View Point

Primum Non-Nocere – Are We Helping or Hurting Patients with Borderline Abnormalities with Aggressive Drug Therapies in the Name of Prevention?

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For centuries medical students have been taught "Primum non-nocere" or translated "Do no harm." The cornerstone to preventive medical care is to prevent problems as much as possible so as to enhance people's quality of life and improve longevity. Yet, with our aggressive pharmacological intervention in patients with borderline problems are we doing more harm than good?

Illnesses that are the result of lifestyle excesses are the particular focus for pharmacological treatments. In the modern world we eat too much, sit too much, and worry too much! This leads to common problems of obesity, diabetes, hypertension, dyslipidemias, osteoporosis, and just plain mental lethargy. Because people want quick fixes to their problems they see doctors to get pills and have procedures. Today many people are influenced by television commercials from drug companies to "Ask your doctor for this drug" campaigns. Doctors are also strongly influenced by drug companies in prescribing habits through marketing efforts by such companies and funding of their research projects by these companies. There is a strong financial incentive for pharmaceutical companies not to cure but to maintain so that patients stay on medications indefinitely.

The diagnostic standards of what is considered "disease" are frequently lowered to include more people at an earlier stage. This leads to earlier pharmacological therapy. However, pharmacological therapy to treat patients with borderline abnormal laboratory values may not have the same beneficial results as lifestyle improvements. Pharmacological treatments stress more and more proactive preventive treatments; but, this aggressive preventive approach is not often based on scientific facts. Often less medication might be better.

Let us review some examples.

First, lowering cholesterol levels has been the main target for prevention of coronary atherosclerosis for many years. In general the treatment recommendation is to get the low-density lipoprotein cholesterol (LDL-C) as low as possible. Epidemiology studies (1) demonstrated that populations that have higher cholesterols have higher incidence of heart attacks, thus the recommendation to lower cholesterol levels whenever possible. However, it must be remembered that not all individuals with high cholesterol get heart disease and that not all patients with low cholesterol are free from heart disease. In fact at the time of heart attack most people do not have markedly elevated cholesterol levels. We now know that coronary inflammation combined with abnormal clotting is the main precipitant for most heart attacks. In other words, the adverse affects of elevated cholesterol may be secondary rather than primary in causing increased heart attacks.

Statin medications have been the main treatment drugs used to lower LDL-C. Statin therapy is very helpful for patients who have hereditary dyslipidemias; however, most people have elevated cholesterol levels as the result of eating an unhealthy diet. Statins can dramatically lower cholesterol levels. This makes both patients and doctors happy. Most people prefer to just take a pill rather than dealing with dietary excesses. Also, physicians prefer to be active prescribing medications rather than trying to motivate patients toward positive dietary and lifestyle changes, which is often more difficult.

It must be remembered that statin therapy is not without risk of significant potential side-effects. These side-

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effects are often under-reported or ignored by treating physicians. The most common side-effects are muscle soreness and fatigue. This can actually limit exercise, which is an important modality in preventative health. On occasion statins can cause severe muscle damage and kidney failure (rabdomyolysis). This may be as a result of taking excessively high doses of statins or interaction with other drugs. Statins can also interact with a wide range of other medications to cause side-effects from those combinations of medications.

On the plus side, statins were shown many years ago to lower recurrent heart attacks in patients with known heart disease (2). It is important to remember that the biggest benefit of statin use was in people who already had a previous heart attack. Using this data, the indications for statin therapy were rapidly expanded to promote their usage for primary prevention in persons with high cholesterol who were otherwise healthy and had no history of heart disease. The goal was to get everyone's LDL-C level below 100 mg/dL. The sales for statins soared while dietary indiscretions mostly continued in patients. Was taking a statin helping them to live better or longer?

A significant study questioning the widespread use of statins was finally published in 2010 by Ray et al. involving 65,229 participants (3). It was meta-analysis of 11 different clinical trials. The participants all had borderline elevated LDL-C, but no history of previous heart disease. The analysis demonstrated that statin therapy does work to lower LDL-C levels. The statin-treated group did change potentially harmful LDL-C levels from average 139 to 98 mg/dL (once again desirable level was considered less than 100 mg/dL). Surprisingly, however, in spite of effective lowering LDL-C with medications this did not result in any significant reduction in mortality! This study was a major blow to the liberal usage of statin therapy for primary prevention.

So how might we identify which patients are truly high risk and may or may not benefit from preventive statin therapy?

Since coronary atherosclerosis is a relatively symptom-free disease until it is far advanced earlier identification of significant atherosclerosis that is more than expected for age has proven to be helpful. Thus electron beam computer tomographic (EBCT) heart scanning was developed to identify and quantify the amount of coronary atherosclerosis in patients at risk for heart attacks. Basically, patients that have higher amounts of coronary calcifications seen on heart scans have increased risk for coronary death. The presence of coronary calcifications, which is atherosclerosis, is a better predictor of death than any cholesterol level (4). Furthermore, it demonstrated that patients who were free of coronary calcifications on heart scan had only 0.1% chance of coronary death regardless of what the cholesterol level was. These same patients had a 20–30% chance of having side-effects from the statin medication (5). Does it make sense to try reducing the risk of a heart attack by less than 0.1% with a statin when the risk of having a side-effect from the medical treatment itself is 20–30% (not to mention the yearly expense of statin medication that is not needed if there is no significant coronary atherosclerosis)?

In spite of these studies use of statins for primary prevention in low-risk patients remains high.

What about correcting other risk factors for heart disease like hypertension or diabetes?

It has long been known that people who have blood pressures greater than 140 mmHg systolic and 90 mmHg diastolic have an increased risk for heart attacks, strokes, and kidney failure. Keeping blood pressure below these levels have been the traditional goal of pharmacological therapy. Hypertensive diabetics are particularly prone to increased cardiovascular mortality. Given this data there was enthusiasm for more aggressive lowering of blood pressure with medications to get systolic levels lower than 120 mmHg.

Did this reduce mortality?

The ACCORD study (6) studied patients with high blood pressure and diabetes. It compared lowering systolic blood pressure to either below 120 mmHg as compared to patients where systolic pressure was just lowered below 140 mmHg. The results demonstrated no significant difference in mortality; however, the adverse reactions to side-effects of antihypertensive medication were twice as high in the more intensively treated group than the standard treated group.

A better long-term therapy for many patients with borderline blood pressure is weight reduction, salt and alcohol restriction, and meditation relaxation. However, these lifestyle options are frequently not emphasized enough by physicians who are quick to give medications and just follow-up on numbers.

Another analysis of 6400 participants in the INVEST study (7) demonstrated that lowering systolic pressure lower than 130 mmHg in diabetic patients with coronary artery disease actually increased mortality 15–20% compared to patients who were treated to get systolic pressure below the standard 140 mmHg systolic pressure. These studies are disturbing for the advocates that lower blood pressure are always better and that more medicine is better than less.

Furthermore, tight control of blood glucose with medications has been promoted to lower cardiovascular disease in patients with diabetes. This makes sense since diabetics that have lower glucose levels tend to have lower incidence of heart disease. (This is probably from more disciplined diet and exercises that result in natural lowering of insulin levels in patients with insulin resistance).

Once again the ACCORD study found that tight control of diabetes may be more harmful than traditional control of diabetes. Glycolated hemoglobin called HbA1c is a useful measurement to assess chronic levels of glucose. A level of greater than 6.5% is considered diabetic by the International Diabetes Association. Newer preventive strategies have been to try to get HbA1c below 6% in diabetics so as to reduce long-term complications of the disease. The ACCORD study demonstrated that HbA1c lower than 6% with medications actually increased mortality rates by 22% when compared to less vigorous standard therapy to get HbA1c levels between 7% to 7.9%.

Here again the standard for disease was lowered and resulting therapy did more harm than good.

Even the mainstay usage of aspirin therapy to prevent cardiovascular incidents in patients should be questioned. If patients do not have significant atherosclerosis they might not have significant benefit from daily aspirin usage (8). The increased risk for bleeding events often outweighs the benefits if patients do not have known atherosclerosis. Once again the nonpharmacological approach of diet and exercise itself has a positive effect to reduce inflammation and abnormal clotting.

Although medications can be beneficial for treatment of diseases they often do not have the same beneficial result of naturally maintaining desirable lean body mass, blood levels of cholesterol, blood pressure, and blood glucose with appropriate diet and exercise.

In our exuberance to help patients we must not be seduced by the shortcuts of pharmacological therapies. The obvious way to treat excesses is to get rid of the excesses. We need to eat less, sit less, and worry less! A prudent diet and a disciplined exercise program needs to remain our first preventive recommendation for everyone. Medications are very beneficial when you need them; however, by taking an overly aggressive pharmacological approach to prevention and giving only a token effort to diet and exercise we are often breaking the golden rule of Primun non-nocere.

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