

**PRACTICAL POINTERS**  
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**JULY 2009**

**MODIFIABLE LIFESTYLES REDUCE LIFETIME RISK OF HEART FAILURE [7-1]**

**DIET AND LIFESTYLE RISK FACTORS ASSOCIATED WITH INCIDENT HYPERTENSION [7-2]**

**BENEFITS OF STATINS IN PEOPLE WITHOUT VASCULAR DISEASE, BUT WITH RISK  
FACTORS [7-3]**

**WHAT PARTS OF THE MEDITERRANEAN DIET ARE MOST BENEFICIAL? [7-4]**

**NEW PAIN MEDICATION GUIDELINES FOR OLDER PATIENTS [7-5]**

**A H-2 BLOCKER TO PREVENT UPPER GI LESIONS IN PATIENTS TAKING LOW-DOSE  
ASPIRIN [7-6]**

**HUMAN PAPILLOMA VIRUS VACCINATION FOR ALL? [7-7]**

**DIABETES COMPLICATIONS AND THE RENIN-ANGIOTENSIN SYSTEM [7-8]**

**IS CONTAINMENT OF THE H1N1 FLU POSSIBLE? [7-9]**

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This document is divided into two parts

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

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

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

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

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

Richard T. James Jr. M.D.

Editor/Publisher.

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## **HIGHLIGHTS AND EDITORIAL COMMENTS JULY 2009**

### ***Maintenance Of Healthy Lifestyles Is Critical To Lowering Risk Of Heart Failure***

#### **7-1 RELATION BETWEEN MODIFIABLE LIFESTYLE FACTORS AND LIFETIME RISK OF HEART FAILURE**

The concept of lifetime risk is important in public health practice. It is defined as the risk of ever developing a disease during one's lifetime.

Several predictors of HF can be influenced by modifiable lifestyle changes: maintaining healthy weight; not smoking; engaging in regular exercise; maintaining a healthy diet. This study examined the association between modifiable lifestyle risk factors and remaining lifetime risk of HF in a large cohort of men.

A prospective cohort study used baseline data from the Physicians' Health Study (1982-2008; over 20 000 individuals; mean age 53 at baseline) to examine the association between modifiable lifestyle factors and remaining lifetime risk of HF. All subjects were apparently healthy at baseline

The study considered 6 healthy lifestyle factors (**HLFs**), which were assessed periodically and dichotomized:

BMI: Under 25 vs overweight (25-29) or obese (30 and over)

Smoking: Never vs ever

Exercise; Regular (5 times a week or more) vs infrequent/ none

Alcohol intake: Moderate 5 drinks per week or more vs less than 5 drinks per week.

(Few drank > 2/day)

Consumption of breakfast cereals: One or more per week vs none

Consumption of fruits and vegetables: 4 or more servings per day vs fewer than 4.

Individuals could have 0 to 6 healthy lifestyles. Since very few men were in the 5 and 6 categories of healthy lifestyles, the investigators collapsed the upper 3 categories and referred to them as the 4 and over group.

Main outcome measure = lifetime risk of HF. Follow-up for 22 years.

Overall, the lifetime risk of HF was 14% at age 40. It remained constant through age 70. At age 80, lifetime risk was 11%. Remaining lifetime risk of HF was 2% to 4% higher in men with hypertension than in men without.

Lifetime risk of HF according to number of HLFs:

Those with 0 had a risk of over 20% for HF. Risks progressively fell to about 10% for those adhering to 4 or more. Each was associated with a lower lifetime risk of HF compared with the corresponding undesirable behavior.

Conversely, each added risk factor increased risk of HF. The lowest risk was observed in those with 4 or more HLFs—a reduction of 50% compared with those with 0. .

Conclusion: In this cohort of apparently healthy men, adherence to healthy lifestyles was associated with lower risk of HF.

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*As the article states, incidence of HF in the general population is much higher than in this physician's group.*

*A number of articles regarding benefits of healthy lifestyles are appearing in the journals.*

*Repeatedly encouraging patients to adopt healthy lifestyles will, if successful, be a necessary step in achieving and maintaining lower costs of our proposed changes in health care. This can be accomplished only by long- time primary care.*

### ***The Potential To Prevent A Large Proportion Of New-Onset Hypertension***

#### **7-2 DIET AND LIFESTYLE RISK FACTORS ASSOCIATED WITH INCIDENT HYPERTENSION IN WOMEN**

Just 37% of individuals with hypertension in the USA have controlled BP; a proportion that increases to 57% with drug intervention.

The second Nurses' Health Study evaluated the association between combinations of low-risk lifestyle factors and risk of developing hypertension during a 14 year period.

Considered six modifiable low-risk lifestyle risk factors:

BMI < 25

Vigorous exercise daily (mean of 30 minutes)

A high score of the DASH diet (Response to a food frequency questionnaire.)

Modest alcohol intake (up to 10 g/d)

Use of non-narcotic analgesics (NSAIDs, aspirin, and acetaminophen) less than once weekly

Intake of 400 ug/d of supplemental folic acid or more.

Follow-up through 2005 (to mean age 50). Main outcome = adjusted hazard ratios for incident self-reported hypertension and population attributable risks of hypertension (**PARs**)

Specific groups of 3, 4, 5, and 6 risk factors were associated with progressively lower HRs of developing hypertension:

	HR	PAR (%)*
3 Highest DASH quintile, daily vigorous exercise, BMI < 25	0.46	53
4 The 3 above + alcohol 0.1 – 10 g/d	0.42	58
5 The 4 above + analgesic use < 1 day per wk	0.28	72

6 The 5 above + folic acid supplementation (only 0.3% of women) 0.22 78

(\* Population attributable risk. The % of women who would have avoided hypertension if all women had been in the low risk groups.)

Hypothetically, compared with women who maintained no beneficial lifestyle factors, risk of hypertension in women who maintained 5 healthy lifestyle factors for 10 years would be lowered by 72%.

Combinations of modifiable risk factors were associated with a dramatically reduced incidence of new-onset hypertension over 10 years. If these associations were causal and independent, lifestyle modification could have the potential to prevent a large proportion of new-onset hypertension occurring in young women,

In this study, BMI was the most powerful predictor of incident hypertension, and the largest single contributor to the hypothetical PAR. Although multiple low-risk factors were significantly associated with lower risk among normal weight and overweight individuals, there was no association among obese women (BMI > 30). Obese women might not benefit from other low-risk behaviors unless weight loss is also addressed.

The study did not have information on plasma 25-OH-vitamin D. Low levels have recently been demonstrated to be related to risk of hypertension, as well as high waist circumference.

Conclusion: Adherence to low-risk dietary and lifestyle factors was associated with significant reductions in the incidence of self-reported hypertension. It could have the potential to prevent a large proportion of new-onset hypertension among young women. This would have major public health benefits.

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*The reference to vitamin D is interesting. Interest in possible beneficial effects persists. Most people, at least in winter, who live at higher latitudes are deficient. Supplement the diet with 1000 to 2000 units daily. It is inexpensive.*

*Without weight loss, obese women derive no benefit from maintaining healthy lifestyles.*

*Lowering risk factors will be a major component of the proposed revision of health care in the US. This would require a sea change in habits of the population. Can this be accomplished? I believe only by continuous medical care by primary care in a medical home. Primary care clinicians must be role models, and abide by all facets of healthy living.*

*If a major proportion of citizens would maintain healthy lifestyles, I believe we would have no more concerns about costs of universal health care coverage.*

*I do not recall hearing about any relation between aspirin, acetaminophen, and folic acid to risk of hypertension.*

***Risk Reduction In All Cause Mortality Of 12% and Major Coronary Events Of 30%, over 4 years***

### **7-3 THE BENEFITS OF STATINS IN PEOPLE WITHOUT ESTABLISHED CARDIO-VASCULAR DISEASE BUT WITH CARDIOVASCULAR RISK FACTORS**

This meta-analysis of randomized trials investigated whether statins reduce all-cause mortality and incidence of major coronary and cerebrovascular events in people without established CVD, but with risk factors.

Included 10 randomized trials of statins (n = over 70 000 persons; 33% women; 23% with diabetes; mean age 63) compared with controls (placebo, active control, or usual care). Reported mortality and CVD events as primary outcomes. .

Mean follow-up = 4 years.

The dose and type of statin varied.

Risk factors included: age over 65, diabetes, smoking, increased BMI, elevated LDL-cholesterol.

All-cause mortality:

Controls: 1925 of 33 793 (5.7%)

Statin group: 1725 of 33 683 (5.1%)

(Odds ratio = 0.88; 12 % reduction; NNTB for 4 years to prevent one death = 166)

Major coronary events:

Controls: 1266 of 23 946 (5.4%)

Statins: 966 of 23 823 (4.1%)

(Odds ratio – 0.70; 30% risk reduction; NNTB for 4 years to prevent one event = 76)

Major cerebrovascular events:

Controls: 2.3%

Statin group: 1.9%

(Odds ratio = 0.81, 19% reduction; NNTB for 4 years to prevent one event = 250)

No significant treatment heterogeneity was found between the sexes, between the elderly and young people, and between people with and without diabetes.

“Given the favorable effect of long-term statin treatment, it would be wrong to deny these benefits to people at increased risk for cardiovascular disease.”

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*Although the NNTB (number needed to treat to benefit one patient) is high, on a population basis, the benefit would be great..*

*Given that age itself is a major risk factor and other risk factors are ubiquitous, would this not lead to near universal statin use?*

*The benefits of statins would be much lower in younger persons without risk factors and in those with few risk factors. Use of statins for these persons would be more problematic. It would depend on a calculation of the risk and the patient's choice after being fully informed. There are risks and costs of statin therapy. In some patients the benefit / harm-cost ratio may be low.*

### ***Moderate Consumption of Ethanol, High Intake Of Vegetables, Fruits And Nuts, Olive Oil, And Legumes.***

#### **7-4 ANATOMY OF HEALTH EFFECTS OF MEDITERRANEAN DIET**

This study investigated the relative importance of individual components of the Mediterranean diet (**MD**) associated with the inverse association between adherence to the diet and mortality.

Entered a population-based cohort of over 23 000 men and women in Greece between 1994 and 1997. All were free of cancer, coronary heart disease, or diabetes. Follow-up for a mean of 8.5 years

Assessed dietary intake by a food frequency questionnaire during the year prior to enrollment:

Vegetables \*

Legumes \*

Fruits and nuts \*

Fish and seafood \*

Cereals \*

High monounsaturated to saturated fat ratio \*

Ethanol \* (For men 10 g a day to less than 50 g a day; Women 5 g and 25 g )

Dairy \*\*

Meat and meat products \*\*

(\* beneficial \*\* not beneficial)

Assessed conformity to the traditional MD with a 10-unit scale based on the 9 variables.

During follow-up, 1075 deaths from any cause occurred.

MD score	Deaths	% of cohort
0-4	652	5.1
5 or more	423	4

Each 2 unit increase in the MD score was associated with a mortality ratio of 0.86. (14% decrease)

Among the 7 presumed beneficial components of the diet, high consumption of all but fish and seafood was inversely associated with mortality.

For meat and meat products and dairy, there was a positive relationship with mortality, which approached statistical significance.

The contribution to the association with lower mortality was largest for moderate consumption of ethanol (24%). Followed by low consumption of meat and meat products (16%), and high consumption of vegetables (16%). Followed by high consumption of fruits and nuts,, high mono-unsaturated to poly-unsaturated fat ratio, and high consumption of legumes (each contributing 10-14%). High consumption of cereals and low consumption of dairy products contributed less (5%).

Close adherence to the traditional MD diet, as indicated by the MD score, was associated with a statistically significant lower overall mortality.

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*Intake of up to 50 g of ethanol daily is not “moderate”. I would advise no more than one glass of wine daily. I would limit intake to one drink daily.*

**“Avoid NSAIDs , Consider Opioids”**

## **7-5 NEW PAIN GUIDELINES FOR OLDER PATIENTS**

Contradicting the guideline of 2002, an updated guideline issued by the American Geriatric Society (AGS) states that physicians treating patients aged 75 and older should avoid NSAIDs,

NSAIDs should be “considered rarely and with extreme caution in highly selected individuals”. Despite improved understanding of risks of NSAIDs, including GI bleeding, they have remained a mainstay of pain therapy in the elderly. Physicians have shied away from opioids. “We feel that NSAIDs in many cases are more risky than many opioid strategies.”

Physicians are advised to anticipate and monitor patients for adverse events associated with opioids, and to continually assess whether the therapy is meeting its goals. Breakthrough pain should be anticipated.

Opioids can induce delirium in older patients. This can be corrected by lowering the dose. Patients starting opioids can also experience anorexia, nausea, or vomiting. These adverse effects may dissipate over time. Constipation can be troublesome.

The guidelines advise against use of other classes of drugs: antidepressants including amitriptyline, imipramine, and doxepine. They cause a high risk of adverse events.

Treating pain in older adults requires an individualized approach. Physical interventions such as applications of heat and cold may help.



Acetaminophen remains the initial drug of choice. Caution against use in patients with liver disease.

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The website [www.americangeriatrics.org/education/pharm\\_management.shtml](http://www.americangeriatrics.org/education/pharm_management.shtml) mentions:

Oxycodone

(eg, Percodan) 2.5-5 mg q 4 to 6 hours

Oxycontin 10 mg q 12 hours

Morphine

Immediate release 2.5 to 10 mg q 4 hours

Sustained release 15 mg q 8 to 24 hours

Hydromorphone

(Dilaudid) 1-2 mg q 3 to 4 hours

Transdermal Fentanyl 12-25 mg q 72 hours

*This is a sea change. Use of opioids in the elderly calls for especial caution. Start with low doses. Monitor carefully. I believe many elderly will prefer NSAIDs because the adverse effects are less evident. Proton pump inhibitors will reduce the risk of GI bleeding. Primary care clinicians must watch for adverse effects of NSAIDs on BP, kidney function and heart failure.*

*I believe judicious use of opioids can offer greater pain relief than NSAIDs*

*On June 30, an advisory committee of the FDA recommended that the maximum daily dose of acetaminophen be lowered from 4000 mg to 2600 mg daily because of liver toxicity. (Individual tablets from 500 mg to 325 mg.)*

*McNeil company, makers of Tylenol, has strong objections. They believe that this will lead patients to switch to O-T-C NSAIDs, which are much more toxic.*

*Acetaminophen is a component of a host of preparations, both O-T-C and by prescription. If these new recommendations are approved, the dose of acetaminophen in many preparations will have to be reduced.*

***Effective for The Prevention Of Peptic Ulcers And Erosive Esophagitis***

## **7-6 FAMOTIDINE FOR THE PREVENTION OF PEPTIC ULCERS AND OESOPHAGITIS IN PATIENTS TAKING LOW-DOSE ASPIRIN**

There have been increasing reports of peptic ulceration, GI bleeding, and esophagitis in patients taking long-term low-dose aspirin (LDA).

This phase III randomized, double-blind, placebo-controlled trial compared efficacy of famotidine (a histamine -2 receptor antagonist; *Pepcid*; Merck; 20 mg twice daily) with placebo in 404 adult patients (mean age 63) for prevention of upper GI (UGI) complications of LDA.

All had been taking long-term LDA at baseline (for a mean of 3 years; the great majority taking 75 mg of aspirin daily). All continued to take LDA.

At baseline, 54% had mucosal scarring; 58% had mucosal erosions. (Subjects at this time had been taking LDA for a mean of 3 years.)

None had peptic ulcers or erosive esophagitis on endoscopy at baseline.

Outcome at 12 weeks:

Peptic ulcers of any size or erosive esophagitis or both	Famotidine + LDA	Placebo + LDA	Odds ratio
	5.4	32.5	0,12

Number needed to treat with famotidine to benefit (NNTB) one patient over 12 weeks =  $32.5 - 5.4 =$  an absolute difference of 27% = NNTB = 3.7 patients treated for 12 weeks to prevent one lesion. (*My calculations RTJ*)

Four patients taking placebo developed upper GI hemorrhage vs 0 in the famotidine group.

Patients taking beta-blockers had a higher risk of GI complications. (24% vs 14%)

The majority of the participants in this trial had erosions or scars at baseline, indicating a high rate of upper GI lesions (including esophagitis) in persons taking LDA. They had a higher risk of UGI complications over 12 weeks.

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*I abstracted this article in part because famotidine is available at some pharmacies for \$10 for 180 twenty mg tablets (3 months supply). Proton pump inhibitors are more expensive.*

*Cimetadine and ranitidine are also available for the same price. Famotidine has the longest plasma half-life and the longest duration of action.*

*In patients taking long-term LDA, upper GI lesions must occur almost universally over time. Lesions must come and go.*

*NSAIDs also frequently cause upper GI lesions. They are less likely to cause bleeding because, unlike aspirin, they have little effect on the clotting mechanism.*

*I did not understand why lesions were more frequent in patients taking beta-blockers.*

*Proton-pump inhibitors are routinely advised for prevention of UGI complications of LDA and NSAIDs. This is an example of newer (presumably more effective, but more expensive) drugs*

*supplanting older drugs (PPIs vs H-2 blockers). Is this a demonstration of the power of the drug industry?*

***“The Only Efficient Way To Stop The Virus Is To Vaccinate The Other Half Of The Sexually Active Population; Boys And Men.”***

### **7-7 HPV VACCINE FOR ALL**

A randomized trial reported in *Lancet* this month reports efficacy of a bivalent HPV vaccine (types 16 and 18 with an aluminum adjuvant in 9000 women age 15-25) for the reduction of high-grade cervical intraepithelial neoplasia (CIN2+/CIN3+),

Over 3 years, CIN2+ associated with HPV 16/18 in those receiving vaccine, vs controls, was reduced by 93%, and CIN2+ associated with HPV 31/33/45/52/58 was reduced by 53% compared with controls.

The neutralizing antibody response to HPV vaccines exceeds the natural immune response to infection with the virus, but life-long immunity is unlikely, making need for a booster probable.

The primary public health goal is to stop the spread of infection, and ultimately disease. “The only efficient way to stop the virus is to vaccinate the other half of the sexually active population; boys and men.” In clinical trials, males show an immune response similar to that of women.

The lifetime risk of HPV infection in the sexually active population is 80% to 90%. Although the virus is eliminated from the body within 2 years in 80% of those infected, infections are more likely to become persistent in older individuals and those with compromised immunity.

“Women have shouldered responsibility for contraception since its inception. The goal to eradicate sexually transmitted carcinogenic viruses can be jointly carried by both women and men, and could be accomplished within a few decades.”

-----

*We need much more information about safety, especially long-term, and effectiveness long-term before application can be made to males.*

### ***No Benefit From ACE Inhibitor or Angiotensin Blocker***

### **7-8 DIABETES COMPLICATIONS AND THE RENIN-ANGIOTENSIN SYSTEM**

The concept has developed that inhibition of the renin-angiotensin system (**R-As**) in patients with diabetes is beneficial in both early and advanced stages of nephropathy.

An extraordinary study in this issue of NEJM challenged the accepted concept. It was the longest study in this field of investigation. It compared strategies for inhibition of the R-As, and evaluated 3

common measures of renal function: microalbuminuria; glomerular filtration rate; and renal morphological features. It also studied the progress of retinopathy.

The findings were surprising. Inhibition of the R-As did not reduce incidence of microalbuminuria, and did not mitigate decline in renal function or renal morphological features. It did reduce progression of retinopathy.

Questions remain.

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*This study was restricted to a selected group of patients with type-1 diabetes.*

*I believe the question of benefit or harm on the kidney from R-A blockade is far from settled.*

*Should primary care clinicians continue to prescribe ACE inhibitors and angiotensin-blockers for patient with diabetes? I would continue because: They are beneficial in treatment of hypertension, which is common in patients with diabetes. They may reduce the complication of retinopathy.*

*We look for further studies.*

### ***“Containment Is No Longer Possible”***

#### **7-9 A/H1N1 INFLUENZA UPDATE (July 25 2009) From the UK Health Protection Agency (HPA)**

##### **This up-to-date review asks:**

- A. What more do we know compared with 2 months ago?
- B. Has advice to healthcare professionals from the HPA changed since the WHO announced pandemic alert 6 in June?
- C. What are the latest predictions on how serious this virus is?
- D. How are current arrangements for administering oseltamivir working?
- E. Is it worth wearing a face mask?
- F. What are the likely arrangements for distribution of the vaccine?
- G. Should pregnant health care workers deal with patients with flu?
- H. Has AH1BN1 mutated?
- I. Is AH1N1 more likely to infect the lungs?
- J. Where can up-to-date information be accessed?

<http://pandemicflu.bmj.com>

[www.dh.gov.uk](http://www.dh.gov.uk)

[www.hpa.org.uk](http://www.hpa.org.uk)

[www.rcgp.org.uk](http://www.rcgp.org.uk)

*Please read the full abstract*

## ABSTRACTS JULY 2009

### *Maintenance Of Healthy Lifestyles Is Critical To Lowering Risk Of Heart Failure*

#### **7-1 RELATION BETWEEN MODIFIABLE LIFESTYLE FACTORS AND LIFETIME RISK OF HEART FAILURE**

Despite improved medical and surgical management, mortality for heart failure (**HF**) remains high. A large part of HF is accounted for by antecedent coronary heart disease and hypertension.

The concept of lifetime risk is important in public health practice. It is defined as the risk of ever developing a disease during one's lifetime.

It is estimated that 1 in every 5 adults over age 40 will develop HF during their remaining years. Primary prevention is essential.

Several predictors of HF can be influenced by modifiable lifestyle changes: maintaining healthy weight; not smoking; engaging in regular exercise; maintaining a healthy diet.

These healthy lifestyles reduce incidence of coronary heart disease, hypertension, and diabetes.

This study examined the association between modifiable lifestyle risk factors and remaining lifetime risk of HF in a large cohort of men.

#### **STUDY**

1. A prospective cohort study used baseline data from the Physicians' Health Study (1982-2008; over 20 000 individuals; mean age 53 at baseline<sup>1</sup>) examined the association between modifiable lifestyle factors and remaining lifetime risk of HF. All subjects were apparently healthy at baseline.
2. The study considered 6 healthy lifestyle factors (**HLFs**), which were assessed periodically and dichotomized:
  - BMI: Under 25 vs overweight (25-39) or obese (30 and over)
  - Smoking: Never vs ever
  - Exercise; Regular (5 times a week or more) vs infrequent/ none
  - Alcohol intake: Moderate: 5 drinks per week or more vs less than 5 drinks per week.  
(Few drank > 2/day)
  - Consumption of breakfast cereals: One or more per week vs none
  - Consumption of fruits and vegetables: 4 or more servings per day vs fewer than 4.
3. Individuals could have 0 to 6 healthy lifestyles. Since very few men were in the 5 and 6 categories of healthy lifestyles, the investigators collapsed the upper 3 categories and referred to them as the 4 and over group.

4. Main outcome measure = lifetime risk of HF. Follow-up for 22 years.

## RESULTS

### 1. Baseline characteristics:

Healthy lifestyle factors	0	1	2	3	4
BMI (mean)	27	26	25	24	23
Never smoker (%)	0	26	46	67	82
Exercise (%)	0	3	9	20	56
Moderate alcohol (%)	0	21	36	45	70
Diet					
Breakfast cereal (%)	0	30	51	77	91
Fruits and vegetables					
Servings/day	1.8	1.9	2.1	2.4	2.8
Hypertension (%)	27	28	24	29	19
Diabetes (%)	2.8	2.7	2.0	1.7	1.7

(At baseline, hypertension and diabetes was more common in those failing to maintain HLFs.)

2. Overall, the lifetime risk of HF was 14% at age 40. It remained constant through age 70. At age 80, lifetime risk was 11%. Remaining lifetime risk of HF was 2% to 4% higher in men with hypertension than in men without.

### 3. Lifetime risk of HF according to number of HLFs:

Those with 0 had a risk of over 20% for HF. Risks progressively fell to about 10% for those adhering to 4 or more. Each was associated with a lower lifetime risk of HF compared with the corresponding undesirable behavior.

4. Conversely, each added risk factor increased risk of HF.

## DISCUSSION

1. In this cohort of apparently healthy male physicians, the remaining lifetime risk of HF was about 1 in 7 at age 40, 50, 60, and 70.
2. The lifetime risk of HF was higher in men with hypertension, antecedent myocardial infarction, and diabetes.
3. Physicians may have lower risks than the general population, given their medical knowledge.
4. The lowest risk was observed in those with 4 or more HLFs—a reduction of 50% compared with those with 0.

5. "Maintenance of healthy lifestyles . . . remains critical to lowering risk of heart failure."

## CONCLUSION

In this cohort of apparently healthy men, adherence to healthy lifestyles was associated with lower risk of HF.

JAMA July 22/29; 302: 394-400 Original investigation, first author Luc Djousse, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass

1 *This reminded me of the original report of the Physicians' Health Study NEJM July 20, 1989:*

*Randomized over 20 000 male physicians to aspirin 325 mg every other day or placebo.*

*Over 5 years: myocardial infarctions occurred in 139 aspirin subjects and 239 placebo subjects.*

*Relative risk = 0.56. Reduction of risk was evident only in those over age 50. Each year, aspirin*

*"prevented" 2 MIs for every 1000 treated.*

*Moderate-severe hemorrhagic stroke over 5 years: aspirin 13; placebo 6.*

*Bleeding from stomach ulcer: aspirin 38; placebo 22. Aspirin was also associated with more easy bruising, hematemesis, melena, and epistaxis.*

*Cardiovascular mortality did not decline.*

*74% of all physicians in the study opted to continue aspirin for primary prevention.*

*This started the interest in low dose aspirin for primary prevention. Apparently, most physicians ignored evidence of the risk of bleeding, and the fact that overall cardiovascular mortality did not decline.*

=====

## ***The Potential To Prevent A Large Proportion Of New-Onset Hypertension***

### **7-2 DIET AND LIFESTYLE RISK FACTORS ASSOCIATED WITH INCIDENT HYPERTENSION IN WOMEN**

"Hypertension contributes to more excess deaths in women than any other preventable factor."

Pharmacological treatment has benefits, but is costly, requires medical intervention, and has adverse effects.

Just 37% of individuals with hypertension in the USA have controlled BP, a proportion that increases to 57% with drug intervention.

Primary prevention is essential.

This prospective cohort study entered, in 1991, over 83 000 women age 27 to 44 (mean age 36).

None had hypertension, cardiovascular disease, diabetes, or cancer. All had reported normal BP (120/80 or lower).

Modifiable risk factors for hypertension include: overweight, obesity; lack of physical activity; poor diet; abstinence from alcohol or excess alcohol; use of non-narcotic analgesics; and low folic acid intake.

The study evaluated the association between combinations of low-risk lifestyle factors and risk of developing hypertension in young women during a 14 year period..

## STUDY

1. Prospective cohort study entered, in 1991, over 83 000 women age 27 to 44 (mean age 36).

None had hypertension, cardiovascular disease, diabetes, or cancer. All had reported normal BP (120/80 or lower).

2. Considered six modifiable low-risk lifestyle risk factors:

BMI < 25

Daily mean of 30 minutes of vigorous exercise

A high score of the DASH diet<sup>1</sup> (Response to a food frequency questionnaire.)

Modest alcohol intake (up to 10 g/d)

Use of non-narcotic analgesics (NSAIDs, aspirin, and acetaminophen) less than once weekly

Intake of 400 ug/d of supplemental folic acid or more.

3. Analyzed combinations of 3, 4, 5, and 6 low risk factors at baseline and on periodic follow-ups.

4. Follow-up through 2005 (to mean age 50). Main outcome = adjusted hazard ratios for incident self-reported hypertension and population attributable risks of hypertension (**PARs**)

## RESULTS

1. During follow-up, over 12 000 women (15%) reported development of hypertension.

2. Distribution of modifiable risk factors and hazard ratios:

	Hazard ratio (HRs) of hypertension
Quintile of DASH score	
1 (lowest)	1.00 (reference)
5 (highest)	0.82
Vigorous exercise d/wk	
<1	1.00
7	0.87



<b>BMI</b>	
<23	1.00
> 30 (obesity)	4.70 (The strongest risk factor)
<b>Mean alcohol intake g/d</b>	
0	1.00
5 to 10	0.84
> 30	1.61
<b>Supplemental folic acid</b>	
0	1.00
> 800 ug/d	0.88
<b>Frequency of acetaminophen d/wk</b>	
< 1	1.00
7	1.44
<b>Frequency of NSAIDs</b>	
<1	1.00
7	1.46
<b>Frequency of aspirin</b>	
<1	1.00
7	1.22

(In between, HRs progressively increased or decreased.)

### 3. Specific groups of 3, 4, 5, and 6 risk factors were associated with progressively lower HRs

of developing hypertension:	HR	PAR (%)*
3 Highest DASH quintile, daily vigorous exercise, BMI < 25	0.46	53
4 The 3 above + alcohol 0.1 – 10 g/d	0.42	58
5 The 4 above + analgesic use < 1 day per wk	0.28	72
6 The 5 above + folic acid supplementation (only 0.3% of women)	0.22	78

(\* Population attributable risk. The % of women who would have avoided hypertension if all women had been in the low risk groups.)

4. Hypothetically, if women maintained 5 healthy lifestyle factors for 10 years, risk of developing hypertension would be lowered by 72%.

5. A family history of hypertension and use of oral contraceptives increased risk only slightly.

## DISCUSSION

1. Combinations of modifiable risk factors were associated with a dramatically reduced incidence of new-onset hypertension over 10 years. If these associations were causal and independent, lifestyle modification could have the potential to prevent a large proportion of new-onset

hypertension occurring in young women, irrespective of a family history of hypertension and use of contraceptive pills.

2. In this study, BMI was the most powerful predictor of incident hypertension, and the largest single contributor to the hypothetical PAR. Although multiple low-risk factors were significantly associated with lower risk among normal weight and obese individuals, there was no association among obese women (BMI > 30). Obese women might not benefit from other low-risk behaviors unless weight loss is also addressed.
3. The study did not have information on plasma 25-OH-vitamin D. Low levels have recently been demonstrated to be related to risk of hypertension, as well as waist circumference.
4. The follow-up lasted for only 14 years (to mean age 50). It is possible that low-risk factors delay rather than entirely prevent hypertension at the rates calculated by PAR.
5. The findings may not be generalisable to the population as a whole. The study population was mostly white, entirely female, and had a higher socioeconomic and educational status.

## CONCLUSION

Adherence to low-risk dietary and lifestyle factors was associated with significant reductions in the incidence of self-reported hypertension. It could have the potential to prevent a large proportion of new-onset hypertension among young women. This would have major public health benefits.

JAMA July 22/27, 2009; 302: 401-11 Original investigation, first author John P Forman, Brigham and Women's Hospital and Harvard Medical School, Boston Mass

1 Dietary Approaches to Stop Hypertension "A clinical trial of the effects of dietary patterns on pressure" NEJM 1997; 336: 1117-1124

The diet includes :

A high intake of fruits, vegetables, nuts, legumes, and low-fat dairy.

Low intake of sodium, sweetened beverages, and red and processed meats.

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***Risk Reduction In All Cause Mortality Of 12% and Major Coronary Events Of 30%, over 4 years***

## **7-3 THE BENEFITS OF STATINS IN PEOPLE WITHOUT ESTABLISHED CARDIOVASCULAR DISEASE BUT WITH CARDIOVASCULAR RISK FACTORS**

Statin drugs are effective in reducing mortality and morbidity in patients with established cardiovascular disease (CVD). They have a place in secondary prevention.

Use in patients without established CVD (primary prevention) has important public health implications.

The reliability of statin treatment in older people (> age 65), women, and those with diabetes is uncertain.

This meta-analysis of randomized trials investigated whether statins reduce all-cause mortality and incidence of major coronary and cerebrovascular events in people without established CVD, but with risk factors.

## STUDY

1. Included 10 randomized trials of statins (n = over 70 000 persons; 33% women; 23% with diabetes; mean age 63) compared with controls (placebo, active control, or usual care). All had a mean follow-up of at least one year, and reported mortality and CVD events as primary outcomes. The study concerned only people without established CVD.
2. The dose and type of statin varied.
3. Risk factors included: age over 65, diabetes, smoking, increased BMI, elevated LDL-cholesterol
4. Primary endpoint = all-cause mortality. Secondary endpoints: major coronary events, (death from coronary heart disease, non-fatal myocardial infarction, and fatal and non-fatal stroke). Mean follow-up = 4 years.

## RESULTS

1. Mean baseline LDL-cholesterol = 140 mg/dL. Mean reductions in total cholesterol = 17%; LDL-c = 26%; and triglycerides = 9% . Mean HDL-cholesterol rose by 3%
2. All-cause mortality:  
Controls: 1925 of 33 793 (5.7%)  
Statin group: 1725 of 33 683 (5.1%)  
(Odds ratio = 0.88; 12 % reduction; NNT for 4 years to prevent one death = 166)
3. Major coronary events:  
Controls: 1266 of 23 946 (5.4%)  
Statins: 966 of 23 823 (4.1%)  
(Odds ratio – 0.70; 30% risk reduction; NNT for 4 years to prevent one event = 76)
4. Major cerebrovascular events:  
Controls: 2.3%  
Statin group: 1.9%

(19% reduction)

5. The association between statins and cancer was not significant.

## DISCUSSION

1. Statins were associated with a (*clinically*) significant risk reduction in all cause mortality of 12% and in major coronary events of 30%, and major cerebrovascular events of 19%.
2. “It is clear from the current analysis that a mortality benefit is a shared characteristic of long-term statin use in people without previous cardiovascular disease.”
3. No significant treatment heterogeneity was found between the sexes, between the elderly and young people, and between people with and without diabetes.
4. “Given the favorable effect of long-term statin treatment, it would be wrong to deny these benefits to people at increased risk for cardiovascular disease.”

## CONCLUSION

A mortality benefit from long-term statin use was evident in people who had no previous history of cardiovascular disease.

BMJ 2009;338: b2376 First author J J Brugts, Erasmus MC Thoraxcenter, Rotterdam Netherlands  
doi:10.1136/bmj.b2376 This study was reported in abridged form in the print issue (BMJ July 4,  
2009;339: 338)

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***Moderate Consumption of Ethanol, High Intake Of Vegetables, Fruits And Nuts, Olive Oil, And Legumes.***

## **7-4 ANATOMY OF HEALTH EFFECTS OF MEDITERRANEAN DIET**

The Mediterranean diet (**MD**) was introduced to the scientific community by the classic studies of Ancel Keys in 1980.

Most studies since have reported an inverse relationship between the MD and overall mortality.

This study investigated the relative importance of individual components of the diet associated with the inverse association between adherence to the diet and mortality.

## STUDY

1. Entered a population-based cohort of over 23 000 men and women in Greece between 1994 and

1997. All were free of cancer, coronary heart disease, or diabetes.

2. Evaluated the contribution of nine widely adopted components of the MD associated with all-cause mortality.
3. Assessed dietary intake by a food frequency questionnaire during the year prior to enrollment:
  - Vegetables \*
  - Legumes \*
  - Fruits and nuts \*
  - Fish and seafood \*
  - Cereals \*
  - High monounsaturated to saturated fat ratio \*
  - Ethanol \* (For men 10 g a day to less than 50 g a day; Women 5 g and 25 g )
  - Dairy \*\*
  - Meat and meat products \*\*(\* beneficial \*\* not beneficial)
4. Assessed conformity to the traditional MD with a 10-unit scale based on the 9 variables.
  - Assigned values of 0 or 1 to each component by using the sex-specific medians in the studied population as cut offs. Assigned 0 to people whose consumption was below the median value of components with a presumably beneficial effect and 1 to those whose consumption was above the median value of components with a presumably beneficial effect.
5. For meat and meat products and dairy, assigned a value of 0 to those whose intake was above the median, and 1 to those below.
6. The total diet score could range from 0 (minimal conformity) to 9 (maximal).
7. Follow-up to 2008. (Mean of 8.5 years).

## RESULTS

1. During follow-up, 1075 deaths from any cause occurred.

MD score	Deaths	% of cohort
0-4	652	5.1
5 or more	423	4
2. Compared to moderate alcohol intake, both high and low intake of alcohol were associated with increased mortality to a statistically significant degree.
3. Among the 7 presumed beneficial components of the diet, high consumption of all but fish and seafood was inversely associated with mortality.

4. For meat and meat products and dairy, there was a positive relationship with mortality, which approached statistical significance.
5. Each 2 unit increase in the MD score was associated with a mortality ratio of 0.86. (14% decrease)
6. The contribution to the association with lower mortality was largest for moderate consumption of ethanol (24%). Followed by low consumption of meat and meat products (16%), and high consumption of vegetables (16%). Followed by high consumption of fruits and nuts,, high mono-unsaturated to poly-unsaturated fat ratio, and high consumption of legumes (each contributing 10-14%). High consumption of cereals and low consumption of dairy products contributed less (5%).
7. “We interpret these findings as suggesting that moderate ethanol intake, low intake of meat and meat products, high lipid ratio, and high intake of plant foods are driving the association of high Mediterranean diet scores with low mortality.”

## DISCUSSION

1. Close adherence to the traditional MD diet, as indicated by the MD score, was associated with a statistically significant lower overall mortality.
3. Actually, the effects of dairy products, cereals, and fish and seafood were largely inconsequential. (Consumption of fish in these participants was generally low.)
4. MD scores in Mediterranean countries assess the impact of large quantities of the components consumed by persons in Mediterranean countries. Persons in non-Mediterranean countries who are on a “MD” may consume relatively lower quantities.

## CONCLUSION

The dominant components of the MD as a predictor of lower mortality are moderate consumption of ethanol, high intake of vegetables, fruits and nuts, olive oil, and legumes. And low consumption of meat and meat products.

BMJ July 4, 2009; 339: 26-29 First author Antonia Trichopoulou, University of Athens Medical School, Athens Greece. Greek European Prospective Investigation into Cancer and nutrition (EPIC) Prospective Cohort Study

BMJ 2009;338:b2337 doi.10.1136/bmj.b2337

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***“Avoid NSAIDs , Consider Opioids”***

**7-5 NEW PAIN GUIDELINES FOR OLDER PATIENTS**

Contradicting the guideline of 2002, an updated guideline issued by the American Geriatric Society (AGS) states that physicians treating patients aged 75 and older should avoid NSAIDs,

NSAIDs should be “considered rarely and with extreme caution in highly selected individuals”.

The new recommendation reflects evidence about serious cardiovascular and gastrointestinal tract risks associated with this class of drugs. NSAIDs may also complicate treatment of common conditions in this age group: hypertension and congestive heart failure.

Acetaminophen remains the initial drug of choice, although caution against using it in patients with liver conditions.

The guideline encourages considering use of opioids in the elderly with persistent pain. Persistent pain is common and often undertreated in the elderly, especially among those with degenerative spine conditions, arthritis, and cancer.

Selecting the appropriate analgesic for older patients, who may have multiple conditions, and who may be taking multiple drugs, requires careful thought.

Despite improved understanding of risks of NSAIDs, including GI bleeding, they have remained a mainstay of pain therapy in the elderly. Physicians have shied away from opioids. “We feel that NSAIDs in many cases are more risky than many opioid strategies.”

Physicians are advised to anticipate and monitor patients for adverse effects associated with opioids, and to continually assess whether the therapy is meeting the goals. Breakthrough pain should be anticipated.

Opioids can induce delirium in older patients. This can be corrected by lowering the dose. Patients starting opioids can experience anorexia, nausea, and vomiting. These adverse effects may dissipate over time. Constipation can be troublesome.

The guidelines advise against use of other classes of drugs: antidepressants including amitriptyline, imipramine, and doxepine, They cause a high risk of adverse events.

Treating pain in older adults requires an individual approach. Physical interventions such as applications of heat and cold may benefit.

JAMA July 1, 2009; 302: 19 Medical News and Perspective by the JAMA Staff.

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## *Effective for The Prevention Of Peptic Ulcers And Erosive Esophagitis*

### **7-6 FAMOTIDINE FOR THE PREVENTION OF PEPTIC ULCERS AND OESOPHAGITIS IN PATIENTS TAKING LOW-DOSE ASPIRIN**

Low-dose aspirin (**LDA**) is one of the most widely used drugs in the world. It has beneficial antithrombotic effects.

There have been increasing reports of peptic ulceration, GI bleeding, and esophagitis in patients taking LDA.

This trial assessed the efficacy of famotidine (a long-acting histamine-2 receptor antagonist) in prevention of these upper GI complications in patients taking LDA.

#### **STUDY**

1. This phase III randomized, double-blind, placebo-controlled trial compared efficacy of famotidine (*Pepcid*; Merck ; 20 mg twice daily) with placebo in 404 adult patients (mean age 63) for prevention of upper GI (**UGI**) complication of LDA.
2. All had been taking long-term LDA at baseline (for a mean of 3 years; the great majority taking 75 mg of aspirin daily).
3. At baseline, 54% had mucosal scarring; 58% had mucosal erosions. (Subjects at this time had been taking LDA for a mean of 3 years.)
4. None had peptic ulcers or erosive esophagitis on endoscopy at baseline. Patients were allowed to continue taking other antiplatelet agents such as clopidogrel and dipyridamole. None were taking proton-pump inhibitors, or other histamine-2 blockers. Antacid pills were given to take prn for symptom relief.
5. All subjects continued to take LDA.
6. Conducted a final endoscopy at 12 weeks. Primary endpoint = development of new upper GI ulcers or erosive esophagitis.
7. Analysis by intention-to-treat.

#### **RESULTS**

1. On the basis of an interim analysis of efficacy of famotidine, the independent data and safety monitoring committee recommended early termination of the trial.
2. At baseline, many patients had upper GI scars or erosions in the GI mucosa. About 1/3 had *H pylori* infection.



3. Outcome at 12 weeks:	Famotidine + LDA (%)	Placebo +LDA (%)	Odds ratio
Gastric ulcer	3.4	15	0.20
Duodenal ulcer	0.5	8.5	0.05
Erosive esophagitis	4.4	18	0.20
Gastric ulcer > 5mm	3.4	13	0.22
Duodenal ulcer >5 mm	0	8.5	
Peptic ulcers of any size or erosive esophagitis or both	5.4	32.5	0,12

4. Number needed to treat with famotidine to benefit (**NNTB**) one patient over 12 weeks =  
 $32.5 - 5.4 =$  absolute difference of 27% = NNTB 3.7 patients for 12 weeks to prevent one lesion.  
*(My calculations RTJ)*

5. Patients taking beta-blockers had a higher risk of GI complications. (24% vs 14%)

6. Patients with baseline erosions and scars had a higher risk of complications.

6. Adverse effects:	Famotidine	Placebo
Drop outs	21	25
Total adverse effects	9	15 (none judged related to the drug)
Upper GI hemorrhage	0	4 (2 admitted to hospital)

## DISCUSSION

1. The risk of developing these lesions was increased in patients taking beta-blockers and in those with GI mucosal scarring or erosions at baseline.
2. Rates of upper GI lesions will vary according to the characteristics of the populations studied. Also with the dose of aspirin, compliance with taking LDA, presence or absence of *H pylori*, and inter-observer variation.
3. The majority of the participants in this trial had erosions or scars at baseline, indicating a high rate of recurrence of UGI lesions (including esophagitis) in persons taking LDA.
4. Beta-blockers acted as an independent factor in increasing the risk of ulceration.
5. GI mucosal damage is equally frequent in patients taking NSAIDs.
6. The UGI lesions were frequently asymptomatic. However, patients assigned to famotidine were less likely to complain of dysphagia. Their overall treatment assessment was better than those assigned to placebo.
7. Proton-pump inhibitors are effective preventive treatment. There have been concerns about costs,

safety, and risk of interaction with other drugs (especially clopidogrel). Famotidine might be a useful alternative in patients taking LDA.

## CONCLUSION

“Famotidine is effective for the prevention of peptic ulcers and erosive esophagitis in patients taking low-dose aspirin.”

Lancet July 11, 2009; 374: 119-25 Original investigation, first author Ali S Taha, University of Glasgow, Scotland. The FAMOUS trial  
Funded in part by Merck

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***“The Only Efficient Way To Stop The Virus Is To Vaccinate The Other Half Of The Sexually Active Population; Boys And Men.”***

## **7-7 HPV VACCINE FOR ALL**

Cervical cancer is the second leading cause of death from cancer in women worldwide. Papanicolaou smear-based screening, introduced in the 1950s, reduced mortality without knowledge about the actual cause of the disease.

The main types of high-risk human papilloma virus (**HPV**) were identified as causal agents 30 years later. This discovery led to development of vaccines.

A study in Lancet<sup>1</sup> reports the efficacy of a bivalent HPV vaccine (types 16 and 18 with an aluminum adjuvant; in 9000 women age 15-25) for the reduction of high-grade cervical intraepithelial neoplasia (CIN2+/CIN3+), and for cross protection against persistent infection with non-vaccine oncogenic types 31, 33, and 45. The adjuvant seems to increase peak antibody response several fold.

Over 3 years, CIN2+ associated with HPV 16/18 in those receiving vaccine, vs controls, was reduced by 93%, and CIN2+ associated with HPV 31/33/45/52/58 was reduced by 53% compared with controls.

(A quadrivalent vaccine contains recombinant protein from types 6, 11, 16, and 18.. How the two vaccines compare in their long-term stimulation of immunity remains to be established.)

The neutralizing antibody response to HPV vaccines exceeds the natural immune response to infection with the virus, but life-long immunity is unlikely, making need for a booster probable.

The vaccine will have a profound effect on invasive and painful secondary prevention such as cryotherapy and loop excision.

The primary public health goal is to stop the spread of infection, and ultimately disease.

“The only efficient way to stop the virus is to vaccinate the other half of the sexually active population; boys and men.” In clinical trials males show an immune response similar to that of women.

One model for assessing HPV strategies supported the inclusion of men as the most cost-effective approach.

The lifetime risk of HPV infection in the sexually active population is 80% to 90%. Although the virus is eliminated from the body within 2 years in 80% of those infected, infections are more likely to become persistent in older individuals and those with compromised immunity.

Eradication of HPV would be accelerated by relaxing the target age to include older women and by including women and men who are seropositive or DNA positive for some HPV types. The vaccine will probably provide protection for the other types.

“Women have shouldered responsibility for contraception since its inception. The goal to eradicate sexually transmitted carcinogenic viruses can be jointly carried by both women and men, and could be accomplished within a few decades.”

Lancet July 25, 2009; 374: 268-70 Editorial, first author Karin B Michels, Harvard Medical School, Boston Mass.

Funded by GlaxcoSmithKline

**1** “Efficacy to Human Papilloma Virus 16/18 ASO4-adjuvant Vaccine against Cervical Infection and Precancer Caused by oncogenic HPV types” The final analysis of a double-blind, randomized study in Young Women (The PATRICIA trial) Lancet July 25, 2009; 374: 301-14 First author J Paavonen, University of Helsinki, Finland

Women (n = over 16 000) age 15-25 were randomized to placebo or HPV-16/18 ASO4-adjuvanated vaccine at months 0, 1 and 6, regardless of their baseline HPV status. Many were not sexually active at the time.

Primary endpoint = vaccine efficacy against cervical intraepithelial CIN2+ that was associated with HPV 16/18 in women who were HPV 16/19 negative at baseline. And DNA negative at baseline and at month 6 for the corresponding types.

Mean follow-up was 35 months after the 3<sup>rd</sup> dose.

Efficacy against CIN2+ associated with HPV-16/18 was 93%.

Efficacy against CIN2+ associated with 12 non-vaccine oncogenic types was 54%.

Efficacy against CIN3+ was 87% in those who had no evidence of oncogenic HPV at baseline.

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## *No Benefit From ACE Inhibitor or Angiotensin Blocker*

### **7-8 DIABETES COMPLICATIONS AND THE RENIN-ANGIOTENSIN SYSTEM**

Animal models and subsequent clinical trials fostered enthusiastic hope that systematic use of agents blocking the renin-angiotensin system (**R-As**) in the management of diabetic nephropathy would reduce the risk of end-stage renal disease. As a result, the concept developed that inhibition of the R-As in patients with diabetes is beneficial in both early and advanced stages of nephropathy.

Studies were then initiated to investigate the role of inhibition of the system in other complications of diabetes—retinopathy and neuropathy.

An extraordinary study in this issue of NEJM<sup>1</sup> challenged the accepted concept. It was the longest study in this field of investigation. It was limited to type-1 diabetes in patients with no or little nephropathy or retinopathy. It compared strategies for inhibition of the R-As, and evaluated 3 common measures of renal function: microalbuminuria; glomerular filtration rate; and renal morphological features. It also studied the progress of retinopathy.

The findings were surprising. Inhibition of the R-As did not reduce incidence of microalbuminuria, and did not mitigate decline in renal function or renal morphological features.

In contrast, it reduced the odds ratio of retinal changes by 60 to 70% compared with placebo, most likely independently of BP reduction.

Questions remain: Most patients in the study had minimal retinopathy, no early proliferative retinopathy. This casts doubt on benefits in patients with more advanced retinopathy.

The duration of these protective effects is not known beyond 5 years.

“The fact that the present study shows a paradoxical increase in the risk of microalbuminuria with long-term angiotensin-receptor blockade (losartan) is a major setback for the dominant concept that inhibition of the renin-angiotensin system is salutary.”

“The normotensive patient with type-1 diabetes and normoalbuminuria in whom retinopathy is minimal or absent, stands to benefit from reduction in the advancement of retinal change through inhibition of the renin-angiotensin system.”

NEJM July 2, 2009; 361: 83-85 Editorial, first author Bruce A Perkins, University of Toronto, Canada.

1 “Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes” NEJM July 2, 2009; 361: 40-51. First author Michael Maurer, University of Minnesota, Minneapolis.

The study randomized 285 normotensive patients with type 1 diabetes. None had microalbuminuria or retinopathy. Randomized to losartan, enalapril, or placebo.

Over 5 years: No change between groups in biopsy-assessed renal structure (mesangial fractional volume, the variable most closely correlated with reduction in GFR). Microalbuminuria was actually greater in the losartan group as compared with placebo—did not differ between placebo and enalapril. GFR declined by about 7 mL per minute in all 3 groups.

As compared with placebo, the odds of retinopathy was reduced by 65% to 70% in the drug groups, independent of changes in BP.

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## **7-9 A/H1N1 INFLUENZA UPDATE (July 25 2009) From the UK Health Protection Agency (HPA)**

A. What more do we know compared with 2 months ago?

The virus is similar to seasonal flu.

Taking oseltamivir (*Tamiflu*) is not a pleasant experience. Side effects that include nausea, diarrhea and hallucinations.

The 2009 pandemic has spread with unexpected speed. (In less than 6 weeks)

The methodology used to estimate fatality could overestimate and underestimate the numbers.

The virus is *not* becoming more virulent.

B. Has advice to healthcare professionals from the HPA changed since the WHO announced pandemic alert 6 in June?

No

The change in the alert refers only to geographical spread, and not to severity.

What has changed is the move from containment of the virus, which is no longer possible, to treatment.

Swabbing in primary care is no longer necessary unless there are special reasons to do so, such as infection control or as part of surveillance.

C. What are the latest predictions on how serious this virus is?

There have been 29 deaths in the UK as of July 19 among persons confirmed to have the virus, although it is not always the cause of death.

The HPA estimates that the UK had 55 000 new cases last week (July 12 – 15) in addition to the 9718 cases previously confirmed. 50 people per 100 000 reported flu like illness between 29 June and 6 July. This rose sharply to 73 per 100 000 between 6 and 12 July.

Globally, there have been 139 5667 cases and 781 deaths according to the European Centre for Disease Prevention and Control.

The Department of Health estimates that about 12% of health care workers and 8% of the entire population are likely to have the virus at any one time. And 0.1 to 0.35% will die.

For most people, AH1N1 is not serious, and can be managed with self-care at home.

The populations should not be unduly alarmed.

Perspective is important—seasonal flu usually kills 8000-9000 people a year.

D. How are current arrangements for administering oseltamivir working?

Usually, general practitioners can diagnose by telephone. If the doctor is satisfied that the patient is describing symptoms of the virus, they can issue an antiviral request form for a friend to pick up at an antiviral collection point. The BMA is concerned that too many people will get antivirals too easily, are being needlessly medicated, and that arrangements for prescribing and administering oseltamivir are too complex.

People in England will be able to bypass their GP by using the National Pandemic Flu Service. If they have symptoms, answer a set of questions and are in one of the high risk groups, they will receive an authorization for a friend to pick up an antiviral. This will allow GPs to deploy their time to other areas of care.

The threshold for getting oseltamivir is low.

E. Is it worth wearing a face mask?

They can help to reduce the spread of respiratory viruses, but their usefulness is limited.

Because the virus is now pandemic, widespread use of face masks by the public is unlikely to stop the disease from spreading. Handwashing is far more effective at preventing spread.

F. What are the likely arrangements for distribution of the vaccine?

GPs will lead on the national immunization program.

Who should get the first vaccine? Frontline clinical staff (healthcare workers) and those involved in frontline support (eg, laboratory workers). Priority groups such as those vulnerable to seasonal flu.

G. Should pregnant health care workers deal with patients with flu?

Pregnant women are at increased risk and should avoid dealing with patients.

H. Has AH1BN1 mutated?

No. it remains the same as it was at onset in Mexico. Surveillance continues.

I. Is AH1N1 more likely to infect the lungs?

One study reported that it does produce a more severe lung infection than can be expected from average seasonal flu.

J. Where can up-to-date information be accessed?

<http://pandemicflu.bmj.com>

[www.dh.gov.uk](http://www.dh.gov.uk)

[www.hpa.org.uk](http://www.hpa.org.uk)

[www.rcgp.org.uk](http://www.rcgp.org.uk)

BMJ July 25, 2009; 339: 196-97 Adrian O'Dowd, freelance journalist, Margate, UK

BMJ 2009;338:b2977













