

**PRACTICAL POINTERS
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INDEX**

JULY - DECEMBER 2010

PRACTICAL CLINICAL POINTS

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

LINKS TO FULL ABSTRACTS

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This index is a reference document based on articles abstracted from 6 flagship journals July - December 2010. It provides a means of reviewing and recalling to memory, in an evening or two, practical clinical points of importance to primary care.

The numbers in the brackets refer to the abstract. For example, [7-6] refers to the sixth article abstracted in July .

It consists of 3 parts:

- 1) “Practical Clinical Points”: This provides an instant reminder of points of clinical interest and importance, which primary care clinicians may wish to advise patients about, consider, and be aware of. Some points are new; some emphasize older points.
- 2) “Medical Subject Headings” (MeSH): A list of medical subject headings from ALCOHOL to WEIGHT arranged alphabetically
- 3) “Highlights of Abstracts and *Editorial Comments*”: linked alphabetically to each MeSH. (There may be several articles listed under a MeSH.) The highlights contain a condensation of each abstract. The *Editorial Comments* are those of the editor alone, based on his years-long experience as a practicing primary care internist and as editor and publisher of *Practical Pointers for Primary Care Medicine*

The full abstracts may be accessed from the monthly issues on the website. They provide more detailed information, and the citation.

Monthly issues for the past 10 years may be found on the website (www.practicalpointers.org).

I hope you find *Practical Pointers for Primary Care* useful and interesting.

Richard T. James Jr. M.D. Editor/Publisher

PRACTICAL CLINICAL POINTS JULY -DECEMBER 2010

Reminders of points of clinical interest and importance which primary care clinicians may wish to consider, be aware of, or advise patients about.

- [7-1] Some patients may be medically illiterate. If you suspect they are, make sure they fully understand your prescription and instructions.
- [7-2] If a patient resists receiving colonoscopy, sigmoidoscopy may be a suitable substitute.
- [7-3] An observational study reported that vitamin D insufficiency is related to greater cognitive decline in elderly adults mean age 74 followed for about 6 years. (*This must be confirmed by a long and large randomized trial. Ed.*)
- [7-4] Diabetes confers about a two-fold excess risk of a wide range of cardiovascular diseases, independent of other risk factors.
- [7-5] Among patients with hypertension, diabetes, and coronary disease, there is no compelling evidence that lowering systolic BP below 130 is beneficial.
- [7-6] Transdermal estrogen may be related to a reduced risk of stroke compared with oral estrogen.
- [7-6] For cardio-respiratory resuscitation, chest compression alone is just as effective as compression + assisted breathing .
- [7-8] For frail old men, risks of testosterone replacement therapy outweigh benefits.
- [7-9] Continuing to aggressively treat men with low grade PSA-diagnosed prostate cancer will do more harm than good.

- [8-1] Waist circumference is associated with higher risk of death, independent of BMI.
- [8-2] Non-optimal lipids are commonly present in young adults, and are associated with increased coronary calcium deposits later in life.
- [8-3] In patients with non-small cell lung cancer, early palliative care must be given early to have any meaningful effect.
- [8-4] Palliative care is appropriate when introduced at the time of diagnosis of serious life-threatening illness.
- [8-5] Adolescents are increasingly developing hearing loss.
- [8-6] Exenatide, a new incretin mimetic given to patients with type-2 diabetes, avoids the twin hazards of hypoglycemia and weight gain.

- [9-1] Routine mammography for women age 40-49 is discouraged. The benefit / harm-cost ratio is low, mainly due to a high false positive rate and low expected benefits.

- [9-2] Non-alcoholic fatty liver disease is a growing health problem. Patients typically meet the diagnostic criteria for the metabolic syndrome and are at increased risk for cardiovascular disease.
- [9-3] Patients with subclinical hypothyroidism may be at increased risk for cardiovascular events and mortality.
- [9-4] Intensive lifestyle interventions over 4 years successfully produced sustained weight loss and improvements in cardiovascular risk factors.
- [9-5] A low carbohydrate, high animal fat diet (The Adkins Diet) was associated with increased all-cause mortality and cardiovascular mortality.
- [9-6] A new automated machine to diagnose *M tuberculosis*.
- [9-7] We are all going to die. Deal with it.
-
- [10-1] Low serum potassium levels are an independent predictor of incident type-2 diabetes.
- [10-2] Tricyclic antidepressants are effective treatment of both migraine and tension headaches.
- [10-3] Dabigatran, a direct thrombin inhibitor, may replace warfarin in reducing risk of thromboembolism in patients with atrial fibrillation.
- [10-4] Combined estrogen-progestin increases risk of breast cancer.
- [10-5] Does severe hypoglycemia increase risk of vascular events and death?
- [10-6] Intensive treatment of type-2 diabetes to achieve an HbA1c of 6% or less seems imprudent. It is associated with increased total and CVD mortality, weight gain, and risk of hypoglycemia.
-
- [11-1] Binge drinking of alcohol increases risk of ischemic heart disease. Wine and regular moderate drinking may lower risk.
- [11-2] More intensive therapy to lower LDL-cholesterol may reduce mortality and major vascular events, regardless of the initial levels.
- [11-3] The author describes the gradual evolution of an addition to classical bedside medicine. “Desktop medicine” considers disease as a risk of future impairment (eg, dyslipidemia as a risk for CVD). The science is based on epidemiology, the laboratory, genetics, and statistics. It emphasizes fostering the patient’s appreciation of risk and then adopting a strategy for risk reduction. It is a clinical-actuarial correlation using the results of risk factor assessment to correlate with models that estimate whether the risk is sufficient to warrant treatment.
- [11-4] In patients with type-2 diabetes, combined resistance-aerobic exercise reduced HbA1c more than either alone.
- [11-5] “Primordial prevention” goes beyond primary prevention. It ensures that the level of CVD risk factors in healthy children are preserved into adulthood.

[12-1] The therapeutic potential of the new oral factor Xa inhibitors.

[12-2. Risk assessment for recurrent venous thromboembolism.

[12-3] Changes in levels of a highly sensitive cardiac troponin T over time correspond with changes in risk of heart failure and cardiovascular death. Higher levels are associated with structural heart disease and subsequent mortality.

[12-4] In a study of 1.4 million white adults, overweight and obesity determined by body mass index, were associated with increased all-cause mortality. Mortality was lowest at BMI 20.0 to 24.9.

[12-5] In the elderly, opioid use as an analgesic increases risk of myocardial infarction, heart failure, falls, fractures, and all-cause mortality compared with NSAIDs.

MEDICAL SUBJECT HEADINGS JULY-DECEMBER 2010

ALCOHOL

ANALGESICS

ANTICOAGULANTS (See **FACTOR Xa INHIBITOR**)

ATRIAL FIBRILLATION

BLOOD GLUCOSE (See **DIABETES** [7-4])

BLOOD PRESSURE (See **DIABETES** [7-5])

BODY MASS INDEX

BREAST CANCER

CANCER (See type: **BREAST**; **COLON**; **PROSTATE**; **LUNG CANCER**)

CARDIAC TROPONIN T

CARDIOPULMONARY RESUSCITATION

CARDIOVASCULAR DISEASE (See **HYPOGLYCEMIA** [10-5]; **HYPERTENSION** [7-5])

CARDIOVASCULAR RISK FACTORS (See **DIABETES** [9-4])

CHOLESTEROL (See **LIPIDS**)

COGNITIVE DECLINE (See **VITAMIN D** [7-3])

COLON CANCER

COLONOSCOPY (See **COLON CANCER** [7-2])

CORONARY CALCIUM (See **CORONARY HEART DISEASE** [8-2])

CORONARY HEART DISEASE.

DABIGATRAN

DEATH

DESKTOP MEDICINE

DIABETES

DIET

ESTROGEN (See **BREAST CANCER** [10-4])

EXENATIDE (See **DIABETES** [8-6])

FACTOR Xa INHIBITORS

FASTING BLOOD GLUCOSE (See **DIABETES** [7-4])

GERIATRICS (See **ANALGESICS** [12-5]; **TESTOSTERONE** [7-8]; **VITAMIN D** [7-3])

HEADACHE

HEALTH INFORMATION (See **LITERACY** [7-1])

HEARING LOSS

HEART FAILURE (See **CARDIAC TROPONIN T** [12-3]

HEMOGLOBIN A1c (See **DIABETES** [11-4])

HORMONE THERAPY (See **BREAST CANCER** [10-4]; **STROKE** [7-6])

HYPERGLYCEMIA (See **DIABETES** [10-6])

HYPERTENSION

HYPOGLYCEMIA

HYPOTHYROIDISM

ISCHEMIC HEART DISEASE (See **ALCOHOL** [11-1])

LIFESTYLE (See **DIABETES** [9-4]))

LIPIDS

LITERACY

LUNG CANCER (See **PALLIATIVE CARE** [8-3])

MAMMOGRAPHY

MICROVASCULAR DISEASE (See **DIABETES** [10-6])

METFORMIN (See **DIABETES** [8-6])

MORTALITY (See **BODY MASS INDEX** [12-4]; **BREAST CANCER** [10-4]; **CARDIAC TROPONIN T** [12-3];; **DIET** [9-5];

CARDIOVASCULAR DISEASE [12-3]; **CORONARY HEART DIESEL** [9-3]; **WAIST CIRCUMFERENCE** [9-1];

HYPOGLYCEMIA [10-5])

NON-ALCOHOLIC FATTY LIVER DISEASE

PALLIATIVE CARE

PATIENT LITERACY

PIOGLITAZONE (See **DIABETES** [8-6])

POTASSIUM

PREVENTIVE STRATEGIES (See **CARDIOVASCULAR DISEASE** [??]

PROGESTIN (See **BREAST CANCER** [10-4])

PROSTATE CANCER

PSA TESTING (See **PROSTATE CANCER** [7-9])

RIFAXIMIN (See **TUBERCULOSIS** [9-6])

SCREENING (See **COLON CANCER** [7-2])

SIGMOIDOSCOPY (See **COLON CANCER** [7-2])

SITAGLIPTIN (See **DIABETES** [8-6])

STROKE

TESTOSTERONE

TRAINING (See DIABETES [11-4])

TRICYCLIC ANTIDEPRESSANTS (See HEADACHE [10-2])

TUBERCULOSIS

VASCULAR DISEASE (See DIABETES [7-4])

VENOUS THROMBOEMBOLISM

VITAMIN D

WAIST CIRCUMFERENCE

WEIGHT (See DIABETES [9-4])

HIGHLIGHTS AND *EDITORIAL COMMENTS* JULY - DECEMBER 2010

ALCOHOL

Binge Drinking Increases Risk. Wine And Regular Drinking Reduce Risk.

11-1 PATTERNS OF ALCOHOL CONSUMPTION AND ISCHEMIC HEART DISEASE IN CULTURALLY DIVERGENT COUNTRIES (PRIME study)

This prospective observational cohort study analyzed the patterns of alcohol consumption and their relation to myocardial infarction and coronary deaths (**MI and CD**) in men age 50-59 in Belfast, Northern Ireland (n = 2745) and in 3 cities in France (n = 7373).

Analyzed weekly alcohol consumption, volume of alcohol intake, frequency of consumption, and type of beverage consumed. One drink of alcohol was standardized as 10--12 g of ethanol.

Assessed the relation between baseline drinking characteristics and incidence of MI and CD and angina over 10 years. Defined groups: non-drinkers, daily drinkers, regular drinkers, and binge drinkers. Regular drinking was arbitrarily defined as intake of at least 3 consecutive drinks on at least one day a week, and if drinking on only one occasion, consuming less than 50 g of alcohol. Binge drinking was set at 50 g or more of alcohol on at least one day a week. It was not an occasional weekly behavior. It occurred regularly each week.

Patterns of drinking differed considerably between Belfast (B) and France (F).

	B (%)	F (%)		B (%)	F (%)
Non-drinkers	39	9	Wine	27	92
Regular drinkers	51	90	Beer	75	56
Daily drinkers	12	75	Spirits	61	73
Binge drinkers	9	0.5			

Men in F were much more likely to drink every day; men in B were much more likely to drink heavily on weekends. Among regular drinkers, the total amount of alcohol consumed was about equal in both B and F (282 g and 255 g weekly). However, the alcohol volume tended to be consumed on 1 or 2 days in B and through the week in F. Mean alcohol consumption in B was 2 to 3 times higher on weekends than in F.

In both countries the *highest* incidence of MI and CD was noted in the *non-drinking* group. Drinkers were *less* prone to MI and CD than non-drinkers. Incidence of angina did not vary in drinkers vs non-drinkers.

Regular drinkers, even those that drank heavily (> 75 g of alcohol daily) had a lower risk of CD and MI than non-drinkers.

Incidence of MI and CD in regular drinkers over 10 years: (%)

	Belfast	France
Non-drinkers	6.4	4.5
75 g daily	3.8	2.9

(Ie, whatever the quantity, regular drinking seemed to be protective.)

Whatever the category of alcohol consumption, the proportion of individuals who experienced MI or CD was always higher in B.

After 10 years of follow-up, a total of 5.3% in B and 2.6% in F had incident MI and CD.

(Ie, in B the rate of MI and CD was twice that of F. Absolute difference = ~ 3 per 100 men in 10 years.)

Conversely, consumption was not associated with angina. The risk of MI and CD in binge drinkers, and in never-drinkers, was similar--about two-fold higher than in regular drinkers.

Wine drinking, compared with no wine drinking was associated with a *lower* risk of MI and CD. Two by two comparisons showed significant differences in risk of MI and CD events between wine and beer drinking and between wine and other types of alcohol.

Hazard ratios for MI and CD in regular drinkers (adjusted): Beer 0.91 Wine 0.57 Other drinks 1.01.

“Our findings have important public health implications. The regions we studied are within countries for which alcohol consumption is the highest recorded worldwide and is of similar order of magnitude (11 to 14 liters of pure ethanol per capita in adults per annum.)”

“From our data alone however, it is difficult to conclude whether the pattern of alcohol intake has a major role in the incidence of ischemic heart disease (**IHD**) independent of other behaviors such as diet.”

Conclusion: Regular and moderate alcohol intake throughout the week, the typical pattern in middle-aged men in France, is associated with a low risk of IHD, whereas the binge drinking pattern more prevalent in Belfast confers higher risk.

This is a long and complex article. I believe it carries an important message for primary care clinical practice.

The investigators carefully pointed out, however, that there may be confounding factors in the French population that contribute to the lower incidence of IHD in France.

The “French paradox” has been noted for years. Despite lifestyles, which are just as unhealthy as other countries, the incidence of IHD has consistently been lower in France. This has been attributed to regular wine-drinking. The present study seems to confirm this.

Heavy regular drinking (> 75 g daily; n = 1134 of 7373 in France mainly wine) seemed protective of IHD. However, it obviously is associated with other diseases and considerable social and family disasters. .

ANALGESICS

12-5 ANALGESIC USE IN THE ELDERLY

Pain is widespread among the general public. It is difficult to treat to the satisfaction of many patients. A recent study from Sweden found the overall presence of pain was 46%, with prevalence increasing to 55% in those over age 70.

About half of patients with chronic pain had not received a formal diagnosis or known the reason for the pain.

In response to perceived inadequacies of pain management, there are efforts to focus more on the treatment of pain and less on the cause. Many clinics now routinely ascertain pain scores along with other vital signs, regardless of the nature of a patient's visit.

The California legislature had enacted several laws stating in patient's bill of rights: "A patient who suffers from severe chronic pain has the option to choose opioid medications, and the patient's physician may refuse to prescribe opioids. However, that physicians shall inform the patient that there are physicians who specialize in the treatment of pain with methods that include use of opioids."

There are few novel treatments to offer for treatment of pain. Most new analgesics are derivatives or reformulations of opioids or aspirin. The development of coxibs marked attempts to develop a somewhat novel class of analgesics. They were met with intense scrutiny and some were removed from the market following an increase in cardiovascular mortality.

Prescribing habits of US physicians for chronic pain has changed in recent years. There has been an increase in prescriptions for opioids for chronic non-cancer pain, especially for women over age 65 with chronic pain. A 2005 study reported that 9% of females over 65 with chronic pain used opioids for more than 90 days, a 35% increase from 2000. Use of opioids in this population is problematic given that users are prone to falls, cognitive impairment, and respiratory depression.

A study in this issue of Archives¹ was based on a large administrative claim database. The cohort consisted of patients diagnosed with osteoarthritis or rheumatic pain who received new prescriptions for an analgesic. Patients were divided into 3 groups according to the analgesic class--NSAIDs, coxibs, and opioids. Those with cancer and in Hospice care were excluded. They were well matched for most baseline characteristics.

The authors found substantial increases in morbidity and mortality in patients who used opioids. Fractures of the hip and pelvis occurred three times as frequently in this group. Humerus fractures were 9 times more frequent, Total fractures were 5 times more frequent than in patients using NSAIDs. There was also an increase in myocardial infarction, a risk that surpassed the risk of MI in users of coxibs.

There was also a statistically significant increase in all-cause mortality, compared with NSAIDs. (Hazard ratio = 1.87) There was no significant difference in mortality between users of coxibs and other NSAIDs.

The investigators did not distinguish between types of opioid used (eg, methadone vs codeine), its dose, or its duration.

Some physicians may prescribe opioids because they perceive them to be less toxic to the gi tract and kidney than NSAIDs and less toxic to the cardiovascular system than coxibs. These assumptions may no longer hold up.

Patients with rheumatoid arthritis make up about 10% of patients with chronic musculo-skeletal pain. Much can be done to relieve pain by use of conventional disease -modifying anti-rheumatic drugs. The chronic pain or knee osteoarthritis can be relieved by non-pharmacological treatment: exercise, weight loss, and physical therapy as well as arthroplasty.

Despite increased awareness of the dangers posed by opioids and other analgesics, the FDA recognizes that the extensive prescribing of these medications will continue, and warrants increased government regulation that we hope balances risk management with the need for adequate access to pain management.

The clinician (*and patient*) will remain responsible for balancing the risks and benefits when choosing the dose and class of analgesic.

Archives Internal Medicine December 13/27 2010; 170: 1976-78 Editorial by Jonathan Graf, University of California, San Francisco.

1 “The Comparative Safety of Analgesics in Older Adults with Arthritis” Annals Internal Medicine December 13/27, 2010:170: 1979-86. Original investigation, first author Daniel H Solomon, Brigham and Women’s Hospital, Boston, Mass

This study examined the comparative safety of non-selective NSAIDs (nsNAIDs), selective cyclo-oxygenase 2 inhibitors, and opioids. It was based on Medicare records 1999 to 2005.

After propensity score matching at baseline, the 3 analgesic cohorts were well balanced of baseline covariates. Mean age was 80; 85% female;

Incident rates per 1000 person-years:

	NSAIDs	HR*	Coxibs	HR	Opioids	HR
Myocardial infarction	14	1.00	20	1.63	29	2.25
Heart failure	30	1.00	34	1.26	45	1.63
GI bleeding	21	1.00	12	0.60	21	1.07
Fracture	28	1.00	19	0.96	101	4.47
Al-cause mortality	48	1.00	47	1.16	75	1.87
Falls	26	1.00	18	0.78	41	1.64

(* Referent Hazard Ratio)

Conclusion : The safety of analgesics varies, depending on the safety event studied. Opioid use exhibits an increased risk of many safety events compared with NSAIDs.

Editors and investigators continue to stress hazard ratios when comparing safety of one drug with another. The introductory abstract often cite hazard ratios (HR) along with confidence intervals, and, sometimes, P values. This jumbles the abstract and, in my view, often makes it unreadable.

HRs may give the patients an indication that one drug is safer than another in some respects. But this information does not allow patients (or clinicians) to make a judgment about accepting or rejecting the risk. Acceptance of risk depends on how great the benefit.

In this study, fractures occurred in 28 of 1000 patients each year vs 101 per 1000 each year for opioids--an increase of about 7 in 100 each year for those taking opioids vs NSAIDs.

I feel sure that some patients would be willing to accept this degree of risk to obtain greater relief from pain.

As usual, patients should be informed so they may make personal decisions.

ATRIAL FIBRILLATION

“May Be An Option To Replace Warfarin”

10-3 DABIGATRAN ETEXILATE IN PEOPLE WITH ATRIAL FIBRILLATION

Dabigatran (*Pradaxa*; Boehringer Ingelheim) has been approved for use in the US by the FDA for preventions of stroke in patients with non-valvular AF. It is a direct thrombin inhibitor.

A large trial in September 2009 (*See Practical Pointers Sept 2009*) reported that, in patients with atrial fibrillation (AF), dabigatran is associated with rates of stroke similar to those of warfarin.

ADVANTAGES COMPARED TO WARFARIN

Taken orally. No monitoring. Dose is constant. Long half-life. More predictable anticoagulant effect. Wide therapeutic range. Much simpler regimen. No interference by foods and other drugs.

Compared with warfarin when used in patients with AF:

Reduces rates of stroke and peripheral embolization as well as, or better than warfarin.

Reduced deaths due to cardiovascular disease.

Fewer intracranial hemorrhage.

Fewer life-threatening bleeds.

Possible use by patients who cannot or will not take warfarin and whose INR is unstable.

DISADVANTAGES

Dose not settled.

Taken twice daily.

Excreted by the kidney. Care when kidney function is impaired.

No antidote. May take several days for effect to lessen.

Possible increased risk of myocardial infarction. May be contraindicated in patients with history of cardiovascular disease.

Increased g.i. bleeding.

Dyspepsia may cause withdrawals.

Generalizability not settled.

Cost \$8.00 a day.

Use for reasons other than AF must be validated.

I believe we require more experience before Pradaxa is used in primary care practice. Other anticoagulants are now approaching approval. We await comparisons for use in indications other than AF.

BODY MASS INDEX

Extending The Validity of BMI as A Prediction Tool

12-4 BODY MASS INDEX AND MORTALITY AMONG 1.4 MILLION WHITE ADULTS

Studies vary in estimating the strength of the relationship between high BMI and all-cause mortality. Inconsistencies could be due to confounding by tobacco use and disease-related weight loss. Differences in age and length of follow-up vary.

Pooled analyses provide the opportunity to examine these issues in a large diverse population with use of standard analytic approaches across studies.

This study examined the relationship between BMI and all-cause mortality in a pooled analysis of 19 prospective studies of predominantly white (non-Hispanic) adults (n = 1.46 million). The study included 160 087 deaths. It examined the extent to which the relationship between BMI and all-cause mortality varied with smoking and prevalent disease.

The principal objectives were to assess the optimal BMI range and to provide stable estimates of the risks associated with being overweight, (BMI 25.0 to 29.9), obese (BMI 30.0 to 39.9), and morbidly obese (BMI > 40) with minimal confounding due to smoking and prevalent disease.

Predefined BMI levels; 15.0 to 18.4; 18.5 to 19.9; 20.0 to 22.4; 22.5 to 24.9; 25.0 to 27.4; 27.5 to 29.9; 30.0 to 34.9; 35.0 to 39.9; and 40.0 to 49.9.

Defined BMI of 22.5 to 24.9 as the reference category. (Hazard ratio [HR] = 1.00)

The age-standardized rate of death from any cause was generally lowest among participants with a BMI 22.5 to 24.9 (the reference group). The HR increased with progressively higher and lower BMI.

There was a contrast in the pattern between healthy subjects who had never smoked and the pattern observed when all subjects were included in the analysis. The nadir of the curve flattened and expanded to the BMI range of 20.0 to 24.5 when the analysis was restricted to healthy participants who never smoked.

Adjustments for alcohol, physical activity, education, and marital status slightly reduced the HR estimates for those with a BMI 25.0 and higher.

When men and women were combined to increase statistical power, the nadir of the HRs remained at 1.00 for BMI 20.0 to 25.5.

The increased HRs for those with BMIs under 20.0, as compared with 22.5 to 24.9, were reduced in those reporting higher-level of physical activity. (Being lean and fit.)

Both overweight (and possibly underweight) were associated with increased all-cause mortality in participant who never smoked and did not have cancer or heart disease at baseline.

These associations were strongest among those whose BMI was ascertained before age 50.

Among healthy persons who had never smoked, the estimated HR for all-cause mortality per 5-unit increase in BMI rose by 1.32

Smoking and preexisting conditions cause weight loss. They are powerful confounders. Analyses that include them lack validity.

The association between underweight and increased mortality was probably, at least in part, due to preexisting disease.

Conclusion: For non-Hispanic white persons, both overweight and obesity are associated with increased all-cause mortality, and underweight may be as well. All-cause mortality is generally lowest within the BMIs range of 20.0 to 24.9. These results are most relevant to white persons living in affluent societies.

BMI is calculated by dividing the weight in kilograms by the height in meters squares.

Several years ago, people were exhorted to: "Know your cholesterol". A good update would be: "Know your BMI". Obviously, overweight and obesity are major public health problems, and knowing that the patient's BMI is high is a major application of primary care.

This information is not new. The study does advance the validity of BMI as a prediction tool, especially since the authors tried to eliminate confounding due to smoking and preexisting disease.

BMI is a valid predictor only for those who, at baseline, are healthy and do not smoke. Smoking and preexisting disease are major confounders.

BMI is a more meaningful predictor for younger persons.

Younger healthy persons who do not smoke can be told that, if their BMI reaches 30, their risk of death is about a third higher than those who are not overweight. If it reaches 35, the risk is increased to two thirds.

The goal should be to maintain BMI between 20 and 25.

Being underweight (BMI under 20) is not necessarily a disadvantage, especially if the individual does not smoke, maintains fitness, and has no underlying disease. The risk of underweight is not as high as the risk of overweight and obesity.

BREAST CANCER

Increases Incidence And Death From Breast Cancer

10-4 ESTROGEN PLUS PROGESTIN AND BREAST CANCER INCIDENCE AND MORTALITY IN POSTMENOPAUSAL WOMEN

The Women's Health Initiative (WHI) followed a total of 16 608 postmenopausal women, age 50-79 (mean age 63) randomly assigned to: 1) 0.625 mg/d of conjugated equine estrogen + 2.5 mg/d medroxyprogesterone acetate (*Prempro*; Wyeth) or 2) placebo. The intervention period lasted from 1993 to 2002, when participants were instructed to stop CHT. Follow-up of 12 788 participants continued until 2009.

During a mean follow-up of 11 years, a total of 678 cases of BC were identified.

In the intention-to-treat analysis, CHT compared with placebo, was associated with an increased incidence of BC: 385 cases (0.42% per year) vs 293 cases (0.35% per year). Hazard ratio (HR) = 1.25.

In the CHT group, a significantly larger fraction of BCs presented with positive nodes: 81 vs 43; HR = 1.78.

Some women prior to entering the trial were taking CRT. These women had a higher risk for BC. HR = 1.85, compared with 1.16 for those without prior use.

More women in the CHT group died of BC: 25 deaths vs 12 deaths. (2.6 deaths per 10 000/year vs 1.3 deaths per 10 000/year. (HR = 1.96)

Following the initial report of the WHI trial, a substantial reduction in use of CHT occurred, followed by a reduction in incidence of BC. Reproductive hormones, especially progestin, are potent stimulators of angiogenesis. Because increased angiogenesis increases both lung and BC metastasis, these findings suggest that angiogenesis stimulation by CHT may facilitate growth and metastatic spread of already-established cancers.

Conclusion: Use of estrogen plus progestin increases the incidence of BC. The cancers are more commonly node positive. Mortality was increased.

I believe the terms hormone replacement therapy (HRT) and hormone therapy (HT) should be abandoned in favor of using the specific terms: estrogen and progestin. HRT and HT are too non-specific. Estrogen and progestin have different benefits and harms. There is good evidence that progestins are the major risk factor for BC.

For discussion, see the following editorial.

Informed Patient-Decisions Are Not Valid When The Information Underlying The Decision Is Speculative

[10-4] POSTMENOPAUSAL HORMONE THERAPY AND BREAST CANCER

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

In 2002, the WHI was stopped early because of evidence of harm. (The WHI reported increased risk of myocardial infarction in addition to BC.) Sales of CHT subsequently fell by 32%.

This contradicted decades of observational studies suggesting that hormone therapy was associated with strong protective effects on the cardiovascular system. The WHI undermined a long and successful campaign by hormone replacement advocates to prescribe hormone therapy as a panacea against heart disease, loss of femininity, and other perils of aging.

This proved once again that only randomized trials can yield insights into harms and benefits.

After many subgroup analyses, a more nuanced explanation emerged. Among the few women who enrolled around the time of menopause, CHT did not increase the risk of cardiovascular disease, and may have reduced it slightly. However, most women in the trial were well past menopause when enrolled.

Ultimately, the only long-term benefit of CHT the FDA allows manufacturers to claim is a reduction in osteoporotic fractures.

It is probable that BC deaths due to CHT has been underestimated. At the end of the study (11 years) the mortality curves appear to be widening, and the difference in cumulative BC between women on CHT and the placebo group appears to be growing.

Since the number of deaths from BC is relatively small, clinicians might conclude that a brief period of treatment given near menopause to relieve symptoms is safe. This is consistent with some guidelines and with the FDA labeling. However, the study does not address the effects of short periods of CHT therapy on risk of BC. The deleterious effects may be underestimated.

Clinicians who prescribe brief courses of CHT for relief of symptoms should be aware that this approach has not been proven to be harmless and the downstream consequences for patients are

uncertain. Discussing the risk-benefit with a patient, in pursuit of an informed decision, may seem, at first blush, to be a reasonable approach, given the lack of evidence. The reality is that informed patient-decisions are not valid when the information underlying the decision is itself speculative. This includes advice to take CHT at lower doses for shorter periods, which assumes that enough is known about how CHT modulates disease risk to be confident that a safe dose is determined.

JAMA October 20, 2010 | 304: 1719-20 Editorial by Peter B Bach, Memorial Sloan-Kettering Cancer Center, New York

I enjoyed this editorial The editorialist takes an interesting conservative view.

How duty bound are primary clinicians to discuss all possible harmful effects of drugs they prescribe even when the harm is very infrequent? (eg, 1 to 2 per 10 000 per year)

All drugs have harmful effects. Many medications we prescribe have adverse effects that occur more frequently than 1 to 2 in 10 000. Discussing all adverse effects would place an unacceptable time-burden on primary care clinicians.

In the case of CHT, I believe it is reasonable to believe that harms of short-low-dose treatment in women near the menopause are likely to be infrequent.

Much depends on the benefit of CHT in reducing symptoms. I believe many women would willingly accept rare risk of harms to gain relief of symptoms of menopause.

While contemplating the editorialist's comments about the often changing fashions of medicine I thought of the current enthusiasm for vitamin D. Enthusiastic endorsement at one period may be withdrawn as more solid evidence becomes available. I await randomized trials for confirmation of benefits of D. Meanwhile, I will continue to recommend oral replacement doses because D is not harmful and costs little.

CARDIAC TROPONIN T

Strongly Associated With Incident HF And CV Death Independent Of Standard Risk Variables

12-3 ASSOCIATION OF SERIAL MEASURES OF CARDIAC TROPONIN T USING A SENSITIVE ASSAY WITH INCIDENT HEART FAILURE AND CARDIOVASCULAR MORTALITY IN OLDER ADULTS.

These investigators hypothesized that, in community-dwelling older patients without a prior diagnosis of heart failure (**HF**), measurable high sensitivity cardiac troponin T (**hs-cTnT**) would be common, and higher concentrations would be associated with greater risk of new onset HF and cardiovascular death (**CV death**) independent of traditional risk factors. Serial measurements over time could reflect a change in risk.

A nation-wide prospective cohort study included 4221 community-dwelling persons age 65 and older. None had prior HF. Main outcome measure = new onset HF and CV death through 2008 with respect to hscTnT concentrations. Measured hscTnT at baseline (1989-1990) and again after 2 to 3 years. The analytical measurement of hscTnT ranges from 3.0 to 10 000 pg/mL

The value at the 99th percentile cutoff in a healthy reference population is 13.5 pg/mL.

Divided participants into 5 equal size categories according to baseline:

Less than 3.0 pg/mL (undetectable); 3.0 to 5.44; 5.45 to 8.16; 8.17 to 12.94; > 12.94

Determined cumulative incidence of HF and CV death for each category over 18 years.

At baseline, higher hscTnT was related to multiple traditional risk factors: age, known CHD, depressed kidney function, ECG abnormalities, abnormal ejection fraction, and increased ventricular mass.

If hscTnT remained undetectable 2 to 3 years after baseline, risk was lower than if it became detectable.

If hscTnT was *detectable* at baseline and *increased* over time, risks *increased*. If hscTnT *decreased* over time, risks *decreased*.

Lower concentrations of hscTnT were associated with a gradient of risk for new-onset HF and CV death in ambulatory persons over age 65, independent of clinical variables. Low hscTnT concentrations frequently change over time. The changes in risk of HF and CV death are concordant with the direction of change.

Concentrations of hscTnT were detectable and of prognostic value in nearly 2/3 of a large geographically and ethnically diverse, stable, but at-risk population of ambulatory older adults without a prior diagnosis of HF.

Baseline levels of hscTnT, below the levels that would be expected to be detected with conventional assays, strongly associate with incident HF and CV death, independent of standard risk prediction variables. Changes in hscTnT determined during 2 to 3 years in subjects who remained free of HF, even when occurring in concentrations well under the 99th percentile of healthy young blood donors, are prognostically significant.

The markedly increased range of measures of hscTnT enables estimation of a gradient of risk across the majority of older individuals, including those with absence of clinical risk factors (other than age), and also permits examination of the significance of changing hscTnT.

Conclusion: Detectable hscTnT levels were present in the majority of community-dwelling older persons without known heart failure. Higher concentrations--within normal range established for younger persons -- reflect a great burden of cardiovascular risk. Changes in hscTnT levels over time were common and corresponded with a change in HF and CV death.

I hesitated to include this article because it is not yet a practical point for primary care. It is provocative, and, I believe, carries promise for the future.

The hscTnT test may lead to increasing sensitivity in detecting risk. It is a more sensitive marker than any risk factor now in use. It is more specific to the heart than C-reactive protein. It may turn out to be relatively simple and inexpensive.

What should the primary care clinician do when the test shows increased risk?

When patients are informed about increased risk, some (perhaps a few) may increase compliance with a more healthy lifestyle. Some may benefit from added medication. I doubt, however, if many would benefit beyond the advice given to patients on the basis of standard risk factors. Poor compliance remains a roadblock. Do we need another risk factor?

The statement that exercise increases the hscTnT levels in patients with ischemic heart disease raises the point: Can hscTnT be used as a inexpensive marker of exercise-induced ischemia?

CARDIO-PULMONARY RESUSCITATION (CPR)

Compression Alone Just As Effective As Breathing + Compression

7-7 CPR WITH CHEST COMPRESSION ALONE OR WITH RESCUE BREATHING.

CPR performed by a lay person has traditionally consisted of chest compression interspersed with rescue breathing.

This randomized trial compared outcomes between chest compression-alone and compression + rescue breathing.

The trial was conducted in two sites in Washington state and one in London. Considered consecutive bystander's calls to 911 for persons in apparent cardiac arrest. Subjects were eligible if the dispatcher determined that they were unconscious and not breathing normally, and that bystander CPR was not underway. If the caller was willing to undertake CPR, the dispatcher opened a randomization envelope containing CPR instructions. Attempts were made to exclude subjects with arrest due to trauma, drowning, or asphyxiation (choking, strangulation, or suffocation), as well as subjects under age 18, and those who had do not resuscitate status. Enrollment took place between 2004 and 2009.

The envelope contained instructions to perform either:

- 1) Chest compression-alone, or
- 2) Chest compression + rescue breathing with 2 initial breaths followed by 15 chest compressions and subsequent cycles of 15 compression and 2 breaths.

Baseline characteristics: Randomized 1941 subjects who met inclusion criteria: mean age 64; 65% male; 71% cardiac arrest, 7% respiratory; arrest witnessed 43%; 87% in residences, 10% public, 4% in nursing homes. Time from dispatch to arrival of the EMS crew at the scene 6.5 minutes; time to advanced support 10 minutes; shockable rhythm 32%.

Bystanders who received instructions for chest compression-alone were more likely to perform CPR than those instructed to breathing + compression. (81% vs 73%)

Pulse present at end of EMS care: compression alone 35%; compression + breathing 31%)

At all three sites combined, there was no statistical difference between the proportions of subjects surviving to hospital discharge according to randomization (12.5% compression-alone; 11% compression + breathing).

At the two sites reporting neurological status, there was no significant difference between those discharged with a favorable neurological status (14.4% vs 11.5%)

Conclusion: Breathing + compression, compared with compression alone, did not improve survival rate or survival with intact neurological status.

Certainly many bystanders would be reluctant to conduct mouth-to-mouth breathing.

There is a tragic downside to CPR. By my calculation, 2.7% of those who survived, had poor neurological outcomes. Would that we could have some indication as to this outcome before starting CPR.

CARDIOVASCULAR DISEASE

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.

Primordial Prevention--The Next Step?

11-5 OPTIMAL CARDIOVASCULAR PREVENTION STRATEGIES FOR THE 21ST CENTURY

Death rates from cardiovascular disease (**CVD**) remains by far the leading cause of morbidity and mortality in the US. CVD chronically affects over 80 million US adults.

Primary prevention reduces the chances of a first event. It is more difficult to implement than secondary prevention. All manifestations of CVD have common predisposing factors, especially smoking, adverse lipids, blood glucose, and high BP. However, most first CVD events occur in individuals with only mildly elevated levels of risk factors who would not typically qualify for preventive efforts. Extensive CVD prevention can be achieved only through lifestyle and environmental modifications

Primordial Prevention goes beyond secondary and primary prevention. It is a more radical concept. It ensures that the levels of CVD risk factors observed in healthy children are preserved into adulthood. Individuals who maintain a profile of ideal CVD risk factors from young adulthood into middle age essentially escape remaining lifetime risk of major CVD events. Both CVD and non- CVD mortality rates are reduced. This results in the addition of 10 years longevity, better health-related quality of life, and lower annual Medicare costs.

The American Heart Association recently endorsed primordial prevention for improving cardiovascular health in all Americans. Barely 5% of the US population now maintain this ideal profile into middle age.

One recent study published in the Bulletin of the World Health Association demonstrated that, if the majority of the US population reached middle-age with an ideal phenotype, more than 90% of coronary heart disease deaths might be prevented.

Population-based strategies aim to improve health of the entire population by favorably shifting the distribution of risk factors.

Vascular surgery, hospitalizations, and expensive drugs for lipid reduction, hypertension and diabetes drive the economic burden of CVD. Medication-based primary prevention is relatively costly. Primordial prevention will generate savings.

Reducing mean population levels of cholesterol or BP by 5%, or legislation to eliminate trans fat, or reducing dietary salt intake by 3 grams per day would generate over a billion dollars of savings per year.

Delays in identifying more effective strategies for CVD prevention will be very costly.

“The status quo is not acceptable politically, ethically, or economically.”

One of the greatest failures of the medical profession has been our inability to convince individual patients to maintain healthy living habits. The failure is not the profession's alone. It is a societal problem requiring continuing educating, reduction in poverty, general awareness of risk and a change in national living habits. This may take decades.

Prevention must begin in early life. Our present risk assessment and reduction models now extend for only 10 years.

Governments may play a role over the objections of the Libertarians.

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benefit beyond the advice given to patients on the basis of standard risk factors. Poor compliance remains a roadblock. Do we need another risk factor?

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COLON CANCER

“Sigmoidoscopy Should Not Be Relegated To A Non-Preferred Screening Test”

7-2 COLONOSCOPY VS SIGMOIDOSCOPY SCREENING: Getting It Right

“The world of cancer screening has been rocked recently by controversy.” Long-standing recommendations on screening for breast, cervical, and prostate cancer have been questioned, based on either new data or reanalysis of old data.

Even though colonoscopy has achieved a predominant role, the logic and justification for its use remains largely theoretical, based on its extended range and increased yield in detecting colon polyps.

“Instead of meeting its expectations, colonoscopy has not yet proven to be more effective than sigmoidoscopy.” Even today, limited evidence demonstrates reduced mortality vs sigmoidoscopy. A case-control study (2009) reported that colonoscopy was associated with reduced mortality, but this reduction was limited to left-sided lesions. Two subsequent observational studies reported that the association between colonoscopy and reduced cancer risk was limited to the distal colon.

“From a public health and policy perspective, these apparent limitations of colonoscopy can no longer be ignored.”

In the absence of convincing data on the superiority of colonoscopy, sigmoidoscopy should not be relegated to a non-preferred screening test.

Because colonoscopy is well established with a high acceptance rate, the level of evidence necessary to modify this existing standard-of-care is higher.

Fashions in medicine change. The public is confused.

A great advantage of sigmoidoscopy is its greater acceptance and uptake by the public. Costs are lower, convenience is greater, discomfort is lessened. Even if more cancers and adenomas were discovered by colonoscopy, I believe the increased willingness of the public to accept and undergo sigmoidoscopy would exceed any possible advantage of colonoscopy.

See Practical Pointers for Primary Care Medicine May 2010 (5-4):

“Once-only Flexible Sigmoidoscopy Screening in Prevention of Colorectal Cancer”

“Significantly reduced incidence of mortality from CRC”

CORONARY HEART DISEASE

“Only 13% Of The Cohort Maintained Normal Lipid Levels Throughout Young Adulthood”

8-2 NON-OPTIMAL LIPIDS COMMONLY PRESENT IN YOUNG ADULTS AND CORONARY CALCIUM LATER IN LIFE

This study evaluated the atherosclerotic consequence of lipid abnormalities during young adulthood.

It is not clear whether cholesterol levels are important earlier in life when short-term risk of CHD is low. Whether early-life lipid levels can cause atherosclerotic damage during young adulthood that persists into middle age is not known.

This prospective cohort study used repeated measurement of fasting lipids, beginning at onset of adulthood and continuing over 20 years of follow-up.

Recruited healthy volunteers (n = 3258) in 4 US cities in 1985-86. Consenting participants underwent baseline examination and repeated follow-up examinations periodically up to 20 years.

Calculated the average lipid levels to estimate the cumulative exposure to each lipid from age 20 to 35. Categorized average exposure for each lipid as normal, borderline, or abnormal according to The National Cholesterol Education Program guidelines.

At year 15 and year 20 all underwent a computed tomography of the coronary arteries to determine calcium content.

Defined lipid levels (mg/dL)	Optimal	Non-optimal	
	Normal	Borderline	Abnormal
LDL-c	<100	100-159	160 & over
HDL-c	60 and over	40-59	39 and under
Triglycerides	<150	150-199	200 and over

Average age at time of coronary calcium score = 45

Average exposure to lipids before age 35 and coronary calcium:

	Participants	% with calcium
Overall	3258	17
Lipid exposure category*		
Normal	434	7
Borderline	2443	17
Abnormal	381	30
Time averaged LDL-c		
<70	116	8
160 and over	123	44
Time averaged HDL-c		
> 70	296	13

< 40	293	26
Time averaged TG		
< 50	592	10
200 and over	24	38

(* Categorized according to their most abnormal lipid level.)

Only 13% of the entire cohort maintained normal lipid levels throughout young adulthood.

Abnormal levels were associated with: male sex; white race; higher income; family history of premature CHD; low levels of self-reported physical activity; diabetes, alcohol consumption; high BMI; high waist circumference; and higher BP.

“Our results suggest that atherosclerotic changes begin during young adulthood as a result of commonly observed non-optimal lipid levels, that these changes persist into middle age, and that maintaining optimal levels of lipids (particularly LDL-cholesterol) throughout young adulthood could provide substantial benefits in terms of CHD prevention.”

Even moderately elevated lipid levels seen in most young adults were associated with coronary calcium later in life.

“Moderate elevations of LDL cholesterol and other lipids are commonly ignored by both patients and physicians during young adulthood.”

These findings reinforce the importance of a heart-healthy diet exercise, and maintenance of normal weight beginning in young adulthood.

This is an important application for primary care and public health. I believe these concerns can be extended to adolescence and even childhood. Atherosclerosis begins at an early age and progresses over the lifetime. Coronary calcium indicates an advanced stage of atherosclerosis.

I would check lipid profiles in the young rarely. However, in extreme circumstances, it might be reasonable. We can easily gauge risk by a number of other factors.

Even more rarely would drug therapy in the young be applicable.

Delaying or preventing its gradual development in early age carries a legacy effect into middle age. Lower risk in middle age is related to reduced risk later in life.

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 SHT 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 SHT.

CHD events, CHD mortality and total mortality were greater in the SHT 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.

SHT is common in primary care.

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

We really do not know whether treatment of SHT 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.

DABIGATRAN

“May Be An Option To Replace Warfarin”

10-3 DABIGATRAN ETEXILATE IN PEOPLE WITH ATRIAL FIBRILLATION

Dabigatran (*Pradaxa*; Boehringer Ingelheim) has been approved for use in the US by the FDA for preventions of stroke in patients with non-valvular AF. It is a direct thrombin inhibitor.

A large trial in September 2009 (*See Practical Pointers Sept 2009*) reported that, in patients with atrial fibrillation (AF), dabigatran is associated with rates of stroke similar to those of warfarin.

ADVANTAGES COMPARED TO WARFARIN

Taken orally. No monitoring. Dose is constant. Long half-life. More predictable anticoagulant effect. Wide therapeutic range. Much simpler regimen. No interference by foods and other drugs.

Compared with warfarin when used in patients with AF:

Reduces rates of stroke and peripheral embolization as well as, or better than warfarin.

Reduced deaths due to cardiovascular disease.

Fewer intracranial hemorrhage.

Fewer life-threatening bleeds.

Possible use by patients who cannot or will not take warfarin and whose INR is unstable.

DISADVANTAGES

Dose not settled.

Taken twice daily.

Excreted by the kidney. Care when kidney function is impaired.

No antidote. May take several days for effect to lessen.

Possible increased risk of myocardial infarction. May be contraindicated in patients with history of cardiovascular disease.

Increased g.i. bleeding.

Dyspepsia may cause withdrawals.

Generalizability not settled.

Cost \$8.00 a day.

Use for reasons other than AF must be validated.

I believe we require more experience before Pradaxa is used in primary care practice. Other anticoagulants are now approaching approval. We await comparisons for use in indications other than AF.

DEATH

“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 GOOD 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 health 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 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.”

DESKTOP MEDICINE

Diagnosis And Treatment Of Disease Before It Is Clinically Manifest--A Clinical-Actuarial Correlation

[11-3] DESKTOP MEDICINE

Concepts of disease are essential for defining medicine. In the early 20th century, the dominant concept was pathology in an individual, the foundation for the bedside model of medicine. Bedside medicine organizes the patient-physician relationship around the chief concern, which guides the focus of history-taking and physical examination. Medical training focused on history-taking and the physical examination, emphasizing laboratory-based science and physical diagnosis.

Today, a new model has emerged--desktop medicine. This describes how a desk with a network computer is transforming medical science and practice. The desktop is the space in which researchers discover risk factors and where patients, as well as physicians, go to gain information to diagnose, prevent, and treat disease. Desktop diseases such as dyslipidemia occupy a substantial portion of

practice, and are leading causes of morbidity and mortality. Medicine may soon require an annual personalized health risk assessment.

Desktop diseases are discovered when studies show a factor (eg, blood pressure) is associated with a negative outcome (eg, stroke) and when a clinical trial shows that an intervention affecting the risk factor reduces the risk of the outcome event. The new technology enables physicians to discover the characteristics of persons at risk and to create models to assess whether a patient is at sufficient risk to warrant intervention.

The clinician gathers risk factors by taking the patient’s history and physical examination and by reviewing published clinical studies; then determining whether the risk is sufficient to recommend treatment. The exercise of gathering risk factors and then assessing how well they predict health outcomes and the benefits of reducing these risks is a clinical-actuarial correlation.

Desktop medicine requires development of skills in probabilistic reasoning, epidemiology, and decision sciences as they apply to clinical practice. Physicians need skills in incorporating desktop and bedside models into the office visit and in shaping patient’s expectations for a visit to include both bedside and desktop diseases.

Bedside diseases are categorical. They are either present or absent. Desktop diseases are dimensional. Risk is continuous. Physicians should discuss disease as a probability. Rather than a disease label compelling treatment, a risk estimate allows patients and physicians to practice clinical-actuarial correlation (eg, Is my risk of cancer death too low to justify surgery?)

In applying desktop medicine, it is essential to improve skills in changing patients’ behaviors.

Educating physicians to practice desktop medicine is especially important for the care of elderly patients who have competing risks.

Comparing desktop medicine and bedside models of medicine

	Bedside	Desktop
Concept	Disease as pathology	Disease as a risk of future impairment
Examples	Alzheimer disease, congestive heart failure, colitis, influenza	Diabetes, dyslipidemia, hypertension, osteoporosis.
Core sciences	Anatomy, biology, histology, chemistry Pathology, physiology	Economics, epidemiology, laboratory science, genetics, psychology, statistics.
Patient-physician Interaction	Emphasizes patient’s chief concern and guides a workup and intervention to address it	Emphasizes fostering patient’s appreciation of risks and then adopting and adhering to strategies for risk reduction
Approach to diagnosis and treatment	Clinical-pathological correlation using results of the history, physical examination and studies to select the disease that best explain the chief concern. Uses judgment to select the best treatment	Clinical-actuarial correlation using the results of the patient’s risk factor assessment to correlate with models that estimate whether risk is sufficient to warrant treatment

I enjoyed this commentary. I have been privileged to experience 7 decades of medical practice. As the editorialist comments, I was taught to elicit the “chief complaint” and then go on to conduct a review of systems in order not to miss any detail of the patient’s history. The physical examination was then paramount.

Over the years, the introduction of determination of risk factors occurred so gradually, we scarcely realized this remarkable change in practice.

Desktop medicine is an addition, not a replacement to bedside medicine. Note the Case Records of the Massachusetts General Hospital published frequently in NEJM. These are examples of pure bedside medicine, beginning with chief concern, history, lab work, imaging, pathology and differential diagnosis.

Now that desktop medicine gives us the ability to predict the likelihood of an adverse event, we face the challenge of persuading the patient to reduce his risk. If risk reduction is in the form of medication, the challenge is relatively easy. If it is in the form of lifestyle change (as it often is) the challenge is difficult.

DIABETES

Diabetes Confers About A 2-Fold Excess Risk Of Vascular Disease

7-4 DIABETES MELLITUS, FASTING BLOOD GLUCOSE CONCENTRATION, AND RISK OF VASCULAR DISEASE

This large meta-analysis reports analysis of people without initial vascular disease, aiming to produce reliable estimates of associations of diabetes (**DM**) and fasting blood glucose (**FBG**) with first-ever ischemic vascular diseases for a wide range of circumstances.

The meta-analysis included 102 studies (n = 698 782), which had information at baseline on history of DM and/or FBS. Overall, at baseline, the mean age was 52; 43% were women; 7% reported history of DM.

Assessed baseline DM status in relation with CHD (first ever myocardial infarction, or fatal coronary heart disease), stroke (ischemic, hemorrhagic or unclassified), and deaths attributed to other vascular disorders (heart failure, sudden death, hypertensive disease, pulmonary embolism, and aortic aneurysm).

Calculated hazard ratios (**HR**) for vascular disease adjusted for age, sex, smoking, systolic BP, and body mass index.

During 8.5 million person-years at risk (median 11 years to first outcome) 52 765 incident fatal

or first-ever non-fatal vascular disease outcomes were recorded.

Relations between FBG and vascular risk in persons *with* DM at baseline:

A. Hazard ratios (HR) in persons *with* DM at baseline compared with those without DM:

Coronary heart disease	2.00
Coronary deaths	2.31
Non-fatal MI	1.82
Ischemic stroke	2.27
Hemorrhagic stroke	1.56
Unclassified stroke	1.84
Other vascular deaths	1.73

B. The overall prevalence of DM in adults was 7.0%. This is lower than same estimates of about 10% in developed countries. Assuming a population-wide prevalence of 10%, 11% of vascular deaths were estimated to be attributable to DM

Relations between FBG and vascular risk in persons *without* DM at baseline:

Vascular risk was non-linearly related to FBG levels.:

FBG (mg/dL)	HR for vascular disease
110 to 125	1.17
100 to 109	1.11
70 to 99	1.00
< 70	1.07

Risk of vascular disease increased as FBG increased in people without DM, but risk increased to a much greater degree as total and non-HDL cholesterol and systolic BP increased.

“Our analysis shows that diabetes confers about a 2-fold excess risk of coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes.”

DM had a stronger association with stroke, both ischemic and hemorrhagic, than LDL-cholesterol.

In contrast with the strong associations observed between DM and vascular outcomes, this study shows much more moderate associations of impaired FBG (100-126) with CHD and stroke.

There were no material associations with vascular risk at FBG 70 to 100 mg/dL.

In those without known DM, total (or non-HDL) cholesterol and systolic BP each had much stronger associations with vascular risk than FBS.

Conclusion: DM confers about a 2-fold excess risk of a wide range of vascular diseases, independently of other risk factors. In people without DM, FBG concentration is modestly and non-linearly associated with risk of vascular disease.

I spent many hours untangling this data. It seems to me that studies reported these days are more complex and convoluted than before. Or, perhaps it is because I am getting older. I do believe authors and editors could present the data more concisely and clearly.

The observation that FBG 70-99 predicts no increased risk of vascular disease is noteworthy. This contrasts with the lack of a definitive lower boundary of risk associated with systolic BP and LDL-cholesterol.

The relation between DM and stroke (both hemorrhagic and ischemic) is much greater than the risk predicted by lipids.

In people without DM, lipids and BP are more important risk factors than FBG.

No Compelling Evidence Indicating That Lowering Systolic Below 130 Is Beneficial For Patients With Diabetes.

7-5 TIGHT BLOOD PRESSURE CONTROL AND CARDIOVASCULAR OUTCOMES AMONG HYPERTENSIVE PATIENTS WITH DIABETES AND CORONARY DISEASE.

In 1993, the 5th report of the Joint National Committee recommended that the treatment goal for blood pressure in patients with diabetes should be less than 130/85. In 2002 and in 2010, the American Diabetes Association recommended that the BP treatment goal for patients with diabetes should be less than 130/80, and as low as 115/75. The ADA, in keeping with epidemiological data, suggested that “there is no threshold value for BP, and risk continues to decrease well into the normal range”.

In 2007, the American Heart Association Scientific Statement recommended that the lower BP treatment goal be expanded to include patients with coronary artery disease (**CAD**), stable or unstable angina, and myocardial infarction without ST elevation.

INVEST¹ (2000-2003) was a prospective randomized multicenter trial of over 22 000 patients with hypertension and CAD.

The present study (1997 extended to 2008) is an observational subgroup (secondary) analysis of 6400 patients with diabetes in the INVEST trial. It was designed to investigate the effects of systolic BP on risk of cardiovascular events in this cohort. Subjects had hypertension and diabetes in addition to CAD. All were over age 50. (Mean age = 66)

Patients received several antihypertension drugs to achieve a BP of less than 130/85.

They were categorized depending on their average BP.

- 1) Tight control if they maintained BP at less than 130.
- 2) Usual control if systolic BP ranged from 130 to less than 140,
- 3) Uncontrolled if systolic BP was 140 or higher.

Primary outcome = first occurrence of all-cause death, non-fatal myocardial infarction, or

non-fatal stroke. The secondary outcome = first all-cause death, non-fatal MI. and non-fatal stroke individually.

The primary outcome occurred in 12.7% of those in tight control; and 12.6% in the usual control; and 19.8% in the uncontrolled group. For all-cause mortality there was significantly increased risk in the tight control group (11% vs 10.2%). In the extended follow-up analysis of all-cause mortality in the group in the USA, after adjustment, all-cause mortality was significantly greater in the tight control group than in the usual control group (22.8% vs 21.8%) Compared with those with a systolic 125-129, those with a systolic BP 110-114 had an increased all-cause mortality. (Hazard ratio = 2.18)

The goal of treating hypertension in patients with diabetes is to prevent macro- and micro-vascular complication. Although for almost 20 years, guidelines have recommended lower BP goals there is a paucity of evidence supporting this recommendation.

“In this observational study, (*of very high-risk patients*) we have shown for the first time, to our knowledge, that decreasing systolic BP to lower than 130 in patients with diabetes and CAD was *not* associated with further reduction in mortality beyond that associated with systolic BP lower than 140 mm Hg, and in fact, was associated with an increase in risk of all-cause mortality.”

Conclusion: Tight control of systolic BP was *not* associated with improved cardiovascular outcomes compared with usual control. At this time there is no compelling evidence indicating that lowering systolic below 130 is beneficial for patients with diabetes. Emphasis should be placed on systolic between 130-139 while focusing on weight loss and other manifestations of cardiovascular morbidity.

Guidelines rarely account for subsets of patients who may have increased risks of complications from the intervention.

I believe the authors of this report have made too broad a conclusion. The results may not apply to young, otherwise healthy patients with diabetes. They may gain benefit over the years in reducing risk of micro- and macro-vascular events from lower BP.

Nevertheless, primary care clinicians should treat elderly diabetic patients at high risk of CVD events with caution. At age 66, they have less to gain from intensive interventions. Too strict control of glycemia also is harmful. Hypoglycemia is a strong risk factor in the elderly.

Treatment of other risk factors (overweight, dyslipidemia) should be emphasized.

Avoids The Twin Hazards Of Hypoglycemia And Weight Gain

8-6 EFFICACY AND SAFETY OF EXENATIDE ONCE WEEKLY VERSUS SITAGLIPTIN OR PIOGLITAZONE AS AN ADJUNCT TO METFORMIN FOR TREATMENT OF TYPE-2 DIABETES

This randomized trial compared the efficacy, safety, and tolerability of three recommended therapies (in addition to metformin) for patients not sufficiently controlled on metformin alone.

Recruited 514 patients in 2008 in 72 hospitals and clinics. All had type-2 diabetes (**DM-2**) but were otherwise healthy. All had been treated with a stable metformin regimen for at least 2 months.

Randomized to: 1) Exenatide 2 mg once weekly subcutaneous injection + oral placebo once daily, + metformin 2) Pioglitazone 45 mg orally once daily + placebo once weekly by injection, + metformin, or 3) Sitagliptin 100 mg orally + once weekly placebo injection + metformin. Stable doses of metformin were continued in all. Doses of sitagliptin and pioglitazone were considered maximum.

At 26 weeks, treatment with exenatide resulted in a greater reduction of HbA1c than sitagliptin. For pioglitazone, the difference was significant only in those with baseline HbA1c 9.0% and above.

Change in HbA1c was determined relative to 2 baseline levels: < 9.0% and 9.0% and above

A. HbA1c < 9.0%

	Exenatide (n = 102)	Sitagliptin (n = 106)	Pioglitazone (n = 109)
Baseline HbA1c	7.8%	7.7%	7.8%
Change in HbA1c	-1.1%	-0.5%	-0.9%
Treatment difference vs exenatide	NA	0.6%	0.2% (Not significant)

B. HbA1c 9.0% and above

	Exenatide (n = 58)	Sitagliptin (n = 60)	Pioglitazone (n = 56)
Baseline HbA1c	9.9%	9.8%	9.7%
Change in HbA1c	-2.0%	-1.3%	-1.5%
Treatment difference vs exenatide	NA	0.7%	0.5%

At 26 weeks, 60% of exenatide patients had HbA1c less than 7.0% and 35% had levels below 6.5%. Fasting blood glucose declined by 32 mg/dL. Fasting insulin levels rose.

In the exenatide group, there were small, but favorable changes in bodyweight, systolic BP, HDL-cholesterol, LDL-cholesterol, triglycerides, albumin / creatinine ratio, C-reactive protein, and quality of life.

Adverse effects of exenatide over 26 weeks: Nausea 23%; diarrhea 18%; vomiting 11%; fatigue 6%; and constipation 6%; 11 patients withdrew because of adverse effects.

There were no episodes of major hypoglycemia; two events of minor hypoglycemia.

“These data suggest that exenatide once weekly offers clinically meaningful improvements in patients not achieving adequate glycemic control on metformin alone.”

Improvements in lipids and markers of cardiovascular risk were noted to varying degrees in all 3 treatments. Exenatide was the only drug associated with favorable mean changes in all the parameters.

Conclusion: Addition of exenatide once weekly to metformin achieved the goal of better glycemic control with weight loss and minimum hypoglycemia more often than did the addition of maximum doses of sitagliptin or pioglitazone.

Because this formulation of exenatide has not been approved by the FDA, this is not a practical point at this time I abstracted the article because of its apparent promise. If we can avoid hypoglycemia and weight gain, we may be able to more safely reduce BP and HbA1c levels.

Exenatide is an incretin mimetic. It increases insulin secretion after a meal, decreases glucagon secretion, delays stomach emptying, and increases satiety.

We await long-term studies about costs, safety, and effect on clinical outcomes.

Exenatide has been available as "Byetta" from Amylin Pharmaceuticals in a short-acting form given twice daily. The exenatide described in this article is long-acting. It is attached to a different type of microsphere, which delays absorption. Half-life is 2 weeks. A steady state is achieved in 6 weeks.

See Practical Pointers March 2010 [3-3] for more details about these drugs.

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 dietitians, 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.

“Serum Potassium Levels -- An Independent Predictor Of Incident DM-2.”

10-1 SERUM AND DIETARY POTASSIUM AND RISK OF INCIDENT TYPE-2 DIABETES

Hypokalemia may be a risk factor for type-2 diabetes (**DM-2**): 1) In studies of thiazide diuretics, lower K levels were associated with higher serum glucose levels. This effect was blunted by oral K supplementation. 2) Experimental studies provide biological plausibility by showing that thiazide-induced hypokalemia leads to diminished insulin secretion. 3) ACE inhibitors, which increase serum K levels, are associated with a decreased risk of DM-2. 4) A reanalysis of the Systolic Hypertension in the Elderly Program (**SHEP**) identified hypokalemia as a mediator of thiazide-related risk of incident

DM-2.

This study analyzed data from ARIC study to test the hypothesis that adults with lower serum K levels (in the normal range) are at higher risk for DM-2, even without diuretic use. It also sought to determine whether higher dietary K intake is associated with lower risk. ARIC is a prospective study of over 15 000 adults age 45-65 (mean 54) at baseline (1986-89) from 4 population probability samples in the US. None had diabetes at baseline. All had serum K determined.

Categorized serum K into 4 clinically meaningful groups: < 4.0 mEq/L; 4.0 to 4.4; 4.5 to 4.9; and 5.0 to 5.5.

Follow-up to 2008. In the first 9 years, subjects were followed by clinic visits; thereafter by telephone consultation.

Mean serum K at baseline was 4.4 mEq/L (range 2.4 to 5.5)

There was a significant inverse relationship between serum K and fasting insulin levels.

	Serum K levels at baseline			
	<4.0	4.0 - 4.4	4.5 - 4.9	5.0 -5.5
Number of participants	1619	4903	4178	1509
Fasting insulin pIU/mL	13.72	11.10	10.76	9.67
Incident DM-2 during the first 9 years of follow-up (n = 1475)				
Rate per 1000 person-years	24.6	16.6	14.2	11.8
Adjusted hazard ratio (HR)	2.05	1.52	1.37	1.00 (referent)

After excluding participants who were prescribed diuretics, beta-blockers, ACE inhibitors, K supplements, and magnesium supplements there was a graded increase in HR of incident DM-2 with lower serum K levels.

Hazard ratios	1.57	1.49	1.38	1.00
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HRs were higher in those receiving diuretics.

	2.91	2.85	1.93	1.00
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The gradient was less evident over 20+ years, but incidence of DM-2 remained higher in those with K levels lower than 5.0

Dietary analysis: Mean K dietary intake was 2655 mg/day (recommended = 4700) The correlation between serum K and dietary intake was modest. But there was a significant graded increase in risk of incident DM-2 with lower dietary K intake. HRs for incident DM-2 by lower to higher K intake quartiles were 1.37; 1.19; and 0.95 compared with the reference highest intake (1.00).

This study is limited by only a single K determination at baseline. However the National Health and Nutrition Examination Survey (NHANES) found that serum K levels have an individual variability of about 5% based on repeated measurements.

I enjoyed this article. It was difficult to cull out the various hazard ratios.

The study emphasizes the importance of a healthy diet--higher intake of fruits and vegetables, the sources of K. The American diet is high in Na and lacking in K. We often forget the importance of K in the pathogenesis of hypertension as well as DM-2.

A study in NEJM May 10, 2007 (See Practical Pointers May 2007) states that "sodium is necessary for development of hypertension, but is not sufficient."

"Potassium is the main intracellular cation. Abundant evidence indicates that a potassium deficit has a critical role in the pathogenesis of hypertension.

"Excess sodium and a deficit of potassium are dominant environmental factors in the pathogenesis.

"Potassium restriction causes a deficit in cellular potassium. This triggers cells to gain sodium in order to maintain their tonicity and volume.

"Sodium retention increases sodium concentration and decreases potassium concentrations in the intra-cellular fluid. This results in a rise in intra-cellular calcium, which triggers contraction of vascular smooth muscle.

"Forms of potassium that do not contain chloride, such as found in fruits and vegetables, offer larger cellular entry in exchange for sodium and greater anti-hypertensive effects.

"Potassium depletion inhibits insulin secretion and is associated with glucose intolerance.

"Thiazide-induced hypokalemia worsens glucose intolerance in type-2 diabetes. Correction of hypokalemia ameliorates the glucose intolerance.

" Primary hypertension and age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium chloride is less than 50 mmol/day (~3 grams of NaCl). It appears then, that sodium intake in excess of 50 to 100 mmol/day is necessary, but not sufficient for the development of primary hypertension.

"Isolated populations that eat natural foods (in which hypertension affects less than 1% of the people) have an individual potassium intake that exceeds about 6 grams per day and a sodium intake of 0.5 to 1.0 grams.

"People in industrialized countries ingest 1.2 to 2.7 grams of potassium per day and as much as 9 grams of sodium.

"Differences in prevalence of hypertension have been attributed to the sodium intake, but could also reflect differences in potassium intake.

"A modified diet that approaches the high potassium /sodium ratio of the diets of our human ancestors is a critical strategy for primary prevention and treatment of hypertension."

The DASH diet is rich in fruits and vegetables.

A HbA1c Target Of 6.0% Or Less With Present Strategies Seems Imprudent.

10-6 EFFECT OF INTENSIVE TREATMENT OF HYPERGLYCEMIA ON MICRO-VASCULAR OUTCOMES IN TYPE-2 DIABETES; An Analysis of the ACCORD Randomized Trial

Epidemiological studies of type-2 diabetes (**DM-2**) have shown that high HbA1c levels are associated with increased risk of diabetic retinopathy and neuropathy.

ACCORD investigated the effects of standard vs intensive control of hyperglycemia on cardiovascular events over 10 years in a large population with DM-2. It also assessed the effect of intensive control on incidence and progression of retinopathy and neuropathy. The study aimed to reduce HbA1c levels to less than 6.0% in the intensive control group vs 7.0-7.9% in the standard group.

Entered 10 251-- 5125 in the intensive group and 5126 in the standard group. At baseline HbA1c levels averaged 8.1% in both groups.

At 4 years, HbA1c levels averaged 6.3% in the intensive group, and 7.6% in the standard group.

Intensive control was stopped at 4 years because of a 22% increase in all-cause mortality. The intensive-control patients were then transferred to standard control and the study continued for another 6 years (total of 10 years) .

At 10 years there were still some benefits remaining in the former intensive group: modest reductions in albuminuria and manifestations of diabetic neuropathy. (*A legacy effect.*) Serum creatinine levels rose equally in both groups.

There was no significant effect of intensive glycemic control on the composite primary micro-vascular outcome. (Renal and retinal)

Analysis of the secondary renal endpoints showed that the risk of development of micro-albuminuria was 20% lower in the intensive group --at both transition and at endpoint.

Targeting HbA1c to 6.0% is not recommended on the basis of micro-vascular benefits. Any benefits should be weighed against the recorded increase in total and CVD-related mortality.

Caution should be exercised in pursuing a strategy of intensive glycemia control for prevention of micro-vascular complications. A HbA1c target of 6.0% or less with present strategies seems imprudent.

Micro-vascular benefits should be weighed against the increase in total and CVD-related mortality, increased weight gain and high risk of severe hypoglycemia

What may primary care clinicians reasonably deduce from ACCORD AND ADVANCE?

- 1. Severe hypoglycemia may occur in those receiving standard treatment. It is more common in those receiving intensive treatment.*
- 2. Adverse CVD effects are more common in patients experiencing severe hypoglycemia.*
- 3. Hypoglycemia is a patho-physiologic stressor. It may be a cause of CVD events and death in*

patients with DM-2, especially in those at high risk for CVD.

- 4. Adverse CVD effects and death may occur in patients with DM-2 who are at high risk of CVD, unrelated to occurrence of hypoglycemia. (Participants in both studies were at high risk at baseline.) Take extra care to avoid hypoglycemia in these patients. Young patients who have no CVD risk factors may better withstand hypoglycemia. Nevertheless, severe hypoglycemia should be avoided at any age.*
- 5. Benefits of intensive glycemc control are much less in older patients with DM-2 than younger patients. Good control starting at an early age and continued will reduce incidence of both micro- and macro-vascular complications*
- 6. There may be considerable benefit offered by the new glucagon-like-peptide drugs (eg, liraglutide) which avoid hypoglycemia and weight gain.*

Combined Aerobic And Resistance Training Was More Effective In Reducing Hba1c

11-4 EFFECTS OF AEROBIC AND RESISTANCE TRAINING ON HEMOGLOBIN A1C LEVELS IN PATIENTS WITH TYPE-2 DIABETES

Regular exercise provides substantial benefits in patients with type-2 diabetes. (DM-2). The benefit related to the exact exercise prescription (aerobic vs resistance) is less clear. For a given amount of time, is the combination of aerobic + resistance better than either alone?

This study was designed to compare the effects of aerobic training, resistance training and the combination on HbA1c levels in previously sedentary persons with DM-2.

Recruited participants (age 30-75; n = 2421 screened for eligibility) from 2007 to 2009 in a community in Louisiana for a 9-month exercise interventions study. After exclusions randomized 262 participants into 4 groups:

- 1) Control (n = 41) were offered weekly stretching and relaxation classes
- 2) Aerobic exercise (n = 72) 140 minutes per week on the treadmill.
- 3) Resistance exercise (n = 73) exercised 3 times a week. Each session consisted of: two sets of 4 upper body exercises; 3 sets of 3 leg exercises; and 2 sets each of abdominal crunches and back exercises.
- 4) Combined aerobic-resistance (n = 76) had 2 resistance periods per week of one set of exercises and the remainder of the time on the treadmill.

Exercise interventions were designed to be of approximately equal time. The exercises were standardized to body weight, Estimated that 150 minutes per week of moderate intensity exercise (50% to 80% of maximum O₂ consumption) would burn 10 to 12 kcal/kg of body weight per week.

Primary outcome = change in HbA1c over 9 months.

Baseline characteristics (means and %): Age 56; female 63%; 47% non-white; HbA1c 7.7%; duration of DM -2 7 years; BMI 35; waist circumference 112 cm; BP 126/76.

Baseline and 9-month changes in HbA1c:	HbA1c %		
	Baseline	9-month	Mean change
A. Intentions -to-treat (n = 262)			
Control	7.62	7.74	+0.12
Resistance	7.58	7.53	--0.05
Aerobic	7.56	7.43	--0.13
Combined exercise	7.59	7.36	--0.23

When intention -to treat group was limited to those with baseline HbA1c 7.0% and over, the difference in HbA1c levels between controls and combined exercise group grew to -0.35%. And when limited to those with a baseline HbA1c 7% or more who actually completed the trial the difference grew to -0.45

The combination group had fewer increases and more reductions in antidiabetes medications.

Cumulative benefit across all outcomes was greater in the combination group compared with either the aerobic or the resistance groups.

The differences in HbA1c between the combination group and the control group occurred even though the control group had increases in use of diabetes medications while the combination group had decreases.

Conclusion: Among patients with DM-2, a combination of aerobic and resistance training, improved HbA1c levels more than aerobic exercise alone and resistance exercise alone.

How generalisable is this trial? One way of judging generalizability is to follow the participant flow chart.

The study began with 2421 individuals screened for eligibility.

After all exclusions, only 262 individuals remained for randomization and the intention-to-treat analysis.

The benefits were indeed modest,

Nevertheless, I believe the trial has some applicability to primary care practice. Some patients may find it more convenient to perform resistance exercises periodically and combine them with brisk walking. A combined program will lead to improved fitness and well-being, and likely lower risks of cardiovascular disease.

There were no dietary restrictions in the trial. If they were applied, benefits would be greater.

DIET

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.

FACTOR Xa INHIBITOR

“Show Great Promise”

12-1 THERAPEUTIC POTENTIAL OF ORAL FACTOR Xa INHIBITORS

Two studies in this issue of NEJM affirm the efficacy and safety of the new oral factor Xa inhibitors, rivaroxaban and apixaban in the management of thromboembolic disease.

One study compared enoxaparin (a low molecular weight heparin) followed by warfarin, with rivaroxaban. Treatment was continued for 3 to 6 months in patients with acute symptomatic deep vein thrombosis (DVT). Rivaroxaban had non-inferior efficacy with respect to recurrent DVT, with similar rates of hemorrhage. A continuing part of the study compared rivaroxaban with placebo for up to 12 months. This confirms the continuing risk of DVT after initial treatment, and lends support to extending the duration of anticoagulation therapy, particularly given the low rates of major bleeding with rivaroxaban (less than 1 in 100).

The second study concerned patients undergoing total hip replacement. Participants were randomized to apixaban orally twice daily, or enoxaparin (a low molecular weight heparin) subcutaneously once daily. Treatment was continued for 35 days after surgery. Apixaban was associated with lower rates of venous thrombosis without any increase in bleeding.

The oral factor Xa inhibitors represent a major advance in prevention and treatment of thromboembolic disease. Factor Xa is situated at the junction of the intrinsic and extrinsic coagulation pathways proximal to thrombin. As compared with warfarin, these new compounds will prove safer in clinical practice. They are highly specific, administered in fixed doses, do not interact with diet, and have fewer interactions with other drugs. Their rapid onset of action obviates the need for heparin at the beginning of treatment. The shorter half-life may improve their overall safety profile, but also may result in increased risks of recurrent VTE if doses are missed.

Subjects in clinical trials are usually younger, have less comorbidity, are likely to be more adherent to taking the drug, and are specifically selected to have less risk of bleeding than real-life patients. Both the risk of hemorrhage and thrombosis increase substantially with age. This may limit generalizability.

The factor Xa inhibitors show great promise.

Big Pharma is hot on the trail after these drugs. It will be interesting to find out which one (or ones) will win. They will have to compete with the direct thrombin inhibitors dabigatran. (See Practical Pointers September 2009 [9-4]). Factor Xa inhibitors are a long-awaited advance. They have many advantages over heparin-warfarin, but the risk of bleeding persists.

HEADACHE

“Substantially Reduced The Pain From Both Migraine And Tension-Type Headache.”

10-2 TRICYCLIC ANTIDEPRESSANTS AND HEADACHES: Systematic Review and Meta-analysis

This inclusive literature search included published randomized clinical trials that evaluated the efficacy of tricyclic anti-depressant drugs in reducing the frequency and severity of migraine headache (**MHA**) and tension-type headaches. (**THA**)

A total of 3176 participants were included in 37 studies., which lasted an average of 10 weeks.. Most studies titrated drug dose. Maximum doses: amitriptyline 150 mg; clomipramine 150 mg; doxepin 100 mg; Mean pooled doses: amitriptyline 80 mg; clomipramine 116 mg; doxepin 50 mg.

1. Tricyclics vs placebo:

A. Tension-type HA (8 studies)

At baseline, participants averaged 16 headaches per month

Tricyclics were more effective than placebo in reducing the burden of THA by an average standard mean difference of 0.99, a clinically large effect.

The number of THA was reduced by an average of 7 per month .

The beneficial effect increased over time.

Participants taking tricyclics for THA were more likely to experience a 50% improvement than those taking placebo.

2. Migraine headache (9 studies)

At baseline, participants averaged 5 headaches per month.

Tricyclics were more effective than placebo in reducing the burden of migraine by an average standard mean difference of 1.00, a clinically large effect.

The number of MHA was reduced an average of 1.4 per month.

The beneficial effects increased over time.

Participants taking tricyclics for MHA were more likely to experience a 50% improvement than those taking placebo

3. Tricyclics reduced the number of doses of analgesics taken for acute HA pain.

4. Adverse effects vs placebo

Relative risk (**RR**)

Those taking tricyclics reported “any” side effect

1.89

Dry mouth 2.91

Drowsiness 1.87

(The only adverse effects that were statistically significant.)

The likelihood of withdrawing due to adverse effects did not differ between groups

4. Tricyclics vs SSRIs.

Despite a low dose (average 50 mg) tricyclics were more likely than SSRIs to produce at least a 50% improvement in THA and MHA .

5. Tricyclics vs other drugs

There were few studies. Three studies compared tricyclics with beta-blockers. There was no difference in reduction in number of HAs. Two studies did not differ in likelihood of experiencing at least a 50% reduction in HA.

Two studies comparing tricyclics with buspirone (an anxiolytic) found no difference.

One study found amitriptyline better than dihydroergotamine for MHA.

6. “We found that tricyclic antidepressants substantially reduced the pain from both migraine and tension-type headache.” Compared with placebo, patients with THA were 40-70% more likely to report at least a 50% improvement. Patients used fewer analgesics.

Tricyclics seem equally effective for MHA. This is useful clinically because differentiation of the two types may not always be straightforward, especially when HAs are frequent.

The benefit seems to increase over time. Clinical practice recommendations suggest that tricyclics be taken for several months before reaching any conclusions on effectiveness for any given patient.

Many clinicians encourage patients to take tricyclics for several months during which the dose is increased before deciding to try a different prophylactic agent.

It is impossible to differentiate whether treatment effect is independent of depression. The relation between depression and physical symptoms is well described. Patients with depression have more physical symptoms and report those symptoms are more serious and more severe and disabling than patients without depression. Depressed patients experience improvements in somatic problems when underlying depression is successfully treated.

7. “Meta-analysis is limited by the problem of aggregate data.” “Heterogeneity in our results was considerable.” “This analysis should be viewed as exploratory rather than definitive.”

Conclusion: Tricyclic antidepressants are effective in preventing migraine and tension-type headache.

Benefits of tricyclics have been described for a half-century.

This is a long, complex article. Abstracting meta-analyses is often unsatisfactory because of heterogeneity between studies. You end up calculating averages.

In eight studies of tension HA, 4 were statistically significant; of 9 studies of migraine, 5 were statistically significant favoring tricyclics over placebo. I believe this adds to the validity of the author's conclusions.

I felt this article was worthy. It deals with patients who are severely afflicted. Some, I am sure, were incapacitated by HA. Tricyclics may be a boon; certainly worth a therapeutic trial. They have the advantage of being effective for tension headaches as well.

It might be reasonable to add short-acting drugs to treat and abort, while patiently continuing amitriptyline. (Eg aspirin with or without metoclopramide.)

Beta-blockers (eg, propranolol) are also effective in prevention of MHA.

Fortunately, amitriptyline is inexpensive. Some pharmacies sell the generic, at any dose for \$4.00 for a monthly supply.

HEARING LOSS

In 2005-06, 1 In 5 US Adolescents Demonstrated Hearing Loss

8-5 CHANGE IN PREVALENCE OF HEARING LOSS IN US ADOLESCENTS

Hearing loss (HL) is a common sensory disorder of millions of individuals in the US. In school-aged children, even slight HL (15-24 dB) can create a need for speech therapy and auditory training. Mild HL in young children can impair speech and language development and decrease educational and social-emotional development.

This study of 12 to 19 year old subjects, compared their health status in The Third National Health and Nutrition Examination Survey (NHANES 1988-94) with NHANES 2005-06. Conducted meticulous audiometry in both groups. Defined HL as low or high frequency loss greater than 15 dB in either ear.

Hearing loss prevalence	NHANES 1989-94 (n = 2928)	NHANES 2005-06 (n = 1771)
Any HL (%)		
> 15 dB	14.9	19.5
15 - 24 dB	11.4	14.2
> 25 dB	3.5	5.3
Bilateral HL (%)		
> 15 dB	3.8	5.5
15 - 24 dB	2.9	4.7
> 25 dB	0.8	0.8

The prevalence of HL increased by 31% over this time. The prevalence of high frequency HL

was higher in 2005-06. The prevalence of low frequency HL did not differ. Males were more likely to have any HL than females.

In 2005-06, 1 in 5 US adolescents demonstrated HL. This represents a 1/3 increase in the prevalence of HL over 10+ years. Most HL was slight. Most HL was unilateral. High frequency HL was more common.

However, the prevalence of HL of 25 dB or greater increased from 3.5% to 5.3%, indicating that one in 20 had mild or worse HL

The reason for the increasing loss is not known. Untreated middle ear disease is not likely to explain the HL. The study did not find a difference in estimated noise exposure between the 2 time periods.

Conclusion: Prevalence of HL among a sample of US adolescents age 12 to 19 was greater in 2005-06 than 1988-94.

Is there an application for primary care here? I believe there is.

Repeated exposure to loud noise does cause hearing loss. Avoiding excess noise is part of a healthy lifestyle, which primary care clinicians constantly advise. So, protect your ears!

Exposure to noise is ubiquitous and growing. Lawn and industrial machinery, traffic, crowds at sports events, and adolescent music are very loud, including the notorious "boom box".

HYPOGLYCEMIA

Adding To the Uncertainty About The Direct Causal Relationship Between Hypoglycemia And Vascular Outcomes.

10-5 SEVERE HYPOGLYCEMIA AND RISKS OF VASCULAR EVENTS AND DEATH: The ADVANCE Study

This 5-year, multicenter, multicountry open-label study examined the relationship between severe hypoglycemia and the subsequent risk of vascular complications and death in patients with DM-2.

Followed a total of 11 140 community-dwelling patients over age 55. All had DM-2 diagnosed after age 30, and had a history of major macro-vascular events or micro-vascular disease, or at least one cardiovascular risk factor in addition to DM-2. (A very high-risk group.)

Compared the effects of intensive glucose-lowering (target HbA1c of 6.5% or lower) with the use of modified-release gliclazide and other glucose-lowering drugs as required, vs standard guideline-based glucose-lowering on the risks of vascular outcomes and death.

Defined hypoglycemia as blood glucose less than 50 mg/dL, or the presence of typical

symptoms and signs of hypoglycemia without other apparent cause. Patients with transient symptoms of the central nervous system who were unable to treat themselves (requiring help of another person) were considered to have severe hypoglycemia.

Severe hypoglycemia was uncommon, but more common in the intensive group. Minor hypoglycemia was common:

	Intensive (n = 5571)	Standard (n = 5569)
Severe hypoglycemia	150 (2.7%)	81 (1.5 %)
Minor hypoglycemia	2898 (52%)	2077 (37%)

The unadjusted risks of a major macro-vascular event, a major micro-vascular event, death from any cause, and death from a CVD cause were significantly increased among patients who had severe hypoglycemia compared with those who did not.

Hazard ratios severe hypoglycemia vs no severe hypoglycemia:

	HR
Major vascular event	3.51
Death (any cause)	3.27
Cardiovascular disease	3.79
Major microvascular event	2.19

But, relatively few patients with severe hypoglycemia had vascular outcomes and death. And outcomes were not closely related to episodes of severe hypoglycemia.

A. During follow-up, 2125 patients had a major macro-vascular or micro-vascular event:

87 of these patients reported severe hypoglycemia (40 before the event, and 47 after the event).

B. Vascular events and death were not closely related to the time of a severe hypoglycemic event. The median time from the episode of severe hypoglycemia to the first major micro-vascular event was 1.56 years and to the first micro-vascular event was 1 year. The median time from severe hypoglycemia to death was 1.05 years; 1.31 years for death from a CVD event and 0.74 years to death from a non-cardiac cause.

C. There was no evidence of a dose-response relationship between repeated episodes of severe hypoglycemia and vascular outcomes and death.

Severe hypoglycemia was associated with increased risks of vascular events and death.

However, neither a close temporal relationship nor a dose-response was observed.

In junction with the absence of a clear dose-response relationship between repeated episodes of hypoglycemia and subsequent macro-vascular events or death, these observations add to the uncertainty about the direct causal relationship between hypoglycemia and vascular outcomes.

In either case, severe hypoglycemia should raise suspicion of adverse outcomes and prompt action to address this possibility.

Severe hypoglycemia was strongly associated with increased risks of adverse clinical outcomes. It is possible that severe hypoglycemia contributes to adverse outcomes, but these analyses indicate that hypoglycemia is just as likely to be a marker of vulnerability to such events.

This is a complex and (to me) a confusing study.

The study began with a group at very high risk for CVD. The mortality rate was high.

The investigators identified many major vascular events. But few were recorded as being associated with severe hypoglycemia. Naturally, patients at very high risk for CVD who do not have DM-2 will die over a short period. The investigators felt that hypoglycemia was not the cause of many of the deaths.

CVD deaths were not related in time with severe hypoglycemia.

There was no evidence of a dose-response relationship between repeated episodes of severe hypoglycemia and death.

They conclude that, although some deaths might have been associated with severe hypoglycemia, many were not associated, and were due to the high risk of CVD in the cohort at baseline.

Nevertheless, the HRs of adverse events in those experiencing severe hypoglycemia (vs those without) were high.

HYPERTENSION

. No Compelling Evidence Indicating That Lowering Systolic Below 130 Is Beneficial For Patients With Diabetes.

7-5 TIGHT BLOOD PRESSURE CONTROL AND CARDIOVASCULAR OUTCOMES AMONG HYPERTENSIVE PATIENTS WITH DIABETES AND CORONARY DISEASE.

In 1993, the 5th report of the Joint National Committee recommended that the treatment goal for blood pressure in patients with diabetes should be less than 130/85. In 2002 and in 2010, the American Diabetes Association recommended that the BP treatment goal for patients with diabetes should be less than 130/80, and as low as 115/75. The ADA, in keeping with epidemiological data, suggested that “there is no threshold value for BP, and risk continues to decrease well into the normal range”.

In 2007, the American Heart Association Scientific Statement recommended that the lower BP treatment goal be expanded to include patients with coronary artery disease (CAD), stable or unstable angina, and myocardial infarction without ST elevation.

INVEST¹ (2000-2003) was a prospective randomized multicenter trial of over 22 000 patients with hypertension and CAD.

The present study (1997 extended to 2008) is an observational subgroup (secondary) analysis of 6400 patients with diabetes in the INVEST trial. It was designed to investigate the effects of systolic BP

on risk of cardiovascular events in this cohort. Subjects had hypertension and diabetes in addition to CAD. All were over age 50. (Mean age = 66)

Patients received several antihypertension drugs to achieve a BP of less than 130/85.

They were categorized depending on their average BP.

- 1) Tight control if they maintained BP at less than 130.
- 2) Usual control if systolic BP ranged from 130 to less than 140,
- 3) Uncontrolled if systolic BP was 140 or higher.

Primary outcome = first occurrence of all-cause death, non-fatal myocardial infarction, or non-fatal stroke. The secondary outcome = first all-cause death, non-fatal MI. and non-fatal stroke individually.

The primary outcome occurred in 12.7% of those in tight control; and 12.6% in the usual control; and 19.8% in the uncontrolled group. For all-cause mortality there was significantly increased risk in the tight control group (11% vs 10.2%). In the extended follow-up analysis of all-cause mortality in the group in the USA, after adjustment, all-cause mortality was significantly greater in the tight control group than in the usual control group (22.8% vs 21.8%) Compared with those with a systolic 125-129, those with a systolic BP 110-114 had an increased all-cause mortality. (Hazard ratio = 2.18)

The goal of treating hypertension in patients with diabetes is to prevent macro- and micro-vascular complication. Although for almost 20 years, guidelines have recommended lower BP goals there is a paucity of evidence supporting this recommendation.

“In this observational study, (*of very high-risk patients*) we have shown for the first time, to our knowledge, that decreasing systolic BP to lower than 130 in patients with diabetes and CAD was *not* associated with further reduction in mortality beyond that associated with systolic BP lower than 140 mm Hg, and in fact, was associated with an increase in risk of all-cause mortality.”

Conclusion: Tight control of systolic BP was *not* associated with improved cardiovascular outcomes compared with usual control. At this time there is no compelling evidence indicating that lowering systolic below 130 is beneficial for patients with diabetes. Emphasis should be placed on systolic between 130-139 while focusing on weight loss and other manifestations of cardiovascular morbidity.

Guidelines rarely account for subsets of patients who may have increased risks of complications from the intervention.

I believe the authors of this report have made too broad a conclusion. The results may not apply to young, otherwise healthy patients with diabetes. They may gain benefit over the years in reducing risk of micro- and macro-vascular events from lower BP.

Nevertheless, primary care clinicians should treat elderly diabetic patients at high risk of CVD events with caution. At age 66, they have less to gain from intensive interventions. Too strict control of glycemia also is harmful. Hypoglycemia is a strong risk factor in the elderly.

Treatment of other risk factors (overweight, dyslipidemia) should be emphasized.

HYPOTHYROIDISM

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.

LIPIDS

“Only 13% Of The Cohort Maintained Normal Lipid Levels Throughout Young Adulthood”

8-2 NON-OPTIMAL LIPIDS COMMONLY PRESENT IN YOUNG ADULTS AND CORONARY CALCIUM LATER IN LIFE

This study evaluated the atherosclerotic consequence of lipid abnormalities during young adulthood.

It is not clear whether cholesterol levels are important earlier in life when short-term risk of CHD is low. Whether early-life lipid levels can cause atherosclerotic damage during young adulthood that persists into middle age is not known.

This prospective cohort study used repeated measurement of fasting lipids, beginning at onset of adulthood and continuing over 20 years of follow-up.

Recruited healthy volunteers (n = 3258) in 4 US cities in 1985-86. Consenting participants underwent baseline examination and repeated follow-up examinations periodically up to 20 years.

Calculated the average lipid levels to estimate the cumulative exposure to each lipid from age 20 to 35. Categorized average exposure for each lipid as normal, borderline, or abnormal according to The National Cholesterol Education Program guidelines.

At year 15 and year 20 all underwent a computed tomography of the coronary arteries to determine calcium content.

Defined lipid levels (mg/dL)	Optimal	Non-optimal	
	Normal	Borderline	Abnormal
LDL-c	<100	100-159	160 & over
HDL-c	60 and over	40-59	39 and under

Triglycerides	<150	150-199	200 and over
Average age at time of coronary calcium score = 45			
Average exposure to lipids before age 35 and coronary calcium:			
	Participants	% with calcium	
Overall	3258	17	
Lipid exposure category*			
Normal	434	7	
Borderline	2443	17	
Abnormal	381	30	
Time averaged LDL-c			
<70	116	8	
160 and over	123	44	
Time averaged HDL-c			
> 70	296	13	
< 40	293	26	
Time averaged TG			
< 50	592	10	
200 and over	24	38	

(* Categorized according to their most abnormal lipid level.)

Only 13% of the entire cohort maintained normal lipid levels throughout young adulthood.

Abnormal levels were associated with: male sex; white race; higher income; family history of premature CHD; low levels of self-reported physical activity; diabetes, alcohol consumption; high BMI; high waist circumference; and higher BP.

“Our results suggest that atherosclerotic changes begin during young adulthood as a result of commonly observed non-optimal lipid levels, that these changes persist into middle age, and that maintaining optimal levels of lipids (particularly LDL-cholesterol) throughout young adulthood could provide substantial benefits in terms of CHD prevention.”

Even moderately elevated lipid levels seen in most young adults were associated with coronary calcium later in life.

“Moderate elevations of LDL cholesterol and other lipids are commonly ignored by both patients and physicians during young adulthood.”

These findings reinforce the importance of a heart-healthy diet exercise, and maintenance of normal weight beginning in young adulthood.

This is an important application for primary care and public health. I believe these concerns can be extended to adolescence and even childhood. Atherosclerosis begins at an early age and progresses over the lifetime. Coronary calcium indicates an advanced stage of atherosclerosis.

I would check lipid profiles in the young rarely. However, in extreme circumstances, it might be reasonable. We can easily gauge risk by a number of other factors.

Even more rarely would drug therapy in the young be applicable.

Delaying or preventing its gradual development in early age carries a legacy effect into middle age. Lower risk in middle age is related to reduced risk later in life.

In High Risk Patients, More Intensive Therapy May Reduce Risk Of Mortality And Major Vascular Events.

11-2 EFFICACY AND SAFETY OF MORE INTENSIVE LOWERING OF LDL-CHOLESTEROL: A Meta-Analysis Of Data From 170 000 Participants In 26 Randomized Trials

This meta-analysis of individual data assessed the benefits and safety of more intensive statin therapy. Trials were eligible if the main effect of the intervention was to lower LDL-c without any other modifications of risk factors.

Five-trials (n = 39 512) compared more intensive statin vs less intensive statin therapy. All had prior CHD. Baseline LDL-c was 96 mg/dL. The mean further reduction in LDL-c at one year = 20 mg/dL. Compared with less intensive therapy, more intensive therapy produced a highly significant 15% reduction in major vascular events at 1 year.

There was no evidence, in the more vs less intensive therapy, that further lowering of LDL-c from 96 mg/dL to 76 mg/dL produced any adverse effects

Twenty-one trials (n = 129 526) compared statin vs placebo. 52% had prior CHD. There was a highly significant reduction of 22% in major vascular events per 38 mg/dL reduction in LDL-c.

Across all 26 trials, all cause mortality was reduced by 10% per year per 38 mg/dL (1 mmol/L) reduction in LDL-c. Absolute benefit = 8 per 1000 per year. This largely reflected significant reductions in death from coronary heart disease.

Overall, the risk reduction in major vascular events was 22% per 38 mg/dL reduction in LDL-c at 1 year, with a significant 12% reduction during the second year, and significant reductions in each year thereafter.

Ischemic stroke was reduced from 0.6% to 0.5%. Absolute benefit = 1 per 1000 per year. Incidence of hemorrhagic stroke may be slightly increased.

In the more vs less statin trials, incidence of rhabdomyolysis was 4 per 10 000; in the statin vs placebo trials, the observed excess was 1 per 10 000.

There was no evidence of any hazard even when LDL-c concentrations lower than 76 mg/dL were reduced further.

The absolute reduction in cardiac mortality produced by lowering LDL-c with statins in a given population depends chiefly on the absolute risk of death due to coronary occlusion.

The size of the proportional reduction in major vascular events was in direct proportion to the absolute reduction in LDL-c. Each 38 mg/dL reduction in LDL-c reduced the risk of occlusive vascular events by about 20% irrespective of the baseline LDL-c concentration.

“These further reductions in vascular risk can be achieved safely.”

“These findings suggest that the primary goal for patients at high risk of occlusive events should be to achieve the largest LDL cholesterol reduction possible.”

Lowering LDL-c further in high-risk patients would produce additional benefits without any increase in non-vascular mortality.

The investigators were very enthusiastic about LDL-c reduction. They agree that a strong intervention is warranted only in those at high risk of CVD.

They tend to downplay risks of statins. (For a detailed account of adverse effects of statin see Practical Pointers June 2009 [6-2]). Adverse events may be anticipated by careful follow-up. This is costly and burdensome.

This presents a challenge for primary care. How should we judge when to augment statin therapy? There is clearly a group of patients for whom aggressive statin treatment is not indicated, and a group for whom aggressive treatment is indicated. The difficult decision lies for those in between. In this group many risk factors must be considered. This includes age of the patient. Young patients will face greater risk of adverse effects of statins because of longer usage. Old patients have less to gain. The patient must be given enough information to enable his informed consent--to balance his risk of IHD vs the possible harms and costs of statins

Investigators and editors stress benefits and risks in relative terms. This may be meaningful when comparing one treatment with another, but is meaningless when applied to the individual patient. Editors may present absolute numbers but leave it to the reader to calculate the absolute risk or benefit. Patients should be told, “If you take this medication or adopt this lifestyle, your chances of benefit are X in 100, and your chances of harm are Y in 100”. The patient may then make a meaningful decisions to accept or reject based on informed consent.

LITERACY

Over 90 Million US Adults Lack The Literary Skills To Effectively Function In The Current Health Care Environment.

7-1 CAN THIS PATIENT READ AND UNDERSTAND WRITTEN HEALTH INFORMATION?

Health literacy is “the degree to which individuals can obtain, process, and understand basic health information and services needed to make appropriate health decisions.”

In 2003, a national assessment of literacy estimated that 14% of adults had below basic literacy, and an additional 22% had only basic literacy. This resulted in over 90 million US adults who may lack the literary skills to effectively function in the current health care environment.

This limitation is most common in older patients, those with lower education levels, immigrants, and racial/ethnic minorities. Up to 20% of high school-educated patients have limited health literacy.

There is an association between literacy and disease knowledge, utilization of preventive services, hospitalizations, overall health status and mortality.

Providing information written at a low literacy level and communicating without medical jargon should be accomplished for all patients, not just those who have limited literacy.

Ensuring patients’ understanding by having them “teach back “ the material would provide universal precautions that ensure comprehension regardless of literacy level. Time limits the individual physicians ability to apply “teach back”.

I did not abstract this article to inform about the likelihood ratios of accuracy of various tests of literacy. I believe seasoned primary care clinicians are fully aware of this problem, but we often forget, and neglect to determine this important application to providing good health care.

In free clinics, inadequate literacy should be assumed universally.

Asking the patient to repeat the instructions (“teach back”) I believe is effective in assuring patients’ understanding.

Most seasoned clinicians will recognize the extent of the problem and attempt to deal with it.

We should not assume medical literacy.

MAMMOGRAPHY

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.)

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

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.

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.

NONALCOHOLIC FATTY LIVER DISEASE

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.

PALLIATIVE CARE

To Have A Meaningful Effect, PC Services Must Be Provided Early In The Course Of The Disease

8-3 EARLY PALLIATIVE CARE FOR PATIENTS WITH METASTATIC NON-SMALL-CELL LUNG CANCER

Palliative care (PC) , with its focus on management of symptoms, psychosocial support, and assistance with decision making, has the potential to improve the quality of care and reduce the use of medical services. However, PC has traditionally been delivered late in the course of disease for patients with uncontrolled symptoms. Late referral to PC is inadequate to alter the quality and delivery of care provided for patients with cancer.

The goal of this study was to examine the effect of early palliative care (EPC) integrated with standard oncologic care on patient-reported outcomes, use of health services, and quality of end-of-life care among patients with terminal cancer.

Enrolled ambulatory patients with newly diagnosed metastatic lung cancer between 2006 and 2009 in a non-blinded randomized trial of 1) EPC integrated with standard oncologic care vs 2) standard oncologic care alone. Patients were enrolled within 8 weeks of diagnosis.

Guidelines from the National Consensus Project for Quality Palliative Care were included in the study protocol. Significant attention was paid to assessing physical and psychosocial symptoms, establishing goals of care, assisting with decision making regarding treatment, and coordinating care on the basis of the individual needs of the patient.

Health care quality of life was measured by several scales which assessed multiple dimensions of

quality-of-life (physical, functional, emotional, and social well-being), and seven symptoms specific to lung cancer.

Early integration of PC resulted in longer survival (about 2 months), and clinically meaningful improvements in quality of life and mood. Rates of depression were lower in the EPC group by about half. EPC was also associated with greater documentation of preferences for resuscitation, an essential step in clarifying and ensuring respect of patient's wishes.

EPC also led to less aggressive end-of-life care including reduced chemotherapy, and longer hospice care. Integration of EPC with standard oncologic care may facilitate the optimal and appropriate administration of anticancer therapy. With earlier referral to hospice, patients may receive care that results in better management of symptoms, leading to prolonged survival.

The study was not able to assess the effect of diversity of race

This study was much more complex than I have indicated.

The results apply to many primary care patients who are terminal, not necessarily from cancer.

I wonder if prolonging life by 2 months is a benefit. These patients, even if they were made more comfortable, must have continued to suffer without hope of cure, and be more dependent. Unless there were some pressing personal or family need, I doubt 2 more months of life would be a reasonable goal.

Note that the subjects in this study were outpatients. The fewer days spent in the hospital is a major achievement.

The author's comment about race is important. Some cultures require that "everything be done" and that life be prolonged as much as possible.

PC Is Appropriate When It Is Introduced At The Time of Diagnosis of A Serious Or Life-Threatening Illness.

8-4 PALLIATIVE CARE--A SHIFTING PARADIGM [Editorial]

Palliative care (PC) focuses on relieving suffering and achieving the best possible quality of life (Q-O-L) for patients and their caregivers. It involves the assessment and treatment of symptoms, support for decision-making, assistance in matching treatments to informed patient and family goals, practical aid of patients and their family caregivers, mobilization of community resources to ensure a secure and safe living environment, and collaborative and seamless models of care across a range of care settings (hospital, home, nursing home, and hospice).

Despite increasing availability of PC, and evidence showing the great distress of the illness, the burdens of caregivers, and the overuse of costly, ineffective therapies during advanced chronic illness, the use of PC by physicians and their patients remains low. Physicians tend to perceive PC as the

alternative to life-prolonging or curative care--what we do when there is nothing more that we can do--rather than a simultaneously delivered adjunct to the disease-focused treatment.

PC is appropriate and potentially beneficial when it is introduced at the time of diagnosis of a serious of life-threatening illness. PC can improve quality-of life outcomes.

The Charlotte, North Carolina region is blessed with a well-organized hospice and palliative care organization. I wish it had been available when I was in active practice.

I agree that the chief obstacle to proper use of PC is delayed calls for assistance.

Support for families of seriously ill patients is an important responsibility of PC.

PATIENT LITERACY

Over 90 Million US Adults Lack The Literary Skills To Effectively Function In The Current Health Care Environment.

7-1 CAN THIS PATIENT READ AND UNDERSTAND WRITTEN HEALTH INFORMATION?

Health literacy is “the degree to which individuals can obtain, process, and understand basic health information and services needed to make appropriate health decisions.”

In 2003, a national assessment of literacy estimated that 14% of adults had below basic literacy, and an additional 22% had only basic literacy. This resulted in over 90 million US adults who may lack the literary skills to effectively function in the current health care environment.

This limitation is most common in older patients, those with lower education levels, immigrants, and racial/ethnic minorities. Up to 20% of high school-educated patients have limited health literacy.

There is an association between literacy and disease knowledge, utilization of preventive services, hospitalizations, overall health status and mortality.

Providing information written at a low literacy level and communicating without medical jargon should be accomplished for all patients, not just those who have limited literacy.

Ensuring patients’ understanding by having them “teach back “ the material would provide universal precautions that ensure comprehension regardless of literacy level. Time limits the individual physicians ability to apply “teach back”.

I did not abstract this article to inform about the likelihood ratios of accuracy of various tests of literacy. I believe seasoned primary care clinicians are fully aware of this problem, but we often forget, and neglect to determine this important application to providing good health care.

In free clinics, inadequate literacy should be assumed universally.

Asking the patient to repeat the instructions (“teach back”) I believe is effective in assuring patients’ understanding.

*Most seasoned clinicians will recognize the extent of the problem and attempt to deal with it.
We should not assume medical literacy.*

POTASSIUM

“Serum Potassium Levels -- An Independent Predictor Of Incident DM-2.”

10-1 SERUM AND DIETARY POTASSIUM AND RISK OF INCIDENT TYPE-2 DIABETES

Hypokalemia may be a risk factor for type-2 diabetes (**DM-2**): 1) In studies of thiazide diuretics, lower K levels were associated with higher serum glucose levels. This effect was blunted by oral K supplementation. 2) Experimental studies provide biological plausibility by showing that thiazide-induced hypokalemia leads to diminished insulin secretion. 3) ACE inhibitors, which increase serum K levels, are associated with a decreased risk of DM-2. 4) A reanalysis of the Systolic Hypertension in the Elderly Program (**SHEP**) identified hypokalemia as a mediator of thiazide-related risk of incident DM-2.

This study analyzed data from ARIC study to test the hypothesis that adults with lower serum K levels (in the normal range) are at higher risk for DM-2, even without diuretic use. It also sought to determine whether higher dietary K intake is associated with lower risk. ARIC is a prospective study of over 15 000 adults age 45-65 (mean 54) at baseline (1986-89) from 4 population probability samples in the US. None had diabetes at baseline. All had serum K determined.

Categorized serum K into 4 clinically meaningful groups: < 4.0 mEq/L; 4.0 to 4.4; 4.5 to 4.9; and 5.0 to 5.5.

Follow-up to 2008. In the first 9 years, subjects were followed by clinic visits; thereafter by telephone consultation.

Mean serum K at baseline was 4.4 mEq/L (range 2.4 to 5.5)

There was a significant inverse relationship between serum K and fasting insulin levels.

	Serum K levels at baseline			
	<4.0	4.0 - 4.4	4.5 - 4.9	5.0 -5.5
Number of participants	1619	4903	4178	1509
Fasting insulin pIU/mL	13.72	11.10	10.76	9.67
Incident DM-2 during the first 9 years of follow-up (n = 1475)				
Rate per 1000 person-years	24.6	16.6	14.2	11.8
Adjusted hazard ratio (HR)	2.05	1.52	1.37	1.00 (referent)

After excluding participants who were prescribed diuretics, beta-blockers, ACE inhibitors, K supplements, and magnesium supplements there was a graded increase in HR of incident DM-2 with lower serum K levels.

Hazard ratios	1.57	1.49	1.38	1.00
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HRs were higher in those receiving diuretics.

2.91 2.85 1.93 1.00

The gradient was less evident over 20+ years, but incidence of DM-2 remained higher in those with K levels lower than 5.0

Dietary analysis: Mean K dietary intake was 2655 mg/day (recommended = 4700) The correlation between serum K and dietary intake was modest. But there was a significant graded increase in risk of incident DM-2 with lower dietary K intake. HRs for incident DM-2 by lower to higher K intake quartiles were 1.37; 1.19; and 0.95 compared with the reference highest intake (1.00).

This study is limited by only a single K determination at baseline. However the National Health and Nutrition Examination Survey (NHANES) found that serum K levels have an individual variability of about 5% based on repeated measurements.

I enjoyed this article. It was difficult to cull out the various hazard ratios.

The study emphasizes the importance of a healthy diet--higher intake of fruits and vegetables, the sources of K. The American diet is high in Na and lacking in K. We often forget the importance of K in the pathogenesis of hypertension as well as DM-2.

A study in NEJM May 10, 2007 (See Practical Pointers May 2007) states that "sodium is necessary for development of hypertension, but is not sufficient."

"Potassium is the main intracellular cation. Abundant evidence indicates that a potassium deficit has a critical role in the pathogenesis of hypertension.

"Excess sodium and a deficit of potassium are dominant environmental factors in the pathogenesis.

"Potassium restriction causes a deficit in cellular potassium. This triggers cells to gain sodium in order to maintain their tonicity and volume.

"Sodium retention increases sodium concentration and decreases potassium concentrations in the intra-cellular fluid. This results in a rise in intra-cellular calcium, which triggers contraction of vascular smooth muscle.

"Forms of potassium that do not contain chloride, such as found in fruits and vegetables, offer larger cellular entry in exchange for sodium and greater anti-hypertensive effects.

"Potassium depletion inhibits insulin secretion and is associated with glucose intolerance.

"Thiazide-induced hypokalemia worsens glucose intolerance in type-2 diabetes. Correction of hypokalemia ameliorates the glucose intolerance.

" Primary hypertension and age-related increases in blood pressure are virtually absent in populations in which individual consumption of sodium chloride is less than 50 mmol/day (~3 grams of NaCl). It appears then, that sodium intake in excess of 50 to 100 mmol/day is necessary, but not sufficient for the development of primary hypertension.

“Isolated populations that eat natural foods (in which hypertension affects less than 1% of the people) have an individual potassium intake that exceeds about 6 grams per day and a sodium intake of 0.5 to 1.0 grams.

“People in industrialized countries ingest 1.2 to 2.7 grams of potassium per day and as much as 9 grams of sodium.

“Differences in prevalence of hypertension have been attributed to the sodium intake, but could also reflect differences in potassium intake.

“A modified diet that approaches the high potassium /sodium ratio of the diets of our human ancestors is a critical strategy for primary prevention and treatment of hypertension.”

The DASH diet is rich in fruits and vegetables.

PROSTATE CANCER

“Continuing To Aggressively Treat Men With Low Grade PC Will Certainly Do More Harm Than Good.”

7-9 THE CAUTIONARY TALE OF PSA TESTING

The initial promise of PSA screening was that a simple accurate blood test would save lives by detecting tumors at an early enough stage to be cured by aggressive treatment. Unfortunately, 2 decades after the PSA era, the promise has been tarnished.

PSA is far from an optimal tumor marker. Early on, PSA screening was found to be relatively nonspecific. The cutoff of 4.0 ng/mL has a positive predictive value of only about 30%. Many men have false positive elevations. The Prostate Cancer Prevention Trial showed many men had false negative tests (15% of subjects with normal PSA had prostate cancer and 15% of these were high grade).

Last year, two large randomized trials reported that PSA screening had little or no effect on PC mortality:

While PSA screening seems likely to have only minimal benefits on survival that takes many years to realize, it is associated with a substantial risk for overdiagnosis (defined as diagnosing cancers that would not otherwise have been detected or caused any harm during a man’s lifetime).

Because there is no way to distinguish an indolent cancer from one likely to progress, most screen-detected PCs are treated with radiotherapy or radical prostatectomy.

There is abundant data showing that attempted curative therapies often lead to urinary, sexual, and bowel dysfunction that can adversely affect quality of life. A major consequence of overdiagnosis--in addition to the psychological burden of overdiagnosis--is the harm from overtreatment.

The concerns that treatment harms outweigh benefits led the US Preventive Services Task Force to strongly advise against screening men older than age 75.

“Prostate-specific antigen testing has led to an epidemic of prostate cancer, but a substantial proportion of PSA-detected cancers will never be clinically significant. Continuing to aggressively treat men with low grade PC will certainly do more harm than good.”

PSA screening reminds me of the dispute about routine mammography screening in women age 40-49. Certainly, some lives will be saved, but at what cost?

Some clinicians and patients will continue to favor routine PSA screening

Primary care clinicians will continue to face decisions for individual men. It is essential that patients fully realize the harms as well as the possible benefits of screening. Full disclosure is essential, and another demand on clinician's time. After fully informing a man about the downside, ask him to think about it twice or three times.

PSA TESTING

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STROKE

No Difference In Stroke In Users Of Low Dose Transdermal Estrogen Compared With Non-Users **7-6 TRANSDERMAL AND ORAL HORMONE REPLACEMENT THERAPY AND THE RISK OF STROKE**

Transdermal estrogen preparations are effective in treatment of postmenopausal symptoms. They may have a different impact on biological cardiovascular risk markers by avoidance of the first pass effect in the liver.

This nested case-control study assessed the risk of stroke associated with oral versus transdermal hormone replacement therapy (**HRT**) on the risk of stroke.

Used a large computerized data base in the UK containing longitudinal records of more than 6 million persons in over 400 general practices. Conducted a nested case-control study within the cohort consisting of all women age 50-79 between 1987 and 2006. None had a history of stroke.

All cohort subjects were followed until the date of stroke (index date), death, or end of the study period, 1) Cases: all individuals with a first stroke (ischemic, hemorrhagic, or not specified).

2) Controls: the investigators selected 4 matched controls on the index date who were still at risk for stroke.

Calculated the number of strokes, adjusted for multiple possible confounders. Main outcome measure: rate ratio (**RR**) of stroke associated with current use of oral and transdermal HRT compared with no use.

Final analysis contained 15 710 cases of stroke and 59 958 controls during 5 650 035 person-years of observation. (Mean age at index date = 70)

All cardiovascular risk factors were more common in cases than in controls.

Use of HRT was more common in cases: 7.7% of cases and 6.9% of controls had used at least

one HRT in the year before the index date.

Direct comparison of transdermal with oral HRT showed the risk of stroke was lower with use of transdermal. (Adjusted rate ratio [RR] = 0.74)

Current use of oral estrogens alone, compared with no use, increased risk of stroke by 35%. Current use of oral estrogen-progestin increased risk by 24% relative to no use. (No added risk with use of progestin.)

Risk of stroke was much lower with use of *low dose* transdermal estrogen vs oral estrogen. Use of *high dose* transdermal estrogen, however, was associated with much higher risk of stroke.

Risk with use of *low-dose* transdermal estrogen was nil in the first year. Risk increased slightly with use after one year.

Conclusion: The use of transdermal HRT containing low doses of estrogen was associated with lower risk of stroke than the oral route. There was no significant difference in stroke rates in users of low doses transdermal estrogen compared with non-users.

I believe the term hormone replacement therapy (HRT) should be abandoned. It can denote, estrogen-alone, progestin-alone or estrogen + progestin. They are two very different drugs. The term is confusing.

I believe the results of this study can be extrapolated to include coronary heart disease and venous thromboembolism. Both have a relation to increased tendency for clotting. The risk would be higher in individuals who have increased risk factors.

The message is much the same:

- 1) Use estrogens in the lowest dose possible*
- 2) Use them for the shortest time possible.*
- 3) In women with high risks for CVD, consider transdermal estrogen.*

Investigators in the UK have a great advantage when considering epidemiological studies. They can use the national coordinated computerized data bases made available by their national health service. This makes the results of studies more generalisable.

My pharmacy informs me that a monthly supply of estradiol patches (once weekly) is less expensive than a monthly supply of Premarin

TESTOSTERONE

In Frail Old Men, Risks Outweigh Benefits

7-8 TESTOSTERONE DEFICIENCY AND REPLACEMENT IN OLDER MEN (Editorial)

“The numbers of older men receiving testosterone are large and increasing.”

Many of the physical and behavioral changes that occur in older men are similar to those that occur in younger men with hypogonadism: decrease in muscle mass, strength, bone mass and sexual function. And increase in body fat, fatigue, and depressed mood.

A population survey of 3369 men age 40-79 compared morning measurements of total and free testosterone with subjects' general, sexual, physical, and psychological health. Among the many symptoms surveyed, 3 sexual symptoms were associated with low levels (poor morning erection, low sexual desire, and erectile dysfunction), and 3 general symptoms (inability to perform vigorous activity, depression, and fatigue) were also associated with low levels. Late onset hypogonadism can be defined by the presence of at least 3 sexual symptoms associated with a total testosterone level of less than 11 nmol/L, and a free testosterone level of less than 220 pmol/L

The difficulty of using symptoms alone to establish a diagnosis of late-onset hypogonadism was highlighted by the finding that 25% of men with normal testosterone levels had similar symptoms. Thus, the combination of low testosterone + symptoms is required for diagnosis.

The second study of frail older men found that replacement increased leg and arm strength, but also had higher rates of cardiovascular events. (10 of 105 men compared with 1 of 103 receiving placebo) over a 6-month period. This led the data and safety monitoring board to recommend early termination of the study. At baseline, these men were at risk due to hypertension, diabetes, hyperlipidemia, and obesity.

It is rare to find a frail elderly man who has no CVD risk factors.

In my view, the risk/benefit ratio of testosterone replacement is too high. I would be very reluctant to prescribe it.

I can see the TV notices now: "If you were taking testosterone and experienced a heart attack you may be eligible for monetary damages. Call the XYZ law firm right away."

If testosterone is prescribed, it should be limited to men who have few or no risk factors, are not frail, and who understand clearly the risks as well as possible benefits.

TUBERCULOSIS

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.

VENOUS THROMBOEMBOLISM

VT Is Chronic Disease. How Do We Prevent Recurrence?

12-2 RISK ASSESSMENT FOR RECURRENT VENOUS THROMBOSIS

Venous thrombosis (VT) is common, with an incidence of about one case in 1000 person-years. In one third of patients deep VT is complicated by pulmonary embolism (PE). Short term mortality from PE is high, and depends on age and presence of underlying co-morbidities such as cancer and cardio-pulmonary disease.

VT is a chronic disease. It often recurs. Risk of recurrence is about 20-25% within 5 years, and is higher in patients with unprovoked VT. Risk of recurrence depends mainly on presence or absence of acquired and congenital risk factors, and may vary substantially between patients. A systematic review reported the case fatality rate of recurrent venous thromboembolism (VTE) was 3.6%

VTE risk assessment is of practical importance. Patients at highest risk of recurrence will benefit from long-term anticoagulation, whereas patients at low risk will be exposed unnecessarily to bleeding.

This review discusses different approaches to assessment of recurrence of VTE in patients with VT of the lower extremity or PE after completion of anticoagulant treatment. It is based on an extensive search of the literature. (97 citations)

A. Clinical features associated with high risk of recurrence of VT:

Unprovoked VT: Risk of recurrence is especially high when the initial VT is unprovoked (ie, the event occurred in the absence of temporary risk factors such as surgery, trauma, pregnancy, or use of female hormones.) Risk of recurrence over 5 years has been as high as 25% in patients with unprovoked VT or PE. Risk of recurrence declines when the temporary cause (eg, estrogen) is removed.

Estrogen use: Women who continue hormone therapy after VT are at high risk of recurrence. Risk of recurrence is less when this temporary cause of VT is removed.

Deep VT: One study reported that all patients with a recurrence had initial proximal deep VT. None with distal (calf) VT had a recurrence. The low rate of recurrence in patients with isolated calf VT has been confirmed by several other observational studies.

Pulmonary embolism. Data from one study showed that the risk of recurrence is more than two-fold higher in patients with symptomatic PE than in patients with asymptomatic PE.

Sex: Risk of recurrent VT is higher in males-- a nearly 4 -fold increase compared with females.

Cancer: Risk of recurrence in patients with cancer is regarded as high.

Residual VT: Recurrence has been reported higher in those with residual VT than in those without.

Weight: The effect of bodyweight on recurrence is nearly linear, so even modest weight loss may reduce risk.

Recurrent VT: Repeated episodes (more than 2 episodes) of VT predisposes to recurrence. It increases the risk of development of post-thrombotic syndrome.

Family history: Investigators who assessed the association between a positive family history of VT and risk of recurrence reported that the family history did not predict recurrence.

B. Laboratory markers associated with increased risk of recurrent VT:

Includes high concentrations of fibrinogen, factor VIII, and factor IX; factor V Leiden; hyperhomocysteinemia; and prothrombin mutations; increased generation of thrombin; partial deficiency of antithrombin, protein C and protein S, and phospholipid antibodies.

C. Relevance of laboratory screening:

“Abnormalities that are associated with an increased risk of venous thrombosis, and that are detectable with laboratory techniques, can be established in more than 50% of patients with a first unprovoked venous thrombosis.” Identification of thrombophilic defects to improve patient care can be a tempting prospect. Screening has been advocated repeatedly, and is now done on a routine basis in many institutions. However-- “Our review shows that these tests have, at most, a small effect on the risk of recurrence.” Screening is indicated only when individuals with increased risk can be identified and there is an effective treatment with a positive benefit-risk balance.

“There is no proof that thrombophilia screening helps patients, neither with regard to treatment of the acute event nor the prevention of recurrence.”

D. D-dimer¹

The D-dimer test has a high negative predictive value.² It has become an integral part of many diagnostic algorithms to exclude acute VT and PE. The test can be used to separate patients into groups of high or low risk of recurrent VT.

D-dimer concentrations measured one month after discontinuation of oral anticoagulants have a high negative predictive value for recurrence irrespective of the presence or absence of hereditary thrombophilia.

Patients with an especially low risk of recurrence can be identified with lower cutoff concentrations of D-dimer. Patients with a first unprovoked VT or PE and concentrations less than 250 pg/mL have a 60% lower risk of recurrence rate than those with concentrations more than 250.

In one study, which measured D-dimer anticoagulation, rather than after discontinuation, a 250 ng/mL cutoff was predictive of a low risk of recurrence in women.

Two systematic reviews of D-dimer have assessed risk stratification. D-dimer is the only laboratory criterion for thrombophilia that has been used to establish the duration of anticoagulation treatment in a large randomized setting. Patients with low concentrations after withdrawal of anticoagulation had a low risk of recurrence (4 per 100 person-years). Persons with high levels who stopped anticoagulation after 6 months had an increased risk of recurrence (10 per 100 person-years) compared with those who received anticoagulation for more than 6 months.

Repeated testing of D-dimer after withdrawal of anticoagulation following a first unprovoked VT could help establish the optimum duration of treatment.

E. Clinical characteristics of patients and laboratory markers:

A prospective cohort study of over 900 subjects with unprovoked VT or PE were followed for a median of 43 months after discontinuation of anticoagulation. Many possible causes of recurrence were included. Only the patient's sex, thrombosis location, and D-dimer were related to increased risk of recurrence.

I believe this is a reasonable assessment of the state of the art regarding VTE. Many points are still not clear. Deciding duration of anticoagulant therapy still requires clinical judgment. D-dimer is a big help.

The reviewer's comment on screening tests is apt. There is no reason to screen for a disease if nothing can be done to treat or change risk. However, some patients may wish to know if they carry a heritable defect in the clotting mechanism.

I wondered why males are more prone to recurrence. Females carry the estrogen.

The new anticoagulants (factor Xa inhibitors and thrombin inhibitors) will, hopefully, bring major improvements.

VITAMIN D

Low Levels Were Associated With Substantial Cognitive Decline

7-3 VITAMIN D AND COGNITIVE DECLINE IN ELDERLY PERSONS

This is the first prospective study examining the association between D levels and cognitive decline or dementia.

Followed 858 randomly selected adults (mean age 74) in the Tuscany, Italy area. Assessed cognitive function every 3 years between 1998-2006. (Mean follow-up = 5.2 years.)

Obtained D levels at baseline. Tested cognitive function every 3 years using the Mini-Mental State Examination (MMSE--range 0 to 30). Also used the Trails Making tests A and B.

(Trails A focuses mainly on attention; Trails B focuses mainly on executive function. In both tests, higher scores represent worse function.)

Divided 25(OH)D levels into quartiles (nmol/L):

< 25 severely deficient; 25-49 deficient; 50 - 74 insufficient; 75 and over, sufficient.

(Corresponds to ng/mL <10 10-19 20-29 30 and over)

At baseline, MMSE, Trails A and B scores were significantly lower in those who were D deficient, than in those who were D sufficient.

Baseline cognitive function scores according to D levels

	75 and over	50-74	25-49	< 25
MMSE	26.3	26	25.2	23.7
Trails A	87.2	94.2	114.9	151.8
Trails B	180.5	188.5	219.8	239.9

Those severely D deficient were more likely to have substantial cognitive decline than those who were sufficient. Significant linear trends between groups suggest a monotonic relationship. Those who were severely deficient were about 60% more likely to experience substantial decline.)

Relative risk of 6-year substantial cognitive decline in baseline non-demented subjects by

D levels:	75 and over	50-74	25-49	< 25
MMSE	1.00 (referent)	1.27	1.26	1.78
Trails A	1.00	0.95	1.25	1.16
Trails B	1.00	0.99	1.11	1.31

(Substantial decline in Trails B. No significant association between D levels and performance of Trails A)

Lower levels of D were associated with greater year-on-year decline in cognitive function.

The MMSE in participants who were severely deficient declined by an average 0.3 points more per year than those who were sufficient.

“In this population-based prospective study, we found that elderly people with low levels of 25 (OH)D were at increased risk of cognitive decline over 6 years.” There was evidence of a monotonic relationship.

The association remained significant after adjustment for a wide range of potential confounders.

Vitamin D is much more than a vitamin. It is a hormone. Interest in its possible functions has been based on its biological associations with multiple organs. And the fact that levels are deficient in many people, especially the elderly, those living at high latitudes, dark-skinned persons, nursing home residents, and patients being admitted to hospitals.

I believe, however, we are placing too heavy a burden on vitamin D. It will take years to understand its true functions. I doubt any drug company will invest in D research. There would be no profit since D is so inexpensive; 1000 IU of D3 can be purchased for 3 cents. I hope that the NIH will step in. Perhaps the recommended daily amount will be upped.

Primary care clinicians have caught on to the D bandwagon and are ordering laboratory determination of blood levels. And prescribing much higher supplementary doses than previously thought sufficient. A dose of 1000 to 2000 IU daily is common. Fortunately, D is a safe drug. Adverse effects are evident only at very high doses.

Since deficiency is so common, and the drug so inexpensive, I have been wondering if it would not be good practice to prescribe it empirically to many patients without the cost and inconvenience of determining blood levels.

Many persons cannot or will not be able to have their blood level confirmed. Some primary care clinicians may be willing to prescribe supplementation without biochemical confirmation. The benefit / harm-cost ratio of empirically prescribed D will be high.

Prescribe D3, not D2, It is a more effective drug.

WAIST CIRCUMFERENCE

“Increased WC Was Associated With Higher Risk Of Mortality Independent Of BMI.”

8-1 WAIST CIRCUMFERENCE AND ALL-CAUSE MORTALITY IN A LARGE U.S. COHORT

A large waist circumference (WC) is associated, independent of BMI, with higher circulating levels of inflammatory markers, insulin resistance, diabetes, dyslipidemia, and coronary heart disease. This may be because WC is strongly correlated with visceral adipose tissue, which is more pathogenic than subcutaneous adipose tissue.

This study focused on examining associations of high levels of WC (> 88 cm in women and >102 cm in men; 35” and 40”) within standard categories of BMI. Quantifying these risks is important because more than 50% of men and 70% of women in the US between ages 50-70 now exceed the WC threshold for abdominal obesity.

Participants in this analysis were drawn from participants in the Cancer Prevention Study II cohort established in 1992. At enrollment (1992 - 1993) participants (mean age 68) completed a 10-page self-administered health questionnaire. WC was first ascertained in 1997. Participants were provided with a tape measure and asked to measure their WC just above their navel to the nearest quarter inch while standing.

Calculated the BMI from weight reported in 1997 and height reported in 1992. After exclusions, a total of 48 500 men and 56 343 women remained for analysis. Recorded deaths from 1997 to 2006.

Relative risks of mortality (**RR**) gradually increased, approximately linearly, as WC increased by 5 cm increments.

RRs of all cause mortality by WC within categories of BMI:

	BMI 18.5-24.9 (normal)	BMI 25 to 29.9 (overweight)	BMI 30 and higher (obese)
WC (cm)			
Men			
< 90	1.00 (reference)	1.00	--
90-109	1.14	1.06	1.00
100 to 110	1.41	1.21	1.38
>110	--	1.50	1.69
Women			
<75	1.00 (reference)	--	--
75-84	1.24	1.00	
85-94	1.52	1.21	1.00
95-104	2.04	1.40	0.94
105 & higher	--	1.77	1.27
(-- not calculated)			

In women, higher levels of WC were more strongly associated with mortality among those with normal BMI than among women who were overweight and obese. Among men, the association between WC and mortality did not vary significantly with BMI.

“In this large prospective cohort, increased WC was associated with higher risk of mortality independent of BMI.”

WC was positively associated with risk of mortality among individuals within all categories of BMI examined (normal, overweight, and obese). The RRs associated with a 10-cm increase ranged from approximately 15% to 25% within various categories of BMI.

This study emphasizes the importance of WC as a risk factor for mortality in older adults regardless of whether BMI is categorized as normal, overweight, or obese.

It may be more impressive to the patients if the abdominal circumference were measured, and the excess girth categorized in inches, and compared with normal. However, primary care clinicians need only eye-ball the abdomen to determine the problem, which is indeed ubiquitous.

Intra-peritoneal fat is metabolically active because it drains directly into the liver leading to non-alcoholic hepatic liver disease. Extra-peritoneal abdominal fat is less metabolically active. It drains into the general circulation.

Risk of cardiovascular disease is increased in patients with non-alcoholic fatty liver disease in proportion to the degree of steatosis. (NEJM September 30, 2010; 363: 1341-50)