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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

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25TH YEAR OF PUBLICATION

This document is divided into two parts

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

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

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of Practical Pointers.*

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

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 10 years can be accessed at www.practicalpointers.org

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* JULY 2010

***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 patents' understanding.

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

We should not assume medical literacy.

"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 pubic 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"

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.

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 the 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 then 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.

INVEST[1] (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 futher 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.

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

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.

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.

"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.

ABSTRACTS JULY 2010

***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.

Written instructions are a key component of health communication. Physicians are often unaware of the patient's literacy and the effects on outcomes. Patients may not volunteer that they have problems with limited literacy. They feel shame about their inability to read.

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".

The authors of this article searched the literature relevant to health literacy.

They selected 2 measures of health literacy as reference standards:

1) Test of Functional Health Literacy in Adults (TOFHLA; also available in Spanish)
   An extensive test requiring up to 22 minutes to administer.
2) Rapid Estimate of Adult Literacy in Medicine (REALM)
   66 English medical words, takes 3 minutes.

They identified and described 6 unique methods for measuring health literacy that met their criteria.. Some presented single word questions (Eg, Do you usually ask someone to help you read materials you receive from the hospital? How would you rate your ability to read? How often do you have problems learning about your medical condition because of difficultly understanding written information?)

Another interesting way of evaluating literary test is asking the patient to read and apply information included on the nutritional label from a pint of ice cream. Patients are asked 6 questions about serving size, nutrition information and ingredients.

Literacy can be measured accurately in health settings with tests that require several minutes to administer. When time is limited, several single-item questions about the patient's confidence with medical forms or whether they use a surrogate reader are moderately effective in identifying those with inadequate and marginal literacy.

When several minutes are available a shortened TOFHLA (7-12 minutes) and the REALM (3 minutes) are accurate tools for identifying patients with limited literacy.

For rapid testing the authors recommend asking patients how comfortable they are filling medical forms, how often they have someone help them read medical information, or rate their own reading ability.

Patients who test positively are at higher risk of poor health outcomes.

JAMA July 7, 2010; 76-84 Original investigation, first author Benjamin J Powers, Durham Veterans Affairs Medical Center, Durham. North Carolina.

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"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.

In the 1980s, sigmoidoscopy screening was common despite lack of evidence for its efficacy. In ensuing decades, case-control studies established that sigmoidoscopy was associated with reduced incidence and mortality from left-sided, but not right-sided colon cancers.

In 1988, opinion emerged that colonoscopy should also be considered a potential tool for screening average risk adults. This was eventually incorporated into screening guidelines. Colonoscopy is reimbursed by Medicare

The USPSTF guidelines stated that sigmoidoscopy and colonoscopy were equally acceptable options. The American College of Gastroenterology gave colonoscopy preferred status. The New York City Department of Health encouraged colonoscopy screening to the exclusion of other modes of screening. Sigmoidoscopy screening declined in the US.

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.

Despite increased adverse effects, higher costs, need for sedation, and greater inconvenience, the presumed mortality benefit of colonoscopy has been used as justification to outweigh the negatives.

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.

"Instead of meeting its expectations, colonoscopy has not yet proven to be more effective than sigmoidoscopy."

Why the apparent lack of efficacy of colonoscopy on right-sided neoplasms? Explanations include difficulty in achieving adequate preparation of the proximal colon, preponderance of flat lesions in the proximal colon, which are difficult to identify, and technical difficulties in reaching the cecum.

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

How should we advise patients? Waiting for randomized trial is not practical. In the absence of the data, 2 initial approaches are in order:

1) The promise of colonoscopy should not be overstated. Patients undergoing colonoscopy should be advised that it is not perfect. A relative risk reduction of 50% to 60% is consistent with observational data.
2) In the absence of convincing data on the superiority of colonoscopy, sigmoidoscopy should not be relegated to a non-preferred screening test.

Much of medicine operates in absence of definitive evidence. As evidence accumulates, physicians must be prepared to reevaluate even a long-standing clinical practice. If de novo decisions were being made today about whether to initiate colonoscopy as a screening tool in place of sigmoidoscopy, in the light of available evidence, doing so would probably be inappropriate.

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

JAMA July 28, 2010; 304: 461-62 "Commentary" first author Alfred J Neugut, Columbia University, New York.

Low Levels Were Associated With Substantial Cognitive Decline

7-3 VITAMIN D AND COGNITIVE DECLINE IN ELDERLY PERSONS

Vitamin D (25[OH]D) (**D)** may help to prevent neurodegeneration. It plays an important role in the expression of neurotrophic factors, neuorgenesis, and beta-amyloid clearance.

Animal and in vitro experiments suggest that D is neuroprotective.

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

STUDY

1. InCHIANTI is a population-based prospective study designed to identify factors for late-life disability.
2. 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.)
3. 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.)
4. Defined substantial cognitive decline as 3 or more points in the MMSE and the worst 10% of decline in Trails.
5. 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)

RESULTS

1. At baseline, MMSE, Trails A and B scores were significantly lower in those who were D deficient, than in those who were D sufficient. They were more likely to be older, female, and to have been tested between December and May, to have significant depressive symptoms, impaired mobility, and lower total energy intake.

2, 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

3. Relative risk of cognitive 6-year decline in all subjects by D levels (adjusted only for baseline cognitive function):

	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

(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.)

4. 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)

5. 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.
6. Additional adjustment for stroke, diabetes and hypertension did not change the pattern of results.

DISCUSSION

1. “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.
2. The association remained significant after adjustment for a wide range of potential confounders (sociodemographic characteristics, clinical status, health behaviors, and dietary factors. And when analyses were restricted to elderly subjects who were non-demented at baseline.
3. Accumulating evidence suggests roles of D in brain development and neuroprotection. D deficiency may be associated with increased risk of other neurological diseases. D receptors are present in a wide variety of cells, including neurons and glial cells. Genes encoding the enzymes involved in the

metabolism of D are also expressed in the brain. D stimulates neurogenesis and regulates the synthesis of neurotrophic factors, which are important for cell division and survival.

4. If future prospective studies and randomized controlled trials confirm that D deficiency is causally related to cognitive decline, then this would open up important new possibilities for treatment and prevention.

CONCLUSION

Low levels of D were associated with substantial cognitive decline in the elderly population over a 6-year period.

Archives Internal Medicine July 11, 2010; 170: 1135-41 First author David J. Llewellyn, University of Exeter, Exeter, UK

An accompanied editorial (pp 1099-1100) first author Andrew Grey, University of Auckland NZ, comments and expands on this article:

Recently, observational studies have reported inverse associations between 25(OH)D, the metabolite that best reflects overall vitamin D status, and the risk of a wide range of diseases.

The results prompted calls for widespread treatment of individuals with low levels, and establishment of public health programs aimed at raising population levels. The proponents of such actions regard “sufficient” levels to be as high as 70 nmol/L (30 ng/mL) based on observational studies,

Current evidence suggests that most individuals have levels below 70 for a substantial part of the calendar year. Achieving sufficient levels will require supplementation, with costs and practical difficulties.

Are such programs justified at present?

It seems intuitively unlikely that a single hormone could play a substantial role in preventing or ameliorating such a diverse range of diseases. A more plausible and prosaic explanation is the presence of common confounders. It is likely that less healthy individuals, who are more likely to experience morbid events, will be heavier, less active, and more sunlight-deprived than healthier ones, and therefore to have lower levels of D. Several indices of poor health are more commonly observed at baseline in those with lower levels. Thus, low D levels may simply be a marker for lower health status rather than the cause of it,. Healthiness is difficult to measure and adjust for.

“We should therefore treat the data from observational studies with caution.”

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

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

Diabetes (**DM**) is a risk factor for coronary heart disease (**CHD**). How much its effect varies by age, sex, or levels of conventional risk factors is uncertain. How much of the effect of diabetes on vascular risk can be accounted for by conventional risk factors is unresolved.

In 2009, the USPSTF stated that prospective data for fasting blood glucose (**FBG**) and CHD were inconsistent and had limitations. Risk beyond conventional risk factors was not established.

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

STUDY

1. The meta-analysis included individual records of DM and FBS and other risk factors in people *without* initial vascular disease. 102 studies had information at baseline on history of DM and/or FBG.
2. Baseline DM was defined as self-reported.
3. 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).
4. Calculated hazard ratios (**HR**) for vascular disease adjusted for age, sex, smoking, systolic BP, and body mass index.

RESULTS

1. The 102 studies included 698 782 participants without a history of myocardial infarction, angina, or stroke;
    - 410 299 had information about self-reported DM, but not FBG
    - 195 390 had information about both self-reported DM and FBG
    - 93 093 had information about FBG, but not DM.
2. 264 353 participants had complete information at baseline for self-reported DM, age, sex. smoking, systolic BP, HDL-cholesterol, total-cholesterol, and triglycerides.
3. Overall, at baseline, the mean age was 52; 43% were women; 7% reported history of DM.

4. 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.

5. 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. HRs for CHD in persons with DM related to baseline FBG levels:

126 mg/dL and greater	2.36
Under 126	1.61

C. Hazard ratios did not change appreciably after further adjustments for lipids, and inflammatory markers, and renal markers

D. HRs for coronary disease with DM were significantly higher in persons age 40-59 than in those age 70; for women; in non-smokers than in smokers; and at below average BMI or below average systolic BP. (*See discussion*)

E. 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

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

A. Among people *without* known DM, FBG concentrations were associated with obesity, BP, lipid concentrations, and inflammatory markers.

B. In people without a history of DM, information about FBS or impaired fasting glucose status did not significantly improve metrics when added to information about several conventional risk factors.

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

FBG	HR for vascular disease
Equal to, or over 126 mg/dL	1.78 *
110 to 125	1.17
100 to 109	1.11

70 to 99	1.00
< 70	1.07

(* *Without known DM at baseline, but likely to have DM. RTJ*)

(To calculate mmol/L multiply by 0.05551)

D. In people without known DM at baseline, risk was only modestly increased in those with FBG 100-125 (pre-diabetes), but was substantially higher in those with FBG 126 and higher.

E. 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.

DISCUSSION

1. "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."
2. This pattern of strong associations of DM with each of several vascular diseases contrasts with that of LDL-cholesterol (or non-HDL-cholesterol) which is strongly related to CHD, but modestly related to ischemic stroke, and unrelated to hemorrhagic stroke.
3. DM is about a third more strongly related to fatal than to non-fatal myocardial infarction, perhaps suggestive of more severe forms of coronary lesions in people with DM than in those without.
4. Although DM was a strong risk factor for CHD in all clinically relevant subgroups assessed in this study, HRs were significantly greater in some subgroups at lower absolute risk of vascular disease--ie, in women, younger ages, non-smokers, and at lower than average BP. The reason for the higher risk in these subgroups, which in the general population carry lower risk, is not known.
5. The data suggest that, in this decade, about 10% of vascular deaths in adults in populations in developed countries are attributable to DM. .
6. 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.
7. There were no material associations with vascular risk at FBG 70 to 100 mg/dL. As FBG increased, risk increased. At FBG concentrations higher than 100 mg/dL, HR per each mmol/L higher glucose (18 mg) was an estimated 1.12.
8. In those without known DM, total (or non-HDL) cholesterol and systolic BP each had much stronger associations with vascular risk than FBS.
9. In people *without* DM, assessment of FBG concentration or impaired FBG .status does not

significantly improve vascular disease prediction beyond the information provided by several other conventional risk factors.

10. The generalizability of the findings to populations in developed countries is supported by the broadly consistent results across 102 cohorts in 25 (mostly high income) countries.
11. There was no information about duration or age of onset of DM

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.

Lancet, June 26, 2010; 375: 2215-22 Original investigation by the Emerging Risk Factors Collaboration, University of Cambridge , Cambridge, UK

Supported by the British Heart Foundation, UK Medical Research Council and Pfizer

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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.

Other studies involving patients with hypertension and CAD reported a J-shaped relationship beween BP and cardiovascular morbidity and mortality.

In 2004, the authors of the present study reported a significant increase in CVD risk among those who achieved a systolic of 110 or lower, questioning the notion that there is no threshold for BP lowering.

The present study investigated systolic BP achieved, and cardiovascular outcomes among elderly patients who had hypertension, diabetes, and CAD. The investigators hypothesized that a systolic below 130 would have *reduced* risk of CVD events compared with those keeping systolic between 130-140.

STUDY

1. INVEST[1] (2000-2003) was a prospective, randomized, multicenter trial of over 22 000 patients with hypertension and CAD.
2. 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)
3. 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.
4. The investigators hypothesized that patients with diabetes who achieved a systolic less than 130 would have *reduced* risk of cardiovascular events compared with those who kept their systolic within the range of 130 to less than 140.
5. 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.

RESULTS

1. Baseline characteristics:

	Tight (35% n - 2255)	Usual (31% n = 1970)	Uncontrolled (34% n = 2175)
Age	65	66	67
BP (mean)	144	149	159
Prior MI %	35	33	34
Prior stroke %	8	9	11

Prior heart failure %	9	7	9

(These patients were sick and elderly and at very high-risk of death and CVD complications.)

2. Outcomes

	Tight	Usual	Uncontrolled
Mean systolic reduction	23	18	13
Primary outcome	12.7%	12.6%	19.8%
All-cause death	11.0	10.2	15,4
Non-fatal MI	1.3	1.7	3/1
Non-fatal stroke	1.0	1.3	2.4
Total MI	4.8	5.1	8.5
Total stroke	1.5	1.7	3.2

3. Mean daily doses of antihypertension drugs were actually lower in the tight control group. Half of the subjects in the tight control group were taking 3 or more drugs (verapamilSR, atenolol, trandolapril, and hydrochlorothiazide); 2/3 in the other two groups were taking 3 or more drugs. About ¾ of participants in both groups were taking a renin-angiotensin system blocker.
4. 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.
5. 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%)
6. 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)

DISCUSSION

1. 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.
2. “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 futher 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.”
3. The UKPDS, which enrolled only patients with diabetes, showed that the patients assigned to the tight

BP control group (<150/85) actually achieved a mean BP of 144/82 over 9 years. This was associated with a significant *reduction* in micro- and macro-vascular events. The benefit observed in tight control in UKPDS was likely due to reduction in systolic from 160 to 144. There was less benefit when the reduction was from 139 to 119.

5. The ACCORD[2] study (2010) of patients with diabetes, compared standard (systolic < 140) with intensive therapy (<120) over a mean of 5 years. The achieved systolic BP in the intensive group was 110 and 133 in the standard group. The intensive group had higher rates of serious adverse events attributed to antihypertension therapy. There was, however, a slight benefit in rate of stroke.
6. The results of the present study cannot be generalized to patients with diabetes, but without CAD.

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.

JAMA July 7, 2010; 304: 61-68 Original investigation, first author Rhonda M Cooper-DeHoff, University of Florida, Gainesville.

1 The International VerapamilSR-Trandolapril Study

2 Action to Control Cardiovascular Risk in Diabetes

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Transdermal HRT Was Associated With Lower Risk Of Stroke Than The Oral Route.

7-6 TRANSDERMAL AND ORAL HORMONE REPLACEMENT THERAPY AND THE RISK OF STROKE

Several studies have suggested that estrogen-alone or estrogen combined with progestogen is associated with increased risk of stroke. A recent meta-analysis reported a 30% increase in risk associated with oral therapy.

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.

STUDY

1. Used a large computerized data base in the UK containing longitudinal records of more than 6 million persons in over 400 general practices.
2. 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.
3. All cohort subjects were followed until the date of stroke (index date), death, or end of the study period.
4. Identified all individuals with a first stroke (ischemic, hemorrhagic, or not specified)--the cases
5. At each case's index date selected 4 matched controls who were still at risk.
6. Identified all prescriptions for HRT issued during the year preceding the index date.
7. Characterized products as estrogens only, estrogen + progestin, and progestin only. Estrogens were further subdivided into oral or transdermal, and according to dose.
8. Determined the duration of use of each prescription. (Under 1 year and over 1 year)
9. Calculated the number of strokes, adjusted for multiple possible confounders.
10. Main outcome measure: ratio of stroke associated with current use of oral and transdermal HRT compared with no use.

RESULTS

1. 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)
2. The rate of stroke in the total cohort (n = 75 668) was 2.85 per 1000 per year.
3. All cardiovascular risk factors were more common in cases than in controls.
4. 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:
5. Direct comparison of transdermal with oral HRT showed the risk of stroke was lower with use of transdermal. (Adjusted rate ratio [**RR**] = 0.74)
6. 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..)

Adjusted RR of stroke associated with current use of HRT by drug type and route of administration:

None	1.00 (referent)
Transdermal route (both)	0.95
Transdermal estrogen only	1.02
Transdermal estrogen + progestin	0.76
Oral route (both)	1.28
Estrogen only	1.35
Estrogen + progestin	1.24

7. 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.

Adjusted RR of stroke associated with current use of estrogen by dose and route of administration:

	RR	
None	1.00	(referent)
Transdermal	0.95	
Low-dose	0.81	(50 ug estradiol and under)
High-dose	1.89	(Over 50 ug; not often used)
Oral	1.28	
Low-dose	1.25	(0.626 equine estrogen or under or 2 mg estradiol or under)
High dose	1.48	(Over 0.625 and over 2 mg)

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

Adjusted RR of stroke associated with current use of estrogen alone, or in combination, by duration of use and route of administration in women not previously exposed to either hormone:

None	1.00
Exclusive transdermal	1.10
One year or less	0.98
Over 1 year	1.13
Exclusive oral	1.28
One year or less	1.02
Over one year	1.35

DISCUSSION

1. This is the first study of the influence of route of administration of HRT on the risk of stroke.
2. Another study reported a lower risk of TIA with use of transdermal vs oral estrogens.
3. The finding of increased risk of stroke with oral estrogens is in accordance with results of randomized controlled trials and a meta-analysis.
4. This study suggests risk is much higher with prolonged use of oral estrogen .
5. There is biological evidence supporting the idea that the risk of vascular events differs according to the route of administration. The transdermal route avoids the first pass effect in the liver, and reduces the induction of hepatic synthesis of clotting factors. However, the biological effect may vary with the dose of estrogen. (The 50 ug dose or less was almost always studied in the past).
6. Information on the risk of ischemic heart disease with different routes of administration of estrogen is scarce.
7. There is more information on the route of administration of estrogen or venous thromboembolism. Recent observational studies and one meta-analysis suggest that transdermal estrogen does not increase risk of VTE. (In contrast to oral administration)
8. The presence of potential residual confounding in this study cannot be excluded. However, any confounding is likely to be non-differential between the two routes of administration.
9. The study was not able to differentiate between ischemic and hemorrhagic stroke.
10. The increased risk of stroke associated with HRT has been a constant finding among most observational studies and randomized, controlled trials.

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.

BMJ 2010l340c2519 doi 10.1136/bmjc2519 First author Christel Renoux, McGill University, Montreal, Canada.

An abbreviated abstract appeared in the print BMJ July 10, 2010; 341:83

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Compression Alone Just As Effective As Breathing + Compression

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

Successful resuscitation is challenging, but achievable. It requires an interdependent set of actions consisting of early arrest recognition, early CPR, early defibrillation, expert advanced life support and timely post-resuscitation care. Early initiation of CPR by a lay person increases the patient's chance of surviving and having a long-term neurological recovery.

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

Interest in chest compression-alone is increasing. It may be more acceptable to a layperson, and has the potential advantage of fewer compression interruptions so that circulation is increased, although at a possible cost to oxygenation.

Studies in animals that involve a primary cardiac cause of arrest and simulate CPR have shown increased circulation and improved survival with compression alone. In contrast, when arrest is due to respiratory causes, breathing may be more beneficial.

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

STUDY

1. The trial was conducted in two sites in Washington state and one in London. Considered consecutive bystanders' calls to 911 for persons in apparent cardiac arrest.
2. 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.
3. 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.
4. The primary outcome was survival to hospital discharge. Secondary outcomes were a return of spontaneous circulation at the end of EMS, and a favorable neurological outcome (good cerebral performance or moderate cerebral disability).

RESULTS

1. 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%.

2. Bystanders who received instructions for chest compression-alone were more likely to perform CPR than those instructed to breathing + compression. (81% vs 73%)
3. Pulse present at end of EMS care: compression alone 35%; compression + breathing 31%)
4. 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).
5. 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%)

DISCUSSION

1. Survival to hospital discharge in subjects given instructions consisting of breathing + compression did not differ from those receiving instructions for compression-alone.
2. There was suggestion that some subsets of subjects receiving compression-alone may have increased survival--those with a cardiac cause of arrest and those with ventricular fibrillation.
3. One possible explanation is that the beneficial physiological effects of continuous compression outweigh the beneficial effects of chest compression + breathing. Alternately, rescue breathing attempted by bystanders may have no physiological effects, so the comparison is essentially between two strategies: continuous compression vs interrupted compression.
4. The investigators suggest that, although there may have been more bystanders willing to perform compression alone, the results favoring compression-alone may have been due to compression's true physiological effects.

CONCLUSION

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

NEJM July20, 2010; 363: 423-33 Original investigation by the Dispatcher-Assisted Resuscitation Trial (DART), first author Thomas D Rea, University of Washington, Seattle.

An accompanying trial in this issue of NEJM (pp 434-42) first author Leif Svensson Karolinska Institutet, Sweden, comes to the same conclusion: 1276 subjects were randomized to bystander compression-alone vs compression + breathing. There was no significant difference in survival at 30 days.

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In Frail Old Men, Risks Outweigh Benefits

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

Average serum testosterone levels gradually decline as men age. The decline, however, is variable. Some men, even in old age, retain levels similar to healthy young men.

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.

It is reasonable to ask whether testosterone deficiency could be causing some changes in age and whether there could be improvement with administration of testosterone.

Clinical presentation of male hypogonadism is non-specific. It overlaps with that of other illnesses and with the aging process itself. It may not be clear that the diagnosis of hypogonadism is appropriate, and whether testosterone replacement might be helpful.

Two articles in this issue of NEJM[1,2] address these important issues.

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

"These results are surprising, since many studies with cumulative numbers of subjects greater than those reported here have not detected substantial increases in cardiovascular risk during testosterone administration."

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.

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.

Among men with deficiency, can testosterone be replaced in an effective and safe manner? Replacement improves muscle mass and strength, increases bone mass, and has other positive effects.

No study has been of sufficient size and duration to adequately address potential harms.

The editorialist comments that this should *not* deter clinicians from prescribing testosterone replacement for men with well-established late-onset hypogonadism, although it should provide some new caution in older men who have extensive history of cardiovascular disease.

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

NEJM July 8, 2010; 189-91 Editorial by William J, Brenner, University of Washington, Seattle.

A brief notice in JAMA August 25, 2010l 304:846 (Health Agency Update by Bridget M Kuehn, JAMA staff), provides an update. The note comments on adverse effects of testosterone noted in study #2 above:

The study supported by the National Institutes on Aging was halted by the Data and Safety Board after preliminary data identified adverse cardiovascular events in the treatment group.

23 of 106 men who received testosterone experienced cardiovascular events including myocardial infarction, heart rhythm disturbances, and elevated BP vs 5 in the placebo group. The risk was constant during the treatment period, (*This commentary cites higher risk than the editorial.)*

1 Identification of Late-onset Hypogonadism in Middle-aged and Elderly Men by the European Male Aging Study (EMAS), first author Frederick C W Wu University of Manchester, UK

2 Adverse Events Associated with Testosterone Administration, the Testosterone in Older Men Trial First author Shehzad Basaria, Boston University School of Medicine, Boston, Mass.

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"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. Widespread testing led to a higher incidence of early-stage disease creating an epidemic of prostate cancer (**PC**) in which the life time risk of diagnosis increased from 9% to 18%.

Even the lowest-risk tumors are often treated aggressively.

A substantial proportion of these PSA-detected cancers likely never would have been found in the absence of screening. An important legacy of the PSA era might be the overdiagnosis and overtreatment of low risk PC.

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:

1) The US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial used 4.0 for PSA (or abnormal findings on digital rectal exam) as the cutoff point for biopsy referral. The study showed no survival benefit from screening. However, there was a limited number of PC deaths, and the follow-up period was short.
2) The European Randomized Study of Screening for Prostate Cancer found an absolute mortality benefit, but only 7 fewer deaths per 10 000 person-years of screening. This implies that over 1400 men had to be screened approximately twice over 9 years to prevent one PC death. The great increase in PC diagnosis implied that an estimated 48 men had to be treated to prevent one PC death.

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).

Over diagnosis occurs because there is a large pool of indolent disease (30% of men over age 50 harbor microscopic prostate cancers, most with histological features suggesting low risk for progression).

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 Scandinavian trial of radical prostatectomy vs watchful waiting found that the disease-specific survival advantage for surgery was achieved only among men age 65 and younger.

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

Once a man is diagnosed with early stage PC, he faces a dilemma: surgery, radiation therapy, androgen deprivation, or watchful waiting. "Given society's bellicose attitude toward cancer, it is also not surprising that men are dissatisfied with watchful waiting."

In recent years, another option has been proposed that may represent a more pragmatic approach -- active surveillance (**AS**). AS is considered an acceptable alternative for men considered at low risk for progression: PSA monitoring every 3 to 6 months, with biopsy every 12 to 23 months. Men who select AS still have the choice to undergo treatment based on rising PSA level, increasing Gleason score, or abnormal digital rectal examination. One study reported that among over 2000 AS patients followed for a median of 43 months disease-specific survival was 99.7%. Only about 1/3 of patients eventually received definitive therapy,

"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."

Archives Internal Medicine July 26, 2010; 170: 1262-63 "Invited Commentary", Editorial, first author Richard M Hoffman, University of New Mexico

A report in BMJ March 20, 2010 page 628 by Nigel Hawkes, freelance journalist, London comments on a New York Times Article March 10. The report extensively quotes comments by Rickard Ablin (University of Arizona College of Medicine, Tucson) discoverer of the PSA test.

The popularity of the test has led to "a hugely expensive public health disaster. The test is hardly more effective than a coin toss". "PSA testing can't detect prostate cancer and, more importantly, it can't distinguish between the two types of prostate cancers--the one that will kill you and the one that won't. Men with low readings might still harbor dangerous cancers, and those with high readings might be completely healthy".

In the USA, PSA testing costs at least 3 billion a year, much of it paid by Medicare and the Veterans Administration.

Dr. Ablin: "PSA is not cancer specific. It is present in the normal, benign, and malignant prostate. Prostate cancer is an age-related disease. If you take men between 60 and 70, 65% or more have prostate cancer. The problem is the lack of specificity. There is no level that tells us the cancer is dangerous. 80% of men with PSA in the range 4-10 have benign prostatic enlargement."

Data from a large study showed that 48 men had to be treated to save one life; 47 men would in all likelihood would no longer function sexually or stay out of the bathroom for long.

Dr. Ablin acknowledges that PSA testing may have benefits in monitoring treatment or in measuring "doubling time" by regular testing. But. "This test should never have been approved for screening by the US Food and Drug Administration. The medical community must confront reality and stop the inappropriate use of PSA screening. Doing so would save billions of dollars and rescue millions of men from unnecessary debilitating treatments."

His stance has not always been popular.

There is some shift in opinion. The American Cancer Society urges a more cautious approach.

The American Urological Society still recommends screening.