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OCTOBER 2009

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PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA

To request monthly issues go to Rjames6556@aol.com

This document is divided into two parts

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

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

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

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

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.

Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* OCTOBER 2009

“An Emerging Risk To Public Health.”

10-1 AMERICAN ROULETTE—CONTAMINATED DIETARY SUPPLEMENTS

In August 2009, the U.S. FDA reported many products containing a wide variety of undeclared active pharmaceutical ingredients. Most of them were labeled as “dietary supplements” (DS) . More than 140 contaminated products have been identified.

These represent only a fraction of the contaminated supplements on the market.

A recent National Health Interview Survey reported that about 114 million people—more than half the adult population of the USA –consume dietary supplements. The supplements, which include botanical products, vitamins and minerals, amino acids, and tissue extracts, are regulated by the FDA under the 1994 Dietary Supplement Health and Education Act (DSHEA). Before 1994, herbal products were considered food additives, and their manufacturers were required to show proof of safety. Since passage of the DSHEA, DS are presumed to be safe and can be marketed with very little oversight.

The DSHEA presents serious obstacles to the FDA’s ability to detect and eliminate contaminated DS. A wide range of DS has been found to be contaminated by toxic plant material, heavy metals, or bacteria. Dozens of DS are contaminated with prescription medications, or drugs rejected by the FDA because of safety concerns. These potential hazardous ingredients have been detected in products marketed for patients with diabetes, high cholesterol, or insomnia. They are most frequently found in products that promise sexual enhancement, optimal athletic performance, and weight loss.

DS marketed for weight loss are consumed by an estimated 15% of U.S. adults.

Individuals and companies that manufacture and distribute these products are very smart. Their intelligence does not include any moral restraint. They will do anything to make a dollar. They must be aware of the potential harm.

Our local newspaper frequently publishes outrageous advertisements for:

“Powerful new diet pills”

“Regain 10-15 years of lost memory power”

“Success in pain relief in over 90%”

“A revolutionary new drug-free formula to regain youthful prostate function”

“Plankton to cure cancer”

Our national pharmacies also advertise these products and make them readily available.

In addition, many homeopathic products are advertised. And many drugs are made available by drug purveyors in Canada without a prescription.

The expenditure of the National Center for Complementary and Alternative Medicine (NCCAM), funded by Congress, is approaching one billion dollars. After 10 years, it has not proved effectiveness of any “alternative” method.

Researchers from the Universities of Exeter and Plymouth (UK) studied over 1300 randomized, controlled trials of herbal medicines. They found only 3 that were of sufficient quality to draw meaningful conclusions. These 3 trials showed no convincing evidence of benefit. Individual herbal medicines (European, Chinese, and Ayurvedic) have an extremely sparse evidence base. There is no evidence supporting use in any indication. (BMJ October 13, 2007: 335: 743)

University medical schools still teach CAM and support professors of CAM. In the USA, CAM and “integrative” medicine has been called “kindly medicine”-- one that takes the whole patient into account.

“The placebo effect can continue to fool scientists and patients alike.”

Primary care physicians should publicize these comments as much as possible.

“Patients With Diabetes Are More Likely To Receive Antidiabetes Medication, Which Has Not Been Shown To Reduce CVD Risk, Rather Than Antihypertensive Medications Or Statins.”

10-2 TRENDS IN MEDICATION USE AMONG U.S. ADULTS WITH DIABETES MELLITUS: Glycemic Control at the Expense of Controlling Cardiovascular Risk Factors

The impact of tight hyperglycemia control on CVD and mortality risk is not clear.

This study examined the competing treatment priorities for adults with diabetes by analyzing the use of antidiabetes, antihypertension, and statin medications reported by the population-based National Health and Nutrition Examination Survey (NHANES) between 1990 and 2006.

The study was limited to adults over age 20 who reported a history of DM.

Between 1999-2000 and 2005-2006, the use of antidiabetes medications increased, with 90% of US persons with diabetes taking antidiabetes drugs in 2005-2006. The use of these drugs substantially exceeded the proportion of eligible adults with diabetes taking antihypertensives and statins.

The higher rates of use of antidiabetes drugs compared with antihypertensive and statin drugs highlights the concern that a disproportionate emphasis is placed on controlling hyperglycemia at the expense of controlling hypertension and high cholesterol. “Patients with diabetes are more likely to receive antidiabetes medication, which has not been shown to reduce CVD risk, rather than antihypertensive medications or statins.”

Control of hyperglycemia frequently takes precedence over control of hypertension and high cholesterol levels among adults with diabetes. This supports the argument for a reprioritization of

diabetes treatment goals emphasizing hypertension and lipid control before tight glycemetic control as part of an evidence-based CVD risk reduction effort.

Medication use:	1999-2000	2005-2006
Taking antidiabetes drugs	82	90
Taking antihypertensive drugs	68	78
Taking statins	26	51

Glucose control is important. Control is beneficial in preventing micro-vascular disease. It is less important than previously thought for control of macro-vascular disease. I believe that good control does have a beneficial effect on reducing risk of atherosclerotic disease, although it may take years of poor control to cause significant arterial disease.

Evidence is Insufficient To Assess The Balance Of Benefits And Harms Of Using Nontraditional Risk Factors

10-3 USING NON-TRADITIONAL RISK FACTORS IN CORONARY HEART DISEASE RISK ASSESSMENT: U.S. Preventive Services Task Force Recommendation Statement

Since 1996, reviews were conducted on 9 proposed nontraditional risk factors:

- High sensitivity C-reactive protein (**hsCRP**)
- Ankle-brachial index (**ABI**)
- Coronary artery calcification score on electron-beam computed tomography (**CAC**)
- Leukocyte count
- Fasting blood glucose
- Periodontal disease
- Carotid intima-media thickness
- Homocysteine
- Lipoprotein (a)

The reviews followed a hierarchical approach aimed at determining which factors could practically and definitively reassign persons who are assessed as intermediate-risk (10% to 20% risk of myocardial infarction and coronary death over the next 10 years according to the Framingham score) to either a high-risk strata, or a low-risk strata. In those reassigned to a high-risk strata, outcomes may be improved by aggressive risk-factor modification. (In the US, about 30% of asymptomatic men and 7% of asymptomatic women fall into the intermediate-risk category.)

“Clinicians should continue to use the Framingham model to assess CHD risk and guide risk-based preventive therapy.”

“The USPTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors discussed in this statement to screen asymptomatic men and women with no history of coronary heart disease to prevent CHD events.”

Clinicians should understand the evidence. And individualize decision making in the specific patient.

This does not say that non-traditional risk factors are valueless. It says merely that we don't know. I expect studies to continue assessing these and other putative risk factors. Note that body mass index, which is a valid risk factor, is not included in the Framingham score.

The study was restrictive. It concerned only those risk factors that might re-classify Framingham risk from intermediate (10-20% risk in the next 10 years) to high (over 20%).

Is the Framingham risk score useful in primary care medicine?

I believe it is not very useful. The score attempts to identify patients who have a 10% to 20% risk of MI or cardiac death over the next 10 years. Primary care clinicians look far beyond 10 years.

Younger persons with a serious risk factor (eg, smoking or high LDL-cholesterol) and no other risk factors may have a low score. Certainly, this should not preclude preventive treatment.

All established risk factors should be treated individually even though the calculated risk is low.

“CRP Levels Are Independently Associated With Incident CHD.” *The Clinical Implications Of The Association Of CRP With CHD Events Are Less Clear.*

10-4 C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE:

Several lines of evidence have implicated chronic inflammation in CHD. Inflammatory markers have received much attention as new or emerging risk factors that could account for some of the unexplained variability in CHD risk.

C-reactive protein (**CRP**) is a sensitive, non-specific systemic marker of inflammation. It is not known, however, if it is involved in pathogenesis of CHD. Elevated levels are associated with traditional risk factors and obesity.

This systematic review and meta-analysis of epidemiologic studies was conducted to help the USPSTF determine whether CRP should be incorporated into guidelines for risk assessment

Risk ratio for CHD associated with CRP levels > 3.0 vs < 1.0:

Pooled RR of eleven good-quality studies combined = 1.58

Risk ratio for CHD associated with CRP 1.0 to 3.0 vs < 1.0:

Pooled RR of twelve good quality studies combined = 1.22

“The body of evidence that CRP level is independently associated with incident CHD is strong.”

Little evidence links changes in CRP to primary prevention of CHD events.

The clinical implications of the association of CRP with CHD events are less clear.

“The viability of CHD as a new factor in global risk assessment of incident CHD is limited by sparse evidence that directly links therapeutic changes in CRP level to primary prevention of CHD events.”

“Current guidelines recommend aggressive therapy only for high-risk patients, such as those with a Framingham score greater than 20%, diabetes, or known cardiovascular disease.”

The implications of the use of CRP in global risk assessment are not clear. The findings have been interpreted to mean that CRP level may represent a different aspect of risk, with complex interrelationships among CRP levels, traditional risk factors, and CHD. Others have concluded that CRP level is largely attributable to traditional risk factors, and CRP may have limited clinical utility.

Conclusion: CRP is independently associated with incident CHD. The clinical implication of this finding is not clear. The pooled risk ratios do not necessarily measure the usefulness of CRP in reclassifying intermediate risk persons. Evidence linking changes in CRP level to primary prevention of CHD is insufficient.

Do we need another risk factor for CHD?

I believe not. We have failed miserably to apply those we have, which we know are valid risk markers. Let us concentrate on those. This does not mean we should quit looking for new risk factors. Premature wide-spread use of a newly described risk factor test, the clinical value of which is dubious, will increase costs of our national health services.

Is high sensitivity CRP a good risk factor?

I believe not. It fails to meet guidelines for a screening test in several respects:

There is no evidence that reducing CRP per se will reduce complications of CHD.

No evidence that a CRP screening program will lead to a reduction in morbidity or mortality from CHD.

CRP has not been adequately evaluated. A suitable cut-off value is not defined and agreed.

The benefit / harm-cost ratio of CRP screening has not been established.

It risks causing harm by overdetection and adverse psychosocial effects.

Will primary care clinicians use CRP for screening?

I believe some will. The lure of the “cutting edge” is strong.

HDL-c is Inversely And Independently Associated With A Reduction In CV Events.

10-5 EVALUATING THE INCREMENTAL BENEFITS OF RAISING HIGH-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS DURING LIPID THERAPY AFTER ADJUSTMENT FOR THE REDUCTIONS IN OTHER BLOOD LIPID LEVELS.

This study analyzed data from individuals treated with lipid-modifying therapy in the Framingham Offspring Study from 1973-2003, focusing only on those individuals who started lipid therapy between the 2nd and 6th visits.

It tested the hypothesis that an elevation in HDL-c levels is inversely and independently associated with a reduction in CV events.

Plasma lipid levels were determined for each individual before therapy was started, and at follow-up visits.

Determined change in HDL-c levels after lipid-modifying therapy for each individual.

Patient characteristics:	Quartiles of change in HDL-c levels (mg/dL)			
	-36 to -3	-2.7 to + 2,3	+2.5 to + 7.0	+ 7.8 to + 35
Number of patients	117	108	121	108
Untreated HDL-c level (mean)	48	40	39	40
Average treated HDL-c	41	40	44	53
Untreated LDL-c level (mean)	171	160	160	160
Average treated LDL-c	126	122	125	127
Untreated TG (mean mg/dL)	209	212	273	293
Change in TG (mg/dL)	-23	-28	-94	-144
No.of events (%)	31 (26)	17 (16)	19 (16)	12 (11)

During an average follow-up of 8 years, 79 individuals experienced a CV event. After adjustment for pretreatment HDL-c levels, age, and sex, the hazard ratio (**HR**) for CV events associated with a 5 mg/dL increase in HDL-c was 0.80.

Overall, a 1% increase in HDL-c level was associated with a 2% drop in CV risk. The lower the pretreatment LDL-c, the greater the risk reduction associated with an increase in HDL-c level.

In this analysis, of individuals starting pharmacotherapy for dyslipidemia, there was an inverse

relationship between changes in HDL-c levels and CV events. The greater the increase in HDL-c level, the lower the CV risk—an observation that persisted after adjustment for changes in LDL-c and triglycerides and other potential confounders.

Conclusion: Although the benefits of raising HDL-c levels remain to be confirmed in randomized trials, it appears the modest changes in HDL-c levels resulting from treatment with commonly used lipid drugs are associated with a reduction in CV risk, independent of the effects of other lipid measures.

Reduces Risk Of Falls In The Elderly By 20%. Use At Least 1000 IU Daily.

10-6 FALL PREVENTION WITH SUPPLEMENTAL AND ACTIVE FORMS OF VITAMIN D: A Meta-Analysis

Vitamin D (**D**) has direct effects on muscle strength, modulated by specific D receptors in muscle. Several trials, of older individuals at risk of D deficiency, reported that supplementation improved strength, function, and balance in a dose-related fashion. This translated into a reduction in risk of falls.

This meta-analysis assessed the efficiency of D supplementation, with and without calcium, for preventions of falls

A systematic search 1995-2008 included 8 randomized trials (n = 2426; 81% women; approximate mean age = 80). All studies were double blind. All subjects were age 65 and older and in stable health living in the community. All received a defined oral dose of: 1) supplemental vitamin D2 (ergocalciferol; 3 studies), or D3 (cholecalciferol; 5 studies), or 2) an active form of vitamin D (1alpha-hydroxy-claciferol or 1,25 dihydroxy-chole-calciferol).

Outcomes analyzed on an intention –to-treat basis. Treatment duration varied from 2 months to 3 years.

Trials assessing D supplements:

The daily dose ranged from 200 IU to 1000 IU.

The pooled relative risk (**RR**) of a fall in studies with 700-1000 IU was 0.81. (A reduction of 19%.)

The RR of falls in those receiving a dose less than 700 IU/d was 1.10.

Achieving a serum 25(OH)D concentration of 24 ng/mL (60 nmol/L) or more resulted in RR of falls of 0.77 (23% reduction). Concentrations of less than 24 ng/mL (60 nmol/L) had no effect on reduction of number of falls.

Trials of oral active forms of D:

Subjects were more likely to experience hypercalcemia than those in the control group.

The pooled RR of fall was 0.77 (Risk reduction = 23%)

No additional benefit compared with supplements.

No fall reduction was seen in subjects receiving a dose of less than 700 IU or serum concentrations less than 24 ng/mL (60 nmol/L). Benefit was noted as soon as 2 to 5 months of treatment.

Fall prevention may not depend on calcium supplementation.

“Active forms cost more and have a higher risk profile, so we believe adequate dosing of supplemental vitamin D should be preferred.”

The renaissance of vitamin D has been fascinating. It is no longer merely for prevention of rickets. It is not really a vitamin.

Benefits in mortality and at least 10 diseases and conditions have been attributed to supplemental D. There have been claims that D improves immune function.

Where do we now stand?

D is a steroid-like hormone derived from dehydro-cholesterol, rather than a vitamin. It has effects on many cells in the body.

Deficiency is widespread, especially in northern latitudes and among the elderly who are not exposed to sunlight. The cutpoint for normal serum levels is not yet established. It is usually cited as 15 to 30 ng/mL. Serum assays are expensive. Some are inaccurate.

D does improve bone strength and lowers risk of fractures in the elderly (along with calcium Supplements).

The benefit / harm-cost ratio of supplemental D is very high. D is not harmless, especially from high doses. Hypercalcemia, hyperphosphatemia and kidney stones may occur. Toxicity from 1000 IU daily is likely to be very low. Years of observations may be required to establish harms and the dose.

Most studies have been observational or epidemiological. They are subject to bias and confounding. Many disagree. It will take years to firmly establish the true benefits.

Randomized, placebo-controlled trials are not ethical. Trials would not be supported by drug companies because D is so inexpensive. There would be no profit motive.

We now treat all individuals routinely and empirically at daily doses recommended by the Institute of Medicine in 1997. The recommended daily supplemental dose has been too low.

It may be safe and advisable to increase the recommended daily dose to 1000 IU. Vitamin D3 (cholecalciferol) is more effective than D2 (ergocalciferol).

Some elderly patients would benefit from empiric treatment with 1000 IU daily .

But, sound evidence of efficacy and effectiveness is limited. What is deficiency? What is

insufficiency?

“Advanced Dementia Is A Terminal Illness”

10-7 THE CLINICAL COURSE OF ADVANCED DEMENTIA

Dementia is a leading cause of death in the U.S. It is under-recognized as a terminal illness. The lack of information characterizing the final stages of dementia may impede the quality of care provided. Under-recognition of prognosis of advanced dementia may lead to suboptimal palliative care.

This study addressed major gaps in knowledge concerning care for patients with advanced dementia.

Recruited and followed subjects (n = 323; mean age 85; 85% female) between 2003-07 from 22 nursing homes. All patients were age 60 or over and had advanced dementia: inability to recognize family members, minimal verbal communication, total functional dependence, incontinence, and inability to ambulate independently.

Over 18 months, 55% died. The probability death within 6 months was 25%. The probability of pneumonia was 41%; febrile episode 53%; eating problem 86%.

Distressing symptoms included dyspnea (46%), pain (39%), pressure ulcers (39%), agitation (54%), and aspiration (41%). Among those who died, the proportion who had these symptoms increased as the end-of-life approached. In the last 3 months of life 41% underwent at least one burdensome intervention: hospitalization (17%), emergency room visit (10%), parenteral therapy (34%), or tube feeding .

Residents whose proxies had an understanding of the expected poor prognosis and clinical complications were much less likely to receive burdensome interventions than were residents whose proxies did not have this understanding. (Odds ratio = 0.12)

Hospice referral: 22% were referred during the 18 month follow-up period; 26% of these were referred in the final week of life.

Patients with advanced dementia had a 6-month mortality rate of 25% and a median survival of 1.3 years. This is similar to the prognosis for more commonly recognized end-of-life conditions such as metastatic breast cancer and advanced congestive heart failure.

Patients with terminal dementia often receive aggressive treatments such as tube feeding and hospitalization. Aggressive interventions may be needed for pain relief, but this is unusual.

As mortality from many leading causes of death has decreased, deaths from dementia have steadily increased.

Conclusion: Pneumonia, febrile episodes and eating problems are common in patients with advanced dementia, and are associated with high 6-month mortality. Distressing symptoms and

burdensome interventions are common. Patients whose health care proxies understand the prognosis and clinical course are likely to receive less aggressive care at end-of-life.

Communication! Communication! Communication! Primary care clinicians who care for demented patients, especially in nursing homes, have the responsibility of determining the chief proxy of the patient and staying in communication with him or her. Try to avoid the difficulties of multiple proxies.

Advanced directives of the patient must be considered. Try to anticipate and solve any intra-family differences about care. Relatives might be asked: "How would you like to be treated if you were in the same condition?"

We should consider early referral to hospice and palliative care. Advanced dementia alone is an adequate reason for referral.

Rates And Subsequent Mortality Among Persons Over Age 65 Have Declined

10-8 INCIDENCE AND MORTALITY OF HIP FRACTURES IN THE UNITED STATES

This observational study of patients age 65 and older examined the trends in hip fracture (HF) incidence and resulting mortality over 20 years in a 20% sample of the US Medicare claims, 1985-2005.

Identified over 786 000 HF in patients discharged from acute care hospitals.

Of the 786 717 hip fractures, 77% occurred in women.

Annual mean number of HF:

957 per 100 000 in women

414 per 1000 000 in men.

The median hospital stay decreased from 12 days to 5 days. The discharge destination changed from going home with self-care (34%) to only 5%. In the last years, 53% were discharged to a skilled nursing facility.

In women, the incidence of hip fractures increased by 9% from 1986 to 1995. It then steadily declined by 25% from 1995 to 2005, In men from an increase of 16% to a decline of 19%.

In women, over the entire study period, the adjusted 30-day mortality decreased from 5.9% to 5.2%; 180-day mortality decreased from 16.8% to 14.3%; 360-day mortality from 24% to 22%. In men the decrease was somewhat larger.

Use of bisphosphonates in women gradually increased over time, with use by few in 1996 to 20% in 2005. Relatively few men took bisphosphonates. Selective estrogen receptor moderators (SERM) use also increased to about 5%. Estrogen use peaked about 2000, and declined thereafter to less than 10%.

This analysis over 20-years reveals two distinct eras: 1) 1986-1998 HF incidence was increasing,

but mortality after HF was falling; 2) 1998-2006 the incidence of HF fell, but mortality remained essentially unchanged.

After 1996, there was a larger decrease in HF in women (decline of 25%) than in men.

The reason for the decline in incidence is not clear. It corresponds temporally with the market release and increasing use of bisphosphonates. (However, a causal relationship has not been demonstrated.) This trend is not likely to explain the entire decline in incidence. HF incidence also fell in men, despite low use of bisphosphonates.

Lifestyle changes may contribute to the decline: calcium and vitamin D supplementation; avoidance of smoking; exercise; moderating alcohol use. And public and physician education and awareness of osteoporosis and fragility fractures.

Surgical and medical management of HF has improved over the past 20 years: improved surgical devices and replacement; earlier weight bearing exercise and improved mobilization; better use of prophylactic antibiotics; increased rates of discharge to non-acute health care settings (rather than to home).

Recurrent fracture is an important risk factor for premature mortality. Increased use of bisphosphonates may reduce incidence of recurrence.

Conclusion: In the US, HF rates and subsequent mortality among persons over age 65 have declined. Co-morbidities among the elderly have increased.

Hip fracture is largely a disease of older women. As women live longer, incidence of HF in those over age 85 is increasing. Prevention rests largely on primary care.

Many changes have improved prognosis. I like to believe that use of bisphosphonates and vitamin D and calcium supplementation have played a role. Has the growing prevalence of obesity also lowered risk of HF?

ABSTRACTS OCTOBER 2009

“An Emerging Risk To Public Health.”

10-1 AMERICAN ROULETTE—CONTAMINATED DIETARY SUPPLEMENTS

“Contaminated supplements represent an emerging risk to public health.”

In August 2009, the U.S. FDA reported many products containing a wide variety of undeclared active pharmaceutical ingredients. Most of them were labeled as “dietary supplements” (DS). More than 140 contaminated products have been identified.

These represent only a fraction of the contaminated supplements on the market.

Lenient regulatory oversight of DS, combined with the FDA’s lack of resources, has created a marketplace in which manufacturers can introduce hazardous new products with virtual impunity.

Although manufacturers have since 2007 been required to report serious supplement-related adverse events to the FDA, the great majority of the estimated 50 000 adverse events that occur annually remain unreported.

A recent National Health Interview Survey reported that about 114 million people—more than half the adult population of the USA—consume dietary supplements. The supplements, which include botanical products, vitamins and minerals, amino acids, and tissue extracts are regulated by the FDA under the 1994 Dietary Supplement Health and Education Act (DSHEA). Before 1994, herbal products were considered food additives, and their manufacturers were required to show proof of safety.

Since passage of the DSHEA, DS are presumed to be safe and can be marketed with very little oversight.

The majority of consumers believe that DS are approved by a government agency and think that the government requires that labels on supplements include warnings about their potential side effects and dangers. Physicians are also misinformed. Some believe that DS require FDA approval. Most do not know that adverse effects suspected to have been caused by DS should be reported to the FDA.

The DSHEA presents serious obstacles to the FDA’s ability to detect and eliminate contaminated DS. A wide range of DS has been found to be contaminated by toxic plant material, heavy metals, or bacteria. Dozens of DS are contaminated with prescription medications, or drugs rejected by the FDA because of safety concerns. These potential hazardous ingredients have been detected in products marketed for patients with diabetes, high cholesterol, or insomnia. They are most frequently found in products that promise sexual enhancement, optimal athletic performance, and weight loss.

DS marketed for weight loss are consumed by an estimated 15% of U.S. adults. In July 2009, the FDA expanded its alert to include 75 tainted products that contain undeclared medications. Sibutramine was found at levels three times the maximum recommended dose. The addition of furosemide and other

diuretics may result in dehydration and hypokalemia. Benzodiazepines and antidepressants mask the side effects of stimulants while conferring a risk of dependence. Some pills combine multiple medications in a single formulation.

Recently, manufacturers have made it more difficult for the FDA to detect undeclared ingredients by modifying the chemical nature of their product by incorporation of chemical analogues (eg, analogues of phosphodiesterase inhibitors for sexual enhancement). The risks of these compounds are not known. An analogue of fenfluramine has been linked to fulminant hepatic failure.

Many of these compounds are sold over the Internet. They are also found in mainstream retail stores.

The DSHEA has *not* ensured the hazardous dietary supplements will be identified or removed from the market in a timely fashion.

Physicians should explicitly ask all patients about the use of such supplements.

NEJM October 15, 2009; 361: “Perspective”, commentary by Pieter A Cohen, Harvard Medical School, Boston, Mass.

To report to the FDA any suspected adverse effects:

www.fda.gov/medwatch/report/hep.htm

www.fda.gov/oc/buyonline/buyonlineform.htm

Sibutramine is marketed in the USA as Meridia (Abbott) It is an appetite suppressant structurally related to amphetamines It is a centrally active serotonin- norepinephrine reuptake inhibitor. Although it has virtually no potential for abuse, the FDA has classified it as a controlled drug.

Rimonabant is an appetite suppressant. It has been linked to suicide. The drug was available in 56 countries, many in Europe. In October 2008, the European Medicines Agency concluded that the benefits did not outweigh the risks. Sanofi-Antis suspended the drug. Approval was withdrawn in January 2009

Fenproporex is an appetite suppressor—a metabolite of amphetamine. An analogue has been linked to fulminant liver failure as well as suicide and addiction. It was withdrawn in many countries due to problems with abuse. It has never been approved in the USA. It is sometimes combined with benzodiazepines and antidepressants and other compounds to create the “Brazilian diet pill”.

“Patients With Diabetes Are More Likely To Receive Antidiabetes Medication, Which Has Not Been Shown To Reduce CVD Risk, Rather Than Antihypertensive Medications Or Statins.”

**10-2 TRENDS IN MEDICATION USE AMONG U.S. ADULTS WITH DIABETES MELLITUS:
*Glycemic Control at the Expense of Controlling Cardiovascular Risk Factors***

Successful reduction of cardiovascular disease (CVD) risk factors among people with diabetes mellitus (DM) is increasing, especially hypertension and dyslipidemia.

The impact of tight hyperglycemia control on CVD and mortality risk is not clear.

This study examined the competing treatment priorities for adults with diabetes by analyzing the use of antidiabetes, antihypertension, and statin medications reported by the population-based National Health and Nutrition Examination Survey (NHANES) between 1990 and 2006.

The study was limited to adults over age 20 who reported a history of DM.

Used the ADA guidelines for standard medical care to determine the eligibility of participants for antidiabetes, antihypertensive, and statin medication. Eligibility for each medication included a HbA1c over 7%; systolic BP over 130 and diastolic over 80; or total cholesterol over 200 mg/dL. Also known CVD, hypertension, cigarette smoking, or albuminuria, or 2 or more CVD risk factors for those under age 40.

Between 1999-2000 and 2005-2006, the use of antidiabetes medications increased, with 90% of persons with diabetes taking antidiabetes drugs in 2005-2006. The use of these drugs substantially exceeded the proportion of eligible adults with diabetes taking antihypertensives and statins. The higher use of antidiabetes drugs may be why the proportion of those with diabetes achieving a HbA1c lower than 7% was 50% and 35% greater than those achieving hypertension and cholesterol control.

The present data also substantiate reports of increasing use of combined antidiabetes drugs, a decline on older generation oral medications such as sulfonylureas, and rising use of metformin and thiazolidinediones.

The higher rates of use of antidiabetes drugs compared with antihypertensive and statin drugs highlights the concern that a disproportionate emphasis is placed on controlling hyperglycemia at the expense of controlling hypertension and high cholesterol. "Patients with diabetes are more likely to receive antidiabetes medication, which has not been shown to reduce CVD risk, rather than antihypertensive medications or statins."

Control of hyperglycemia frequently takes precedence over control of hypertension and high cholesterol levels among adults with diabetes. This supports the argument for a reprioritization of diabetes treatment goals emphasizing hypertension and lipid control before tight glycemic control as part of an evidence-based CVD risk reduction effort.

Medication use (%):

	1999-2000	2005-2006
Taking antidiabetes drugs	82	90
Taking antihypertensive drugs	68	78

Taking statins	26	51
HbA1c, BP, and cholesterol levels, and control rates (%)		
HbA1c (mean)	7.8	7.2
Controlled HbA1c	41	58
Controlled hypertension*	16	29
Controlled cholesterol*	24	43

(* Controlled hypertension and controlled cholesterol are limited to those with diabetes who had hypertension and high cholesterol)

Archives Internal Medicine October 12, 2009; 169: 1718-20 Research Letter, first author Devin M Mann, Mount Sinai School of Medicine, New York.

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Evidence is Insufficient To Assess The Balance Of Benefits And Harms Of Using Nontraditional Risk Factors

10-3 USING NON-TRADITIONAL RISK FACTORS IN CORONARY HEART DISEASE RISK ASSESSMENT: U.S. Preventive Services Task Force Recommendation Statement

The USPSTF makes recommendations about preventive care services for patients who have no recognized signs or symptoms of the target condition. It bases its recommendations on systematic reviews of the evidence of the benefits and harms, and an assessment of the net benefit of the service.

This recommendation considers non-traditional novel risk factors for coronary heart disease (**CHD**) risk in asymptomatic patients.

Since 1996, reviews were conducted on 9 proposed nontraditional risk factors:

- High sensitivity C-reactive protein (**hsCRP**)
- Ankle-brachial index (**ABI**)
- Coronary artery calcification score on electron-beam computed tomography (**CAC**)
- Leukocyte count
- Fasting blood glucose
- Periodontal disease
- Carotid intima-media thickness
- Homocysteine
- Lipoprotein (a)

Treatment to prevent CHD by modifying risk factors is currently based on the Framingham risk model, which sorts individuals into low- intermediate- and high-risk groups. If the classification of individuals at intermediate risk could be improved by using additional risk factors, treatment to prevent CHD might be targeted more effectively.

The reviews followed a hierarchical approach aimed at determining which factors could practically and definitively reassign persons who are assessed as intermediate-risk (10% to 20% risk of myocardial infarction and coronary death over the next 10 years according to the Framingham score) to either a high-risk strata, or a low-risk strata. In those reassigned to a high-risk strata, outcomes may be improved by aggressive risk-factor modification. (In the US, about 30% of asymptomatic men and 7% of asymptomatic women fall into the intermediate-risk category.)

There is insufficient evidence to determine the percentage of intermediate-risk individuals who would be reclassified by screening with non-traditional risk factors. Data are not available to determine whether they would benefit from additional treatments.

Regarding the coronary artery calcification score on electron-beam computed tomography, there is no convincing evidence that CAC adds information about intermediate-risk persons.

Regarding ABI: Evidence is insufficient to assess the value of ABI for cardiac risk assessment in asymptomatic intermediate-risk patients.

“Clinicians should continue to use the Framingham model to assess CHD risk and guide risk-based preventive therapy.”

Clinicians should understand the evidence. And individualize decision making in the specific patient.

“The USPTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors discussed in this statement to screen asymptomatic men and women with no history of coronary heart disease to prevent CHD events.”

Annals Internal Medicine October 6, 2009: 474-82 “Clinical Guidelines” by the U.S. Preventive Services Task Force

http://www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.htm

<http://hp2010.nhlbihin.net/atp/iii/calculator.asp?usertype=prof>

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“CRP Levels Are Independently Associated With Incident CHD.” The Clinical Implications Of The Association Of CRP With CHD Events Are Less Clear.

10-4 C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE:

A Systematic Review And Meta-Analysis For The USPSTF

The factors that make up the Framingham risk score account for most of the excess risk for incident CHD. However, these factors do not explain all the excess risk. About 40% of CHD deaths occur in persons with cholesterol levels that are lower than population average.

Several lines of evidence have implicated chronic inflammation in CHD. Inflammatory markers have received much attention as new or emerging risk factors that could account for some of the unexplained variability in CHD risk.

C-reactive protein (**CRP**) is a sensitive, non-specific systemic marker of inflammation. It is not known, however, if it is involved in pathogenesis of CHD. Elevated levels are associated with traditional risk factors and obesity.

In the Framingham risk scoring system, intermediate-risk persons are those with a 10% to 20% 10-year risk for non-fatal MI or coronary death (“hard” events). Further stratification by use of new markers might reclassify some intermediate-risk persons to low risk (< 10%) or to high risk (>20%). This would permit more aggressive risk reduction therapy in persons reclassified as high-risk, and may reduce incident CHD events.

This systematic review and meta-analysis of epidemiologic studies was conducted to help the USPSTF determine whether CRP should be incorporated into guidelines for risk assessment. Is CRP independently predictive of incident CHD, specifically among intermediate-risk persons?

STUDY

1. Literature search (1966-2007) selected prospective cohort and case-control studies relevant to the independent predictive ability of CRP when used in intermediate-risk persons.
2. Identified 23 principal articles for the meta-analysis. The body of evidence was of good quality, consistency, and applicability.
3. All studies measured CRP using a high-sensitivity assay (hsCRP).

RESULTS

1. CRP has desirable test characteristics and good data exist on the prevalence of elevated CRP in intermediate-risk persons.
2. Risk ratio for CHD associated with CRP levels > 3.0 vs < 1.0:
Pooled RR of eleven good-quality studies = 1.58
3. Risk ratio for CHD associated with CRP 1.0 to 3.0 vs < 1.0:
Pooled RR of twelve good quality studies = 1.22

4. Little evidence links changes in CRP to primary prevention of CHD events.
5. The meta-analysis could not assess how well risk ratios derived from the entire population apply to intermediate-risk participants, or how those participants would be reclassified if CRP were used.

DISCUSSION

1. “The body of evidence that CRP level is independently associated with incident CHD is strong.”
2. The clinical implications of the association of CRP with CHD events are less clear. The pooled risk ratio does not necessarily measure the usefulness of CRP in reclassifying intermediate risk persons.
3. Establishing the independent predictive ability of a new risk factor is necessary, but not sufficient for assessing its potential usefulness in screening. Other criteria must be considered, such as the prevalence of the factor in the target population, the reliability and cost of the test, potential harm of testing, and the effect that treatment of the risk factor has on modifying risk.
4. Weight loss, exercise, and smoking cessation (*and statin drugs*) can reduce CRP levels.
5. “The viability of CRP as a new factor in global risk assessment of incident CHD is limited by sparse evidence that directly links therapeutic changes in CRP level to primary prevention of CHD events.”
6. “Current guidelines recommend aggressive therapy only for high-risk patients, such as those with a Framingham score greater than 20%, diabetes, or known cardiovascular disease.”
7. Studies do not directly test whether lowering CRP reduces cardiovascular risk.
8. The implications of the use of CRP in global risk assessment are not clear. The findings have been interpreted to mean that CRP level may represent a different aspect of risk, with complex interrelationships among CRP levels, traditional risk factors and CHD. Others have concluded that CRP level is largely attributable to traditional risk factors, and CRP may have limited clinical utility.
9. The causal relationship between CRP and traditional risk factors is not clear. The findings of many studies, including this meta-analysis, suggest that the degree of correlation between CRP and traditional risk factors is not so great that CRP loses its independent effect. However, statistical independence does not establish causality.

CONCLUSION

CRP is independently associated with incident CHD. The clinical implication of this finding is not clear. The pooled risk ratios do not necessarily measure the usefulness of CRP in reclassifying intermediate risk persons.

Evidence linking changes in CRP level to primary prevention of CHD is insufficient.

Annals Internal Medicine October 56 2009; 151: 483-95 Original investigation, first author David I Buckley, Oregon Health and Science University, Portland .

C-reactive protein was discovered by Tillett and Francis in 1930 as a protein in the serum of patients with inflammation. It reacts with the Capsular polysacchararide of pneumococcus. (Hence “C-peptide)

It is an acute phase reactant produced in the liver. Levels rise dramatically during inflammatory processes. This is secondary to a rise in interleukin-6 (IL-6), which is produced predominantly by macrophages, as well as adipocytes. CRP is believed to have a role in innate immunity.

High-sensitivity CRP test measures low levels of CRP, giving results in 30 minutes, with a sensitivity down to 0.04 mg/L.

Many types of inflammation in humans will raise CRP levels. It is not specific.

White blood cell invasion and inflammation of, and damage to, the arterial wall, as in atherosclerosis, leads to increases in CRP.

Source: Wikipedia

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HDL-c is Inversely And Independently Associated With A Reduction In CV Events.

10-5 EVALUATING THE INCREMENTAL BENEFITS OF RAISING HIGH-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS DURING LIPID THERAPY AFTER ADJUSTMENT FOR THE REDUCTIONS IN OTHER BLOOD LIPID LEVELS.

Several population studies have reported that for every 1 mg/dL increase in HDL-cholesterol (**HDL-c**) there is a 2% to 3% decrease in the risk of future cardiovascular (**CV**) events. This inverse relationship is independent of levels of low-density lipoprotein cholesterol (**LDL-c**). And remains apparent even when levels of LDL-c have been reduced by aggressive statin therapy to below 70 mg/dL.

HDL-c has several known functions with the potential to protect against development of atherosclerosis and its sequellae:

Promoting efflux of cholesterol from cells in the artery wall

- Promotion of endothelial function
- Repair and inhibition of thrombosis
- Stimulation of endothelial nitric oxide production
- Antioxidant and anti-inflammatory functions.

Thus, there is a compelling case for considering interventions to raise HDL-c levels as a strategy to reduce CV risk.

In contrast to the consistent trial data showing the cardioprotective effects of reducing LDL-c levels, the evidence that raising HDL-c levels translates into a reduction in CV events is at best circumstantial, and remains controversial.

This study analyzed data from individuals treated with lipid-modifying therapy in the Framingham Offspring Study. It tested the hypothesis that an elevation in HDL-c levels is inversely and independently associated with a reduction in CV events.

STUDY

1. Analyzed data from the Framingham Offspring study from 1973-2003, focusing only on those individuals who started lipid therapy between the 2nd and 6th visits.
2. Plasma lipid levels were determined for each individual before therapy was started, and at follow-up visits.
3. Determined change in HDL-c levels after lipid-modifying therapy for each individual. Averaged all lipid measurements to estimate levels during treatment.
4. Divided the cohort into quartiles of change in HDL-c levels.
5. Recorded development of all CV events.
6. Estimated the association between HDL-c levels and CV events after adjustment for baseline lipid levels and changes during treatment.

RESULTS

1. Patients included in the analysis (n = 454; mean age 61) started lipid-modifying therapy between the 2nd and 6th examination cycles. 96% were taking only one drug: statins (72%); fibrates (17%); resins, or niacin.

2. Patient characteristics:	Quartiles of change in HDL-c levels (mg/dL)			
	-36 to -3	-2.7 to + 2,3	+2.5 to + 7.0	+ 7.8 to + 35
Number of patients	117	108	121	108
Untreated HDL-c level (mean)	48	40	39	40

Average treated HDL-c	41	40	44	53
Untreated LDL-c level (mean)	171	160	160	160
Average treated LDL-c	126	122	125	127
Untreated TG (mean mg/dL)	209	212	273	293
Change in TG (mg/dL)	-23	-28	-94	-144
No.of events (%)	31 (26)	17 (16)	19 (16)	12 (11)

3. During an average follow-up of 8 years, 79 individuals experienced a CV event.
4. After adjustment for pretreatment HDL-c levels, age, and sex, the hazard ratio (**HR**) for CV events associated with a 5 mg/dL increase in HDL-c was 0.80.
5. The HR remained stable after adjustment for multiple other possible confounding factors.
6. Overall, a 1% increase in HDL-c level was associated with a 2% drop in CV risk.
7. The lower the pretreatment LDL-c, the greater the risk reduction associated with an increase in HDL-c level.

DISCUSSION

- 1, “It is well established that HDL-c level is an inverse predictor of CV risk.”
2. In this analysis, of individuals starting pharmacotherapy for dyslipidemia, there was an inverse relationship between changes in HDL-c levels and CV events. The greater the increase in HDL-c level, the lower the CV risk—an observation that persisted after adjustment for changes in LDL-c and triglycerides and other potential confounders.
3. “We found that a 1% increase in HDL-c level was associated with a 2% reduction in CV risk.”
This is consistent with the epidemiological data from previous cohort studies of individuals not receiving lipid therapy.
4. “Additional unforeseen cofounders remain a concern.”
5. “Despite the obvious shortcomings of this analysis, these data provide some of the strongest evidence currently available to support the hypothesis that raising HDL-c levels is associated with a reduction in CV risk.”
6. The conclusion that raising HDL-c levels is associated with lower CV risk does not appear to be uniquely associated with a specific class of drugs.

CONCLUSION

Although the benefits of raising HDL-c levels remain to be confirmed in randomized trials, it appears the modest changes in HDL-c levels resulting from treatment with commonly used lipid drugs are associated with a reduction in CV risk, independent of the effects of other lipid measures.

Archives Int Med October 26, 2009; 169: 1775-80 Original investigation, first author
Steven A Grover, McGill University Health Centre, Montreal, Quebec, Canada

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Reduces Risk Of Falls In The Elderly By 20%. Use At Least 1000 IU Daily.

10-6 FALL PREVENTION WITH SUPPLEMENTAL AND ACTIVE FORMS OF VITAMIN D: A Meta-Analysis

Vitamin D (**D**) has direct effects on muscle strength, modulated by specific D receptors in muscle. Several trials, of older individuals at risk of D deficiency, reported that supplementation improved strength, function, and balance in a dose-related fashion. This translated into a reduction in risk of falls.

Overall, however, results of studies of fall prevention by D have been mixed. This may have been due to use of low doses.

This meta-analysis assessed the efficiency of D supplementation, with and without calcium, for preventions of falls.

STUDY

1. A systematic search 1995-2008 included 8 randomized trials (n = 2426; 81% women; approximate mean age = 80). All studies were double blind. All subjects were age 65 and older and in stable health living in the community. All received a defined oral dose of: 1) supplemental vitamin D2 (ergocalciferol; 3 studies), or D3 (cholecalciferol; 5 studies), or 2) an active form of vitamin D (1alpha-hydroxy-cholecalciferol or 1,25 dihydroxy-cholecalciferol).
2. In all trials: (a) falls were the primary or secondary end-point, (b) included a definition of falls and how they were assessed, (c) falls had to be assessed for the entire trial period.
3. Primary outcome = relative risk of having at least one fall among persons receiving D with or without calcium vs persons receiving placebo or calcium supplementation alone.
4. Outcomes analyzed on an intention –to-treat basis. Treatment duration varied from 2 months to 3 years.

RESULTS

1. Trials assessing D supplements:

The daily dose ranged from 200 IU to 1000 IU.

Calcium dose varied from 500 mg/d to 1200 mg/d.

The pooled relative risk (**RR**) of a fall in 7 studies with 700-1000 IU was 81%. (A reduction of 19%).

The RR of falls in those receiving a dose less than 700 IU/d was 1.10.

Achieving a serum 25(OH)D concentration of 24 ng/mL (60 nmol/L) or more resulted in RR of falls of 0.77 (23% reduction). Concentrations of less than 24 ng/mL (60 nmol/L) had no effect on reduction of number of falls.

2. Trials (n = 2) of oral active forms of D:

Subjects were more likely to experience hypercalcemia than those in the control group.

The pooled RR of fall was 0.77 (Risk reduction = 23%)

No additional benefit compared with supplements.

DISCUSSION

1. The efficacy of supplemental D for fall prevention depended on dose and achieved 23(OH)D concentrations. No fall reduction was seen in subjects receiving a dose of less than 700 IU or serum concentrations less than 60 nmol/L. Benefit was noted as soon as 2 to 5 months of treatment.
2. At a high dose, the benefit was not significantly affected by the type of supplemental vitamin D.
3. Fall prevention may not depend on calcium supplementation.
4. This study confirms a meta-analysis of 2006¹ Five double-blind trials have been reported since then.
5. Active forms cost more and have a higher risk profile, so we believe adequate dosing of supplemental vitamin D should be preferred.”

CONCLUSION

Supplemental vitamin D in a dose of 700-1000 IU daily reduced risk of falling among older individuals by 19%. Doses less than 700 IU or serum concentrations less than 24 ng/mL (60 nmol/L) may not reduce risk of falls.

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“Advanced Dementia Is A Terminal Illness”

10-7 THE CLINICAL COURSE OF ADVANCED DEMENTIA

Dementia is a leading cause of death in the U.S. It is under-recognized as a terminal illness. The lack of information characterizing the final stages of dementia may impede the quality of care provided. Under-recognition of prognosis of advanced dementia may lead to suboptimal palliative care. . The clinical course of advanced dementia has not been described in a rigorous, prospective manner. The incidence of clinical complications, the extent of physical suffering, and the use of burdensome interventions are not well understood.

A better understanding of the clinical trajectory of end-stage dementia is critical for improving care.

STUDY

1. This study obtained data from a prospective cohort study of nursing home residents¹ and their families (health care proxies). The study addressed major gaps in knowledge concerning care for patients with advanced dementia.
2. Recruited and followed subjects (n = 323; mean age 85; 85% female) between 2003-07 from 22 nursing homes. All patients were age 60 or over and had advanced dementia: inability to recognize family members, minimal verbal communication, total functional dependence, incontinence, and inability to ambulate independently.
3. Collected data characterizing survival, clinical complications, symptoms, and treatments. Determined proxies' understanding of residents' prognosis, and the expected clinical complications.

RESULTS

1. Over 18 months, 55% died. The probability death within 6 months was 25%.
2. The probability of pneumonia was 41%; febrile episode 53%; eating problem 86%.
3. The 6-month mortality rate for those who had pneumonia was 47%; a febrile episode 45%; and an eating problem 39%.
4. Distressing symptoms included dyspnea (46%), pain (39%), pressure ulcers (39%), agitation (54%), and aspiration (41%). Among those who died, the proportion who had these symptoms increased as the end-of-life approached.
5. In the last 3 months of life 41% underwent at least one burdensome intervention:

- hospitalization (17%), emergency room visit (10%), parenteral therapy (34%), or tube feeding (8%).
6. Residents whose proxies had an understanding of the expected poor prognosis and clinical complications were much less likely to receive burdensome interventions in the last 3 months of life than were residents whose proxies did not have this understanding. (Odds ratio = 0.12)
 7. Hospice referral: 22% were referred during the 18 month follow-up period; 26% of these were referred in the final week of life. .
 8. Health care proxies perceptions: Among proxies, 96% believed that comfort was the primary goal of care. At the last assessment, 20% of proxies believed that the resident for whom they were responsible had less than 6 months to live. Only 18% stated they had received prognostic information from a physician; 81% felt they understood which clinical complications to expect, but only 32% stated that a physician had counseled them about complications.

DISCUSSION

1. Patients with advanced dementia have a high rate of infections, eating problems, and death.
2. Distressing symptoms are common as death approaches.
3. Many undergo burdensome interventions of questionable benefit.
4. When health care proxies were aware of the poor prognosis and expected clinical complications, residents were less likely to undergo these interventions in the final days of life.
5. Patients with advanced dementia had a 6-month mortality rate of 25% and a median survival of 1.3 years. This is similar to the prognosis for more commonly recognized end-of-life conditions such as metastatic breast cancer and advanced congestive heart failure.
6. “Advanced dementia is a terminal illness.” Most deaths are not precipitated by other terminal diseases such as cancer, heart failure, and myocardial infarction.
7. Patients with terminal dementia often receive aggressive treatments such as tube feeding and hospitalization. Aggressive interventions may be needed for pain relief, but this is unusual.
8. As mortality from many leading causes of death has decreased, deaths from dementia have steadily increased.

CONCLUSION

Pneumonia, febrile episodes and eating problems are common in patients with advanced dementia, and are associated with high 6-month mortality.

Distressing symptoms and burdensome interventions are common.

Patients whose health care proxies understand the prognosis and clinical course are likely to receive less aggressive care at end-of-life.

NEJM October 15, 2009; 361: 1529-38 Original investigation, first author Susan L Mitchell, Hebrew Senior Life Institute for Aging Research, Boston Mass

1 “Choices, Attitudes, and Strategies for Care of Advanced Dementia at End-of-life” (CASCADE) Alzheimer Dis Assoc Disord 2006; 20: 166-75

An editorial in the is issue of NEJM (pp 1595-96) by Greg A Sachs, Indiana University School of Medicine, Indianapolis, comments and expands on this article:

Many demented patients have little in the way of either comfort or company toward the end. End-of-life care for many patients with dementia does not look all that different from that of 30-years ago. They are at risk for undertreatment of pain and treatments with burdensome and possibly non-beneficial interventions, which may add to suffering.

They are referred to hospice and palliative care at rates far lower than those with cancer.

Hospice care in nursing homes during the last 30 days of life has been associated with a reduction in hospitalization of almost 50%, and with improvements in pain assessment and management. Patients also have milder psychiatric symptoms.

Families of patients who receive hospice care report greater satisfaction with care.

One barrier to hospice in these patients is the failure to recognize that advanced dementia is a terminal illness.

Given the information in this study, it would clearly be possible to anticipate the death of patients in similar circumstances.

“Clinicians, patients’ families, and nursing home staff need to recognize that advanced dementia is a terminal illness requiring palliative care” These patients do not need another serious illness to qualify for hospice care.

Discussions with proxies could modify their perceptions about prognosis and expected complications, alter decisions about use of burdensome interventions, and increase referral to palliative programs and hospice.

Rates And Subsequent Mortality Among Persons Over Age 65 Have Declined

10-8 INCIDENCE AND MORTALITY OF HIP FRACTURES IN THE UNITED STATES

About 30% of people with a hip fracture (**HF**) will die in the following year. Many more will experience significant functional loss.

Some studies have shown excess long-term mortality even 10 years after the episode.

HF is extremely expensive.

Concern exists that because of the aging of the population, the incidence of HF will increase.

This study assessed trends in age-and sex-specific incidence and risk adjusted mortality of HF among elderly individuals in the US.

STUDY

1. Observational study of patients age 65 and older examined the trends in HF incidence and resulting mortality over 20 years in a 20% sample of the US Medicare claims. 1985-2005.
2. Identified over 786 000 HF in patients discharged from acute care hospitals.
3. Obtained medication data from over 109 000 respondents in a Medicare survey between 1992 and 2005.
4. A one-year look-back identified the presence of co-morbid conditions.
5. Main outcome measures = age-and sex-specific incidence of the HF and age- and risk-adjusted mortality rates at 30, 180, and 360 days. And trends in pharmaceutical use over time—specifically use bisphosphonates, estrogens and selective estrogen receptor modulators. **(SERM)**

RESULTS

1. Study population:

Of the 786 717 hip fractures, 77% occurred in women.

Annual mean number of HF:

957 per 100 000 in women

414 per 1000 000 in men.

The majority of fractures occurred in persons age 75-84.

The percentage of hip fractures in those age 85 years or older increased from 38% in 1986 to 44% in 2005. (A 6% increase) In contrast, the proportion of people age 85 and older in the general population increased by 4%.

The median hospital stay decreased from 12 days to 5 days. The discharge destination changed from going home with self-care (34%) to only 5%. In the last years, 53% were discharged to a skilled nursing facility.

2. Hip fracture incidence:

In women, the incidence of hip fractures increased by 9% from 1986 to 1995. It then steadily declined to 2005 by 25%, In men from an increase of 16% to a decline of 19%.

3. Trends in patient co-morbidities:

The most common co-morbidities were congestive heart failure, chronic pulmonary disease,

and diabetes. These co-morbidities have increased over time.

4. Trends in hip fracture mortality:

Most co-morbidities as well as age were associated with increased mortality.

In women, over the entire study period, the adjusted 30-day mortality in women decreased from 5.9% to 5.2%; 180-day mortality decreased from 16.8% to 14.3%; 360-day mortality from 24% to 22%. In men the decrease was somewhat larger. However, since 1996, mortality rates have not changed.

5. Trends in medication use:

Use of bisphosphonates in women gradually increased over time, with use by few in 1996 to 20% in 2005. Relatively few men took bisphosphonates.

SERM use also increased to about 5%. Estrogen use peaked about 2000, and declined thereafter to less than 10%.

DISCUSSION

1. This analysis over 20-years reveals two distinct eras: 1) 1986-1998 HF incidence was increasing, but mortality after HF was falling; 2) 1998-2006 the incidence of HF fell, but mortality remained essentially unchanged.
2. After 1996, there was a larger decrease in HF in women (decline of 25%) than in men.
3. The reason for the decline in incidence is not clear. It corresponds temporally with the market release and increasing use of bisphosphonates. (However, a causal relationship has not been demonstrated.) This trend is not likely to explain the entire decline in incidence. HF incidence also fell in men, despite low use of bisphosphonates.
4. Lifestyle changes may contribute to the decline: calcium and vitamin D supplementation; avoidance of smoking; exercise; moderating alcohol use. And public and physician education and awareness of osteoporosis and fragility fractures.
5. Surgical and medical management of HF has improved over the past 20 years: improved surgical devices and replacement; earlier weight bearing exercise and improved mobilization: better use of prophylactic antibiotics; increased rates of discharge to non-acute health care settings (rather than to home).
6. Recurrent fracture is an important risk factor for premature mortality. Increased use of bisphosphonates may reduce incidence of recurrence.

CONCLUSION

In the US, HF rates and subsequent mortality among persons over age 65 have declined. Co-morbidities among the elderly have increased.

JAMA October 14, 2009; 302: 1573-79 Original investigation, first author Carmen A Brauer, University of Calgary, Alberta, Canada.

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