

Mortality and adverse event reduction with lifestyle modification

Randomized trials of secondary prevention programs in CHD: A systematic review

- 12 trials with 9,803 patients
- Summary risk ratios were:
 - 0.91 (0.79-1.04) for all-cause mortality
 - 0.94 (0.80 – 1.10) for recurrent myocardial infarction
 - 0.84 (0.76 – 0.94) for admission to a hospital
- “Disease management programs improve processes of care, reduce admissions to hospital, and enhance quality of life or functional status in patients with coronary heart disease.”

The INTERHEART Study

- Standardized case-control study of myocardial infarction in 52 countries on every continent
- 15,152 cases and 14,820 controls were enrolled
- Nine risk factors measured:
 - Daily consumption of fruits and vegetables
 - Smoking
 - Lipids (ApoB/ApoA1 ratio)
 - Hypertension
 - Psychosocial factors
 - Abdominal obesity
 - Diabetes
 - Alcohol consumption
 - Exercise

Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study). Lancet. 2004;364:937-52.

The INTERHEART Study

- Collectively, these nine risk factors accounted for 90% of the population attributable risks in men and 94% in women
- These associations were noted in men and women, old and young, and in all regions of the world.
- “Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity account for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions. This finding suggests that approaches to prevention can be based on similar principles worldwide and have the potential to prevent most premature cases of myocardial infarction.”

Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study). Lancet. 2004;364:937-52.

Complications of bypass surgery and angioplasty increase with age, whereas the benefits of diet and lifestyle modification occur as much in older as younger patients.

Thus, diet and lifestyle changes are especially beneficial for Medicare patients.

Post Bypass Surgery Mortality

Hospital stays, complications, and mortality following coronary bypass surgery all increase in direct correlation to age.

Peigh et al. Ann Thorac Surg 1994;Nov;58(5): 1362-7.

Post Bypass Surgery Mortality

Mortality difference following coronary bypass surgery is 5.5% for the elderly vs. 1.0% in younger patients during the first 5 days following bypass surgery.

Paone et al. Circulation 1998; Nov. 10;98 (19 suppl): 1141-5.

Post Angioplasty (PTCA) Mortality

The conclusions of a 10 year follow up study of 21,516 patients aged 50-79:

- "Age was the most important correlate of death after PTCA, with a 65% increase in hazard of death for each 10 year increase in age.
- Age has an independent effect on early and late survival after PTCA.

Taddei CF et al. Am J of Cardiology 1999; Aug; 84(3): 245-51.

Complications with Stents

Elderly patients, post PTCA with stent, have higher:

- Mortality (2.2 vs. 1.2%)
- Myocardial infarction during stent placement (2.9 vs. 1.7%)
- Emergency CABG (3.7 vs. 1.4%).

De Gregario et al., J Am Coll Cardiol. 1998; Sep; 32(3): 577-83.

Post PCI (Percutaneous Coronary Intervention) Angina

After PCI, chest pain may occur in as many as 50% of patients.

Sidney Smith, MD et al, ACC/AHA Guidelines for Percutaneous Coronary Intervention, Circulation. 2001;103:3019

“Lifestyle modification is the nationally recognized, first-line treatment of choice for primary and secondary cardiovascular risk management.”

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002; 106: 3143–3421.

Bypass and angioplasty compared to lifestyle and risk reduction therapies

Intensive risk management is
equivalent or better than
bypass surgery or angioplasty
for the treatment of heart
disease in stable patients.

Coronary Artery Surgical Study (CASS)

- 24,958 patients with ischemic CAD
- Randomized to CABG & medical therapy
- 16 year follow up
- Only 2.1% of bypasses yield improved mortality – only in those with left main and left main equivalent disease *and* poor left ventricular function

Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASS experience. *Circulation*. 1995;91:2325-34.

PTCA vs. Lipid-Lowering Therapy: The AVERT Trial

- 341 patients who had been referred for PTCA were randomly-assigned to receive either lipid-lowering therapy or PTCA
- Patients had stable CAD, normal LVEF, low symptoms or asymptomatic, LDL>115
- 18 month follow-up.

AVERT Results:

- 13% of patients receiving lipid-lowering therapy but 21% of patients who underwent angioplasty had ischemic events (PTCA, repeat PTCA, CABG, or unstable angina)
- There were 36% fewer ischemic events after lipid-lowering therapy than after angioplasty
- “In patients with stable coronary artery disease, aggressive lipid-lowering therapy is at least as effective as angioplasty and usual care in reducing the incidence of ischemic events.”

Pitt B et al, NEJM 1999;Jul 8; 341(2): 70-6.

PTCA vs. Lipid-Lowering Therapy: The TIME trial

- Patients aged 75 years or older – one year follow up – PTCA vs. lipid-lowering therapy
- 282 patients with Canadian Cardiac Society class 2 or higher angina despite treatment with 2 or more anti-anginal drugs
- 1-year mortality and death or nonfatal myocardial infarction rates were not significantly different between the groups.
- This study shows equivalent outcomes in PTCA versus medical therapy in the Medicare population.

Pfisterer M, Buser P, Osswald S, et al. JAMA. 2003;289:1117-23.

PTCA vs. Exercise

- 101 male patients ages ≤ 70 years, post PTCA
- Randomized to 12 months of exercise training (20 minutes of bicycle ergometry per day) or to PTCA.
- Exercise training was associated with a higher event-free survival (88% versus 70% in the PTCA group, $P = 0.023$)
- “Compared with PTCA, a 12-month program of regular physical exercise in selected patients with stable coronary artery disease resulted in superior event-free survival and exercise capacity at lower costs, notably owing to reduced re-hospitalizations and repeat revascularizations.”

Hambrecht R, Walther C, Mobius-Winkler S, et al. *Circulation*. 2004;109:1371-8.

Summary

- Angioplasty (including stents) has never been shown to prolong life or prevent heart attacks in stable CHD patients
- Bypass surgery prolongs life only in 2-3% of patients with severe left main coronary artery disease and poor left ventricular function. These patients are excluded from this lifestyle program.

Summary

- These findings are consistent with the latest understanding of the pathophysiology of CHD, which reveals that the less severe coronary artery lesions are more likely to cause MI and sudden cardiac death than the more severe ones, and these moderate lesions are not bypassed or angioplastied.
- In contrast, diet and lifestyle interventions, as well as lipid-lowering drugs, affect *all* lesions.

Ornish D. "Intensive Lifestyle Changes in Management of Coronary Heart Disease. In: Braunwald E. *Harrison's Advances in Cardiology*. New York: McGraw Hill, 2002.

Summary

- Thus, an evidenced-based approach reveals that the most justifiable reason for undergoing revascularization is to reduce angina.
- However, this reduction in angina can be accomplished to a greater degree in only a few weeks (91% reduction in angina) by making comprehensive lifestyle changes with much less trauma and at lower cost.

Ornish DM, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary atherosclerosis? The Lifestyle Heart Trial. *The Lancet*. 1990; 336:129-133.

Summary

- At best, revascularization provides a temporary benefit, but lesions tend to reocclude and/or restenose.
- In contrast, diet and lifestyle interventions, as well as lipid-lowering drugs, cause continued regression of coronary atherosclerosis over time.

Ornish D. Concise Review: Intensive lifestyle changes in the management of coronary heart disease. In: *Harrison's Principles of Internal Medicine* (online), edited by Eugene Braunwald et al., 1999.

Summary

- Therefore, comprehensive lifestyle changes are equivalent or superior to PTCA and CABG for reducing angina and event rates at lower costs and morbidity

Ornish D. Concise Review: Intensive lifestyle changes in the management of coronary heart disease. In: *Harrison's Principles of Internal Medicine* (online), edited by Eugene Braunwald et al., 1999.

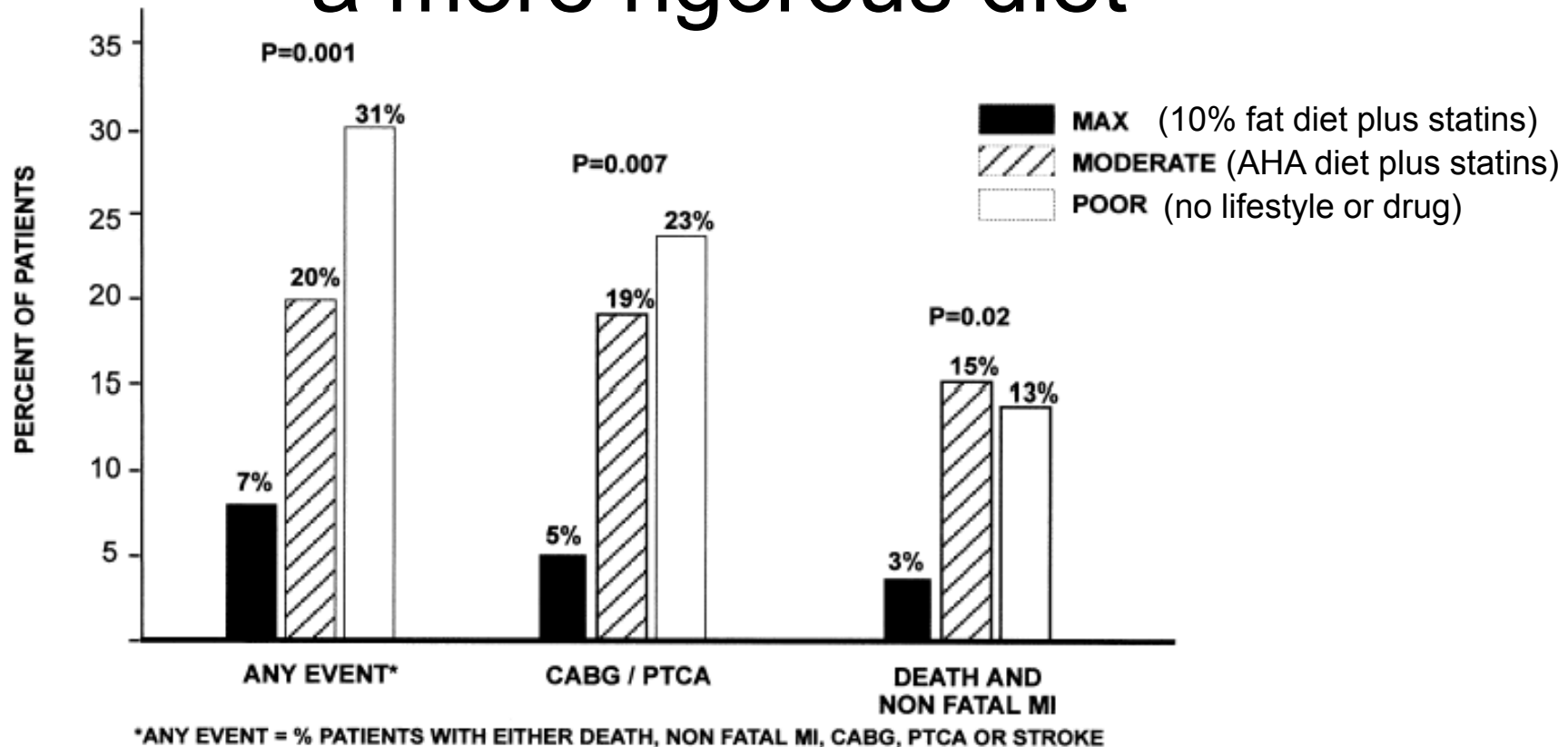
Event and mortality reduction:
very low fat diet

Low fat diet

- 409 patients with CHD, observational study
- 5 year follow-up for cardiac events
- Categorized blindly
 - “poor” treatment without diet or lipid drugs, or smoking
 - “moderate” treatment on AHA/NCEP 30% fat diet and lipid-lowering drugs or strict low-fat diet (10% of calories) without lipid drugs
 - “maximal” treatment with diet 10% of calories as fat, regular exercise, and lipid active drugs

Sdringola S, Nakagawa K, Nakagawa Y, et al. *J Am Coll Cardiol.* 2003;41:263-72.

The relative gains of a more rigorous diet



Coronary event rates were 30.6%, 20.3% & 6.6% for groups 1-3

Death rates were 13%, 15% & 3.3% for groups 1-3

Improvements in perfusion by PET (reversal) only occurred with maximal therapy

Sdringola S, Nakagawa K, Nakagawa Y, et al. *J Am Coll Cardiol.* 2003;41:263-72.

Event and mortality reduction: exercise

Exercise and decreased mortality in women

- 5,721 asymptomatic women who underwent baseline examinations in 1992, mean age at baseline was 52 ± 11 years, Follow up in 8 years
- The Framingham Risk Score—adjusted mortality risk decreased by 17% for every 1-MET increase in that time frame

Exercise and decreased mortality in men

- 6213 men referred for treadmill exercise testing for clinical reasons
- Exercise capacity is a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease.
- Each 1-MET increase in exercise capacity conferred a 12% improvement in survival.
- PMRI lifestyle program improved MET level by 2.7 (10.1 to 12.8), therefore, predicted mortality risk reduction = $12 \times 2.7 = 32.4\%$

Myers J, Prakash M, Froelicher V, et al. NEJM, 2002;346:793-801.

Predicted mortality reduction with exercise benefit due to the PMRI lifestyle program

- In Women
 - The Framingham Risk Score—adjusted mortality risk decreased by 17% for every 1-MET increase
 - PMRI lifestyle program improved MET level by 2 (8.1 to 10.1), therefore, predicted mortality risk reduction = 34%
- In Men
 - Each 1-MET increase in exercise capacity conferred a 12% improvement in survival
 - Lifestyle program improved MET level by 2.7 (10.1 to 12.8), therefore, predicted mortality risk reduction = 32.4%

Event and mortality reduction
depression

Depression and risk of CHD

- 4493 elderly Americans (65 years or older) free of cardiovascular disease at baseline
- Followed for 6 years
- Risk of CHD increased by 40% and risk of death by 60% compared with those who had the lowest mean scores (greatest depression).
- Among elderly Americans, depressive symptoms constitute an independent risk factor for the development of CHD and total mortality.

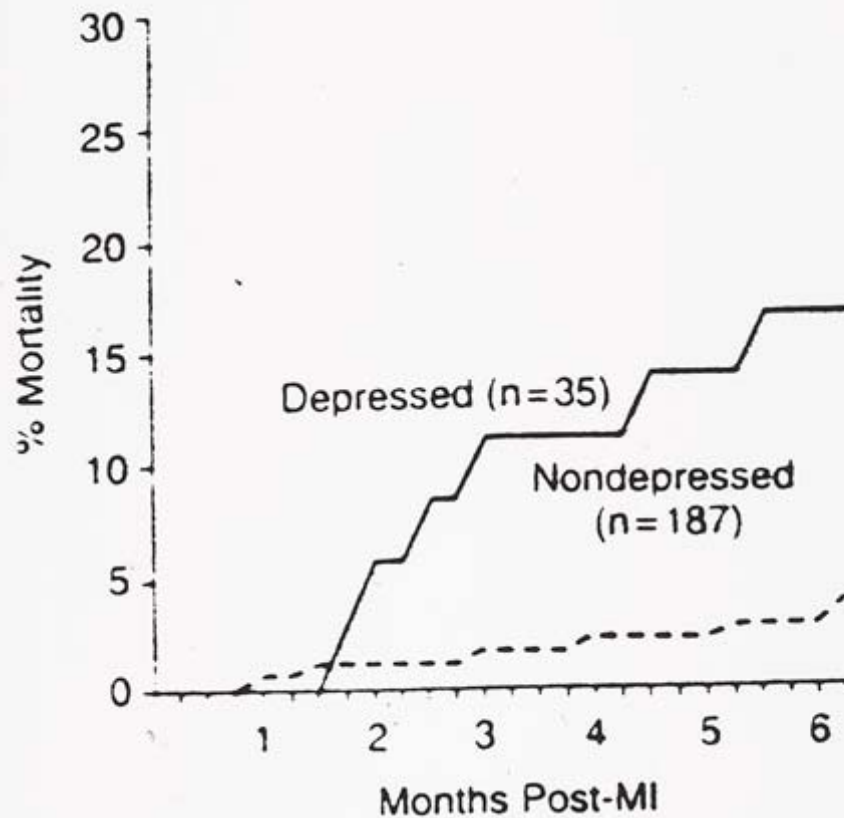
Ariyo AA, Haan M, Tangen CM, et al. *Circulation*. 2000;102:1773-9.

Depression and cardiac events

- 222 patients were interviewed 5-15 days post-MI
- 24-88 years in age, mean = 60 years old
- Depression assessed using National Institute of Mental Health Diagnostic Interview Schedule
- After 6 months, 17% of depressed patients but only 4% of other patients had died, all from cardiac causes
- Depression was a significant predictor of mortality (hazard ratio, 5.74; 95% confidence interval, 4.61 to 6.87; $P = .0006$)

Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. JAMA. 1993 Oct 20;270(15):1819-25.

JAMA 1993; 270:1819-25



Cumulative mortality for depressed and nondepressed patients. MI indicates myocardial infarction.

Depression and cardiac events

- Generally healthy men and women aged 60 years or older over 4.5 years in the SHEP study
- 25% increased risk of death per 5-unit increase in the CES-D score (relative risk [RR], 1.25; 95% confidence interval [CI], 1.15 to 1.36)
- In the 3 demonstration projects, there was a 4-6 unit decrease in the CES-D score

Wassertheil-Smoller S et al, Arch Intern Med 1996; 156(5):553-61.

Predicted mortality reduction with depression benefit due to lifestyle program

- Total average reduction in CESD score in the demonstration projects = 11.6 to 6.5 (43.9%)
- Using the SHEP study findings, this reduction in CESD score predicts a 25% decrease in depression-related mortality due to lifestyle changes

Wassertheil-Smoller S et al, Arch Intern Med 1996; 156(5):553-61.

Event and mortality reduction;
lipid lowering

Lipid lowering in elderly

- The Scandinavian Simvastatin Survival Study (4S Study)
- 827 women and 1021 men 65 years or older
- Simvastatin group: relative risks for clinical events were as follows (based on LDL reduction of 35%):
 - all-cause mortality, 0.66 (0.48 to 0.90)
 - CHD mortality, 0.57 (0.39 to 0.83)
 - major coronary events, 0.66 (0.52 to 0.84)
 - revascularization procedures, 0.59 (0.41 to 0.84)

Miettinen TA, Pyorala K, Olsson AG, et al. *Circulation*. 1997;96:4211-8.

Predicted mortality reduction with lipid control benefit - Lifestyle program

- 62% of “All Participants,” 70% of “65 and Older,” and 87% of “Medicare” patients were taking lipid-lowering medications at baseline.
- Unlike other interventions, medication compliance was maintained at one year (no drop off)
- In “All Participants,” lifestyle changes after one year further reduced LDL from 111 to 101 mg/dl (9.0%)
- This represents an additional predicted mortality reduction of at least 9.0%

Event and mortality reduction;
hypertension control

ALLHAT Analysis

- “First and foremost, the lowering of blood pressure, and not the drug used to achieve this, remains the key variable in preventing future cardiovascular events”
- “BP control, not vascular mechanism of action, is the primary determinant of clinical outcome”

ALLHAT Analysis: Hypertension, What Has It Taught Us So Far?
Canadian Medical Association Journal. 2004;171.

ALLHAT Review Can J Cardiol. 2004 Aug; 20 (Suppl) B: 77-82 B

Controlling hypertension to decrease mortality

- SYST-EUR Study
- N =4695, Over 60 years old, 2 year RCT
- Mixed medical therapy to lower BP
 - Systolic by 10mm, diastolic by 4.5mm
- Event reductions
 - Reduction: Stroke (NF) - 44%
 - Cardiac Endpoints (NF) - 33%
 - MI - 56%
 - CHF - 24%
 - cardiac mortality - 27%

Staessen JA et al; Lancet. 1997; 350: 757-764.

Controlling hypertension to decrease mortality

- STOP Trial (1991)
- 1627, RCT, 70-84 yrs using beta blocker and diuretic
- Drop in systolic/diastolic = 19.5mm Hg/8.1mm Hg
- Relative Risk Reduction*
 - All MI
 - All Stroke
 - Fatal Stroke

* (All statistically significant)

Lancet Nov 23 1991; 339: 1281
0.86
0.53
0.27

Controlling hypertension to decrease mortality

- SHEP study
- 4736; Min age: 60 yrs mean 72 yrs
- RCT, 4.5 years duration
- Treatment Group Reductions:
 - Syst. BP 10 mm more vs placebo
 - Total Stroke Relative Risk 0.64
 - NF MI + Coronary Death
 - Major CV events

0.73
JAMA V 265 No 24, June 26, 1991

0.68

Predicted mortality reduction with hypertension benefit - Lifestyle program

- Lifestyle program effect, in comparable patients with HTN, reduced systolic BP by 19.6 mm Hg and diastolic BP by 9.5 mm Hg
- Estimated benefits based on:
 - SYST-EUR Study – twice the effect on systolic and diastolic
 - STOP Trial – Equivalent outcome
 - SHEP study – twice the effect on systolic and diastolic
- Therefore, the lifestyle program should reduce mortality and cardiac events at least as much as in these three studies

Cardiac rehabilitation and weight reduction

Cardiac Rehabilitation attracts fewer women

- Cardiac rehab programs serve few women (3%)
 - Ades, NEJM, 2001;345:892; Mosca et al, Circulation 1997;96:2468; Franklin et al in Wenger: Women and HD, 1997; Toobert et al, J Women Health 1998; 7: 685
- Lifestyle program serves a greater percentage of women (20-30%)
 - Koertge, Weidner, Elliot-Eller et al. AJC, 2003;91:1316-22

Prevalence of Obesity in Cardiac Patients

- 40% of patients with cardiac disease are obese
- obese patients were younger ($p < 0.0001$) and had more systemic hypertension ($p < 0.01$), and diabetes mellitus ($p < 0.05$) and higher percent body fat ($p < 0.0001$), total cholesterol ($p = 0.02$), triglycerides ($p < 0.0001$), fasting glucose ($p = 0.04$), and low-density lipoprotein (LDL)-high-density lipoprotein (HDL) cholesterol ($p < 0.0001$), but had lower HDL cholesterol ($p < 0.01$) and exercise capacity ($p = 0.07$) than patients not classified as obese

Lavie CJ, Milani RV. Am J Cardiol. 1997 Feb 15;79(4):397-401.

Poor Weight Loss Outcomes in Cardiac Rehabilitation

- 0-2% loss of body weight in standard cardiac rehabilitation programs
 - Mendoza 1991, Lavie, 1995, 1997, Brochu, 2000)
- WHY?
 - Low caloric expenditure (Shairer, 1998)
 - 270 (=/- 112)kcal (Savage, 2000)
 - Absence of behavioral modification strategies (Harvey-Benino, 1998)

Event and mortality reduction:
weight loss

Predicted mortality reduction with weight loss benefit - Lifestyle program

- There was a 6.2% weight loss, sustained at one year.
- This is substantially better than most weight loss programs
- This represents a stroke rate decrease of 1-8%
- This represents a CHD rate decrease of 7-24%

Oster G, Thompson D, Edelsberg J, et al. *Am J Public Health*. 1999; 89:1536–1542.

Event and mortality reduction;
diabetes management

Intensive lifestyle modification program for diabetes works better than medication + standard lifestyle changes

- 3,234 patients at risk for diabetes were randomly-assigned to lifestyle modification program (diet + exercise), metformin (850 mg bid), or placebo for 2.8 years
- Mean age 51, 68% women, 32% men
- Intensive lifestyle change alone - 58% reduction in the risk of developing type 2 diabetes mellitus vs. placebo
- Metformin plus standard lifestyle – 31% reduction in the risk of developing type 2 diabetes mellitus vs. placebo

Knowler WC, Barrett-Connor E, Fowler SE, et al. N Engl J Med. 2002; Feb 7;346(6):393-403.

Risk reduction in diabetics: Meta-analysis of randomized controlled trials

- 18 randomized controlled trials analyzed
- CHD death and nonfatal MI were reduced by:
 - Cholesterol lowering (RR) = 0.75;
95% CI: 0.61 to 0.93)
 - Blood pressure lowering (RR = 0.73;
95% CI: 0.57 to 0.94)

Reducing Hb(A)1C reduces morbidity and mortality in diabetics (UKPDS 35)

- 4,585 Type II diabetics
- 10 year follow-up
- Endpoints:
 - Primary - Mortality (diabetic + all-cause)
 - Secondary - myocardial infarction, stroke, amputation (including death from peripheral vascular disease), and microvascular disease

Stratton IM, Adler AI, Neil HA, et al. BMJ. 2000; 12;321(7258):405-12.

Reducing Hb(A)1C reduces morbidity and mortality in diabetics (UKPDS 35)

- Each 1% reduction in mean Hb(A)1c reduced risks:
 - 21% for deaths related to diabetes (15% to 27%, $P<0.0001$)
 - 21% for any end point related to diabetes (95% confidence interval 17% to 24%, $P<0.0001$)
 - 14% for myocardial infarction (8% to 21%, $P<0.0001$)
 - 37% for microvascular complications (33% to 41%, $P<0.0001$)
- The lower the Hb(A)1c, the lower the risk—
no glycemic threshold

Stratton IM, Adler AI, Neil HA, et al. BMJ. 2000; 12;321(7258):405-12.

Predicted mortality reduction with diabetic control - Lifestyle program

- Lifestyle program reduced Hb(A)1c from 7.4% to 6.6% after 12 weeks (0.8%, n = 157) and from 7.4% to 7.0% after 1 year (0.4%, n = 133)
- Using the UKPDS 35 data, a 0.4% reduction in Hb(A)1c would mean an additional reduction of:
 - 12.6% for deaths related to diabetes
 - 12.6% for any end point related to diabetes
 - 8.4% for myocardial infarction
 - 22.2% for microvascular complications

Summary:

MCAC Evaluative Questions