PRACTICAL POINTERS

FOR

PRIMARY CARE MEDICINE

ABSTRACTED MONTHLY FROM THE JOURNALS

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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 25-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
10 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.

Editor/Publisher.

9-1 LESSONS FROM THE MAMMOGRAPHY WARS

We, as a profession, have often failed to acknowledge that every medical intervention, no matter how beneficial for some patients, will provide diminishing returns as the threshold for intervention is lowered. For women 40-49, the false positive rate of mammography is high and the expected benefits are low.

As the risk of BC rises, the benefits of mammography increase, and the relative harms decrease.

Generally, the net benefit of all medical interventions is a continuous function of 3 factors: risk of morbidity and mortality if untreated ; the treatment's relative risk reduction; and the treatment's net harm. (Risk; Relative risk reduction [RRR]; and harms.)

Net benefit = $(\text{Risk}_{noRx} \ \text{X} \ \text{RRR}_{Rx})$ - (Harms_{Rx})

As the risk of no treatment (Risk_{noRx}) decreases, the net benefit of treatment will decrease,, even if the treatment's RRR remains constant.

Despite this continuing gradient of treatment benefit vs harm, medical decision-making is necessarily discrete. For any individual patient we must choose to treat or not to treat, to screen or not to screen. We are constantly trying to elucidate clear thresholds for intervention (eg, level of HbA1c and LDL-cholesterol). What we often do not remember is that these thresholds are to some degree subjective and arbitrary and are necessarily a value judgment.

We need to distinguish between choices that are clear-cut and those that require individualized decision-making. Rather than seeking a single universal threshold for intervention, we should define two distinct thresholds: 1) One above which benefits clearly outweigh the harms, and 2) One below which concern about harms clearly outweighs benefit.

Between 1) and 2) there is 3) a grey area of indeterminate net benefit, in which clinicians should defer to individual patient's preference.

When a given service is successfully extended to more people with more intensity, those providing the service tend to grow in importance and profitability.

"In the United States, where medical specialists often enjoy the exalted status in the minds of the public, if experts shout loudly that every woman 40 years of age must be screened annually for breast cancer, then breast cancer must be important, screening must be a basic human right, and doctors who provide this service must have greater value and authority."

But what if those experts are basing their recommendations on more than the interest of the patient?

This is an important article .

Age is an important determinant of the value of screening. Benefit from mammography is much greater between ages 60-69 than between 40-49. What about much older age--say 80-89? I believe we should also set an age for discontinuing screening.

At old-old age, we gain much less benefit from screening colonoscopy, lipid levels, HbA1c, and mammography simply because the length of life is shorter and preventive interventions are less effective.

The editorial briefly mentions monetary costs. Almost 2000 women would need to be invited for mammography to prevent one death from BC during 11 years of follow-up at a direct cost of more than 20 000 visits for imaging and about 2000 false positives.

I attempted a rough estimate of costs of screening 2000 women age 40-49 every year for 11 years to save one life:

Number of mammograms -- 2000 X 11 = 22 000

If costs for a single mammogram is $255 $255 X 22 000 = $5 610 000

False Positive (callback mammograms) 2000 X $255 =   500 000

Biopsies 500 at $1000 =   500 000

Mastectomies 50 at $10000 =   500 000
                                                          $7 110 000

Society must decide if the value of one life is without price, or whether $7 110 000 could be better spent on other public health interventions.

If I may describe a personal hospitalization:

Recently I developed massive diarrhea and vomiting (An intestinal virus?) I collapsed at home because of dehydration. I had no abdominal pain or tenderness.

I received excellent treatment in the hospital for which I am most grateful. I left the hospital within 48 hours.

Before I was admitted I was transported to the X--ray department and received a CT scan of the abdomen. Later the ER physician recommended a carotid artery ultrasound, which I refused.

I ask: Was the CT necessary? Would it be safe to defer this decision until the clinical picture became cleared? Would CT have been recommended if the hospital had no CT equipment and I had to be transported to a nearby facility where a scanner was available? Was a carotid ultrasound indicated?

If a hospital or practice has a state-of-the art machine available, it will be used.

NAFLD Has Emerged As A Growing Public Health Problem.

9-2 RISK OF CARDIOVASCULAR DISEASE IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Patients with the non-alcoholic fatty liver disease (**NAFLD**), both children and adults, typically meet the diagnostic criteria for the metabolic syndrome (abdominal obesity, hypertension, dyslipidemia, and dysglycemia). Thus, they have multiple risk factors for cardiovascular disease.

A large meta-analysis confirmed that NAFLD is strongly associated with increased carotid artery medial-intimal thickness and an increased prevalence of carotid atherosclerotic plaques.

Given the strong association between NAFLD and markers of subclinical cardiovascular disease (**CVD**), it is not surprising that patients with NAFLD have a higher prevalence of clinically manifest CVD.

Many large population-based studies using elevated liver enzyme levels as surrogate markers of NAFLD (and should therefore be interpreted cautiously) have shown that NAFLD is associated with an increased risk of CVD, independent of alcohol consumption and several established CVD risk factors.

One meta-analysis concluded that gamma-glutamyltransferase levels were an independent long-term predictor of incident CVD events. (Elevated levels of serum alanine transferase failed to show any independent association.)

Expanded and inflamed visceral adipose tissue releases a wide array of molecules potentially involved in development of insulin resistance and atherosclerosis. This includes free fatty acids and various inflammatory cytokines. These cytokines may derive from adipocytes or infiltrating macrophages, or both.

Hepatic steatosis results from increased hepatic intake of free fatty acids derived mainly from hydrolysis of adipose-tissue triglycerides and also from dietary chylomicrons and hepatic lipogenesis.

Cardiovascular risk is greater among patients with non-alcoholic steato-*hepatitis* than in those with simple steatosis. Ample evidence indicates that NAFLD, especially its necro-inflammatory form (non-alcoholic steatohepatitis) can exacerbate both hepatic and systemic insulin resistance and promote the development of atherogenic dyslipidemia, thus favoring progression of CVD.

The growing body of evidence suggests that CVD is the leading cause of death in patients with advanced NAFLD, and that it is associated with an increased risk of incident CVD independent of traditional risk factors and the metabolic syndrome.

 Current recommendations for treatment are limited to weight reduction by means of diet and exercise, treatment of individual components of the metabolic syndrome, insulin sensitizers (metformin and pioglitazone), and bariatric surgery for obesity.

It is not known whether ameliorating NAFLD, will ultimately prevent or slow development and progression of CVD. The prognostic value of NAFLD in CVD risk-stratification remains debatable.

Nevertheless, the strong association between NAFLD and CVD risk deserves particular attention in view of its potential implication for primary care practice. The current body of evidence argues for careful monitoring and evaluation of the risk of CVD in all patients with NAFLD.

Two key questions remain: 1) Is NAFLD associated with CVD as a consequence of shared risk factors, or does NAFLD contribute to CVD independently of these factors? 2) Is the risk of CVD increased in patients with simple steatosis, or is the necro-inflammatory milieu of non-alcoholic steatohepatitis a necessary pro-atherogenic stimulus?

NAFLD has emerged as a growing public health problem.

Obviously, we have much more to learn.

I enjoyed this review. I had not realized before the importance of inflammation in the intra-peritoneal-fatty liver disease process..

I have argued in the past that we do not need any more risk factors for CVD until we fully utilize the ones we have. I would now add NAFLD as an important risk factor--risk added to that of the obese abdomen. We have long recognized that the fatty abdomen is a risk factor--the key to the metabolic syndrome. Both the metabolic syndrome and NAFLD are common. Thus, they must co-exist in many individuals.

Now we add a series of risk factors: abdominal obesity + hepatic steatosis, + steato-hepatitis, + diabetes. Each step adds to risk. High alcohol consumption brings added damage to the liver.
I believe it would be prudent for primary care to measure liver enzyme levels in patients with obvious abdominal obesity. And, if high,, go on to ultrasound to determine the extent of steatosis.

Perhaps patients' knowledge of this added risk would encourage them to adopt more healthy lifestyles.

Associated With Increased Risks Of CHD Events And CHD Mortality
9-3 SUBCLINICAL HYPOTHYROIDISM AND RISK OF CORONARY HEART DISEASE AND MORTALITY

Subclinical hypo-thyroidism (**SCHT)** is defined as elevated serum thyroid stimulating hormone (TSH) and normal thyroxine (**T4**) concentrations.

Because SCHT has been associated with hyper-cholesterolemia and atherosclerosis, screening and treatment have been advocated to prevent CHD. Three recent meta-analyses found moderately increased risk, but with heterogeneity among individuals.

This study determined individual data of 55 287 participants with over 500 000 years of follow-up (1972-2007) supplied from 11 prospective cohorts. All reported total deaths and CHD deaths. All had a comparison group with euthyroidism. 25 977 participants from 7 of the cohorts also reported CHD events.

Measured serum TSH levels and T4 levels at baseline. Followed participants over time. (Medians ranged from 2,5 to 20 years).

Defined subclinical hypothyroidism as serum TSH of 4.5 mIU/L or greater and a normal T4.

Among the 55 287 participants, 6.2% had SCHT.

CHD events, CHD mortality and total mortality were greater in the SCHT groups: (4.3%; 2.4%; and 0.9%)

The overall hazard ratio (**HR**) adjusted for age and sex compared with those with normal

thyroid function:	HR	Per 1000 person years
For CHD events	1.18	4 more events
CHD mortality	1,14	1,.5 more deaths
Total mortality	1.09	2 more deaths

. As TSH values rose, HRs for CHD events and mortality rose. Participants with TSH levels of 10 and above had significantly increased risk of CHD events. (HR = 1.89)

The study could not address whether the risks are attenuated by thyroxine replacement.

Subclinical hypothyroidism was associated with increased risks of CHD events and CHD mortality in those with higher TSH levels, particularly those with TSH of 10 mIU/L or greater.

SCHT is common in primary care.

The study begs the question about treatment. Generally, treatment of SCHT has been discouraged, although there is some disagreement on this point.

We really do not know whether treatment of SCHT will benefit.

It seems to me that, in view of the increased risk of high TSH levels, treatment may be indicated in this group.

Before any treatment is proposed, primary care clinicians should determine if there are any suggestive symptoms compatible with hypothyroidism, and assess the patients' preference about treatment.

If thyroxine replacement is prescribed, I believe it should go low and slow, with careful follow-up.

If the decision is made not to treat, the patient should also be followed carefully. Some patients will go on to develop clinical hypothyroidism.

9-4 LONG-TERM EFFECTS OF A LIFESTYLE INTERVENTION ON WEIGHT AND CARDIOVASCULAR RISK FACTORS IN INDIVIDUALS WITH TYPE-2 DIABETES

The Look AHEAD is the longest multidisciplinary lifestyle study examining the long-term effects of lifestyle interventions in patients with DM-2.

This multi-centered randomized trial followed 5145 obese and overweight individuals (age 45-76) with DM-2.

Randomized participants to: 1) Intensive lifestyle interventions (**LI**), or 2) Diabetes support and education (**DSE;** the controls)

The LIs included changes in diet and physical activity designed to induce at least a 7% weight loss:

1) A calorie goal of 1200 to 1800 kcal/d with less than 30% fat. (< 10% saturated fat) and a minimum of 15% from protein.

2) Exercise goal of 175 minutes per week of brisk walking or similar.

3) Patients in the LI group were seen weekly for the first 6 months by registered dieticians, behavioral counselors, or exercise specialists; 3 times a month for the next 6 months. Thereafter, at least once a month.

The DSE patients were invited to 3 group sessions each year, focusing on diet, physical activity and social support.

At 4 years: (Means)	LI	DSE
Weight loss (%)	4.7	1.1
Fitness (% METs over baseline)	+5.1%	+1.1%%
HbA1c (goal of < 7%)	57%	51%
BP (less than 130/80)	63%	61%
LDL-cholesterol (< 100 mg/dL)	61%	65%
HDL-cholesterol (%)	+3.5%	+2%

In general, benefits were greater at one year than at 4 years. Effects on weight, fitness, HbA1c and systolic BP gradually decreased from year 1 to year 4, although some benefit remained.

The positive impact of the intervention on several of the risk factors was greatest at year one, followed by recidivism toward the baseline over the next 3 years.

The DSE group also experienced benefits over 4 years.

Conclusion: Intensive lifestyle interventions over 4 years were successful in producing sustained weight loss and improvements in CVD risk factors and glycemic control in patients with DM-2.

I congratulate the investigators on completion of a difficult study. I look forward to follow-up reports of clinical benefits and whether benefits are sustained over a longer period. Although reducing risk factors over 4 years may improve clinical outcomes for a long time (legacy effect), benefits would be much greater if risk factors were reduced permanently.

Is this intervention applicable to primary care practice? I believe not for several reasons:

The intervention time required would be exceptionally long for both clinicians and patients. The investigators screened 16 000 individuals before 5145 agreed to participate.
Costs would be very high --much higher than most could afford.
The DSE group did obtain some benefit. This approach would be more applicable to primary care.

We continue to struggle to prevent DM-2 (it is preventable). Our efforts have been unsuccessful. It will require the general public to take more responsibility for their own health.

Higher Animal-Based Fat, Lower Carbohydrate Diet Was Associated With A Higher Mortality.
9-5 LOW CARBOHYDRATE DIETS AND ALL-CAUSE MORTALITY AND CAUSE-SPECIFIC MORTALITY

Low carbohydrate diets (**LCD; the Atkins Diet**) have been claimed to promote weight loss and improve cholesterol levels and BP. Weight-loss trials have found that LCD are as effective, or more effective, than diets with higher carbohydrate content.

However, effects on lipid profiles of LCDs containing substantial animal products were mixed, resulting in greater improvements in HDL-cholesterol with perhaps less favorable changes in LDL--cholesterol. These diets can be high in red meat and low in fruits, vegetables and whole grains.

Prospectively examined the relationship between different types of LCDs and all-cause and cause-specific mortality in 2 large cohorts: After excluding subjects with cancer, heart disease, and diabetes, the database included 85 168 women and 44 548 men.

These investigators developed scores to characterize LCDs on the basis of the proportions of carbohydrates, fat, and protein from animal or vegetable sources. They previously found that women on a LCD emphasizing vegetable sources of fat and protein were associated with lower risk of type-2 diabetes and coronary heart disease. However, long-term data of LCDs on mortality are scarce.

Overall, the low-carbohydrate diets were associated with a modest *increase* in overall mortality. (Hazard ratio [HR] = 1.12)

The animal-fat low carbohydrate score (comparing extreme deciles) was associated with a *higher* all-cause mortality (HR = 1.23). And cancer mortality (HR = 1.28)

In contrast, a higher vegetable fat low carbohydrate score was associated with lower all-cause mortality (HR = 0.80) and cardiovascular mortality) HR = 0.77)

. "In our two cohorts of U.S. men and women who were followed for 20 to 26 years, we observed that the overall low-carbohydrate diet score was only weakly associated with all-cause mortality. However, a higher animal low-carbohydrate score was associated with higher all-cause and cancer mortality, whereas a higher vegetable low carbohydrate diet was associated with lower mortality, particularly CVD mortality."

The health effects of a low-carbohydrate diet may depend on the type of protein and fat. A diet that includes mostly vegetable sources of protein and fat is preferable to a diet with mostly animal sources of protein and fat.

Conclusion: Consumption of a vegetable-based low carbohydrate diet was associated with a lower risk for all-cause mortality and CVD mortality. High scores for the animal-based low carbohydrate diet were associated with a higher risk of overall mortality.

The study is more complex than I have indicated. It makes sense.

The study did not mention fish fat.

There was no mention of weight loss.

I have not read anything about the Atkins diet recently. I do not know if it remains popular.

A Remarkable New Automated Machine For Detecting M Tuberculosis And Rifampin Resistance

9-6 RAPID MOLECULAR DETECTION OF TUBERCULOSIS AND RIFAMPIN RESISTANCE

This article describes a new automated machine which has high sensitivity and specificity in detection of *M tuberculosis* and rifampin resistance in sputum.

Please read the full abstract.

We await confirmation. If the machine is dependable, and not too costly, it may be a major advance.

"Would I Be Surprised If This Patient Died Within The Next Year?"

9-7 WE'RE ALL GOING TO DIE.   DEAL WITH IT

In the years since Cicely Saunders opened St. Christopher's Hospice in 1967, palliative care has blossomed into one of the glories of British medicine.

Although much had been learnt about caring for cancer patients at the end of their lives, these lessons have been inadequately appreciated by doctors treating patients dying from causes other than cancer.

Eventually everyone dies--many more of gradual physical and mental decline than cancer. Early recognition of those patients with advanced illness who would benefit from supportive and palliative care is the key to good management. A positive answer to the question: "Would I be surprised if this patient died within the next year?" is one trigger indicating that such care should begin.

After that decision come the difficult conversations. Not everyone will want to talk about the end of their life, but "the right conversations with the right people at the right time can enable patients and their loved ones to make the best use of the time that is left and prepare for what lies ahead."

The obstacles to plain speaking and clear thinking about death are legion. We live in a culture in which people are uncomfortable with their own mortality. This needs to change "so that dying, death and bereavement will be accepted as a natural part of everyone's life cycle."

Doctors seem to find this message harder to accept than others, with some of them regarding any death as a failure. In a dramatic attempt to stave off the inevitable, typically more money is spent on health care during a patient's last year of life than any other year.

The UK's General Medical Council recommends that death should become an explicit discussion point when patients are likely to die within 12 months. Frank discussion of the topic throws up many challenges. These include where a patient wants to die, and who should provide palliative care and recognition of the spiritual needs of patients facing death.

BMJ September 25, 2010; 341: 645 Commentary by Tony Delamothe, Deputy Editor BMJ, London

The best way I have read to approach the subject of death is to ask "Are you at peace?"
Without death there would be no life. RTJ

BMJ presents 6 commentaries on death and dying in this issue. Some quotes:

DYING MATTERS: LET'S TALK ABOUT IT First author Jane E Seymour, University of Nottingham, UK

"As death has been less common in our daily lives, it has become harder to consider our own mortality, or that of those close to us. Lack of openness about death has negative consequences to the quality of care provided to the dying and

bereaved. Eradicating ignorance about what can be achieved with modern palliative care and encouraging dialogue about end of life care issues are important means of changing attitudes."

RECOGNIZING AND MANAGING KEY TRANSITIONS IN END OF LIFE CARE First author Kristy Boyd, University of Edinburgh, Scotland

"Prognostic paralysis may delay a change in gear for too long. Being alert to the possibility that a patient might benefit from supportive and palliative care is central to delivering better end of life care."

HAVING THE DIFFICULT CONVERSATIONS ABOUT THE END OF LIFE   First author Stephen Barklay, Institute of Public Health, Cambridge, UK

"Clinicians need to create repeated opportunities for patients to talk about the future and the end of life care, guided by the patient as to timing, pace, and content of such talks, and respecting the wishes of those who do not want to discuss such matters."

ACHIEVING A GOD DEATH FOR ALL   First author John Ellershaw, Marie Curie Cancer Care London, UK

"A good death for all is now recognized as a priority at societal and political levels. To achieve this goal we need a fundamental shift of emphasis to train and educate heath care professionals to ensure rigorous assessment of new end of life care services that aim to improve quality and choice, and to explore best use of resources."

SPIRITUAL DIMENSIONS OF DYING IN PLURALISTIC SOCIETIES First author Liz Grant, St. Columba's's Hospice,

"Despite the decline of formal religion many people still regard the idea of spirituality as essential to their sense of self, especially at times of stress."

9-1 LESSONS FROM THE MAMMOGRAPHY WARS

Since 2002, annual mammography has been recommended for women age 40 and older. Suddenly, an independent government-funded panel suggested that this schedule might be too much--that less might be better.

Advocates of breast-cancer (**BC**) screening immediately took action, denouncing the panel's statement as government rationing, suggesting that the panel members had ignored the medical evidence, and even implying that the panel members were guilty of a callous disregard for life.

In reality, this independent panel simply recommended that routine screening begin at age 50, and women age 40-49 should make individual decisions with their doctors advice.

The panel also recommended that screening be performed every other year, which would halve the number of screens while maintaining most of the benefits. The panel concluded that we had previously over estimated the value of mammography, that mammography is good, but not that good.

We, as a profession, have often failed to acknowledge that every medical intervention, no matter how beneficial for some patients, will provide diminishing returns as the threshold for intervention is lowered. For women 40-49, the false positive rate is high and the expected benefits are low. Almost 2000 women would need to be invited for mammography to prevent one death from BC during 11 years of follow-up at a direct cost of more than 20 000 visits for imaging and about 2000 false positives.

These ratios are much more favorable in women age 60-69.

As the risk of BC rises, the benefits of mammography increase, and the relative harms decrease.

Generally, the net benefit of all medical interventions is a continuous function of 3 factors: risk of morbidity and mortality if untreated ; the treatment's relative risk reduction; and the treatment's net harm. (Risk; Relative risk reduction [RRR]; and harms.)

Net benefit = $(\text{Risk}_{\text{noRx}} \text{ X } \text{RRR}_{\text{Rx}})$ - $(\text{Harms}_{\text{Rx}})$

As the risk of no treatment ($\text{Risk}_{\text{noRx}}$) decreases, the net benefit of treatment will decrease,, even if the treatment's RRR remains constant.

Despite this continuing gradient of treatment benefit vs harm, medical decision-making is necessarily discrete. For any individual patient we must choose to treat or not to treat, to screen or not to screen. We are constantly trying to elucidate clear thresholds for intervention (eg, level of HbA1c and LDL-cholesterol). What we often do not remember is that these thresholds are to some degree subjective and arbitrary and are necessarily a value judgment.

We need to distinguish between choices that are clear-cut and those that require individualized decision-making. Rather than seeking a single universal threshold for intervention, we should define two

distinct thresholds: 1) One above which benefits clearly outweigh the harms, and 2) One below which concern about harms clearly outweighs benefit.

Between 1) and 2) there is 3) a grey area of indeterminate net benefit, in which clinicians should defer to individual patient's preference.

It is just such a grey area into which women in their 40s are assigned by the new mammography guidelines.

In our pursuit of excellence, we have generally preferred to ignore these grey areas. It is easier to simply lower the threshold for intervention and recommend mammography for all women age 40-49 rather than rely on individual judgment.

When a given service is successfully extended to more people with more intensity, those providing the service tend to grow in importance and profitability.

 "In the United States, where medical specialists often enjoy the exalted status in the minds of the public, if experts shout loudly that every woman 40 years of age must be screened annually for breast cancer, then breast cancer must be important, screening must be a basic human right, and doctors who provide this service must have greater value and authority."

But what if those experts are basing their recommendations on more than the interest of the patient?

NEJM September 8, 2010; 363: 1076-79 "Sounding Board", Editorial, first author Kenneth H Quanstrum, the University of Michigan, Ann Arbor.

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NAFLD Has Emerged As A Growing Public Health Problem.

9-2 RISK OF CARDIOVASCULAR DISEASE IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Patients with the non-alcoholic fatty liver disease (**NAFLD**), both children and adults, typically meet the diagnostic criteria for the metabolic syndrome (abdominal obesity, hypertension, dyslipidemia, and dysglycemia). Thus, they have multiple risk factors for cardiovascular disease.

A large meta-analysis confirmed that NAFLD is strongly associated with increased carotid artery medial-intimal thickness and an increased prevalence of carotid atherosclerotic plaques. The medial-intimal thickness seems to be associated with the severity of the NAFLD.

CLINICALLY MANIFEST CVD

Given the strong association between NAFLD and markers of subclinical cardiovascular disease (**CVD**), it is not surprising that patients with NAFLD have a higher prevalence of clinically manifest CVD.

In a large study of 3000 unselected patients with type-2 diabetes, the prevalence of coronary, cerebrovascular, and peripheral vascular disease was remarkably higher among patients with NAFLD, independent of traditional risk factors.

In another large study of unselected patients with type-2 diabetes, the prevalence of coronary, cerebrovascular, and peripheral vascular disease was remarkably higher among patients with NAFLD.

An autopsy study of over 700 children showed that the prevalence of coronary heart disease (**CHD**) was increased by a factor of 2 among those with NAFLD.

SERUM LIVER ENZYMES

Many large population-based studies using elevated liver enzyme levels as surrogate markers of NAFLD (and should therefore be interpreted cautiously) have shown that NAFLD is associated with an increased risk of CVD, independent of alcohol consumption and several established CVD risk factors.

One meta-analysis concluded that gamma-glutamyltransferase levels were an independent long-term predictor of incident CVD events. (Elevated levels of serum alanine transferase failed to show any independent association.)

LIVER ULTRASOUND

NAFLD diagnosed on ultrasonography in a community-based cohort of over 1600 healthy adults was associated with an increased risk of non-fatal CVD events independently of CVD risk factors.

To date, the evidence suggests that patients with NAFLD have multiple risk factors for CVD, and that CVD as a cause of death is more common than liver disease as a cause of death in such patients. NAFLD is linked to increased risk of CVD events both in patients with type-2 diabetes and in those without. However, more study is needed to determine whether NAFLD poses an independent risk above and beyond that of known CVD risk factors.

PUTATIVE MECHANISMS LINKING NAFLD TO CVD

Two key questions ask: 1) Is NAFLD associated with CVD as a consequence of shared risk factors, or does NAFLD contribute to CVD independently of these factors? 2) Is the risk of CVD increased in patients with simple steatosis, or is the necro-inflammatory milieu of non-alcoholic steatohepatitis a necessary pro-atherogenic stimulus?

The close correlations of NAFLD, abdominal obesity, and insulin resistance make it extremely difficult to distinguish the precise causal relationships underlying the increased risk.

The biological mechanisms potentially responsible for the accelerated atherogenesis probably have their origin in the expanded visceral adipose tissue, with the liver being both the target of the resulting systemic abnormalities and a source of proatherogenic molecules that amplify the arterial damage.

Expanded and inflamed visceral adipose tissue releases a wide array of molecules potentially involved in development of insulin resistance and atherosclerosis. This includes free fatty acids and various inflammatory cytokines. These cytokines may derive from adipocytes or infiltrating macrophages, or both.

The resulting adipose-tissue inflammation is one of the earliest steps in the chain of events leading to insulin resistance.

INFLAMMATION, COAGULATION, AND DISORDERED METABOLISM

Hepatic steatosis results from increased hepatic intake of free fatty acids derived mainly from hydrolysis of adipose-tissue triglycerides and also from dietary chylomicrons and hepatic lipogenesis.

Insulin resistance is a pathogenic factor in the development and progression of NAFLD. It also plays a major role in the development of the metabolic syndrome and cardiovascular disease.

In the presence of increased free fatty acid flux and chronic low-grade inflammation, the liver is both the target of, and a contributor to, systemic inflammatory changes.

Hepatic steatosis is associated with increased production of inflammatory cytokines. Increased intrahepatic cytokine expression is likely to play a key role in the progression of NAFLD, and CVD.

Circulating levels of several inflammatory markers are highest in patients with non-alcoholic steato-*hepatitis,* intermediate in those with simple steatosis and lowest in control subjects without steatosis.

Men with NAFLD have higher levels of C-reactive protein and fibrinogen than did overweight men without NAFLD. NAFLD, can contribute to a more atherogenic risk profile over and above the contribution of visceral obesity.

Patients with non-alcoholic steatohepatitis and those with chronic viral hepatitis have markedly greater carotid artery intimal-medial thickness than healthy subjects. This is consistent with the hypothesis that liver inflammation plays a role in the pathogenesis of CVD.

Ample evidence indicates that NAFLD, especially its necro-inflammatory form (non-alcoholic steatohepatitis) can exacerbate both hepatic and systemic insulin resistance and promote the development of atherogenic dyslipidemia, thus favoring progression of CVD.

CONCLUSION

NAFLD has emerged as a growing public health problem.

Increases in CVD morbidity and mortality are important clinical features. The growing body of evidence suggests that CVD is the leading cause of death in patients with advanced NAFLD, and that it is associated with an increased risk of incident CVD independent of traditional risk factors and the metabolic syndrome.

The pathogenic process may occur through the systemic release of proatherogenic mediators from the steatocic and inflamed liver.

The treatment strategies for NAFLD and CVD are similar. Current recommendations are limited to weight reduction by means of diet and exercise and to the treatment of individual components of the metabolic syndrome. Bariatric surgery for obesity, insulin sensitizers (metformin and thiazolidinediones-- pioglitazone is probably the drug of choice) for type-2 diabetes, and drugs directed at the renin-angiotensin-aldosterone system to control hypertension may have beneficial hepatic effects..

There is no convincing evidence that lipid-lowering agents, including statins, are beneficial for patients with NAFLD, but they can be safely prescribed for conventional indications such as diabetes and high CVD risk.

It is not known whether ameliorating NAFLD, will ultimately prevent or slow development and progression of CVD. The prognostic value of NAFLD in CVD risk-stratification remains debatable.

Nevertheless, the strong association between NAFLD, and CVD risk deserves particular attention in view of its potential implication for primary care practice. The current body of evidence argues for careful monitoring and evaluation of the risk of CVD in all patients with NAFLD.

NEJM September 30, 2010; 363: 1231-40 Review article, first author Giovanni Targher, University of Verona, Italy

A short article in BMJ August 2009, first author Neeraj Bhala, University of Sydney, NSW Australia stresses some points.

NAFLD is the most common cause of liver dysfunction. Biopsy is the gold standard for diagnosis.

The disease may progress to cirrhosis, liver decompensation and liver cancer.

Some authorities have found that alanine aminotransferase is elevated (in addition to gamma glutamyltransferase. Alanine amino transferase levels are usually greater than aspartate aminotransferase. No biochemical thresholds have been specified for diagnosis of NAFLD.

Patients with advanced NAFLD can have normal liver function.

Increases in bilirubin occur with development of cirrhosis.

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9-3 SUBCLINICAL HYPOTHYROIDISM AND RISK OF CORONARY HEART DISEASE AND MORTALITY

Subclinical hypo-thyroidism (**SCHT)** is defined as elevated serum thyroid stimulating hormone (TSH) and normal thyroxine (**T4**) concentrations.

Controversy persists on the indication for TSH screening and treatment of SCHT. Data on the association between SCHT and CHD are conflicting.

Because SCHT hs been associated with hyper-cholesterolemia and atherosclerosis, screening and treatment have been advocated to prevent CHD. Three recent meta-analyses found moderately increased risk, but with heterogeneity among individuals.

STUDY

1 Individual data on 55 287 participants with over 500 000 years of follow-up (1972-2007) were supplied from 11 prospective cohorts. All reported total and CHD deaths. All had a comparison group with euthyroidism.

2. 25 977 participants from 7 of the cohorts also reported CHD events.

3. Measured serum TSH levels and T4 levels at baseline, Followed participants over time. (Medians ranged from 2,5 to 20 years).

4. Defined subclinical hypothyroidism as serum TSH of 4.5 mIU/L to 19.9, with a normal T4. level. Euthyroidism was defined as a TSH of 0.5 mIU/L to less than 4.5 mIU/L. Stratified subclinical hypothyroidism as: mild -- TSH 4.5 to 6.9; moderate -- 7.0 to 9.9; and severe -- 10.0 -19.9. All with normal T4 levels.

5. The investigators analyzed individual participant data to synthesize evidence across the studies. This eliminated bias and allowed performance of time-to-event analyses.

6. Outcome measures = CHD events, CVD mortality, and total mortality.

RESULTS

1. Among the 55 287 participants, 6.2% had SCHT.

2. During follow-up, 2168 died of CHD, and 4479 (among 7 cohorts) had CHD events.

3. CHD events, CHD mortality and total mortality were greater in the SCHT groups:

	SCHT	Euthyroid	Difference
CHD events	430/2020	4040/23 952	
	21.2%	16.9%	4.3%

CHD mortality	210/3348	1958/50 953	
Total mortality	6/2%	3.8%	2.4%
	915//3450	8749/51837	
	2.6%	1.7%	0.9%

4. The overall hazard ratio (**HR**) adjusted for age and sex compared with those with normal

thyroid function:

	HR	Per 1000 person-years
For CHD events	1.18	4 more events
CHD mortality	1,14	1,.5 more deaths
Total mortality	1.09	2 more deaths

5. As TSH values rose, HR for CHD events and mortality rose. Participants with TSH levels of 10 and
above had significantly increased risk of CHD events.

	CHD events	CHD mortality	Total mortality
TSH levels		Hazard ratios	
0.5 - 4.49	1.00	1.00	1.00
4.5 - 6.9	1.00	1.09	1.06
7.0 - 9.9	1.12	1,17	1.12
10 - 19.9	1.89	1.58	1.22

DISCUSSION

1. SCHT was associated with increased risk of CHD events and CHD deaths in those with higher
   TSH levels. Risk was significantly increased in those with TSH of 10 mIU/L and above.
2. These associations persisted after adjustment for traditional CHD risk factors and did not differ
   significantly with age.
3. Minimal TSH increases were not associated with increased risks. This is important because
   many adults with minimal TSH elevations are treated in clinical practice.
4. There was no significant effect of preexisting CHD at baseline on outcomes.
5. These results are generally consistent with previous studies.
6. SCHT may be a milder form of overt hypothyroidism, which has been associated with increased
   arterial stiffness, altered endothelial function, increased atherosclerosis and altered coagulability.
   (Adults with higher TSH levels are more likely to develop overt hypothyroidism.)
7. The study could not address whether the risks are attenuated by thyroxine replacement.

CONCLUSION

Subclinical hypothyroidism was associated with increased risks of CHD events and CHD mortality in those with higher TSH levels, particularly those with TSH of 10 mIU/L or greater.

JAMA September 22-29;304; 1365-74 Review article for the Thyroid Studies Collaboration, first author Nicholas Rodondi, University of Lausanne Switzerland.

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9-4 LONG-TERM EFFECTS OF A LIFESTYLE INTERVENTION ON WEIGHT AND CARDIOVASCULAR RISK FACTORS IN INDIVIDUALS WITH TYPE-2 DIABETES

Improving glycemic control and risk factors for cardiovascular disease (**CVD**) in patients with type-2 diabetes (**DM-2)** is critical for preventing long-term vascular complications.

The Look AHEAD is the longest multidisciplinary lifestyle study examining the long-term effects of lifestyle interventions in patients with DM-2.

STUDY

1. This multi-centered randomized trial followed 5145 obese and overweight individuals (age 45-76) with DM-2.

2. Randomized participants to: 1) Intensive lifestyle interventions (**LI**), or 2) Diabetes support and education (**DSE;** the controls)

3. Examined the effect of intensive LIs on weight, fitness, glycemic control, and CVD risk factors over a 4-year period.

4. The LIs included changes in diet and physical activity designed to induce at least a 7% weight loss:

   1) A calorie goal of 1200 to 1800 kcal/d with less than 30% fat. (< 10% saturated fat) and a minimum of 15% from protein.

   2) Exercise goal of 175 minutes per week of brisk walking or similar.

   3) Patients in the LI group were seen weekly for the first 6 months by registered dieticians, behavioral counselors, or exercise specialists; 3 times a month for the next 6 months. Thereafter at least once a month.

5. The DSE patients were invited to 3 group sessions each year, focusing on diet, physical activity and social support.

6. For both groups, the patients' own physician provided all needed medical care and made

changes in medications as needed.

7. Participants were paid $100 annually.

RESULTS

1. At baseline, 60% were women, 37% from racial minorities, 14% had a history of CVD. The average age was 59 and BMI was 36. The average duration of DM-2 was 7 years. 93% completed the entire 4 years.

2. Participants in both groups continued to be treated individually by various drugs prescribed by their own physician

3. At 4 years: (Means)

	LI	DSE
Weight loss (%)	4.7	1.1
Fitness (% METs over baseline)	+5.1%	+1.1%%
HbA1c (goal of < 7%)	57%	51%
BP (less than 130/80)	63%	61%
LDL-cholesterol (< 100 mg/dL)	61%	65%
HDL-cholesterol (%)	+3.5%	+2% *(My calculation from figure 2 RTJ)*

They state that the LDL-c changes in the DSE group were due to greater use of lipid-lowering drugs.)

4. There were no differences in diastolic BP and triglycerides at 4 years.

5. In general, benefits were greater at one year than at 4 years. Effects on weight, fitness, HbA1c and systolic BP gradually decreased from year 1 to year 4, although some benefit remained.

DISCUSSION

1. Lifestyle interventions can produce long-term weight loss, improvement in fitness, and sustained beneficial effects on CVD risk factors.

 2. Although the differences between the 2 groups were greatest in the first year, and decreased over time, the differences between those groups averaged across the 4 years were substantial.

3. The lifestyle interventions produced positive changes in glycemic control, BP, and lipid levels simultaneously.

4. The weight losses are impressive in light of the perception that individuals with DM-2 have more difficulty losing weight than their non-diabetic counterparts.

5. The positive impact of the intervention on several of the risk factors was greatest at year one,

followed by recidivism toward the baseline over the next 3 years.

6. The DSE group also experienced benefits over 4 years.

7. Of particular interest is the sustained effect on HDL-cholesterol over 4 years.

8. The study will continue to determine cost effectiveness and effect on CVD morbidity
   and mortality.

CONCLUSION

Intensive lifestyle interventions over 4 years were successful in producing sustained weight loss and improvements in CVD risk factors and glycemic control in patients with DM-2.

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Higher Animal-Based Fat, Lower Carbohydrate Diet Was Associated With A Higher Mortality.
9-5 LOW CARBOHYDRATE DIETS AND ALL-CAUSE MORTALITY AND CAUSE-SPECIFIC MORTALITY

Low carbohydrate diets (**LCD; the Atkins Diet**) have been claimed to promote weight loss and improve cholesterol levels and BP. Weight-loss trials have found that LCD are as effective, or more effective, than diets with higher carbohydrate content.

However, effects on lipid profiles of LCDs containing substantial animal products were mixed, resulting in greater improvements in HDL-cholesterol with perhaps less favorable changes in LDL--cholesterol. These diets can be high in red meat and low in fruits, vegetables and whole grains.

In contrast, the "Eco-Adkins" diet--low calorie, low carbohydrate with high amounts of plant protein and oils have shown to lower LDL-cholesterol.

Long-term studies of LCDs are needed to evaluate effects on mortality. However, such trials are not feasible because of the difficulty in maintaining adherence and follow-up over many years.

These investigators developed scores to characterize LCDs on the basis of the proportions of carbohydrates, fat, and protein from animal or vegetable sources. They previously found that women on a LCD emphasizing vegetable sources of fat and protein were associated with lower risk of type-2 diabetes and coronary heart disease. However, long-term data of LCDs on mortality are scarce.

STUDY

1. Prospectively examined the relationship between different types of LCDs and all-cause and cause-specific mortality in 2 large cohorts:

    1) The Nurses Health Study is a cohort study of 121 700 female nurses age 30-55 living in the US in 1976. All answered periodic questionnaires about medical, lifestyle, and other health related information. In 1980 and periodically thereafter, participants completed a 61-item food frequency questionnaire.

    2) The Health Professionals Follow-up Study of 51 529 males age 40-75,, established in 1986, also completed periodic food-frequency questionnaires.

2. After excluding subjects with cancer, heart disease, and diabetes, 85 168 women and 44 548 men were followed to 2006.

3. The food-frequency questionnaires accessed the average food intake during the preceding year.

4. Total energy and nutritional intake were calculated.

5. Created a vegetable low carbohydrate score on the basis of the percentage of energy of carbohydrate, vegetable protein, and vegetable fat. Created an animal low-carbohydrate score on the basis of the percentage of carbohydrate, animal protein and animal fat.

6. Identified deaths (all-cause mortality, CVD deaths, and death from cancer).

RESULTS

1. In the NHS, over 26 years,, there were 12 555 deaths;, of which 2458 were CVD deaths, and 5780 were cancer deaths. In the HPFS, over 20 years, there ware 8678 deaths;\; 2746 CVD and 2960 cancer.

2. Both men and women who had the highest animal low-carbohydrate scores had higher BMIs and lower intakes of fruits and vegetables. Those with higher vegetable low-carbohydrate diets tended to have higher whole grain intake.

3. Overall, the low-carbohydrate score was associated with a modest increase in overall mortality. (Hazard ratio [HR] comparing extreme deciles = 1.12)

4. The animal-fat low carbohydrate score (comparing extreme deciles) was associated with a higher all-cause mortality (HR = 1.23). And cancer mortality (HR = 1.28)

5. In contrast, the vegetable-fat low carbohydrate score was associated with lower all-cause mortality (HR = 0.80) and cardiovascular mortality) HR =0.77)

DISCUSSION

1. "In our two cohorts of U.S. men and women who were followed for 20 to 26 years, we observed that the overall low-carbohydrate diet score was only weakly associated with all-cause mortality. However, a higher animal low-carbohydrate score was associated with higher all-cause and cancer mortality, whereas a higher vegetable low carbohydrate diet was associated with lower mortality, particularly CVD mortality."

2. Because low-carbohydrate diets may have variable amounts of plant or animal fat, this may explain why low-carbohydrate diets showed mixed results on lipid profiles.

3. There was a positive association between animal low-carbohydrate score and mortality. Diets high in red meats and processed meats have been associated with higher risk for lung cancer and colorectal cancer.

4. The health effects of a low-carbohydrate diet may depend on the type of protein and fat. A diet that includes mostly vegetable sources of protein and fat is preferable to a diet with mostly animal sources of protein and fat.

CONCLUSION

Consumption of a vegetable-based low carbohydrate diet was associated with a lower risk for all-cause mortality and CVD mortality. High scores for the animal-based low carbohydrate diet were associated with a higher risk of overall mortality.

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A Remarkable New Automated Machine For Detecting M Tuberculosis And Rifampin Resistance
9-6 RAPID MOLECULAR DETECTION OF TUBERCULOSIS AND RIFAMPIN RESISTANCE

Only a small fraction of the large numbers of persons worldwide who develop HIV-associated TB and multi-resistant TB have access to sensitive detection.

Diagnostic delay, aggravated by the disproportionate frequency of smear-negative disease in patients with TB, is common. The failure to recognize and treat leads to increased mortality, secondary resistance, and ongoing transmission.

This article describes a fully automated molecular test for TB detection and drug resistance. The machine uses real-time polymerase-chain-reaction (**PCR**) to amplify M. tuberculosis (**MTB**) to diagnoses of the presence of MTB and resistance to rifampin. Resistance is determined by PCR amplification of a specific source of a rifampin-resistance gene.

Testing is carried out in a **MTB/RIF** machine (Gene-Xpert , Cepheid), which integrates sample processing and PCR in a disposable plastic cartridge containing all reagents required for sputum lysis, nucleic acid extraction, amplification and detection.

The only manual step is the addition of a bactericidal buffer to sputum before transferring a defined volume to the cartridge. The cartridge is then inserted into the device, which provides results within 2 hours.

This multicenter prospective evaluation of the MTB/RIF determined its sensitivity and specificity as compared with the best available reference standard--culture.

In this study, 1730 patients with suspected pulmonary TB provided 3 sputum specimens each. Two specimens were processed for microscopy, solid and liquid culture, and the MTB/RIF test. One specimen was used for direct testing with microscopy and the MTB/RIF test.

The MTB/RIF test was specific in 99.2% of the patients without TB. (0.8% false positives,) The sensitivity of MTB/RIF was 99.2% (9.8% false negatives.)

MTB/RIF correctly identified 97.6% with rifampin-resistant bacteria (2.4% false negatives) and 98.1% with rifampin-sensitive bacteria (1.9% false positives).

Conclusion: The test provided sensitive detection of TB and rifampin-resistant TB directly from untreated sputum in less than 2 hours with minimal hands-on time.

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