

PRACTICAL POINTERS

FOR PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JULY 2006

MEDICAL ILLITERACY “Screening for Literacy May Become the Next Vital Sign”

FDA APPROVES SHINGLES VACCINE

BENEFITS OF EXTRA OLIVE OIL AND NUTS ADDED TO THE MEDITERRANEAN DIET.

NEW GUIDELINES FOR HYPERTENSION FROM THE UK

VARENICLINE A NEW DRUG TO AID SMOKING CESSATION How Effective if Given for 3 Months?

BENEFITS OF MAINTENANCE VARENICLINE Given For 6 Months

STARTING INSULIN THERAPY A Rational Approach

A “POLYPILL” FOR PATIENTS WITH DIABETES.

NEW INJECTABLE DRUGS FOR DIABETES Exenitide and Pramlintide

OUTCOME OF HEART FAILURE WITH “PRESERVED EJECTION FRACTION”

“DIASTOLIC” HEART FAILURE Heart Failure by Any Name is Lethal

ADHERENCE TO A PLACEBO LOWERS MORTALITY The “Healthy Adherer Effect”

TOTAL DAILY ACTIVITY ENERGY EXPENDITURE VS PURPOSEFUL ENERGY EXPENDITURE

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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

Rjames6556@aol.com

This document is divided into two parts

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

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

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

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

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 5 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 2006

Screening For Literacy May Become A New “Vital Sign”.

7-1 ILLITERACY: The Silent Epidemic

A large survey conducted by the National Center for Education Statistics estimated that 14% of adults in the US have “below basic” level of “prose literacy”, defined as the ability to use printed and written information in order to function in society, to achieve one’s goals, and to develop one’s knowledge and potential.

Adults with below basic skills have no more than the most simple literacy skills. They lack ability to read documents such as drug and food labels.

Survey results indicate that more than a third of English-speaking patients, and half of Spanish-speaking patients at US public hospitals have low health literacy.

People with low literacy are more likely to be in poor health, and are more likely to have diabetes, poorly controlled diabetes, and heart failure. They are often ashamed of their problem and are adept at hiding it.

Our vast medical literature presents studies which enter only literate subjects. We in primary care are usually the clinicians who meet non-literate patients.

Our patients may be literate in non-English languages. I believe more primary care clinicians should learn to speak basic Spanish—a beautiful language.

All the applications of modern medicine (advances in dietary and drug therapy) are useless if the patient cannot adhere to a prescribed regimen, whether it be due to lack of understanding, lack of will, lack of social support, or lack of financial means.

A Major Boon for the Elderly

7-2 FDA APPROVES SHINGLES VACCINE

On May 26, 2006; the FDA approved the vaccine (Oka/Merck; *Zostavax*). It is indicated for persons age 60 and over who are not immunocompromised, (about 44 million) and who have not had a history of shingles.

A major study reported the vaccine reduced incidence of shingles of 51%; reduced severity of the disease by 61%, and decreased incidence of post-herpetic neuralgia of 67%.

The company said the vaccine is available now, priced at about \$150. Who will pay? If the CDC advisory Committee on Immunization Practices votes in October on recommendations for whom the vaccine is appropriate, Medicare coverage may follow. Coverage is not available “at this time”.

I will certainly take the vaccine. And advise my wife to take it as well.

The Healthy Diet Is Not A Low Fat Diet, It Is A Selected Fat Diet.

7-3 EFFECTS OF A MEDITERRANEAN-STYLE DIET ON CARDIOVASCULAR RISK FACTORS

Incidence rates of cardiovascular disease (CVD) have marked geographical differences. One factor may be diet. High adherence to the Mediterranean diet (MD) is associated with a reduction in mortality. The diet

may also be associated with a reduced BP and improved lipid profiles.

Olive oil, a rich source of mono-unsaturated fatty acids is a main component of the MD.

Frequent nut intake has been associated with a decrease in rates of CVD.

This study randomized subjects to one of 3 diets:

- 1) Low fat diet: Subjects were advised to reduce intake of all types of fat. They were given a leaflet describing the American Heart Association recommendations. Diet was similar to the DASH diet.
- 2) MD with added olive oil: Participants were given one liter of olive oil to consume each week.
- 3) MD with added nuts: Participants were given sachets of nuts to take 30 g / day.

Compared with the low fat diet, the 2 MDs produced beneficial changes BP, fasting glucose, insulin levels, and lipids. Not much difference between olive oil and nut groups.

The diets (except for olive oil and nut content) were similar to the DASH diet which is associated with lowering of BP. The authors state that if salt were restricted (as in the low sodium DASH diet) BP would likely be lowered still more.

Compared with a low-fat diet (similar to the DASH diet), a MD supplemented with virgin olive oil or nuts had beneficial effects on cardiovascular risk factors.

I would assume that a combination of olive oil and nuts would produce the same benefits, and would be easier to adhere to. Why not consider other mono-unsaturated oils (peanut; canola) beneficial as well? They may be less expensive than olive oil.

For prevention of CVD, the "low-fat" diet is no longer considered the most beneficial. The most beneficial diet is a moderately high mono-unsaturated fat, very low saturated fat; no trans fat diet.

I believe poly-unsaturated fats may be substituted for mono-unsaturated fats and produce similar benefits. Some would add low-salt and low glycemic load to the diet.

The added nut and olive oil diet would likely increase weight over time. If one adopts these diets, energy intake must not be increased. This may be difficult for individual patients.

For patients and physicians who are interested in a detailed description of the MD go to:

www.postgradmed.com/issues/2002_02/curtis.htm Accessed August 28, 2006

Google also presents a variety of information.

7-4 EVOLUTION OF HYPERTENSIVE DISEASE: A Revolution In Guidelines

The National Institute for Health and Clinical Excellence (NICE) of the UK presents these guidelines”

Drug treatment is stratified by age.

A. Older patients:

Step 1: A calcium channel blocker or a thiazide diuretic.

Step 2: ACE* + CCB, or CCB + diuretic

Step 3: ACE + CCB + diuretic

* Angiotensin converting enzyme inhibitor. An angiotensin II blocker may be substituted.

In older patients the two most clinically effective and cost-effective drugs for initial lowering of BP are a calcium-channel blocker and a thiazide-type diuretic. BP in older patients is more resistant to therapy. The need for 2 or more drugs in most people was acknowledged.

B. Younger patients:

Step 1: ACE inhibitor

Step 2: ACE + CCB. or ACE + diuretic

Step 3: ACE + CCB + diuretic

Start with lifestyle changes.

When (at what age) to add drugs is a clinical decision based on the individual. A firm diagnosis of hypertension should be made. Monitoring with a 24-hour machine or repeated self-measurements at home are the most reliable diagnostic methods.

I believe that many patients are treated unnecessarily with drugs, and many more who require treatment do not receive them. I also believe that many patients receive too-high doses of antihypertension drugs. Lower doses can be effective, especially if a combination of drugs is used.

I would not eliminate beta-blockers from the protocol. They are beneficial and inexpensive drugs. Small doses should be used and titrated.

I believe that doses of all drugs should be carefully titrated. (Younger patients have more time to do so.)

Titration can be done in two ways:

1) Start with the usual recommended doses and titrate down according to home measurements of BP.

2) Start with low doses and gradually increase.

Starting with low doses and titrating upward would lead to fewer adverse effects and reduce costs. I would add low doses of a second and a third drug before titrating the first drug up to full doses.

A pill cutter is essential. A home monitor is essential.

The criterion for the drugs used and their doses = what works for the individual. I would add a second and a third drug at low doses rather than increase the dose of the first drug.

Since these drugs are used for a lifetime, expense is a consideration.

NICE can be accessed at www.nice.org.uk Search for clinical guideline 34 hypertension

The appendix pages 44 and 45 present a management flowchart for hypertension and the guideline for choosing drugs for newly diagnosed patients

Six In One Hundred Taking Varenicline Achieved Continuing Abstinence At One Year

7-5 VARENICLINE, A NICOTINE ACETYLCHOLINE RECEPTOR PARTIAL AGONIST, VS SUSTAINED RELEASE BUPROPION AND PLACEBO FOR SMOKING CESSATION.

Varenicline is a non-nicotine high affinity agonist, and simultaneously a partial antagonist, of the nicotine acetylcholine receptor located in the nucleus accumbens. It may be beneficial for smoking cessation. Varenicline acts by 1) stimulating release of sufficient dopamine to reduce craving and withdrawal symptoms which occur after

abrupt cessation of nicotine, while 2) simultaneously acting as a partial antagonist by blocking the binding of nicotine and reducing smoking satisfaction.

This study randomized 1025 smokers to: 1) varenicline 1 mg twice daily, 2) bupropion SR 150 mg twice daily, or 3) placebo. Before randomization, 30% of over 1400 persons screened were excluded because they did not meet inclusion criteria.

Twenty six % of those assigned to varenicline did not complete the 12 week treatment phase; another 18% did not complete the 12 to 52 week phase.

Continuing abstinence at one year:

Varenicline	28% (not statistically different from bupropion)
Bupropion SR	23%
Placebo	14%

Adverse effects included: weight gain, nausea, headache, and insomnia. Four % discontinued due to adverse effects.

The investigators conclude that “Varenicline is an efficacious therapy for smoking cessation.” The hypothesis that a partial nAChR agonist-antagonist would effectively reduce craving and smoking satisfaction was supported.

I calculated the absolute 52-week benefit of varenicline vs placebo. (See the complete abstract) Compared with placebo, an additional 10% of subjects who present to primary care and have no exclusion criteria for varenicline, and remain on varenicline for 52 weeks remain abstinent. Permanent cessation would likely be lower.

I would not underestimate, however, the benefit to society of achieving a one in 10 goal of permanent cessation. The benefit/harm-cost ratio of varenicline cannot be calculated until we have more information on cost and continuing evidence of harms.

We need much more observation: Could varenicline be combined with bupropion or nicotine replacement? Would sequential administration benefit? Could therapy with varenicline be continued for a longer period?

Taking varenicline for 6 months (vs 3 months) led 7 of 100 subjects to remain abstinent at one year

7-6 EFFECT OF MAINTENANCE THERAPY WITH VARENICLINE ON SMOKING CESSATION

The majority of cigarette smokers who achieve abstinence relapse within the first year and require many more attempts before achieving permanent abstinence.

This trial determined whether smokers who remained abstinent after 12 weeks of varenicline therapy would maintain greater continuous abstinence rates at one year if varenicline was continued for another 12 weeks.

	Varenicline given for 6 months	Varenicline given for 3 months
Abstinent at 3 months	100%	100%
Abstinent at 13 weeks	95%	88%
Abstinent at 6 months	70%	50%
Abstinent at 1 year	44%	37%

(Note the increasing relapse rate over the year.)

The benefit of varenicline given for 6 months (vs 3 months) in promoting abstinence at 1 year is 7 out

of 100 (7%).

Of 100 patients taking varenicline for 6 months (vs 3 months), 7 more remained abstinent at one year due to the effect of an additional 3 months of varenicline.

Varenicline is at best a modest help. The success rates in primary care would be more modest. Patients in primary care would be less motivated to abstain than the volunteers screened for the trials in academic centers. They would receive less support and encouragement, and would be more likely to withdraw.

The major problem would remain—how to discourage young persons from starting to smoke.

I applaud drug companies and investigators for maintaining interest in smoking cessation. I hope their efforts will continue.

Varenicline has been approved by the FDA. It will be marketed as Chantix by Pfizer. I expect a flurry of advertisements from the company to the general public. I expect many smokers to request this therapy, relying on a pill to solve their addiction. It takes more than a pill. But, even if few achieve permanent abstinence, achieving abstinence for even one patient is a welcome accomplishment. And helping 7 of 100 patients to achieve abstinence is a major accomplishment.

“It Is Now Easier To Achieve The Recommended HbA1c Goal Of Under 7%”.

7-7 STARTING INSULIN THERAPY: A Rational Approach

This article reviews the pharmacological characteristics of currently available insulin products and suggests initial insulin regimens, especially for type 2 diabetes (**DM-2**). Patients with type 1 diabetes are generally more homogenous in terms of underlying pathophysiologic characteristics than those with DM-2. The review begins by describing the pharmacologic characteristics of some of the most commonly used insulin products.

It describes 3 common blood glucose profiles of patients with DM-2 that represent typical patterns. The authors suggest an initial insulin regimen for each profile that would then be modified according to individual responsiveness. The need for an individualized approach to insulin therapy cannot be overemphasized.

All patients with type 1 diabetes require insulin. Indications for DM-2 include: symptomatic hyperglycemia, failure of oral therapy, pregnancy, acute illness necessitating surgery, cardiovascular surgery, acute myocardial infarction, and admission to intensive care.

I believe insulin should be more frequently used in patients with DM-2 to help achieve recommended HbA1c levels.

This is a helpful guide for primary care clinicians. I will file it for reference. Read the full abstract.

“To Be Taken By All Patients With Diabetes”

7-8 “POLYPILL” FOR PATIENTS WITH DIABETES

“A daily cocktail of inexpensive drugs for individuals with diabetes could save 1.2 million lives, prevent 4.5 million myocardial infarctions, reduce cases of renal failure by 600 000, and result in 1 million fewer cases of

blindness or eye surgeries over the next 30 years.” (Robert A Rizza, president of the American Diabetes Assn. at the June 2006 meeting.) There is a need to overcome “physician inertia” and encourage all clinicians to treat patients with diabetes aggressively.

The “Polypill”, to be taken daily, contains metformin 1000 mg; aspirin 75 mg; a generic statin drug (eg, simvastatin 40 mg); and a generic angiotensin-converting enzyme inhibitor (eg, captopril).

The “Polypill” concept remains alive. It was first proposed by Wald and Law (BMJ 2003; 326: 1419-23 Practical Pointers June 2003)—“A Strategy To Reduce Cardiovascular Risk By More Than 80%”. Their Polypill contains 6 drugs to be taken daily: simvastatin 40 mg; hydrochlorothiazide 12.5 mg; atenolol 25 mg; enalapril 5 mg; folic acid 800 micrograms; and aspirin 75 mg. Patients with established cardiovascular disease, diabetes, and smokers are not the only individuals who might benefit. They also proposed that the pill would be beneficial if taken by all persons over age 55.

The diabetes polypill contains 3 of the cardiovascular polypill components (statin, aspirin, and ACE-inhibitor in addition to metformin).

7-9 NEW INJECTABLE DRUGS FOR DIABETES: Incretin mimetics—Exenatide and Pramlintide

Incretins are natural insulinotropic substances originating in the g.i. tract that are released by meals.

- A. Glucagon-like peptide-1 (GLP-1): Naturally released after a meal. It promotes insulin production, reduces production of glucose, and promotes a feeling of fullness. (The natural half life = less than a minute)
- B. Amylin: A natural hormone that, along with insulin, is produced by the beta cells. It helps slow the flow of sugar from the stomach into the blood and contributes to post prandial glucose control

This abstract from the 2006 PDR outlines actions of two new incretin mimetics which have recently been approved by the FDA.

1) Exenatide (*Byetta*) is a 39 amino acid peptide in which several amino acids of the natural human GLP-1 are replaced by others. It is given twice daily in microgram amounts, reaching peak levels in 2 hours. Blood levels are detectable up to 10 hours. It activates the GLP-1 receptor and, especially when added to metformin or a sulfonylurea, improves glucose control.

2) Pramlintide (*Symilin*) is a synthetic analogue of, and adjunct to, human amylin. Injected s.c. separately with insulin before meals. Approved by FDA in 2005. It is for use in patients who require insulin. It is reported to lower HbA1c slightly and to weight reduction.

“May Become the Most Common Form of Heart Failure.”

7-10 OUTCOME OF HEART FAILURE WITH PRESERVED EJECTION FRACTION.

HF with preserved ejection fraction (**HFwPEF**) is increasingly recognized. It has been attributed to abnormalities of diastolic function, although the exact mechanism is debated. The term “heart failure with preserved ejection fraction” has replaced the older term “diastolic heart failure”.

This study enrolled over 2800 patients (mean age 73) admitted to hospitals from 1999 to 2001. All had a discharge diagnosis of heart failure as defined by the Framingham Study criteria. Ejection fractions (**EF**) had been measured in all patients

Categorized patients into 3 groups:

- 1) EF less than 40% [HF with reduced EF—classical HF. Mean EF = 26%]
- 2) EF 40% to 50% [HF with borderline EF]
- 3) EF over 50% [HF with preserved EF—“diastolic” HF. Mean EF = 62%]

Clinical characteristics:

Presenting symptoms were largely similar between the groups

Patients with HFwPEF were more likely to be older (age 75 vs 72), to be female (66%), to have had hypertension (55% vs 49%) , and atrial fibrillation (32% vs 24%).

Mortality rates between group 1) and group 3) at one year were similar: 26% and 22%. Readmission rates for HF were also similar.

Thirty day mortality rates were also similar between the two groups.

A substantial proportion of patients admitted with heart failure had an ejection fraction over 50%.

Their mortality rate was similar to those with reduced ejection fraction.

The association with hypertension may be due to myocardial hypertrophy which leads to limitation of ventricular filling.

The basic abnormality of congestive heart failure is a reduction in the volume of blood ejected into the general circulation from the left ventricle (stroke volume), not diastolic function. According to PeterLiu, Toronto University (personal communication) there have not been good specific studies documenting stroke volume as related to development of congestive heart failure. We have been locked into the concept of ejection fraction because it is easily determined. One can have a deficit of stroke volume from either decreased proportion being ejected, or decrease filling volume to start with.

What's in A Name? Heart Failure by Any Name Is Just as Deadly

7-11 DIASTOLIC HEART FAILURE—A Common and Lethal Condition

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

Although the AHA has revised the terminology to “heart failure with preserved ejection fraction”, this editorialist still prefers the term “diastolic heart failure” (**DHF**). DHF describes the dominant underlying pathophysiological features, and has connotations familiar to clinicians. Virtually all patients with DHF will show abnormalities in diastolic function and elevated left ventricular filling pressure.

Treatments for DHF are emerging (eg, the use of angiotensin-receptor blockers). Preventive measures have proven efficacy (eg, treatment of hypertension).

Early treatment of hypertension is becoming more urgent in recognition of its role in DHF.

The basic abnormality of congestive heart failure is a reduction in the volume of blood ejected into the general circulation from the left ventricle (stroke volume), not diastolic function. According to Peter Liu, Toronto University (personal communication) there have not been good specific studies documenting stroke volume as related to development of congestive heart failure. We have been locked into the concept of ejection fraction because it is easily determined. One can have a deficit of stroke volume from either decreased proportion being ejected, or decrease filling volume to start with.

7-12 A META-ANALYSIS OF THE ASSOCIATION BETWEEN ADHERENCE TO DRUG THERAPY AND MORTALITY

Poor adherence to therapy is considered a critical barrier to treatment success. Good adherence to a beneficial drug must be associated with good health outcomes. Individual studies have reported that good adherence (even to placebo) is associated with a reduction in risks. “This is contrary to the proposition that placebo has little effect on health outcomes, and has led to the speculation that adherence to drug therapy may act as an identifiable marker for overall healthy behavior, the so called ‘healthy adherer’ effect.”

This study evaluated the relation between adherence to drug therapy, including placebo, and mortality.

A. Deaths overall to drug therapy:

Good adherers 1462 of 31 439 (4.7%)

Poor adherers 1317 of 15 408 (8.5%)

(Good adherence [vs poor adherence] to a beneficial drug therapy resulted in 3.8% reduction in death. Of 1000 patients with good adherence, 38 (one in 26) would have their lives extended merely because of some attribute good adherers possess.)

B. Deaths in the placebo groups--eight studies with a placebo arm (19 633 participants):

Good adherers to placebo 4.3% (584 of 13 429)

Poor adherers to placebo 6.5% (415 of 6204)

(Ie, good adherence to placebo was associated with a reduction in mortality of 2.2%

Of 1000 subjects, some attribute of good adherers prolonged life in 22 (one in 45).

C. Conversely, Good adherence to a therapy which eventually was proven to be *harmful* resulted in an *increased* mortality.

Good adherence may be a marker of overall healthy behavior.

By definition, placebos have no pharmacological effects. They may have profound psychological effects. If one believes in a treatment (which is really a placebo), will outcomes be better than if one does not believe? It depends, I suspect, on the nature of the disease and the power of the practitioner. (Consider the power of the Shaman.) I believe also that patients adhere better if they and the clinician have a good relationship. They also tend to report good effects when they wish to please the practitioner.

Take 1000 patients receiving placebo: 1) 500 adhere conscientiously; 2) 500 do not adhere regularly. Outcomes will be better in 1).

Over Time, Risks Of The Former Smoker Tend To Approach The Risk Of The Never Smoker.

7-13 REVERSAL OF RISK UPON QUITTING SMOKING

In March 2006, 17 scientists from 8 countries met in Lyon, France to assess the evidence on the reversal of health risks after quitting smoking cigarettes. They considered 10 diseases linked to cigarettes.

The group sought evidence to answer 3 questions:

- 1) Is the risk for disease lower in former smokers than in continuing smokers?
- 2) What is the time course of the reduction in risk with continued abstinence?
- 3) Does the risk return to that of never smokers after long periods of abstinence?

The answers:

- 1) Yes
- 2) It may take many years.
- 3) It may or may not, depending on the disease in question. Risks do decline dramatically over 10 to 20 years.

“There are overwhelming health benefits of quitting smoking that accrue with increasing duration of abstinence for most diseases reviewed.” Rarely does the risk for disease decline to that of never smokers, but, with longer and variable periods of abstinence, the risk of the former smoker tends to approach the risk of the never smoker.

“Unequivocally, quitting smoking avoids the further increase in death from cancer, cardiovascular disease, and pulmonary disease caused by continuing smoking.”

The article did not mention any connection between pack-years and risks. Quitting at a younger age will confer two advantages: 1) Fewer pack-years of smoking will likely be associated with a greater reduction in risks.

2) Individuals will live longer to experience the reduction in risks.

The sooner you quit, the better. It may take 15 to 20 years to lower risk to normal. But it is likely to do so.

The Higher the FLAEE, the Lower the Risk Of Death.

7-14 DAILY ACTIVITY ENERGY EXPENDITURE AND MORTALITY AMONG OLDER ADULTS

The most accurate method of determining free-living energy expenditure uses isotopes of ^2H and ^{18}O ($^2\text{H}^{18}\text{O}$ —doubly labeled water). ^2H is eliminated as water, and ^{18}O is eliminated as water and carbon dioxide. The excess disappearance rate of ^{18}O relative to ^2H is a measure of the carbon dioxide production rate, a direct measure of total energy expenditure.

To calculate the “free living activity energy expenditure” (**FLAEE**—the amount an individual expends in any activity per day), the investigators determined resting metabolic rate and calculated the thermic effect of meals, and subtracted these energy expenditures from the total. This objectively determined the FLAEE.

FLAEE captures *any form* of physical activity ranging from purposeful exercise to simple fidgeting. Physical activity questionnaires generally address only the former.

Over a 2-week period, this study determined the FLAEE of over 300 adults (mean age 75) twice over a 2-week period in 1997-98. All were healthy enough to climb stairs and walk, and to perform activities of daily living independently. None had mobility disabilities.

Divided the subjects into 3 categories, depending on their FLAEE:

High > 770 kcal/day

Middle 521 – 770 kcal / day

Low < 521 kcal / day.

Followed subjects for all-cause mortality over a mean of 6 years.

Absolute risk of death was 12% in the highest tertile of FLAEE; 18% in the middle tertile; and 25% in the lowest tertile. For every 287 kcal / day of FLAEE, there was about a 30% lower risk of mortality. This would be attained by performing about 1 ¼ hours of activity per day at a metabolic rate of 3.0—household chores, vacuuming, mopping, washing windows, lawn work, walking at 2.5 MPH, and non-sitting work. In this study, the total self reported activity duration was about 30 to 60 minutes longer on average in the 2nd and 3rd tertiles than in the 1st.

This study, which suggests that *any activity* expenditure in older adults can lower mortality rates, seemingly contradicts reports that exercise needs to be performed at a specific intensity.

“More important, this accumulation is from usual daily activities that expend energy and not necessarily for volitional exercise.” Simply expending energy through any activity may influence survival.

OK, all you senior citizens, keep moving !

ABSTRACTS JULY 2006

Screening For Literacy May Become A New “Vital Sign”.

7-1 ILLITERACY: The Silent Epidemic

A large survey conducted by the National Center for Education Statistics estimated that 14% of adults in the US have “below basic” level of “prose literacy”, defined as the ability to use printed and written information in order to function in society, to achieve one’s goals, and to develop one’s knowledge and potential.

Adults with below basic skills have no more than the most simple literacy skills. They lack ability to read documents such as drug and food labels. They may be able to sign a form, but they cannot use “a television guide to find out what programs are on at a specific time”.

In addition, 22% of adults are estimated to have between low basic “quantitative literacy”. They may be able to sum the numbers on a bank deposit slip, but they cannot compare the ticket prices for two events.

Older adults fared poorest—23% of those over age 64 had below basic prose literacy; 34% had below basic quantitative skills.

Survey results indicate that more than a third of English-speaking patients, and half of Spanish-speaking patients at US public hospitals have low health literacy. Patients with reading problems may avoid outpatient offices and clinics because they are intimidated by paperwork. They may be more likely to use emergency departments for their care. “Emergency rooms are user-friendly if you can’t read because somebody else asks the questions and somebody else fills out the form.”

People with low literacy are more likely to be in poor health, and are more likely to have diabetes, poorly controlled diabetes, and heart failure. They are often ashamed of their problem and are adept at hiding it.

Many physicians and other health care workers remain unaware that their patients may have reading problems. It may be difficult for some physicians to believe the patient cannot read.

One method to assure understanding is the “teach-back” approach—asking the patients to explain what they have been told.

Some authorities suggest that screening for literacy may become a new “vital sign”.

“The health care system does not help physicians who treat low-literacy patients”.

Physicians who recognize their patient’s difficulty in reading may take the opportunity to encourage the patient to enroll in an adult reading program.

NEJM July 27, 2006; 355: “Perspective”, commentary by Erin N Marcus, University of Miami Miller School of Medicine, Miami, FL

A Major Boon for The Elderly

7-2 FDA APPROVES SHINGLES VACCINE

An estimated million persons suffer shingles each year in the US. Most are over age 60. Up to 20% of all older persons will have an episode of shingles at some point in their lives. They suffer most from post-herpetic neuralgia.

On May 26, 2006; the FDA approved the vaccine (Oka/Merck; *Zostavax*). It is indicated for persons age 60 and over who are not immunocompromised, (about 44 million) and who have not had a history of shingles.

Zostavax is a live-attenuated varicella-zoster vaccine. It is given subcutaneously as a single dose. Each dose contains about 14 times the amount of antigen found in the childhood chickenpox vaccine. It differs from most vaccines which are usually given to persons with no prior exposure to an organism in order to prevent infection. *Zostavax* is used after a pathogen (varicella) has infected the body. (*Albeit years prior.*)

A major study ¹ reported the vaccine reduced incidence of shingles of 51%; reduced severity of the disease by 61%, and decreased incidence of post-herpetic neuralgia of 67%.

Additional studies are in progress on long-term safety, and applicability to younger persons.

The company said the vaccine is available now, priced at about \$150. Who will pay? If the CDC advisory Committee on Immunization Practices votes in October on recommendations for whom the vaccine is appropriate, Medicare coverage may follow. Coverage is not available “at this time”.

JAMA July 2006; 296: 157 “Medical News and Perspective”, commentary by Mike Mitka, JAMA staff.

1 NEJM 2005; 353: 2271-84 See *Practical Pointers* June 2005 [6-1]

The Healthy Diet Is Not A Low Fat Diet, It Is A Selected Fat Diet.

7-3 EFFECTS OF A MEDITERRANEAN-STYLE DIET ON CARDIOVASCULAR RISK FACTORS

Incidence rates of cardiovascular disease (CVD) have marked geographical differences. One factor may be diet. High adherence to the Mediterranean diet (MD) is associated with a reduction in mortality. The diet may also be associated with a reduced BP and improved lipid profiles.

Olive oil, a rich source of mono-unsaturated fatty acids is a main component of the MD.

Frequent nut intake has been associated with a decrease in rates of CVD.

This study compared effects of 2 different MDs (one containing added olive oil, and one containing added nuts) vs a low-fat diet on risk factors for CVD.

Conclusion: MDs supplemented with olive oil or nuts had beneficial effects above those of a low fat diet.

STUDY

1. Multicenter primary prevention trial in Spain entered 772 community dwelling subjects (mean age 69).

All subjects had type 2 diabetes, or 3 or more CHD risk factors. (A high risk group). None had a history of CVD.

2. Randomized subjects to one of 3 diets:

- 1) Low fat diet: Subjects were advised to reduce intake of all types of fat. They were given a leaflet describing the American Heart Association recommendations.
- 2) MD with added olive oil: Participants were given one liter of olive oil to consume each week.
- 3) MD with added nuts: Participants were given sachets of nuts (walnuts [2/4], hazelnuts [1/4],

and almonds [1/4]) to take 30 g / day. [Walnuts differ from all other nuts through their high content of polyunsaturated fatty acids, especially alpha linolenic acid (an n-3 plant fatty acid)]. The added nuts increased alpha-linolenic acid by 1 g per day.

3. No energy restrictions were suggested. No mention of intake of wine in the groups.
4. Follow-up for 3 months.

RESULTS

1. The main dietary changes were the large increases in consumption of virgin olive oil and nuts in groups 2) and 3)..
2. Body weight and BMI were slightly reduced in all 3 groups with no between-group differences.
3. Compared with the low fat diet, the 2 MDs produced (mean) beneficial changes in most outcomes: ²

Systolic BP	- 6.5 mm Hg
Diastolic BP	- 2 mm Hg
Fasting glucose	- 20 mg/dL
Fasting insulin	- 20 pmol/L
Total cholesterol	- 6 mg/dL
LDL-cholesterol	- 3 mg/dL
HDL cholesterol	+ 2 mg/dL
Triglycerides	-13 mg/dL

3. Not much difference between olive oil and nut groups.

DISCUSSION

1. The MD is a high fat diet. Large amounts of mono-unsaturated fatty acids (olive oil) are used in Mediterranean cultures.
2. The diets (except for olive oil and nut content) were similar to the DASH diet which is associated with lowering of BP. The authors state that if salt were restricted (as in the low sodium DASH diet) BP would likely be lowered still more.
3. If the MD is useful in primary care cardiovascular prevention, one would expect the diet to show reductions in risk factors. This study provides evidence that it does indeed reduce multiple risk factors.
4. When nutritional advice is given to overweight people, clinicians are reluctant to recommend high mono-unsaturated fat diets as an alternative to low fat diets because of fear of promoting obesity. “Because many participants in our study were obese or had diabetes, our results are reassuring in the lack of weight gain when supplementing ad libitum diets with sizable amounts of unsaturated fats, such as those contained in olive oil and nuts.” (*The trial lasted only 3 months. RTJ*).
5. Diets enriched with virgin olive oil¹ have more beneficial effects on lipids than refined olive oil. The reason is not known.
6. Longer follow-up will be required to determine clinical outcomes.

CONCLUSION

Compared with a low-fat diet (similar to the DASH diet), a MD supplemented with virgin olive oil or nuts had beneficial effects on cardiovascular risk factors.

Annals Int Med July 4, 2006; 145: 1-11 Original investigation by the Prevencion con Dieta Mediterranea (PREDIMED) study, first author Ramon Estruch, Hospital Clinic, Barcelona, Spain.

- 1 “Virgin olive oil” is the first cold-pressed from olives. I do not know what is so special about it.
- 2 Admittedly surrogate outcomes. I believe they are clinically important.

7-4 EVOLUTION OF HYPERTENSIVE DISEASE: *A Revolution In Guidelines*

The UK National Institute for Health and Clinical Excellence (NICE), in collaboration with the British Hypertension Society, has updated recommendations for drug treatment. They recommended 3 important developments in guidelines:

1) Initial selection of drugs according to age:

A. Older patients:

Step 1: A calcium channel blocker or a thiazide diuretic.

Step 2: ACE* + CCB, or CCB + diuretic

Step 3: ACE + CCB + diuretic

* Angiotensin converting enzyme inhibitor. An angiotensin II blocker may be substituted..

In older patients the two most clinically effective and cost-effective drugs for initial lowering of BP are a calcium-channel blocker and a thiazide-type diuretic. BP in older patients is more resistant to therapy. The need for 2 or more drugs in most people was acknowledged.

B. Younger patients:

Step 1: ACE

Step 2: ACE + CCB, or ACE + diuretic

Step 3: ACE + CCB + diuretic

For younger people, NICE concluded that initial therapy with an ACE-inhibitor is more likely to reduce BP than is initial therapy with a calcium blocker or a thiazide. However, structured research evidence for treatment of younger persons with hypertension is a worry.

Heretofore, treatment of hypertension was focused mainly on people over the age of 55 who had established cardiovascular disease. There is an alarming lack of data on the best treatment of hypertension in patients under age 55. Hypertensive injury evolves over decades. The early stages are characterized by modest rises in BP and subtle disturbances in lipid and glucose profiles which progress over the years. Damage to the vascular wall in multiple organs is potentially preventable. It progresses to damage the heart, kidney and brain. Vascular wall damage leads to stiffening of arteries and progressive rise in systolic BP. This makes hypertension more resistant to treatment. The patient's risk, although lowered, is never restored to normal. And will probably require two or more drugs.

Why do we wait so long? Hypertension is easy to identify. Why do we miss the opportunity to prevent the evolution of the disease rather than struggle to treat the consequences? This is because prior guidelines have focused on treatment of older people with established organ damage or concomitant disease. Younger people do not usually have clinical events. Trials are done in patients who do.

The potential to prevent evolution of hypertensive disease and thereby limit treatment to a single drug was recently highlighted. Many might consider this approach preferable to a more complex multidrug treatment later in life.

The disease evolves over the years from prehypertension to hypertension + organ damage, to hypertension + clinical disease. With time, the risk of cardiovascular disease rises, and the number of drugs needed to control BP increases.

2) A reappraisal of the role of beta-blockers

Beta-blockers were relegated as a less suitable *initial* therapy for the routine treatment of hypertension because they are less effective than other drugs at preventing major cardiovascular events, especially stroke. They are more likely to induce development of diabetes (especially if combined with diuretics). They are the least cost-effective.

“Whether this conclusion applies to all beta-blockers, or only to those used in clinical trials of hypertension (mainly atenolol) is unknown. “

3) A formal cost-effectiveness analysis of treatment of hypertension.

The analysis showed that treatment is one of the most cost-effective interventions evaluated in health care.

Lancet July 1, 2006; 368: 6-8 “Comment” by Bryon Williams, University of Leicester School of Medicine, Leicester, UK

Six In One Hundred Taking Varenicline Achieved Continuing Abstinence At One Year

7-5 VARENICLINE, A NICOTINE ACETYLCHOLINE RECEPTOR PARTIAL AGONIST, VS SUSTAINED RELEASE BUPROPION AND PLACEBO FOR SMOKING CESSATION.

Nicotine replacement therapy and bupropion (*Zyban*; Generic) have had important, albeit moderate efficacy.

Recent evidence supports a primary role of a nicotine-acetylcholine receptor (**nAChR**) in reinforcing the effects of nicotine. The dependence-producing effects of nicotine are believed to be mediated by the nAChR located in the nucleus accumbens. When activated, the nAChR releases dopamine, the pleasurable effects of which are linked to maintaining smoking behavior.

Varenicline, a non-nicotine high affinity agonist, and simultaneously a partial antagonist, of the nAChR may be beneficial for smoking cessation. Varenicline acts by 1) stimulating release of sufficient dopamine to reduce craving and withdrawal symptoms which occur after abrupt cessation of nicotine, while 2) simultaneously acting as a partial antagonist by blocking the binding of nicotine and reducing smoking satisfaction.

In animal studies, the agonist effect on dopamine release was 35% to 60% of the maximal response to nicotine.

This study assessed the efficacy and safety of varenicline for smoking cessation compared with placebo and bupropion.

Conclusion: At one year, varenicline was slightly more effective than placebo. Not statistically different from bupropion.

STUDY

1. Randomized, double-blind phase 3 clinical trial conducted at 19 US centers screened over 1400 smokers (mean age 43; mean years of smoking 24; mean number of cigarettes smoked per day = 21). The great majority had made at least one prior attempt to quit. All received brief counseling and were followed periodically throughout the trial.
2. Subjects were generally healthy. Exclusion criteria included a number of physical and psychiatric diseases.
Thirty percent of individuals screened for the study were excluded.
3. After exclusions, 1025 smokers were randomized to: 1) varenicline titrated to 1 mg twice daily, 2) bupropion SR titrated to 150 mg twice daily, or 3) placebo.
4. Subjects were advised to take the first dose on day one, and set the smoking cessation date on day 8. Active therapy lasted 12 weeks, with subsequent 40 weeks of non-drug follow-up.
5. Determined continuous abstinence for weeks 9 through 52 verified by exhaled carbon monoxide.¹

RESULTS (intention to treat):

1. Twenty six % of those randomized to varenicline did not complete the 12 week treatment phase; another 18% did not complete the 12 to 52 week phase. Most of these were lost to follow-up or refused to participate further.
2. Continuous abstinence at one year

Varenicline	22% (not statistically different from bupropion)
Bupropion SR	16%
Placebo	8%
3. Varenicline reduced craving and withdrawal symptoms. It increased appetite more than placebo.
4. Adverse effects of varenicline:
Weight gain from baseline to week 12 = 2.4 kg.
Discontinued due to adverse effects 4%
Nausea 28%; insomnia 14%; headache 15%. These were generally mild to moderate and diminished over time.

DISCUSSION

1. Nicotine dependence is a chronic, relapsing disease. Abstinence rates declined in all three groups after drug treatment ended. The difference between groups diminished at 52 weeks.
2. All subjects received initial counseling and encouragement during careful follow-up. This would not be generally available in primary care.

CONCLUSION

“Varenicline is an efficacious therapy for smoking cessation.”

The hypothesis that a partial nAChR agonist-antagonist would effectively reduce craving and smoking satisfaction was supported.

JAMA July 5, 2006; 296: 47-55 Original investigation by the Varenicline Phase 3 Study Group, first author David Gonzales, Oregon Health and Science University, Portland.

Pfizer funded the study. Varenicline will be marketed as *Chantix*.

1 The investigators set abstinence from week 9 through 12 as the primary outcome. Abstinence for this period is clinically meaningless. The only clinically significant result would be sustained cessation. No data in the study indicated cessation long-term (after one year).

I tried to estimate the applicability and effectiveness of varenicline in primary care based on their data in figure 3 page 51:

1000 patients present with the desire to stop smoking

30% are excluded for physical and psychiatric problems

700 remain. Varenicline is prescribed.

25% of these patients discontinue the 12 week treatment phase

525 remain

18% of these discontinue week 12 to 52 follow-up phase

430 would remain and complete 52 weeks of the study..

Continuing abstinence at 52 weeks, varenicline (12 weeks) compared with placebo (12 weeks):

At the end of one year, 28% of 700 (n = 196) varenicline subjects remained abstinent

At the end of one year, 14% of 700 (n = 98) placebo patients remained abstinent

In absolute terms, 98 of 1000 (10%) patients achieved continuing abstinence at 1 year due to the effect of varenicline.

A similar multicenter trial by an entirely different group of investigators was published in this issue of JAMA (pp 56-63), first author Douglas E Jorenby, University of Wisconsin School of Medicine, Madison. Results were almost identical.

In addition, two studies (by many of the same investigators) comparing varenicline to placebo in the August 14/28 issue of Archives Internal Medicine reported similar outcomes

Taking varenicline for 6 months (vs 3 months) led 7 of 100 subjects to remain abstinent at one year

7-6 EFFECT OF MAINTENANCE THERAPY WITH VARENICLINE ON SMOKING CESSATION

The majority of cigarette smokers who achieve abstinence relapse within the first year and require many more attempts before achieving permanent abstinence.

This trial determined whether smokers who remained abstinent after 12 weeks of varenicline therapy would maintain greater continuous abstinence rates at one year if varenicline was continued for another 12 weeks.

Conclusion: Seven of 100 subjects taking varenicline for 6 months (vs 3 months) achieved abstinence due to the effect of varenicline.

STUDY

1. Multicountry trial screened over 2400 smokers to determine suitability for varenicline therapy. Of these, about 500 were excluded mainly because they did not meet inclusion criteria. 1928 were assigned to receive open-label varenicline for 12 weeks.
2. Of these, 1210 achieved abstinence at the end of 12 weeks, and were entered into the trial.
3. Randomized (double-blind) to: 1) continued varenicline for a second 12 weeks, or 2) placebo.
4. The trial continued, lasting from week 24 to week 52 during which no subject received treatment.

RESULTS

1.	Varenicline given for 6 months	Varenicline given for 3 months
Abstinent at 3 months	100%	100%
Abstinent at 13 weeks	95%	88%
Abstinent at 6 months	70%	50%
Abstinent at 1 year	44%	37%

(Note the increasing relapse rate over the year.)

2. Benefit of varenicline given for 6 months (vs 3 months) in promoting abstinence at 1 year was 7 out of 100 (7%).
3. The number needed to treat for 24 weeks to achieve abstinence for a total of 52 weeks was 14.
4. The median time to the first relapse after randomization was 198 days for varenicline vs 87 days for placebo.
5. Adverse events were similar to the preceding trial.

DISCUSSION

1. Smokers who were abstinent after 12 weeks of open treatment with varenicline, and then received another 12 weeks of blinded treatment with varenicline vs placebo experienced a reduced rate of relapse over a subsequent 9 months.
2. "Varenicline may be an efficacious, safe, and well tolerated agent for maintaining abstinence for smoking."

CONCLUSION

Smokers who achieved abstinence after 12 weeks of varenicline therapy and subsequently received a second 12 weeks of therapy had greater abstinence rates over 1 year than those receiving placebo over a second 12 weeks.

JAMA July 5, 2006; 296: 64-71 Original investigation, by the Varenicline Phase 3 Study Group, first author Serena Tonstad, Ulleval University Hospital, Oslo, Norway

“It Is Now Easier To Achieve The Recommended Hba1c Goal Of Under 7%”.

7-7 STARTING INSULIN THERAPY: A Rational Approach

The emergence of new insulin products has provided opportunities to achieve better diabetes control.

This article reviews the pharmacological characteristics of currently available insulin products and suggests initial insulin regimens, especially for type 2 diabetes (**DM-2**). Patients with type 1 diabetes are generally more homogenous in terms of underlying pathophysiologic characteristics than those with DM-2.

This review describes 3 common blood glucose profiles of patients with DM--2 that represent typical patterns. The authors suggest initial insulin regimens for each profile that would then be modified according to individual responsiveness. The need for an individualized approach to insulin therapy cannot be overemphasized.

The review begins by describing the pharmacologic characteristics of some of the most commonly used insulin products. (*I selected individual examples to be brief. Consult the original for the entire list. RTJ*)

The advent of recombinant DNA technology made it possible to improve the time-action profile of regular insulin. Human insulin analogues have less variability of action than the older human insulin. But, a clinically significant variability between individual patients remains.

- A. Insulin lispro (*Humalog*, Eli Lilly) is rapidly absorbed after sc administration < 30 minutes; peaks at 1 hour; has a short duration of action (3 to 4 hours). Individual variability is less than with regular human insulin. It should be injected 5 to 15 minutes before meals. It can be administered after meals without excessive deterioration of glycemic control.
- B. Neutral protamine Hagedorn (NPH) has a delayed onset of action (2 to 4 hours) Reaches peaks at 6 to 7 hours, and lasts up to 20 hours. When used as basal insulin, the peak and trough effect requires 2 or more injections to minimize excursions of insulin levels.
- C. Insulin glargine is a long acting analogue, with onset of action at 2 hours, reaches a peak at 4 to 6 hours, and lasts up to 24 hours. The time of day of the injection is minimally important as long as it is administered at the same time each day. Glargine has a more stable, less variable pharmacokinetic profile than NPH. Compared with bedtime NPH, it is associated with less nocturnal hypoglycemia.
- D. Insulin detemir is another long-acting basal analog with a unique mechanism of action (*See text*). Detemir is administered twice daily in most patients.
- E. . Mixtures (insulin analogues):
 - 1) 75/25 Humalog (75% neutral protamine lispro [NPL] + 25% lispro)
 - 2) 50/50 Humalog (50% neutral protamine lispro [NPL] + 50% lispro)These premixed human insulins have an onset of about 15 minutes, and peak at 1 to 4 hours, and last up to 24 hours.

Choosing the insulin preparation:

All patients with type 1 diabetes require insulin. Indications for DM-2 include: symptomatic hyperglycemia, failure of oral therapy, pregnancy, acute illness necessitating surgery, cardiovascular surgery, acute myocardial infarction, and admission to intensive care.

The authors present common profiles of blood glucose levels who are not candidates for, or who have had treatment failure with oral agents. (*I simplified the suggested regimens for simplicity and clarity, and present their first choice only. RTJ*)

Profile 1: fasting and postprandial hyperglycemia:

	Recommended initial insulin
Type 1	Glargine + premeal rapid acting (eg, lispro)
Type 2 with insulinopenia	NPH twice daily
Gestational diabetes	NPH twice daily + premeal regular human insulin.

Profile 2: fasting hyperglycemia and daytime euglycemia. .DM-2 with large supper and bedtime snacking, active during daytime,

Insulin NPH or insulin Demeter at bedtime

Profile 3: postprandial hyperglycemia and fasting euglycemia. DM- 2 with partial failure of oral agents:

NPH or Demeter in the morning. *

Profile 4: Gestational diabetes with postprandial hyperglycemia and fasting euglycemia

NPH in the morning and premeal regular human insulin.

(All recommendations except * are evidence-based; * is based on expert opinion.)

Adding insulin to oral agents: In patients with type 2, intermediate or long-acting insulin may be added to oral agents to control fasting blood glucose. In general, a starting dose of 10 to 15 units of glargine at bedtime is appropriate. Increase by 1 to 2 units for every 20 mg/dL of fasting blood glucose over 100 mg/dL

The authors present helpful tables (pp 130 and 131) recommending titration schedules for basal and preprandial insulin doses and for premixed insulins, depending on blood glucose levels.

As inhaled insulin becomes generally available, persons with predominantly postprandial hyperglycemia may benefit from its convenience.

Monitoring glucose control in insulin-treated patients includes daily self-monitoring and periodic determinations of glycated hemoglobin (HbA1c). At initiation, 4 determinations daily (before meals and bedtime) are generally recommended.

“Prescribing insulin is a dynamic process, and the patients should be prepared to adjust the regimen as additional information about blood glucose becomes available.” It is now easier to achieve the recommended HbA1c goal of under 7%.

Annals Int Med July 18, 2006; 145: 125-34 “Narrative Review”, first author Arshag D Mooradian, St. Louis University School of Medicine, St. Louis MO.

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“To Be Taken By All Patients With Diabetes”

7-8 “POLYPILL” FOR PATIENTS WITH DIABETES

“A daily cocktail of inexpensive drugs for individuals with diabetes could save 1.2 million lives, prevent 4.5 million myocardial infarctions, reduce cases of renal failure by 600 000, and result in 1 million fewer cases of blindness or eye surgeries over the next 30 years.” (Robert A Rizza, president of the American Diabetes Assn. at the June 2006 meeting.) There is a need to overcome “physician inertia” and encourage all clinicians to treat patients with diabetes aggressively.

The “Polypill”, to be taken daily, contains metformin 1000 mg; aspirin 75 mg; a generic statin drug (eg, simvastatin 40 mg); and a generic angiotensin-converting enzyme inhibitor (eg captopril). [Of course, smoking would be prohibited.] The aim is to reduce HbA1c to under 7%; and to reduce the BMI to under 25.

Even if the BMI goal were not reached, such a program could still reduce millions of complications of diabetes.

“Such a pill would cost about \$100 per year and could reduce total serious diabetes complications by 23%.” Reduction in medical costs would be considerable.

The article reports other issues considered at the meeting: continuous glucose monitoring, diabetes and depression, bariatric surgery, and genetic aspects of diabetes.

JAMA July 26, 2006; 296: 377-80 “Medical News and Perspectives” by Bridget M Kuehn, JAMA Staff.

7-9 NEW INJECTABLE DRUGS FOR DIABETES: Incretin mimetics—exenatide and Pramlintide.

A definition of terms:

- 1) Incretin: Generic term for all natural insulinotropic substances originating in the g.i. tract that are released by meals.
 - A. Glucagon-like peptide-1 (GLP-1): Naturally released after a meal. It promotes insulin production, reduces production of glucose, and promotes a feeling of fullness. (The natural half life = less than a minute)
 - B. Amylin: A natural hormone that, along with insulin, is produced by the beta cells. It helps slow the flow of sugar from the stomach into the blood and contributes to post prandial glucose control.

(To add to the confusion, the pharmaceutical company producing incretin-like drugs is named Amylin pharmaceuticals.)

- 2) Incretin mimetic: a drug that mimics the action of incretin. Exenatide and pramlintide are examples.

Exenatide (*Byetta*; Amylin pharmaceuticals and Lilly):

Byetta is a 39 amino acid peptide in which several amino acids of the natural human GLP-1 are replaced by others. It is given twice daily in microgram amounts, reaching peak levels in 2 hours. Blood levels are detectable up to 10 hours. It is cleared by the kidney. Severe kidney disease is a contraindication. It should not be used in type 1 diabetes. Approved by FDA in 2005. Now being heavily advertised.

Actions:

- A. It activates the GLP-1 receptor and mimics its action. It restores the first phase insulin response.
(Normally, a robust insulin response occurs during the first minute following iv glucose administration. This response is lost in patients with type 2 diabetes. It also increases second phase insulin response—10 minutes to 2 hours after a glucose load.
- B. Improves glycemic control in type 2 diabetes. Decreases fasting and p.c. blood glucose.
- C. Increases insulin secretion by beta-cells, but only in the presence of an elevated blood glucose. Its action subsides as blood glucose level falls.
- D. Decreases inappropriately elevated glucagon secretion.
- E. Slows gastric emptying. Food intake may be reduced.

Clinical studies:

A 30 week study of patients with type 2 who were inadequately controlled by metformin, a sulfonylurea, or both. When *Byetta* was added:

HbA1c was reduced by 0.5% to 0.9%

30% to 40% achieved HbA1c under 7%

Hypoglycemia

With metformin 5% (no more than placebo)

With sulfonylurea 14% to 36%

Fasting blood glucose - 8 mg/dL

2-h blood glucose -63 to -71mg/dL

Weight - 1.6 to 2.8 kg

Nausea 40%

(Weight loss and lack of hypoglycemia are pluses when exenatide was added to metformin.)

Pramlintide (Symilin; Amylin pharmaceuticals)

A synthetic analogue of, and adjunct to, human amylin. Injected s.c. separately with insulin before meals. Approved by FDA in 2005.

For use in diabetic patients requiring insulin. May reduce amount of insulin needed.

Slows gastric emptying. Moderates appetite.

Suppresses glucagon secretion.

Given alone, does not produce hypoglycemia. Increases risk of insulin-induced severe hypoglycemia

Clinical studies:

HbA1c reduced by -0.4%; weight reduced by 1.7 kg.

Nausea common

Data abstracted from PDR 2006 by the editor of *Practical Pointers for Primary Care*

I was led to this abstract by an article in Medical News and Perspectives, JAMA July 26, 2006; 296: 380 by Bridget M Kuehn "New Diabetes Drugs Target Gut Hormones"

“May Become the Most Common Form of Heart Failure.”

7-10 OUTCOME OF HEART FAILURE WITH PRESERVED EJECTION FRACTION.

Heart failure (HF) has classically been considered to be a clinical syndrome associated with cardiac dilatation and impaired cardiac contractility.

HF with preserved ejection fraction (HFwPEF) is increasingly recognized. It has been attributed to abnormalities of diastolic function, although the exact mechanism is debated. The term “heart failure with preserved ejection fraction” has replaced the older term “diastolic heart failure”.

This population-based study evaluated the epidemiological features and outcomes of patients with HFwPEF
Conclusion: HFwPEF is common and prognosis is just as bad as HF with low ejection fraction.

STUDY

1. Enrolled over 2800 patients (mean age 73) admitted to hospitals from 1999 to 2001. All had a discharge diagnosis of heart failure as defined by the Framingham Study criteria. Ejection fractions (EF) had been measured in all patients by echo, left ventricular angiography, or radionuclide angiography. None had severe valvular disease.
2. Categorized patients into 3 groups:
 - 1) EF less than 40% [HF with reduced EF—classical HF. Mean EF = 26%]
 - 2) EF 40% to 50% [HF with borderline EF]
 - 3) EF over 50% [HF with preserved EF—“diastolic” HF. Mean EF = 62%]
3. Only groups 1) and 3) were studied in detail in order to more clearly define two distinct groups.
4. Main outcome measures = death within 1 year, and readmission to hospital for HF.

RESULTS

1. Numbers of patients:

Group 1) 1570 (56%)

Group 2) 352 (13%)

Group 3) 880 (31%)

(Ie, about 1/3 had HFwPEF)

2. Clinical characteristics:

Presenting symptoms were largely similar between the groups

Patients with HFwPEF were more likely to be older (age 75 vs 72), to be female (66%), to have had hypertension (55% vs 49%) , and atrial fibrillation (32% vs 24%).

They had lower rates of other modifiable risk factors: smoking, diabetes, hyperlipidemia, peripheral arterial disease, angina, and prior myocardial infarction.

Mortality rates between group 1) and group 3) at one year were similar: 26% and 22%. Readmission rates for HF were also similar.

DISCUSSION

1. “We found that about one third of patients admitted with heart failure in whom left ventricular function was measured had an ejection fraction of more than 50 percent.”
2. These patients were more likely to be women, were older, and were more likely to have a history of hypertension.
3. Those with a reduced ejection fraction had higher rates of diabetes, coronary artery disease, and hyperlipidemia. This is in keeping with the concept that myocardial infarction or ischemia constitutes a major cause of heart failure associated with a low ejection fraction.
4. The subtle differences in physical examination and presenting symptoms were not helpful in distinguishing between groups. Imaging methods are the mainstay for distinguishing.
5. Thirty day mortality rates were also similar between the two groups.

CONCLUSION

A substantial proportion of patients admitted with heart failure had an ejection fraction over 50%. Their mortality rate was similar to those with reduced ejection fraction.

NEJM July 20, 2006; 355: 260-69 Original investigation, first author R Sacha Bhatia, University of Toronto, Canada.

1 I found a helpful web site www.medicalcriteria.com/azindex.htm. It lists criteria for a long list of medical conditions ranging from agoraphobia to Zollinger-Ellison. The Framingham Criteria for Congestive Heart Failure are included.

A similar natural history study of heart failure over 15 years appeared in this issue of NEJM (pp 251-59), first author Theophilus E Owan, Mayo Clinic, Rochester, MN. Their findings were similar to the preceding study:

53% had a reduced EF: 47% had a preserved EF.

The prevalence of recognized HFwPEF increased over time likely due to improved methods of measuring ejection fractions.

Patients with preserved EF were more likely to be older, female, obese, and to have hypertension and atrial fibrillation.

Survival trends were similar when preserved EF was defined as greater than 60%, and reduced EF as less than 40%. (Only about 1/3 in each group survived 5 years)

The study concerned only patients with HF who were at an advanced stage and sick enough to be admitted to the hospital. The natural history of patients with lesser severity was not studied.

“No agents have been proven to improve survival among patients with preserved ejection fraction. Thus it is not unexpected that survival among patients with preserved ejection fraction did not change significantly over the study period.”

“Heart failure with preserved ejection fraction may become the most common form of heart failure.”

What's in A Name? Heart Failure by Any Name Is Just as Deadly

7-11 DIASTOLIC HEART FAILURE—A Common and Lethal Condition

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

Although the AHA has revised the terminology to “heart failure with preserved ejection fraction”, this editorialist still prefers the term “diastolic heart failure” (**DHF**). DHF describes the dominant underlying pathophysiological features, and has connotations familiar to clinicians. Virtually all patients with DHF will show abnormalities in diastolic function and elevated left ventricular filling pressure. In DHF, congestive symptoms are more closely related to the filling (diastolic) properties of the ventricle than to the ejection (systolic) properties.

New data challenge the widely held perception that the survival rate among patients with most forms of heart failure is inversely related to the ejection fraction.

The ejection fraction in patients with DHF does not appreciably change between hospital admission and discharge, despite dramatic changes in patients’ clinical status.

The clinical recognition of DHF has increased over time. This may be due to the increasing age of patients with HF, but also due to increasing awareness. The term “diastolic heart failure” (and related terms) in the literature now appears twenty times more commonly than 20 years ago. The growing availability of echocardiography probably increases the likelihood that patients with dyspnea will be diagnosed as having DHF.

We are facing a lethal condition regardless of its name. About 25% of patients with DHF will die within one year. 2/3 die within 5 years. There has been little improvement in survival rate, in contrast with the improvements in patients with systolic HF.

Treatments for DHF are emerging (eg, the use of angiotensin-receptor blockers). Preventive measures have proven efficacy (eg, treatment of hypertension).

NEJM July 20, 2006; 355: 308-10 Editorial by Gerard P Aurigemma, University of Massachusetts Medical School, Worcester.

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7-12 A META-ANALYSIS OF THE ASSOCIATION BETWEEN ADHERENCE TO DRUG THERAPY AND MORTALITY

Poor adherence to therapy is considered a critical barrier to treatment success. Good adherence to a beneficial drug must be associated with good health outcomes. Individual studies have reported that good adherence (even to placebo) is associated with lower risk. “This is contrary to the proposition that placebo has little effect on health outcomes, and has led to the speculation that adherence to drug therapy may act as an identifiable marker for overall healthy behavior, the so called ‘healthy adherer’ effect.”

This study evaluated the relation between adherence to drug therapy, including placebo, and mortality.

Conclusion: Good adherence (including adherence to placebo) was associated with positive health outcomes. The “healthy adherer” effect may be a surrogate marker for overall healthy behavior.

STUDY

1. Systematic review selected 21 studies (over 46 000 participants) to include in a meta-analysis. Eight studies were randomized, placebo-controlled (n= 19 633). Thirteen were cohort studies.
2. All studies described the method used to measure adherence, provided a clear definition for good adherence and poor adherence, and reported mortality according to adherence groups.

RESULTS

1. Deaths overall to drug therapy:

Good adherers 1462 of 31 439 (4.7%)

Poor adherers 1317 of 15 408 (8.5%) (*I could find no mean time-frame of treatments. RTJ*)

Good adherence [vs poor adherence] to a beneficial drug therapy resulted in 3.8% reduction in death.

Of 1000 patients with good adherence, 38 (one in 26) would have their lives extended merely because of some attribute good adherers possess.)

2. Deaths in the placebo groups--eight studies with a placebo arm (19 633 participants):

Good adherers to placebo 4.3% (584 of 13 429)

Poor adherers to placebo 6.5% (415 of 6204)

(Ie, good adherence to placebo was associated with a reduction in mortality of 2.2%

Of 1000 subjects, some attribute of good adherers prolonged life in 22—one in 45.

3. In two trials the study drug actually was proven to be harmful. Good adherers to the harmful drug had a 7.5% death rate; poor adherers a 3.2% death rate. (Ie, in this case, being a poor adherer actually saved lives.)

DISCUSSION

1. There was a consistent association between participants with good adherence to a beneficial drug and lower mortality.
2. There was also a consistent relation between participants with good adherence to a placebo and lower mortality.
3. Conversely, good adherence to a *harmful* drug *increased* mortality. Poor adherence was protective.
4. “Our observation suggests that stratification by adherence groups may facilitate earlier detection of harmful therapies if the rate of adverse events is higher in participants with good adherence.”
5. Persons with good adherence (even placebo) may also have healthier behaviors—the “healthy adherer” effect. Good adherence is a marker of overall healthy behavior.

CONCLUSION

Good adherence (vs poor adherence) to a placebo and to a drug regimen is associated with decreased mortality. The “healthy user” effect.

Over Time, Risks Of The Former Smoker Tend To Approach The Risk Of The Never Smoker.

7-13 REVERSAL OF RISK UPON QUITTING SMOKING

In March 2006, 17 scientists from 8 countries met in Lyon, France to assess the evidence on the reversal of health risks after quitting smoking cigarettes. They considered 10 diseases linked to cigarettes.

The group sought evidence to answer 3 questions:

- 1) Is the risk for disease lower in former smokers than in continuing smokers?
- 2) What is the time course of the reduction in risk with continued abstinence?
- 3) Does the risk return to that of never smokers after long periods of abstinence?

A. Lung cancer:

In 5 to 9 years after cessation, a lower risk for LC becomes evident, and then risk decreases progressively.

However, there is a persistent increased risk for LC in former smokers compared with never smokers even after long duration of abstinence.

B. Laryngeal cancer:

Risk decreases rapidly with time since stopping. In 10 years, risk is reduced by about 60%. However, former smokers continue to have higher risks as compared with never smokers.

C. Oral and pharyngeal cancers:

Relative risk declines with increasing duration of cessation. Risk reaches the level of never smokers after 20 years.

D. Squamous-cell cancer of the esophagus and stomach, pancreatic, renal cell, cervical, and bladder cancers:

Risk is lowered as time of cessation increases. It still takes decades to approach that of never smokers.

E. Coronary heart disease:

Former smokers have substantially lower risk than continuing smokers. Risk decreases by about 35% in 2 to 4 years. Risk may reach that of never smokers after 10 to 15 years.

F. Cerebrovascular disease:

There is a marked reduction in risk after 2 to 5 years. Some studies report the risk returns to that of never smokers after 15 years.

G. Abdominal aortic aneurysm:

Former smokers have a lower risk than continuing smokers. The scarce data suggest that cessation is associated with a slow decline in risk over 20 years.

H. Peripheral arterial disease;

Relative risk remains greater even after 20 years.

I. COPD:

FEV-1 may increase after one year of cessation. In the following years, the rate of decline in FEV-1 is about half that of continuing smokers. Cohort studies show that the accelerated decline in FEV-1 in current smokers reverts to the age-related rate of decline seen in never smokers within 5 years.

J. Chronic bronchitis:

Symptoms decrease rapidly within a few months after cessation. Prevalence is similar to that of never smokers within 5 years.

“There are overwhelming health benefits of quitting smoking that accrue with increasing duration of abstinence for most diseases reviewed..” Rarely does the risk for disease decline to that of never smokers, but, with longer and variable periods of abstinence, the risk of the former smoker tends to approach the risk of the never smoker.

“Unequivocally, quitting smoking avoids the further increase in death from cancer, cardiovascular disease, and pulmonary disease caused by continuing smoking.”

Lancet July 29, 2006; 368: 348-49 “Comment” first author Carolyn M Dresler, International Agency for Research on Cancer, Lyon, France.

The Higher the FLAEE, the Lower the Risk Of Death.

7-14 DAILY ACTIVITY ENERGY EXPENDITURE AND MORTALITY AMONG OLDER ADULTS

Observational studies suggest that older adults who report moderate or high physical activity are at lower risk of death than those who report low levels of activity. These studies were based on questionnaire assessments, and are subject to recall bias, typically overestimating actual amounts of physical activity.

The most accurate method of determining free-living energy expenditure uses isotopes of ^2H and ^{18}O ($^2\text{H}^{18}\text{O}$ —doubly labeled water). ^2H is eliminated as water, and ^{18}O is eliminated as water and carbon dioxide. The excess disappearance rate of ^{18}O relative to ^2H is a measure of the carbon dioxide production rate, a direct measure of total energy expenditure.

To calculate the “free living activity energy expenditure” (**FLAEE**—the amount an individual expends in any activity per day), the investigators determined resting metabolic rate and calculated the thermic effect of meals, and subtracted these energy expenditures from the total. This objectively determined the FLAEE.

FLAEE captures *any form* of physical activity ranging from purposeful exercise to simple fidgeting. Physical activity questionnaires generally address only the former.

Conclusion: The higher the FLAEE, the lower the risk of death.

STUDY

1. Over a 2-week period, determined the FLAEE of over 300 adults (mean age 75). All were healthy enough to climb stairs and walk, and to perform activities of daily living independently. None had mobility disabilities.
2. Determined the FLAEE twice over a 2-week period in 1997-98.
3. Divided the subjects into 3 categories, depending on their FLAEE:

High	> 770 kcal/day
Middle	521 – 770 kcal / day
Low	< 521 kcal / day.
4. Followed subjects for all-cause mortality over a mean of 6 years.

RESULTS

1. Eighteen % (n = 55) died over 6 years.

2. As a continuous risk factor, a standard deviation of one FLAEE (287 kcal / day) was associated with a 32% lower risk of mortality after multiple adjustments for other risk factors.
3. Absolute risk of death was 12% in the highest tertile of FLAEE; 18% in the middle tertile; and 25% in the lowest tertile.
4. Self-reported high intensity exercise, volunteering, and caregiving did not differ significantly between groups. However, participants reporting higher FLAEE were more likely to report climbing stairs and working for pay. They self-reported longer duration of activity, and expended a greater number of kilocalories in total activity.

DISCUSSION

1. Higher FLAEE demonstrated a strong association with lower risk of death among older adults.
2. The major strength of the study was the direct measurement of both total energy expenditure and resting metabolic rate, giving an objective evaluation of FLAEE. (Biases occur with self-reported physical activity questionnaires.)
3. Previous studies which shaped our understanding of the relation between physical activity and longevity have typically quantified activity such as walking, vigorous exercise, or regularity of activity. This ignores a large component of energy expended during usual daily activities.
4. This study, which suggests that *any activity* expenditure in older adults can lower mortality rates, seemingly contradicts reports that exercise needs to be performed at a specific intensity.
5. For every 287 kcal / day of FLAEE, there was about a 30% lower risk of mortality. This would be attained by performing about 1 ¼ hours of activity per day at a metabolic rate of 3.0—household chores, vacuuming, mopping, washing windows, lawn work, walking at 2.5 MPH, and non-sitting work. In this study, the total self reported activity duration was about 30 to 60 minutes longer on average in the 2nd and 3rd tertiles than in the 1st.
6. “More important, this accumulation is from usual daily activities that expend energy and not necessarily for volitional exercise.”
7. Higher levels of physical activity are associated with reductions in coronary heart disease, cancer, falls, and physical disability.
8. FLAEE is influenced by bodyweight, age, and sleep duration.
9. Previous self-reported measurements may have underestimated the benefits of higher levels of physical activity in older adults.

CONCLUSION

Objectively measured FLAEE was strongly associated with lower risk of mortality in healthy older adults. Simply expending energy through any activity may influence survival.

JAMA July 12, 2006; 296: 171-79 Original investigation, first author Todd M Manini, National Institute of Aging, Bethesda MD.
