PRACTICAL POINTERS

FOR
PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

NOVEMBER 2006

STATINS REDUCE RISK OF DEATH IN PATIENTS WITH CHRONIC HEART FAILURE

AT WHAT AGE SHOULD WE STOP PSA SCREENING FOR PROSTATE CANCER?

LIFESTYLE INTERVENTIONS TO REDUCE INCIDENCE OF DIABETES IN PATIENTS WITH GLUCOSE INTOLERANCE

LOW CARBOHYDRATE, HIGHER FAT DIETS DO NOT INCREASE RISK OF CORONARY HEART DISEASE. HIGH GLYCEMIC LOAD DIET INCREASES RISK OF CHD

THIAZIDE DIURETICS INCREASE FASTING GLUCOSE MORE THAN OTHER ANTIHYPERTENSION DRUGS, BUT DO NOT INCREASE RISK OF CLINICAL EVENTS

"THIAZIDES BECOME THE CORNERSTONE OF TREATMENT OF HYPERTENSION"

PIOGLITAZONE FOR TREATMENT OF NON-ALCOHOLIC STEATOHEPATITIS.

NON-ALCOHOLIC FATTY LIVER DISEASE, THE MOST COMMON FORM OF LIVER DISEASE. SHOULD WE TREAT IT WITH THIAZOLIDINEDIONES?

INTERMITTENT CLAUDICATION: A REVIEW ARTICLE

DUAL DRUG THERAPY FOR MEN WITH LOWER URINARY TRACT SYMPTOMS AND OVERACTIVE BLADDER.

ANALOGIES BETWEEN READING OF MEDICAL AND RELIGIOUS TEXTS. AN ESSAY COMPARING MEDICAL "FUNDAMENTALISM" WITH RELIGIOUS "FUNDAMENTALISM"

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE
www.practicalpointers.org

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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

   HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

   EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 5 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
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HIGHLIGHTS AND *EDITORIAL COMMENTS* NOVEMBER 2006

A Major Therapeutic Application—If Confirmed

11-1 STATIN THERAPY AND RISKS OF DEATH AND HOSPITALIZATION IN CHRONIC HEART FAILURE

Increasing attention has focused on potentially "pleotropic" effects of statin drugs. (Ie, effects other than on lipids.)

This study assessed whether statin therapy has beneficial effects on clinical outcomes in patients with HF.

Entered a cohort of over 24 000 patients with documented chronic HF (mean age = 70; age range 20 to > 80) to evaluate any association between *initiation* of statin therapy (after diagnosis of HF) and death and hospitalization for HF.

None had taken statins before onset of HF and entrance into the study.

Follow-up = a median of 2.4 years.

Using an intent-to –treat approach, incident statin use was associated with lower risk of death and hospitalizations (adjusted for multiple possible confounding variables).

Risks per 100 person-years	Statin use	No statin
Death	15	25
Hospitalizations for HF	22	31

(Absolute differences = ~ 10% per year; NNT to benefit one patient = 10)

Alterations of lipid levels are the major reason for prescribing statins. Other, non-lipid effects of statins may be beneficial in patients with HF (Eg, reduction in inflammatory factors and detrimental cytokines; improvement of endothelial function; stabilization of coronary plaques.)

The observed beneficial association was prominent among patients with coronary heart disease (**CHD**) as well as without known CHD.

Conclusion: Among adults who had no prior statin use, *incident* statin use after diagnosis of HF was independently associated with lower risks of death or hospitalization among patients with or without coronary heart disease.

These results are startling. I believe they call for confirmation as soon as possible. This could be a major therapeutic intervention. What should primary care clinicians do in the meantime? Since statins would be indicated for lipid control in most patients with HF, I believe we should prescribe them for almost everyone with HF.

Inappropriate Screening Is Common Among The Elderly.

11-2 PSA SCREENING AMONG ELDERLY MEN WITH LIMITED LIFE EXPECTANCIES

Most guidelines do not recommend PSA screening for prostate cancer (**PC**) in elderly men with limited life expectancy. The potential harms, which occur immediately, outweigh potential benefits. Potential harms include:

additional procedures due to false positive results, psychological distress, and morbidity associated with treating clinically insignificant PC.

The American Urological Society recommends annual PSA screening for men over age 50 and older if they have more than a 10-year life expectancy, usually defined as having a greater than a 50% probability of surviving 10 years. The US Preventive Services Task Force concluded that evidence is *insufficient* to recommend *routine* PSA screening, and that men with a low probability of surviving 10 years are unlikely to benefit from screening, even under favorable assumptions.

"All agree that currently there is no conclusive evidence that PSA screening reduces prostate mortality at any age or life expectancy, and convincing evidence of benefit is unlikely to ever exist for elderly men because ongoing randomized trials of PSA screening have excluded men older than 75 years."

This cohort study of over 550 000 male veterans age 70 and older (median age = 77) seen in Veterans Affairs facilities in 2003. None had a history of PC, elevated, PSA, or symptoms of PC.

In 2003, 56% of these elderly men received a PSA test.

Screening decreased with advancing age within each 5-year age group, ranging from 64% in men age 70-74 to 36% in men age 85 or older.

The percentage of men who received PSA screening did not substantially decline with worsening health. (Eg, among men age 85 and older, 34% in best health had a PSA compared with 36% of those in worst health.)

There is strong evidence that few men age 70 or more who are in the poorest health due to co-morbidity will survive 10 years. Yet 51% of these men were screened with PSA.

Conclusion: PSA screening among elderly veterans with limited life expectancy should be much lower, given the known harms of screening. More attention to prognosis is needed when recommending screening for elderly men.

This advice extends to other screening and interventions. Like an expert poker player, the expert clinician should know "When to hold and when to fold". When should we stop colonoscopy? Lipid screening? Routine physical examinations? Mammography? Pelvic examinations and Pap Smears? When should we stop some of the many multiple drugs old patients take?

How should we respond when an elderly patient requests screening?

I believe, as primary care clinicians, we sometimes order a screening procedure (especially PSA) without adequately informing the patient about potential harms as well as benefits.

Benefits Were Sustained for At Least 3 Years After Active Counseling Was Stopped

11-3 SUSTAINED REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES BY LIFESTYLE INTERVENTION: The Finnish Diabetes Prevention Study.

Lifestyle interventions can prevent deterioration of impaired glucose tolerance to manifest type 2 diabetes (**DM2**), at least as long as the intervention continues.

This study assessed whether the originally-achieved risk reductions from lifestyle interventions remain after discontinuation of active counseling.

The first phase of the study entered 522 overweight men and women (mean age = 55; BMI = 31) between 1993 and 1998. All had impaired glucose tolerance, based on a 75 gram oral glucose tolerance test. (2-hour plasma glucose between 140 and 199 mg/dL; 7.8 and 11.0 mmol/L)

The intervention cohort received individualized, detailed counseling about diet and exercise. Counseling continued intermittently for the 4 years. Controls were given general health behavior information without specific, individualized advice.

The first phase of the study lasted a median of 4 years at which time the incidence of DM2 was lower in the intervention group. This second phase of the study reports outcomes of the 2 groups for the additional 3 years (years 4 to 7) during which subjects received no counseling.

During years 4 to 7, incidence rates per 100 person-years = 4.3 in the former intervention group, and 7.4 in the former control group

A modest difference in body weight between intervention and control groups was maintained during the final 3 years (- 1.8 kg vs 0 kg loss). The benefits of the intervention were largely, but not entirely, mediated through weight loss.

This is an important message from the public health point of view. Interventions can have long-term effects on lifestyle.

Conclusion: Lifestyle intervention in people at high risk for DM2 resulted in sustained lifestyle changes and a reduction in incidence of DM2, which remained after individual lifestyle counseling was stopped.

I spent considerable time studying and abstracting this study. I believe the message is important. Patients can achieve and maintain favorable lifestyles which will reduce risk of DM2 and (more importantly) reduce average glucose levels. I doubt, however, that most primary care clinicians have the time to devote to an intensive effort. But they can constantly remind their high-risk patients about their risky lifestyles. And help to arrange continuing counseling by other health-care workers.

"A Higher Glycemic Load Was Strongly Associated With An Increased Risk Of CHD"

11-4 LOW-CARBOHYDRATE-DIET SCORE AND THE RISK OF CORONARY HEART DISEASE IN WOMEN

This study evaluated data in the Nurses Health Study (> 82 000 women) which permitted comparison of a low carb, higher fat, higher protein diet with a high carb, lower fat, lower protein diet.

All subjects had completed validated food-frequency questionnaires several times during the study.

Divided mean daily intakes of carbohydrate, protein and fat into deciles beginning with the lowest intake of carbs, and progressing to the highest. (*1990 questionnaire data*):

Decile with lowest carb intake

Total kcal	Energy from carb	Energy from fat	Energy from protein
1539	37%	40%	23%

Glycemic load

73

Decile with highest carb intake

Total kcal	Energy from carb	Energy from fat	Energy from protein
1814	59%	26%	15%

Glycemic load

145

Also determined the % of energy of animal fat and vegetable fat, and animal protein and vegetable protein for each decile of carb intake:

Over 20 years (over 1 500 000 person-years), documented 1994 new cases of CHD.

On average, body mass index increased from baseline over 20 years by about 2.5 units *regardless* of the carbohydrate intake.

After controlling for multiple potential confounders, the relative risk (RR) of coronary heart disease between those in the highest intakes of carbohydrate (lowest fat) vs those in the lowest intake of carbohydrate (highest fat) was 0.94. (No statistically significant difference.) "Total dietary fat has not been associated with a risk of coronary heart disease." *(Ie, in this study, no evidence that diets low in carb and higher in fat and protein were associated with increased risk of CHD.)*

A higher glycemic load was strongly associated with an increased risk of CHD. (RR of highest glycemic load vs lowest = 1.90 vs 1.00, (*Almost double*)

"We found that, after taking into account confounding variables, a low carbohydrate diet (*higher fat*) was *not* associated with a risk of coronary heart disease in this large prospective cohort of women."

When vegetable sources of fat were chosen, a low carbohydrate intake was associated with a moderately *lower* risk of CHD than when animal sources of fat were chosen. (RR = 0.70)

Conclusion: Diets lower in carbohydrate and higher in protein and fat were *not* associated with increased risk of CHD in women. When vegetable source of fat and protein were chosen, the RR of CHD was lower than when animal fat and animal protein were chosen. Low glycemic load diets were associated with a lower risk of CHD.

This remarkable study is more complicated than I have indicated. It was difficult to abstract. I believe I have captured the essence of the outcomes.

The study points out that a low glycemic load diet is part of a healthy diet. Higher levels of plasma glucose are a risk factor.

It confirms that a low saturated fat diet is healthier, and that vegetable fats (oils; mono-unsaturated fat) and polyunsaturated fats are also important parts of the healthy diet.

It also confirms how difficult it is to lose weight on any diet, and to maintain the loss.

The healthy diet:

1) Low glycemic load

2) Low saturated fat; high poly- unsaturated fat, and mono-unsaturated fat

3) Zero trans fat

4) Total calories adjusted to maintain BMI under 25

Add a glass of wine before dinner, and this is similar to the Mediterranean diet.

No Reason To Be Concerned About Diuretic-Associated Increase In Risk Of Diabetes.

11-5 FASTING GLUCOSE LEVELS AND INCIDENT DIABETES MELLITUS IN OLDER NON-DIABETIC ADULTS RANDOMIZED TO RECEIVE 3 DIFFERENT CLASSES OF ANTI-HYPERTENSIVE TREATMENT

Elevated blood glucose levels have been associated with thiazide-type diuretics.

This post-hoc subgroup study compared the effects of *first-step* therapy with a thiazide (chlorthalidone), an angiotensin converting enzyme-inhibitor **(ACE-I;** lisinopril), and a calcium channel blocker (**CCB;** amlodipine**)** on fasting glucose and incident type 2 diabetes (**DM2**) in elderly patients with hypertension. And determined associated cardiovascular and renal disease risks.

The differences in mean fasting glucose (**FG)** were small: +3 mg/dL between chlorthalidone and amlodipine and + 5 mg/dL between chlorthalidone and lisinopril.

There was no effect of these changes in FG on cardiovascular (**CVD**) and renal outcomes." This suggests that diuretics lead to elevated glucose levels by mechanisms different from those associated with DM."

Development of DM2 (% with FG above 125 mg/dL): chlorthalidone 14; amlodipine 12; lisinopril 11.

Hazard ratios associated with subjects who developed DM2 vs those who did not develop DM2 during the first 2 years with subsequent cardiovascular disease:

	Chlorthalidone	Amlodipine	Lisinopril
CHD	1.46	1.71	2,23
Stroke	1.83	2.63	0.48
Heart failure	0.96	1.29	3.66
Combined cardiovascular disease	0.96	1.14	1.31
Total mortality	1.05	1.92	1.31

Although none were statistically significant, this suggests that outcomes in patients taking chlorthalidone may be more favorable than in patients taking the other drugs.

Conclusion: FG levels increase in older adults with hypertension regardless of the treatment type. Compared with the other drugs, chlorthalidone modestly increased the risk of FG above 125 mg/dL (DM) There was no conclusive or consistent evidence that this chlorthalidone-associated increase in DM increased risk of clinical events over 5 years.

I believe this is an important clinical point, well worth the time I spent studying and abstracting the article. I believe that judicious use of thiazides remain the cornerstone of treatment for hypertension. Start low and go slow (eg, up to 25 mg hydrochlorothiazide). I would add a second and third drug rather than increasing the dose of the thiazide.

There must have been two different types of DM in the chlorthalidone group: 1) That as a result of the drug, and 2) That which, as age of the cohort increased, occurred spontaneously – not related to the diuretic. The study concerned only group 1).

"Thiazides Become The Cornerstone"

11-6 NEW-ONSET DIABETES MELLITUS LESS DEADLY THAN ELEVATED BLOOD PRESSURE?

The evidence that thiazide therapy is effective for treatment of hypertension passes numerous standards, including pharmacological and mechanistic plausibility, robust outcomes in heterogeneous groups of patients, favorable results in head-to-head comparison with other agents, and efficacy in combination therapy trials.

In all stages of hypertension and in the elderly population, thiazide-based therapy significantly reduces risk of stroke, coronary events, congestive heart failure, renal failure, and malignant hypertension.

While the occurrence of new-onset DM is an independent predictor of cardiovascular risk, administration of diuretics is not independently associated with cardiovascular risk. The recent guidelines from the British Hypertension Society state: "It is not clear that an elevated blood glucose developing as a consequence of drug treatment has the same long-term health impact as in other circumstances."

"Indeed, evidence is mounting that diuretic-induced DM may be completely benign".

"This finding bolsters the concept that thiazide-induced DM is a different and benign disease entity compared with either do novo DM, or that which develops in the context of other antihypertensive agents."

ALLHAT found that thiazide was more effective in lowering BP than either CCB or ACE. We might conclude that the benefit of BP reduction outweighs any risk associated with development of DM.

"Viewed through the wide-angle lens of outcomes research, thiazides become the cornerstone on which blood pressure-lowering treatment should be built."

I believe the benefit / harm –cost ratio of judicious use of thiazides as a first-line drug for hypertension is higher than other antihypertension drugs.

A 'Proof of Concept': Pioglitazone Efficacious In Patients With Nonalcoholic Steatohepatitis."

11-7 A PLACEBO-CONTROLLED TRIAL OF PIOGLITAZONE IN SUBJECTS WITH NON-ALCOHOLIC STEATOHEPATITIS

Non-alcoholic steato-*hepatitis* (**NASH**) is characterized by: insulin resistance, accumulation of hepatic fat, and a predominantly lobular necro-inflammation of the liver. It may or may not include centrilobar fibrosis. It may progress to cirrhosis. It is commonly associated with type 2 diabetes (**DM2**) and obesity.

Thiazolidinediones may reverse many of these abnormalities by ameliorating insulin resistance in adipose tissues, in the liver, and in muscles. They increase adiponectin levels in the plasma, stimulate fatty acid oxidation, and inhibit hepatic fatty acid synthesis. They also have anti-inflammatory effects.

This study followed 55 patients (mean age 51; BMI 33). All had a liver biopsy. All had histological features of NASH. All had impaired glucose tolerance or DM2, increased plasma insulin levels, increased plasma free fatty acids, and increased hepatic fat content (assessed by MRI).

Randomized to: 1) a hypocaloric diet + pioglitazone 45 mg daily, or 2) a hypocaloric diet + placebo

Subjects with NASH who received pioglitazone for 6 months had improved insulin sensitivity, a reversal of

the metabolic milieu permissive of steatosis of the liver, and amelioration of cytokine-mediated systemic inflammation (tumor necrosis factors). Also had improved hepatic insulin sensitivity and glucose clearance, reductions in plasma free fatty acids, plasma glucose, and insulin levels

The histological features of steatohepatitis (steatosis, ballooning necrosis, and centrilobular inflammation) also improved.

Read the following editorial

"The Most Common Form Of Chronic Liver Disease"

11-8 THIAZOLIDINEDIONES FOR NON-ALCOHOLIC STEATOHEPATITIS—PROMISING, BUT NOT READY FOR PRIME TIME

(This editorial comments and expands on the preceding article.)

Nonalcoholic fatty liver disease is the most common form of chronic liver disease. It begins with hepatic steatosis, an accumulation of excess fat in hepatocytes. Steato*hepatitis*, the most severe form of the disease, develops in about 5% of patients with steatosis.

The prognosis of steato*hepatitis* is poor, rivaling that of hepatitis C. Once it develops, many patients will die of liver-related causes (cirrhosis, hepatocellular cancer, and liver failure).

Thiazolidinediones are more effective treatment than metformin. (Although a recent study reported that rosiglitazone was of little benefit.) Unfortunately thiazolidinediones may be associated with weight gain. The author suggests adding the two drugs as first treatment of nonalcoholic fatty liver disease in patients with type 2 diabetes. The combination may provide the same benefits as thiazolidinedione alone, and may avoid the weight gain associated with thiazolidinediones.

Many other approaches to treatment of hepatic steatosis and steatohepatitis have been proposed. None, except bariatric surgery has changed the natural history

Nevertheless, "Until results of large controlled studies of at least one to two years are available, dietary modification, exercise, and treatment of co-existent conditions should be the preferred strategy for managing nonalcoholic steatohepatitis." *(Although I believe the author would agree that this strategy has little chance of success in most obese patients. RTJ)*

Thiazolidinediones are an approved therapy for DM2. If a patient with DM2 is obese (BMI > 30), I believe it would be reasonable to include pioglitazone therapy for the DM2, expecting it to improve any associated hepatic steatosis-steatohepatitis. I believe it is reasonable to combine it with metformin.

"An Important Warning Signal To Start Measures To Reduce Risk Of Cardiovascular Events"

11-9 INTERMITTENT CLAUDICATION A *Clinical Review*

In the vast majority of cases of IC, atherosclerosis is the underlying pathology.

Patients with peripheral arterial disease have the same risk of death from cardiovascular causes as those with a history of coronary or cerebrovascular disease.

Cigarette smoking is by far the most potent risk factor. Other risk factors are age, diabetes, hypertension, dyslipidemia, and hyperhomocysteinemia.

Early diagnosis and risk factor control by primary care clinicians is critical in reducing the mortality associated with IC.

Primarily, treatment should be targeted at reducing factors for atherosclerosis risk of cardiovascular events through secondary prevention (smoking cessation, hypertension control, statin drugs, antiplatelet drugs, diabetes control). Secondarily, treatment should aim to improve symptoms.

Regular exercise, at least 3 times a week, has been shown to improve walking distance and maximal exercise time.

The work "peripheral" may explain why the importance of the disease as a manifestation of general atherosclerotic disease. IC should not be seen as "peripheral", but as an important "central" warning signal to start measures to reduce risk of cardiovascular events. Primary care doctors have a major role in prevention of cardiovascular complications.

11-10 TOLTERODINE AND TAMSULOSIN FOR TREATMENT OF MEN WITH LOWER URINARY TRACT SYMPTOMS AND OVERACTIVE BLADDER

Overactive bladder syndrome (**OABS**) is characterized by urinary urgency, and increased frequency during the day and night—with or without incontinence. An estimated 10 million men over age 40 have symptoms consistent with OABS. The symptoms are often attributed to detrusor overactivity, characterized by involuntary detrusor contractions during bladder filling. Detrusor overactivity may co-exist with bladder outlet obstruction due to benign prostatic hyperplasia (**BPH**)[1].

The resultant increased pressure leads to structural changes in the bladder, which in turn increases the excitability of detrusor smooth muscle. Outlet obstruction may cause urinary hesitancy, intermittency, weak stream, and other lower urinary symptoms.

This randomized, double-blind, placebo-controlled trial followed 879 men (mean age 62). All had documented symptoms of overactive bladder with 8 or more micturations daily, and urgency symptoms 3 or more times daily, with or without incontinence.

Randomized to: 1) tolterodine ER (*Detrol ER* 4 mg daily; blocks the muscarine receptor of acetylcholine;) 2) tamsulosin (*Flomax* 0.4 mg daily; blocks adrenergic action on the prostate smooth muscle), 3) both together, or 4) placebo. Follow-up for 12 weeks:

	Placebo	Tolterodine ER	Tamsulosin	Both
Treatment benefit (%)	62	65	71	80

(In absolute terms, the difference between placebo and two drugs combined was 18%; NNT to benefit one patient = 6.)

Conclusion: Treatment with combined tolterodine ER + tamsulosin resulted in clinically significant benefit for men with moderate to severe lower urinary tract symptoms.

Primary care clinicians might choose to prescribe one drug to test its benefit, and add the second drug if response is not satisfactory.

"Most Proponents Of E-BM Adopt A Balanced View."

11-11 ANALOGIES BETWEEN READING OF MEDICAL AND RELIGIOUS TEXTS

Conventional medicine can be seen as a belief system characterized by a profession of faith in evidence-based medicine (**E-BM**). Faith in E-BM follows from the benefits it has delivered in the past, and continues to deliver. It is the best method we have for navigating our way through potential new treatments.

E-BM is analogous to many religious traditions. It is a canon of sacred texts (medical literature). Differences in interpretation can often be traced to different assumptions underlying our reading of the literature.

Just as there are fundamentalist, conservative, and liberal views of religious texts, there are fundamentalist, conservative, and liberal views of E-BM.

The editorialist goes on to describe some analogies between religious fundamentalism and medical fundamentalism.

Most proponents of E-BM adopt a balanced view. They emphasize the limitations of E-BM, the need for judgment in applying it to individual patients, and the validity of evidence other than randomized, controlled trials. They tend to see the literature as a guide, establishing principles that need to be applied to specific situations.

Randomized, controlled trials may show a consistent improved survival for a defined period. "The main difficulty in applying these data is the external validity." How should we treat the patients with serious co-morbidity? And patients who do not meet inclusion criteria of the trial?

I enjoyed abstracting this commentary. I felt, however, that the editorialist painted the analogy with too broad strokes. Medical fundamentalism is not that "fundamental". I do not believe that primary care clinicians are strict "medical fundamentalists". Most will be selective in applying the treatment provided to subjects in a randomized-controlled trial (RCT). They know that their individual patient may vary from patients entered into the trial. Their individual patient may well be an outlier.

Some individuals will gain a more favorable response than the mean response to the intervention. Some will gain less. Some may be at greater risk of developing an adverse outcome if not treated. Some will be at greater risk of harms if treated.

There are also many social and economic reasons why the treatment recommended by the RCT cannot be applied to an individual patient.

Primary care practice is difficult to do well.

Read the full abstract. Read the original article.

ABSTRACTS NOVEMBER 2006

A Major Therapeutic Application—If Confirmed

11-1 STATIN THERAPY AND RISKS OF DEATH AND HOSPITALIZATION IN CHRONIC HEART FAILURE

Outcomes for the growing numbers of elderly people with heart failure **(HF**) remain poor.

Patients with HF have largely been excluded from trials of statin therapy.

Increasing attention has focused on potentially "pleotropic" effects of statin drugs. (Ie, effects other than that on lipids.)

This study assessed whether statin therapy has beneficial effects on clinical outcomes in patients with HF.

Conclusion: Among adults diagnosed with HF who had not taken statins prior to onset of HF, incident statin use was associated with lower risks of death and hospitalizations.

STUDY

1. Entered a cohort of over 24 000 patients with documented chronic HF (mean age = 70; age range 20 to > 80) to evaluate any association between *initiation* of statin therapy (after diagnosis of HF) and death and hospitalization for HF. About ¼ had HF with preserved ejection fraction. ("Diastolic" HF)
2. All had clinical indications for statin use. But, only about half of the subjects actually received statins.
3. None had taken statins before onset of HF and entrance into the study.
4. Main outcome = all-cause death and hospitalization for HF.
5. Follow-up = a median of 2.4 years.

RESULTS

1. About 50% of the 24 000 subjects received statins. Half did not.
2. At baseline, the group receiving statins were more likely to be younger (age 70 vs 73) , to be male, and to have known cardiovascular disease, diabetes, and hypertension.
3. Deaths during follow-up = 8200.
4. Using an intent-to –treat approach, incident statin use was associated with lower risk of death and hospitalizations (adjusted for multiple possible confounding variables).

Risks per 100 person-years	Statin use	No statin
Death	15	25
Hospitalizations for HF	22	31

(Absolute differences = ~ 10% per year; NNT to benefit one patient = 10)

5. Even after adjustment for patient's propensity to take the statin prescribed, and after adjustment for cholesterol levels, and for use of other cardiovascular medications, statin use was associated with lower risks of outcomes—regardless of whether the patients did or did not have known coronary heart disease.
6. Risk of death and hospitalization was even lower in patients who took the prescribed statin regularly.

DISCUSSION

1. Alterations of lipid levels are the major reason for prescribing statins. Other, non-lipid effects of statins may be beneficial in patients with HF. (Eg, reduction in inflammatory factors and detrimental cytokines; improvement of endothelial function; stabilization of coronary plaques.)
2. "We found that, within a large population of adults with heart failure who were eligible for lipid-lowering therapy, initiation of statin therapy was associated with lower risks of death and hospitalization, even after adjusting for expected differences in patients taking or not taking a statin with regard to cholesterol levels, other potential confounders, concurrent therapies, and the propensity to take a statin."
3. The observed beneficial associations were prominent among patients with CHD, as well as without known CHD.
4. The authors repeat the admonition that, because of the observational nature of the study, the possibility of confounding factors is not ruled out, and the magnitude of benefits from statins may be overestimated.

CONCLUSION

Among adults who had no prior statin use, *incident* statin use after diagnosis of HF was independently associated with lower risks of death or hospitalization among patients with or without coronary heart disease.

JAMA November 1, 2006; 296: 2105-2111 Original investigation, first author Alan S Go, Kiser Permanente of Northern California, Oakland, and University of California, San Francisco.

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11-2 PSA SCREENING AMONG ELDERLY MEN WITH LIMITED LIFE EXPECTANCIES

Most guidelines do not recommend PSA screening for prostate cancer (**PC**) in elderly men with limited life expectancy. The potential harms, which occur immediately, outweigh potential benefits. Potential harms include: additional procedures due to false positive results, psychological distress, and morbidity associated with treating clinically insignificant PC.

The American Urological Society recommends annual PSA screening for men over age 50 and older if they have more than a 10-year life expectancy, usually defined as having a greater than a 50% probability of surviving 10 years. The US Preventive Services Task Force concluded that evidence is *insufficient* to recommend *routine* PSA screening, and that men with a low probability of surviving 10 years are unlikely to benefit from screening, even under favorable assumptions.

"All agree that currently there is no conclusive evidence that PSA screening reduces prostate cancer mortality at any age or life expectancy, and convincing evidence of benefit is unlikely to ever exist for elderly men because ongoing randomized trials of PSA screening have excluded men older than 75 years."

This study characterized the extent of PSA screening among elderly men, including those with limited life expectancy.

Conclusion: Screening rates are much too high.

STUDY

1. Cohort study of over 550 000 male veterans age 70 and older (median age = 77) seen in Veterans Affairs facilities in 2003. None had a history of PC, elevated, PSA, or symptoms of PC.
2. Used comorbidity scores to stratify men into 3 groups ranging from best health to worst health.
3. Most PSA screening tests were listed in progress notes as “health care maintenance”, “routine laboratory work ups”, or had no documented reason.
4, Main outcome = numbers of men receiving a PSA screen.

RESULTS

1. In 2003, 56% of these elderly men received a PSA test.
2. Screening decreased with advancing age within each 5-year age group, ranging from 64% in men age 70-74 to 36% in men age 85 or older.
3. The percentage of men who received PSA screening did not substantially decline with worsening health. (Eg, among men age 85 and older, 34% in best health had a PSA compared with 36% of those in worst health.
4. Screening rates exceeded 60% in some subgroups of men in the worst health.

DISCUSSION

1. PSA screening rates were high among veterans age 70 and older.
2. Advancing age and poor health status had minimal influence on screening rates.
3. Even when 10-year survival based on age became extremely low, PSA screening rates remained substantial (Of the men age 85 and older who were screened, fewer than 10% were expected to survive for 10 years.)
4. There is strong evidence that few men age 70 or more who are in the poorest health due to co-morbidity will survive 10 years. Yet 51% of these men were screened with PSA.
5. Several non-clinical factors, such as region of the country, had greater impact on PSA screening rates than health.

   Screening exceeded 60% in some subgroups of men in worst health.
6. The high PSA rates in the study “suggests considerably inappropriate screening in elderly veterans with potentially harmful consequences”.
7. Modeling studies suggest that 2 out of every 3 cancers identified by screening would never have produced symptoms during their lifetime.
8. If PC identified by screening is treated, elderly men suffer more complications from treatment, including incontinence, bowel dysfunction, and death.
9. Similar factors associated with screening have been reported in the general US population. “Inappropriate screening similarly extends beyond the VA health care system.”

CONCLUSION

PSA screening among elderly patients with limited life expectancy should be much lower, given the known harms of screening. More attention to prognosis is needed when recommending screening for elderly men.

JAMA November 15, 2006; 296: 2336-42 Original investigation, first author Louise C Walter, San Francisco VA Medical Center and University of California, San Francisco.

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Benefits Were Sustained for At Least 3 Years After Active Counseling Was Stopped

11-3 SUSTAINED REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES BY LIFESTYLE INTERVENTION: The Finnish Diabetes Prevention Study.

Lifestyle interventions can prevent deterioration of impaired glucose tolerance to manifest type 2 diabetes (**DM2**), at least as long as the intervention continues. Two major studies have demonstrated that lifestyle changes as a result of intensive counseling, over a period of 3 years, reduced risk of progression from impaired glucose tolerance to DM2 by over 50%.

This study assessed whether the originally-achieved risk reductions from lifestyle interventions remain after discontinuation of active counseling.

Conclusion: Benefits were sustained for at least 3 years after active counseling was stopped.

STUDY

1. The first phase of the study entered 522 overweight men and women (mean age = 55; BMI = 31) between 1993 and 1998. All had impaired glucose tolerance, based on a 75 gram oral glucose tolerance test. (2-hour plasma glucose between 140 and 199 mg/dL; 7.8 and 11.0 mmol/L)
2. At baseline, mean fasting plasma glucose = 110 mg/dL[1] (6.1 mmol/L); mean 2-h glucose = 160 mg/dL[2] (8.9 mmol/L).
3. During the first 4 years, the cohort was randomized to: 1) an intensive lifestyle intervention group, and 2) a control group.
4. The intervention cohort received individualized, detailed counseling about diet and exercise. Counseling continued intermittently for the 4 years. Controls were given general health behavior information without specific, individualized advice. The main goals of the intervention were weight reduction of 5% or more; less than 30% of daily energy from saturated fat; fiber intake of 15 g per 1000 kcal; and moderately intense physical activity 30 minutes a day or more.
5. The first phase of the study lasted a median of 4 years at which time the incidence of DM2 was lower in the intervention group.
6. After 4 years, active counseling was discontinued, and subjects free of diabetes were followed by observation only for an additional 3 years. (Median total follow-up = 7 years.)
7. This second phase of the study reports outcomes of the 2 groups for the additional 3 years (years 4 to 7) during which subjects received no counseling.
8. Primary endpoint = development of diabetes[3] during years 4 to 7.

RESULTS

1. During years 4 to 7, incidence rates per 100 person-years = 4.3 in the former intervention group, and 7.4 in the former control group. Total number of cases of diabetes at 7 years: intervention group = 75 (163 without diabetes); control group = 110 (127 without diabetes). NNT for one year to benefit one patient = 33.
2. Mean body weight and intake of total and saturated fat remained lower, and physical activity and fiber intake remained higher in the intervention group during the post intervention period (years 4 to 7) despite lack of continued counseling.

DISCUSSION

1. The difference in the cumulative incidence of diabetes was sustained after counseling was discontinued. The absolute difference in diabetes risk between the intervention group and controls remained the same (15%) during the final 3 years of observation as during the first 4 years.
2. A modest difference in body weight between intervention and control groups was maintained during the final 3 years (- 1.8 kg vs 0 kg loss).
3. This is an important message from the public health point of view. Interventions can have long-term effects on lifestyle.
4. The benefits of the intervention were largely, but not entirely, mediated through weight loss.[4]
5. Oral anti-diabetes drugs could be an option for those who do not respond to lifestyle interventions.[5] However, much of their effect dissipates as soon as the drug is discontinued.
6. About 50% of persons with inspired glucose tolerance will develop diabetes within 10 years. Although lifestyle interventions alone, even if successful, do not necessarily prevent DM2 in all persons, they will postpone onset of the disease.
7. “Adherence to the intervention is a specific challenge for future diabetes prevention programmes.” About one third of participants in the intervention group did not meet predefined goals after one year.
8. “The high diabetes incidence even in the intervention group of our study suggests that preventive actions should probably be targeted to all high-risk individuals, even before impaired glucose tolerance is present.”

CONCLUSION

Lifestyle intervention in people at high risk for DM2 resulted in sustained lifestyle changes and a reduction in incidence of DM2, which remained after individual lifestyle counseling was stopped.

Lancet November 11, 2006; 368: 1673-79 Original investigation, by the Finnish Diabetes Prevention Study Group, first author Jaana Lindstrom, National Public Health Institute, Helsinki, Finland.

1 Now, this fasting level is considered to be abnormal. Normal fasting plasma glucose is below 100 mg/dL

2 Abnormal glucose tolerance is defined as a 2-h post 75 g glucose challenge between 140 and 199.

3 Diabetes is now defined as a fasting plasma glucose of 126 mg/dL and above, and /or a 2-h post challenge plasma glucose of 200 and above. I would judge that, if the study had defined DM2 as 126 and above, the results of lifestyle changes would be more impressive.

4 Modest weight reduction can provide benefits.

5 Metformin also reduces risk of development of DM2 in patients with impaired glucose tolerance.

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"A Higher Glycemic Load Was Strongly Associated With An Increased Risk Of CHD"

11-4 LOW-CARBOHYDRATE-DIET SCORE AND THE RISK OF CORONARY HEART DISEASE IN WOMEN

Low-fat, high-carbohydrate, energy-deficient diets have been advocated by leading research and medical societies to manage obesity.

Despite these recommendations, diets low in carbohydrates and high in fat and protein, remain popular (eg, the Atkins diet). The long-term safety of these carbohydrate-restricted diets remains controversial. Several professional organizations have cautioned against their use. The diets usually contain high amounts of saturated fat and cholesterol. This may cause dyslipidemia and increase risk of coronary heart disease (**CHD**).

This study evaluated data in the Nurses Health Study which permitted comparison of a low carb, higher fat, higher protein diet with a high carb, lower fat, lower protein diet.

Conclusion: Low carb, higher fat, higher protein diets were *not* associated with increased risk of CHD.
High glycemic load diets increased risk of CHD.

STUDY

1. Evaluated data on over 82 000 women in the NHS. All had completed validated food-frequency questionnaires several times during the study
2. Divided mean daily intakes of carbohydrate, protein and fat into deciles beginning with the lowest carb intake and progressing to the highest.

Decile with lowest carb intake

Total kcal	Energy from carb	Energy from fat	Energy from protein
1539	37%	40%	23%

Glycemic load
73

Decile with highest carb intake

Total kcal	Energy from carb	Energy from fat	Energy from protein
1814	59%	26%	15%

Glycemic load
145

(From their table 2 (pp 1994-95) which reports intakes in the year 1990. I present it to illustrate some differences in the diets in quantitative terms. As the carb intake rose, intake of fat and protein fell.)

3. Glycemic load per day varied from 73 in the lowest carb decile to 145 in the highest carb decile. (It doubled.) *(Total dietary glycemic load was calculated by multiplying the carbohydrate content of each food by its glycemic index. (The glycemic index of glucose is 100.) Then multiplied this value by the frequency of consumption. Then summed these values for all foods. Dietary glycemic load therefore represents both the quality and quantity of carbohydrate consumed. Each unit of glycemic load represents the equivalent blood glucose-raising effect of 1 gram of pure glucose.)*
4. Saturated fat varied between 14% of energy in the low carb decile, and 9% in the highest decile.
5. Trans fat as % of energy intake = 1.7% and 1.4%--little difference between deciles.
6, Also determined the % of energy of animal fat and vegetable fat, and animal protein and vegetable protein for each decile of carb intake:

	Animal fat % of energy	Vegetable fat % of energy
Lowest decile of carb intake	27%	19%
Highest decile of carb intake	13%	10%

7. Outcome = incident CHD, including non-fatal myocardial infarcts and fatal coronary events.
8. Follow-up = 20 years.

RESULTS

1. Over 20 years (over 1 500 000 person-years), documented 1994 new cases of CHD.
2. On average, body mass index increased from baseline over 20 years by about 2.5 units *regardless* of the carbohydrate intake.
3. After controlling for multiple potential confounders, the RR of coronary heart disease between those in the highest intakes of carbohydrate (lowest fat) vs those in the lowest intake of carbohydrate (highest fat) was 0.94. (No statistically significant difference), *(Ie, in this study, no evidence that diets low in carb and higher in fat and protein were associated with increased risk of CHD.)*
4. The RR of CHD on the basis of the percentage of energy intake from vegetable fat and vegetable protein vs animal fat and animal protein was 0.70. *(Ie, again demonstrating the beneficial effect of unsaturated oils.)*
5. A higher glycemic load was strongly associated with an increased risk of CHD. (RR of highest glycemic load vs lowest = 1.90 vs 1.00, (*Almost double*)

DISCUSSION

1. "We found that, after taking into account confounding variables, a low carbohydrate diet (*higher fat*) was *not* associated with a risk of coronary heart disease in this large prospective cohort of women."
2. When vegetable sources of fat were chosen, the low carbohydrate intake was associated with a moderately *lower* risk of CHD than when animal sources of fat were chosen.
3. Few people in the cohort followed the strict version of the Atkins diet (very low carb; high fat) long term. However, the amount of carb in the lowest decile of intake (< 29% of calories) was similar to that consumed by participants in clinical trials of the Atkins diet.
4. The low carb diet did not have a significant effect on weight. On average, BMI increased by 2.5 units

from baseline. The effects of a low carbohydrate diet on outcomes in this trial were not mediated by weight loss.

5. Saturated fat and trans fat have been associated with increased risk of CHD. “Total dietary fat, however, has not been associated with a risk of coronary heart disease.”
6. A low carbohydrate diet tends to have a lower glycemic load than a high carbohydrate diet. In this investigation, there was a direct association between glycemic load and CHD.

CONCLUSION

Diets lower in carbohydrate and higher in protein and fat were *not* associated with increased risk of CHD in women. When vegetable sources of fat were chosen, the low carbohydrate intake was associated with a moderately *lower* risk of CHD than when animal sources of fat were chosen.

Low glycemic load diets were associated with a lower risk of CHD.

NEJM November 8, 2006; 355: 1991-2002 Original investigation, first author Thomas L Halton, Harvard School of Public Health, Boston, Mass.

See also: “Global and Regional Mortality from Ischemic Heart Disease and Stroke Attributable to Higher-than-Normal Blood Glucose Concentration” Lancet November 11, 2006; 368: 1651-59. First author Goodorz Danaei, Harvard School of Public Heath, Boston Mass.

This remarkable study compared cardiovascular mortality related to blood glucose levels in populations around the world. The investigators conclude that higher-than optimum blood glucose is a leading cause of cardiovascular mortality. There was a continuous association between blood glucose and risk of CHD beginning at fasting blood glucose levels of 88 mg/dL (4.9 mmol/L) Each 18 mg/dL rise above 88 mg/dL was associated with a 1.1 to 1.4 increase in mortality. Ie, there is a graded risk beginning at a low level.

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No Reason To Be Concerned About Diuretic-Associated Increase In Risk Of Diabetes

11-5 FASTING GLUCOSE LEVELS AND INCIDENT DIABETES MELLITUS IN OLDER NON-DIABETIC ADULTS RANDOMIZED TO RECEIVE 3 DIFFERENT CLASSES OF ANTI-HYPERTENSIVE TREATMENT

Type 2 diabetes **(DM2**) and hypertension share several common antecedents, including obesity and insulin resistance. Treatment of one disorder may affect the other.

Elevated blood glucose levels have been associated with thiazide-type diuretics. It has been suggested that angiotensin-converting enzyme-inhibitors (**ACE-I**) may result in lower rates of incident DM2.

This study compared the effects of *first-step* therapy with a thiazide, an ACE-I, and a calcium channel blocker (**CCB**) on fasting glucose (**FG**) and incident DM2 in elderly patients with hypertension. And determined associated cardiovascular and renal disease risks.

Conclusion: FBS increased in all 3 groups. The diuretic (chlorthalidone) was associated with a modestly higher FBS and risk of development of DM2. There was no conclusive evidence that this chlorthalidone-associated increase in risk of DM2 increased risk of clinical events.

STUDY

1. This was a post-hoc subgroup analysis from the ALLHAT[1] trial among hypertensive patients (mean age 66) randomized to *first-step* treatment with chlorthalidone (*Generic*; a thiazide diuretic), amlodipine (*Caduet; Lotrel; Norvasc*; a CCB), or lisinopril (*Prinivil; Zestril*; an ACE-I). None had DM2 at baseline.
2. The cohort included only patients for whom FG levels were reported during follow-up (n = over 9500). Determined differences in FBS levels, incident DM2, and risk of cardiovascular and renal disease.
3. Follow-up for a mean of 5 years.

RESULTS

1. Mean FG levels increased in all 3 treatment groups.
2. Change in FG at 2 years: (mg/dL): chlorthalidone + 9; amlodipine + 6: Lisinopril + 4
3. Development of DM2 (% with FG above 125 mg/dL): chlorthalidone 14; amlodipine 12; lisinopril 11.
4. There was no significant association between FB level change at 2 years and subsequent coronary heart disease, stroke, cardiovascular disease, or end-stage renal disease.
5. Hazard ratios associated with subjects who developed DM2 vs those who did not develop DM2 during the first 2 years with subsequent cardiovascular disease:

	Chlorthalidone	Amlodipine	Lisinopril
CHD	1.46	1.71	2,23
Stroke	1.83	2.63	0.48
Heart failure	0.96	1.29	3.66
Combined cardiovascular disease	0.96	1.14	1.31
Total mortality	1.05	1.92	1.31

(Although none were statistically significant, this suggests that outcomes in patients taking chlorthalidone may be more favorable than in patients taking the other drugs.)

DISCUSSION

1. In these older non-diabetic adults, the FG rose with time in all 3 groups of drugs.
2. Patients randomized to chlorthalidone had a significantly higher FG and increased incidence of DM2 at 4 years of follow-up compared with the other 2 drugs. The differences in mean FG were small— +3 mg/dL between chlorthalidone and amlodipine and + 5 mg/dL between chlorthalidone and amlodipine. (This suggests that chlorthalidone has a detrimental effect on glucose metabolism, or that the other drugs have a neutral or protective effect, or both.)
3. The findings that chlorthalidone-induced hyperglycemia and DM2 do *not* result in increased CVD and renal outcomes is similar to the results of other studies.

4. “Our findings are consistent with other studies in that hazard ratios for endpoints (CHD, total mortality, heart failure and combined cardiovascular disease) tended to be *lower* in the chlorthalidone group compared with the other groups.”
5. Other studies have demonstrated that cessation of long-term use of thiazide diuretics is associated with prompt improvement in glucose metabolism. This suggests that diuretics lead to elevated glucose levels by mechanisms different from those associated with DM2.
6. Low potassium levels did not increase odds of DM2 development in this analysis. However, other studies have reported that low levels of potassium caused by thiazide treatment are related to an increase in FG and increased risk of developing DM2. Careful attention to potassium levels in patients receiving thiazides may reduce risk of hyperglycemia.
7. This study did not measure 2-h postprandial blood glucose levels. Some cases of DM2 may have been missed.
8. These findings cannot be extrapolated beyond 5 years. The effects of hyperglycemia on progression of atherosclerosis may occur over many decades.

CONCLUSION

FG levels increase in older adults with hypertension regardless of the treatment type.

Compared with the other drugs, chlorthalidone modestly increased the risk of FG above 125 mg/dL (DM2)

There was no conclusive or consistent evidence that this chlorthalidone-associated increase in DM2 increased risk of clinical events over 5 years.

Archives Int Med November 13, 2006; 166: 2191-2202 Original investigation by the Antihypertensive and Lipid-lowering Treatments to Prevent Heart Attack Trial (ALLHAT Collaborative Research Group), first author Joshua I Barzlay, Emory University School of Medicine, Atlanta, GA

1 “Antihypertensive and Lipid-lowering Treatments to Prevent Heart Attack Trial” JAMA 2002; 288: 2981-97

All subjects were hypertensive and at high risk of cardiovascular disease. First-step therapy with a thiazide diuretic was as effective in reducing cardiovascular events as were amlodipine (CCB) and lisinopril (ACE). Chlorthalidone was associated with lower risk of heart failure.

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“Thiazides Become The Cornerstone”

11-6 NEW-ONSET DIABETES MELLITUS LESS DEADLY THAN ELEVATED BLOOD PRESSURE?

(This editorial comments and expands on the preceding study.)

The evidence that thiazide therapy is effective for treatment of hypertension passes numerous standards, including pharmacological and mechanistic plausibility, robust outcomes in heterogeneous groups of patients, favorable results in head-to-head comparison with other agents, and efficacy in combination therapy trials.

Thiazides have a dual mechanism of action which addresses the volume-vasoconstriction mismatch by its 1) natriuretic properties and 2) by its less-appreciated vasodilatory properties.

In all stages of hypertension and in the elderly population, thiazide-based therapy significantly reduces risk of stroke, coronary events, congestive heart failure, renal failure, and malignant hypertension.

Decades ago, legitimate concerns were raised about the hypokalemia-induced metabolic and pro-arrhythmic consequences of thiazides. These were related mainly to high doses (eg, chlorthalidone 100 mg). Now thiazides are administered at much lower doses which provide almost as great a reduction in BP as higher doses. (The dose-response is relatively flat.)

Concerns persist about the increased risk of elevated fasting glucose (**FG**) and diabetes (**DM**) related to thiazides. While the occurrence of new-onset DM is an independent predictor of cardiovascular risk, administration of diuretics is not independently associated with cardiovascular risk. The recent guidelines from the British Hypertension Society state: "It is not clear that an elevated blood glucose developing as a consequence of drug treatment has the same long-term health impact as in other circumstances."

"Indeed, evidence is mounting that diuretic-induced DM may be completely benign." In the preceding study, while the risk development of DM was greater in the thiazide group, the diuretic did not seem to be responsible for the increase in coronary heart disease (**CHD**) risk associated with new-onset DM. Rather, development of DM during treatment with ACE inhibitors was associated with an increased risk of CHD and congestive heart failure. Development of DM during treatment with the CCB was associated with increased mortality. "This finding bolsters the concept that thiazide-induced DM is a different and benign disease entity compared with either de novo DM or that which develops in the context of other antihypertensive agents."

ALLHAT found that thiazide was more effective in lowering BP than either CCB or ACE. We might conclude that the benefit of BP reduction outweighs any risk associated with development of DM.

In the 19th and 20th centuries medical education, practice and therapies were based primarily on pharmacological and pathophysiological precepts. Now, outcomes research and evidence-based medicine teach us that, when possible, pharmacological and pathophysiological principles must be tested in systematically conducted clinical research studies in generalisable patient populations.

"Viewed through the wide-angle lens of outcomes research, thiazides become the cornerstone on which blood pressure-lowering treatment should be built."

Archives Int Med November 13, 2006, 199: 2174-76 Editorial by Robert A Phillips, University of Massachusetts Memorial Medical Center, Worcester

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A 'Proof of Concept': Pioglitazone Efficacious In Patients With Nonalcoholic Steatohepatitis."

11-7 A PLACEBO-CONTROLLED TRIAL OF PIOGLITAZONE IN SUBJECTS WITH NON-ALCOHOLIC STEATOHEPATITIS

Non-alcoholic steato-*hepatitis* (**NASH**) is characterized by: insulin resistance, accumulation of hepatic fat, and a predominantly lobular necro-inflammation of the liver. It may or may not include centrilobar fibrosis. It may progress to cirrhosis. It is commonly associated with type 2 diabetes (**DM2**) and obesity.

Weight loss remains the standard of care.

Insulin resistance in NASH is frequently associated with chronic hyperinsulinemia, and an excessive supply of plasma free fatty acids to the liver. This promotes hepatic lipogenesis. Patients with NASH have low plasma adiponectin[1] levels.

Thiazolidinediones may reverse many of these abnormalities by ameliorating insulin resistance in adipose tissues, in the liver, and in muscles. They increase adiponectin levels in the plasma, stimulate fatty acid oxidation, and inhibit hepatic fatty acid synthesis. They also have anti-inflammatory effects.

Pioglitazone (*Actos*; Takeda Pharmaceuticals) is a thiazolidinedione which ameliorates insulin resistance and improves glucose and lipid metabolism in DM2.

This study assessed the effect of pioglitazone on NASH

Conclusion: Pioglitazne led to improved metabolic parameters and liver histology.

STUDY

1. Followed 55 patients (mean age 51; BMI 33). All had a liver biopsy. All had histological features of NASH.
2. All had impaired glucose tolerance or DM2, increased plasma insulin levels, increased plasma free fatty acids, and increased hepatic fat content (assessed by MRI).
3. Randomized to: 1) a hypocaloric diet (500 kcal per day less than that calculated to maintain body weight) + pioglitazone 45 mg daily, or 2) a hypocaloric diet + placebo
4. Ten healthy subjects with normal glucose tolerance served as controls.
5. Repeated metabolic studies and liver biopsy after 6 months of treatment.

RESULTS

1. Diet + pioglitazone
   - A. Improved all metabolic variables:
     - Improved fasting plasma glucose and insulin levels
     - Improved glycemic control and glucose tolerance
     - Reduced level of free fatty acids
     - Normalized liver aminotransferase levels
     - Increased plasma adiponectin levels
     - Reduced levels of tumor necrosis factor
   - B. Improved histological changes in the liver:
     - Decreased hepatic fat content
     - Improved all histological variables including a necro-inflammation score
   - C. Subjects in this group actually *gained* weight—a mean of +2.5 kg over 6 months. And increased body fat content.[2]
2. Diet + placebo:
   - A. Subjects *lost* an average of 3.2 kg
   - B. Limited effect on metabolic variables

C. Reduced steatosis, ballooning necrosis, and lobular inflammation in some subjects, but not as great an improvement as in the pioglitazone group

DISCUSSION

1. Subjects with NASH who received pioglitazone for 6 months had improved insulin sensitivity, a reversal of the metabolic milieu permissive of steatosis of the liver, and amelioration of cytokine-mediated systemic inflammation (tumor necrosis factors). Also had improved hepatic insulin sensitivity and glucose clearance, reductions in plasma free fatty acids, plasma glucose, and insulin levels
2. The histological features of steatohepatitis (steatosis, ballooning necrosis, and centrilobular inflammation) also improved. Fibrosis did not improve.
3. By improving insulin sensitivity of adipose tissue, thiazolidinediones reduce excessive rates of lipolysis, and also reduce substrate supply to the liver, and mitigate hepatic lipid synthesis.
4. In patients with NASH, adiponectin levels are decreased. Levels increased markedly as a result of pioglitazone administration.
5. Treatment of patients with both DM2 and NASH may be particularly challenging because weight loss and metformin therapy do not increase adiponectin levels, and administration of insulin may increase steatosis.
6. "Taken together, these results serve as a 'proof of concept' that pioglitazone has efficacy in patients with nonalcoholic steatohepatitis."

CONCLUSION

Pioglitazone led to metabolic and histological improvement in subjects with nonalcoholic steatohepatitis.

NEJM November 30, 2006; 355:2297-307 Original investigation, first author Renata Belfort, University of Texas Health Science Center at San Antonio,

1 Adiponectin is a protein hormone produced and secreted by adipocytes. Plasma levels are *decreased* in subjects with visceral obesity. *(I do not understand this point. If fat cells produce adiponectin, and there are more intraabdominal fat cells in patients with steatohepatitis, why are plasma levels decreased? Anyone out there with an explanation? RTJ)*

It influences the body's response to insulin, and regulates the metabolism of lipids and glucose

It augments glucose uptake in muscle cells

It may be a protective marker for DM2

It has anti-inflammatory effects of the cells lining walls of blood vessels

It exhibits pleotropic effects on vascular cells—modifying endothelial cell function, proliferation of smooth muscle, and lipid accumulation in macrophages

High levels are associated with reduced risk of myocardial infarction; low levels with higher risk

Low plasma levels may be related to development of the metabolic syndrome

(Adiponectin is new to me. I gleaned this information from GOOGLE. I will watch for further information.)

2 This is discouraging. The following article suggests adding metformin to a thiazolidinedione in patients with DM2. . Metformin may be associated with better weight control. We await more experience on effects of incretins, including the recently approved sitagliptin, an incretin enhancer.

Supported in part by a grant from Takeda.

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"The Most Common Form Of Chronic Liver Disease"

11-8 THIAZOLIDINEDIONES FOR NON-ALCOHOLIC STEATOHEPATITIS—PROMISING, BUT NOT READY FOR PRIME TIME

(This editorial comments and expands on the preceding article.)

Mostly unrecognized before 1980, non-alcoholic fatty liver disease now affects all fields of clinical medicine. It is the most common form of chronic liver disease in the U.S. It begins as hepatic steat-*osis* an accumulation of fat in hepatocytes. Data based on ultrasonographic and serum enzyme measurements indicate that the prevalence of non-alcoholic liver disease in the U.S. population is about 30%--as many as 90 million cases.

Prevalence is expected to increase with the epidemic of obesity and DM2.

It is suggested that steato-*hepatitis*—the most severe form of non-alcoholic fatty liver disease—has a prevalence of 5%.

The histologic features of steatohepatitis (the end of a large clinical spectrum of non-alcoholic liver disease) includes fatty hepatocytes + hepatocyte injury (ballooning degeneration), with or without fibrosis, polymorpho-nuclear infiltrates and Mallory's hyaline.

Once it develops, up to 50% of patients with steatohepatitis die from a liver-related cause as the disease decompensates into cirrhosis, subacute liver failure, and to hepatocellular cancer. The mortality rate is similar to, or worse than, hepatitis C. (Steatosis alone is much more benign.)

Insulin resistance is the first step in development of hepatic steatosis. This has led to the concept that the disease is the hepatic component of the metabolic (insulin-resistance) syndrome. The second step is progression from steatosis to steatohepatitis (which is facilitated by cytokines).

Metformin and thiazolidinediones have been studied to test the hypothesis that lessening insulin resistance may be beneficial. Thiazolidinediones have been more efficacious than metformin.

The preceding study was correctly termed a "proof of concept". The sample was small, and the study period short. A recent study reported that rosiglitazone had little or no benefit in patients with steatohepatitis.

Thiazolidinediones do have adverse effects, although they are usually well tolerated.

Many other approaches to treatment of hepatic steatosis and steatohepatitis have been proposed. None, except bariatric surgery has changed the natural history.

For initial therapy of patients with DM2 a combination of metformin + a thiazolidinedione may provide the same benefits as thiazolidinedione alone, and may avoid the weight gain associated with thiazolidinediones.

"Until results of large controlled studies of at least one to two years are available, dietary modification, exercise, and treatment of co-existent conditions should be the preferred strategy for managing nonalcoholic steatohepatitis."

NEJM November 30, 2006; 355: 2361-63 Editorial by Arthur J McCullough, Cleveland Clinic, Ohio

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11-9 INTERMITTENT CLAUDICATION A *Clinical Review*

Pathogenesis:

In the vast majority of cases of IC, atherosclerosis is the underlying pathology.

Cigarette smoking is by far the most potent risk factor. Other risk factors are age, diabetes, hypertension, dyslipidemia, and hyperhomocysteinemia.

Diagnosis:

The diagnosis is based on the classical history of cramping muscle pain that occurs after the same degree of exercise, and is relieved by rest.

Many persons with IC do not consult a doctor. Often the doctor is not aware that their patient has IC.

Early diagnosis and risk factor control by primary care clinicians is critical in reducing the mortality associated with IC.

Other conditions may mimic these symptoms: nerve root compression, spinal stenosis, hip arthritis, Baker's cyst, venous claudication. Typically nerve root compression pain radiates down the back of the lower extremity, and is often described as sharp and lancinating. In some patients, it may be relieved by change in position such as leaning forward. In spinal stenosis, motor weakness may be present. Concomitant lumbosacral pain disease may cause difficulty in identifying which of the two conditions is the main cause of symptoms.

Absent or reduced peripheral pulses supports the diagnosis, but some patients with IC have foot pulses which are apparently normal. A low ankle-brachial pressure index (**A-BPI** < 0.9) supports the diagnosis. The presence of palpable pulses and a normal resting A-BPI does not rule out IC. If the symptoms are highly suggestive, and the A-BPI is normal, an exercise A-BPI should be performed. If a substantial drop in ankle pressure is observed after exercise and at the same time symptoms develop, a diagnosis can be confidently made.

In patients with an A-BPI of >1.3, the result is likely to be artifactual, secondary to heavily calcified vessels.

Treatment:

Primarily, treatment should be targeted at reducing factors for atherosclerosis risk of cardiovascular events through secondary prevention (smoking cessation, hypertension control, statin drugs, antiplatelet drugs, diabetes control. Secondarily, treatment should aim to improve symptoms.

There is clear evidence that antiplatelet drugs reduce major cardiovascular events. They reduce risk of arterial occlusion, and requirement of revascularization.

Statins reduce risk of cardiovascular complications. There is some evidence that statins reduce symptoms of IC, and increase walking distance and pain free walking time.

Regular exercise, at least 3 times a week, has been shown to improve walking distance and maximal exercise time.

Intensive diabetes control reduces incidence of cardiovascular disease, but has no effect on risk of peripheral arterial disease. BP control confers protection against cardiovascular events. There is no evidence that lowering BP alters the natural course of IC.

The role of treatment with percutaneous angioplasty is controversial. A Cochrane review concluded that angioplasty may have some benefit, but only short term. There is insufficient evidence for use of stents in addition to angioplasty.

Bypass surgery: There is a wide variation in opinions about effectiveness of bypass. There is little doubt that, for patients with debilitating symptoms who are not suitable for angioplasty, surgery may provide effective treatment—but, may increase morbidity and mortality.

Prognosis:

People with IC have a significantly increased mortality risk.

Patients with peripheral arterial disease have the same risk of death from cardiovascular causes as those with a history of coronary or cerebrovascular disease. Patients with IC have a significantly higher mortality than age-matched controls (about 12% per year). Most deaths are due to heart disease; about 10% are due to strokes.

The natural course of IC is benign for the leg affected, with few patients ever requiring interventions or amputation. Only one in four will develop any deterioration in symptoms.

Conclusion:

The word “peripheral” may explain why the importance of the disease as a manifestation of general atherosclerotic disease. IC should not be seen as “peripheral”, but as an important “central” warning signal to start measures to reduce risk of cardiovascular events. Primary care doctors have a major role in prevention of cardiovascular complications.

BMJ November 11, 2006; 333: 1002-05 “Clinical Review” by Kevin Cassar, Aberdeen Royal Infirmary, UK.

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11-10 TOLTERODINE AND TAMSULOSIN FOR TREATMENT OF MEN WITH LOWER URINARY TRACT SYMPTOMS AND OVERACTIVE BLADDER

Overactive bladder syndrome (**OABS**) is characterized by urinary urgency, and increased frequency during the day and night—with or without incontinence. An estimated 10 million men over age 40 have symptoms consistent with OABS. The symptoms are often attributed to detrusor overactivity, characterized by involuntary detrusor contractions during bladder filling. Detrusor overactivity may co-exist with structural bladder outlet obstruction due to benign prostatic hyperplasia (**BPH**)[1]. The resultant increased pressure leads to structural changes in the

bladder, which in turn increases the excitability of detrusor smooth muscle. Outlet obstruction may cause urinary hesitancy, intermittency, weak stream, and other lower urinary symptoms.

Antimuscarinic agents (muscarine blockers, eg, tolterodine; *Detrol*-Pharmacia-Upjohn)[2] block the action of acetylcholine on its muscarinic receptors, reducing detrusor overactivity.

Alpha-adrenergic receptor antagonists (alpha-blockers, eg, tamsulosin; *Flomax*; Boehinger-Ingelheim)[3] block the action of the sympathetic (adrenergic) nervous system on adreno-receptors in the bladder and prostate, reducing smooth muscle tone and decreasing bladder outlet resistance.

Some men may not respond to monotherapy. This trial assessed the efficacy and safety of two agents combined in men with both overactive bladder and BPH.

Conclusion: Treatment with both drugs benefited men with moderate to severe lower urinary tract symptoms.

STUDY

1. Multicenter, randomized, double-blind, placebo-controlled trial followed 879 men (mean age 62). All kept a diary noting bladder symptoms. All had: a high prostate symptom score indicating BPH, and were at least moderately bothered with urinary symptoms. All had documented symptoms of overactive bladder with 8 or more micturations daily, and urgency symptoms 3 or more times daily, with or without incontinence. (Ie, symptoms due to involuntary contraction of smooth muscle in the bladder and prostate.)
2. Excluded men with significant structural bladder obstruction (postvoid volume over 200 mL, maximum urinary flow less than 5 ml/sec, and prostate specific antigen greater than 10 ng/mL).
3. Randomized to: 1) tolterodine ER (4 mg daily) 2) tamsulosin (0.4 mg daily), 3) both together, or 4) placebo.
4. Determined patient's perception of benefit, bladder diary variables, prostate symptom score, and safety and tolerability.
5. Primary endpoint = patient's perception of treatment benefit. (A global response.)
6. Follow-up for 12 weeks. Analysis based on the intent- to-treat. Defined the cohort as patients who received at least one dose of study medication, who had at least one baseline assessment, and had at least one post baseline assessment.

RESULTS

1. At 12 weeks:

	Placebo	Tolterodine ER	Tamsulosin	Both
Treatment benefit (%)	62	65	71	80

(In absolute terms, the difference between placebo and two drugs combined was 18%; NNT to benefit one patient = 6.)

2. Compared with placebo, significant reductions of all bladder diary variables occurred in the combined drug group,
4. Patients receiving tolterodine ER alone demonstrated significant reductions in episodes of urgency-related incontinence. For other bladder variables, only patients receiving both drugs demonstrated significant reductions compared with placebo.
5. Adverse events: All active interventions were well tolerated. Few patients discontinued because of lack

of efficacy, urinary retention, or decreased urinary flow. (No difference between groups.) The most frequent adverse symptom was dry mouth—a frequent adverse effect of muscarine blockers.

DISCUSSION

1. Urinary function is affected by detrusor contractility and urethral resistance, including that imparted by smooth muscle of the prostate and bladder neck.
2. Symptoms of urgency, incontinence, and frequency of daily and nocturnal micturations were significantly improved in the combined-drug group.
3. Changes in postvoid residual volume and maximum urinary flow rate did not differ between the 4 groups.
4. A large placebo effect was observed for all endpoints of the study. The investigators make an interesting suggestion: "The placebo group cannot be viewed as a non-treatment group, principally because patients were required to complete bladder diaries." These diaries provide insight into behavioral modifications that may improve symptoms by enhancing patient's awareness of their bladder habits. This may have provided a training effect.

CONCLUSION:

Treatment with combined tolterodine ER + tamsulosin resulted in clinically significant benefit for men with moderate to severe lower urinary tract symptoms.

JAMA November 15, 2006; 296: 2319-28 Original investigation, first author Steven A Kaplan, Weill Cornell Medical College, New York, NY.

1 Obstruction from BPH can be 1) structural, due to blockage of the outlet, and 2) functional, due to contraction of smooth muscle within the gland. A third drug (5-alpha-reductase inhibitor; finasteride; *Proscar*) may be added to reduce prostate volume.

Cost: My pharmacy quotes: Detrol ER 4 mg $3.77 each; $1375.00 per year
Flomax 0.4 mg $2.67 each; $ 973.00 per year.

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"Most Proponents Of E-BM Adopt A Balanced View."

11-11 ANALOGIES BETWEEN READING OF MEDICAL AND RELIGIOUS TEXTS

Conventional medicine can be seen as a belief system characterized by a profession of faith in evidence-based medicine (**E-BM**). Faith in E-BM follows from the benefits it has delivered in the past, and continues to deliver. It is the best method we have for navigating our way through potential new treatments.

E-BM is analogous to many religious traditions. It is a canon of sacred texts (medical literature). Differences in interpretation can often be traced to different assumptions underlying our reading of the literature.

Just as there are fundamentalist, conservative, and liberal views of religious texts, there are fundamentalist, conservative, and liberal views of E-BM.

Religious fundamentalism:

Has been defined as the strict maintenance of the ancient or fundamental doctrines of a religion.

Fundamentalism is associated with literal readings of sacred texts. Fundamentalism sees truth as unified, revealed, absolute, and inerrant.

Supporters have a black and white view, seeing themselves as the true keepers of the faith, with good reasons for an absolute belief that they are right.

Critics of religious fundamentalists see the world in shades of grey, and view fundamentalism as righteous and simplistic. Texts can be interpreted in different ways.

Medical fundamentalism:

Variation in interpretation of the medical literature shares many of the features of variation of interpretation of religious texts.

Medical fundamentalists take a strict and literal view of the literature. They give little allowance for individualization, show little skepticism about limitations of the literature, and tend to undervalue non-randomized evidence. Their approach sees the literature as law—a series of "sacred texts" that are treated with great respect and are to be applied literally. Any deviation from the text is seen as heresy. They tend to be self righteous and denigrate other interpretations.

"Of course, the analogy is not to be taken too far. Violence and fanaticism are not features of most medical decision making."

Most proponents of E-BM adopt a balanced view. They emphasize the limitations of E-BM, the need for judgment in applying it to individual patients, and the validity of evidence other than randomized, controlled trials. They tend to see the literature as a guide, establishing principles that need to be applied to specific situations.

Randomized, controlled trials may show a consistent improved survival for a defined period. "The main difficulty in applying these data is the external validity." How should we treat the patients with serious co-morbidity? And patients who do not meet the inclusion criteria of the trial?

Conclusions:

Belief systems in medicine are analogous to those of religious interpretations.

Attitudes of medical and religious literature can be characterized as fundamentalist, conservative, or liberal.

E-BM and the scientific medical literature are the bedrock of modern medical practice.

Interpretation of the evidence is not clear cut.

The advantage of the conservative position is that it is clear and well defined. The advantage of the liberal position is that it is flexible. But, if you allow a large degree of latitude to interpretation, where does it stop?

"One of the difficulties of the debate in both religious and medical contexts is that attitudes tend to be polarized."

"We need to be aware of our differing assumptions, avoid self-righteousness, and conduct these discussions in an atmosphere of tolerance."

BMJ November 18, 2006; 333: 1068-70 Editorial by Matthew Links, University of New South Wales, Kogarah Australia.

Comments by the editor of Practical Pointers:

Investigators, by defining entrance and exclusion criteria, try to choose subjects for RCTs as similar to each other as possible. But, subjects included in RTCs are not uniform. They are not clones. They differ in many respects from each other.

1) Some are at greater risk for the outcome studied. They may benefit more from the intervention as indicated by the mean.
2) Some are at lesser risk for the outcome. They will not benefit as much from the intervention as indicated by the mean.
3) Some are more susceptible to harms of the treatment. They may have more frailty, and more co-morbidity.
4) Some are at lesser risk of harms of the treatment. They may be more robust and have less co-morbidity.

The conclusions of the RTC are expressed as the means of benefits and harms. They do not necessarily apply to the next patient seen by a primary care clinician. An editorial in Annals Int Med November 2006 (page 700) quotes Stephen Jay Gould as remarking “The median is not the message”.

RCTs always include subjects who are excluded, and many who withdraw from the trial for lack of compliance and other reasons. The primary care clinician still has to make the decision about a patient who fits this group.

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