental causes and biological mechanisms leading to disease: changes in gene expression, which modulate inflammation, oxidative stress, and metabolic dysfunction. An unhealthy lifestyle and environment, not a statin deficiency, are the real reasons for cardiovascular disease.

Ignoring or giving lip service to the underlying causes and treating only risk factors is somewhat like mopping up the floor around an overflowing sink rather than turning off the faucet, which is why medications usually have to be taken for a lifetime. When the underlying lifestyle causes are addressed, patients often are able to stop taking medication and avoid surgery.

Dyslipidemia and hypertension are only a couple of many factors that lead to cardiovascular disease, and they may not even be the most important ones. Inflammation and insulin resistance are the primary drivers of cardiovascular disease and are driven by what we eat, how much we exercise, how we deal with stress, and our body burden of environmental toxins. We focus on cholesterol or glucose or hypertension because they are the risk factors for which we have the best medication. As the evidence shows, they may be only the downstream symptoms of a much more important biological process of insulin resistance that must be treated directly. Insulin resistance is a complex metabolic dysregulation that results from multiple insults, including a high-glycemic load, low-fiber, nutrient-poor diet, sedentary lifestyle, chronic stress, environmental toxins, latent infections, and allergens. These factors must be the targets for primary and secondary prevention of chronic disease.

A comprehensive approach to treating the system and not the symptom using a whole-food, plant-based diet rich in omega-3 fats, antioxidants, and phytonutrients; supplements; exercise; stress management; and strategies for treating chronic low-level environmental toxicity can have a dramatic impact on the risk of heart disease. And there is a good side effect—this approach reduces the risk of nearly all chronic diseases.
22. Cziraky MJ, Watson KE, Talbert RL. Targeting low HDL-cholesterol to decrease residu-


25. Ford ES, Bergmann MM, Kriger J, Schienkarwitz A, Weikert C, Boeing H. Healthy liv-
