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FOR

PRIMARY CARE MEDICINE

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26th 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 reviews of the current literature and his 26-year publication of Practical Pointers.

2) The **FULL 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* MARCH 2012

Primordial Prevention Begins In Early Life

3-1 IMPROVING CARDIOVASCULAR HEALTH IN THE US POPULATION

The American Heart Association has announced a new strategy to improve cardiovascular health by 20% by 2020 while reducing death from CVD by 20%.

Seven health behaviors and health factors define cardiovascular health: Not smoking; being physically active; having normal BP, blood glucose, total cholesterol, and weight; and eating a healthy diet.

Two key concepts are central to the development and achievement of the AHA goals:

1) At present, prevention efforts focus on unhealthy individuals and populations. But, most CVD events occur in the large proportion with average or only mildly elevated levels of risk factors, rather than the small subset with marked elevations. Thus, in addition to the "high risk" strategies, population strategies must shift the entire population distribution of risk factors toward more favorable levels. When population strategies are successful, small changes in population levels can result in large reductions in disease rates.

2) Population strategies that prevent risk factor development in the first place are called *primordial prevention.* Once a risk factor has developed, it is difficult to reduce risk back to a low level. Pharmacological and lifestyle interventions for primary and secondary prevention, while effective, will not reduce cardiovascular (**CV**) event rates to levels seen in patients who maintain optimal risk profiles from youth into middle and older age.

An article in this issue of JAMA[1] reported secular trends in CVD health metrics in the US over the past 20 years. The prevalence of all 7 factors at ideal levels was less than 2%. There were some positive trends; Increases in physical activity; reductions in smoking, BP, and cholesterol levels. There were alarming trends: Decreased proportion of adults following a healthy diet; and increased prevalence of obesity and impaired fasting glucose.

The data indicate the critical importance of attempting to shift the population toward greater CV health. There was an association between the numbers of ideal health metrics and mortality over 15 years. Compared with individuals with 0 or 1 metrics at ideal levels, those with 6 or 7 had over 50% lower all-cause mortality, lower risk of premature CVD death, and even a reduction in some cancers.

Why do so few Americans have ideal CV health? The answer is clear.

Data from all of the studies indicate that the face of ideal CV health is young, educated, white women. The pattern of ideal CV health is normal in most infants, but it is lost, sometimes rapidly, during childhood, adolescence, and young adulthood through adoption of adverse behaviors related to diet,

weight, and sedentary lifestyle, particularly in populations with lower socio-economic status. Thus the nature of the problem transcends the public health care system. Solutions must come from improvements in the environment and better access to healthy food and activity, which should reduce the alarming disparities in cardiovascular health.

A concerted effort is needed to improve health behaviors in all segments of the population. Opportunities abound for physicians, policymakers, and consumers to support improvements in CV health.

JAMA March 28, 2012; 307: 1314-16 Commentary by Donald M Lloyd-Jones, Northwestern University Feinberg School of Medicine. Chicago, IL

1 "Trends in Cardiovascular Health Metrics and Associations with All-cause Mortality Among US Adults" JAMA March 28, 2012; 307: 1273-83 Original investigation, first author Quarnhe Yang, CDC. Atlanta, GA.

Most interventions have been focused on primary and secondary prevention. The term "primordial prevention" is new to me. Primordial prevention is the real goal.

This is a challenge for primary care. We relate to the general population to a greater extent than any other specialty. But each of us relates to one patient and family at a time. We can make a difference by educating individuals and families, especially those with young children.

Our efforts, however, will be meaningless unless we act as role models and adopt all 7 metrics ourselves.

I believe there is a role for government in improving the food supply to lower adverse fats, salt, and sugar. There is also a great challenge for our school systems to teach primordial prevention.

I have abstracted several articles recently promoting preventive care, especially lifestyle interventions. I make no apology for the repetition. The subject is so important.

A Risk Factor For All-Cause Mortality

3-2 SITTING TIME AND ALL-CAUSE MORTALITY RISK IN 227 497 AUSTRALIAN ADULTS

This study focused on the dose-response relationship between total sitting time and all-cause mortality.

Over 220 000 participants, representing 11% of the population of a state of Australia, completed a baseline questionnaire (2006). All were over age 44.

Sitting time was assessed by asking: 1) About how many hours in each 24-hour day do you usually spend sitting?

Determined all-cause mortality (2006-2010) in relation to sitting time, adjusted for potential confounders. Daily sitting time (hours / day) was divided into 4 categories: 1) 0 to 3.9; 2) 4 to 7.9; 3) 8 to 10.9; and 4) 11 or more. Determined hazard ratios of all-cause death related to 0 to 3.9 hours per day.

During 621 695 person-years of observation (mean follow-up 2. 8 years) 5405 deaths were registered.

Relationship between sitting and all-cause mortality after adjustment for sex, age, BMI, smoking, and other possible confounding factors:

Hazard ratios	Sitting time h/d			
	0-3.9	4.0 to 7.9	8.0 to 10.9	11 and over
All subjects	1.00*	1.02	1.15	1.40

* Referent

The trend in the 4 groups showed a significant hazard ratio for all-cause mortality.

The population-attributable deaths due to sitting was 7%. Inactive participants with high levels of sitting had the highest mortality rate. “The results show that prolonged sitting is associated with higher all-cause mortality risk independent of physical activity.”

Sitting less than 8 hours per day, and meeting the physical activity recommendations of the WHO independently protected against all-cause mortality.

In the USA, less than half the adult population meets the WHO recommendations for physical activity. The potential public health gains of interventions to change activity are substantial.

Conclusion: Prolonged sitting was a risk factor for all-cause mortality, independent of physical activity.

(See the full abstract for details and the citation. Ed.)

Practical Pointers has abstracted many articles demonstrating benefits of healthy lifestyles. This is a major responsibility and opportunity for primary care medicine.

The difficulty is: how to change patient-behaviors. This is difficult, but keep on trying.

We are a sitting society. A commentary attached to the full abstract suggested that incidental standing-walking around activity during the day, instead of sitting, would be beneficial. Physical activity does not require planning. Pretend you are on a cruise. Instead of sitting on a deck chair, walk around the deck. While waiting in an airport, don’t sit, get up and walk around. When traveling to work in a car, park several blocks from the office. Keep active. Emulate the busy housewife.

*This study has all the difficulties related to observational studies. Duration was less than 3 years—a short time. Longer duration may have demonstrated more differences between the groups***.**

At Present, Clinicians Will Need To Rely On Their Clinical Judgment And Well-Meaning, But Necessarily Vague Clinical Practice Guidelines And Expert Opinion.

3-3 SUBCLINICAL HYPOTHYROIDISM

"Subclinical" denotes the presence of a disease without obvious symptoms—an early stage of evolution of a disease. Subclinical hypothyroidism (**SCHOT**) occurs when thyroid stimulating hormone (**TSH**) is high and free thyroxin (**T4**) and T3 levels remain within the normal reference range.

Diagnosis is based on the exquisite sensitivity of the hypothalamic-pituitary- thyroid axis. Serum TSH changes logarithmically. Free T4 changes arithmetically. Therefore changes in free T4 that are within the normal range will cause increases or decreases in TSH that are likely to be outside the reference range. Most experts agree that SCHOT represents early mild thyroid failure. Depending on the size of the increase in serum TSH it can be mild (TSH 4.5-9 mU/L), or severe (TSH 10 mU/L and over). Most patients with SCHOT have the mild form.

Transient increases in SCHOT may occur. The TSH level should be repeated in 3-6 months to rule out laboratory error and a transient increase.

Antithyroid antibodies, a marker of chronic autoimmune lymphocytic thyroiditis (Hashimoto) are present in 60% to 80% of persons with elevated TSH. High antithyroid autoantibody titers are associated with persistent raised serum TSH.

The NHANES III study reported 4% of the US population had SCHOT. Overall incidence increases with age and in females.

Although dyslipidemia (especially elevated total- and LDL-cholesterol) is associated with overt hypothyroidism, the relationship with SCHOT is controversial. The association may be stronger in patients with TSH levels above 10 mU/L.

Maternal SCHOT can lead to serious obstetric complications including increased risk of miscarriage, placental abruption, low birth weight, and premature delivery. Impaired mental function has been reported in children born of inadequately treated women with SCHOT.

Generally, treatment does not improve mood, cognition, or symptoms unless the TSH is more than 10. In a meta-analysis of 13 studies of levothyoxin therapy, the effects of therapy were proportional to both the severity of SCHOT and the increase in serum lipids. Both total- and LDL-cholesterol were modestly reduced.

Population screening (of asymptomatic patients) is controversial because the benefits of treatment are unproven for most individuals who might be diagnosed through screening programs.

Conclusion: SCHOT is common in clinical practice. Since most patients are asymptomatic, screening is the only way that most patients will be identified. Yet, experts do not agree about whether screening is worthwhile because no large population-based randomized, controlled trials show that intervention is beneficial. The data are sufficient, however, to recommend treatment of patients who are over age 65, and have TSH levels of 10 and over. Treatment can also be recommended for pregnant women with TSH levels above the reference range for pregnancy. For most patients with TSH concentrations between.5.0-10, no firm recommendations can be made. The decision to treat will be made on various clinical factors. At present, clinicians will need to rely on their clinical judgment and well-meaning, but necessarily vague clinical practice guidelines and expert opinion.

(See the Full Abstract for a levothyoxin treatment algorithm. Ed.

I abstracted this article in detail and at length because I knew little about SCHOT and considered it an important clinical application. World-wide, thyroid disease is becoming epidemic.

One word describes the state of our knowledge about SCHOT—"uncertainty".

At present, decisions about screening and treatment rely on clinical judgment. Pay attention to new or unusual symptoms .Increased suspicion related to pregnancy is warranted.

I believe many primary care clinicians screen frequently.

Should we screen for antithyroid antibodies? I do not believe it will aid decisions about treatment in primary care practice. Routine screening will exceed our efforts to practice good stewardship of medical interventions and costs.

A n = 1 trial may be helpful. Try a short time of low dose levothyoxin. Are symptoms improved? Do symptoms improve as well on a placebo? A short course of low-dose levothyroxin is likely harmless. Carefully follow-up for effect on symptoms and TSH.

My laboratory cites a reference range for TSH of 0.30 to 3.0.

The article also includes discussion of subclinical hyperthyroidism, equally interesting. I omit this.

Non-HDL-C Had A Stronger Association With Risk Of Major CV Events Than LDL-C And Apo-B

3-4 **ASSOCIATION OF LDL-CHOLESTEROL, NON-HDL CHOLESTEROL, AND APOLIPOPROTEIN- B LEVELS WITH RISK OF CARDIOVASCULAR EVENTS AMONG PATIENTS TREATED WITH STATINS: A Meta-analysis**

All current guidelines state that low-density lipoprotein cholesterol (**LDL-c)** levels should be used as the target to initiate and titrate lipid-lowering therapy.

LDL- c may not be the best lipid parameter to predict CV risk or to quantify the atheroprotective effect of statin therapy.

This study was based on 8 randomized controlled trials including 38 153 participants. All participants included were taking statin drugs.

(This was a high risk group of patients who were receiving primary or secondary preventive therapy. Many had experienced a CV event. Ed.)

Measured total-c, LDL-c, Apo-B, HDL-c, and triglycerides at baseline and at 1 year. Non-HDL-c was calculated as total-c minus HDL-c.

Followed for major CV events: Myocardial infarction (fatal and non-fatal), coronary artery disease, unstable angina, stroke (fatal and non-fatal), peripheral arterial disease, and congestive heart failure.

Calculated hazard ratios (**HR**) for risk of major CV events by 1 standard deviation (**SD**) from the mean of LDL-c, Apo-B, and non-HDL-c. Determined one SD for non-HDL-c to be 36 mg/dL; LDL-c to be 32 mg, and Apo-B to be 27 mg.

During follow-up, among the 38 153 participants 14% experienced a CV event.

LDL-c, non-HDL-c and Apo-B were statistically associated with risk of major CV events:

	One standard deviation: mg/ dL	HR for each 1 SD increase
LDL-c	32	1.13
Non-HDL-c	36	1.16
Apo-B	27	1.14

HRs for risk of major CV events for 4 patient categories comparing non-HDL-c with LDl-c defined by target levels of 130 mg/dL and 100 mg/dL.

Target		HP
LDL-c	HDL-c	
> 100 mg/dL	> 130	1.21
<100	>130	1.32
>100	<130	1.02
<100	<130	1.00 (Referent)

Compared with those who reached both targets, statin treated patients reaching the non-HDL-c target of < 130, but not the LDL-c target of <100, had a HR of major CV disease of 1.02. Patients reaching the LDL-c target, but not the non-HDL-c target had a HR of 1.32.

(Ie, reaching the non-HDL-c target seems much more protective. ED.)

"Our observation in statin-treated patients extended prior results from large population-based studies showing that non-HDL-c is more strongly associated with risk of future major cardiovascular events than LDL-c." The study did not find evidence that Apo-B performed better than LDL-c or non-HDL-c.

Conclusion: Among high-risk, statin-treated patients, on-treatment levels of LDl-c, Apo-B and non-HDL-c were each associated with risk of future major CV events. The strength of the association was greater for non-HDL-c than for LDL-c and Apo-B.

(See the full abstract for details and the citation. Ed.)

A provocative study, but not conclusive. Determination of the best and least expensive marker for effectiveness of statin therapy is an important challenge for primary care. To abide by the ethical principle of good stewardship of medical interventions and costs, we must choose the simplest and most cost effective marker. Certainly it will not be the combined LDL-c + non-HDL-c. I would bet on non-HDL-c.

Dementia And Dependency Relentlessly Continued

3-5 DONEPEZIL AND MEMANTINE FOR MODERATE-TO SEVERE ALZHEIMERS DISEASE

Guidelines advocate cholinesterase inhibitors (eg, donepezil [**D**]) for treatment of Alzheimer disease (**AD**). Some recommend discontinuation when AD becomes severe. The FDA has approved D for treatment of severe AD.

Memantine (**M**) has been reported to be effective in patients with moderate or severe AD.

There is limited evidence to guide the difficult decision regarding continuation of treatment when AD progresses. Continuing treatment is associated with adverse outcomes.

This study of AD patients, who were already taking D, asks whether continuation of D-alone, M-alone, M + D, or no drug therapy would be the superior treatment.

This double-blind, placebo-controlled trial entered 295 community dwelling patients (mean age 77) with moderate to severe AD and followed them for 52 weeks. All had been taking D for between 3 months and 5 years.

All had a baseline score between 5 and 13 (mean = 9) on the Mini-Mental State Examination (**MMSE**). Possible scores ranged from 0 to 30, with higher scores indicating better cognitive function. Score of 5 to 9 indicated severe AD; 10 to 13, moderate AD.

All also had a baseline caregiver score on The Bristol Activities of Daily Living Scale (**BADLS**) ranges from 0 to 60, with higher scores indicating greater impairment. Mean baseline score was 28.

Randomized to: 1) Continuation of D-alone; 2) M; alone; 3) D + M; or 4) No drug therapy. Placebos were added as needed to blind treatments.

Over one year, mean scores on the MMSE in all 4 groups relentlessly continued to deteriorate from a mean baseline score of 9:

	D-alone	M alone	D + M	No drug	
MMSE from 9 to	5.5	5.0	5.5	3.5	(Worsening)
BADLS from 28 to	35	36	34	41	(Worsening)

The primary outcome measure: The overall mean differences between drug and no drug across all visits (weeks 6, 18, 30, and 52):

D alone +1.9 points on MMSE; - 3 points on BADLS

M-alone +1.2 points of MMSE; -1.5 points on BADLS

Both drugs showed better scores compared to no drug treatment, but both drugs were associated with a continuing decline in cognitive function and activities of daily living.

There was no clinically important difference between groups in behavioral and psychological symptoms.

"This double-blind, placebo –controlled trial involving community living patients with moderate or severe Alzheimer's disease who were already receiving treatment with a cholinesterase inhibitor, showed that there was modest cognitive and functional benefit of continuing donepezil over the course of 12 months."

There was no significant benefit from adding M to D.

The improvements in cognition and function associated with D and M were small relative to the overall size of the decline in cognition and functional status that was seen in all patients.

Conclusion: In patients with moderate or severe AD, continuing treatment with D was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over 12 months.

This complex article was difficult to abstract.

Casual readers may miss the important outcomes.

I believe it stresses the wrong outcomes. Although D was "better" than the other interventions, cognitive function and difficulties with daily living progressed relentlessly over the year.

The authors did not stress this point. They stressed the difference between the 4 interventions and the advantages of D over the rest. This is not a valid clinical point for primary care.

Both D and M have a wide variety of adverse effects. Benefits, if any, are small. The benefit/harm-cost ratio is, in many patients, less than 1/1.

I believe these drugs have been over prescribed, overused. They may retard progressing of dementia to a small degree in those with beginning AD, but they are continued without benefit.

They are costly, especially if used for years.

Why are these drugs used so frequently? I believe because family members latch onto any intervention which promises some benefit and hope, no matter how small. And because drug companies advertise them so forcefully.

"New Drugs Have Dangers That Become Apparent Long After The Relatively Pristine Data Of Clinical Trials Has Given Way To The Gritty Reality Of Daily Clinical Drug Use"

3-6 DABIGATRAN: "Do we have sufficient data?

Dabigatran (*Pradaxa*), a new direct thrombin inhibitor, has certainly been in the news recently. These editorialists identified over 500 publications. It has also been widely advertised to the general public.

A change in anticoagulant therapy seems likely and imminent.

Seven randomized, controlled trials have been published to make dabigatran the primary contender among several new anticoagulants.

Case reports have noted increased bleeding associated with advanced age, renal impairment, and low body weight.

Left ventricular thrombus formation has also been reported.

A meta-analysis in this issue of Archives[1] suggests that we step back and retain a critical view as powerful new drugs enter clinical use on a potential massive scale.

An unexpected finding emerged from the RE-LY[2] trial. There was a 38% increase in myocardial infarctions (**MI**) , and higher risks of several other safety outcomes including a few major hemorrhages and systemic embolic events.

After FDA approval, a review of efficacy and safety data of RE-LY identified 32 previously undiagnosed unidentified MIs, 28 of which were clinically silent, and diagnosed only by new pathologic Q waves.

The meta-analysis[1] of the 7 RCTs, which compared dabigatran with warfarin, enoxaparin and placebo repeatedly found an increased rate of MI in the dabigatran groups.

"The robust finding that dabigatran is associated with increased rates of MI is alarming and emphasizes the need for continuing critical appraisals of drugs after phase 3 trials."

Why might adverse effects be under-reported in clinical trials and subsequently occur in clinical use? This issue is complex, ranging from the responsibility of individual clinicians and the role of regulatory bodies and legislative measures. Methodologic issues that contribute to under-reporting of adverse events include: Large size of clinical trials are required to detect all but the most common adverse effects, problems of data collection, poor statistical analysis, delayed reporting of negative findings, and publication bias in favor of positive findings.

Some critics argue that much of our prescribing habits may be based on myth, built on a body of literature that is, at best, flawed methodologically and , at worst, silenced or manipulated by interested parties.

New drugs have dangers that become apparent long after the relatively pristine data of clinical trials has given way to the gritty reality of daily clinical drug use.

As long-term management of multiple comorbid chronic diseases among an increasingly older population becomes the face of modern medicine, disentangling adverse drug events will become more blurred by the growing epidemic of polypharmacy.

Archives Internal Medicine Mach 12, 2012; 172: 403-04 Commentary, first author Jeremy M Jacobs, Hadassah-Hebrew University Medical Center, Mount Scopus, Jerusalem, Israel

1 " DABIGATRAN ASSOCIATED WITH HIGH RISK OF ACUTE CORONARY EVENTS" Meta-analysis of Non- inferiority Randomized, Controlled Trials

Archives Internal Medicine March 17, 2012; 172: 397-402 Cleveland Clinic, Cleveland, Ohio.

Selected seven trials (N = 30 514) of dabigatran compared with warfarin, enoxaparin, or placebo. Dabigatran was significantly associated with a higher risk of myocardial infarction or acute coronary syndromes than the control groups. In absolute terms, the risk with dabigatran was 1.19% vs 0.79%. (Absolute difference = 0.40% or 4 out of every 1000 patient treated.)

2. RE-LY "DABIGATRAN VERSUS WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION" NEJM September 17, 2009; 361: 1139-51. See Practical Pointers September 2011 for abstract.

A chance of MI of 4 in 1000 might seem acceptable to some patients. But when multiplied by the potentially large numbers of the population potential receiving the drug, risk is very high. We wait until more data is available to determine the place of dabigatran in primary care.

This again points out the risk of immediately using newly approved drugs. All drugs have harmful effects. And the harms may not be evident for years. Primary care clinicians would be wise to wait for several years until the benefit / harm-cost ratio of the new drug is clearer. Do not be the first to prescribe the drug unless it has an important indication and there is no reasonable substitute drug.

If an adverse effects occurs in a primary care patient taking X drug, we may not know if there is a relationship. Reporting such events, especially in newly introduced drugs, is essential. I believe many primary care clinicians fail to do this.

Underreporting may be more common in trials sponsored by drug companies.

Many patients, especially the elderly, may take 6 or 7 or more drugs. There is absolutely no way to determine which, if any drug , may be associated with an adverse effect in these patients.

Several points in the article puzzled me. Why should a patient taking an anticoagulant suffer increased risk of thrombotic events? Why would Q-wave infarction be more common?

FULL ABSTRACTS MARCH 2012

A Risk Factor For All-Cause Mortality

3-2 SITTING TIME AND ALL-CAUSE MORTALITY RISK IN 227 497 AUSTRALIAN ADULTS

The benefits of a physically active lifestyle are established. Physical inactivity is estimated to account for 6% of global deaths. The WHO has recommended that adults participate in at least 150 minutes of moderate exercise per week to reduce the risk of chronic diseases such as CVD, type-2 diabetes, and certain cancers.

Even when individuals engage in physical activity 150 minutes/week, increasing evidence suggests that what happens in the remaining 6500 minutes of awake time per week is important for health. All-cause mortality may be increased with TV viewing, recreational (computer) screen time, sitting during leisure time, sitting in a car or in an airport, sitting at school or during housework, and occupations that involve prolonged sitting.

This study focused on the dose-response relationship between total sitting time and all-cause mortality.

STUDY

1. Over 220 000 participants, representing 11% of the population of a state of Australia, completed a baseline questionnaire (2006). All were over age 44.
2. Sitting time was assessed by asking: 1) About how many hours in each 24-hour day do you usually spend sitting?
3. Also assessed total activity (moderate and vigorous).
4. The outcome variable (all-cause death; 2006-2010) was determined from the public registry.
5. Determined all-cause mortality in relation to sitting time, adjusted for potential confounders.
6. Daily sitting time (hours / day) was divided into 4 categories: 1) 0 to 3.9; 2) 4 to 7.9; 3) 8 to 10.9; and 4) 11 or more. Determined hazard ratios of all-cause death related to 0 to 3.9 hours per day.

RESULTS

1. At baseline, 25% were sitting at least 8 h/d; 25% failed to meet the 150-minute per week physical activity guideline.
2. Duration of sitting time tended to be greater in the <u>younger</u> groups, and in those with **higher**

education levels, poorer self- rated health, lower physical activity, and higher BMI. And in those requiring help with daily tasks.

3. During 621 695 person-years of observation (mean follow-up 2. 8 years) 5405 deaths were registered.
4. Relationship between sitting and all-cause mortality after adjustment for sex, age, BMI, smoking, and other possible confounding factors:

Hazard ratios	Sitting time h/d			
	0-3.9	4.0 to 7.9	8.0 to 10.9	11 and over
All subjects	1.00*	1.02	1.15	1.40

* Referent

5. The trend in the 4 groups showed a significant hazard ratio for all-cause mortality.
6. The population-attributable deaths due to sitting was 7%.
7. Inactive participants with high levels of sitting had the highest mortality rate. The strong relationship of increased sitting time to mortality persisted even among persons with relatively high levels of physical activity.
8. Healthy participants had lower absolute all-cause mortality compared with those with existing CVD or diabetes. Reduced sitting and increased physical activity were associated with reduced mortality rates in both groups,

DISCUSSION

1. “The results show that prolonged sitting is associated with higher all-cause mortality risk independent of physical activity.”
2. The association between sitting and mortality appeared to be relatively consistent across women and men, age groups, BMI categories, physical activity levels, and across healthy participants compared with those with preexisting CVD and diabetes.
3. People who sat the most and performed no weekly physical activity had the highest mortality
4. Sitting less than 8 hours per day, and meeting the physical activity recommendations of the WHO independently protected against all-cause mortality.
5. This further builds on the accumulating evidence of the association between sedentary behaviors and health.
6. Prolonged sitting has been shown to result in increased plasma triglycerides, decreased levels of high density lipoproteins, and decreased insulin sensitivity.
7. In the USA, less than half the adult population meets the WHO recommendations for physical

activity. The potential public health gains of interventions to change activity are substantial.

CONCLUSION

Prolonged sitting was a risk factor for all-cause mortality, independent of physical activity.

Archives Internal Medicine March 26, 2012 Original investigation, first author Hide P van der Ploeg, University of Sydney, Australia for The 45 and Up Study

A commentary in this issue of Archives, first author David W Dunstan, Baker ID Heart and Diabetes Institute, Melbourne, Australia expands on this article:

Reducing total sitting time may be as important as increasing participation in physical activity.

This observation that prolonged sitting is hazardous to health is not new. It was noted in the 17th century by Francisco Ranazziini. In the 1960s Morris reported that workers in occupations requiring sitting (London bus drivers) had higher incidence of CVD than workers who were required to stand and ambulate (Bus conductors).

Homans reported in 1954 that the incidence of venous thrombosis in the legs increases with prolonged sitting. This led to the recommendation that " such matters are important enough to suggest the advisability of making movements of the toes, feet, and lower legs when one is sitting for long periods, and getting up and exercising when opportunity offers".

There are weaknesses in this observational study. It was based on self-reported sitting time.

Newer measurements made by accelerometers—small electronic devices worn on the hip during working hours—provide further insights. The US-NHANE Survey (2010) examined 7-days of use of the machine in over 1700 individuals to determine awake-time activity. Most of the time was spent on sedentary behavior (58%) or light-intensity activity (strolling, washing dishes, and gardening (39%), and only 3% on moderate-vigorous physical activity time.

There is an inverse relationship between sitting time and light-to-moderate activity. Increasing light-to moderate activity will decrease sitting time. One study reported an almost perfect inverse correlation between the two. Therefore, in addition to the benefits of moderate-to-vigorous activity, health gains should accrue through redressing the imbalance between sitting time and light-intensity activity. Sitting consumes less energy than light-to-moderate activity,

Increasing light activity may be a feasible goal for many and may increase health benefits.

At Present, Clinicians Will Need To Rely On Their Clinical Judgment And Well-Meaning, But Necessarily Vague Clinical Practice Guidelines And Expert Opinion.

3-3 SUBCLINICAL HYPOTHYROIDISM

"Subclinical" denotes the presence of a disease without obvious symptoms—an early stage of evolution of a disease. Subclinical hypothyroidism (**SCHOT**) occurs when thyroid stimulating hormone (**TSH**) is high and free thyroxin (**T4**) and T3 levels remain within the normal reference range.

Diagnosis is based on the exquisite sensitivity of the hypothalamic-pituitary- thyroid axis. Serum TSH changes logarithmically. Free T4 changes arithmetically. Therefore changes in free T4 that are within the normal range will cause increases or decreases in TSH that may be outside the reference range. Each individual seems to have a specific set point for the h-p-t axis, which is to a large extent genetically determined.

Most experts agree that SCHOT represents early mild thyroid failure. Depending on the size of the increase in serum TSH it can be mild (TSH 4.5-9 mU/L), or severe (TSH 10 mU/L and over). Most patients with SCHOT have the mild form. However, there is some controversy over the upper limit of the reference range.

Cause:

Antithyroid antibodies, a marker of chronic autoimmune lymphocytic thyroiditis (Hashimoto) are present in 60% to 80% of persons with elevated TSH. Hashimoto's thyroiditis is more common in girls and women.

Epidemiology:

SCHOT is more common in iodine sufficient countries. Iodine supplementation might increase incidence. It occurs in 4-20% of the adult population. The wide range is due to differences in age, sex, body mass index, race (whites have greater incidence than blacks) and the cutoff concentrations of TSH used to define the condition. The NHANES III study reported 4% of the US population had SCHOT. Overall incidence increases with age and in females. The increase in TSH with age may not be an indication of thyroid hormone deficiency as it has been recorded in individuals without circulating thyroid antibodies.

Diagnosis:

Predisposition to SCHOT maybe increased by familial and genetic factors such as family history of autoimmune thyroid disease, systemic autoimmune disorders, or genetic disorders (eg, Down syndrome). High antithyroid autoantibody titers are associated with persistent raised serum TSH. Transient increases in SCHOT may occur. The TSH level should be repeated in 3-6 months to rule out laboratory error and a transient increase. TSH levels are raised in obese individuals and falsely suggest SCHOT. This mild increase is usually associated with free T3 levels at the upper normal level. This may be due to increased de-iodinase activity as a compensation for fat accumulation to raise energy expenditure.

Progression to overt hypothyroidism:

SCHOT is usually progressive, although it is often reversible, especially when TSH levels are less than 10 mU/L. Levels above 10 and the presence of antithyroid antibodies are associated with increased risk of progression to overt hypothyroidism. The presence of thyroid antibodies at any level of TSH (even as low as 2.5) predicted long-term risk of hypothyroidism The annual rate of progression to overt disease is about 4% in women with raised TSH and antithyroid antibodies and 2-4% in those without antibodies. In a population study of over 400 000 patients, progression from slightly increased TSH (5-9) mU/L) to higher levels occurred in less than 10% over 5 years. Levels tend to return to normal in patients with lower levels (4-6) than in those with higher levels.

Symptoms:

Symptoms of SCHOT are neither sensitive nor specific. It is difficult to distinguish SCHOT subjects from euthyroid patients. Symptoms are affected by disease severity, disease duration, and individual sensitivity. Patients who report many, or newly developed symptoms are more likely to have SCHOT.

Decreased quality-of-life, anxiety, depression, cognitive dysfunction, and memory loss have been reported, although contrasting findings have also been reported. Symptoms seems to be les severe in the elderly. In two large cross sectional studies of patients age 65-79, SCHOT was not associated with cognitive dysfunction, anxiety, or depression.

Cardiovascular risk:

Cardiac dysfunction may occur in patients with SCHOT—both depressed systolic function and left ventricular diastolic dysfunction. Patients might complain of reduced exercise tolerance. A slow rate of left ventricular relaxation might critically impair filling during exercise, leading to ventricular systolic dysfunction. SCHOT can impair relaxation of vascular smooth muscle, increasing systemic vascular resistance. However, the clinical significance of this is not known. In one study, systolic and diastolic BP and total cholesterol levels were higher than controls. In another study, heart disease and all-cause mortality did not increase during an 11-year follow-up. Although dyslipidemia (especially elevated total- and LDL-cholesterol) is associated with overt hypothyroidism, the relationship with SCHOT is controversial. The association may be stronger in patients with TSH levels above 10 mU/L and in smokers, and patients with insulin resistance. In a large meta-analysis, the risk of coronary heart disease increased with the severity of SCHOT. But there was no interaction between mortality due to CHD and age.

Risk of heart failure (**HF**):

One study of elderly patients reported a relative risk of HF of 2.6 in those with TSH 7-9.9 and 3.3 in those with TSH of 10 and greater. In another study, increased incidence of HF was recorded only in patients with TSH greater than 10.

Women of reproductive age and during pregnancy:

Prevalence of SCHOT is 0.5 to 5%. Maternal SCHOT can lead to serious obstetric complications including increased risk of miscarriage, placental abruption, low birth weight, and premature delivery, although at a lower rate than with overt hypothyroidism. Increased rate of fetal death has been reported in some studies, but not in others. Thyroid hormone is essential for fetal development especially during the first months of pregnancy. The fetal thyroid does not produce thyroxin until the 13^{th} week. Impaired mental function has been reported in children born of inadequately treated women with SCHOT, but not in those receiving adequate treatment.

Treatment:

1. TSH 5 to 9:
   A. Consider treatment of young and middle-aged patients, especially if they have recent onset of symptoms, goiter, or antithyroid antibodies, dyslipidemia or other cardiovascular risk factors, or if pregnant. Treat with levo-thyroxin with a goal of TSH of 0.5 to 2.5 in young patients and possibly higher (4 to 6 in older patients).
   B. No treatment in patients older than age 85. In patients older than 65, treat to TSH under 7. In asymptomatic patients under age 65, who do not have goiter, dyslipidemia, or other CVD risk factors, are not pregnant and do not intend to become pregnant, treatment or observation are both reasonable. However, treatment could be considered if there is a progressive increase in TSH.
2, TSH 10 and above:
   Treat with levo-thyroxin with a goal of 0.5 to 2.5 in young and middle-aged individuals and possibly higher levels (4 to 6) in the elderly .

Effects of replacement therapy:

Various placebo-controlled studies have assessed effects of replacement with levothyroxin on symptoms and signs in patients with SCHOT. Comparisons of these studies is difficult because enrolled

patients differ in age and degree. Studies also differ in terms of symptom score, duration of replacement therapy, and levothyroxin dose. Generally, however, treatment does not improve mood, cognition, or symptoms unless the TSH is more than 10. Studies concur that replacement therapy improves systolic and diastolic function, endothelial function, and carotid intima-media thickness. Studies reported treated patients had lower risk of HF and lower all-cause mortality than untreated individuals. In a meta-analysis of 13 studies of levothyoxin therapy the effects of therapy were proportional to both the severity of SCHOT and the increase in serum lipids. Both total- and LDL-cholesterol were modestly reduced. The reductions were proportional to the dyslipidemia and the SCHOT. Triglycerides and HDL-c did not change. Miscarriage rates and premature delivery were much lower in adequately treated women. The effect of treatment on neurological development of the children has not been established, but guidelines recommend it.

Screening:

Population screening (of asymptomatic patients) is controversial because the benefits of treatment are unproven for most individuals who might be diagnosed through screening programs. Recommendations for screening differ substantially between professional societies and expert panels. Case finding has been advocated in pregnant women and those who might become pregnant. Many are not diagnosed. One randomized trial of pregnant women showed that universal screening did not reduce the rate of adverse events compared with case finding. In anther trial, only 1% of middle aged and older women individuals had improved quality of life from screening and treatment.

Conclusion:

SCHOT is common in clinical practice. Since most patients are asymptomatic, screening is the only way that most patients will be identified. Yet, experts do not agree about whether screening is worthwhile because no large population-based randomized, controlled trials show that intervention is beneficial. The data are sufficient, however, to recommend treatment of patients who are over age 65, and have TSH levels of 10 and over. Treatment can also be recommended for pregnant women with TSH levels above the reference range for pregnancy. For most patients with TSH concentrations between 5.0-10 no firm recommendations can be made. The decision to treat will be made on various clinical factors. At present, clinicians will need to rely on their clinical judgment and well-meaning, but necessarily vague clinical practice guidelines and expert opinion.

Lancet March 24, 2012; 379: 1142-54 "Subclinical Thyroid Disease: Seminar, first author David S Cooper, Johns Hopkins School of Medicine, Baltimore MD,

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Non-HDL-C Had A Stronger Association With Risk Of Major CV Events Than LDL-C And Apo-B

3-4 ASSOCIATION OF LDL-CHOLESTEROL, NON-HDL CHOLESTEROL, AND APOLIPOPROTEIN- B LEVELS WITH RISK OF CARDIOVASCULAR EVENTS AMONG PATIENTS TREATED WITH STATINS: A Meta-analysis

All current guidelines state that low-density lipoprotein cholesterol (**LDL-c)** levels should be used as the target to initiate and titrate lipid-lowering therapy. However, trials investigating the efficacy of statins have shown that the cardiovascular (**CV**) benefit of statins may go beyond their influence on LDL-c levels.

LDL- c may not be the best lipid parameter to predict CV risk or to quantify the atheroprotective effect of statin therapy.

Population-based studies have shown that non-HDL-c and Apo-B are more strongly associated with CV risk than LDL-c. The role of particles other than LDL-c as targets for statin therapy remains debatable.

This study assessed whether, among statin-treated patients, non-HDL-c and Apo-B were more strongly associated with the risk of future CV events than LDL-c. And whether non-HDL-c and Apo-B explained a larger proportion of the atheroprotective effects of statins than LDL-c.

STUDY

1. Literature search found 8 randomized controlled trials including 38 153 participants. All participants included were taking statin drugs.
   (This was a high risk group of patients who were receiving primary or secondary preventive therapy. Many had experienced a CV event. Ed.)
2. Measured total-c, LDL-c, Apo-B, HDL-c, and triglycerides at baseline and at 1 year. Non-HDL-c was calculated as total-c minus HDL-c.
3. Followed for major CV events: Myocardial infarction (fatal and non-fatal), coronary artery disease, unstable angina, stroke (fatal and non-fatal), peripheral arterial disease, and congestive heart failure.
4. Calculated hazard ratios for risk of major CV events by 1 standard deviation (**SD**) increase from the mean of LDL-c, Apo-B, and non-HDL-c. Determined one SD from the mean for non-HDL-c to be 36 mg/dL; LDL-c to be 32 mg, and Apo-B to be 27 mg.

RESULTS

1. During follow-up, among the 38 153 participants:

   158 fatal MI; 615 fatal MI, 615 fatalities for other coronary artery disease, 2806 hospitalizations for unstable angina, and 1029 fatal or non-fatal strokes. Event rate = 14%. Some experienced more than one event.

2. LDL-c, non-HDL-c and Apo-B were statistically associated with risk of major CV events. The HRs per 1 standard deviation (SD) from the mean:

	One standard deviation: mg/ dL	HR for each 1 SD increase
LDL-c	32	1.13
Non-HDL-c	36	1.16
Apo-B	27	1.14

3. Lipid and Apo-B levels and risks of major CV events in statin-treated patients stratified by quartiles of lipids and Apo-B:

	Quartile				HR per 1 SD increase
	1	2	3	4	
LDL-c					
Mean (mg/dL)	49	74	97	129	
Event rate (%)[b]	7	14	17	18	
Hazard ratio[c]	1.00[a]	1.06	1.15	1.26	1.13
Non-HDL-c					
Mean (mg/dL)	69	98	124	151	
Event rate (%)	7	14	16	19	
Hazard ratio	1/00	1.12	1.17	1.42	1.16
Apo-B					
Mean (mg/dL)	60	80	97	127	
Event rate (%)	9	13	16	20	
Hazard ratio	1.00	1.05	1.12	1.33	1.14

   (a referent; b number of events per number of study patients; c adjusted for sex, age, smoking, diabetes, and systolic BP)

4. When participants were divided into quartiles, those in the top quartiles had stronger association with CV events than those in the bottom quartile. Hazard ratio (**HR**), comparing quartile 4 with quartile 1, was higher for non-HDL-c (1.42) than for LDl-c (1.26) and for Apo-B (1.33)

5. Associations with risk of major cerebrovascular events were not as strong.
6. The strength of the associations did not differ between subgroups including those with and without diabetes and hyper-triglyceridemia**.**
7. HRs for risk of major CV events for 4 patient categories comparing non-HDL-c with LDl-c defined by target levels of 130 mg/dL and 100 mg/dL.

Target		HP
LDL-c	HDL-c	
> 100 mg/dL	> 130	1.21
>100	<130	1.02
<100	>130	1.32
<100	<130	1.00 (Referent)

Compared with those who reached both targets, statin treated patients reaching the non-HDL-c target of < 130, but not the LDL-c target of <100, had a HR of major CV disease of 1.02. Patients reaching the LDL-c target, but not the non-HDL-c target had a HR of 1.32

(Ie, reaching the non-HDL-c target seems much more protective. ED.)

DISCUSSION

1. Among statin-treated patients, non-HDL-c had a stronger association with risk of major CV events than LDL-c and Apo-B.
2. The predictive value of different lipids and Apo-B has been debated for years. A 1980 study suggested that Apo-B levels were more closely associated with presence of coronary atherosclerosis compared with LDL-c and triglycerides. Other studies have had varying results regarding the predictive value of lipids and Apo-B.
3. “Our observation in statin-treated patients extended prior results from large population-based studies showing that non-HDL-c is more strongly associated with risk of future major cardiovascular events than LDL-c.” The study did not find evidence that Apo-B performed better than LDL-c or non-HDL-c.
4. In participating trials, HDL-c was measured according to the protocol of the Centers for Disease Control and Prevention. It is important to recognize this when extrapolating results of this study to clinical practice because many clinical laboratories do not currently use this method to measure HDL-c.

CONCLUSION

Among high-risk, statin-treated patients, levels of LDl-c, Apo-B and non-HDL-c were each associated with risk of future major CV events. The strength of the association was greater for non-HDL-c than for LDL-c and Apo-B.

JAMA March 28, 2012; 1302-09 Original investigation, first author S Matthjus Boekholdt, Academic Medical Center, Amsterdam, Netherlands.

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Dementia and Dependency Relentlessly Continued

3-5 DONEPEZIL AND MEMANTINE FOR MODERATE-TO SEVERE ALZHEIMERS DISEASE

Guidelines advocate cholinesterase inhibitors (eg, donepezil [**D**]) for treatment of Alzheimer disease (**AD**). Some recommend discontinuation when AD becomes severe. The FDA has approved D for treatment of severe AD.

Memantine (**M**) has been reported to be effective in patients with moderate or severe AD.

One study reported that combined therapy (D + M) was more effective than D alone.

There is limited evidence to guide the difficult decision regarding continuation of treatment when AD progresses. Continuing treatment is associated with adverse outcomes including hip fractures and syncope leading to insertion of pacemakers.

This study of AD patients, who were already taking D, asks whether continuation of D-alone, M-alone, M + D, or no drug therapy would be the superior treatment.

STUDY

1. This double-blind, placebo-controlled trial entered 295 community dwelling patients (mean age 77) with moderate to severe AD and followed them for 52 weeks. All had been taking D for between 3 months and 5 years.
2. All had a baseline score between 5 and 13 (mean = 9) on the Mini-Mental State Examination (**MMSE**). Possible scores ranged from 0 to 30, with higher scores indicating better cognitive function. Score of 5 to 9 indicated severe AD; 10 to 13, moderate AD.
3. All also had a baseline caregiver score on The Bristol Activities of Daily Living Scale (**BADLS**) ranges from 0 to 60, with higher scores indicating greater impairment. Mean baseline score was 28.
4. Patients were excluded if they had severe or unstable medical conditions, were receiving

M, or were considered unlikely to adhere to the study regimen.

5. Randomized to: 1) Continuation of D-alone; 2) M; alone; 3) D + M; or 4) No drug therapy. Placebos were added as needed to blind treatments.

RESULTS

1. Completion rates at 52 weeks in the 4 groups were low, ranging from 20 of 72 to 38 of 72.
2. Over one year, mean scores on the MMSE in all 4 groups relentlessly continued to deteriorate from a mean baseline score of 9 and the mean scores on BADLS deteriorated from a mean baseline score of 28

	D-alone	M alone	D + M	No drug	
MMSE from 9 to	5.5	5.0	5.5	3.5	(Worsening)
BADLS from 28 to	35	36	34	41	(Worsening)

Over one year, the mean scores on the MMSE and BADLS continued to worsen, despite drug treatment (*My estimates from their figure 3. Ed.)*

3. The primary outcome measure:

The overall mean differences between drug and no drug across all visits (weeks 6, 18, 30, and 52):

D alone +1.9 points on MMSE; - 3 points on BADLS

M-alone +1.2 points of MMSE; -1.5 points on BADLS

(Both drugs showed better scores compared to no drug treatment, but both drugs were associated with a continuing decline in cognitive function and activities of daily living.)

4. No significant added benefit of D + M over D alone and over M alone. The efficacy of D and M did not differ significantly in the presence or absence of the other.
5. Secondary outcomes: There was no clinically important difference between groups in behavioral and psychological symptoms.
6. Patients who withdrew from the study were more cognitively impaired and had more difficulty with daily living.

DISCUSSION

1. “This double-blind, placebo –controlled trial involving community living patients with moderate or severe Alzheimer’s disease, who were already receiving treatment with a cholinesterase inhibitor, showed that there was modest cognitive and functional benefit of continuing donepezil over the

course of 12 months." *(Benefit was not absolute. There was a small benefit compared with M and no drug. . Ed.)*

2. The difference in scores of the MMSE between those who continued D and those who discontinued D exceeded the prespecified minimum clinically important difference of 1.4 points. The BADLS scores did not show a clinically important difference.
3, M-alone benefited, but the benefit was smaller than the benefit from D-alone.
4. There was no significant benefit from adding M to D.
5. The improvements in cognition and function associated with D and M were small relative to the overall size of the decline in cognition and functional status that was seen in all patients.

CONCLUSION

In patients with moderate or severe Alzheimer's disease, continuing treatment with donepezil was associated with cognitive benefit that exceeded the minimum clinically important difference and with significant functional benefit over the course of 12 months.

ALTERNATIVE CONCLUSION (by the editor of *Practical Pointers*)

In patients with moderate or severe Alzheimer's disease who were already taking D, continued treatment with D over the next year was associated with continuing increases in dementia and dependency, but not as rapidly as in those taking M or no drug.

NEJM March 8 2012; 366: 893-903 Original investigation , first author Robert Howard, Kings College. London. The Donepezil and Memantine in Moderate to Severe Alzheimer Disease (DOMINO) study (Funded by the U.K. Medical Research Council)