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FOR

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26th YEAR OF PUBLICATION

This document is divided into two parts

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

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

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

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

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

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* JUNE 2011

6-1 NEW GUIDELINE COVERS WAYS TO PREVENT AND TREAT HYPERTENSION IN ELDERLY PEOPLE

For the first time, clinicians have a guideline on the prevention and treatment of hypertension specifically in individuals older than 65. This came in April 2011 from the American College of Cardiology and the American Heart Association.

Although hypertension is prevalent in this older population (64% of men and 78% of women) control is less common. Many clinicians are reluctant to treat these patients because they believe it will increase mortality. Moreover, rigorous study of hypertension in those over 80 has been nonexistent.

A study in 2008 (Hypertension in the Very Elderly Trial [HYVE][1] changed the landscape. It looked at 3845 patients, age 80 and over, randomized to antihypertensive therapy with a diuretic and, if necessary to reach target, an added angiotensin converting enzyme (ACE) inhibitor.

Compared with the placebo, the active treatment reduced systolic BP by 15 mmHg with a reduction in the rate of death from cardiovascular causes of 23% and a 21 % reduction in death from any cause.

The trial was stopped for ethical reasons at the end of 2 years. The findings were compelling enough to warrant new guidelines. However, the lack of rigorous research on prevention and management of individuals age 65 and older with hypertension resulted in the panel's statement that the recommendations were based largely on expert opinion.

(Go to the full abstract to access the guideline Ed.)

JAMA June 15, 2011; 305: 2394 "Medical News and Perspective" by Mike Mitka, JAMA staff

1 "Treatment of Hypertension Patients 80 Years of Age and Older" NEJM May 1. 2008; 358: 1887 First author Nigel S Beckett, Imperial College, London.

This international trial randomized 3848 patients age 80 and over who had a sustained systolic BP 160 and over to receive either a diuretic (indapamide) alone or with, if necessary, an added angiotensin converting enzyme (ACE) inhibitor (perindopril) vs placebo. Target was a systolic of 150.

At baseline, mean age was 83, mean systolic BP 173. At 2 years mean systolic was 15 mmHg lower in the active treatment group than in the placebo group.

In the intention-to-treat analysis, active treatment was associated with a 30% reduction in fatal or non-fatal stroke, 21% reduction in death from any cause, a 23% reduction in death from cardiovascular causes, and a 64% reduction in heart failure.

Few serious adverse effects were reported.

The investigators concluded that antihypertensive treatment in persons over age 80 is beneficial.

This is another example of investigators and editors reporting benefits in terms of percentage reduction in risk. This looks impressive but may have little clinical meaning.
To detect absolute risk reductions, readers must go to the data published in the article and calculate it themselves.

According to my calculations, for every 1000 persons treated for one year, 5 patients would avoid stroke, 5 would avoid death from any cause, 7 avoid any CVD event, and 10 avoid heart failure.

Considering the severity of these outcomes, I believe treatment is worthwhile.

Journals almost always cite BP as systolic / diastolic. And almost always the diastolic is irrelevant, especially for patients over age 50. Outcomes depend on systolic. Patients get confused when told their BP is X/Y. What is systolic? What is diastolic? They will understand more clearly and remember when told their BP is X.

What is "hypertension" ? At present, the best we can do is to define it as a number. Alternatively, hypertension could be defined as that BP, which in an individual will increase risk of organ damage, mortality, and morbidity.

Decision about whether, and how, to treat a given BP in an elderly person would then become a matter of clinical judgment instead of depending on numbers. Certainly, many persons over age 80 should not be treated.

The subjects in this trial were generally in good health for their age.

If the decision is made to treat, I believe home BP monitoring is essential to guide therapy.

"It's Time To Get Serious About BP Measurement"

6-2 IMPROVING THE MEASUREMENT OF BLOOD PRESSURE: Is it time for regulated standards?

Ideally, BP should be measured using an appropriately-sized cuff, with the patient resting for 5 minutes in a seated position, with the feet on the floor, with the back supported.

Deviations from this standard are common. In practice, BP measurements are remarkably casual. Cuffs are applied over clothing. BP is obtained without allowing the patient to rest. Measurements are taken while patients are sitting hunched over the examining table with their legs dangling. Training is minimal. Devices are not checked, and not recalibrated.

Even in research settings, the most experienced personnel can become sloppy, as manifested by digital preference—an unexpected high percentage of readings ending in "0".

Frequency of measurement also matters. Random measurement error and inherent biological fluctuations lead to within-patient variability of measurement. Assessment of BP requires several measurements over separate patient encounters. Averaging BP across several clinic visits enhances precision even more than several readings at a single visit.

The percentage of patients with controlled BP (< 140) may vary with the type of measurement. A study in this issue of *Annals*[1] reported 28% of patients were considered controlled by clinic measurements; 49% by home measurements; and 68% by research methods. Only 33% of patients were correctly classified as having BP that was in or out of control. A single measurement of 120 to 157 was not sufficiently precise to correctly classify a patient as having BP that was in control with 80% certainty.

Greater precision (lower within-patient variation) can be obtained with additional measurements. This benefit was present when the measurements were taken at up to 4 visits. There was little benefit in additional measurements. (Averaging BP across visits reduces within-patient variability.) However, the cost and patient-burden of several visits is of concern. Hence determination of BP at home will benefit by enabling repeated measurements. Reasons may be—elimination of the white coat effect, and clinic measurements that do not conform to recommended standards.

The implications of this discordance are substantial for both patients and clinicians. Spuriously high clinic readings could lead to inappropriate escalation of drug treatment and adverse effects.

The importance of accurate BP measurement has largely been neglected. High quality measurements should be averaged over several visits

"It is time to get serious about BP measurement."

Annals Internal Medicine June 21, 2011; 154: 838-39 Editorial, first author Laurence J Appel, Johns Hopkins University, Baltimore MD.

1. "Measuring Blood Pressure for Decision-making and Quality Reporting: When and How Many Measurements?" Original investigations, first author Benjamin J Powers, Durham Veterans Affairs Medical Center, Durham NC

This strengthens my belief that home BP measurement is necessary for good BP control. The usual busy primary care office may not take time to assess BP properly. Home measurement can be done with the patient relaxed and in the proper position. Multiple readings can easily be taken and averaged over time.

My experience with home BP—the third reading in a 10 minute series is often the lowest.

The article did not mention diastolic pressure. I believe only systolic is important in the vast majority of older patients seen in primary care. Focusing on systolic will save time and avoid patient-confusion.

Prolonged Daily TV Viewing Was Consistently Associated With Increased Risk

6-3 TELEVISION VIEWING AND RISK OF TYPE-2 DIABETES, CARDIOVASCULAR DISEASE, AND ALL-CAUSE MORTALITY

On average, 40% of daily free time (about 4 hours) is occupied by TV viewing.

TV viewing displaces more active energy expenditure.

This meta-analysis summarized all published cohort studies on the incidence of type-2 diabetes (**DM-2**), non-fatal and fatal cardiovascular disease (**CVD**), and all-cause mortality related to the amount of daily TV viewing.

A systematic search (1970-2011) found 8 relevant studies (Europe, Australia, and the US). Some studies reported outcomes for more than one endpoint (eg, DM-2 and CVD). All were prospective. The study population was healthy at baseline.

Total numbers in the 8 studies:

	Individuals	Person-years	Cases	Mean years
DM-2	175 938	1 100 000	6428	8.5
CVD (fatal & non-fatal	34 253	-	1052	10.4
All-cause mortality	26 509	202 353	1879	6.8

(Adjusted for multiple confounding factors)

Adjusted relative risk (RR) per each 2-hours of TV viewing per day:

	RR (pooled)
DM-2	1.20
CVD	1.15
All-cause mortality	1.13

Each 2-hours of daily TV viewing was associated with 176 cases of DM-2; 38 cases of CVD; and 104 cases of all-cause mortality per year.

There was a linear dose response for each outcome.

Conclusion: Prolonged daily TV viewing was consistently associated with increased risk of DM-2, CVD, and all-cause mortality

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We live in a sedentary society. We work at desks, at computers, study, and read. All non-physical activities. All could be added to judge total adverse effects of sedation.

Most of us have to make conscious efforts to increases physical activity. Many, including primary care physicians, fail to do so. Of course, primary care clinicians should encourage continuing physical fitness as part of the healthy lifestyle. They must first act as a role model and maintain fitness themselves.

"Potentially Highly Cost-Effective"

6-4 AN INTERNATIONAL RANDOMIZED PLACEBO-CONTROLLED TRIAL OF A FOUR COMPONENT COMBINATION PILL ("POLYPILL") IN PERSONS WITH RAISED CARDIOVASCULAR RISK.

In 2000, the World Health Organization and the Welcome Trust convened a meeting of experts to discuss evidence-based and affordable interventions for non-communicable diseases. A major impetus was the potential of a fixed-dose combination pill containing low doses of aspirin, a statin

drug, and two BP-lowering drugs. The use of one pill daily containing all components would reduce cost and increase compliance.

In 2002, the WHO outlined the substantial potential public-health benefits and cost-effectiveness of such a pill, which was expected to substantially reduce cardiovascular risk in persons with cardiovascular disease.

This trial assessed the short-term efficacy and adverse effects of the polypill among people at raised risk of CVD. It was conducted in 7 countries 2008-2009. All subjects (n = 378; 13 subjects in the US; age range 50-70) had increased risk over 5-years determined by the Framingham risk function.

Randomized to low daily doses of 4 drugs:

1) Aspirin 75 mg
   Lisinopril 10 mg
   Hydrochlorothiazide 12.5 mg
   Simvastatin 20 mg, or
2) Placebo

Followed participants periodically for 12 weeks.

Expected reductions in CVD risk were estimated using data from systematic reviews, which have shown that each medication class confers approximately similar proportional reductions in cause-specific outcomes across a wide range of patient populations.

There was a wide range of baseline systolic BP (**SBP**) and LDL-cholesterol levels; 33% were regarded as hypertensive, 52% as pre-hypertensive, and 14% as normal ; 22% of participants had a 5.0-7.5% 5-year risk of CVD; 3% had a risk over 20%.

Over the 12-week follow-up, reductions were on average:

	Baseline	12-week change
SBP	134	-9,9
LDL-c	140	-31

Tolerance and adverse effects:

	Polypill	Placebo
Discontinued treatment	23%	18%
Reported adverse effects	58%	42%

Most adverse effects in the polypill group were attributed to the well-known adverse effects of aspirin—gastric irritation and bleeding, and to the ACE inhibitor—cough, headache, dizziness, and hypotension.

Predicted effects: One would expect a 60% reduction in CVD risk and a 50% increase in extra-cranial bleeding. (The adverse effects of aspirin balanced out the beneficial effects of BP-lowering.) In a patient group at a risk similar to the average in this trial, one would expect, over 5 years, about 1 in 18 would benefit in terms of avoiding a major event, largely due to SBP and LDL-c reduction. Among untreated patients with established CVD, the absolute benefit would be higher.

Most adverse effects, including virtually all major ones, were due to aspirin, which provided modest benefits. Even among patients with moderately elevated risk, the absolute benefit of aspirin was small.

Trials showing hard CVD end-points (eg, myocardial infarction and CVD death) would take years to complete.

Most all the benefits in the trial were due to BP and cholesterol lowering.

Conclusion: Over 12 weeks, the polypill achieved sizable reductions in SBP and LDL-cholesterol. It caused adverse effects in 1 of 6 people. The halving of predicted CVD risks was modestly lower than previous estimates, and the adverse effects modestly higher. Substantial benefit would be expected among patients at high risk.

The polypill principle is fascinating. It was first proposed by Wald and Law "A Strategy to Reduce Cardiovascular Risk by More than 80%" BMJ June 28, 2003; 326: 1419-23 (See www.practicalpointers.org June 2003 for an abstract.)

The original polypill consisted of low doses of 6 drugs: simvastatin, hydrochlorothiazide, atenolol, enalapril, folic acid and aspirin. The pill was to be given to all persons over age 55 without pre- or post-testing.

In view of advances in drug efficacy and knowledge about adverse effects, most of the drugs have been changed;

The present article suggests that the adverse effects of aspirin balance out the beneficial effects. Thus, an updated pill would omit aspirin. It would contain a statin, (eg simvastatin 20 mg) and 2 antihypertensive drugs. Some authorities would prefer a calcium blocker, instead of an ACE

inhibitor, in patients over age 50, and chlorthalidone instead of hydrochlorothiazide. An updated pill would then contain: Simvastatin 20 mg, amlodipine 2.5 mg, and chlorthalidone 12.5 mg. All are available as generics. With a little trouble, the combination could be obtained at a modest cost.

Present "normal" (ie, target) BP and LDL-c levels are arbitrary. Many patients with levels below normal will benefit from further reductions in BP or LDL-c. And many will benefit by lowering a high level to a level still above target. The extent of the benefit depends on baseline risk. Lowering population SBP from 140 to 130 will benefit more (in absolute terms) than lowering it from 130 to 120.

Should primary care clinicians in the US ever prescribe the pill?

For patients who are compliant, but have limited resources and difficulty accessing medical care, I believe prescribing a polypill would be justified. It would still require some pre-testing and some post-testing.

I believe the principle of treating only patients with "abnormal" target levels will gradually be relaxed.

At What Cost?

6-5 EXEMESTANE FOR BREAST CANCER PREVENTION IN PREMENOPAUSAL WOMEN

Estrogen contributes to normal breast development, and can also promote breast cancer (BC).

Aromatase inhibitors[1] (eg, exemestane) profoundly suppress estrogen levels in postmenopausal women.

This international randomized, double-blind placebo-controlled trial (2004-2010) was designed to detect effects of exemestane in reducing risk of primary invasive BC.

All subjects (n = 4560) were postmenopausal (mean age 62). All were at increased risk of BC due to:

1) Age over 60
2) Gail risk score for BC greater than 1.66% chance (mean 2.3%) of invasive BC within 5 years (www.cncer.gov/bcrisktool)
3) Prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ
4) Ductal carcinoma in situ treated with mastectomy

Randomized to:

1) Exemestane 25 mg/d +placebo

2) Placebo + placebo

Invasive BC at a median of 35 months number):

Exemestane 11

Placebo 32

The hazard ratio (treated vs placebo) = 0.35, a reduction in risk of 65%[2]

The number needed to treat (NNT) with exemestane for 3 years to prevent one BC = 94.

Exemestane reduced annual incidence of invasive BC from 0.55% to 0.19% and also reduced the incidence of known BC precursors (eg, ductal carcinoma in situ). This suggests possible further reductions in long-term incidence of BC.

Menopausal symptoms (hot flashes, sweating, insomnia) and arthritis were more common in the exemestane group.

Endometrial cancers and venous thromboembolism did not occur with exemestane.

Conclusion: Exemestane significantly[3] reduced invasive BC in postmenopausal women who were at moderate risk. During 3-years of therapy, there were no serious toxic effects and only minimal changes in health-related quality-of-life.

Clinicians should be aware of the cost component (to the patient and to society) of the benefit / harm-cost ratio of treatments they advise.

My pharmacist quotes a cost of $354.00 for 30 25 mg generic exemestane tablets.

= $11/80 per day per person

= $4,307.00 per year per person

= $12 921 for 3 years

= $29 521 485 to treat 2285 persons for 3 years

= $1 405 922 to prevent one BC over 3 years (21 of 2285 persons)

(This at a downside of frequent menopausal symptoms.)

1 *Some BCs require estrogen to grow.*

Aromatase is an enzyme that synthesizes estrogen.

The ovaries are the major source of estrogen in premenopausal women. In postmenopausal women, most estrogen is produced by conversion of androgen into estrogen by aromatase in percutaneous tissue (mainly adipose tissue) where it acts locally.

Circulating estrogen in postmenopausal women is the result of estrogen escaping local metabolism.

Exemestane (Aromatasin) is an aromatase inhibitor. It is used to treat postmenopausal BC. It is an oral steroid, which irreversibly binds to aromatase and inactivates it. The suppression rate is 85%for estradiol and 95% for estriol.

It is available as a generic. Source: Wikpedia

2 *Editors and authors persist in reporting risk reductions as percentages. This is clinically meaningless and misleading. The absolute risk reduction was about 1 per 100 treated for 3 years.*

3 *They also persist in mentioning "significance", meaning statistical significance, which can also be clinically meaningless and misleading.*

"No Significant Threat Of Radiation From The Scan"

6-6 AIRPORT FULL BODY SCANNING: What is the Risk?

The Transportation Security Agency (TSA) has deployed 486 full body scanners (FBS) in airports in the US. More are on the way.

There are two types of FBS. Each generates a detailed outline of the human body:

The millimeter-wave scan emits extremely low-energy waves—each scan delivers a small fraction of the energy of a cell phone. The scan captures reflected energy.

The backscatter scanning machine (the most commonly used type) uses very low doses of X-rays. Scans used in medical imaging transmit energy *through* the body and deposit it *in* the body. Backscatter scanners detect radiation that *reflects off* the person's body. Some energy is absorbed by the most superficial tissues of the body such as skin.

Both machines have the capacity to create extremely detailed and revealing images. They generate outlines that reveal genitalia, buttocks, breasts, fat creases and all types of prostheses. The TSA has taken several steps to ensure the privacy of passengers—blurring the face, installing software to make the image less provocative, and ensuring that the operator never sees the passengers directly. Scans in airports cannot be saved or exported.

Another concern is the safety of the backscatter X-ray, which uses ionizing radiation. The potential for this to cause damage depends on dose. Low doses do cause biological damage, but the cells rapidly repair the damage. Moderate doses can change cells to become cancerous and can cause birth defects.

The dose of ionizing radiation emitted by the backscatter scan is extremely low—so low that it is really not known if there is a potential to cause harm. But even if the dose is low, the cancer risk merits consideration, given that there are 750 million enplanements in the US each year, and even a small risk per person could potentially translate into a significant number of cancers.

All of us are routinely exposed to ionizing radiation from many different sources—an average of 6 *milli*-sieverts (mSv) annually. The 2 most common sources are medical procedures and ubiquitous background radiation (natural sources) from the sun and cosmic rays, and from the earth.. The backscatter X-ray scan exposes individuals to 0.03 to 0,10 *micro*-sieverts (uSv)—the equivalent of 3 to 9 minutes received from natural radiation in daily life.

One backscatter scan adds radiation equivalent to about 1 to 3 minutes of flight time.

A frequent flier would have to undergo 50 scans to equal the radiation from a dental X-ray; 1000 scans to equal that of one chest X-ray; 4000 to equal one mammogram; and 20 000 to equal a single abdominal-pelvic CT scan.

Extrapolating cancer risk from high levels of X-ray exposure to the small amounts of radiation from backscatter scan is questionable, and may be inappropriate. If one assumes a "linear-no-threshold" model (ie, there is no threshold) every exposure carries some risk.

The authors estimate that risk from a backscatter scan, given the limitations of cancer prediction, to be about 6 cancers over the lifetime of all US passengers. This contrasts with the hundreds of thousands of cancers that occur in the country every year.

Based on what is known about scans, passengers should not fear going through the scanners for health reasons, as the risks are truly trivial. However, continuing independent testing of the machines is necessary.

Conclusion: There is no significant threat of radiation from the scan.

I enjoyed this article, although it does not directly pertain to primary care medicine. Patients may ask about it.

It does contrast the concerns about very low doses of radiation from the scans with seeming

unconcern about the relatively massive radiation doses from CT scans and mammograms.

As the authors mention, we can gauge the benefit / harm-cost ratio of backscatter scans. In my opinion, the benefit is great (peace of mind) and the harm nil. Costs may be significant, but when spread over millions of passengers, it becomes small.

FULL ABSTRACTS JUNE 2011

6-1 NEW GUIDELINE COVERS WAYS TO PREVENT AND TREAT HYPERTENSION IN ELDERLY PEOPLE

The guideline:

- Evaluation should begin with accurate BP measurement, which in this population should include the patient standing up for 1 to 3 minutes to evaluate possible hyper- or hypo-tension.
- Once a BP reading is taken, the physician needs to determine if it represents hypertension. Systolic BP increases naturally in the elderly due to age-related stiffening of the large vessels. The panel suggests a target of 140 mmHg for age 65 and older. It is not clear whether systolic goal should be the same in patients age 65 to 75 as in patients older than 80.
- If hypertension is determined, identify reversible and treatable causes. Evaluate for organ damage. Assess other CVD risk factors and comorbid conditions affecting prognosis, and identify barriers to adherence. Pay particular attention to quality-of-life factors. Symptomatic well-being, cognitive function, and physical activity diminish with age and disease.
- Suggest life-style modifications. This may be the only treatment necessary. Focus on smoking, cessation, reducing excess weight and mental stress, and modifying excess sodium and alcohol intake. Increase physical activity.
- If drug therapy is warranted, prescribe the lowest dose and increase the dose gradually. "Go slow; go low" Add a second drug from another drug class if target BP is not reached. For initial therapy, a low dose thiazide diuretic is recommended.
- Be conservative in treatment, going by the individual patient's tolerance rather than trying to achieve target levels.
- For patients over age 80, a target systolic of 140-145 is acceptable.
- Check frequently for orthostatic hypotension. BP lower than 130 should be avoided.
- Remember that chronological age does not define "elderly", and that the elderly are more prone to adverse effects.

Since this is the first guideline for the elderly, the authors recognize that work remains to be done.

JAMA June 15, 2011, 305: 2394 "Medical News and Perspective" by Mike Mitka, JAMA staff.

Prolonged Daily TV Viewing Was Consistently Associated With Increased Risk

6-3 TELEVISION VIEWING AND RISK OF TYPE-2 DIABETES, CARDIOVASCULAR DISEASE, AND ALL-CAUSE MORTALITY

On average, 40% of free time (about 3 to 4 hours) is occupied by TV viewing.

TV viewing displaces more active energy expenditure. It is associated with unhealthy eating in both children and adults. (Influenced at times by TV advertising.) Both sedentary lifestyle and unhealthy diet are independent risk factors for type-2 diabetes (DM-2), cardiovascular disease and all-cause mortality.

This meta-analysis summarized all published prospective cohort studies on the incidence of DM-2, non-fatal and fatal CVD, and all-cause mortality related to amount of daily TV viewing.

STUDY

1. A systematic search (1970-2011) found 8 relevant studies (Europe, Australia, and the US), Some studies reported outcomes for more than one endpoint. (eg, DM-2 and CVD) All were prospective. The study populations were healthy at baseline.
2. Presented relative risks (RR) and odds ratios (OR).
3, Pooled estimates of risk in increments of 2 hours of TV viewing.

RESULTS

1. Total numbers in the 8 studies:

	Individuals	Person-years	Cases	Mean years
DM-2	175 938	1 100 000	6428	8.5
CVD (fatal and non-fatal)	34 253	-	1052	10.4
All-cause mortality	26 509	202 353	1879	6.8

(Adjusted for multiple confounding variables.)

2. Adjusted relative risk for each 2-hour increase in TV viewing daily:

	RR (pooled)
DM-2	1.20
CVD	1.15
All-cause mortality	1.13

3. TV viewing and risk of DM-2:

As daily-hours of viewing increased from 2 to 6, risk increased linearly.

The RR = 1.20 for each 2-hour viewing per day.

The absolute risk for DM-2 per 100 000 individuals per year per 2-hours of daily viewing = 176.

4. TV viewing and risk of CVD:

RR = 1.15 per each 2-hours viewing per day.

There was a linear dose response.

The corresponding absolute risk, based on estimates of CVD mortality in the US, was 38 cases of fatal CVD per 100 000 individuals per year for every 2-hours per day of viewing.

When data from dietary factors and BMI were included, the results were not substantially changed.

5. TV viewing and risk of all-cause mortality:

RR = 1.13 for each 2-hours of viewing per day.

The absolute risk increase was estimated to be 104 per 100 000 per year for each 2-hours of daily viewing. Risk increased especially after the first 3-hours. The RR was then 1.30.

DISCUSSION

1. TV viewing was consistently associated with higher risk of DM-2, CVD, and all-cause mortality.
2. The dose-response was linear for each 2-hours of viewing per day.
3. There was still a possibility of publication bias and residual confounding. There was a relatively small number of studies. Subgroups of individuals who were more susceptible to risk were not determined.
4. Although all studies excluded subjects with chronic disease at baseline, there may be some reverse causality. Ie, subjects with increased disease may become more sedentary.
5. In some studies, the assessment of TV viewing relied on self-report at baseline.
6. Not all studies controlled for physical activity.
7. However, studies included large sample size, long duration of follow-up, and prospective analysis.
8. Numerous studies have reported associations of sedentary life-style with biological risk

factors—adverse lipid levels and obesity

9. Three randomized trials have shown benefits by reducing TV time. The studies were short. They suggested that reduced TV viewing time may lead to improvements in diet, physical activity, and BMI. It is possible that some of the benefit was explained by reducing the caloric intake associated with TV viewing. The present study did not confirm this.

CONCLUSION

Prolonged TV viewing was consistently associated with increased risk of DM-2, CVD, and all-cause mortality.

JAMA June 15, 2011; 2448-55 Original investigation, first author Andrew Grontved, University of Denmark, Odense, Denmark.

"Potentially Highly Cost-Effective"

6-4 AN INTERNATIONAL RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF A FOUR-COMPONENT COMBINATION PILL ("POLYPILL") IN PERSONS WITH RAISED CARDIOVASCULAR RISK

In 2000, the World Health association and the Welcome foundation convened a meeting of experts to discuss evidence-based and affordable interventions for non-communicable disease. A major impetus was the potential of a fixed-dose combination pill containing low-doses of aspirin, a statin, and two BP-lowering drugs. The use of one pill daily containing all components would reduce costs and improve compliance.

In 2002, the WHO outlined the potential public health benefits and cost-effectiveness of such a pill, which was expected to substantially reduce cardiovascular risk in persons with vascular disease.

The polypill has gained widespread attention. It was originally recommended to treat everyone over age 55 in developed countries. Now, major cross-disciplinary guidelines recommend targeting use on the basis of global risks of cardiovascular disease (CVD), making global intervention rather than single risk modification the standard of care.

This trial assessed the short-term efficacy and adverse effects of the polypill among people at raised global risk of CVD.

The trial was also planned to inform people with established CVD. But, the use of placebo is not appropriate for this group.

STUDY

1. Conducted in 7 countries 2000-2009. All subjects (n = 278; 13 in the US; age range 50-70) had increased CVD risk over 5-years determined by the Framingham risk function. No subject had contraindications to any components of the pill
2. Randomized to low doses of 4 drugs:
   1) Aspirin 75 mg
   Lisinopril 10 mg
   Hydrochlorothiazide 12,5 mg
   Simvastatin 20 mg
   2) Placebo
   The pill was taken once daily in the evening with food.
3. Followed participants periodically for 12 weeks.
4. Primary outcome = change in systolic BP (SBP), and LDL-cholesterol. (Intention-to-treat)
5. Expected reductions in CVD risk were estimated using data from systemic reviews, which have shown that each medication class confers approximately similar proportional reductions in cause-specific outcomes across a wide range of patient populations. There are no major differences between agents. For example, lowering LDL by 39 mg, lowering systolic BP by 10 mmHg, and aspirin individually lower CVD by 42%, 27% and 20%. The expected joint effect of reducing LDL by 20 mg, systolic by 5 mmHg, and aspirin would be approximately a 40% lower risk of CVD.

RESULTS

1. There was a widespread range of SBP and LDL levels; 33% would be regarded as having "hypertension"; 52% as "prehypertension"; and 14% normal; 22% of participants had a 5-7.5% 5-year risk of CVD; 3% had a 20% risk. At 12 weeks, data on LDL and SBP were available for 88% of participants.
2. Over the12-weeks of follow-up, reductions were on average:

	Baseline	12-week change

SBP	134	-9.9 mmHg
LDL	140	-31 mg

3. Reductions also occurred in DBP, total cholesterol, and triglycerides. No clear evidence of change in HDL.
4. Tolerance and adverse effects:

	Polypill	Placebo
Discontinued treatment	23%	18%
Reported adverse effects	58%	42%

The adverse effects of the polypill group were attributed to the well-known adverse effects: aspirin—gastric irritation,; bleeding tendency, and to ACE inhibitors—cough; headache; dizziness; and hypotension..

Most adverse effects did not necessitate stopping treatment. Most occurred early, within 2 to 6 weeks. No deaths, major vascular events, major bleeds, or gastric ulceration occurred.

Few serious adverse effects were noted in each group.

5. Predicted effect on CVD risk:

One would expect an approximate 60% reduction in CVD risk. And a 5% increase in the risk of extra-cranial bleeding. (The beneficial effects of BP reduction balanced out the adverse effects of aspirin.)

In a patient group at similar risk to the average in this trial, one would expect, over 5 years, about 1 in 18 would benefit in terms of avoiding a major event, largely due to SBP and LDL reduction.

Among untreated patients with established CVD, the benefits would be greater.

DISCUSSION

1. Treatment with the polypill achieved sizable reductions in SBP and LDL. The treatment could be expected to more than halve cardiovascular risk.
2. The pill caused adverse effects sufficient to stop treatment in 1 of 20 participants. Lesser adverse effects occurred in about 1 in 8.
3. There are limitations of the study: Short follow-up; a high drop-out rate; inability to determine which adverse effect was due to which drug; the patient population represented a relatively narrow group, having raised CVD risk and no existing contraindications to any drug. The predicted reductions in risk are based on reductions in risk factor levels—indirect estimates.

4. Several previous trials have assessed the effect of a polypill. The results are compatible to the present study, although the components of the pill varied. One 12-week trial in India (n = 2053) reported the reductions from each treatment modality were essentially the same. A second trial from Iran (n =475) lasted 12 months. Both trials were more prone to bias. A recent trial (n = 216) in Sri Lanka suggested similar reductions in risk factors and predicted CVD risk.
5. What are the implications for clinical practice?

Among patients at low to modest global CD risk, future work is required on the polypill formula. The present trial suggested that tolerability is not as good as previous trials have suggested, although still causing no symptoms in 5 of 6 persons treated.

More adverse effects, including virtually all major ones, were due to aspirin, which provided modest benefits. Even among patients with moderately elevated risk levels, the absolute benefit of aspirin would be small. Polypill based on BP and cholesterol reduction are therefore required, along with research on the benefits and risks compared with usual care.

Trials showing hard CVD end-points (eg, myocardial infarction and CVD death) would take years to complete.

Most or all the benefits in this trial were due to the extent of BP and LDL lowering. Efficacy of treating BP and cholesterol-lowering well below historic “hypertension” and “dyslipidemina” levels is established. Will clinical practice still be restricted to treatment of persons with BP and cholesterol levels considered to be hypertensive and hyper-cholesterolemic? (Regardless of CVD risk).

Among patients with established CVD, further evidence on efficacy of individual classes of drugs is not required. Effectiveness has been established in clinical trials over the past half century. All major guidelines recommend BP and cholesterol lowering and antiplatelet therapy in patients with vascular disease. Research is therefore required only on the comparative role of polypill-based treatment in patients whose BP and LDL levels now do not reach the threshold for treatment.

The vast majority of high-risk people are presently not treated. Increasing access to treatment is potentially highly cost-effective.

CONCLUSION

The polypill achieved sizable reductions in SBP and LDL-cholesterol. It caused adverse effects in 1 of 6 people.

The halving of predicted CVD risk was modestly lower than previous estimates, and the adverse effects moderately higher.

Substantial benefit would be expected among patients at high risk.

BMJ June 4, 2011; 342: 1229 (BMJ 2011;342:d3355) presented a brief notice of the trial
Author Susan Mayor. The full article is published in PLoS

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At What Cost?

6-5 EXEMESTANE FOR BREAST CANCER PREVENTION IN POSTMENOPAUSAL WOMEN

Estrogen contributes to normal breast development and can also promote breast cancer (BC). To date, chemoprevention of BC has focused on the selective estrogen-receptor modulators (SERM) tamoxifen and roloxifen, which exert antiestrogen effects on the breast as well as on other organs.

Tamoxifen has been shown to reduce the number of invasive BCs by 50% compared with placebo. The estimated number needed to treat with tamoxifen for 5 years to prevent one BC is 95, falling to 57 at 10 years.

Tamoxifen increases risk of endometrial cancer and venous thromboembolism.

The acceptance of SERMs to reduce risk has been poor because they are associated with rare but serious adverse effects. A 2002 expert assessment concluded that tamoxifen lacked overall health benefits.

Aromatase inhibitors (eg, exemestane) profoundly suppress estrogen levels in postmenopausal women. In early trials of therapy for BC, AI reduced contralateral primary BC more than tamoxifen.

STUDY

1. This international, randomized, placebo-controlled trial (2004-2010) was designed to detect effect of exemestane in reducing risk of primary invasive BC.
2. All subjects (n= 4560) were postmenopausal (median age 62).

All were at increased risk of BC due to:

1) Age over 60.

2) Gail risk score of BC greater than 1.66% chance (median 2.3%) of invasive BC within 5 years.

3) Prior atypical ductal lobular hyperplasia or lobular carcinoma in situ

4) Ductal carcinoma in situ treated with mastectomy

3. Mammography was required within 12 months before randomization and every 12 months thereafter.
4. Randomized to:
   1) Exemestane 25 mg daily + placebo
   2) Placebo + placebo
5. Primary outcome = incidence of invasive cancer.

RESULTS

1. Invasive BC at median of 35 months (number):

   Exemestane n = 11

   Placebo n = 32

   (Relative risk reduction of 65% (21 BCs prevented over 3 years by treating over 2000 patients.)
2. Incidence of ductal carcinoma in situ (number):

   Exemestane n = 10

   Placebo n = 27
3. Exemestane appeared to be superior in all prespecified subgroups.
4. The number needed to treat (NNT) to prevent one invasive BC over 3 years = 94.
5. Symptoms and adverse effects occurred in 88% of the exemestane group and 85% of the placebo group, with no difference in new osteoporotic fractures, cardiovascular or other cancers. Five % in both groups discontinued protocol treatment early due to adverse effects. More hot flashes in the exemestane group (18%vs 11.9%). Worsened menopausal symptoms occurred in7% of the exemestane group. There were 19 deaths in each group.

DISCUSSION

1. Exemestane reduced annual incidence of invasive BC from 0.55% to 0.19% and also reduced the incidence of known BC precursors (eg, ductal carcinoma in situ). This suggests possible further reduction in long-term incidence of BC.
2. Menopausal symptoms (hot flashes, sweating, insomnia) and arthritis were more common in the exemestane group.
3. Endometrial cancers and venous thromboembolism did not occur with exemestane.
4. The trial has limitations. The follow-up was short. The numbers of BC were small. The optimal duration of therapy is not known. The NNT to prevent one BC over 3 years was high (94).

CONCLUSION

Exemestane significantly reduced invasive BC in postmenopausal women who were at moderate risk During 3 years, there were no serious toxic effects and only minimal changes in health-related quality-of-life.

NEJM June 23, 2011; 364: 2381-91 Original investigation be the National Clinical Trial Group MAP.3, first author Paul E Goss, Massachusetts General Hospital, Boston Mass.
Supported in part by Pfizer.

"No Significant Threat Of Radiation From Scans"

6-6 AIRPORT FULL BODY SCANNING: What is the Risk ?

The Transport Security Administration (TSA) has deployed 486 full body scanners (FBS) in 78 airoports in the US. More are on the way.

Thee are 2 types of FBS. Each generates a detailed outline of the human body:

The millimeter-wave scanner emits low-energy waves—each scan delivers a small fraction of the energy of a cell phone.

The backscatter scanning machine (the most commonly used type) uses very low doses of X-rays. Scans used in medical imaging transmit X-rays *through* the body and deposit energy *in the body*. Backscatter scanners detect radiation that *reflects off* the person's image. Some energy is absorbed by the most superficial tissue in the body, such as skin.

Both machines have the capacity to create extremely detailed and revealing images. They generate outlines that reveal genitalia, buttocks, breasts, fat creases , and all types of prostheses. The TSA has takes several steps to ensure the privacy of passengers—blurring the face, installing software to make the images less provocative, and ensuring that the operator never sees passengers directly. Scans in airports cannot be saved or exported.

Nevertheless, groups such as The American Civil Liberties Union have objected to scanning on the basis of the 4th amendment *(illegal search and seizure*) and the Religious Freedom Restoration Act.

Another concern is the safety of the backscatter X-ray, which does use ionizing radiation. The potential for this to cause damage depends on dose. Low doses do cause biological damage, but cells rapidly repair the damage. Moderate doses can change cells to become cancerous and cause birth defects.

The dose of ionizing radiation emitted by the backscatter scanner is extremely low—so low that it is really not known if there is a potential to cause harm. But, even if the dose is low, the cancer risk merits consideration, given that there are 750 million enplanements in the US each year, and even a small risk per person could potentially translate into a significant number of cancers.

Exposure to ionizing radiation: full body airport scans vs ubiquitous background exposure:

All of us are routinely exposed to ionizing radiation from many different sources--- an average of 6 *milli*-sieverts (mSv) annually. The 2 most common sources are medical procedures and ubiquitous background radiation (natural sources) from the sun and cosmic rays. The backscatter X-ray scanner exposes individuals to 0.03 to 0.10 *micro* sieverts (uSv)—the equivalent of 3 to 9 minutes of natural radiation received daily

Natural radiation increases as distance from the earth increases. Altitudes of commercial flights are high enough to increase natural radiation received from the sun. Overall, air travel is associated with an exposure of about 0.04 *micro*-sieverts per minute of flight time. The backscatter scan adds radiation equivalent to about 1 to 3 minutes of flight time.

Comparing risk associated with backscatter scan with other sources of radiation:

A frequent flier would have to take more than 50 airport scans to equal the radiation for a dental X-ray; 1000 to equal that of one chest X-ray; 4000 for one mammogram; and 20 000 to equal a single abdominal-pelvic CT scan.

Cancer risk associated with backscatter scans:

Estimating cancer risk from very small X-ray doses is difficult. Studies that have demonstrated an association have been performed at doses much higher than levels emitted by the scan. Extrapolation from high levels of X-ray exposure to small amounts of radiation from backscatter scans is questionable, and may be inappropriate.

If one assumes a "linear-no-threshold" model, (ie, there is no threshold) every exposure carries some risk.

Energy from the scan is concentrated in the skin. There is no model for understanding the relationship between skin exposure and risk of skin cancer.

The backscatter scan radiation will also be concentrated in breast tissue, so breast exposure from the scan can be used to predict breast cancer risk.

The authors estimated risk, given the limitations of cancer prediction, in 3 groups of passengers.

1) All fliers: Among the millions of enplanements per year, 6 cancers over the lifetime of those screened could result from backscatter radiation. This contrasts with the 40 million cancers that would develop in these individuals over their lifetimes.
2) Frequent fliers: Making some assumptions, 6 additional cancers could occur from the scans. This contrasts with an estimated 400 000 cancers that would be expected over the lifetimes of persons in this group.
3) Five year old frequent fliers: Children are more sensitive to radiation.
   The breast dose from backscatter scan is 0.004 *micro*-sieverts.
   An estimated 9140 cases per 100 000 5-year old girls would occur in those exposed to *one* sievert of radiation. For every 2 million girls who travel one round trip per week, an estimated 1 additional breast cancer would occur over the lifetimes of these children. This contrasts with the 250 000 breast cancers that would occur over the lifetimes of these children.

These examples show the difficulty in using epidemiological estimates of extremely low doses of radiation.

In medicine, we try to balance risks and benefits of everything we do. Airport scanning should not be deployed until they provide benefit—improving national security and safety. (This is outside the expertise of the authors.) Based on what is known about scans, passengers should not fear going through the scans for health reasons, as the risk is truly trivial. However, continuing independent testing of the machines is necessary.

Conclusion: There is no significant threat from radiation from the scans.

Archives Internal Medicine June 27, 2011; 171: 1112-14 "Special article", first author Patrick Mehta, University of California, Berkley

1 *The sievert [Sv-after Rolf Sievert, a Swedish physicist) attempts to quantify the biological effects of ionizing radiation as opposed to the physical aspects, which are characterized by the absorbed dose, measured in gray.*

The SI unit gray (Gy) is a measure of the absolute dose of radiation—absorbed by any material. The unit Sv measures the equivalent dose of radiation supposed to have a damaging effect equal to the same dose of gamma rays as the gray.

Both units are defined as energy (joules) per unit mass (kilograms)

An older unit for the equivalent dose is the roentgen equivalent man (rem), still used in the US. One sievert is equivalent to 100 rem. Use of the term rem is strongly discouraged.

Single dose examples in milli-Sv

Dental X-ray	*2.0*
Mammogram	*4 to 5*
Chest CT scan	*6 to 18*
GI series X-ray	*14*

Maximum yearly acceptable dose from any man made facility = 1 milli-SV

Source: Wikpedia