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This document is divided into two parts

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

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

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

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

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

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* NOVEMBER 2009

"All Screening Programs Do Harm. Some Do Good As Well."

11-1 EFFECTS OF MAMMOGRAPHY SCREENING UNDER DIFFERENT SCREENING SCHEDULES: Model Estimates of Potential Benefits and Harms.

This study was based on 6 models of breast cancer (**BC**) incidence and mortality in the U.S. These models were ideally suited for estimating the effect of screening under a variety of policies, and for facilitating comparisons of strategies. The models were developed independently\y by prestigious Medical Schools and Universities, and Cancer centers.

They predicted a cumulative probability of BC mortality developing over a woman's lifetime, starting at age 40 vs starting at age 50

They also predicted probability of death from BC from annual screening vs biennial screening (every 2 years).

Without screening, the median probability of dying from BC after age 40 is 3%. If a particular screening strategy leads to a 10% reduction in BC mortality, then the probability of BC mortality would be reduced to 2.7%, or 3 deaths prevented per 1000 women screened. [10% X 3 = 0.3%; 3% - 0.3% = 2.7%]

A. Comparison of different STARTING ages:

1) Starting at age 40 averted 6.2 cancer deaths per 1000 screened.
2) Starting at age 50 averted 5.4 cancer deaths per 1000 screened.
3) One additional life saved per 1000 screened at the expense of 470 false positives and recalls, 33 unnecessary biopsies, and an additional 4000 mammograms

B. Comparison of ANNUAL screening vs screening every 2 YEARS:

1) Screening every year from age 40 to age 69 resulted in a reduction of cancer mortality of 8.3 per 1000 screened
2) Screening every 2 years from age 40 to age 69 resulted in a reduction in cancer mortality of 6.2 pre 1000 screened.
3) A difference of 2 lives saved per 1000 screened.
4) This advantage was at the expense of 1000 false positives and recalls, 70 unnecessary biopsies, and 14 000 more mammograms.

C. Comparison of different STOPPING ages:

1) Screening every 2 years from age 50 and stopping at age 69 averted 5 deaths for every 1000 screened.
2) Screening every 2 years from age 50 and stopping at age 79 averted 9 deaths for every

1000 screened.

3) Four additional deaths per 1000 screened were averted by extending screening to age 79 at the expense of 230 false positives and call backs, 16 unnecessary biopsies, and 3000 mammograms.

"The conclusion of this modeling analysis is that biennial intervals are more efficient and provide a better balance between benefits and harms than annual intervals."

Substantial increases in false-positive results and unnecessary biopsies were associated with annual intervals. These harms are reduced by almost 50% with biennial intervals.

Slow-growing tumors are much more common than fast-growing tumors. The ratio of slow- to fast-growing tumors increases with age, so little survival benefit is lost between screening every 2 years vs every year.

Screening strategies that include an upper age limit beyond age 69 remain efficient albeit with low incremental gains over strategies that stop at earlier ages, and with greater harms.

These models provide estimates of the average benefits and harms expected across a cohort of women. They do not reflect personal data for individuals.

The models do not capture differences in outcomes among certain subgroups such as women with BC genetic susceptibility, women who are sicker or healthier than average, or black women.

The models do not capture the morbidity associated with surgery for screen-detected disease or decrements in quality of life associated with false positive results, living with earlier knowledge of cancer diagnosis and overdiagnosis.

The study did not include costs.

Conclusion: Starting mammography screening at age 50 instead of age 40, and every 2 years instead of every year achieves most of the benefits with much less harm. Decisions about the best strategy depend on individual objectives, and the weight placed on harms, benefits, and resource considerations.

To put this into perspective helping women to choose, I believe we can inform them that the best scientific knowledge indicates:

By choosing to start screening mammography at age 50 instead of age 40, you will increase risk of death from BC by 1 in 1000. This will be at the expense of 4 additional mammograms, and 470 chances in 1000 of a false positive and call-back, and 33 chances in 1000 of receiving a biopsy.

By choosing screening every 2 years instead of every year, you will increase your chances of dying from BC by 2 in 1000. This will reduce the number of mammograms and false positives by about half, and decrease the number of biopsies.

By extending screening from age 69 to age 79, you will reduce the chances of death from BC by 4 in 1000 screened. This will be at the expense of 5 extra mammograms, increasing the chance of false positives by at least 2 in 10, and increasing the number of unnecessary biopsies.

The study did not address monetary costs.

"Thus, The Recommendation Against Routine Screening At Ages 40-49"

11-2 SCREENING FOR BREAST CANCER: U.S. PREVENTIVE TASK FORCE (USPSTF) RECOMMENDATION STATEMENT

This is an update of the 2002 USPSTF recommendation statement on screening for breast cancer (**BC**) in the general population. The USPSTF makes recommendations about preventive care services for patients who have no recognized signs or symptoms of the target condition.

The USPSTF recognizes that clinical or policy decisions involve more considerations than the body of evidence alone. Clinicians should understand the evidence, but *individualize decision making* to the specific patient or situation.

Summary of recommendations and evidence:

1) The USPSTF recommends against *routine* screening mammography in women age 40-49. The decision to start screening before age 50 should be an individual one, taking patient context into account, including the patient's values regarding specific benefits and harms.
2) The USPSTF recommends screening *every 2 years* for women age 50-74.
3) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening in women age 75 and older.
4) The USPSTF recommends against teaching breast self-examination.
5) The USPSTF concludes the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination *beyond screening mammography* in women age 40 and older.
6) The USPSTF concludes that the current evidence of benefits and harms of either digital mammography or magnetic resonance mammography (MRI) instead of film mammography is insufficient.

The USPSTF reasoned that the additional benefit gained by starting at age 40 rather the age 50 is small, and that moderate harms from screening remain at any age. Thus, the recommendation against routine screening at ages 40-49.

Potential harms of mammography:

False positive results are common and lead to additional imaging, and unnecessary biopsy.

(False negative results occur at a relatively low rate for all ages.)

Anxiety, distress, and other psychosocial effects can occur, but usually are transient.

Overdiagnosis can occur when screening detects early-stage invasive BC or ductal carcinoma in situ (DCIS) in a woman who is likely to die from another cause before the BC would be clinically detected. Over diagnosis can also occur if a detected DCIS or other early-stage lesion never progresses to invasive cancer.

Unnecessary earlier treatment can occur at any age when screening detects a slower-growing cancer that would have eventually become clinically evident, but would never have caused death.

Radiation exposure may increase risk of BC, but usually at much higher doses than those used in mammography, although regular mammography could contribute to cumulative radiation doses from additional imaging.

I struggled to abstract the 2 articles on screening for BC in a concise and meaningful way.

The report from the USPSTF raised considerable ire among some women, particularly those in their 40s in whom BC had been detected by mammography. They completely misread the recommendation. They raised the specter of "rationing" by interpreting it to mean that the USPSTF recommended against screening between ages 40-49. The USPSTF did no such thing. It recommended against routine screening at this age. (Ie, against universal screening—against automatically recommending screening for everyone beginning at age 40.)

Physicians and patients should consider the individual's decisions about screening after she has been adequately informed about harms as well as benefits. Some women are so fearful of BC that they will request frequent screening beginning at an early age. Their decisions should be honored.

The recommendations against breast self-examination, I doubt will persuade those who do self-examine to stop.

The recommendation about examination of the breasts in the physician's office during a routine physical examination pertains only if a mammogram is not contemplated. I presume most primary care clinicians will continue to examine the breasts during a routine check up.

Regarding DCIS, I believe that most young women would opt for surgery and not temporize by watchful waiting. The risk of progression to malignancy is too great.

No Need To Fast; No Need To Measure Triglycerides

11-3 MAJOR LIPIDS, APOLIPOPROTEINS, AND RISK OF VASCULAR DISEASE

Uncertainty persists about the merits of measurement and modification of triglycerides with the risk of vascular disease. It is not clear to what extent these relationships depend on cholesterol levels or vary with the fasting state.

This study assessed the relationship between major lipids and apo-lipoproteins and vascular risk.

Individual records were supplied on over 302 000 people in 22 countries (2.79 million person-years; mean age 59; 57% male) from 68 long-term prospective studies. No person had known vascular disease initially. At baseline, all had determinations of total cholesterol, HDL-cholesterol (HDL-c), and triglycerides (TG), and conventional risk factors (age, sex, smoking, diabetes, systolic BP, and body mass index).

Twenty-two studies (> 91 000 participants) had information on apo A-1 and apo B, and 8 studies (> 44 000 participants) had directly measured low-density cholesterol (LDL-c) values.

During 2.79 million person-years of follow-up there were 8857 non-fatal myocardial infarctions (MI), 3928 CHD deaths, 2534 ischemic strokes, and 513 hemorrhagic strokes..

Calculated non-HDL-c by subtracting HDL-c from total cholesterol. This measure encompasses low-intermediate- and very-low density lipoprotein cholesterol.

Hazard ratios for CHD of apo-lipoproteins compared with non-HDL-c

A. Apo-B compared with non-HDL-c

The mean lowest quintile level of apo B = 85mg/dL; the highest = 137

As apo B (*the Bad cholesterol*) rose, the hazard ratio for CHD increased from 1.0 to 2.0

The mean lowest quintile non-HDL-c = 125; the highest = 198

As non-HDL-c rose, the hazard ratio increased from 1.0 to 2.0

(Ie, the two were equally predictive of increasing harm as levels rose.)

B. Apo A1 compared with HDL-c

The mean lowest quintile level of apo A1 = 126 mg/dL; the highest = 178

As apo A1 increased the hazard ratio for CHD decreased from 1.0 to 0.7

The mean lowest quintile level of non-HDL-c = 125; the highest = 196

As HDL-c increased, the hazard ratio for CHD decreased from 1.0 to 0.7

(Ie, the two were equally predictive of increasing benefit as levels rose.)

Similar relationships were calculated for ischemic stroke. The absolute risks and benefits were much lower, but still in the same direction.

"The current analysis of more than 300 000 people has demonstrated that lipid assessment in

vascular disease can be simplified by measurement of either cholesterol levels or apolipoproteins without the need to fast and without regard to triglycerides."

In contrast with previous finding based on much less data, triglyceride concentration was not independently related with CHD risk after controlling for HDL-c, non-HDL-c, and other standard risk factors. "Hence, for population-wide assessments of vascular risk, triglyceride measurement provides no additional information about vascular risk given knowledge of HDL-c and total-c levels."

Concentrations of HDL-c and non-HDL-c were each strongly associated—in opposite directions—with CHD risk.

HDL-c and non-HD-c levels were largely independent of each other as well as from triglyceride concentrations and other risk factors. "Hence, whereas prevailing therapeutic strategies focus on lowering LDL-c (or approximately analogously, non-HDL-c) the current findings suggest that therapy directed at *raising* HDL-c as well as *lowering* non-HDL-c may generate substantial additional benefit."

"The current prospective data contrast sharply with those of some large retrospective case-control studies that reported that apolipoproteins have much stronger associations with CHD risk than cholesterol levels."

Conclusion: Lipid measurements in vascular disease can be simplified by measurement of total-c and HDL-c or apolipoproteins without the need to fast and without regard to triglyceride.

This study was much more complicated than I have indicated. It included many statistical applications.

I believe I have captured the results and the meaning of the study. The study was large and included many countries. This would favor generalizability.

The message is:

Aim for a ratio of HDL-c to non-HDL-c as high as possible. (The study did not calculate ratios.)

No need to fast or measure triglycerides.

This simplifies calculation of risks and benefits of therapy and adds to convenience of testing.

"A Diuretic Should Be Part Of Any Multidrug Regimen."

11-4 FIFTY YEARS OF THIAZIDE DIURETIC THERAPY OF HYPERTENSION

"Thiazides and thiazide-like diuretics have remained a cornerstone in the management of hypertension for more than half a century since their introduction in 1958. Very few agents used for the treatment of any disease can boast such staying power."

This is a testament both to the efficacy and safety of these compounds, and to the relevance of salt and volume contraction to the management of essential hypertension.

This 50th anniversary article reviews the history of the discovery and development of thiazides, mechanism of action, important trials documenting their role in prevention of cardiovascular disease, and the possible few limitations to the use of diuretics.

Please read the full abstract.

I abstracted this article with pleasure. I lived and practiced though the entire history of thiazide development. Indeed, I remember when weekly mercuhydrin injections were standard therapy for congestive heart failure.

I believe the development of thiazides was one of the major advances in medicine in the past century.

The article repeats the importance of BP control in patients with diabetes.

Chlorthalidone and hydrochlorothiazide are very inexpensive. Some pharmacies sell them for $10 for a 3-month's supply.

The benefit / harm - cost ratio of thiazides is very high.

Should The Availability Of An Inexpensive, Safe And Effective Preventive Treatment Be Widened?

11-5 PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

In the 1980s, Rose coined the term "prevention paradox" to describe the fact that a large proportion of cardiovascular disease (**CVD**) events occur among the many individuals with average risk factor values. He distinguished between 2 approaches to CVD prevention:

1) The high-risk strategy aims to truncate the upper tail of the normal distribution of risk factors. It focuses on individuals who are most likely to benefit personally from preventive treatment..

2) The population-based strategy aims to shift the entire risk distribution.

Soon, the high-risk approach came to be synonymous with the use of drugs. (Targeting high-risk individuals with preventive drug therapy benefits the individuals, but does little to reduce the overall burden of CVD on the population.)

The population approach was identified with efforts to shift norms of diet, physical activity, and smoking. Modest lifestyle changes could be recommended to the population at large because sensible interventions such as low-salt diet may be presumed to be safe.

Risk models were then developed to estimate individual risk at the point of care. The models accurately assigned individuals to different risk groups. But they failed to efficiently distinguish or discriminate between individuals who will or will not experience a CVD event.

Two recent developments provide an opportunity for a fresh approach:

1) The cost of the original statins has decreased precipitously.

2) The efficacy and safety of statins, especially at low to moderate doses, is established.

The widely accepted threshold of a 10-year CVD risk of 20% means that a large proportion of men 50 years and older is already eligible for statins. As a result, long-term mass preventive therapy would occur de facto in this group.

"Because 96% of all CVD events occur in persons older than 55 years, and because risk equations are poor at discriminating events, an alternative proposal is simply to offer generic statins, perhaps as part of a combination-drug polypill to all adults on the basis of age threshold regardless of the level of LDL-cholesterol, CRP, or absolute risk."

Preparations containing a statin and effective and safe BP-lowering agents such as low-dose diuretics are already being evaluated for wider use. An age-based approach obviates the need for a resource-intensive check for CVD risk, and would extend preventive drug therapies to individuals at lower individual risk.

Lifestyle interventions are generally ineffective.

The "polypill" concept refuses to die. Applying a preventive intervention to the general population is already an accepted application in the U.S. (Eg, the administration of vaccines.)

Traditional Western medicine relies on 1) testing for risk, 2) prescribing for individual patients with risk above a defined, but arbitrary level, 3) monitoring for adverse effects and effectiveness of response by retesting. Should the response be less than predicted by the arbitrary level, the dose of the drug is increased.

The polypill concept relies on evidence that, at any BP or LDL-c level, reducing that level will result in a constant relative risk reduction, but with an ever-diminishing absolute risk reduction.

Clinicians can often tell at a glance, without testing, individuals who are at increased risk of CVD. (Mall watching will reveal how high the risk of CVD is in the general population.)

Simply checking the BP will augment reliability of the predication.

I would judge that acceptability of a pill would be greater than a life-style change. People find it easier to take a pill. But, would the population comply with taking a daily pill for years without any obvious benefit?

Primary care clinicians may consider it risky to prescribe without pre-testing and follow-up.

Would there be legal risks?

I believe the benefit / harm-cost ratio of a polypill would be very high, especially in some populations.

"Offers A New Mode Of Action For The Treatment Of Obesity"

11-6 EFFECTS OF LIRAGLUTIDE IN THE TREATMENT OF OBESITY

Liraglutide is a glycogen-like peptide (**GLP**). It is 97% structurally analogous to native GLP, a gut-derived incretin hormone. Native GLP has a short elimination half-life (~ 1-2 minutes). Liraglutide has a half-life of about 13 hours. This allows once-a-day administration by subcutaneous injection. It was developed for treatment of type-2 diabetes.

Native GLP suppresses appetite and energy intake in both normal-weight and obese persons, as well as in patients with type-2 diabetes. There are several GLP receptors in brainstem nuclei, which are involved in appetite regulation.

This study assessed the effect of liraglutide on body weight (combined with low-fat diet and physical activity and counseling) on obese persons *without* diabetes.

Entered 564 men (n = 135) and women (n = 429) mean age 45, from 19 clinical research sites,

Body mass index of 30-40 (mean = 35) , stable body weight, and fasting plasma glucose less than 126 mg/dL. (Ie, none had known diabetes) None had major medical conditions. During the trial about 4% were diagnosed with type-2 diabetes; about 33% with prediabetes.

Randomly assigned to:

1) Liraglutide (1.2 mg; 1.8 mg; 2.4 mg; and 3.0 mg) s.c, once daily.

2) Placebo once daily s.c.

3) Orlistat 120 mg three times daily orally. (Open–label)

(I omitted data on the lower doses of liraglutide; the 3.0 mg dose was the most effective. RTJ)

All participants were instructed to adhere to a low-fat diet. (30% fat; 20% protein; 50% carbohydrate; about a 500 kcal / day deficit). They were encouraged to maintain or increase physical activity.

Outcomes:	Placebo (n = 98)	Liraglutide 3.0 mg(n = 93)	Orlistat (n = 95)
Completed trial (%)	79	82	79
Mean weight loss (kg)	-2.8	- 7.2	-4.4
Metabolic syndrome (%)			
Baseline	34	28	23

Week 20	21	11	20
Prediabetes (%)			
Baseline	36	31	29
Week 20	35	5	31
Safety data (Withdrawals %):			
Overall	19	12	17
With serous adverse events	1	1	0
Due to adverse events	3	5	3

Nausea and vomiting occurred within the first month in up to 33% of patients on 3.0 mg liraglutide Prevalence declined to about 10% at 5 months. Five withdrew because of nausea.

"Treatment with liraglutide, in addition to an energy-deficit diet and exercise program led to a sustained, clinically relevant, dose-dependent weight loss that was significantly greater than with placebo and orlistat."

Weight loss was accompanied by reductions in waist circumference, BP, and frequency of metabolic syndrome and prediabetes.

"Liraglutide was generally well tolerated. However, nausea and vomiting were more frequent than with other treatments, although these events were mostly transient and of mild or moderate intensity."

. "Liraglutide offers a new mode of action for the treatment of obesity, and improved efficacy compared with currently available therapies. Its effect on prediabetes suggests that it might be important for treating obese prediabetic individuals."

Conclusion: Liraglutide treatment over 20 weeks was well tolerated, induced weight loss, improved certain obesity-related risk factors, and reduced prediabetes.

I detected and was amused by the usual degree of "spin":

"Adverse events were generally mild and transient"

"Liraglutide was generally well tolerated"

(Primary care clinicians treat one patient at a time)

I wonder—Did the nausea and vomiting contribute to the weight loss?

The effect on prediabetes was encouraging.

I abstracted this article because GLPs may be an effective alternative to treatment of obesity.

"If At First You Don't Succeed . . . "

11-7 THE IMPACT OF REPEATED CYCLES OF PHARMACOTHERAPY ON SMOKING CESSATION

This study tested the impact of repeated courses of pharmacotherapy to help smokers recover from relapses and engage in new cessation efforts. It followed a cohort of smokers offered up to 4 courses of pharmacotherapy over 2 years.

Recruited smokers (n = 726), regardless of their interest in quitting, from 50 rural primary care clinics in Kansas. All were over age 18 and had smoked over 10 cigarettes daily.

At months 0. 6, 12, and 18, participants were asked if they wanted to receive a 6-week course of 21 g/d nicotine patch, or a 7-week course of buproprion sustained-release 150 mg twice daily.

Defined cessation as a self-reported 7-day abstinence at the end of each 6-month cycle.

Cessation rates were consistently higher for users of pharmacotherapy compared with nonusers.

Association between multiple consecutive cycles and cessation rates:

	720 smokers	
First cycle	464 requested medications (64%)	262 did not request meds (36%)
	81 quit (17%)	20 quit (8%)
Second cycle	202 requested medications (53%)	
	25 quit (12%)	
Third cycle	81 requested medications (46%)	
	13 quit (16%)	
Fourth cycle	44 requested meds (65%)	
	7 quit (16%)	

(Total of 27% [126 of 464] quit vs 8% of untreated group)

Many smokers persisted in requesting drugs for up to 4 cycles. Between 12% and 17% quit at each cycle. (The probability of quitting was not related to the number of previous drug-assisted attempts.)

One of 2 smokers was willing to make a second drug-assisted attempt within 6 months of a treatment failure. Willingness to reengage in treatment did not diminish over time.

"These results support a model of care in which smokers in whom treatment initially fails are quickly reengaged in a new pharmacotherapy-assisted quit attempts."

The goal is permanent abstinence,

This study defined abstinence as cessation for only 7 days.

Nevertheless, I believe some patients will indeed stop permanently after one or more attempts to quit. Some, of course, will relapse. By my calculation, in this study, the NNT to achieve one cessation for 7 days = 5

This is a possible practical application for primary care practice. Some clinicians and patients will be willing to try again and again. And after several attempts, some will succeed.

Subjects in the study were-selected regardless of their interest in cessation. This makes the study more generalisable.

Would not a primary-care clinician's success in getting one person to quit be equivalent to one coronary bypass operation?

ABSTRACTS NOVEMBER 2009

"All Screening Programs Do Harm. Some Do Good As Well."

11-1 EFFECTS OF MAMMOGRAPHY SCREENING UNDER DIFFERENT SCREENING SCHEDULES: Model Estimates of Potential Benefits and Harms.

This study was based on 6 models of breast cancer (**BC**) incidence and mortality in the U.S. These models were ideally suited for estimating the effect of screening under a variety of policies, and for facilitating comparisons of strategies. The models were developed independently by prestigious Medical Schools and Universities, and Cancer centers.

They predicted a cumulative probability of BC mortality developing over a woman's lifetime, starting at age 40 vs starting at age 50

They also predicted probability of death from BC from annual screening vs screening every 2 years.

Without screening, the median probability of dying from BC after age 40 is 3%. If a particular screening strategy leads to a 10% reduction in BC mortality, then the probability of BC mortality would be reduced to 2.7%, or 3 deaths prevented per 1000 women screened. [10% X 3 = 0.3%; 3% - 0.3% = 2.7%]

Benefits and harms of different screening programs:

A. Comparison of different STARTING ages:

Screening every 2 years starting at age 40 vs age 50 and continuing to age 69

	Average screenings Per 1000 women (rounded)	Percentage mortality reduction	Cancer deaths averted per ` 1000 screened	False positives per 1000	Unnecessary biopsies per 1000
Ages 40-69	13 000	16%	6.2	1250	88
Ages 50-69	9000	15%	5.4	780	55

1) Starting at age 40 averted 6 cancer deaths per 1000 screened.

2) Starting at age 50 averted 5 cancer deaths per 1000 screened.

3) One additional life saved at the expense of 470 false positives and recalls,

33 unnecessary biopsies, and an additional 4000 mammograms

B. Comparison of ANNUAL screening vs screening every 2 YEARS:

	Average screenings Per 1000 women (rounded)	Percentage mortality reduction	Cancer deaths averted per ` 1000 screened	False positives per 1000	Unnecessary biopsies per 1000
Screening every 2 years					
Ages 40-69	14 000	16%	6.2	1250	88
Ages 50-69	9000	15%	5.4	780	55
Screening every year					
Ages 40-69	28 000	22%	8.3	2250	158
Ages 50-69	18 000	20%	7.3	1350	95

1) Screening every year from age 40 to age 69 resulted in a reduction of cancer mortality of 8.3 per 1000 screened

2) Screening every 2 years from age 40 to age 69 resulted in a reduction in cancer mortality of 6.2 pre 1000 screened.

3) A difference of 2 lives saved per 1000 screened.

4) This advantage was at the expense of 1000 false positives and recalls, 70 unnecessary biopsies, and an additional 14 000 mammograms.

C. Comparison of different STOPPING ages:

Screening every 2 years					
Ages 50-69	9000	15%	5.4	780	55
Ages 50-79	12 000	25%	9.4	1020	71

1) Screening every 2 years from age 50 and stopping at age 69 averted 5.4 deaths for every 1000 screened.

2) Screening every 2 years from age 50 and stopping at age 79 averted 9.4 deaths for every 1000 screened.

3) Four additional deaths per 1000 screened were averted by extending screening to age 79 at the expense of 230 false positives and call backs, and an additional 16 unnecessary biopsies.

DISCUSSION

1. “The conclusion of this modeling analysis is that biennial intervals are more efficient and provide a better balance between benefits and harms than annual intervals.”
2. Substantial increases in false-positive results and unnecessary biopsies were associated with annual intervals. These harms are reduced by almost 50% with biennial intervals.

3. Slow-growing tumors are much more common than fast-growing tumors. The ratio of slow- to fast-growing tumors increases with age, so little survival benefit is lost between screening every 2 years vs every year.
4. For the small numbers of women with aggressive fast-growing tumors, even annual screening is not likely to confer a survival advantage.
5. Conclusions about the optimal *starting* age depend more on the measure chosen for evaluating outcomes: If the goal of a national screening program is to reduce mortality in the most efficient manner, then programs that screen every 2 years from age 50 to age 69, 74, or 79 are the most efficient on the basis of the ratio of benefits to the number of screening examinations. If the goal is to maximize the number of life-years gained, then the preferred strategy would be to screen every 2 years starting ate age 40.
6. In all models, some reduction in BC mortality, albeit small, was seen with strategies that started screening at age 40 vs age 50.
7. Choices about optimal ages of initiation ultimately depend on program goals, resources, weight attached to the presence of trial data, the balance of harms and benefits, and considerations of efficiency and equity.
8. Decisions about starting and stopping ages also depend on tolerance for false-positive results and rates of overdiagnosis.
   (Overdiagnosis can occur when screening detects ductal carcinoma in situ or early-stage invasive BC in women, typically older, who are likely to die from another cause before the BC would be clinically detected. Over diagnosis can also occur in younger women if a detected DCIS or other early-stage lesion never progresses to invasive cancer. Unnecessary treatment can occur at any age when screening detects a slower-growing cancer that would have eventually become clinically evident, but would never have caused death.)
9. Screening strategies that include an upper age limit beyond age 69 remain efficient albeit with low incremental gains over strategies that stop at earlier ages, and with greater harms.
10. Any benefits of screening older women must be balanced against possible harms. The probability of overdiagnosis increases with age, and increases dramatically for the oldest age groups.
11. We need better data on the natural history of DCIS to draw reliable conclusions on the absolute magnitude of overdiagnosis associated with different screening schedules.
12. These models provide estimates of the average benefits and harms expected across a cohort of women. They do not reflect personal data for individuals.
13. The models do not capture differences in outcomes among certain subgroups such as women

with a positive family history or genetic susceptibility for BC, women who are sicker or healthier than average, or black women.

14 The models do not capture the morbidity associated with surgery for screen-detected disease or decrements in quality of life associated with false positive results, living with earlier knowledge of cancer diagnosis and overdiagnosis.

15. The study assumed 100% adherence to screening and treatment. Benefits will always fall short of projected results because adherence is not perfect.

16. The study did not include costs.

CONCLUSION

Mammography screening every 2 years achieves most of the benefit of annual screening with less harm.

Decisions about the best strategy depend on individual objectives, and the weight placed on harms, benefits, and resource considerations.

Annals Internal Medicine November 17, 2009; 151: 738-47 "Clinical Guidelines" first author Jeanne S Mandelblatt, Lombardi Comprehensive Cancer Center, Washington DC

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"Thus, The Recommendation Against Routine Screening At Ages 40-49"

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The USPSTF recognizes that clinical or policy decisions involve more considerations than the body of evidence alone. Clinicians should understand the evidence, but *individualize decision making* to the specific patient or situation.

Summary of recommendations and evidence:

1) The USPSTF recommends against *routine* screening mammography in women age 40-49. The decision to start screening before age 50 should be an individual one, taking patient context into account, including the patient's values regarding specific benefits and harms.

There is moderate or high certainty that net benefit of starting at age 40 is small. (C recommendation)

2) The USPSTF recommends screening *every 2 years* for women age 50-74. There is high certainty that the net benefit is moderate. There is moderate certainty that the net benefit is moderate to substantial. (B recommendation)

3) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening in women age 75 and older. Evidence is lacking, of poor quality, or conflicting. (I recommendation)

4) The USPSTF recommends against teaching breast self-examination. There is moderate or high evidence the service has no net benefit, and that the harms outweigh the benefits. (D recommendation)

5) The USPSTF concludes the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination *beyond screening mammography* in women age 40 and older. Evidence is lacking, of poor quality, or conflicting. (I recommendation)

6) The USPSTF concludes that the current evidence of benefits and harms of either digital mammography or magnetic resonance mammography (MRI) instead of film mammography is insufficient. Evidence is lacking, of poor quality, or conflicting. (I recommendation)

The review confirms that screening mammography reduces mortality:

The relative risk for death due to BC mammography vs usual care:

Age 40-49	0.85
Age 50-59	0.85
Age 60-69	0.68
Older women	Uncertain

"The precise age at which the benefits from screening mammography justify the potential harms is a subjective judgment and should take into account patient preferences." Clinicians should inform women about the potential benefits (reduced chances of dying from BC), and potential harms (false-positive results, unnecessary biopsies), and limitations of the test. Women should be told that the balance of benefits and potential harms of mammography improves with increasing age for women between ages of 40 to 70.

This updated recommendation is now further informed by a new systematic review, which incorporates a new randomized, controlled trial that estimates the number needed to invite for screening to prevent one BC death

Age	40-49	1904
Age	50-59	1339
Age	60-69	377

The risk of BC increases with age. National Cancer Institute estimates the 10-year risk of BC for a woman:

Age 40	1 in 69
Age 50	1 in 42
Age 60	1 in 29

Lifetime risk for all women to develop BC = 12%

The USPSTF reasoned that the additional benefit gained by starting at age 40 rather the age 50 is small, and that moderate harms from screening remain at any age. Thus, the recommendation against routine screening at ages 40-49.

Potential harms of mammography:

- False positive results are common, cause anxiety, and lead to additional imaging, and biopsy.
- False positive results leading to additional imaging studies are more common in younger women.
- Anxiety, distress, and other psychosocial effects can occur, but usually are transient.
- False negative results occur at a relatively low rate for all ages.
- Overdiagnosis can occur when mammography screening detects early-stage invasive BC or ductal carcinoma in situ (DCIS) in a woman, typically older, who is likely to die from another cause before the BC would be clinically detected. Over diagnosis can also occur in younger women if a detected DCIS or other early-stage lesion never progresses to invasive cancer.
- Unnecessary earlier treatment can occur at any age when screening detects a slower-growing cancer that would have eventually become clinically evident, but would never have caused death.
- Radiation exposure may increase risk of BC, but usually at much higher doses than those used in mammography, although regular mammography could contribute to cumulative radiation doses from additional imaging.

Estimate of magnitude of net benefit of mammography screening:

In 2002, the USPSTF concluded that there was fair evidence that mammography screening every 12 to 33 months could significantly reduce BC mortality. The evidence was strongest for women age 50-69, with weaker evidence for women age 40-49.

Since the estimates of 2002, two studies have added data specifically for women age 40-49. The relative risk for death from BC (screened vs not-screened) = 0.85. The number needed to invite for screening to prevent one BC death = 1904

An analysis projected that screening every 2 years produced from 70% to 99% of the benefit of annual screening, with a reduction in the number of mammograms required, and therefore a reduction in harms.

Screening women age 50-69 projected a 17% reduction in mortality (compared with no screening). Extending the age beyond 70 produced an additional 7% reduction.

The USPSTF noted with moderate certainty that the net benefit of mammography in women aged 50-74 were at least moderate and the greatest benefits were seen in age 60-69. For women age 40-49, there was moderate certainty that the net benefits were small. For women over age 74, trial data were lacking, and the certainty of net benefit was low.

The effectiveness of mammography screening presumably results from the early detection of smaller, earlier-stage tumors, which are more responsive to available treatment.

Although the most common BC occurs in the epithelial cells that line the duct system (ductal carcinoma), the sequence of development to invasive cancer is not entirely known. Ductal carcinoma in situ (**DCIS**) does not always represent a precursor to invasive ductal cancer. Progression of DCIS to invasive ductal cancer occurs in half or fewer of the cases. Because DCIS is found only by mammography, its incidence has increased steadily. Because the likelihood that DCIS will progress to invasive cancer is unknown, surgical removal may represent over diagnosis and over treatment.

Recommendations of others:

The Canadian Task Force on Preventive Health Care (2001) recommended mammography every 1 to 2 years beginning at age 40.

The American Cancer Society (2003) recommended annual mammography beginning at age 40.

The American Medical Society (2002) and the National Comprehensive Cancer Network (2009) recommendations were similar to the ACS.

The American College of Physicians (2007) recommended the mammography decisions for women age 40-49 should be based on individualized assessment of risk of BC. Clinicians should inform these women about potential benefits and harms of screening, and be aware of the woman's preference.

The WHO (2009) recommended mammography every 1 to 2 years for women age 50-69.

Annals Internal Medicine November 17,2009; 151: 716-727 From the U.S. Preventive Services Task Force. Supported by the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services.

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No Need To Fast; No Need To Measure Triglycerides

11-3 MAJOR LIPIDS, APOLIPOPROTEINS, AND RISK OF VASCULAR DISEASE

Reliable assessment of the separate and joint associations of major blood lipids and apo-lipoproteins is important for development of screening and therapeutic strategies.

Expert opinion is divided about whether assessment of apo-lipoprotein A1 (apo-A1) and apo-lipoprotein B (apo B) should replace assessment of high-density lipoprotein cholesterol (HDL-c), and total cholesterol levels in assessment of vascular risk.

Uncertainty persists about the merits of measurement and modification of triglycerides with the risk of vascular disease. It is not clear to what extent these relationships depend on cholesterol levels or vary with the fasting state.

This study assessed the relationship between major lipids and apo-lipoproteins and vascular risk.

STUDY

1. Individual records were supplied on over 302 000 people in 22 countries (2.79 million person-years; mean age 59; 57% male) from 68 long-term prospective studies. No person had known vascular disease initially.
2. At baseline, all had determinations of total cholesterol, HDL-cholesterol (HDL-c), and triglycerides (TG), and several conventional risk factors (age, sex, smoking, diabetes, systolic BP and body mass index).
3. Twenty-two studies (> 91 000 participants) had information on apo A-1 and apo B, and 8 studies (> 44 000 participants) had directly measured low-density cholesterol (LDL-c) values.
4. During 2.79 million person-years of follow-up there were 8857 non-fatal myocardial infarctions

(MI), 3928 CHD deaths, 2534 ischemic strokes, and 513 hemorrhagic strokes.

5. Calculated non-HDL-c by subtracting HDL-c from total cholesterol. This measure encompasses low- intermediate- and very-low density lipoprotein cholesterol. The study used this measure as the principal marker of cholesterol content in pro-atherogenic lipoproteins in order to avoid biases that may arise when using LDL-c value estimated by the Friedwald formula.[1]

RESULTS

1. Hazard ratios for CHD:

A. Triglycerides:

Comparing levels between 70 and 250 mg/dL, after adjustment for multiple risk factors, including HDL-c and non-HDL-c, the hazard ratio for CHD of the highest level to the lowest level remained about 1.0. (Ie, no increased risk for TG.)

B HDL-c:

The hazard ratio for CHD, comparing the highest (60 mg/dL) to lowest level (35 mg/dL) was 1.6. (Ie, an inverse relationship. The higher the level, the lower the risk.)

C Non HDL-c

Comparing levels of non-HDL-c from 130 to 210 mg/d, the hazard ratio for CHD of the highest level to the lowest was 2.4. (Ie, a direct relationship. The higher the level of non-HDL-c , the higher the risk.)

(*These are my calculations from Figure 1 page 1995. RTJ*)

2. Similar relationships were calculated for ischemic stroke. The absolute risks and benefits were much lower, but still in the same direction. There was no relation of the lipids studied to hemorrhagic stroke.

3. Hazard ratios of apo-lipoproteins compared with non-HDL-c

A. Apo-B compared with non-HDL-c

The mean lowest quintile level of apo B = 85mg/dL; the highest = 137

As apo B rose, the hazard ratio for CHD increased from 1.0 to 2.0

The mean lowest quintile non-HDL-c = 125; the highest = 198

As non-HDL-c rose, the hazard ratio increased from 1.0 to 2.0.

(Ie, the two were equally predictive of increasing harm as levels rose)

B. Apo A1 compared with HDL-c

The mean lowest level of apo A1 = 126 mg/dL; the highest = 178

As apo A1 increased the hazard ratio for CHD decreased from 1.0 to 0.7

The mean lowest quintile level of non-HDL-c = 125; the highest = 196

As HDL-c increased, the hazard ratio for CHD decreased from 1.0 to 0.7

(Ie, the two were equally predictive of increasing benefit)

(*These are my calculations from Figure 3 page 1997. RTJ*)

4. Non-HDL-c by levels of HDL-c:
   A. As non-HDL-c levels rose from 120 mg/dL to 200, a lower HDL-c level (< 50) was associated with less benefit (increase in hazard ratio from 1.0 to 2.2)
   B. As non-HDL-c levels rose from 120 mg/dL to 200, a higher HDL-c level (> 50) was associated greater benefit (increase in hazard ratio from 1.0 to 1.9).
   C. At any non-HDL-c level, a higher HDL-c was associated with greater benefit.
5. HDL-c by levels of non-HDL-c
   A. A low HDL-c level correlated with a higher non-HDL-c level was associated with less benefit than a low HDL-c level correlated with lower non-HDL-c
   B. A high HDL-c level correlated with a lower non-HDL-c level was associated with a greater benefit than a high HDL-c level correlated with a high non-HDL-c.
   C. At any non-HDL-c level, a higher HDL-c was associated with greater benefit

   (*My calculations from figure 2 page 1996*)

DISCUSSION

1. "The current analysis of more than 300 000 people has demonstrated that lipid assessment in vascular disease can be simplified by measurement of either cholesterol levels or apolipoproteins without the need to fast and without regard to triglycerides."
2. Whether to measure cholesterol levels or apolipoproteins in vascular risk assessment should hinge more on practical considerations (eg, cost, availability and standardization of assays) than on major differences in strength of epidemiological associations.
3. Hazard ratios for vascular disease associated with lipid levels were as strong in participants who did not fast as in those who fasted.
4. Hazard ratios were similar with non-HDL-c as with directly measured LDL-c.
5. In contrast with previous finding based on much less data, triglyceride concentration was not independently related with CHD risk after controlling for HDL-c, non-HDL-c, and other standard risk factors.
6. "Hence, for population-wide assessments of vascular risk, triglyceride measurement provides no additional information about vascular risk given knowledge of HDL-c and Total-c levels."

7. Concentrations of HDL-c and non-HDL-c were each strongly associated—in opposite directions—with CHD risk.
8. HDL-c and non-HDL-c were largely independent of each other as well as from triglyceride concentrations and other risk factors. Whereas prevailing therapeutic strategies focus on lowering LDL-c (or approximately analogously, non-HDL-c) the current findings suggest that therapy directed at raising HDL-c as well as lowering non-HDL-c may generate substantial additional benefit.
9. CHD risk is approximately two-thirds lower in people with a 15 mg/dL higher HDL-c and 80 mg/dL lower non-HDL-c, which are attainable with extended-release-niacin plus a potent statin.
10. Hemorrhagic stroke was not related to any of the lipids studied here. Pro-atherogenic lipids appear to be associated with ischemic stroke, albeit modestly.
11. "The broad consistency of results across 68 studies in 21 countries support their generalizability."
12. "The current prospective data contrast sharply with those of some large retrospective case-control studies that reported that apolipoproteins have much stronger associations with CHD risk than cholesterol levels."
13. The current findings cannot confirm or refute causality.

CONCLUSION

Lipid measurements in vascular disease can be simplified by measurement of total-c and HDL-c, or apolipoproteins, without the need to fast and without regard to triglyceride.

JAMA November 11, 2009; 302: 1993-2000 Original investigations, by the Emerging Risk Factors Collaboration, corresponding author John Danesh, University of Cambridge, Cambridge, UK

1 [LDL-c] = [Total-c] – [HDL-c] – [TG/5]

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"A Diuretic Should Be Part Of Any Multidrug Regimen."

11-4 FIFTY YEARS OF THIAZIDE DIURETIC THERAPY OF HYPERTENSION

"Thiazides and thiazide-like diuretics have remained a cornerstone in the management of hypertension for more than half a century since their introduction in 1958. Very few agents used for the treatment of any disease can boast such staying power."

This is a testament both to the efficacy and safety of these compounds, and to the relevance of salt and volume contraction to the management of essential hypertension.

This 50th anniversary article reviews the history of the discovery and development of thiazides, mechanism of action, important trials documenting their role in prevention of cardiovascular disease, and the possible few limitations to the use of diuretics.

HISTORY

Until 1957, the only effective diuretics were mercurial agents (restricted mainly to treatment of heart failure). In 1937, research on the mechanisms of acidemia produced by sulfonamides demonstrated that they had a diuretic effect. Later, the development of the carbonic anhydrase inhibitor acetazolamide helped us to understand the mechanisms for urinary acidification and diuresis.

Novello and Sprague (Merck Sharpe and Dohme) synthesized a large number of compounds in search of a better carbonic anhydrase. They came upon cholrothiazide, which is in fact a sulfonamide as well as a carbonic anhydrase inhibitor. Unexpectedly, its potent diuretic activity distinguished it from carbonic anhydrase. It caused an increase in chloride, rather than bicarbonate excretion. In the late 1950s, M. M. (one of the authors of this article) obtained supply of cholrothiazide, then used to treat congestive heart failure. Within 2 weeks, after use in a few patients; it became obvious that it lowered BP.

MECHANISM OF ACTION

The initial decrease in BP results from a diuretic-induced reduction in plasma volume and cardiac output, with a slight increase in peripheral vascular resistance. This is followed by a decrease in vascular resistance, perpetuating the lower BP. The cardiac output returns to normal, with a continuing slight decrease in plasma volume. (The reduction in volume explains the ongoing increase in the action of the renin-angiotensin system.)

It was hypothesized that the blood vessels of hypertensive individuals were “waterlogged” with excessive sodium and water, making them more susceptible to sympathetic nervous system stimuli. Thiazides reversed this effect, making the vessels less sensitive to vasoconstriction.

Actually, while these explanations have experimental support, they are not definitive. The precise mechanism of long-term action of thiazides is not known.

It is well known that up to 40% of individuals (especially the elderly and blacks) in the U.S. are salt-sensitive. (They respond to a high sodium intake with increases in BP, and to sodium restriction with decreases in BP. Many of these persons respond readily to thiazides. However, all ages and ethnic groups respond to some extent with BP lowering.

CURRENT ROLE OF DIURETICS IN THE PREVENTION OF CV EVENTS

The Veterans Cooperative Study (1964-1967) proved that lowering severe hypertension by medications (combined thiazide, reserpine, and hydralazine) caused a remarkable decrease in death, stroke, and other CV events associated with diastolic BP > 105.

The Hypertension Detection and Follow-up Program (1979) extended this observation to mild and moderate hypertension. It demonstrated that a "stepped-care approach" with diuretics as initial therapy, lowered BP and decreased incidence of strokes, coronary heart disease, and death in patients with then-termed "mild hypertension" (diastolic 90-104).

Many subsequent trials relied on a diuretic as a major component of treatment. The simple conclusion was that diuretics prevent CV events.

The Systolic Hypertension in the Elderly Program (SHEP; 1991) was the first blinded trial that demonstrated that lowering isolated systolic BP (> 160 with a diastolic < 90) reduced strokes and major CV events.

"Notwithstanding all of the positive evidence in favor of diuretics from many trials in older and middle-aged groups, the use of diuretics in the United States declined in the 1980s and 1990s, as heavily promoted medications were introduced. Were these drugs any better?

The Antihypertensive and Lipid-lowering Treatment of Prevent Heart Attack Trial (ALLHAT, 2002) was the largest hypertension trial ever undertaken. It compared the efficacy of initiating therapy with a diuretic, a calcium channel blocker, or an ACE inhibitor on fatal and non-fatal cardiovascular disease events. Patients who received chlorthalidone (12.5-25 mg) as initial therapy experienced fewer strokes than those initiated on an ACE inhibitor, and fewer heart failure events than those initiated on a calcium blocker. The diuretic-based program was as effective, and possibly more effective in some subgroups than treatment programs based on ACE inhibitor or calcium blocker.

Based on these results, diuretics were recommended as first-step treatment for most patients with hypertension by the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2003).

Many U.S. trials have used chlorthalidone. Compared with hydrochlorothiazide (both act on the same nephron site) the BP-lowering efficacy of chlorthalidone may exceed that of hydrochlorothiazide, especially at night. Doses of 12.5 to 25 mg are as effective in reducing clinic BP as 25 to 50 mg hydrochlorothiazide. There is data suggesting that the doses of hydrochlorothiazide used in some recent trials were too low. Many physicians are reluctant to use higher doses of hydrochlorothiazide because of concerns about metabolic problems.

The Blood Pressure Lowering Treatment Trialists' Collaboration (2000), a meta-analysis of 31 trials reported no differences between drug classes in prevention of major CV events, and no differences in their preventive effectiveness in older compared with younger patients.

While the possible metabolic effects of diuretics (hypokalemia and hyperglycemia) have been repeatedly emphasized, they appear to have been overemphasized and do not obviate the benefit of thiazides. In the SHEP trial, chlorthalidone-based, there was a more marked reduction in fatal and non-fatal myocardial infarctions (54% and 26%) and all-cause mortality in patients with diabetes compared with non-diabetics. In patients whose potassium levels decreased to below 3.5 mmol/L the outcome was better than in the placebo group. Hypokalemia was more common when high doses of chlorthalidone were used. The doses presently used are lower and result in less hypokalemia.

"There is limited evidence at present that the metabolic effects of diuretic therapy, at the dosages presently used are of major clinical significance." Nevertheless, physicians may still consider the metabolic effects to be clinically significant.

Lack of promotion of diuretics and heavy promotion of other classes of drugs may have contributed to their decline in use. (The desire to "be up-to-date") Because angiotensin II receptor blockers are associated with fewer metabolic effects, while providing approximately the same BP-lowering efficacy, some physicians may believe they represent better initial control.

"At present, data clearly demonstrate that the degree of BP lowering is a more important determinant of outcome than the specific medication."

When diuretics are used in combination with other drugs (eg, beta-blockers ACE inhibitors, ARBs) BP lowering is greater and racial differences in response are reduced. (When diuretics are added to ACE inhibitors in black patients, BP lowering is greater and outcomes are improved.)

"The Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure has suggested that a diuretic should be part of any multidrug regimen."

Preponderant evidence favors achievement of a goal BP level as the most important factor in determining outcome in most patients.

When renal dysfunction is present (creatinine over 2 mg/dL), or GFR less than 50 mL/min, thiazides may become ineffective, and a loop diuretic should be used instead, both as a diuretic and a BP lowering agent.

CONCLUSION

Thiazide diuretics have stood the test of time for more than 50 years. Their use as monotherapy, or in combinations, has resulted in dramatic decreases in cerebrovascular and cardiovascular events.

Compared with other antihypertension agents with different mechanisms of action, diuretics are as effective, and in some instances, more effective in event reduction.

Archives Internal Medicine November 9, 2009; 169: 1851-56 Review article, first author Marvin Moser, Yale University School of Medicine, New Haven Conn.

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Should The Availability Of An Inexpensive, Safe And Effective Preventive Treatment Be Widened?

11-5 PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

In the 1980s, Rose coined the term "prevention paradox" to describe the fact that a large proportion of cardiovascular disease (**CVD**) events occur among the many individuals with average risk factor values. He distinguished between 2 approaches to CVD prevention:

1) The high-risk strategy aims to truncate the upper tail of the normal distribution of risk factors. It focuses on individuals who are most likely to benefit personally from preventive treatment..

2) The population-based strategy aims to shift the entire risk distribution.

At that time, the available lipid-lowering therapies were limited. None was well tolerated, and the risk / benefit profile for clofibrate argued against its widespread use.

Soon, the high-risk approach came to be synonymous with the use of drugs. (Targeting high-risk individuals with preventive drug therapy benefits the individuals, but does little to reduce the overall burden of CVD on the population.)

The population approach was identified with efforts to shift norms of diet, physical activity, and smoking. Modest lifestyle changes could be recommended to the population at large because sensible interventions such as low-salt diet may be presumed to be safe. The real world effects of such recommendations have been limited.

In the 1990s, statins were introduced as potent LDL-cholesterol lowering agents. They were used first for secondary prevention of patients with CVD. Then for primary prevention. They resulted in a 25% relative reduction in CVD events in both primary and secondary prevention, and in patients with varying risk factor profiles. For this reason, the number needed to treat to benefit one patient depends largely on the baseline absolute risk. Cost and uncertainty about long-term adverse effects of statins limited their use at that time.

Risk models were then developed to estimate individual risk at the point of care. The models accurately assigned individuals to different risk groups. But they failed to efficiently distinguish or discriminate between individuals who will or will not experience a CVD event.

Over time, new markers for risk have been developed and proposed. Neither new markers nor new metrics have managed to completely evade the prevention paradox.

Two recent developments provide an opportunity for a fresh approach:

1) The cost of the original statins has decreased precipitously.

2) The efficacy and safety of statins, especially at low to moderate doses, is established.

For an inexpensive treatment known to be safe and effective, should its availability be widened?

The widely accepted threshold of a 10-year CVD risk of 20% means that a large proportion of men 50 years and older is already eligible for statins. As a result, long-term mass preventive therapy would occur de facto in this group.

Woman with average risk may not pass the 20% threshold until they are well advanced in years.

"Because 96% of all CVD events occur in persons older than 55 years, and because risk equations are poor at discriminating events, an alternative proposal is simply to offer generic statins, perhaps as part of a combination-drug polypill to all adults on the basis of age threshold regardless of the level of LDL-cholesterol, CRP, or absolute risk."

Preparations containing a statin and effective and safe BP-lowering agents such as low-dose diuretics are already being evaluated for wider use. An age-based approach obviates the need for a resource-intensive check for CVD risk, and would extend preventive drug therapies to individuals at lower individual risk.

Scant information is available on the cost and public acceptability of a policy of widening the eligibility of generic drugs with minimal monitoring of response vs a resource-intensive individualized risk management together with treatment targets.

Whether a less personalized approach to CVD risk stratification improves health outcomes at an acceptable cost can and should be asked and answered by trials and studies.

JAMA November 18, 2009; 302: 2144-45 Commentary, first author Aroon D Hingorani, University College London, London UK

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"Offers A New Mode Of Action For The Treatment Of Obesity"

11-6 EFFECTS OF LIRAGLUTIDE IN THE TREATMENT OF OBESITY: *A Randomized, Double-Blind, Placebo-Controlled Study*

Few safe and effective drugs are currently available for the treatment of obesity. Alternative approaches to weight loss that are safe and well tolerated, and that can lower the risks associated with obesity are needed.

Liraglutide is a glycogen-like peptide (**GLP**). It is 97% structurally analogous to native GLP, a gut-derived incretin hormone. Native GLP has a short elimination half-life (~ 1-2 minutes). Liraglutide has a half-life of about 13 hours. This allows once-a-day administration by subcutaneous injection. It was developed for treatment of type-2 diabetes. It has shown benefits for glycemic control.

Native GLP suppresses appetite and energy intake in both normal-weight and obese persons, as well as in patients with type-2 diabetes. There are several GLP receptors in brainstem nuclei, which are involved in appetite regulation.

Liraglutide causes a dose-dependent weight loss, improves beta-cell function, delays gastric emptying, lowers systolic BP, and decreases concentration of glycated hemoglobin,

This study assessed the effect of liraglutide on body weight (up to 3.0 mg per day combined with low-fat diet and physical activity and counseling) on obese persons *without* diabetes. The effect of liraglutide was compared with that of orlistat, a GI lipase inhibitor, as well as placebo.

STUDY

1. Entered 564 men (n = 135) and women (n = 429) mean age 45, from 19 clinical research sites,
   Body mass index of 30-40 (mean = 35) , stable body weight, and fasting plasma glucose less than 126 mg/dL. (Ie, none had known diabetes) None had major medical conditions. During the trial about 4% were diagnosed with type-2 diabetes; about 33% with prediabetes.
2. Randomly assigned to:
   1) Liraglutide (1.2 mg; 1.8 mg; 2.4 mg; and 3.0 mg) s.c, once daily.
   2) Placebo once daily s.c.
   3) Orlistat 120 mg three times daily orally. (Open–label)
   (I omitted data on the lower doses of liraglutide; the 3.0 mg dose was the most effective. RTJ)
3. All participants were instructed to adhere to a low-fat diet. (30% fat; 20% protein; 50% carbohydrate; about a 500 kcal / day deficit). They were encouraged to maintain or increase physical activity measured by pedometers. They were taught to self-administer the liraglutide.
4. Trial duration = 20 weeks; Analysis by intention-to-treat.

5. Primary end-point = change in weight.

RESULTS

1. Outcomes:	Placebo (n = 98)	Liraglutide 3.0 mg(n = 93)	Orlistat (n = 95)
Completed trial (%)	79	82	79
Mean weight loss (kg)	-2.8	- 7.2	-4.4
Lost > 5% weight (%)	29	76	44
Lost > 10%weught (%)	2	28	9
Metabolic syndrome (%)			
Baseline	34	28	23
Week 16	21	11	20
Prediabetes (%)			
Baseline	36	31	29
19 weeks	35	5	31
2. Safety data (Withdrawals %):			
Overall	19	12	17
With serous adverse events	1	1	0
Due to adverse events	3	5	3

3. Mean HbA1c, mean plasma glucose, waist circumference, and systolic BP decreased slightly with liraglutide. Beta-cell function increased.
4. Quality of life, physical function and self-esteem improved with liraglutide.
5. Adverse events:

   Nausea and vomiting occurred within the first month in up to 33% of patients on 3.0 mg liraglutide Prevalence declined to about 10% at 5 months. Five withdrew because of nausea.

DISCUSSION

1. “Treatment with liraglutide, in addition to an energy-deficit diet and exercise program led to a sustained, clinically relevant, dose-dependent weight loss that was significantly greater than with placebo and orlistat.” More than 50% of patients achieved a target 5% to 10% weight reduction after 20 weeks.
2. Weight loss was accompanied by reductions in waist circumference, BP, and frequency of metabolic syndrome and prediabetes.
3. “Liraglutide was generally well tolerated. However, nausea and vomiting were more frequent

than with other treatments, although these events were mostly transient and of mild or moderate intensity."

4. "Liraglutide offers a new mode of action for the treatment of obesity, and improved efficacy compared with currently available therapies. Its effect on prediabetes suggests that it might be important for treating obese prediabetic individuals."
5. Long-term risk-benefit profile of liraglutide remains to be established.

CONCLUSION

Liraglutide treatment over 20 weeks was well tolerated, induced weight loss, improved certain obesity-related risk factors, and reduced prediabetes.

Lancet November 7, 2009; 374: 11606-16 Original investigation, first author Arne Astrup, University of Copenhagen, Denmark

Funded by Novo Nordisk

Liraglutide has been approved in Europe for treatment of type-2 diabetes. Approval is pending in the U.S.

Liraglutide, and other GLPs, act in a glucose-dependent manner. (Ie, stimulates insulin production only when blood glucose is higher than normal. It has little tendency to produce hypoglycemia. It decreases appetite and tends to maintain body weight. It lowers blood triglycerides

Byetta, another GLP, is available in the US. It has a shorter half-life and must be given twice daily [Source—Wikipedia]

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"If At First You Don't Succeed . . . "

11-7 THE IMPACT OF REPEATED CYCLES OF PHARMACOTHERAPY ON SMOKING CESSATION

Smoking cessation pharmacotherapy can increase quit rates.

Smokers often fail a single quit attempt.

This study tested the impact of repeated courses of pharmacotherapy to help smokers recover from relapses and engage in new cessation efforts. It followed a cohort of smokers offered up to 4 courses of pharmacotherapy over 2 years.

STUDY

1. Recruited smokers (n = 726), regardless of their interest in quitting, from 50 rural primary

care clinics in Kansas. All were over age 18 and had smoked over 10 cigarettes daily.

2. At months 0. 6, 12, and 18, participants were asked if they wanted to receive a 6-week course of 21 g/d nicotine patch, or a 7-week course of buproprion sustained-release 150 mg twice daily. Drugs were supplied free of charge. Smokers who chose to use pharmacotherapy were self-selected.
3. All participants received telephone counseling to promote cessation and to encourage prevention of relapse.
4. Defined cessation as a self-reported 7-day abstinence at the end of each 6-month cycle.
5. Follow-up included over 82% of participants. Subjects were censored at the end of any cycle in which they failed to request medication.
6. Because the investigators wanted to examine the impact of repeated cycles on smokers who had failed to quit during a prior medication-assisted attempt, they also censored subjects who had stopped smoking at the end of a previous cycle.

RESULTS

1. Cessation rates were consistently higher for users of pharmacotherapy compared with nonusers.
2. Association between multiple consecutive cycles and cessation rates:

	720 smokers	
First cycle	464 requested medications (64%)	262 did not request meds (36%)
	81 quit (17%)	20 quit (8%)
Second cycle	202 requested medications (53%)	
	25 quit (12%)	
Third cycle	81 requested medications (46%)	
	13 quit (16%)	
Fourth cycle	44 requested meds (65%)	
	7 quit (16%)	

3, Many smokers persisted in requesting drugs for up to 4 cycles.
4. Between 12% and 17% quit at each cycle. (The probability of quitting was not related to the number of previous drug-assisted attempts.)
5. Of those who did not wish to participate, 8% quit without drug help.
6. Odds ratio of quitting with aid of drugs vs not receiving drugs at each cycle = 1.53, 1.83, 1.85, and 2.08.
7. Over the entire course of treatment, a total of 126 of 464 (27%) using drugs quit vs 8% in the untreated group. [Difference = 19%]

DISCUSSION

1. One of 2 smokers was willing to make a second drug-assisted attempt within 6 months of a treatment failure. Willingness to reengage in treatment did not diminish over time.
2. Drug therapy seemed to remain effective even in the presence of multiple prior treatment failures.
3. “These results support a model of care, in which smokers in whom treatment initially fails, are quickly reengaged in a new pharmacotherapy-assisted quit attempt.”

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