GUIDELINES FOR TREATING THE ELDERLY WITH MULTIPLE CONDITIONS
Many Elderly Patients Take Too Many Drugs

CARDIOVASCULAR OUTCOMES AND ANTIHYPERTENSIVE DRUG TREATMENT
Diuretics and Beta-Blockers First.

HEPATOBILIARY DISEASE COMMON IN TYPE 2 DIABETES

THE POLYMEAL: MORE NATURAL, SAFER, AND TASTIER (THAN THE POLYPILL)

ASPIRIN IS UNDERUSED IN PATIENTS WITH DIABETES

CAN ECONOMISTS HELP WITH THE OBESITY EPIDEMIC?

HEAVY METAL CONTENT OF AYURVEDIC HERBAL MEDICINE PRODUCTS

BALANCING THE RISKS AND BENEFITS OF FISH CONSUMPTION

A HOPEFUL TREATMENT FOR MACULAR DEGENERATION
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12-1 POTENTIAL PITFALLS OF DISEASE-SPECIFIC GUIDELINES FOR PATIENTS WITH MULTIPLE CONDITIONS

Primary care clinicians are encouraged to adhere to evidence-based guidelines for the management of specific diseases. The goal is to maximize benefits, including prevention of disease-specific outcomes, deaths, and hospitalizations.

For patients with several coexisting health conditions, the long-term net benefits and harms of the combination of all medications taken in adherence to disease-specific guidelines is less clear. Twenty percent of Medicare beneficiaries have 5 or more chronic conditions, and 50% are receiving 5 or more drugs. Take, for instance, a 70-year old woman who has hypertension, a past myocardial infarction, depression, diabetes, and osteoporosis. According to guidelines she should be receiving aspirin, a beta-blocker, and ACE inhibitor, a bisphosphonate, calcium, a diuretic, a SSRI, a statin, a sulfonylurea, and perhaps a thiazolidinedione and vitamin D.

What added benefit (and added harm) does the 7th, 8th, or 9th medication provide over the 2nd or 3rd? The risk of adverse effects increases as the number of medications (and the length of time they are taken) increases.

The prevalence of problems associated with multiple medications is probably underestimated. The broader physical, cognitive, psychological, and other effects remain unknown and unexplored. Patients, especially the elderly, and those with multiple complaints, vary in regard to the importance they place on health outcomes such as longer survival, the prevention of specific disease events, physical and cognitive functioning, and the amount of inconvenience and risk of adverse effects (and costs) they are willing to tolerate.

Elderly patients with multiple health problems who are receiving long-term, multiple-drug therapy present an important clinical problem. I believe older patients take too much medicine.

We have no way of knowing the benefits or adverse effects of multiple-drug combinations. No randomized trial has considered (or can consider) effects of a particular combination of 10 drugs with another 10 drugs, or with placebo. For example, an elderly patient takes 10 different drugs. [1, 2, 3, 4, 5, 6, 7, 8, 9,10]. Does drug 4 (even though medically indicated) add to her quality and length of life? We have no way of determining this. No conclusive randomized trial will, or can, be conducted comparing: 1) a group taking 9 drugs (omitting drug 4) with 2) a group taking all 10 drugs. I believe the benefit obtained from each of the 10 drugs would be much less for a patient taking 10 drugs than for a patient taking only one drug for one indication. I also believe that taking all 10 would be associated with more adverse effects than taking 9.
Clinicians (including myself), when presented with a new complaint by an elderly patient often automatically prescribe a drug for which the basis of benefit is established when prescribed for a lone condition. Multiple conditions and multiple drugs confuse the clinical picture. We should think twice.

Will adding a new drug really increase length and quality of life? Will it provide additional comfort? By how much? At what cost? Certainly many drugs given to younger patients for a specific condition do effectively prolong quality and length of life. But for elderly patients receiving multiple drugs little may be gained and much lost. Consider an elderly patient with limited life expectancy who is receiving multiple drugs, all with established benefits when used as lone therapy for a younger person. Will lowering her LDL-cholesterol from 130 to 100 enhance his length and quality of life? Will lowering his systolic BP from 170 to 140? Will increasing her bone density by 3%? Will lowering her HbA1c from 8% to 7%?

Periodically, I read in the newspaper of an elderly, economically disadvantaged, couple who must choose between paying for their medications or paying the rent. I feel compassion. I also think—How necessary are the drugs they are struggling to pay for? Do all of them add length and quality to their lives?

How should clinicians respond to this problem? There is no “scientific” answer. It depends on “clinical judgment” by the clinician and the informed preference of the patient. Patients should be able to judge for themselves the risks vs costs and harms. (Although at the practical clinical level this maybe impossible.) I believe short-term symptom-relieving drugs are more likely to improve quality-of-life in an elder than long-term risk-reducing medication. Regarding the illustrative patient, the SSRI may be the most important drug she receives.

When consulting with an elderly patient with multiple complaints who is receiving multiple medications ask--How do you feel? If “poorly”, perhaps it might best to remove a drug instead of adding one.

What is the primary care clinician to do when consulting with 80-year-old Mrs. Jones who is already receiving multiple medications and presents with a new complaint which may lead to her receiving yet another long-term drug? “Mrs. Jones, I can prescribe a drug for your condition, but I do not know if, when added to the other drugs your are taking, you will be benefited or harmed. If you do wish to take an added drug, it is very important that you let me know soon whether it really makes you feel better.”
ASSOCIATION BETWEEN CARDIOVASCULAR OUTCOMES AND ANTIHYPERTENSIVE DRUG TREATMENT IN OLDER WOMEN

This study, limited to postmenopausal women with hypertension, asked - 1) What single drug is most effective in lowering risk of cardiovascular events? 2) What 2-drug combination is most effective?

Over a 6-year follow-up determined relationship between incidence of CVD and baseline use of 1) Diuretics, 2) ACE inhibitors, 3) Beta-blockers, 4) Calcium channel blockers, as monotherapy; and 5) dual therapy (combinations of two).

Used as monotherapy, the hazard ratio of CVD death calcium blocker vs diuretic = 1.55 (Ie, calcium blocker was more hazardous than diuretic, a statistically significant difference.) Neither of the other two drugs had statistically significant differences in risk as compared with diuretics.

In the subset of patients receiving dual therapy at baseline, those taking a calcium blocker + diuretic had an 85% greater risk of CVD death as compared with beta-blocker + diuretic. There were no statistically significant differences between other combinations and risk of CVD.

In prevention of CVD in women with hypertension (and no history of cardiovascular disease) monotherapy with diuretics was equal or superior to monotherapy beta-blockers, ACE inhibitors or calcium blockers in preventing CVD complications.

Dual combination therapy with a calcium blocker + a diuretic was associated with higher CVD mortality than ACE inhibitors + diuretics and beta-blocker + diuretics.

The practical point for primary care clinicians: The less expensive diuretics and beta-blockers and the combination is in no way inferior to any other antihypertension drugs. Unless there is a strong indication for ACE inhibitors or calcium blockers, or unless there is intolerance to diuretics or beta-blockers, a diuretic or a beta-blocker or the combination should be first-line therapy.

I would use relatively low-dose of thiazide (not over 25 mg hydrochlorothiazide), and then add a beta-blocker.

HEPATOBILIARY DISEASE IN TYPE 2 DIABETES: A Narrative Review

This article discusses the spectrum of liver disease in DM2: non-alcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma, hepatitis C, acute liver failure, and cholelithiasis.

The insulin resistance and relative insulin deficiency in patients with DM2 affects lipid as well as carbohydrate metabolism. Insulin resistance decreases glucose uptake in the skeletal muscle and increases lipolysis from adipocytes. Lipolysis increases circulating free fatty acids. This in turn may lead to more insulin resistance and more lipolysis. Thus a vicious cycle is started. The net effect is increased storage of fat in the liver.
“Non-alcoholic fatty liver disease is the most prevalent liver disease in the USA.” NAFLD is a broad spectrum. It ranges from steatosis (bland fatty infiltration of hepatocytes), to non-alcoholic steatohepatitis (steatosis plus inflammation, necrosis, and fibrosis) and, in some patients, to end-stage liver disease and hepatocellular carcinoma. Prevalence of NAFLD is as high as 50% in patients with DM2 and obesity. (Of these, up to 50% have steatohepatitis; 19% cirrhosis).

The diagnosis is suspected in persons who do not use alcohol and have mildly elevated aminotransferase levels (AST and ALT; AST/ALT ratio greater than 1). Clinical features are non-descript. Some patients report malaise and a sense of fullness. Hepatomegaly may be present.

Imaging studies reveal a diffuse increase in echogenicity (“bright liver”). But only liver biopsy can assess the severity of damage and prognosis.

Treatment: Good metabolic control; caloric restriction (low glycemic index foods may be especially important); weight loss; exercise. Alcohol should be avoided. It is recommended that drug therapy begin with a secretogogue (a sulfonylurea) with rapid advancement to insulin therapy if control is not established. Insulin-sensitizing agents such as pioglitazone and rosiglitazone may be especially useful. The alpha-glucosidase inhibitors are also useful.

Cirrhosis, hepatocellular carcinoma, hepatitis C, acute liver failure, and cholelithiasis are also more common in patients with diabetes.

I was not aware of the frequency of NAFLD associated with DM2

Biochemical profiles sometimes unexpectedly report mildly increased liver enzymes. In the past, if I did not know of any clinical indication for the elevations, I would ignore the report. This article changes my approach. They may be indicating a significant illness which can be treated. Glucose tolerance should be checked in these patients.

12-4 THE POLYM EAL: A More Natural, Safer, and Tastier Strategy to Reduce Cardiovascular Disease by More than 75%

The concept of the Polypill was introduced in 2003. It was based on the premise that everyone in Western societies is at risk for cardiovascular disease. The investigators suggested it would immeasurably benefit if it were taken by everyone over age 50. The pill contained 6 individual drugs: a statin drug; 2) folic acid 800 micrograms; 3) aspirin 75 mg; 4), 5), 6) three antihypertension drugs at half dose (choose from a thiazide, beta-blocker, ACE inhibitor or angiotensin II blocker, and a calcium blocker).

The objective of the present study was to define a safer non-pharmacological and tastier alternative to the Polypill (a Polymeal) for use by the general population. The foods to be ingested daily: Wine, fish, dark chocolate, fruit and vegetables, garlic, and almonds.
Combining all ingredients of the Polymeal was calculated to reduce CVD in men by 76% and increase life expectancy free of cardiovascular disease by 9 years. In patients with CVD, life would be extended by 2.4 years.

The FDA would not approve any combination of drugs to be given to the general population without determination of individual risk. The Polymeal, although somewhat fanciful, is much more acceptable. Indeed, it has merit in reminding us of the benefits of diet in reducing risk of CVD. Except for garlic and dark chocolate, I believe the ingredients would be acceptable to many persons on a daily basis.

Note that wine is the most beneficial component of the diet. Some epidemiologists are so convinced of its benefits that they consider abstinence to be a risk factor.

12-5 ASPIRIN USE AMONG PATIENTS WITH DIABETES

Adults with diabetes, but with no clinical cardiovascular disease, may have risk of CVD events similar to non-diabetic adults with established CVD.

Strategies to prevent CVD events in persons with diabetes are underused. Aspirin effectively reduces risk of first and subsequent myocardial infarction in patients with diabetes as well as in those without. Many adults with diabetes do not use it.

This study assessed regular aspirin use among adults with diabetes between 1997 and 2001. Use remained less than ideal for patients with CVD. One quarter of diabetic patients with established heart disease or stroke did not use aspirin. Among those with risk factors for CVD (hypertension, dyslipidemia, smoking) 60% did not use aspirin. Almost 2/3 of those without CVD did not use aspirin.

Overall use by women was lower than by men.

Although aspirin use in patients with diabetes is increasing, use is suboptimal, especially in women, younger patients, and in those with major CVD risk factors.

The benefit/harm-cost ratio of aspirin is among the highest of any drug.

Should all patients with diabetes take aspirin? I believe in the great majority the benefits outweigh risks. Risks of aspirin in younger persons with no other risk factors for CVD may outweigh benefits. But even in younger persons the duration of diabetes should be considered.

I believe at times primary care clinicians simply forget to recommend aspirin.

12-6 ECONOMICS OF OBESITY

Traditional health promotion efforts have focused on the individual, relying on education, skills training, and building social support to help people change behavior. In the case of obesity, these approaches are failing. Public health officials are wondering—Why do people not listen?
This essay suggests that economics plays a large part in the obesity epidemic. Food, especially foods high in fat and sugar, have become cheaper as obesity rates have risen. Obesity rates among the poor are substantially higher than among those in higher income groups. The poor are more likely to depend on high fat, high sugar, less expensive foods. As income drops, choice of foods contracts. From economists’ perspective, people are rational beings who try to attain the maximum happiness within the constraints of their circumstances such as their income, available time, and other resources. The economic situation of low-income people forces them to adopt “obesogenic” diets. Economists say if you want to change behavior, change costs.

Obesity is a low-income problem, yet we offer middle-class solutions. “We say you need to eat more fresh fruits and vegetables and to exercise more. Well, if you live in the inner city you aren’t going to suddenly start eating mangos and playing tennis.”

Another important factor affecting diet is time. In order to prepare so-called “thrifty” diets you need 20 hours a week for food preparation. The typical working mother spends 5 hours a week on this task. The poor often work long hours and have long commutes. They are “time poor” as well as cash poor.

Ultimately the solution to the problem of obesity is to improve the socioeconomic situation of the poor by providing better jobs, wages, and social services. “Obesity is, profoundly, a socioeconomic issue, and medical approaches will not work.”

I enjoyed this perspective. I believe it contains much truth. But it is certainly not the whole truth. Many economically advantaged persons are obese. Observe in any upscale mall. (I wonder what the poor/rich ratio is regarding obesity.)

The article will make me more compassionate and less critical when discussing the “overweight problem” of the majority of my patients. Some have great limitations regarding their choices of foods, convenience of shopping, and time to prepare. For many, eating fat and sweets is one of the pleasures of their lives. They do not want to give it up. Cultural influences remain strong.

Disadvantaged persons are also greatly limited in their choices of exercise. Walking through the neighborhood may be unsafe, unpleasant, and stressful. Sidewalks may be broken and uneven. Walkers may be harassed.

The just-published changes in the food pyramid call for more of the same expensive foods and for more exercise. Costs, time, and opportunity have become more limiting. Three daily glasses of skim milk are recommended. A gallon of milk now costs me over $4. For a family 4 or 5, this adds up.

Obviously the root causes of the obesity epidemic have not been addressed.

A note about children: There is an effective means of limiting fat and sweets from their diet through changes in the school meal programs. I believe we are making headway in this regard.
Ayurvedic medicine originated in India more than 2000 years ago. It relies heavily on herbal medicine products (HMP). HMPs are marketed as dietary supplements under the Dietary Supplement Health and Education Act. Proof of safety and efficacy is not required.

Ayurvedic HMPs containing heavy metals are readily available in the USA. This study determined the prevalence and concentrations of heavy metals in Ayurvedic HMPs.

Fourteen of 70 (20%) HMPs tested contained heavy metals:

<table>
<thead>
<tr>
<th>Metal</th>
<th>No. containing</th>
<th>Median concentration—mg/gram</th>
<th>Range mg/gram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>13</td>
<td>0.040</td>
<td>0.005 to 37</td>
</tr>
<tr>
<td>Mercury</td>
<td>6</td>
<td>20</td>
<td>0.03 to 104</td>
</tr>
<tr>
<td>Arsenic 6</td>
<td>0.4</td>
<td></td>
<td>0.037 to 8</td>
</tr>
</tbody>
</table>

Taken as recommended by the manufacturer, heavy metal intoxication may result. One in 5 Ayurvedic HMPs produced in South Asia contains potentially harmful levels of lead, mercury, and/or arsenic. Users are at risk.

Traditional medicines from China, Malaysia, Mexico, Africa, and the Middle East have also been shown to contain heavy metals.

*The recent furor over unreported adverse effects of Merck’s Vioxx led me to include this study. Can you imagine the furor which would occur if a product of Merck was reported to contain arsenic, mercury, or lead? Our drug oversight system is schizophrenic.*

The term Ayur-veda comes from the Sanskrit meaning Life (health) and knowledge. Google presents over 1 million citations. The wide range of products available, which are said to be all “natural”, include nostrums for vitality and strength; healthy blood and skin; healthy hair growth; proper function of the immune system, heart, joints, muscles, kidneys, adrenal, liver, lung, and reproductive system; mental clarity; control of blood glucose; and depression.

**12-8 BALANCING THE RISKS AND BENEFITS OF FISH CONSUMPTION**

Studies from the past 2 decades have repeatedly linked consumption of fish—especially fish high in omega-3 fatty acids—with healthier hearts in the aging population. A reduced risk of stroke, dementia, kidney disease, asthma, and diabetes has also been reported.

There are risks stemming from 2 toxins—mercury and polychlorinatedbiphenyls (PCBs) which are found in fish living in polluted waters and in some farmed fish.

*Mercury exposure and the role of the internist:*

The only important source of organic mercury (methylmercury) is contaminated fish. Methylmercury reaches its highest levels in large predatory species such as shark, tilefish, swordfish...
king mackerel, and tuna; and in bottom feeders such as crab. A single serving of highly contaminated fish can contain more than 200 ug of mercury. Five of the most commonly eaten fish that are low in mercury are shrimp, canned light tuna, salmon, pollock, and catfish.

Fish sticks and “fast food” sandwiches are commonly made from fish low in mercury.

**PCB exposure and the role of the internist:**

PolyChlorinated Biphenyls (eg, dioxin) are a mixture of individual chemicals which are no longer produced in the USA. Prior to 1979 their use was widespread in industry. There are no known natural sources of PCBs. They do not break down in the environment, and may remain there for very long periods.

Fish are the main sources of concentrated PCB exposure. The highest levels have been found in farmed salmon. (90% of salmon consumed in the USA are farmed.) In the past they were fed PCB-contaminated ground-up fish. The fishing industry has started to change the way it feeds farmed fish. Contamination levels in salmon have declined by 90%. As of March 2004, the FDA maintained that the level of PCBs in farm-raised salmon is well below the safety standard.

The FDA emphasizes that the benefits of eating salmon on cardiovascular health outweigh the risk from PCBs, especially for those at highest risk.

*I consider this a legitimate point for primary care clinicians to address. Patients may be asking about it.*

* I have wondered about the omega-3 content of fish, especially farm-fed fish. The natural content of omega-3 in fish comes up in the food chain beginning with plankton. How much omega-3 is contained in the food fed to farmed fish?

*The relation between PCBs and cancer is very tenuous. The article cites a risk of one additional case of cancer in 100 000 people over a 70-year lifetime.*

*It is impossible for individual consumers to know the mercury and PCB content of the fish they consume.*

*I believe it reasonable for primary care clinicians to advise pregnant women and children against eating large predatory fish. For elders, the benefits of any fish far outweigh any risk. The good news is that older adults are the most likely to benefit from fish consumption. I will continue to eat fish at least twice a week.*

*The recent furor over the outrageous dioxin poisoning of the now President of Ukraine will allow us to follow the adverse effects of mega-doses in one individual.*

*The Internet is packed with information about contamination of fish. Go to Google and access salmon and mercury; and polychlorinatedbiphenyls. I included a few points from the Internet in the abstract.*
Extensive evidence has suggested a causal role of vascular endothelial growth factor (VEGF) in diseases of the eye in which neovascularization and increased vascular permeability occur.

Neovascularization in ARMD is dependent on VEGF. It is characterized by choroidal neovascularization that involves the subretinal space, often leading to exudation and hemorrhage, followed by a fibrovascular scar. Loss of central vision results.

Now a specific antagonist to VEGF (Peg-aptanib) is being tested in the treatment of neovascular ARMD. Peg-aptanib binds to and blocks activity of extracellular VEGF.

Results favored peg-aptanib. Fewer patients lost more than 15 letters. Fewer patients had severe visual loss. Some maintained or gained visual acuity.

This, of course, is not a practical point at this time. I considered the ray of hope to be interesting enough to include.
ABSTRACTS DECEMBER 2004

Is What is Good for the Diseases Always Best for The Patient?

12-1 POTENTIAL PITFALLS OF DISEASE-SPECIFIC GUIDELINES FOR PATIENTS WITH MULTIPLE CONDITIONS

Primary care clinicians are encouraged to adhere to evidence-based guidelines for the management of specific diseases. The goal is to maximize benefits, including prevention of disease-specific outcomes, deaths, and hospitalizations.

Some multidrug regimens clearly provide added disease-specific benefits, at least for some subpopulations of patients. For patients with several coexisting health conditions, the long-term net benefits and harms of the combination of all medications taken in adherence to disease-specific guidelines is less clear. Twenty percent of Medicare beneficiaries have 5 or more chronic conditions, and 50% are receiving 5 or more drugs. Take, for instance, a 70-year old woman who has hypertension, a past myocardial infarction, depression, diabetes, and osteoporosis. According to guidelines she should be receiving aspirin, a beta-blocker, and ACE inhibitor, a bisphosphonate, calcium, a diuretic, a SSRI, a statin, a sulfonylurea, and perhaps a thiazolidinedione and vitamin D. In addition, she may be taking over-the-counter drugs for allergies, pain, dyspepsia, and insomnia.

Is what is good for the diseases always best for the patient? There is a tension between the standardized treatment of diseases and the individualized care of patients with multiple health problems.

Guidelines are based on randomized, controlled trials (RCTs) which typically provide evidence of modest reductions in risk of disease-specific outcomes associated with the use of individual medications. Older patients and patients with multiple health conditions are usually excluded from trials. In most RCTs, adverse events are evaluated with less rigor and precision than are benefits. Health preferences of patients and the outcomes related to their quality-of-life are seldom mentioned.

Furthermore, clinical trials supporting the recommendations of guidelines are conducted over a few months or a few years. This precludes the ability to detect the benefits and harms associated with medications which may be taken for decades. What added benefit (and added harm) does the 7th, 8th, or 9th medication provide over the 2nd or 3rd? The risk of adverse effects increases as the number of medications (and the length of time they are given) increases.

In judging benefits and harms of multiple drugs, we should use absolute, rather than relative, scales. A 30% reduction in risk may represent a 3% absolute reduction.
The prevalence of problems associated with multiple medications is probably underestimated. The broader physical, cognitive, psychological, and other effects remain unknown and unexplored. Patients, especially the elderly, and those with multiple complaints, vary in regard to the importance they place on health outcomes such as longer survival, the prevention of specific disease events, physical and cognitive functioning, and the amount of inconvenience and risk of adverse effects (and costs) they are willing to tolerate.

The proliferation of multidrug regimens demands that we consider health priorities as well as the marginal benefits and harms associated with all medications when translating guidelines into prescribing decisions for individual patients with multiple problems. The focus should change from disease-driven to patient-driven.

NEJM December 30, 2004; 351: 2805-16  “Sounding Board”, commentary, first author Mary E Tinetti, Yale School of Medicine, New Haven, Conn.

First Use A Diuretic or A Beta-Blocker as Monotherapy and the Combination as Dual Therapy.

12-2 ASSOCIATION BETWEEN CARDIOVASCULAR OUTCOMES AND ANTIHYPERTENSTIVE DRUG TREATMENT IN OLDER WOMEN

Based on clinical trial results, diuretics or beta-blockers are considered to be first-step monotherapy for high BP. Newer classes of drugs (ACE inhibitors and calcium blockers) are also effective in lowering BP. They are increasingly used as first-step monotherapy.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) provided clinical trial data on monotherapy, and indicated that diuretics were equal or superior to other agents as first-line therapy. Most patients, however, require more than one drug class to control hypertension.

This study, limited to postmenopausal women with hypertension, asked - 1) What single drug is most effective in lowering risk of cardiovascular events? 2) What 2-drug combination is most effective?

Conclusion: Monotherapy with diuretics was equally or more effective than other monotherapies. The combination of beta-blockers + diuretics was superior to, or equally effective as other combinations.

STUDY

1. This large multicenter observational study assessed a subset of women (n = over 15 000) enrolled in the Women’s Health Initiation-Observation Study (WHI-OS) age 50 to 79 at baseline.
2. All had history of hypertension (BP > 140/90). None had a history of cardiovascular disease (CVD). At baseline, all had been treated with antihypertension drugs for 4 to 7 years.

3. Over a 6-year follow-up determined relationship between incidence of CVD and baseline use of 1) Diuretics, 2) ACE inhibitors, 3) Beta-blockers, 4) Calcium channel blockers, as monotherapy; and 5) dual therapy (combinations of two).

RESULTS
1. Only about 1/3 of women in the entire cohort of the WHI-OS (n = 93 000) with hypertension were treated and controlled. One third had BMI over 30.

2. Subset receiving mono-therapy at baseline (n = 11 294):

<table>
<thead>
<tr>
<th></th>
<th>ACE-I</th>
<th>Beta-B</th>
<th>Calcium-B</th>
<th>Diuretic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary disease</td>
<td>0.99</td>
<td>1.18</td>
<td>1.22</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.89</td>
<td>0.82</td>
<td>1.34</td>
<td>1.00</td>
</tr>
<tr>
<td>CVD death</td>
<td>0.95</td>
<td>0.83</td>
<td>1.55</td>
<td>1.00</td>
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</table>

(a Hazard ratio of CVD death calcium blocker vs diuretic = 1.55 (i.e., calcium blocker more hazardous than diuretic a statistically significant difference. None of the other associations was statistically significant.)

3. Subset receiving dual therapy at baseline (n = 4493)

   A. Those taking a calcium blocker + diuretic had an 85% greater risk of CVD death as compared with beta-blocker + diuretic.
   
   B. There were no statistically significant differences between other combinations and risk of CVD.

DISCUSSION
1. Over 6 years, patients treated with a calcium blocker alone were more likely to experience CVD morbidity and morality than those taking a diuretic alone.

2. Among patients using a 2-drug combination, those taking a diuretic + a calcium blocker were at twice the risk of CVD death compared with those taking a diuretic + a beta-blocker.

3. The Joint National Committee recommends a thiazide-type diuretic as preferred initial therapy for most patients with stage 1 hypertension (140-159/90-99). And combined therapy, usually including a thiazide diuretic, for patients with stage 2 hypertension (> 160/100).

4. Other studies have reported that prescriptions of calcium blockers have increased while the use of diuretics has declined in spite of the higher costs and lack of evidence of superior tolerability or health outcomes of calcium blockers.
5. Obtaining a BP under 140/90 (and under 130/80 in those with diabetes) most often requires a combination of 2 or 3 drugs. In this study, most women were not treated aggressively enough to control their BP to recommended levels.

CONCLUSION

In prevention of CVD in women with hypertension (and no history of cardiovascular disease) monotherapy with diuretics was equal or superior to monotherapy beta-blockers, ACE inhibitors or calcium blockers in preventing CVD complications.

Dual combination therapy with a calcium blocker + a diuretic was associated with higher CVD mortality than ACE inhibitors + diuretics and beta-blocker + diuretics.

Risks were similar for ACE inhibitors + diuretics and beta-blocker + diuretics.

JAMA December 15, 2004; 292: 2849-59 Original investigation, first author Sylvia Wassertheil-Smoller, Albert Einstein College of Medicine, Bronx, NY.


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“Non-Alcoholic Fatty Liver Disease is the Most Prevalent Liver Disease in The USA.”

12-3 HEPATOBILIARY DISEASE IN TYPE 2 DIABETES: A Narrative Review

“Only recently has liver disease been recognized as a major complication of type 2 diabetes.”

(DM2)

This article (based on a MEDLINE search) discusses the spectrum of liver disease in DM2: non-alcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma, hepatitis C, acute liver failure, and cholelithiasis.

Metabolic effects of DM2 on the liver

The insulin resistance and relative insulin deficiency in patients with DM2 affects lipid as well as carbohydrate metabolism. Insulin resistance decreases glucose uptake in the skeletal muscle and increases lipolysis from adipocytes. Lipolysis increases circulating free fatty acids. This in turn may lead to more insulin resistance. Thus a vicious cycle is started. The net effect is increased storage of fat in the liver.

The frequent occurrence of dyslipidemia in DM2 is characterized by elevated plasma triglycerides, reduced HDL-cholesterol, and a predominance of small, dense, lipoprotein particles, a pattern frequently seen in non-alcoholic fatty liver disease. The major cause of hypertriglyceridemia is hepatic overproduction of triglyceride-rich very-low-density lipoprotein (VLDL), and
apolipoprotein B secondary to the increased availability of free fatty acids. Due to the relative lack of insulin, hepatic VLDL and apoB production is not adequately suppressed.

*Non-alcoholic fatty liver disease*

“Non-alcoholic fatty liver disease is the most prevalent liver disease in the USA.”

NAFLD is a broad spectrum. It ranges from steatosis (bland fatty infiltration of hepatocytes), to non-alcoholic steatohepatitis (steatosis plus inflammation, necrosis, and fibrosis) and, in some patients, to end-stage liver disease and hepatocellular carcinoma.

Prevalence of NAFLD is as high as 50% in patients with DM2 and obesity. (Of these, up to 50% have steatohepatitis; 19% cirrhosis).

The diagnosis is suspected in persons who do not use alcohol and have mildly elevated aminotransferase levels (AST and ALT; AST/ALT ratio greater than 1). Clinical features are non-descript. Some patients report malaise and a sense of fullness. Hepatomegaly may be present.

Serum ferritin levels are elevated in half of the patients.

Imaging studies reveal a diffuse increase in echogenicity (“bright liver”). But only liver biopsy can assess the severity of damage and prognosis.

Treatment: Good metabolic control; caloric restriction (low glycemic index foods may be especially important); weight loss; exercise. Alcohol should be avoided. It is recommended that drug therapy begin with a secretogogue (a sulfonylurea) with rapid advancement of insulin therapy if control is not established. Insulin-sensitizing agents such as pioglitazone and rosiglitazone may be especially useful. The alpha-glucosidase inhibitors are also useful.

Weight loss improves insulin sensitivity and results in reduction of steatosis. But, the necroinflammation and fibrosis may worsen if the weight reduction is rapid. This paradoxical effect may be caused by the increased lipolysis leading to increased circulating free fatty acids. Limiting loss to no more than 1.5 kg/wk has been suggested.

*Cirrhosis in DM2*

“Cirrhosis is one of the leading causes of death in patients with diabetes.”

The most common cause of cryptogenetic cirrhosis is steatohepatitis. The most common cause of steatohepatitis is DM2.

*Hepatocellular carcinoma in DM2*

Incidence is increased in patients with DM2.

*Hepatitis C in DM2*

Strong epidemiological evidence shows that prevalence of hepatitis C is greater in DM2 than in the general population. The hepatitis C virus may contribute to the development of DM2. Patients with hepatitis C have a higher incidence of DM2 than do patients with hepatitis B infection.

*Acute liver failure in DM2*
Risk of liver failure is increased in DM2.

*Cholelithiasis in DM2*

A two- to 3-fold increase in risk. Obesity is a strong co-factor, but DM2 alone is an independent risk factor. 


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**Quantifying the Benefits of Diet**

**12-4 THE POLYMEAL: A More Natural, Safer, and Tastier Strategy to Reduce Cardiovascular Disease by More than 75%**

The concept of the Polypill was introduced in 2003. The investigators suggested it would immeasurably benefit Western society if it were taken by everyone over age 50. Six pharmacological components were combined into one pill. By modifying different risk factors for cardiovascular disease (CVD), the pill was considered to multiplicatively reduce risks of CVD. In general, the medical community has welcomed the concept, but questioned the potential adverse effects and costs of the drugs.

The objective of this study was to define a safer non-pharmacological and tastier alternative to the Polypill for use by the general population.

Conclusion: Daily ingestion of 6 food components was calculated to reduce risk of CVD by 76%

**STUDY**

1. Used an evidence-based conceptional framework to calculate the individual and combined effects of various foods on reduction of risk of CVD.
2. Conducted a literature search of randomized trials and meta-analyses of benefits of 6 different foods. All the foods had been reported to reduce risk of CVD through their effects on BP and lipids.
3. The foods to be ingested daily: Wine, fish, dark chocolate, fruit and vegetables, garlic, and almonds.
4. Calculated the individual benefit and the combined benefit of all six foods on individuals starting at age 50 and closing at age 100.
RESULTS
1. Combining all ingredients of the Polymeal was calculated to reduce CVD in men by 76% and increase life expectancy free of cardiovascular disease by 9 years. In patients with CVD, life would be extended by 2.4 years.
2. Benefits extended to women, but by somewhat fewer years.
3. Effects of ingredients of the Polymeal in reducing risk of CVD:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Mean percentage reduction in risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wine (150 mL/day)</td>
<td>32</td>
</tr>
<tr>
<td>Fish (114 g 4 times/wk)</td>
<td>14</td>
</tr>
<tr>
<td>Dark chocolate (100 g/day)</td>
<td>21</td>
</tr>
<tr>
<td>Fruit and vegetables (400 g/day)</td>
<td>21</td>
</tr>
<tr>
<td>Garlic (2.7 g/day)</td>
<td>25</td>
</tr>
<tr>
<td>Almonds (68 g/day)</td>
<td>12</td>
</tr>
<tr>
<td>Combined effect</td>
<td>76</td>
</tr>
</tbody>
</table>

4. The effects were based on calculations of benefits on lipids and BP.
5. Adverse effects: No serious adverse effects were reported in any of the papers selected. Garlic produces a body odor and has adverse effects on breath as well as some GI disturbances; fish (especially large fish such as swordfish and shark) in large quantities have been related to increased ingestion of mercury. No adverse effects of wine at the level recommended, including no association with breast cancer. Additional alcohol should not be included.

DISCUSSION
1. All persons in Western societies have CVD risk factors. Everyone is at risk.
2. “The Polymeal is an effective, natural, probably safer and tastier alternative to the Polypill.” It would reduce CVD and increase life expectancy in the general population.
3. Moderate physical exercise and lipid- and BP-controlling drugs can be added. (Eg, combined with components of the Polypill.)
4. Individual ingredients may be taken at different times of the day.
5. Some other ingredients could be added to enhance benefits: olive oil, soy, oat bran, cereals, nuts, tea.

CONCLUSION
The Polymeal promises to be an effective non-pharmacological, safe, and tasty alternative to reduce CVD mortality and increase life expectancy in the general population.
Aspirin is Underused in Prevention of CVD in Patients With Diabetes

12-5  ASPIRIN USE AMONG PATIENTS WITH DIABETES

Adults with diabetes, but with no clinical cardiovascular disease, may have risk of CVD events similar to non-diabetic adults with established CVD.

Among women with diabetes, CVD-mortality actually increased during the time CVD-mortality fell among non-diabetic women.

Strategies to prevent CVD events in persons with diabetes are underused. Aspirin effectively reduces risk of first and subsequent myocardial infarction in patients with diabetes as well as in those without. Many adults with diabetes did not use it.

This study assessed regular aspirin use among adults with diabetes between 1997 and 2001.

Conclusion: Aspirin use increased over 4 years, but many diabetics, especially women, and those younger than age 50 did not take it.

STUDY

1. Analyzed data from the Behavioral Risk Factor Surveillance System, a federally funded telephone survey of non-institutionalized adults in the USA.

2. Determined self-reported regular aspirin use in a total of over 5000 patients with diabetes in 1997, and 2001. All were over age 35.

RESULTS

1. Regular aspirin use among diabetics over age 35 increased from 1997 to 2001:

<table>
<thead>
<tr>
<th></th>
<th>1997 (%)</th>
<th>2001 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All respondents</td>
<td>37</td>
<td>49</td>
</tr>
<tr>
<td>No CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No risk factors</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>One or more risk factors</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Those with CVD</td>
<td>52</td>
<td>74</td>
</tr>
</tbody>
</table>
2. Women with diabetes less likely to take aspirin:

<table>
<thead>
<tr>
<th></th>
<th>No CVD (%)</th>
<th>CVD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>83</td>
</tr>
</tbody>
</table>

3. Use increased with age:

<table>
<thead>
<tr>
<th>Age</th>
<th>No CVD (%)</th>
<th>CVD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-49</td>
<td>21</td>
<td>60</td>
</tr>
<tr>
<td>50-64</td>
<td>39</td>
<td>78</td>
</tr>
<tr>
<td>65 and over</td>
<td>48</td>
<td>74</td>
</tr>
</tbody>
</table>

DISCUSSION

1. There has been an encouraging increase in use of aspirin in adults with diabetes. But, use remained less than ideal for patients with CVD. (One quarter of patients with established heart disease or stroke did not use aspirin.)
2. Almost 2/3 of those without CVD did not use aspirin.
3. Among those with risk factors for CVD (hypertension, dyslipidemia, smoking) 60% did not use aspirin.
4. Overall use by women was lower than by men.
5. Why is aspirin underused?
   - The CVD risk associated with diabetes is underappreciated.
   - Concerns about safety.
   - Physicians may appreciate the CVD risk but place greater emphasis on glucose, lipid, and BP control.
   - Physicians may be concerned that aspirin may not be as effective for prevention of CVD in diabetics. (It is effective.)
   - Physicians may underestimate the risk of CVD in women. (Diabetes greatly increases risk in younger females as well as in older.)
   - Physicians may think that the risk of CVD in young patients with diabetes who have no additional risk factors is too low to recommend aspirin. (This may be true for women with diabetes under age 45 who lack other risk factors, but over this age risk becomes equal among men and women, and benefits may outweigh harms.)

CONCLUSION

Although aspirin use in patients with diabetes is increasing, use is suboptimal, especially in women, younger patients, and in those with major CVD risk factors.
Is the Epidemic Based on Economic Factors?

12-6 ECONOMICS OF OBESITY

Doctors tell patients to lose weight. Public health campaigns urge the public to eat right and exercise more. TV, newspapers and magazines serve up a steady diet of slimming tips. Diet books abound. Yet more and more people grow fat.

Traditional health promotion efforts have focused on the individual, relying on education, skills training, and building social support to help people change behavior. In the case of obesity, these approaches are failing. Public health officials are wondering—Why do people not listen?

These approaches cannot combat the powerful environmental factors that influence eating and physical activity. Public health workers are now beginning to enlist the help of economists to combat the obesity epidemic.

There is evidence that economics plays a large part in the obesity epidemic. Food, especially foods high in fat and sugar, have become cheaper as obesity rates have risen. Obesity rates among the poor are substantially higher than among those in higher income groups. The poor are more likely to depend on high fat, high sugar, less expensive foods. As income drops, choice of foods contracts.

From economists’ perspective, people are rational beings who try to attain the maximum happiness within the constraints of their circumstances such as their income, available time, and other resources. The economic situation of low-income people forces them to adopt “obesogenic” diets. Economists say if you want to change behavior, change costs.

There is a tendency to blame obese individuals for not exerting a strong will, for making the wrong choices, for being uneducated and stupid. But healthy diets are expensive. The difference in cost per calorie between high sugar, high fat foods and fresh fruits and vegetables is large.

Obesity is a low-income problem, yet we offer middle-class solutions. “We say you need to eat more fresh fruits and vegetables and to exercise more. Well, if you live in the inner city you aren’t going to suddenly start eating mangos and playing tennis.” The first thing that falls out of the market basket is fruit, followed by fresh vegetables, followed by fish, followed by meat and cheese. You are left with sweetened grains, sugar, and fat. These are the food choices of low-income groups.

Another important factor affecting diet is time. In order to prepare so called “thrifty” diets you need 20 hours a week for food preparation. The typical working mother spends 5 hours a week on
this task. The poor often work long hours and have long commutes. They are “time poor” as well as cash poor.

“Simply exhorting people of limited means to eat better is a waste of time.” To improve their diets, healthy foods must be made available and cheap. Instead of subsidizing sugar and grain product, fruits and vegetables should be subsidized.

Ultimately the solution to the problem of obesity is to improve the socioeconomic situation of the poor by providing better jobs, wages, and social services. “Obesity is, profoundly, a socioeconomic issue, and medical approaches will not work.”


=======================================================================

Contain Potentially Harmful Levels of Lead, Mercury, and/or Arsenic. Users Are at Risk.

12-7 HEAVY METAL CONTENT OF AYURVEDIC HERBAL MEDICINE PRODUCTS

Ayurvedic medicine originated in India more than 2000 years ago. It relies heavily on herbal medicine products (HMP). About 80% of India’s 2 billion population uses Ayurvedic. Its popularity in the USA has increased. In the USA, products are now available from South Asian markets, Ayurvedic practitioners, health food stores, and the Internet.

HMPs are marketed as dietary supplements under the Dietary Supplement Health and Education Act. Proof of safety and efficacy is not required.

Lead, mercury, and arsenic intoxication have been associated with the use of Ayurvedic HMPs. This study determined the prevalence and concentrations of heavy metals in Ayurvedic HMPs.

Conclusion: One of 5 Ayurvedic HMP contained potentially harmful levels of lead, mercury, and/or arsenic.

STUDY

1. Identified all stores in the Boston area that sold Ayurvedic HMPs. The investigators visited each store and purchased unique Ayurvedic HMPs. (N = 70) All had been manufactured in South Asia. Many were recommended for children.

2. Determined the prevalence and concentrations of heavy metals in each.

3. Estimated the intake of the metals using the manufacturer’s dosage recommendations.

4. Compared dosages with the recommended maximum allowable daily ingestion recommended by US Pharmacopeia and US Environmental Protection Agency standards.
RESULTS

1. Fourteen (20%) contained heavy metals:

<table>
<thead>
<tr>
<th>Metal</th>
<th>No. containing</th>
<th>Median concentration - mg/gram</th>
<th>Range - mg/gram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>13</td>
<td>0.040</td>
<td>0.005 to 37</td>
</tr>
<tr>
<td>Mercury</td>
<td>6</td>
<td>20</td>
<td>0.03 to 104</td>
</tr>
<tr>
<td>Arsenic</td>
<td>6</td>
<td>0.4</td>
<td>0.037 to 8</td>
</tr>
</tbody>
</table>

2. If taken as recommended by the manufacturers, each of the 14 could result in heavy metal intakes above published regulatory guidelines.

DISCUSSION

1. Ayurvedic HMPs containing heavy metals are readily available in the USA.
2. Taken as recommended by the manufacturer, heavy metal intoxication may result.
3. Other studies have also reported Ayurvedic HMPs contain heavy metals. In England, 40% of Ayurvedic HMPs contained a heavy metal. Of 22 purchased in India, 64% contained lead, and 41% arsenic.
4. Traditional medicines from China, Malaysia, Mexico, Africa, and the Middle East have also been shown to contain heavy metals.
5. Epidemiological evidence suggests a relation of heavy metal intake (even at levels previously thought to be acceptable) and insidious adverse effects—decreased childhood IQ, increased BP, and chronic renal insufficiency.
6. Ayurvedic experts estimate that about 1/3 of Ayurvedic HMPs intentionally contain at least one metal. The metals are purportedly detoxified through multiple heating/cooling cycles and the addition of “specific” herbs.
7. A recent analysis of the US National Health Interview Survey estimated that 750,000 adults in the USA consulted Ayurvedic practitioners in 2002. In India 80% of the population uses Ayurveda.

CONCLUSION

One in 5 Ayurvedic HMPs produced in South Asia contains potentially harmful levels of lead, mercury, and/or arsenic. Users are at risk.

**Risks of Mercury and PCBs vs Benefit of Omega-3 Fatty Acids.**

**12-8 BALANCING THE RISKS AND BENEFITS OF FISH CONSUMPTION**

Studies from the past 2 decades have repeatedly linked consumption of fish—especially fish high in omega-3 fatty acids—with healthier hearts in the aging population. A reduced risk of stroke, dementia, kidney disease, asthma, and diabetes has also been reported.

Fish consumption in the USA is increasing.

There are risks stemming from 2 toxins—mercury and polychlorinatedbiphenyls (PCBs) which are found in fish living in polluted waters and in some farmed fish.

Certainly, many fish pose no known health risks to any consumers. Those include flounder, farmed rainbow trout, sole, anchovies, and farmed clams and shrimp. Other fish (cod, farmed catfish, mahi mahi, wild salmon, tilapia, and canned chunk tuna) are fine to eat in moderation, about once a week. Environmental health experts generally agree that most Americans would benefit from consuming more of these safe fish.

*Mercury exposure and the internist:*

The only important source of organic mercury (methylmercury) is contaminated fish. Methylmercury reaches its highest levels in large predatory species such as shark, tilefish, swordfish king mackerel, and tuna; and in bottom feeders such as crab. A single serving of highly contaminated fish can contain more than 200 ug of mercury. Five of the most commonly eaten fish that are low in mercury are shrimp, canned light tuna, salmon, pollock, and catfish.

Fish sticks and “fast food” sandwiches are commonly made from fish low in mercury.

In adults, symptoms such as tremor, difficulty with concentration, vision deficits, and tingling have been described, usually at blood levels of 200 ug per liter or more. Some individuals have elevated mercury levels yet have no symptoms.

Children may be more susceptible. Pregnant women should be cautious because of the possibility of transmission to the child.

*PCB exposure and the role of the internist:*

PolyChlorinated Biphenyls (eg, dioxin) are a mixture of individual chemicals which are no longer produced in the USA. Prior to 1979 their use was widespread in industry. There are no known natural sources of PCBs. They do not break down in the environment, and may remain there for very long periods.

The EPA has identified PCBs as a probable carcinogen. However, because of the long latency period required for cancer induction, the effects on adults are poorly understood. They also appear to have adverse effects on the CNS.
Fish are the main sources of concentrated PCB exposure. The highest levels have been found in farmed salmon. (90% of salmon consumed in the USA are farmed.) In the past they were fed PCB-contaminated ground-up fish. The fishing industry has started to change the way it feeds farmed fish. Contamination levels in salmon have declined by 90%. As of March 2004, the FDA maintained that the level of PCBs in farm-raised salmon is well below the safety standard. The FDA emphasizes that the benefits of eating salmon on cardiovascular health outweigh the risk from PCBs, especially for those at highest risk.

The article mentions other sources of omega-3 fatty acids. Flaxseed, canola, soybeans, and walnuts are high in short-chain alpha-linolenic acid. They are believed to be as beneficial as omega-3 from fish. Purified omega-3 acids are also available as supplements.


A Ray of Hope

12-9 PEGAPTANIB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

In the developed world, age-elated macular degeneration (ARMD) is the leading cause of irreversible, severe loss of vision in people over age 55. It remains an area of unmet medical need. Almost 1 million people in the USA are expected to develop ARMD over the next 5 years. It is a major public health issue in the increasing population of older persons.

Extensive evidence has suggested a causal role of vascular endothelial growth factor (VEGF) in diseases of the eye in which neovascularization and increased vascular permeability occur. Neovascularization in ARMD is dependent on VEGF. It is characterized by choroidal neovascularization that involves the subretinal space, often leading to exudation and hemorrhage, replaced, after several months, by a fibrovascular scar. Loss of central vision results.

Now a specific antagonist to VEGF (Peg-aptanib) is being tested in the treatment of neovascular ARMD. Peg-aptanib binds to and blocks activity of extracellular VEGF. [Peg denotes polyethylene glycol which is added to increase half-life.]

Prospective, randomized, double-blind trial (n = 1186) assessed 1) intra-vitreous injection of peg-aptanib (3 different doses) into one eye, or 2) placebo injection every 6 weeks for 48 weeks. Primary end point = proportion of patients who lost fewer than 15 letters of visual acuity.
Efficacy was demonstrated without a dose-response relationship:

<table>
<thead>
<tr>
<th></th>
<th>Peg-aptanib</th>
<th>Placebo</th>
<th>Absolute difference</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients losing more than 15 letters</td>
<td>30%</td>
<td>45%</td>
<td>15%</td>
<td>7</td>
</tr>
<tr>
<td>Severe loss (&gt; 30 letters)</td>
<td>10%</td>
<td>22%</td>
<td>12%</td>
<td>8</td>
</tr>
<tr>
<td>Maintained or gained visual acuity</td>
<td>33%</td>
<td>23%</td>
<td>10%</td>
<td>10</td>
</tr>
</tbody>
</table>

Benefit appeared as early as 6 weeks and remained during all subsequent points.
Retinal detachment, endophthalmitis, and traumatic injury occurred in a few patients.

NEJM December 30, 2004; 351: 2805-16 Original investigation by the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group, first author Evangelos S Gragoudas, Harvard Medical School, Boston Mass.