How to Prevent A Broken Heart

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Although physicians have been successful in reducing the incidence of cardiovascular disease (CVD), it is still the number-one killer according to the American Heart Association's 2002 *Heart and Stroke Statistical Update*. The reason is that our population is getting older. Americans have aged into their heart disease. Future efforts to reduce death and disability from heart disease are jeopardized by a growing worldwide epidemic of obesity and sedentary activity coupled with the increasing incidence of diabetes (DM). This *Heartbeat* will cover the risks presented by obesity, the metabolic syndrome and DM along with a treatment plan to prevent DM and reduce the incidence of CVD.

NCEP ATP III

The recently released National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines have an increased focus on primary prevention.[1] While patients at highest risk are still those with known coronary heart disease (CHD) or other vascular disease, the new guidelines recognize CHD risk equivalents that raise the risk for a CHD event in patients without CHD to that of patients with established disease (Table I).

Table I: CHD Risk Equivalents

- Other clinical forms of atherothrombotic disease: peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease
- Diabetes
- Multiple risk factors that confer a 10 year risk for CHD > 20%

All of these patients should have aggressive LDL-C reduction (<100mg/dL). Intensity of therapy should be matched to CHD risk.

Maintaining focus on primary prevention, NCEP ATP III recognizes the metabolic syndrome, also known as insulin resistance syndrome (IRS) or cardiovascular dysmetabolic syndrome CDS), as a secondary target of therapy (Table II). Evidence is accumulating that risk for CHD can be reduced beyond LDL-C lowering therapy by modification of other lipid risk factors (increased TG or low HDL-C) along with diet and exercise.

Metabolic Syndrome – Increased Risk

Table II: Clinical ID of the Metabolic Syndrome*

Risk factor	Defining Level
Abdominal Obesity	Waist Circumference
Men	>40 in
Women	>35 in
Triglycerides (TG)	≥ 150mg/dL
HDL –C	
Men	<40mg/dL
Women	<50mg/dL
Blood pressure	≥130/≥85mmHg
Fasting glucose	≥ 110mg/dL

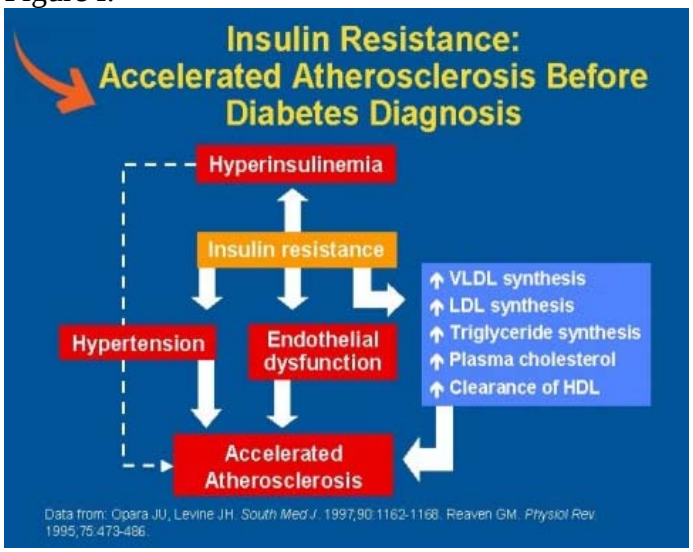
*Diagnosis is dependent on 3 or more

Other factors associated with the metabolic syndrome or the IRS that have been identified are (1) increased plasminogen activator inhibitor (PAI-1) levels, (2) tumor necrosis factor α, (3) C reactive protein (CRP), (4) increased free fatty acids (FFA), (5) polycystic ovarian syndrome and (6) small dense LDL-C.

Excess body fat and physical inactivity promote the development of insulin resistance, clinically diagnosed with android (central obesity), acanthosis nigricans (hyperpigmentation) and acrochordons (skin tags).

All of the components of IRS are in themselves independent risk factors for CVD events. The risk factors of this syndrome act synergistically to accelerate the progression of disease and enhance the risk for a CHD event at any given LDL-C level. IRS antecedes frank, overt DM by years if not decades.[2] Unfortunately, by the time the diagnosis of DM is made, the attendant CV risks of accelerated atherosclerosis have already been established (Figure 1), increasing the risk of events and worsening the prognosis CVD.

Figure I.



The increased risk of CHD in DM is significant. Nearly 75% of deaths among diabetics are attributable to CHD (more broken hearts), and type II DM is associated with a two (men) to fourfold (women) increased risk of CHD.[3]

Big, Bad News: Obesity in Younger People Increases Risk of Early MI

The American Heart Association recently classified obesity as an independent risk factor for DM.[4] Being obese or overweight greatly increases chances of having an MI at an earlier age according to researchers from the Mayo clinic.[5] The authors write, "Even after adjustment for confounding variables, obese patients were likely to present with MI nearly a decade younger than normal weight patients." Overweight and obesity are directly associated with insulin resistance and the metabolic syndrome and the resultant increased risk.

Prevention

DM is a serious, costly disease affecting approximately 8 % of adults in the US.[6] Treatment prevents some of its devastating complications but does not eliminate all adverse consequences. The diagnosis is often delayed until complications are present. Since risk of CV complications are so high and treatment remains inadequate, *prevention is preferable*. The following three treatment modalities work through the amelioration of endothelial dysfunction, the common denominator of all high-risk states.[7]

Diabetes Prevention Program: Lifestyle change, metformin treatment prevent progression to type II DM

The long awaited results of the **D**iabetes **P**revention **P**rogram (DPP) show a dramatic 58% reduction in new type II DM with an intensive lifestyle intervention program focused on weight loss with diet and regular exercise, and a 31% reduction with metformin (Glucophage-Bristol-Myers Squibb) treatment, among patients at high risk for developing the disease (i.e. metabolic syndrome).[8] The researchers estimate that about 10 million Americans resemble DPP participants and that, if the study's interventions were implemented, there would be a substantial reduction in the incidence of DM (7 patients treated with lifestyle intervention or 13.9 with metformin to prevent 1 case). The results corroborate a similar (intensive lifestyle intervention) Finnish diabetes prevention study.[9]

The authors feel that type II DM can be prevented by either lifestyle modification, which is particularly effective, or metformin in high-risk patients, regardless of gender, age or ethnic group. This study is ongoing and CV outcomes data will be forthcoming.

ACE inhibitors to prevent DM? Wait for DREAM to come true

Several studies have shown the cardio and renal protective effect of ACE inhibitors in subgroups of patients with DM, including those with prior MI, hypertension, and left ventricular dysfunction or heart failure. A new analysis of the **H**eart **O**utcomes **P**revention **E**valuation (HOPE) trial[10] indicates that the tissue ACE inhibitor ramipril (Altace – King pharmaceuticals) reduces the risk of new diagnosis of DM among high-risk individuals with no previous history of DM.[11]

Yusuf and colleagues are the first to admit that their findings, based on prospectively collected data, but not a primary or secondary endpoint of the HOPE trial, need further investigation. To this end, they have begun the **D**iabetes **RE**duction **A**ssessment with **R**amipril and **R**osiglitozone **M**edication (DREAM) trial, with a target enrollment of 4000 people with no DM at baseline. It will evaluate the effects of ramipril and rosiglitozone (one of the thiazolidinediones [TZDs]—a drug class that has several non-hypoglycemic effects that offset IRS decreasing the development of DM) in people with impaired glucose tolerance, with a follow-up of 5.5 years.

ACE inhibitors should be used as a first line treatment in high-risk patients (CHD, any vascular disease, HF, DM, and renal disease). For the present, because of improvements in endothelial dysfunction (ED)—(secondary to increased bradykinin and increased plasminogen activator etc.), the proven outcome benefits and the possible reduction in incidence of DM, ACE inhibitors should be considered for first line treatment of hypertension in IRS.

Statins for Prevention of DM?

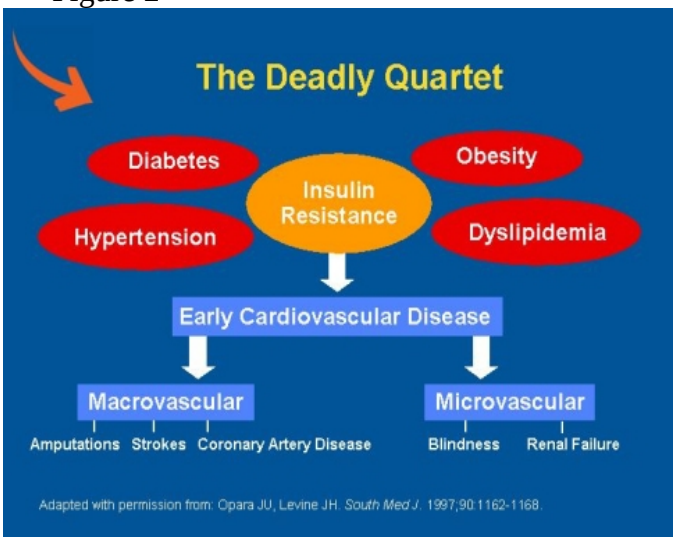
The benefits of the statins for primary and secondary prevention of CVD events are documented and well known. Statin benefits are thought to be due to their LDL-C lowering effects and their more nebulous non-lipid lowering effects (improvement of ED). Lesser known is the decreased incidence of DM in people treated with statins in some of the sub-analysis of the primary prevention studies.[12] Statins should be another therapy considered for treatment in these high-risk patients.

And the Point is……

In the drive to prevent CV events, it appears that the earlier we identify the risk, the greater the potential benefit of treatment. These steps will help identify those at risk, prevent the development of DM and subsequent increased CV risk.

1) Identify patients with a constellation of risk factors ("The Deadly Quartet"—Figure 2) that include abdominal obesity atherogenic dyslipidemia (high LDL-C, high TG and low HDL-C), hypertension, and insulin resistance (i.e. metabolic syndrome (IRS) which frequently precedes the diagnosis of DM).

Figure 2



2) Initiate therapeutic lifestyle changes including diet, weight reduction and increased physical activity, with the combined objective of reducing underlying causes of the metabolic syndrome and preventing the development of DM and it's underlying increased CV risk.

3) Consider adding metformin if needed for those refractory to weight loss.

4) Many endocrinologists including Dr Haenal feel that TZDs should be added early when IRS is identified.

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5) Definitely consider adding an ACE inhibitor especially as first line treatment for hypertension, adding other medication as needed to reach a goal blood pressure of <130/85).

6) Use statins aggressively, to get to a minimum goal LDL-C of < 100mg/dL. Consider these even in those without high LDL-C to assist in correcting high TG and low HDL-C because of their other beneficial effects. If TG or HDL-C goals are not reached with a statin, consider adding niacin or a fibrate to increase low HDL-C or decrease high TG. A just released study demonstrates that combination statin-fibrate and-statin niacin regimens are safe, well tolerated in most patients, and quite effective in managing dyslipidemias in most patients at risk for CV events who are inadequately treated with one of these agents alone. [13]

This proactive approach could prevent a lot of broken hearts.

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