

# **PRACTICAL POINTERS**

## **FOR PRIMARY CARE**

**ABSTRACTED MONTHLY FROM THE JOURNALS**

### **FEBRUARY 2007**

**VENOUS THROMBOEMBOLISM: A Clinical Practice Guideline**

**HEADACHES: Master Classes for GPs**

**DEFINING LIMITS IN CARE OF TERMINALLY ILL PATIENTS**

**SEAFOOD CONSUMPTION IN PREGNANCY: Beneficial or Harmful?**

**OFF-LABEL USE OF DRUGS**

**LIVE FLU VACCINE VS INACTIVATED VACCINE IN CHILDREN: Important to Adults as Well**

**RESISTANCE OF STREPTOCOCCI TO MACROLIDES OCCURS RAPIDLY**

**SIESTA REPORTED TO REDUCE CORONARY MORTALITY**

**HUMAN PAPILLOMA VIRUS: High Prevalence among Females in the US**

**IS THE “ANNUAL PHYSICAL EXAMINATION” HELPFUL?**

**SHOULD CLINICIANS REFUSE AN APPLICATION TO A PATIENT ON THE BASIS OF**

**THEIR RELIGIOUS CONVICTIONS?**

**DOES GARLIC REDUCE CHOLESTEROL?**

JAMA, NEJM, BMJ, LANCET

ARCHIVES INTERNAL MEDICINE

ANNALS INTERNAL MEDICINE

[www.practicalpointers.org](http://www.practicalpointers.org)

PUBLISHED BY PRACTICAL POINTERS, INC.

EDITED BY RICHARD T. JAMES JR. MD

400 AVINGER LANE, SUITE 203

DAVIDSON NC 28036 USA

[Rjames6556@aol.com](mailto:Rjames6556@aol.com)

---

---

This document is divided into two parts

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

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

-----

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

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

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 5 years can be accessed at [www.practicalpointers.org](http://www.practicalpointers.org)

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

---

Practical Pointers is published every month on the internet as a public service. It is available on a more timely basis by e-mail attachment. It contains no advertising. It is completely without bias. There is never any charge.

Requests for "subscription" to [rjames6556@aol.com](mailto:rjames6556@aol.com)

# HIGHLIGHTS AND *EDITORIAL COMMENTS* FEBRUARY 2007

*LMWH Carries the Day.*

## **2-1 VENOUS THROMBOEMBOLISM: a Clinical Practice Guideline**

This concise review considers;

Initial inpatient treatment of deep venous thrombosis.

Outpatient treatment of deep venous thrombosis.

Initial treatment of pulmonary embolism.

Duration of anti-coagulation.

Anti-coagulation for management of venous thromboembolism pregnancy.

Compression stockings to prevent post-thrombotic syndrome.

Read the full abstract

-----

*I enjoy articles such as this which present recommendations in concise, simple, and clear fashion. The guideline considers deep venous thrombosis (DVT) and pulmonary embolism (PE) separately. I believe venous thromboembolism (VTE) is a more accurate and inclusive term because risk of PE (asymptomatic as well as symptomatic) is very high (almost universal) in patients with DVT of the lower extremities.*

## **2-2 HEADACHES: Master Classes for GPs**

This is a straightforward and practical review.

It includes comments on migraine, medication overuse HA, cluster HA, dangerous HA, and temporal arteritis.

Also practical management tips and common pitfalls.

Some may find it useful to save as reference.

Read the full abstract.

***“Despite What They Might Say, People At The End Of Life Rarely Want Everything Or Nothing.”***

## **2-3 DEFINING LIMITS IN CARE OF TERMINALLY ILL PATIENTS**

Invasive procedures in terminally ill patients often fail to change the course of the disease. Interventions can become inappropriate overtreatment. Untimely referral to hospice, poor technical performance, overuse of interventions inconsistent with preferences and prognosis, and poor communication, increase the likelihood of inappropriate clinical intervention.

Surrogates usually do not realize that “doing everything” may lead to overtreatment. Doctors often do not take the time to clarify the nature of such requests. Surrogates may not have any idea about the wishes of the patient. Doctors should provide an accurate, sensitively presented account of the predictable consequences of

“doing everything”, and follow up by exploring how these consequences may not serve the goal of providing the best care.

It is imperative for good end-of-life decision-making to identify, explain, and negotiate consensus goals to ensure that appropriate treatment occurs. This requires effective communication skills and cultural sensitivity. The first step in preventing overtreatment of terminally ill patients is for both sides to collect and share information. Doctors must listen to, and focus on, what the patient and family understands about the patient’s condition:

What are you hoping we can achieve?

What do you think the patient would want?

Read the full abstract.

-----

*If you practice primary care medicine long enough, you will encounter surrogates who demand that ‘everything’ be done for their relative. I believe, however, that this situation occurs less frequently now than in the past. Suggestions about how to deal with it are welcome.*

### ***No Evidence To Support The Warning Of The US Advisory That Pregnant Women Should Limit Their Seafood Consumption***

#### **2-4 MATERNAL SEAFOOD CONSUMPTION IN PREGNANCY AND NEURODEVELOPMENT OUTCOMES IN CHILDHOOD**

Optimum fetal development is dependent on specific nutrients derived solely from dietary sources. These include essential fatty acids, of which seafood is a major source. In the USA, women are advised to limit their seafood intake during pregnancy to 340 grams per week to avoid fetal exposure to trace amounts of neurotoxins (especially mercury).

Such limitation of seafood consumption could cause intake of long-chain essential fatty acids to fall below quantities adequate for optimum fetal neurodevelopment.

This observational cohort study (over 11 500 women) assessed the possible benefits and hazards to a child’s development related to levels of maternal seafood intake during pregnancy.

Postal questionnaires were sent during pregnancy, and then at specific time points after birth of the child to obtain information about diet, education, social circumstances, behavior, and developmental outcomes. Detailed questions about seafood consumption were included.

Compared developmental, behavioral, and cognitive outcomes of children from ages 6 months to 8 years of women consuming 1) no seafood, 2) some seafood (1 -340 g per week) and 3) over 340 g per week

After adjustment, maternal seafood intake during pregnancy of less than 340 g per week was associated with increased risk of their children being in the lowest quartile for verbal IQ compared with mothers who consumed more than 340 g per week. Low maternal seafood intake was also associated with increased risk of suboptimum outcomes for prosocial behavioral, fine motor, communication, and social development scores.

There was no evidence that consumption of more than 3 portions of seafood a week during pregnancy has an adverse effect on the behavior or development of the child. (No evidence of harm.)

By contrast, maternal consumption of more than 340 g of seafood a week was beneficial to the child's neurodevelopment.

Advice that limits seafood consumption might reduce the intake of nutrients necessary for optimum neurological development.

Although methyl mercury undoubtedly has harmful effects on the developing brain, the harm is unlikely to be greater than the overall benefits of nutrients at the concentrations usually present in seafood.

Conclusion: Children of mothers who ate larger amounts of seafood were likely to have more optimum neurodevelopment. This study found no evidence to support the warning of the US advisory that pregnant women should limit their seafood consumption.

***Be Well Informed; Base Use On Firm Rationale; Keep Good Records***

**2-5 OFF-LABEL DRUGS: *Experts Weigh In On Promotion and Prescription***

“Off-label drug use has been around for decades. It is perfectly legal for practitioners to prescribe them for a condition not described in the approved labeling if it seems reasonable or appropriate.”

According to the FDA, when prescribing a product for an indication not in the approved labeling, physicians “have the responsibility to be well informed about the product, to base its use on firm scientific rationale, and on sound medical evidence, and to maintain records of the product's usefulness and effects”.

“Inappropriate off-label prescribing could have an effect on many patients because 21% of the 725 million total drug prescriptions reported in the study lacked FDA approval for the condition they were used to treat.”

The FDA Modernization Act of 1997 permitted drug companies to disseminate valid information—such as peer-reviewed studies published in scientific journals—about the safety and effectiveness of off-label uses that have been or will be studied and submitted for FDA approval. The FDA deemed other forms of off-label promotion illegal. However, a number of companies have falsely marketed their drugs for treatment of a variety of other conditions.

***“Successful Control Of Annual Influenza Epidemics Depends On Vaccinating A High Proportion Of Children.”***

**2-6 LIVE ATTENUATED versus INACTIVATED INFLUENZA VACCINE IN INFANTS AND YOUNG CHILDREN**

This study compared the safety and efficacy of live attenuated vaccine administered by nasal spray vs killed vaccine administered by injection.

During the 2004-05 flu season, randomly assigned over 7800 children age 6 months to 5 years to:  
1) live attenuated vaccine (*FluMist*), or 2) killed vaccine (*Fluzone*).

Influenza attack rates (confirmed by culture):

Live vaccine	Killed vaccine
(N = 3916)	(N = 3936)

A/H1N1	3 (0.1%)	27 (0.7%)	
A/H3N2	37 (0.9%)	178 (4.5%)	
B	115 (2.9%)	136 (3.5%)	
Regardless of match	153 (3.9%)	338 (8.6%)	[NNT = 21]

Serious adverse effects were more common in children age 6 months to age 1 year. Live vaccine was related to a higher risk of significant wheezing in infants age 6 months to 1 year.

“Many believe that the successful control of annual influenza epidemics depends on vaccinating high proportion of children.”

In addition to its high acceptability because of the mode of administration, the significantly higher efficacy of this live attenuated vaccine than the licensed inactivated vaccine suggests that it can play an important role in the control of influenza.

Conclusion: Among young children, live attenuated vaccine had better efficacy than the inactivated vaccine. Live vaccine should be a highly effective, safe vaccine for children *age 12 months to 5 years* who do not have a history of asthma or wheezing.

-----

*This study did not include a placebo group. It assumed that flu vaccine does provide protection.*

*Practical Pointers is addressed mainly to adult primary care medicine. Articles of pediatric interest are rarely abstracted. I abstracted this study because it does indeed pertain to adult medicine. Immunization of very young children against flu not only protects them, but extends protection to the family. The “herd” immunity effect benefits not only the recipients of the vaccine, but persons who have not been immunized. The goal remains—to attain universal vaccination against flu.*

*The antigenic effect of live virus depends on establishment of viral replication in the recipient (a mild infection). It is more effective in persons who do not have antibodies against the virus. (eg, young children). Live virus is less effective in adults who have some degree of immunity, which blocks the replication process. In adults, the immune response to killed vaccine is greater than the response to live vaccine. See Practical Pointers December 2006.*

### ***Resistance Developed Within A Few Days***

#### **2-7 EFFECT OF AZITHROMYCIN AND CLARITHROMYCIN THERAPY ON PHARYNGEAL CARRIAGE OF MACROLIDE-RESISTANT STREPTOCOCCI IN HEALTHY VOLUNTEERS.**

Two macrolides, clarithromycin and azithromycin are among the drugs of choice for treatment of respiratory infections. Respiratory pathogens (*Streptococcus pneumoniae*, *Streptococcus pyogenes*) are commonly resistant to macrolides. Resistance is increasing. This is most likely due to their inappropriate use.

This randomized, double-blind trial followed 204 healthy volunteers (mean age 24) for 42 days. Obtained pharyngeal swabs at baseline, and periodically, to culture and determine macrolide resistance by growth characteristics on erythromycin containing plates.

Randomized subjects to: 1) clarithromycin—500 mg twice daily for 7 days, 2) azithromycin—500 mg once daily for 3 days, and 3) matching placebo groups.

At baseline, macrolide resistance, determined by this method, was present in about 25% to 30% of each of the 3 groups. Immediately after macrolide use, a large increase in the proportion of macrolide resistance was noted in both clarithromycin and azithromycin groups, but not in the placebo groups.

Resistance peaked to over 80% at day 4 in the azithromycin group, and at day 8 in the clarithromycin group. Over 42 days, resistance decreased to 60%-70% in the antibiotic groups. Resistance in the placebo groups remained stable.

The study followed a subgroup of subjects for a total of 180 days. Resistance fell slightly from day 42, but continued to remain higher than in the placebo groups.

Conclusion: Antibiotic use was an important driver of the emergence of antibiotic resistance. “Physicians prescribing antibiotics should take into account the striking ecological side-effects of such antibiotics.”

-----

*I abstracted this article because several points impressed me:*

- 1) The high percentage (25%-30%) of streptococci considered by the study to be resistant at baseline, before any antibiotic had been given.*
- 2) The immediate (within days) development of resistance.*
- 3) The duration of resistance (months).*
- 4) The gradual waning of resistance (over 180 days in this study).*
- 5) The possible extension of resistance of bacteria, other than streptococci, induced by macrolides.*

*The study does not link antibiotic exposure (and development of resistance to the antibiotic in an individual) to the clinical outcome of illness in that individual. I believe both antibiotics would be curative in many patients despite presence of resistance. I doubt that the 25% to 30% of patients who carry resistant organisms who develop clinical illness would fail to respond to either antibiotic.*

**“May Reduce Coronary Mortality”**

## **2-8 SIESTA IN HEALTHY ADULTS AND CORONARY MORTALITY IN THE GENERAL POPULATION**

This study evaluated the association between siesta and CHD mortality in adults in Greece over a follow-up mean of 6 years. . No subject had a history of CHD, stroke, or cancer.

At baseline, all individuals were asked whether they took midday naps, the average duration, and the weekly frequency.

Categorized participants into:

Never taking naps

Systematic napping:

Occasional napping:

The association between naps and CHD mortality was stronger in working men

Adjusted CHD mortality ratios in men according to nap-taking and current working status:

Taking midday naps	Currently working (28 deaths)	Currently not working (n = 57) (57 deaths)
No	1.00	1.00
Occasional	0.36	0.86
Systematically	0.36	0.61
Occasional + systematic	0.36	0.64

“We interpret our findings as indicating that among healthy adults, siesta, possibly on account of stress-releasing consequences, may reduce coronary mortality.”

Conclusion: After controlling for potential confounders, siesta of apparently healthy individuals, particularly working men, was associated with lower CHD mortality.

-----

*This article gathered considerable interest by the lay press in the US.*

*The authors mention that the Mediterranean population has two benefits going: diet and siesta.*

*I was unable to calculate the absolute benefit of siesta in working men from the data presented. As there were only 28 deaths among 7300 subjects, the absolute benefit must have been very small.*

**Overall Prevalence Of HPV Types Included In The Vaccine = 3.4% (3 million women)**

## **2-9 PREVALENCE OF HPV INFECTION AMONG FEMALES IN THE UNITED STATES**

Human papilloma virus (HPV) is the most common sexually transmitted infection. Prevalence is highest among young persons, within the first few years after sexual debut.

HPV types are categorized according to their epidemiological association with cervical cancer (types 16 and 18); and genital warts (types 6 and 11). Worldwide, approximately 70% of cervical cancers are due to HPV 16 and 18.

A highly efficacious quadrivalent prophylactic vaccine against types 6, 11, 16, and 18 was licensed in June 2006. It is recommended for routine use in females age 11 to 12 years. It is close to 100% effective in preventing the infection and cervical cancer precursors and genital lesions associated with the types included.

In 2003-04, The National Health and Nutrition Examination Survey (NHANES) used a representative sample of US non-institutionalized women (age 14 to 59; n = 1921) to determine baseline population prevalence of HPV before widespread availability of a vaccine.

Women provided a self-collected vaginal swab specimen for determination of HPV DNA by polymerase chain reaction, followed by determination of the type(s).

Overall prevalence = 27%. (42 types; corresponds to 25 million females in the US.)

Overall, 3.4% of the study participants had infections with types included in the quadrivalent vaccine (HPV 6, 11, 16, 18; 3 million women). Of women age 14 to 19, 6% had at least 1 of the 4 types

Overall prevalence of high risk types 16 and 18 was 2.3%

Conclusion: Overall HPV prevalence in the US is high (27%)—highest in ages 20-24. The prevalence of types included in the HPV vaccine was relatively low.



-----  
*The health, social, and economic burden of HPV infections are considerable. This includes the expense, bother, and anxiety produced by positive Pap smears.*

*I was unable to determine the length of immunity from the vaccine or whether a booster will be necessary.*

*There is controversy about efforts to make vaccination against HPV mandatory for girls age 11 to 12. Why not vaccinate boys? Certainly “herd” immunity would play a large role here.*

### ***Schedule for a “Complete Physical”, or Deliver Preventive Services in The Context of Ongoing Clinical Care?***

#### **2-10 THE VALUE OF THE PERIODIC HEALTH EVALUATION: Systematic Review**

The PHE consists of one or more visits to a health care provider to assess patients’ overall health and risk factors. It results in delivery of clinical preventive services that are tailored to a patient’s age, sex, and clinical risk factors and laboratory testing. The PHE may improve patient outcomes and the public’s health.

It could, however, induce unnecessary costs and patient harms. Early studies of the PHE, performed before the adoption of current preventive services guidelines, were costly and demonstrated minimal improvements in clinical outcomes. Because of concern over the value of the PHE, some experts have advocated episodic targeted delivery of preventive services in the context of ongoing clinical care.

In light of conflicting opinions regarding the PHE’s impact on health, costs, and non-uniformity of its implementation, these investigators performed a systematic review of the evidence to ascertain benefits and harms.

This systematic review selected 21 studies assessing the delivery of preventive services, clinical outcomes, and costs among patients receiving the PHE versus those receiving usual care. Defined “usual care” as the delivery of clinical preventive services in the absence of a health care provider visit designated for the primary purpose of assessing the patient’s health and risk factors for disease.

Compared with usual care, the PHE had consistently beneficial association with patients’ receipt of gynecological examination and Pap smears, cholesterol screening, and fecal occult blood testing.

The PHE had a beneficial effect on patient “worry” in one randomized trial, but had mixed effects on other outcomes and costs.

Conclusion: The PHE has a beneficial effect on the delivery of some preventive services, and may have a beneficial effect on patients’ worry.

-----  
*This is not a strong study. There is too much heterogeneity. I believe it does concur with the experience of most primary care clinicians. I believe also that, since primary care clinicians care for many patients with chronic diseases over a long-term, there will be ample opportunity to apply the goals of the PHE episodically. This approach may be time- and expense-saving.*

*We should focus on long-term control of the “big 5” risk factors (in addition to any acute and continuing health problems the patient may present).*

*Smoking and alcohol*

*Diet and lipid control*

*Exercise*

*Body mass index*

*Blood pressure.*

*Some patients may wish to schedule an appointment for a periodic “check up” focused on their general health. This may provide them reassurance and possibly uncover previously undiagnosed risk factors. I would not deny this service. Indeed, patients who schedule PHEs may be more compliant and interested in continuing to focus on reduction of risk factors.*

*Some risk factors should not be routinely investigated without full informed consent of the patient. (g, PSA testing)*

*There comes a time when we should limit investigations usually considered part of the PHE. Elderly patients may not live long enough to gain any benefit from continuing risk reduction, and may not wish to be bothered or worried any longer, but to enjoy to the fullest possible each day granted them.*

***The Doctor-Patient Relationship Should Retain The Moral Agency Of Both The Physician And The Patient***

## **2-11 RELIGION, CONSCIENCE, AND CONTROVERSIAL CLINICAL PRACTICES**

Should health professionals refuse to provide treatments to which they object on moral grounds?

Recent controversies regarding physicians and pharmacists who refuse to prescribe or dispense emergency and other contraceptives have sparked a debate about moral objections in providing some types of health care.

Most people believe that health professionals should *not* have to engage in medical practices about which they have moral qualms. On the other hand, most people also believe that patients should have access to legal treatments, even in situations in which their physicians are troubled about moral implications of those treatments.

Is it ethical for physicians to describe their objections to the patient? Should physicians have the right to refuse to discuss, provide, or refer patients for legal medical interventions to which they have religious or moral objections?

Historically, doctors and nurses have not been required to participate in abortions or suicide, even where those interventions are legally sanctioned.

This study aimed at understanding how physicians think about their ethical rights and obligations when conflicts emerge in clinical practice.

Conclusion: On moral grounds, many physicians refuse to provide some services which society considers legal, and do not consider themselves obligated to disclose information about, or to refer patients, for legal but morally controversial, medical procedures.

-----

*Read the entire abstract.*

*The message of this article extends far beyond the limited circumstances described. It extends to*

*placing judgments on others under many circumstances. Many physicians and pharmacists apparently consider providing a service they consider immoral (or refusing to refer to another professional who will provide the service) a form of aiding and abetting immoral behavior. It is a form of imposition of one's belief on another.*

*When an authoritarian professional refuses to discuss alternatives, or to refer to another professional, patients (and especially teenagers) are placed at an overwhelming disadvantage. What if the clinician does not know, or will not disclose the name of another professional who will provide the service? What if the patient cannot, for economic or practical reasons, consult with a second provider?*

*The article suggests that patients who want information about, and access to, such procedures may need to inquire proactively to determine whether their physician would accommodate such requests. Is this practical?*

*I can imagine this scenario between patient and a professional:*

*Physician or pharmacist: "I can not provide this service to you."*

*Patient: "Why not, Dr. Jones?"*

*Physician: "I believe it is immoral".*

*Patient: "Do you believe it is a sin?"*

*Dr. Jones: "Yes, I do."*

*Patient: "Dr. Jones, are you a sinner?"*

***"Unlikely To Produce Lipid Benefits."***

## **2-12 EFFECT OF RAW GARLIC VS COMMERCIAL GARLIC SUPPLEMENTS ON PLASMA LIPID CONCENTRATING IN ADULTS WITH MODERATE HYPERCHOLESTEROLEMIA**

This study compared the effects of raw garlic, and 2 garlic supplements with distinctly different formulations on the plasma lipid concentrations in adults with moderate hyper-cholesterolemia..

Recruited and randomized 192 adults (age 30-65) from the community who had a fasting LDL-cholesterol concentration of 130 to 190 mg/dL (mean = 151), a triglyceride level under 250 mg/dL, and a body mass index of 19 to 30.

Provided garlic in 3 forms: 1) raw garlic, 2) *Garlicin*, and 3) *Kyloic-100*. *Garlicin* was selected to represent powdered garlic supplements. *Kyloic* was selected because it is one of the most popular brands. It is an aged powdered garlic supplement. 4) A placebo group was added.

The products were consumed 6 days a week for 6 months: raw garlic as a crushed average size clove; *Garlicin* and *Kyloic* given at 1 1/2 to 3 times the recommended dose.

There were no clinically or statistically significant effects of the 3 garlic forms on LDL-c.

Six month changes in LDL-c (means; mg/dL)

Raw garlic	+0.4
Garlicin	+3.2
Kyloic	+0.2
Placebo	-3.9

Conclusion: None of the forms of garlic tested, when given at an approximate dose of a 4-g garlic clove daily for 6 months, had significant effects on LDL-c.

-----

*It is difficult to prove a negative. Proponents of natural products can readily cite reasons why a trial does not disprove efficacy.*

*Garlic is widely advertised to lower cholesterol. I believe this property is now disproved. Such advertisements should not be allowed. As the editorialist states, there remains a possibility that garlic does reduce risk of cardiovascular disease for other reasons. Admittedly, LDL-c is an intermediate endpoint, but a good one.*

*It would take a large, long, and expensive randomized trial of garlic products, with the endpoint of cardiovascular disease incidence, to prove or disprove this point. I doubt if such a trial will be completed. Meanwhile garlic will likely continue to be widely used.*

# ABSTRACTS FEBRUARY 2007

*LMWH Carries the Day.*

## **2-1 VENOUS THROMBOEMBOLISM: A Clinical Practice Guideline**

*This guideline provides the most recent evidence-based recommendations for management of venous thromboembolism<sup>1</sup> (VTE). It is based on a more detailed practice guideline for management of VTE which details the background for these recommendations, published in this issue of Annals (pp 211-22), first author Jodi B Segal, Johns Hopkins University School of Medicine, Baltimore MD.*

### 1. DVT (Initial inpatient treatment):

It is critical to treat deep venous thrombosis (**DVT**) at an early stage to avoid complications such as pulmonary embolism (PE), recurrent DVT, and the post-thrombotic syndrome. Consistent evidence demonstrates that low-molecular-weight heparin (**LMWH**) is superior to unfractionated heparin (UFH) for initial treatment of DVT, particularly for reducing mortality and the risk of major bleeding. LMWH is less likely than UFH to cause antibody formation and heparin-induced thrombocytopenia. It is cost-effective compared with UFH.

### 2. DVT (Outpatient treatment):

LMWH is safe and cost-effective for carefully selected patients. It should be considered if the required support services are in place. Several trials allowed a brief inpatient admission for stabilization of patients before randomization to the outpatient group. Most studies excluded patients with previous venous thromboembolism (VTE), thrombophilic conditions, significant co-morbidity, pregnancy, and those unlikely to adhere to outpatient therapy. Therefore, this recommendation cannot be generalized.

### 3. Pulmonary Embolism (**PE**) (Initial inpatient treatment):

Reviews of existing trials indicate that LMWH is at least as effective as UFH for patients with PE. The rates of recurrent DVT, major bleeding, and death are similar between groups. Many patients treated with UFH receive too low- or too high-doses. LMWH has the advantage of being consistently therapeutic. Several trials allowed a brief inpatient admission for stabilization of patients before randomization to the outpatient group.

### 4. Optimal duration of anti-coagulation:

VTE recurs in about 20% of patients during 5 years observation. For VTE secondary to transient risk factors, anti-coagulation should be maintained for 3 to 6 months. Patients with DVT due to transient risk factors benefit little from more than 3 months therapy. For idiopathic or recurrent VTE, the appropriate duration of treatment is not definitely known. There is evidence of substantial benefit of extended-duration therapy. Length of therapy in trials varied widely, for up to 4 years. The benefit/risk ratio for longer periods is not known. Patients' preferences should help decide on duration. LMWH is safe and effective for long-term treatment of VTE in selected patients (and may be preferable for patients with cancer). Long-term

LMWH is comparable to oral anticoagulation for treatment of VTE in selected patients. It may be useful in patients in whom control of the international normalized ratio for warfarin therapy is difficult.

5. Anticoagulation for management of VTE in pregnancy:

Compared with non-pregnant women, pregnant women have a 5-fold increased risk of VTE. There is insufficient evidence to make specific recommendations for types of anti-coagulation. But, vitamin K antagonists (eg, warfarin) should be avoided because they cross the placenta and may cause fetal bleeding and embryopathy. LMWH and UFH do not cross the placenta. Neither is associated with these fetal complications.

6. Compression stockings;

Most post-thrombotic syndrome patients are diagnosed within 2 years after DVT. The post-thrombotic syndrome may result in life-long limb pain and edema. Compression stockings should be used routinely to prevent the post-thrombotic syndrome, beginning soon after diagnosis of proximal DVT, and continuing for at least one year. Evidence demonstrates a marked reduction in the incidence and severity of the post-thrombotic syndrome, whether with over-the-counter stocking or custom-fit stockings.

Annals Internal Medicine February 6, 2007; 146: 204-10 “Clinical Guidelines” from the American College of Physicians and The American Academy of Family Physicians, first author Vincenza Snow, American College of Physicians, Philadelphia, PA.

1 The guideline considers deep venous thrombosis (DVT) and pulmonary embolism (PE) separately.

*I believe venous thromboembolism (VTE) is a more accurate and inclusive term because risk of PE (asymptomatic as well as symptomatic) is very high (almost universal) in patients with DVT of the lower extremities.*

=====

**2-2 HEADACHES: Master Classes for GPs**

In the UK, 15% of the adult population has migraine; 80% has episodic tension –type headache from time to time. Prevalence is higher in women.

This article provides a concise overview.

1. Migraine:

Make an acute treatment plan

Treatment ladder for migraine.

Step 1

Try to identify triggers using a diary. (food, stress, lack of sleep).

Start with NSAID (aspirin or ibuprofen).

Give these with an antiemetics—oral metoclopramide (*Reglan*)<sup>1</sup> or prochlorperazine

(*Compazine*)<sup>2</sup> as a buccal tablet, given before the NSAID.

Advise treatment as soon as possible after an attack starts.

## Step 2

### Triptans:

All triptans are associated with relapse of symptoms after 48 hours (20-50% of patients).

Give oral metoclopramide (*Reglan*) before the triptan.

Do not prescribe with ergotamine.

Recommend taking when the HA starts rather than at the time of aura.

Sumatriptan (*Imitrex*)<sup>3</sup> is the most commonly prescribed, and has the most evidence about effects. Recommend starting with a 50 mg tablet. (Also available as a rapidly dispersing preparation.) If necessary increase dose to 100 mg, or 20 mg as a nasal spray. The spray is not useful if vomiting occurs, as the drug's bioavailability depends partly on ingestion.

If a rapid response is needed, subcutaneous sumatriptan relieves migraine in 80% within one hour.

Patients respond differently to different triptans. If ineffective, recommend another triptan.

Triptans are contraindicated in patients with ischemic heart disease, uncontrolled hypertension, and those with risk factors for coronary heart disease and cerebrovascular disease.

### Prophylaxis for migraine:

First line = beta-blocker

Second line = topiramate (*Topamax*)<sup>4</sup> or valproic acid (*Depakene*)<sup>5</sup>

One dose of topiramate 100 mg daily has been reported to be effective and well tolerated.

Continue taking effective drugs for 4 to 6 months, then withdraw over 2 to 3 weeks to see if the drugs are still necessary.

## 2. Medication overuse HA:

Is an important cause of HA.

More common in patients who overuse triptans. These patients typically have a daily migraine type HA, or an increase in frequency of HA.

Overusers of analgesics and ergotamine typically have a daily tension-type HA.

Patients using analgesics or triptans for 17 days a month are at risk.

## 3. Cluster HA:<sup>A</sup>

Are unilateral and severe. They occur in clusters over 6 to 12 weeks. More common in men, and in people who smoke. They tend to occur daily and wake the patient if they occur within a few hours of falling asleep. They are associated with ipsilateral watering of the eye, conjunctival redness, rhinorrhea, nasal blockage, and ptosis. Prevalence in the UK is 7 in 10 000.

## 4. Dangerous HA :

Subarachnoid hemorrhage, meningitis, temporal arteritis, and raised intracranial pressure of whatever reason occur in fewer than 1% of patients referred to outpatient clinics. They tend to be "first and worst", of sudden onset, progressive, and with onset later in life.

## 5. Temporal arteritis:

Consider temporal arteritis in any older patient who has a new-onset HA. Only a minority have temporal pain. Jaw claudicating (pain during talking or chewing) is virtually diagnostic.

## 6. Practical management tips:

Recognize that patients may have more than one type of HA.

Be alert for medication overuse HA. Codeine based drugs are common culprits.

Be aware that the patient may have a rare primary HA disorder (most commonly cluster HA).

Consider prophylaxis for migraine.

First line: beta-blocker.

Second line: topiramate (*Topamax*).or valproate (*Depakene*).

Start at low doses and slowly titrate upward.

## 7. Common pitfalls:

Causing medication overuse HA by treating chronic HA with regular analgesia rather than suggesting prophylaxis.

Undertreating migraine.

Missing unusual primary HA variants.

Blaming HA on stress.

BMJ February 3, 2007; 33: 254-56 "Practice", Review article, first author Geraint Fuller, Gloucester Royal Hospital, London UK

I have amended the article to include only drugs readily available in the U.S.

**1** Metoclopramide (*Reglan*; *Generic*) is a true prokinetic drug. It causes coordinated contractions of the upper g.i. tract (antrum and upper small bowel) and increases lower esophageal sphincter tone. It is used as an anti-emetic. Extrapyramidal adverse effects are rare.

**2.** Compazine is a phenothiazine. Utility against psychosis is questionable. It is available only as a generic. It is used as an anti-emetic. .

**3.** Sumatriptan (*Imitrex*) is a selective 5-hydroxytryptamine (serotonin) agonist. It acts by reducing the vasoconstriction associated with migraine. Safety and efficacy are better than ergotamine.

**4** Topiramate (*Topamax*) is an anti-seizure drug, recently approved for prevention of migraine. It is not effective for treating acute attacks. It is a carbonic anhydrase inhibitor. Titrate up from 25 mg daily to 100 mg. Mechanism unknown. Reported to reduce the number of acute attacks of migraine.

**5.** Valproate (*Depakene*; *Generic*) is an anti-epilepsy drug. Reported to reduce frequency of acute migraine attacks. Paresthesias are a common adverse effect.

Topiramate and valproate are complex drugs, with many adverse effects. Primary care clinicians who prescribe them should be familiar with them and well aware of adverse effects. I would not prescribe them. I would leave this to HA consultants.

**A** As a primary care clinician you will encounter a patient with CHA if you practice long enough.



CHA is extraordinarily distressing and disabling. Patients will be most grateful if you can help them gain relief.

A few additional points: (Gathered from GOOGLE and www.mayoclinic.com)

CHA may be a disorder of the hypothalamus, related to its biological clock function.

Onset is usually sudden (thunderclap), often at the same time of day. Offset may also be sudden.

Rarely CHA does not remit, and may occur daily for long periods.

Many patients with CHA are heavy smokers

Patients tend to be restless and pace around (in contrast to migraine).

Alcohol may trigger a CHA

Treatment of acute attack

Start treatment immediately

Injected medications act more quickly and are recommended.

Oxygen

Sumatriptan

Lidocaine nasal drops

Prevention

Avoid alcohol and tobacco

For short term use:

Corticosteroids

Ergotamine

Long term use

Calcium blocker

Lithium

Depakote

Topiramate

---

***“Despite What They Might Say, People At The End Of Life Rarely Want Everything Or Nothing.”***

### **2-3 DEFINING LIMITS IN CARE OF TERMINALLY ILL PATIENTS**

Invasive procedures in terminally ill patients often fail to change the course of the disease. Interventions can become inappropriate overtreatment. Untimely referral to hospice, poor technical performance, overuse of interventions inconsistent with preferences and prognosis, and poor communication, increase the likelihood of inappropriate clinical intervention.

The authors present a clinical scenario in which a terminally ill elderly father with lung cancer, COPD, congestive heart failure, and pneumonia had been admitted for the 3<sup>rd</sup> time in 10 months. He had told his wife (and the therapy team) several times he never wanted to be placed on a respirator again. But, he did not

complete an advanced directive. He was confused. His son (who had not been previously involved) wanted “everything” done for his father.

Surrogates usually do not realize that “doing everything” may lead to overtreatment. Doctors often do not take the time to clarify the nature of such requests. Surrogates may not have any idea about the wishes of the patient. Doctors should provide an accurate, sensitively presented account of the predictable consequences of “doing everything”, and follow up by exploring how these consequences may not serve the goal of providing the best care.

It is important to clarify the patient’s and surrogate’s expectations regarding outcomes, to resolve misunderstandings, and to correct unfounded expectations. To facilitate appropriate care, doctors must, at times, anticipate discordance between their views and those of patients or surrogates, and use the informed consent process to prevent potential discordance from becoming actual discordance. Doctors should respond quickly when conflicts do arise.

It is imperative for good end-of-life decision-making to identify, explain, and negotiate consensus goals to ensure that appropriate treatment occurs. This requires effective communication skills and cultural sensitivity. The first step in preventing overtreatment of terminally ill patients is for both sides to collect and share information. Doctors must listen to, and focus on, what the patient and family understands about the patient’s condition:

What are you hoping we can achieve?

What do you think the patient would want?

Doctors need to identify what is important to the patient including any religious beliefs and what his or her values and goals might be. If a surrogate is involved, his substituted judgment must be based as much as possible on what the patient might want. (The substituted judgment standard.)

Patients and surrogates need to understand the potential adverse effects of treatment and their prevalence, both short- and long-term. Doctors should make clear that good medical care does not always mean doing “everything” that is technically possible. In fact, what is technically possible may be clinically inappropriate. Doctors should clearly convey that inappropriate treatment is not benign, but almost always associated with appreciable burdens and little or no clinical benefits. Overtreatment can cause suffering.

Families need to understand that not doing “everything” is not equivalent to doing “nothing”. The doctor should set realistic goals which ensure comfort and maintain dignity of the patient. When discussing treatments we should always return to what the patient’s and goals would be, and why inappropriate intervention might not support these values.

Doctors should not use words that might contribute to conflict—“stopping treatment” and withdrawing care”. Doctors should focus on effective palliation and helping patients maintain their dignity.

After acknowledging the situation’s difficulty, doctors should not shy away from making recommendations based on their expert opinion. A surrogate may appreciate such recommendations because they can reduce guilt and the feeling of being solely responsible for the outcome. A personal empathetic approach to recommend against certain procedures may enhance trust and credibility, and reduce the burden of decision making. “If the patient were my father, I would . . . .”

When doctors offer all technically possible alternatives unedited by clinical judgment about which ones are clinically beneficial or simply acquiesce to requests to “do everything” they yield their proper role in the informed consent process. It does not violate the terminally ill patient’s or a surrogate’s autonomy to recommend against clinically inappropriate interventions and to provide an evidence-based explanation that justifies the recommendation. A successful approach requires doctors, guided by professional integrity, to exercise responsible influence over the informed consent process.

Curative and palliative care should not be dichotomous. Patients should not have to forego curative treatments to have access to palliative care, nor should they have to forego palliative care just because they are still undergoing curative treatments.

Once consensus has been reached, it is important to document the discussion, and write appropriate orders immediately. And to make sure that other professionals who care for the patient understand. If the patients is to be discharged from the hospital, those who follow-up should be made aware of the consensus agreement.

BMJ February 3,2007; 334: 339-41 “Analysis”. Commentary, first author Ursula K Braun, Michael DeBakey VA Medical Center, Houston TX

=====

***No Evidence To Support The Warning Of The US Advisory That Pregnant Women Should Limit Their Seafood Consumption***

**2-4 MATERNAL SEAFOOD CONSUMPTION IN PREGNANCY AND NEURODEVELOPMENT OUTCOMES IN CHILDHOOD**

Optimum fetal development is dependent on specific nutrients derived solely from dietary sources. These include essential fatty acids, of which seafood is a major source. In the USA, women are advised to limit their seafood intake during pregnancy to 340 grams per week to avoid fetal exposure to trace amounts of neurotoxins (especially mercury).

Such limitation of seafood consumption could cause intake of long-chain essential fatty acids to fall below quantities adequate for optimum fetal neurodevelopment.

This observational cohort study<sup>1</sup> assessed the possible benefits and hazards to a child's development related to levels of maternal seafood intake during pregnancy.

Conclusion: Compared with outcomes in women who ate no fish, beneficial effects on childhood development were recorded with maternal seafood intakes of more than 340 g per week. There was no evidence of harm at higher intakes of seafood.

## STUDY

1. At 32 weeks gestation, over 11 500 women living in Bristol UK completed a food frequency questionnaire. Postal questionnaires were also sent 4 more times during pregnancy, and then at specific time points after birth of the child to obtain information about diet, education, social circumstances, behavior, and developmental outcomes. Detailed questions about seafood consumption were included.
2. Considered 28 potential confounders assessing social disadvantage, perinatal, and dietary items when comparing outcomes.
3. Compared developmental, behavioral, and cognitive outcomes of children from ages 6 months to 8 years of women consuming 1) no seafood, 2) some seafood (1 -340 g per week) and 3) over 340 g per week. Measured the IQs of children at age 8. (n = 5549).

## RESULTS

1. Twelve % of women ate no fish during pregnancy; 65% ate 1-340 g per week; 23% ate more than 340 g .per week.
2. Intakes of omega-3 fatty acids ranged from 0 to 16 grams.
3. After adjustment, maternal seafood intake during pregnancy of less than 340 g per week was associated with increased risk of their children being in the lowest quartile for verbal IQ compared with mothers who consumed more than 340 g per week.
4. Low maternal seafood intake was also associated with increased risk of suboptimum outcomes for prosocial behavioral, communication, and social development scores.
5. In the group with seafood intake of 1-340 grams per week, outcomes were more favorable than in the group who ate no fish, but less favorable than those who ate over 340 g per week.
6. As mother's intake of omega-3 fatty acids increased, verbal IQ scores in their children at age 8 were higher than in children of mothers whose intake was less. About 30% of children whose mothers consumed no omega-3 acids had low verbal IQ scores compared with about 16% of children with low scores whose mothers consumed more omega-3.
7. Although relatively few women who ate no fish but took fish oil supplements, outcomes of their infants were close to those of mothers who did eat fish.

## DISCUSSION

1. This shows no evidence that consumption of more than 3 portions of seafood a week during pregnancy has an adverse effect on the behavior or development of the child. (No evidence of harm.)

2. By contrast, maternal consumption of more than 340 g of seafood a week was beneficial to the child's neurodevelopment.
3. As with any observational study, the possibility exists that some confounders had not been taken into account. The study did not have information about specific species of seafood.
4. The study was reasonably representative of the British population, which has a higher mean consumption of mercury than the US population. Seafood eaten in this cohort was likely to have contained greater quantities of mercury than the species from the US that were used to formulate the 2004 US advice.
5. Advice that limits seafood consumption might reduce the intake of nutrients necessary for optimum neurological development.
6. Although methyl mercury undoubtedly has harmful effects on the developing brain, the harm is unlikely to be greater than the overall benefits of nutrients at the concentrations usually present in seafood.

## CONCLUSION

Children of mothers who ate larger amounts of seafood were likely to have more optimum neurodevelopment.

This study found no evidence to support the warning of the US advisory that pregnant women should limit their seafood consumption. (No evidence of harm.)

Lancet, February 17, 2007; 369: 578-85 Original investigation, first author Joseph R Hibbeln, US National Institute of Health, Bethesda MD, USA.

### 1 Avon Longitudinal Study of Parents and Children (ALSPAC)

An editorial in this issue of Lancet (pp 537-38), first author Gary J Myers, University of Rochester Medical Center, NY comments and expands on the study:

The fetal brain grows rapidly in size and complexity during gestation. In the first two decades of life the brain triples in size. The brain accounts for about 25% of the basal metabolic rate at birth, and is about 50% lipid, predominantly polyunsaturated long-chain fatty acids, some of which are essential fatty acids.

Two of the most important essential fatty acids are docosahexaenoic acid and arachidonic acid.<sup>a</sup> The developing brain needs large quantities of these nutrients, especially docosahexaenoic acid which the human body cannot synthesize in adequate quantities from precursors. Consequently, they are mostly obtained from the diet. Fish and other seafoods and breast milk contain essential fatty acids. The fatty acid content of mother's breast milk is determined mostly by her diet.

This lends support to the popular opinion that "fish is brain food".

All fish contain small amounts of methylmercury. Although it can be neurotoxic, the amount of mercury exposure that constitutes a toxic dose is not known. The only confirmed case of prenatal mercury human poisoning by methylmercury occurred in Japan in the 1950s-60s after massive industrial pollution of nearby water.

About two-thirds of Americans believe that thousands of US children are poisoned by mercury every year from eating fish. “In fact, there has never been even one child with prenatal mercury poisoning from consuming fish documented outside Japan.”

In 2004 the FDA and the Environmental Protection Agency published an advisory recommending that people should restrict their consumption of specific fish <sup>b</sup> that accumulate higher concentrations of methylmercury. Are such advisories in the public interest? Will people really reduce consumption of only these named species? A recent survey suggested that many Americans presented with this advice reduced their intake of all fish.

**a** Docosahexaenoic acid is an 18 carbon omega-3 acid; arachidonic acid is an 18 carbon omega-6 acid.

Both are essential fatty acids.

**b** Especially shark, swordfish, king mackerel and tile fish.

=====

***Be Well Informed; Base Use On Firm Rationale; Keep Good Records***

### **2-5 OFF-LABEL DRUGS: *Experts Weigh In On Promotion and Prescription***

“Off-label drug use has been around for decades. It is perfectly legal for practitioners to prescribe them for a condition not described in the approved labeling if it seems reasonable or appropriate.” <sup>1</sup>

Potentially dubious promotions from drug companies, pressure from patients and their advocacy groups, and hurdles to reimbursement by insurance providers make determining the appropriateness of such prescribing difficult.

According to the FDA, when prescribing a product for an indication not in the approved labeling, physicians “have the responsibility to be well informed about the product, to base its use on firm scientific rationale, and on sound medical evidence <sup>2</sup>, and to maintain records of the product’s usefulness and effects”.

The basis for off-label use usually comes from clinical trials in similar diseases. For example, if a drug has been tested and approved for one type of cancer, and a different type of cancer arises due to the same mechanism (such as a mutation of a particular gene), then logic would suggest that the therapy may be effective against both malignancies.

It is estimated that 50% to 75% of all uses of drugs in cancer care are off-label. About 90% of patients with rare diseases are given at least one off-label drug. The majority of drugs on the market do not have labeling indications for children, leaving their use in children to physician’s discretion.

A study in 2001 reported that 73% of off-label uses lacked evidence of clinical efficacy. The greatest disparities between supported and non-supported off-label use were found among prescriptions for psychiatric uses and allergies. “Inappropriate off-label prescribing could have an effect on many patients because 21% of the 725 million total drug prescriptions reported in the study lacked FDA approval for the condition they were used to treat.”

There is also a presumption that FDA approval provides widespread or general endorsement of a drug. But, some of the situations in which these drugs are used off-label are so different that this presumption is erroneous.

When a drug is newly approved for indication (#1), it is not wise to immediately use it for an off-label indication (#2). This is because new safety issues for indication (#1) may crop up in the post-marketing years. Using the drug immediately for an off-label indication (#2) could then add to risk.

The FDA Modernization Act of 1997 permitted drug companies to disseminate valid information—such as peer-reviewed studies published in scientific journals—about the safety and effectiveness of off-label uses that have been or will be studied and submitted for FDA approval. The FDA deemed other forms of off-label promotion illegal. However, a number of companies have falsely marketed their drugs for treatment of a variety of other conditions.

The United States Pharmacopoeia Drug Information (USP DI) is a compendium providing scientific documentation for labeled and off-labeled use of prescription drugs. ([www.micormedex.com](http://www.micormedex.com))

JAMA February 21, 2007; 297: 683-84 “Medical News and Perspectives” commentary by Tracy Hampton, JAMA Staff.

- 1 Who decides if it is reasonable or appropriate?
- 2 If use requires “firm scientific rationale and sound medical evidence” why is the drug not approved?

---

***“Successful Control Of Annual Influenza Epidemics Depends On Vaccinating A High Proportion Of Children.”***

## **2-6 LIVE ATTENUATED versus INACTIVATED INFLUENZA VACCINE IN INFANTS AND YOUNG CHILDREN**

Hospitalization rates for culture confirmed influenza among young children are similar to those among the elderly. Outpatient visits for confirmed influenza are more frequent among infants and young children than in any other age group.

U.S. advisory bodies have recommended routine universal vaccination of all children 6 months to 5 years.

This study compared the safety and efficacy of live attenuated vaccine administered by nasal spray vs killed vaccine administered by injection.

Conclusion: Live attenuated vaccine had better efficacy than killed vaccine.

### **STUDY**

1. During the 2004-05 flu season, randomly assigned over 7800 children age 6 months to 5 years to:
  - 1) live attenuated vaccine (*FluMist*), or 2) killed vaccine (*Fluzone*). Children not previously vaccinated received a second dose of the assigned vaccine, 28 to 42 days later.
2. No child had a recent episode of wheezing or severe asthma.
3. Monitored influenza-like illness with culture.

## RESULTS

### 1. Influenza attack rates (confirmed by culture):

	Live vaccine (N = 3916)	Killed vaccine (N = 3936)
A/H1N1	3 (0.1%)	27 (0.7%)
A/H3N2	37 (0.9%)	178 (4.5%)
B	115 (2.9%)	136 (3.5%)
Regardless of match	153 (3.9%)	338 (8.6%) [NNT = 21]

2. The superior efficacy of the live vaccine was observed for both the antigenically well-matched and the antigenically-drifted virus.

3. Significant reductions were also seen in overall attack rates of acute otitis media and lower respiratory tract infections. (Relative efficacy live vs killed = 51% and 46%

4. Among previously unvaccinated children, wheezing occurred within 42 days in 3.8% receiving the live vaccine, vs 2.1% among those receiving the killed vaccine, primarily among those age 6 months to 1 year.

5. Adverse effects (AE) overall	Live (%)	Killed (%)
Runny or stuffy nose	46	57
Fever > 100	5	2
Fever > 102	<1	<1
Hospitalization any cause	3.1	2.9
Number of serious AE	6	5

7. Serious adverse effects were more common in children age 6 months to age 1 year.

	Live (%)	Killed (%)
Significant wheezing		
6-11 months	14	10
12 months - 5 years	8	7
Any serious AE		
6-11 months	7	3
12 months - 5 years	3	3
Hospitalization any cause		
6-11 months	6	3
12 months - 5 years	3	3

## DISCUSSION

1. "Many believe that the successful control of annual influenza epidemics depends on vaccinating a high proportion of children."

2. In addition to its high acceptability because of the mode of administration, the significantly higher efficacy of this live attenuated vaccine than of the licensed inactivated vaccine suggests that it can play an important role in the control of influenza



3. The higher efficacy was seen not only for well-matched strains but also for viruses that were antigenically drifted from the antigen in the vaccine.
4. Live vaccine was related to a higher risk of significant wheezing in infants age 6 months to 1 year.

## CONCLUSION

Among young children, live attenuated vaccine had better efficacy than the inactivated vaccine. Live vaccine should be a highly effective, safe vaccine for children age 12 months to 5 years who do not have a history of asthma or wheezing.

NEJM February 15, 2007; 356: 685-96 Original investigation, first author Robert B Belshe, Saint Louis University Health Sciences Center, St. Louis, MO

Study supported by Med Immune, maker of FluMist

---

### ***Resistance Developed Within A Few Days***

#### **2-7 EFFECT OF AZITHROMYCIN AND CLARITHROMYCIN THERAPY ON PHARYNGEAL CARRIAGE OF MACROLIDE-RESISTANT STREPTOCOCCI IN HEALTHY VOLUNTEERS.**

Resistance to antibiotics is a major public health problem.

Two macrolides, clarithromycin (*Biaxin*) and azithromycin (*Zithromax*) are among the drugs of choice for treatment of respiratory infections. Respiratory pathogens (*Streptococcus pneumoniae*, *Streptococcus pyogenes*) are commonly resistant to macrolides. Resistance is increasing. This is most likely due to their inappropriate use.

Azithromycin has a long half-life, and therefore is often given once a day for 3 days. Clarithromycin has a shorter half life, and is often given twice daily for 7 days. Theoretically, shorter drug exposure duration would decrease the chance of development of resistance.

This study used the oral commensal streptococcal flora as models to study the effect of clarithromycin and azithromycin on selecting macrolide resistance in a healthy population.

Conclusion: Resistance developed rapidly.

## STUDY

1. Randomized, double-blind trial followed 204 healthy volunteers (mean age 24) for 42 days.
2. Obtained pharyngeal swabs at baseline, and periodically, to culture and determine macrolide resistance.
3. The proportion of macrolide-resistant streptococci was determined by comparing the number of colonies growing on erythromycin-containing plates (2 ug/mL) by the number of colonies on plates without erythromycin.
4. Randomized to: 1) clarithromycin—500 mg twice daily for 7 days, 2) azithromycin—500 mg once daily for 3 days, and 3) matching placebo groups.

5. Primary outcome = the change in proportion of streptococci that were macrolide-resistant.

## RESULTS

1. At baseline, macrolide resistance, determined by this method, was present in about 25%-30% of each of the 3 groups.
2. Immediately after macrolide use, a large increase in the mean proportion of macrolide resistance was noted in both clarithromycin and azithromycin groups, but not in the placebo groups.
3. Resistance peaked to over 80% at day 4 in the azithromycin group, and at day 8 in the clarithromycin group.
4. Over 42 days, resistance decreased to 60%-70% in the antibiotic groups. Resistance in the placebo groups remained stable.
5. Changes in mean proportion of macrolide-resistant streptococci from baseline:

	Azithromycin (%)	Clarithromycin (%)	Placebo (%)
Day 4	60		
Day 8	57	52	4
Day 24	54	33	3
Day 42	41	28	4

(Compared with the 25% to 30% of streptococci resistant to erythromycin present at baseline in all 3 groups, resistance in both antibiotic groups increased to over 80%.)

4. Resistance to azithromycin remained higher than resistance to clarithromycin over 42 days.
5. The study followed a subgroup of subjects for a total of 180 days. Resistance fell slightly from peak levels and from day 42, but continued to remain higher than in the placebo groups.
6. The investigators also determined the molecular basis for resistance based on the carriage of two macrolide-resistance genes in the streptococci. *(I do not have enough experience to comment on this aspect of the study. Those who are comfortable with genetic expression in bacteria may find this meaningful. RTJ)*

## DISCUSSION

1. Macrolide use is the single most important driver of emergence of macrolide resistance in humans.
2. Quantitatively, azithromycin selected more resistant organisms in the early post-therapy phase than clarithromycin
3. The effect of a single course of antibiotics on the oral commensal flora lasted for more than 180 days. Commensal flora could serve as a reservoir of resistance for potentially pathogenic flora.
4. Both antibiotics achieve high extracellular concentrations in respiratory tissue. They are commonly used as first-line therapy for community-acquired infections.
5. The plasma half-life and tissue persistence of azithromycin (68 hours) is much longer than that of clarithromycin (7 hours). Azithromycin might persist in vivo for 3 to 4 weeks. This may explain why azithromycin selected for significantly more macrolide-resistant streptococci for a longer period.

6. Despite the large increase in the proportion of macrolide resistant streptococci after macrolide use, at no point did the proportion of resistant bacteria reach 100%. Within 48 hours of the end of therapy, 18% of the streptococcal flora were still susceptible to macrolides.
7. A longer time period would be needed to determine the time needed for the resistant oral flora to revert to baseline levels.

## CONCLUSION

Antibiotic use is an important driver of the emergence of antibiotic resistance. “Physicians prescribing antibiotics should take into account the striking ecological side-effects of such antibiotics.”

Lancet February 10, 2007; 369: 482-90 Original investigation, first author Surbhi Malhotra-Kumar, University of Antwerp, Belgium.

The article is more detailed than I have indicated. It presented data on the distinctive selection pressures related to each of the antibiotics based on development of their resistance-conferring genes. (Primary care clinicians more familiar than I am with applications of resistance-conferring genes may be interested.)

An accompanying editorial in this issue of Lancet (pp 442-43) by Stephanie J Dancer, Southern General Hospital, Glasgow, UK comments:

Exposure to macrolides could encourage resistance to other bacteria in the community.

The UK has had a concerted drive to reduce antimicrobial prescribing in the community, especially for infections of the upper respiratory tract. The drive has succeeded to some extent.

However, if macrolide use is discouraged because of concern over their resistance potential, patients might end up receiving a drug that is more toxic, more expensive, and perhaps even better at selecting for resistance.

Antibiotics consumed on hospital wards can affect the amount and type of resistance in environmental organisms found on floors and hand-touch surfaces.

“The key message is that antibiotic prescribing affects the patient, their environment, and all the people that come in contact with that patient or with their environment.”

---

### *“May Reduce Coronary Mortality”*

## **2-8 SIESTA IN HEALTHY ADULTS AND CORONARY MORTALITY IN THE GENERAL POPULATION**

Ecological evidence has indicated that mid-day napping may reduce the risk of coronary heart disease (CHD) in countries where the habit is common. Mediterranean and several Latin countries (where daytime napping is common) tend to have low mortality rates for CHD.

However, epidemiological studies regarding the effect of siesta on CHD have been conflicting.

This study evaluated the association between siesta and CHD mortality in adults in Greece.

Conclusion: Siesta-taking by apparently healthy adults was associated with a lower CHD mortality.

## STUDY

1. The EPIC study (European Prospective Investigation into Cancer and Nutrition) enrolled over 28 000 healthy volunteers aged 20-86 in 1994-99. (EPIC is being conducted in 10 European countries.)
2. This subset to the study (done in Greece) followed over 23 500 subjects for a mean of 6 years determine if midday naps had any effect on mortality from CHD. None had a history of CHD, stroke, or cancer.
3. At baseline, all individuals were asked whether they took midday naps, the average duration, and the weekly frequency.
4. Categorized participants into:
  - Never taking naps
  - Systematic napping:
    - Taking naps regularly (at least 3 times weekly) with average duration of at least 30 minutes.
  - Occasional napping:
    - Taking naps irregularly (either once or twice weekly, frequently on week-ends)
    - Average duration less than 30 minutes.

## RESULTS

1. During follow-up, 792 deaths occurred; 133 due to CHD.
2. Mortality ratio from CHD among men and women, controlling for potential confounders (co-morbidity, diet, and physical activity):

No siesta	1.00
Siesta of any frequency	0.66
Occasional	0.88
Systematic	0.63

3. The association between naps and CHD mortality was stronger in working men

Adjusted CHD mortality ratios in men according to nap-taking and current working status:

Taking midday naps	Currently working (28 deaths)	Currently not working (n = 57 (57 deaths)
No	1.00	1.00
Occasional	0.36.	0.86
Systematically	0.36	0.61
Occasional + systematic	0.36	0.64

## DISCUSSION

1. The lower risk of CHD associated with siesta-taking was evident in men, among whom 85 CHD deaths occurred. In women (48 CHD deaths; only 6 in working women) the association was only marginal.
2. Among men who were currently working the association was striking; among retirees, it was not

significant.

3. "We interpret our findings as indicating that among healthy adults, siesta, possibly on account of stress-releasing consequences, may reduce coronary mortality."
4. "The existence of a stronger inverse association among working men is compatible with the fact that occupational stress is common in many manual and non-manual professions."

## CONCLUSION

1. After controlling for potential confounders, siesta of apparently healthy individuals, particularly working men, was associated with lower CHD mortality.

Archives Int Med February 12,2007; 167: 296-301 Original investigation, first author Androniki Naska, University of Athens, Greece.

=====  
***Overall Prevalence Of HPV Types Included In The Vaccine = 3.4% (3 million women)***

## **2-9 PREVALENCE OF HPV INFECTION AMONG FEMALES IN THE UNITED STATES**

Human papilloma virus (HPV) is the most common sexually transmitted infection. Prevalence is highest among young persons, within the first few years after sexual debut.

HPV types are categorized according to their epidemiological association with cervical cancer (types 16 and 18); and genital warts (types 6 and 11). Worldwide, approximately 70% of cervical cancers are due to HPV 16 and 18.

Approximately 90% of infections clear within 2 years (due to immune response).

A highly efficacious quadrivalent prophylactic vaccine against types 6, 11, 16, and 18 was licensed in June 2006 (*Gardasil*; Merck). It is recommended for routine use in females age 11 to 12 years. (The Advisory Committee on Immunization Practices recommended that females 11 to 26 be vaccinated with the quadrivalent vaccine.) Three doses are necessary (0, 3 months. And 6 months).

It is close to 100% effective in preventing the infection and cervical cancer precursors and genital lesions associated with the types included.

This study determined the prevalence of HPV among females in the U.S. to determine baseline population prevalence before widespread availability of a vaccine.

Conclusion: HPV is common; highest in females, most prevalent in ages 20-24. The prevalence of the HPV vaccine types was relatively low.

## STUDY

1. In 2003-04, The National Health and Nutrition Examination Survey (NHANES) used a representative sample of US non-institutionalized women (age 14 to 59; n = 1921) to determine prevalence of HPV.
2. Women were examined in a mobile examination center. They provided a self-collected vaginal swab

specimen for determination of HPV DNA by polymerase chain reaction, followed by determination of the type(s).

## RESULTS

### 1. Prevalence (42 types) among females age 14 to 59:

Age	14-19	25%
	20-24	45%
	25-29	27%
	30-39	28%
	40-49	25%
	50-59	20%

(The article cites 20 “low-risk” HPV, and 22 “high-risk” types. )

### 2. Overall prevalence = 27%. (Corresponds to 25 million females in the US.)

### 3. Prevalence was higher in women classified as sexually active. Five % of females who reported never having had sex had positive tests.

### 4. There was a trend for increased prevalence with each year of age from 14 to 24, followed by a gradual decline through age 59.

### 5. Prevalence of types included in the vaccine:

HPV-6	1.3%
HPV-11	0.1%
HPV- 16	1.5%
HPV-18	0.8%
Total	3.4% (Corresponds to 3 million women)

### 6. Most participants had only 1 type (60%); 24% had 2 types; 16% had 3 or more.

### 7. Overall, 3.4% of the study participants had infections with types included in the quadrivalent vaccine (3 million women). In women age 14 to 19, 6% had at least 1 of the 4 types

## DISCUSSION

### 1. HPV infection (42 types) was present in 27% of US females age 14 to 59. Prevalence in the 14 to 24 age group was 34%.

### 2. Overall prevalence of high risk types 16 and 18 was 2.3%

## CONCLUSION

Overall HPV prevalence (42 types) in the US is high (27%)—highest in ages 20-24 (45%).

The prevalence of types included in the HPV vaccine = 3.4%.

I accessed additional information about HPV and the vaccine from [www.merck.com](http://www.merck.com):

Merck estimates that:

- A. ~ 70% of cervical cancers; ~ 50% of high-grade cervical dysplasias, and ~ 25% of low-grade cervical dysplasias are due to HPV types 16 and 18,
- B. HPV types 6 and 11 are responsible for ~ 90% of genital warts, and ~10% of low-grade cervical dysplasias.
- C. About 10 000 new cases of HPV-related cervical cancers occurred in the US in 2006; 330 000 new cases of HPV-related high-grade cervical dysplasia (CIN 2/3) occur each year; and 1.4 million new cases of low-grade cervical dysplasia (CIN 1). (Both oncogenic and non-oncogenic HPV types can cause abnormal results.)
- D. One million new cases of genital warts each year. Of these, ~ 30% regress spontaneously and ~ 25% recur.

Pap and HPV screening prior to vaccination are not necessary. Females can receive the vaccine regardless of whether they previously had an abnormal Pap test, a positive HPV test, or genital warts.

The FDA approved the vaccine for the prevention of cervical cancer; cervical intraepithelial neoplasia (CIN2 and 3); adenocarcinoma in situ; vulvar pre-cancers; and vaginal precancers.

Also for prevention of genital warts and low grade cervical lesions (CIN 1).

There are about 5 million abnormal Pap tests that require follow-up each year in the US. At least 3 million are caused by some type of HPV.

The vaccine is not intended to be used as treatment of active disease.

Vaccination does not substitute for routine cervical cancer screening.

Adverse effects were mainly local reactions at the site of vaccination, occasional fever, and pruritis.

The vaccine may reduce the human and economic burden of HPV-related diseases.

---

## **Schedule Patients for a “Compete Physical” or Deliver Preventive Services in the Context of Ongoing Clinical Care?**

### **2-10 THE VALUE OF THE PERIODIC HEALTH EVALUATION: Systematic Review**

The periodic health evaluation (**PHE**) has been a fundamental part of medical practice for decades—despite a lack of consensus regarding its value in health promotion and disease prevention.

The PHE consists of one or more visits to a health care provider to assess patients’ overall health and risk factors. It results in delivery of clinical preventive services that are tailored to a patient’s age, sex, and clinical risk factors and laboratory testing. The PHE may improve patient outcomes and the public’s health.

It could, however, induce unnecessary costs and patient harms. Early studies of the PHE, performed before the adoption of current preventive services guidelines, were costly and demonstrated minimal improvements in clinical outcomes. Because of concern over the value of the PHE, some experts have advocated episodic targeted delivery of preventive services in the context of ongoing clinical care.

In light of conflicting opinions regarding the PHE's impact on health, costs, and non-uniformity of its implementation, these investigators performed a systematic review of the evidence to ascertain benefits and harms.

Conclusion: The PHE improves delivery of some recommended preventive services, and may lessen patient worry.

## STUDY

1. Systematic review selected 21 studies assessing the delivery of preventive services, clinical outcomes, and costs among patients receiving the PHE versus those receiving usual care.
2. Because the PHE is tailored to individual patients, and is delivered in a highly heterogeneous fashion, the investigators developed a definition of the PHE that could be widely applied to a majority of clinical practices:
  - 1) One or more visits to a health care provider for the primary purpose of assessing overall health and risk factors for disease that may be prevented by early intervention.
  - 2) It consists only of the history, risk assessment, and a *tailored* physical examination that could lead to delivery of preventive services.
  - 3) As defined, the PHE did not include the delivery of clinical preventive services that the patient could receive after the visit for the PHE. (Eg, a 50 year old woman receiving the PHE could undergo a detailed history, risk assessment, and physical examination (including a gynecological exam) during the visit. But subsequent studies (eg, mammogram or colonoscopy) were considered to be the result of the PHE and not a part of the PHE.
3. Defined "usual care" as the delivery of clinical preventive services in the absence of a health care provider visit designated for the primary purpose of assessing the patient's health and risk factors for disease. Under this definition, preventive health services were considered to have been delivered opportunistically (ie, in the setting of a visit designated for the ongoing care of acute or chronic illnesses.)

## RESULTS

1. The best available evidence assessing benefits or harms of the PHE consisted of 21 studies published from 1973 to 2004. Considered evidence to show a clear beneficial effect of the PHE when the investigators reported that the PHE consistently resulted in greater benefits or a reduction in harms compared with usual care.
2. The contents of the PHE were heterogeneous. They reported a wide range of outcomes.

The most frequently cited types of history and risk assessment were alcohol and substance abuse, tobacco use, and dietary risks. The least frequently cited included assessment of folic acid and calcium intake.

The most frequently cited components of the physical examination were BP, weight and height, breast exam, gynecologic exam, and rectal exam. The least frequently cited included neurological exam and foot exam.



3. Compared with usual care, the PHE had consistently beneficial association with patients' receipt of gynecological examination and Pap smears, cholesterol screening, and fecal occult blood testing.
4. The PHE had a beneficial effect on patient "worry" in one randomized trial, but had mixed effects on other outcomes and costs.
5. Overall, the strength and consistency of the evidence varied widely among outcomes, as did the magnitude and direction of results.

## DISCUSSION

1. The best available evidence suggests that patients benefit from the PHE through its association with improved delivery of some recommended clinical preventive services, and through reduction of patient worry.
2. The available evidence does not reveal harms associated with the PHE.
3. "Given that short- and long-term studies have shown that appropriate implementation of currently recommended preventive services improves health . . . and that elimination of worry or concern regarding illness may represent a powerful motivator for action on the part of patients, our findings provide health care providers and payers with justification for the continued implementation of the PHE."

## CONCLUSION

The PHE has a beneficial effect on the delivery of some preventive services, and may have a beneficial effect on patients' worry.

The current evidence demonstrating clear benefits (despite considerable heterogeneity of studies) could provide clinicians with confidence that the PHE may confer benefits in their own practices while they use individual judgment regarding the optimal way to implement the PHE.

Annals Internal Medicine February 20, 2007; 144: 289-300 Original investigation, first author L Ebony Boulware, Johns Hopkins School of Medicine, Baltimore MD.

---

### ***The Doctor-Patient Relationship Should Retain The Moral Agency Of Both The Physician And The Patient*** **2-11 RELIGION, CONSCIENCE, AND CONTROVERSIAL CLINICAL PRACTICES**

Should health professionals refuse to provide treatments to which they object on moral grounds? Recent controversies regarding physicians and pharmacists who refuse to prescribe or dispense emergency and other contraceptives have sparked a debate about moral objections in providing some types of health care.

Most people believe that health professionals should *not* have to engage in medical practices about which they have moral qualms. On the other hand, most people also believe that patients should have access to legal treatments, even in situations in which their physicians are troubled about moral implications of those treatments.

Is it ethical for physicians to describe their objections to the patient? Should physicians have the right to refuse to discuss, provide, or refer patients for legal medical interventions to which they have religious or moral objections?

Historically, doctors and nurses have not been required to participate in abortions or suicide, even where those interventions are legally sanctioned.

This study aimed at understanding how physicians think about their ethical rights and obligations when conflicts emerge in clinical practice.

## STUDY

1. Conducted a cross-sectional mail survey of a random sample of practicing U.S. physicians from all specialties.
2. Asked physician's judgments about their ethical rights and obligations when patients request a legal medical procedure to which the physician objects for religious or moral reasons, including terminal sedation in dying patients, providing abortion for failed contraception, and prescribing birth control to adolescents without parental approval.

## RESULTS

1. A total of 1140 physicians responded.
2. Opinions about controversial clinical practices:

Terminal sedation (% of respondents)

Do not object	83
Object	17

Abortion due to failed contraception

Do not object	48
Object	52

Prescriptions of birth control pills to adolescents without parental consent

Do not object	58
Object	42

3. Opinions about the ethical obligations of a physician who objects to a legal medical procedure requested by a patient:

A. Would it be ethical for the physician to plainly describe to the patient why he or she objects

to the requested procedure?	%
Yes	63
No	22
Undecided	15

B. Does the physician have an obligation to present all possible options to the patient, including information about obtaining the requested procedure?

Yes	86
-----	----

No 8

Undecided 6

C. Does the physician have an obligation to refer the patient to someone who does not object to the requested procedure?

Yes 71

No 18

Undecided 11

4. Opinions about ethical obligations according to religious characteristics:

Odds ratio:	May describe their moral objections	Obligated to disclose all possible options	Obligated to refer
Intrinsic religiosity:			
Low	1.0 (referent)	1.0	1.0
Moderate	1.4	0.4	0.6
High	2.5	0.3	0.3
Attendance at religious services:			
Never	1.0 (referent)	1.0	1.0
Once a month	1.5	0.5	0.7
Twice a month	2.7	0.3	0.3

5. On the basis of results:

Twenty two % of physicians believe that it is *not* ethically permissible for doctors to explain their moral objections; 18% believe it is unethical to refer patients to another clinician who does not object to the requested procedure; 8% believe that physicians are not obligated to present all options.

Physicians who were male, those who were religious, and those who had personal objections to morally controversial clinical practices were less likely to report that doctors must disclose information about, and to refer patients for medical procedures to which the physician objected on moral grounds.

6. Physicians who objected to all 3 controversial practices were less likely to report that doctors must present all options and refer to other providers.

## DISCUSSION

1. When a patient requests a legal medical intervention to which the physician objects on religious or moral grounds, most physicians felt that it is ethically permissible for the physician to describe the reason for the objection, and also believe that the physician must disclose information about the intervention and refer the patient.
2. The number of physicians who disagreed about these majority opinions was not trivial. The proportion of physicians who object is substantial. Fifty-two percent reported objections to abortion for failed contraception; and 42% reported objections to contraception for adolescents without parental permission.
3. If physician's ideas translate into their practices, millions of Americans may be cared for

by physicians who do not believe they are obligated to disclose information about medically available treatments, or to refer to another provider for treatments they consider objectionable.

4. Physician's judgments about their obligations are associated with their own religious characteristics and beliefs about morally controversial clinical practices.
5. Although patients who wish to receive these services may consult a doctor who does not object to providing these services, this may be difficult for some patients.
6. These controversial practices primarily concern sexual and reproductive health of women. This is perhaps why more female doctors are more supportive of full disclosure and referral.
7. Medical "paternalism" is based on the assumption that physicians know what is best for their patients, and therefore make decisions without informing the patient of all the facts, alternatives, and risks. Paternalism is widely criticized for violating the right of adults to self-determination.
8. The inverse of paternalism is a strict emphasis on patient autonomy, which suggests that physicians must disclose all options and allow patients to choose among them. This, many declare, makes physicians mere technicians or vendors of health care goods and services.
9. This study suggests that the balance most physicians strike between paternalism and autonomy involves both full disclosure and an open dialogue about the options. Ethicists have recommended models for the doctor-patient relationship that retain the moral agency of both the physician and the patient by encouraging them to engage in a dialogue and negotiate mutually acceptable accommodations that do not require either party to violate their own convictions. These interactive models retain a role for the influence of "the physician's values, the physician's understanding of the patient's values, and his or her judgment of the worth of the patient's values".
10. They do not require physicians to be value-neutral. They do allow the physician to explain the reasons for their objections.
11. Ethicists are ambivalent about referrals for a controversial procedure. This ambivalence stems from a long-standing concern that physicians not be asked to act in ways that "would violate their personal sense of responsible conduct".

## CONCLUSION

Many physicians do not consider themselves obligated to disclose information about, or to refer patients for, legal but morally controversial, medical procedures.

NEJM February 8, 2007; 356: 593-600 Original investigation, first author Farr A Curlin, University of Chicago. IL

=====  
*"Unlikely To Produce Lipid Benefits."*

**2-12 EFFECT OF RAW GARLIC VS COMMERCIAL GARLIC SUPPLEMENTS ON PLASMA LIPID CONCENTRATING IN ADULTS WITH MODERATE HYPERCHOLESTEROLEMIA**

Garlic has been used medicinally since antiquity. Garlic supplements are promoted as cholesterol-lowering agents. They are among the top selling herbal supplements.

Despite promising in vitro studies and a strong plausibility of effect demonstrated in animal studies, the clinical trial evidence supporting a hypo-cholesterolemic effect of various forms of garlic is highly inconsistent.

This study compared the effects of raw garlic, and 2 garlic supplements with distinctly different formulations on the plasma lipid concentrations in adults with moderate hyper-cholesterolemia..

Conclusion: None of the tested forms of garlic had clinically significant effects on plasma lipid concentrations.

## STUDY

1. Recruited and randomized 192 adults (age 30-65) from the community who had a fasting LDL-cholesterol concentration of 130 to 190 mg/dL (mean = 151), a triglyceride level under 250 mg/dL, and a body mass index of 19 to 30.
2. Provided garlic in 3 forms: 1) raw garlic, 2) *Garlicin*, and 3) *Kyloic-100*. *Garlicin* was selected to represent powdered garlic supplements. *Kyloic* was selected because it is one of the most popular brands. It is an aged powdered garlic supplement. 4) A placebo group was added.
3. The products were consumed 6 days a week for 6 months: raw garlic as a crushed average size clove; *Garlicin* and *Kyloic* given at 1 1/2 to 3 times the recommended dose.
4. Assessed LDL-c monthly.

## RESULTS

1. There were no statistically significant effects of the 3 garlic forms on LDL-c.
2. Six month changes in LDL-c (means; mg/dL)

Raw garlic	+0.4
Garlicin	+3.2
Kyloic	+0.2
Placebo	-3.9
3. No difference in effects among subjects with LDL-c above the median.
4. No statistically significant effects on HDL-c, total cholesterol, triglycerides, and the HDL-c/total C ratio.
5. Adverse effects: bad body and breath odor only in the raw garlic group (57%).

## DISCUSSION

1. The garlic products, all extensively characterized chemically, had neither a statistically detectable effect nor a clinically relevant effect on plasma lipids, , in adults with moderate hypercholesterolemia.
2. “Based on our results, and those of other recent trials, physicians can advise patients with moderately elevated LDL-c concentrations, that garlic supplements or dietary garlic in reasonable doses are unlikely to produce lipid benefits.”

3. Garlic may have other health effects, such as increased fibrinolysis, decreased atherosclerosis, or anti-carcinogenic properties. These possible effects should be scrutinized in larger trials.

## CONCLUSION

None of the forms of garlic tested, when given at an approximate dose of a 4-g garlic clove daily for 6 months, had significant effects on LDL-c.

Annals Int Med February 26, 2007; 167: 346-353 First author Christopher D Gardner, Stanford University Medical School, Stanford CA

Study supported by the National Institutes of Health

An editorial in this issue of Archives (pp 325-26), first author Mary Charleston, Center for Complementary and Integrative Medicine, Weill Cornell Medical College, New York comments:

The results do not demonstrate that garlic has no usefulness in the prevention of cardiovascular disease. A key general problem is how to define the end point for clinical trials to test efficacy. For any cardiovascular disease prevention, dyslipidemia is a key contributor to atherosclerosis, but many investigators have hypothesized that it is not the amount of native LDL that contributes to atherosclerosis, but the amount of oxidized LDL, that directly influences atherogenesis. Some studies have demonstrated that garlic increases resistance to oxidation of LDL.

Atherosclerosis is a complex phenomenon in which inflammation, hypertension, platelet aggregation, dyslipidemia, endothelial dysfunction, diabetes, and a host of other factors such as previous infections, smoking, and genetics may have a role.

The selection of a single compound for the purpose of standardization when the exact mechanisms of action are unknown continues to hinder our ability to evaluate the health effects of natural products.

Does garlic prevent cardiovascular disease? The jury is still out.

=====













