

# **PRACTICAL POINTERS**

## **FOR PRIMARY CARE**

**ABSTRACTED MONTHLY FROM THE JOURNALS**

### **NOVEMBER 2005**

**“OH, BY THE WAY, DOCTOR” SYNDROME ---- SETTING THE AGENDA FOR THE CLINICAL INTERVIEW**

**THE WAIST/HIP RATIO MORE PREDICTIVE OF MYOCARDIAL INFARCTION THAN BMI**

**SUPPLEMENTS ARE NECESSARY FOR ADEQUATE VITAMIN D LEVELS**

**THE LOW BENEFIT/HARM-COST RATIO OF SCREENING FOR CERVICAL CANCER AT AGE 21**

**HUMAN PAPILOMA VIRUS, THE ROOT CAUSE OF CERVICAL CANCER: THE PROMISE OF GLOBAL-CERVICAL-CANCER PREVENTION**

**VALUE AND LIMITATIONS OF CHEST PAIN HISTORY**

**INHALED INSULIN – THE LATEST**

**AFTER MI, HIGH DOSE ATORVASTATIN (LIPITOR) NOT MORE BENEFICIAL THAN STANDARD DOSE SIMVASTATIN (ZOCOR) TO PREVENT MAJOR CORONARY EVENTS**

**REMARKABLE BENEFITS OF A PUBLIC-HEALTH INTERVENTION TO REDUCE SECONDHAND SMOKE**

**MORE NOVEL EFFECTS OF DIET ON BLOOD PRESSURE AND LIPIDS**

**HABITUAL CAFFEINE INTAKE DOES NOT INCREASE RISK OF HYPERTENSION.**

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This document is divided into two parts

1) The **HIGHLIGHTS AND EDITORIAL COMMENTS**

**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 5 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 NOVEMBER 2005

### *How To Avoid The “Oh, By The Way, Doctor” Syndrome.*

#### 11-1 “WHAT ELSE” SETTING THE AGENDA FOR THE CLINICAL INTERVIEW

A too common ending of a medical interview:

*Dr: “It looks like you have a bad virus cold and not a bacterial sinus infection. Antibiotics don’t help. I will treat your symptoms and you can expect to get better. Let me know if you do not improve in a few days.”*

*(Doctor then stands and gets ready to leave the room.)*

*Patient: “Before you go there is one more thing I would like to mention. I have been passing a little blood in my stool.” “Should I do anything about it.”?*

*Dr: “Why didn’t you tell me this before”*

*Patient” “You didn’t ask me.”*

The syndrome occurs at the end of the interview. “We believe it has its origin at the beginning.”

If the physician jumps into an exploration of the first problem the patient mentions before knowing all of the patient’s worries, he will often be confronted with these unvoiced concerns at the end of the interview. Open ended questions such as “What else?”; “What other problems do you wish to attend to today?”; “What specific requests do you have today?” are most helpful in eliciting the patient’s entire list of concerns.

We should not blame the patient for a defective interview process.

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*This article should be read in its entirety. See the abstract.*

*I believe some patients would respond if asked to list their agendas before coming to the office.*

*The same question “Is there anything else?” may also be asked at the end of the interview to reach completion.*

*This is important advice. I wish I had received it at the beginning of my medical career.*

### ***Waist/Hip Ratio Showed A Graded And More Highly Significant Association With Risk Of MI Than BMI.***

#### **11-2 OBESITY AND THE RISK OF MYOCARDIAL INFARCTION IN 27 000 PARTICIPANTS FROM 52 COUNTRIES: The INTERHEART Study**

This study postulated that markers of central obesity (especially the W/H ratio) are more strongly related to the risk of myocardial infarction (MI) than BMI.

Case-control study entered over 27 000 subjects world-wide.

A. Cases: Over 12 000 subjects with a first MI

B. Controls: Over 14 000 age and sex-matched subjects who did not have an MI.

Measured waist and hip circumferences and BMI

Results: Cases had a strikingly higher W/H ratio than controls. This observation was consistent for all regions of the world.

BMI: There was a modest and graded association with MI between quintiles (odds ratio top quintile compared with bottom quintile (1.44). However, when adjusted for other risk factors, odds ratio became insignificant (0.98)

W/H ratio: The odds ratios for MI for every successive quintile of the W/H ratio was significantly greater than that of the previous one:

1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	4 <sup>th</sup>	5 <sup>th</sup>
1.00	1.15	1.39	1.90	2.52

The population-attributable risk of MI in the two top quintiles of W/H ratio was 24%.

The population-attributable risk of MI in the top two quintiles of BMI was only 8%.

“The INTERHEART study clearly indicates that, of the various anthropometric measures commonly used, the waist-to-hip ratio shows the strongest relation with the risk of myocardial infarction.”

“The global burden of obesity has been substantially *underestimated* by the reliance on BMI in previous studies.” If a raised W/H ratio were to be used to assess the risk of cardiovascular disease, the proportion classified as obese would increase substantially.

The best anthropometric index of obesity as a predictor of MI is the W/H ratio. It shows a graded and highly significant association with MI risk.

Redefinition of obesity based on waist-to-hip ratio instead of BMI increases the estimate of MI attributable to obesity. For a rule of thumb, a cut point of a W/H ratio above 8.5/10 for women and 9/10 for men would be considered to increase risk.

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*This remarkable study was carried out by many investigators in all continents and supported by many drug companies and heart associations.*

*Being a case-control study, it is not definitive and requires confirmation.*

*Its important contribution is to point out that the danger of obesity is not due to fat in the extremities, but to intra-peritoneal fat which drains directly into the liver. This results in adverse metabolic effects which increase the risk of cardiovascular disease.*

***Vitamin D Supplements Are Necessary For Adequate Vitamin D Status In Northern Climates.***

### **11-3 RELATIONSHIP BETWEEN SERUM PARATHYROID HORMONE LEVELS, VITAMIN D SUFFICIENCY, AND CALCIUM INTAKE.**

This study used the serum parathyroid hormone (PTH) level as a marker of sufficiency or insufficiency of vitamin D and calcium. (If vitamin D and calcium levels are insufficient, PTH will be high; if sufficient, PTH will be low.) The investigators examined calcium intake and serum levels of 25-hydroxyvitamin D (25-OH-D) with respect to optimal serum PTH levels in a healthy adult population living in a northern latitude where sunshine is limited.

The lowest PTH (most favorable) levels were observed in the group with the highest serum 25-OH-D (18 ng/mL and above) In this group, the intake of calcium made little difference in the PTH levels. (Ie, when comparing intake of less than 800 mg with over 1200 mg. )

The highest PTH (least favorable) was observed in the group with 25-OH-D less than 10 ng/mL. In this group, calcium did make a difference in PTH levels. PTH was higher when the calcium intake was less than 800 mg, and lower when intake was over 1200 gm. (Ie, calcium intake may be more important in persons with lower vitamin D intake.)

“The significance of our study was demonstrated by the strong negative association between sufficient serum levels of 25-hydroxyvitamin D and PTH with calcium intake varying between 800 mg/d, and to more than 1200 mg/d.” Vitamin D sufficiency can ensure ideal serum PTH values even when the calcium intake level is less than 800 mg/d.

“There is already sufficient evidence from numerous studies for physicians to emphasize the importance of vitamin D status and to recommend vitamin D supplements for the general public when sun exposure and dietary sources are insufficient.”

No vitamin D biosynthesis occurs during the winter months at latitudes of 42° north (Boston) and 52° north (Edmonton, Alberta). Iceland is 64° north. Only subjects who took supplements maintained a serum level of 25-OH-D above 18 ng/mL during the winter.

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*The study does not suggest that intake of calcium should be limited even though vitamin D may compensate for modest intakes of calcium. I believe generous intakes are warranted (> 1000 mg daily). The study does suggest that vitamin D, not calcium, is the main determinate of bone health .*

*Vitamin D is the key to adequate bone metabolism. Higher dietary calcium intake can only partially compensate when vitamin D is not sufficient.*

*The main point of the study for primary care is that intake of vitamin D is often not sufficient for optimum metabolic needs. Supplementation is needed, not only in northern climates, but also for other circumstances. Individuals in nursing homes and those confined to indoors need supplements. Adolescents need all the bone in their bone-banks they can get to maintain best bone health in older age. I believe supplementation would be reasonable in this group as well as in the elderly.*

*A daily multivitamin supplement is convenient, safe, and inexpensive. It contains 400 IU vitamin D, which is likely to ensure adequate serum levels when added to the dietary intake.*

***“Exercise Restraint and Prudence in Screening Initiation”.***

#### **11-4 A 21-YEAR-OLD WOMAN WITH ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE**

The decision to begin cervical cancer screening is of greater significance than clinicians often appreciate. Beginning too soon may set in motion a series of interventions and investigations that do not yield a beneficial health outcome.

Cervical-vaginal HPV prevalence is less than 2% before initiation of vaginal intercourse.

Prevalence of HPV: 71% in age 18-22; 31% in age older than 29; 29% in ages over 40. The decline is due to the immune response.

An abnormal cytology (ASC-US) occurs in up to 1 in 6 of sexually active young women.

Acute HPV infection causes cervical changes that can manifest as low-grade abnormal cytology, but such cytology does *not* indicate the presence of underlying cervical intraepithelial neoplasia (CIN).

HPV infections and ASC-US often regress spontaneously.

“Young women enthusiastic about cervical cancer screening need to be made aware of the projected benefits and potential harms of screening and treatment.” Screening young women often elicits anxiety and a cascade of clinical interventions of no clinical value. We should . . . “exercise restraint and prudence in screening initiation”. “Just because we can test doesn’t mean we should test. “

Patient’s preferences and values should be integrated into clinical decision about screening. This requires explanation of risks, benefits, and burdens.

Women should be told that cigarette smoking increases risk of CC.

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*This and the preceding article would suggest delay in screening until age 30.*

*Why wait?*

*Prevalence of cervical cancer is very low in younger women*

*HPV and ASC-US are very common in sexually active women age 21. The burden of following, treating, and advising them would be considerable.*

*Between ages 21 and 30, many HPV infections and ASC-US will regress leading to avoidance of colposcopy and biopsy. Considerable anxiety will be avoided if screening were delayed.*

*It takes about 10 years for dysplasia to develop into cancer. The risk of developing cancer during the 20-30 decade is small.*

*So. . .the benefit/harm-cost ratio of screening at age 21 is extremely low. The ratio increased by age 30.*

### ***There Is A Single Root Cause Of Cervical Cancer Is the Venerable PAP Test Outdated?***

#### **11-5 THE PROMISE OF GLOBAL-CERVICAL-CANCER PREVENTION**

“Because there is a single root cause of cervical cancer, we can envision both primary prevention through vaccination against HPV in young women, and secondary preventive screening directly for carcinogenic HPV in older women.”

“HPV DNA testing is more sensitive and the results more easily reproducible than cytologic screening and colposcopy for the detection of extant and incipient cervical precancerous conditions and cancer.”

A negative test for carcinogenic HPV types provides a degree and duration of reassurance not achievable by any other diagnostic method.

We can target the optimal age at which screening should be performed; determine the most cost-effective testing intervals; which HPV types to screen for (strongly carcinogenic vs weakly carcinogenic); and the threshold of viral loads (very low loads only minimally raise the risk).

Because of the greater accuracy of HPV DNA testing, screening should be focused on reaching women at the time of the peak risk of treatable precancerous conditions, and before the average age at which incurable invasive CCs occur. Screening women once at age 35, or twice at ages 35 and 40 with current HPV DNA tests targeting 13

carcinogenic types can achieve more cost-effective reductions in cancer than can conventional cytological methods.

The peak prevalence of transient infections occurs among women during their teens and 20s, after the initiation of sexual activity. The peak prevalence of cervical pre-cancerous lesions occurs about 10 years later; the peak prevalence of invasive CC at age 40 to 50. The conventional model of CC prevention is based on repeated rounds of cytological examinations and colposcopy. Alternative strategies include HPV vaccination of adolescents, or one or two rounds of HPV screening at the peak ages of treatable precancerous lesions and early cancer.

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*Would universal vaccination against HPV make cervical HPV testing unnecessary?*

*In regard to HPV we will soon have for primary care:*

*1) Early and more definitive screening.*

*2) Prophylaxis with vaccination.*

*Remarkable advances in immune therapy are in the offing:*

*HPV vaccine*

*Herpes Zoster vaccine*

*Improved TB vaccine*

*Malaria vaccine*

*Vaccine for H5N1 Flu*

*HIV is the holdout. Many persons still have high hopes.*

***“No Single Element Of Chest Pain History Is A Powerful Enough Predictor Of Non-ACS To Allow the Clinician To Make Decisions According To It Alone.”***

#### **11-6 VALUE AND LIMITATIONS OF CHEST PAIN HISTORY IN THE EVALUATION OF PATIENTS WITH SUSPECTED ACUTE CORONARY SYNDROMES: A Systematic Review**

Despite diagnostic advances, missed acute coronary syndromes (ACS) and acute myocardial infarctions (AMI) remain problematic. The diagnosis is missed in 2% to 10% of patients.

Conversely, a large proportion of patients with chest pain who are admitted do *not* turn out to have an ACS. This has enormous economic implications.

Chest pain must be used in conjunction with other markers to determine disposition.

##### **A. Low risk of ACS**

Pain that is pleuritic, positional, stabbing, or reproducible with palpation.

##### **B. Probable low risk**

Pain not related to exertion or that occurs in a small inframammary area.

##### **C. Probable high risk**

Pain described as pressure, is similar to that of a prior MI, or worse than prior anginal pain.

##### **D. High risk**

Pain that radiates to one or both shoulders or arms,, or is related to exertion.

Despite limitations, the chest pain history allows the clinician to establish approximate probabilities for acute cardiac ischemia.

Overall, the likelihood ratios of positive tests (the presence of an individual descriptor of pain) varies from 0.2 to 4.7. That is, the discomfort described can be present in 2 out of 12 patients with ACS. Or can be present in 5 out of 6. This is not robust enough to be independently useful in establishing a diagnosis. There will always be patients without ACS who have discomfort similar to that of patients with ACS.

**“Overall The Inhaled Insulin Approach Seems Effective And Safe.”**

### **11-7 INHALED INSULIN IMPROVES GLYCEMIC CONTROL WHEN SUBSTITUTED FOR OR ADDED TO ORAL COMBINATION THERAPY IN TYPE 2 DIABETES.**

This study examined the effect of a preparation of inhaled, dry-powdered human insulin (*Exubera*) which is currently in development. The inhaled insulin delivers aerosolized powdered insulin to the small airways and alveoli. This enables rapid absorption. Its effect lasts 4 to 6 hours.

Does inhaled insulin improve glycemic control when taken alone, or when added to oral agents?

Open label parallel-group followed over 300 patients with DM2 (mean age 57; mean BMI = 30). All were receiving two oral antidiabetes medications (predominantly a sulfonylurea and metformin). All had a HbA1c of 8% or greater (mean = 9.5%). All were considered to have failed on dual oral therapy. None had significant respiratory disease. None were smokers.

Randomized to:

- A. Inhaled insulin alone given 3 times daily before meals.
- B. Inhaled insulin + continued oral agents
- C. Oral agents alone.

HbA1c reduction compared with oral agents alone:

- A. Inhaled insulin alone = -1.18 %
- B. Inhaled insulin + continued oral agents = - 1.67 %

HbA1c levels less than 7% :

- A. Inhaled insulin + continued oral agents = 32%
- B. Oral agents alone = 1%.

In the insulin groups, fasting glucose and 2-hour postprandial glucose mean levels improved by up to 50 mg/dL and 75 mg/dL. Triglyceride levels improved by 40 to 54 mg/dL

Hypoglycemia occurred at a rate of 1.3 to 1.7 episodes per month in the insulin groups; 0.1 in the oral agents-alone group. No patient discontinued insulin due to hypoglycemia.

Cough was more common in the insulin groups. It was generally mild and decreased in incidence and prevalence during the trial. No patients discontinued for this cause.

Mean body weight increased in the insulin groups over 3 months (+ 6 pounds); did not change in the oral-alone group.

Withdrawals were similar in all 3 groups (about 6%--none due to adverse events).

Pulmonary function remained similar in all groups.



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*One would expect inhaled insulin to be more rapidly absorbed into the general circulation than subcutaneous insulin. It has a faster onset of action and thus a more rapid glucose-lowering effect. Its duration of action is longer than the short-acting insulin lispro and is similar to regular insulin. This makes it suitable for administration before meals.*

*I included this abstract to follow-up on this new technology, which I believe is of great interest to many patients with DM2. There is a long road ahead before inhaled insulin becomes freely available. I believe we will reach the end of the road.*

**No Difference in Cardiovascular and All-Cause Mortality.**

**11-8 HIGH-DOSE ATORVASTATIN VS USUAL-DOSE SIMVASTATIN FOR SECONDARY PREVENTION AFTER MYOCARDIAL INFARCTION The IDEAL Study**

Statins are part of the standard treatment regimen after myocardial infarction (MI). Incremental benefits have been demonstrated with intensive lowering of LDL-cholesterol (LDL-c) among patients with the acute coronary syndrome (ACS). The National Cholesterol Education Program now recommends a LDL-c level less than 70 for patients at very high risk of ACS.

The IDEAL study hypothesized that intensive lowering of LDL-c with atorvastatin (*Lipitor*) at the highest recommended dose would yield incremental benefits compared with the usual recommended dose of simvastatin (*Zocor*).

Prospective, randomized, open label, multicenter trial enrolled over 8500 patients (mean age = 61). All had a history of acute MI. (*This is a secondary prevention study.*)

Subjects were randomized to 1) atorvastatin 80 mg daily, or 2) simvastatin 20 mg daily.

Over 4.8 years:	Atorvastatin (n = 4439)	Simvastatin (n = 4449)	Absolute difference	NNT*
LDL-c (mean mg/dL)	81	100		
Major cardiac event	9.3%	10.4%	1.1%	90**
Non-fatal acute MI	6.0 %	7.2%	1.2%	
(* Number needed to treat for 5 years to benefit one patient.)				
(** not statistically significant)				
Non-cardiovascular death	3.2%	3.5%		
Death from any cause	8.2%	8.4%		

Adverse effects: Adverse event resulting in permanent discontinuation were more common in the atorvastatin group (9.6% vs 4.2%). Transaminase elevation in 1% vs 0.1%. Serious myopathy and rhabdomyolysis were rare in both groups.

When standard and intensive LDL-c lowering were compared in patients at high risk (past MI), there was no statistically significant reduction in major coronary events. There was no difference in cardiovascular and all-

cause mortality. There was a reduction in other composite secondary endpoints and non-fatal MI. (NNT for 5 years = 26 to 62.)

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*When I first noted the title of the investigation, I expected much more favorable results in the atorvastatin group.*

*Note that the recommended level of LDL-c of 70 was not reached in either group.*

*Lipitor therapy is more burdensome (more discontinuation; need to follow more closely for transaminase).*

*Note that at baseline, hypertension was present in 33% of subjects, mean body mass index was 27, and 20% were current smokers. I believe clinicians have focused too much on cholesterol lowering as a preventive measure and have neglected the other risk factors. This study did not mention any interventions for the other risk factors other than to state that subjects received dietary counseling.*

*I believe a primary prevention trial would report better results from atorvastatin. It is too late to gain much benefit after a severe cardiovascular event has occurred.*

### ***A Public Health Intervention Producing Remarkable Benefits.***

#### **11-9 LEGISLATION FOR SMOKE-FREE WORKPLACES AND HEALTH OF BAR WORKERS IN IRELAND: Before And After Study**

In March 2004, The Republic of Ireland introduced a comprehensive smoke-free law covering all indoor workplaces. This created a natural experiment for identifying effects of the ban.

This study compared exposure to secondhand smoke and respiratory health in bar staffs before and after the law was passed.

Enrolled staff working in pubs in the Republic (n = 111) six months before the smoking ban went into effect.

The study considered non-smokers only.

Followed the cohort for one year after to assess changes in exposure to secondhand smoke and symptoms.

Salivary cotinine concentrations fell by 71%. Levels fell in 106 of 111 subjects

Self reported exposure to secondhand smoke was high before the ban, with smoke at work accounting for by far the greatest exposure. Exposure fell from 40 hours a week to zero.

At baseline, 65% reported one or more respiratory symptoms. This dropped to 49% on follow-up. Fewer reported cough and production of phlegm, red eyes, and sore throat.

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*I included this article because it illustrates an important public health intervention. It certainly can be more widely applied.*

### ***The Basic DASH Diet Modified By Increased Protein and Monounsaturated Fat Improved BP and Lipid Levels***

#### **11-10 MORE NOVEL EFFECTS OF DIET ON BLOOD PRESSURE AND LIPIDS:**

**Results of the OmniHeart Randomized Trial “Effects of Protein, Monounsaturated fat, and Carbohydrate Intake on Blood Pressure and Serum Lipids”**

This issue of JAMA presents the OmniHeart randomized trial which represents the latest effort by members of the DASH Trials group to examine the effect of varying protein, monounsaturated fat, and carbohydrate intakes on BP.

The Trial recruited subjects with BP 120-159/80-99. It used a complex crossover design which continued the basic DASH diet and modified it to contain:

- A. 58% of kcal as carbohydrate, or
- B. 25% of kcal as protein, or
- C. 37% of kcal as monounsaturated fat (olive oil, canola oil, safflower oil).

Compared with the carbohydrate diet, the high protein decreased systolic by 3.5 in those with hypertension, decreased LDL-c by 3.3 mg/dL and decreased triglycerides by 15.7 mg/dL, but *decreased* HDL-c by 1.3 mg/dL

Compared with the carbohydrate diet, the high monounsaturated fat diet decreased systolic in those with hypertension by 2.9; had no significant effect on LDL-c; *increased* HDL-c by 1.1 mg/dL, and lowered triglycerides by 9.6 mg

Overall, the high monounsaturated diet seemed to produce the greatest benefit with the least adverse effects.

The authors suggest that a basic DASH diet modified by increased protein or monounsaturated fat content improved BP and lipid levels and reduced risk of estimated cardiovascular disease.

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*The investigators suggested that their results . . . "Should be widely applicable to the US population" But note that the subjects were relatively young and enthusiastic, the trial periods lasted only 6 weeks, the diets were prepared in research kitchens and under controlled circumstances. Nevertheless, about 10% to 15% dropped out of the study.*

*I applaud the noble effort, but I do not believe the results are applicable to primary care. Certainly, diet does play an important part in control of lipids and BP. For the latter, I believe salt restriction is the most important and achievable component.*

*Weight loss per se (calorie restriction + exercise) is more relevant to lowering BP than is the type of diet.*

*Most primary care clinicians, I believe, would emphasize treatment of lipid and BP disorders with drugs.*

### **Coffee Lovers—Be Reassured. Cola Drinkers—Some Reason For Concern**

#### **11-11 HABITUAL CAFFEINE INTAKE AND THE RISK OF HYPERTENSION IN WOMEN**

Much clinical lore about the possible association between caffeine intake and the risk of hypertension is available. Some have reported an increased risk. But studies have been limited by short observation periods. Information about prolonged, regular intake is not available.

This study prospectively examined the association between caffeine intake and incident hypertension in a large cohort of women over many years.

- A. Caffeine consumption: Those in the third quintile had a 13 % increased risk of hypertension.

Interestingly, those in the 4<sup>th</sup> and 5<sup>th</sup> quintiles were not at increased risk –an *inverse U-shaped* curve.) Trend was non-linear.

- B. Caffeinated coffee consumption: No increase in the risk between quintiles. Actually, those in the

4<sup>th</sup> and 5<sup>th</sup> quintile had a lower risk than those in the 1<sup>st</sup> quintile.

C. Decaffeinated coffee: Similar to caffeinated.

D. Sugared caffeinated cola: There was a definite linear increase in incidence of hypertension with increasing intake between quartiles—highest quartiles had 28% to 44% higher risk.

E. Diet caffeinated cola: also a linear trend with increasing intake—highest quartiles had 16% to 19% greater risk.

Caffeine consumption does not appear to increase risk of incident hypertension.

Consumption of coffee (caffeinated and decaffeinated) does not appear to increase risk of developing hypertension.

Caffeinated soft drink (sugared and diet) appear to be associated with increased risk of hypertension. Whether the association is causal will require further study.

# ABSTRACTS NOVEMBER 2005

## *How To Avoid The “Oh, By The Way, Doctor” Syndrome.*

### 11-1 “WHAT ELSE” SETTING THE AGENDA FOR THE CLINICAL INTERVIEW

A too common ending of a medical interview:

*Dr: “It looks like you have a bad virus cold and not a bacterial sinus infection. Antibiotics don’t help. I will treat your symptoms and you can expect to get better. Let me know if you do not improve in a few days.”*

*(Doctor then stands and gets ready to leave the room.)*

*Patient: “Before you go there is one more thing I would like to mention. I have been passing a little blood in my stool.” “Should I do anything about it.”*

*Dr: “Why didn’t you tell me this before”*

*Patient” “You didn’t ask me.”*

In the USA this frustrating interaction is usually called the “Oh, by the way, Doctor” syndrome.

The French call it “a propos, Docteur”.

The Dutch may call it “tussen haakjes” (“between two brackets”, or as we say “parenthetically”).

The Spanish “Pues, ya que estoy aqui” (Well, since I am still here”)

The syndrome occurs at the end of the interview. “We believe it has its origin at the beginning.”

Although clinicians tend to blame the patient for this distressing syndrome, in fact it is frequently the result of a defective interview technique—failure to elicit the patient’s entire agenda early in the visit.

If the physician jumps into an exploration of the first problem the patient mentions before knowing all of the patient’s worries, he will often be confronted with these unvoiced concerns at the end of the interview. Open ended questions such as “What else?”; “What other problems do you wish to attend to today?”; “What specific requests do you have today?” (eg, prescription refills, referrals, of forms that need completion) are most helpful in eliciting the patient’s entire list of concerns.

Once the physician has a clear picture, she may find it necessary to prioritize concerns and negotiate with the patient how to, and when, to attend to them. Time limitations may prevent covering all issues at that visit.

Incomplete and incorrect agenda-setting is common in the medical interview. Many concerns are not elicited. The doctor and the patient may not agree on the nature of the main presenting problem (this is most common when the chief symptoms is psychological). The clinician may interrupt the patient almost immediately after the interview starts, preventing the patient from fully voicing all concerns.

What the model of a complete interview is not:

- 1) a single chief symptom, 2) further elaboration of the history of the symptom; 3) a family history,
- 4) a personal medical history, 5) a drug and allergy history, and 6) a systems review.

This format does not match the reality of many visits in which patients bring more than one symptom, and want attention and advice about each. The concern the patient considers the most pressing is often not the first-voiced concern. If the concern is psychosocial, it is even less likely to come up first.

“From our patient’s perspective, our cardinal flaw as clinicians consists of neither listening to, nor understanding their issues.”

A practical approach may be to have the medical assistant or nurse start the process by fully eliciting and listing the patient’s agenda before the consultation: 1) What are your main concerns today?; 2) What other concerns do you have?; 3) Do you have any specific needs such as prescription refills, referrals, of forms that need completion? (*Some patients may feel more comfortable with, and be more forthcoming in confiding in, an empathetic nurse.*)

The physician may acknowledge the list and ask again, “Is there anything else?”

Does this take more time? The editorialists say just the opposite. A dysfunctional consultation may end up taking more time.

Even though the clinician’s concerns may have prompted the visit (eg, to check on BP, follow-up on studies), the patient is still the one who decides to come in for that appointment and will probably have additional questions and needs.

If the patient’s list is long, the physician may need to take the lead in prioritizing the list—ie, negotiate with the patient which items will be addressed in the present visit and which may be saved for another time.

If the patient seems to demand more time, the physician may set time limits with a simple apology—“I am sorry I must stop for now. I know it can be frustrating, but I don’t feel right about asking other patients to wait too long.” (*And agree on another time to continue.*)

We should not blame the patient for a defective interview process.

Annals Int Med November 5, 2005; 143: 766-70 “Medical Writings” commentary, first author Laurence H Baker, Foregone Health Sciences University, Portland.

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***W/H Ratio Showed A Graded And More Highly Significant Association With Risk Of MI Than BMI.***

**11-2 OBESITY AND THE RISK OF MYOCARDIAL INFARCTION IN 27 000 PARTICIPANTS FROM 52 COUNTRIES: The INTERHEART Study**

Obesity increases the risk of cardiovascular disease and diabetes. We do not know which measure of obesity (body mass index [**BMI**]), waist circumference, hip circumference, or waist/hip ratio (**W/H ratio**) shows the strongest relation to risk.

This study postulated that markers of central obesity (especially the W/H ratio) would be more strongly related to the risk of myocardial infarction (**MI**) than BMI.

Conclusion: W/H ratio showed a graded and more highly significant association with risk of MI than BMI.

**STUDY**

1. Case-control study entered over 27 000 subjects world-wide.

A. Cases: Over 12 000 subjects with a first MI

B. Controls: Over 14 000 age and sex-matched subjects who did not have an MI.

2. Measured waist and hip circumferences with a non-stretchable tape.

Waist circumference at the abdomen at the narrowest point between the costal margin and the iliac crest.

Hip circumference at the level of the widest diameter around the buttocks.

*(No other descriptions of the protocol of measurement were described except to state that the tape was attached to a spring scale at a tension of 750 g. [ Which I do not understand] I presume measurements were taken in the upright position. Were they taken post prandially? )*

3. Determined associations of BMI and W/H ratio with MI.

RESULTS (For the North America Group)

1.	Cases	Controls	Difference cases vs controls
BMI 25 -29.9	40%	35%	
BMI 30 and over	40%	35%	
Total	80%	70%	10%

High and moderate W/H ratio

> 10/10 in men;

> 9.5/10 in women)

*9.5/10 to 10/10 in men*

*9.0/10 to 9.5/10 in women*

	33%	10%	
Total	60%	28%	32%

*(My estimates from Figure 1 p 1641 and figure 2 p 1642. Note the differences between cases of MI and controls:*

$$\text{High BMI difference} = 80\% - 70\% = 10\%$$

$$\text{High-moderate W/H ratio difference} = 60\% - 28\% = 32\%$$

2. Cases had a strikingly higher W/H ratio than controls. This observation was consistent for all regions of the world.

3. BMI: There was a modest and graded association with MI between quintiles (odds ratio top quintile compared with bottom quintile (1.44). However, when adjusted for other risk factors, odds ratio became insignificant (0.98)

4. W/H ratio: The odds ratios for MI for every successive quintile of the W/H ratio was significantly greater than that of the previous one:

1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	4 <sup>th</sup>	5 <sup>th</sup>
1.00	1.15	1.39	1.90	2.52

5. As quintiles rose from 1 to 5, both waist circumference alone and hip circumference alone were also associated with increasing odds of having a MI The associations were not as strong as for the W/H ratio.

6. The population-attributable risk of MI in the two top quintiles of W/H ratio was 24%.

The population-attributable risk of MI in the top two quintiles of BMI was only 8%.

## DISCUSSION

1. "The INTERHEART study clearly indicates that, of the various anthropometric measures commonly used, the waist-to-hip ratio shows the strongest relation with the risk of myocardial infarction."
2. The ratio was evident across all ages and ethnic groups; in smokers and non-smokers; and in those with and without diabetes, dyslipidemia, and hypertension.
3. "The global burden of obesity has been substantially *underestimated* by the reliance on BMI in previous studies."
4. If a raised W/H ratio were to be used to assess the risk of cardiovascular disease, the proportion classified as obese would increase substantially.
5. "The opposing effects on cardiovascular risk between abdominal and lower-body fat tissue are probably related to different biochemical characteristics of fat in these regions."
6. Previous studies have demonstrated that removal of *subcutaneous* abdominal fat results in large reductions in weight and waist circumference but has no effect on cardiovascular risk factors. By contrast surgical removal of even small amounts of *intra-abdominal* fat (within the peritoneal cavity) results in substantial improvements in oral glucose tolerance, insulin sensitivity, and fasting plasma glucose and insulin despite similar weight loss in controls.
7. Treatment could focus on both 1) loss of abdominal fat, and 2) increase in skeletal muscle mass.

## CONCLUSION

The best anthropometric index of obesity as a predictor of MI is the W/H ratio. It shows a graded and highly significant association with MI risk.

Redefinition of obesity based on waist-to-hip ratio instead of BMI increases the estimate of MI attributable to obesity.

Lancet, November 5, 2005; 1640-49 original investigation by the INTERHEART Study investigators, first author Salim Yusuf, McMaster University, Hamilton, Ontario, Canada.

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*Vitamin D Supplements Are Necessary For Adequate Vitamin D Status In Northern Climates.*

### **11-3 RELATIONSHIP BETWEEN SERUM PARATHYROID HORMONE LEVELS, VITAMIN D SUFFICIENCY, AND CALCIUM INTAKE.**

Recently, higher doses of supplementary vitamin D (*eg, 800 IU*) have been recommended for optimum bone health. The ideal intake is not known.

The serum 25-hydroxyvitamin D (**25-OH-D**) level is the generally accepted indicator of vitamin D status, but no universal consensus has been reached regarding which serum values constitute sufficiency.

This study used the serum parathyroid hormone (**PTH**) level as a marker of sufficiency or insufficiency of vitamin D and calcium. (If vitamin D and calcium levels are insufficient, PTH will be high; if sufficient, PTH will be low.)



Accordingly, the study investigated the relative importance of 1) calcium intake, and 2) serum 25-OH-D levels, as determined by serum PTH levels.

Conclusion: Vitamin D supplements are necessary for adequate vitamin D status in northern climates. Vitamin D is more important than calcium intake to maintain a low (favorable) PTH.

## STUDY

1. Cross-sectional study entered and followed over 900 healthy Icelandic adults.
2. All completed a food frequency questionnaire which assessed vitamin D and calcium intake.
3. Divided participants according to calcium intake:
  - A. Less than 800 mg per day
  - B. 800 to 1200
  - C. Over 1200
4. Further divided according to serum 25-OH-D levels:
  - A. Less than 10 ng/mL
  - B. 10 to 18 ng/mL
  - C. Over 18 ng/mL
5. Main outcome measure = serum intact PTH as determined by calcium and vitamin D intake.

## RESULTS

1. About 60% of subjects were taking vitamin D supplements. (Very popular in Iceland.) Those taking vitamin D supplements had higher serum 25-OH-D levels, especially during the winter months.
2. Serum PTH levels were significantly lower in supplement users. (The higher the serum vitamin D; the lower the PTH—up to a certain point.) At levels of 25-OH-D more than 18 ng/mL no further decrease in serum PTH occurred. Therefore the study used a serum level of 25-OH-D of 18 ng/mL to define vitamin D sufficiency.
4. There was a strong inverse relationship between serum 25-OH-D and PTH levels.
  - A. Only subjects who took supplements maintained a serum level of 25-OH-D above 18 ng/mL during the winter.
  - B. The lowest PTH levels were observed in the group with the highest 25-OH-D (18 ng/mL and above). In this group, the intake of calcium made little difference in the PTH levels. (Ie, when comparing intake of less than 800 mg with over 1200 mg. )
  - B. The highest PTH (least favorable) was observed in the group with 25-OH-D less than 10 ng/mL. In this group, calcium did make a difference in PTH levels. A high calcium intake was associated with lower PTH levels. PTH was higher when the calcium intake was less than 800 mg, and lower when intake was over 1200 gm. (Ie, calcium intake may be more important in persons with lower vitamin D intake.)
  - C. But even in the group with high calcium intake, PTH was higher in those with low 25-OH-D levels, and lower in those with high 25-OH-D levels.

## DISCUSSION

1. PTH is the major hormone maintaining normal serum calcium and phosphorus. It is the principal systemic determinant of bone remodeling. Normally, it is itself regulated through levels of vitamin D and calcium. An insufficiency of either is generally associated with an increase in PTH.
2. The authors comment that other studies have reported that no vitamin D biosynthesis occurs during the winter months at latitudes of 42° north (Boston) and 52° north (Edmonton, Alberta). Iceland is 64° north.
3. “Our results suggest that vitamin D sufficiency can ensure ideal serum PTH values even when the calcium intake level is less than 800 mg/d, while high calcium intake (> 1200 mg/d) is not sufficient to maintain ideal serum PTH as long as vitamin D status is insufficient.”
4. “The significance of our study was demonstrated by the strong negative association between sufficient serum levels of 25-hydroxyvitamin D and PTH with calcium intake varying between 800 mg/d and to more than 1200 mg/d.”
5. High calcium intake does ameliorate the increase in serum PTH that accompanies vitamin D insufficiency, and does permit somewhat lower serum 25-OH-D levels to maintain ideal serum PTH.
- 6 “There is already sufficient evidence from numerous studies for physicians to emphasize the importance of vitamin D status and recommend vitamin D supplements for the general public when sun exposure and dietary sources are insufficient.”

## CONCLUSION

Vitamin D supplements are necessary for adequate vitamin D status in northern climates.

As long as vitamin D status is ensured, calcium intake levels of more than 800 mg/d may not be necessary to maintain calcium metabolism.

JAMA November 9, 2005; 294: 2366-41 Original investigation, first author Laufey Steingrimsdottir, Public Health Institute of Iceland.

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*‘Exercise Restraint and Prudence in Screening Initiation’.*

### **11-4 A 21-YEAR-OLD WOMAN WITH ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE**

The American Cancer Society (2002), the American College of O and G (2003), and the US Preventive Services Task Force (2003) all recommend that cervical cancer screening begin at age 21 regardless of whether the woman is sexually active. *(These recommendations may be changed. RTJ)*

This article describes a 21 year old woman who had a positive PAP smear (atypical squamous cells-undetermined origin—**ASC-US**) at age 21. This entered her into the “medical system” and led to considerable anxiety, and subsequently, over the next 3 years, to 6 PAP smears and colposcopy with a biopsy. No cervical disease was found.

Amazingly, the women became very enthusiastic about cervical screening and advised her friends to have it.

The editorialist makes several appropriate comments:

1) The decision to begin cervical cancer screening is of greater significance than clinicians often appreciate.

Beginning too soon may set in motion a series of interventions and investigations that do not yield a beneficial health outcome.

2) Human papilloma virus (**HVP**):

A. “We live in a society of sexually active people, at least 50% of whom will acquire genital HPV infections in their lifetime.”

B. Cervical-vaginal HPV prevalence is less than 2% before initiation of vaginal intercourse. Prevalence of HPV declines with age: 71% in age 18-22; 31% in age older than 29; 29% in ages over 40.

C. HPV infections often regress spontaneously.

D. Acute HPV infection causes cervical changes that can manifest as low-grade abnormal cytology, but such cytology does *not* indicate the presence of underlying cervical intraepithelial neoplasia (**CIN**).

3) ASC-US and CIN:

A. An abnormal cytology occurs in up to 1 in 6 of sexually active young women.

B. ASC-US is diagnosed in more than 2 million women annually. Many clinicians use ASC-US as the threshold for colposcopy. Colposcopy can be painful and expensive. Cervical excisional treatments have been associated with adverse obstetrical outcomes.

D. Many ASC-US abnormalities will resolve spontaneously and will never be clinically relevant. (Due to the immune response against HPV.) About 10% can be expected to have underlying CIN

E. Some CIN also resolve spontaneously and will never be clinically relevant.

4) Cervical cancer:

A. Cervical cancer prevalence in women under age 20 is one in a million. Squamous cell cervical cancer ranges from 1.3 per 100 000 women age 20 to 24; to 14.8 per 100 000 in women over age 50.

B. Prevention is achieved by removing CIN grades 2 & 3 (high grade dysplasia).

“Young women enthusiastic about cervical cancer screening need to be made aware of the projected benefits and potential harms of screening and treatment.” Screening young women often elicits anxiety and a cascade of clinical interventions of no clinical value. We should . . . “exercise restraint and prudence in screening initiation”. “Just because we can test doesn’t mean we should test. “

Patient’s preferences and values should be integrated into clinical decision about screening. This requires explanation of risks, benefits, and burdens.

Women should be told that cigarette smoking increases risk of CC.

JAMA November 2,2005; 294: 2210-18 “Clinical Crossroads”, commentary by George F Sawaya, Beth Israel Deaconess Medical Center, Boston , Mass

An editorial in this issue of JAMA, first author Paul D Blumenthal, Johns Hopkins University, Baltimore MD comments and expands

CC is unique for several reasons. (*In some ways similar to screening for cancer of the colon by colonoscopy. RTJ*)

There is an identifiable precancerous condition.

The transition from precancer to cancer occurs over an extended period, on average over 10-years.

Screening tests for detecting cancer and pre-cancer are available and are safe and effective. They can be done on outpatients.

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***There Is A Single Root Cause Of Cervical Cancer Is the Venerable PAP Test Outdated?***

**11-5 THE PROMISE OF GLOBAL-CERVICAL-CANCER PREVENTION**

Cervical cancer (CC) remains a leading form of cancer among women in low-resource regions of the world. It often kills women at young ages, when they are still raising families.

At present, screening is unavailable or underfunded in many parts of the world.

*Single* cytological screenings are insensitive and do not provide sustained reassurance with regard to risk of CC.

Promising new prevention strategies are based on improved knowledge of the pathogenesis of CC. *Persistent* cervical infection with one of approximately 15 types of human papilloma virus (HPV) causes virtually all cases of CC as well as the preceding changes which are evident on cytological and visual examination.

“Because there is a single root cause of cervical cancer, we can envision both primary prevention through vaccination against HPV in young women, and secondary preventive screening directly for carcinogenic HPV in older women.”

“HPV DNA testing is more sensitive and the results more easily reproducible than cytologic screening and colposcopy for the detection of extant and incipient cervical precancerous conditions and cancer.”

A negative test for carcinogenic HPV types provides a degree and duration of reassurance not achievable by any other diagnostic method.

We can target the optimal age at which screening should be performed; determine the most cost-effective testing intervals; which HPV types to screen for (strongly carcinogenic vs weakly carcinogenic); and the threshold of viral loads (very low loads only minimally raise the risk).

Because of the greater accuracy of HPV DNA, screening should be focused on reaching women at the time of the peak risk of treatable precancerous conditions, and before the average age at which incurable invasive CCs occur. Screening women once at age 35, or twice at ages 35 and 40 with current HPV DNA tests targeting 13 carcinogenic types can achieve more cost-effective reductions in cancer than can conventional cytological methods.

It is not necessary to detect *transient* HPV infection or the associated mild pathological or visible epithelial abnormalities of *young* women among whom acute and resolving HPV infections are extremely common in the decade after initiation of sexual activity.

The peak prevalence of transient infections occurs among women during their teens and 20s, after the initiation of sexual activity. The peak prevalence of cervical pre-cancerous lesions occurs about 10 years later; the peak prevalence of invasive CC at age 40 to 50. The conventional model of CC prevention is based on repeated rounds of cytological examinations and colposcopy. Alternative strategies include HPV vaccination of

adolescents, or one or two rounds of HPV screening at the peak ages of treatable precancerous lesions and early cancer.

HPV DNA tests are now being developed into rapid, robust, easy-to-use formats. This will allow one-visit “screen and treat” strategies.

Women who are HPV negative can be considered at low risk.

Those who are HPV positive can undergo further assessment with visualization of the cervix to determine the appropriate management. Most can be treated with cryotherapy which is easy to perform on site.

Only women with severe or extensive precancerous conditions or obvious cancer that is not treatable with cryotherapy need be referred to specialist care.

Vaccines against HPV types 16 and 18 have been shown to have very high efficacy against new, persistent infections. (These types account for 70% of CCs.) Because vaccination is not designed to treat infection once it has occurred, women would have to be vaccinated at a young age. (eg, age 15, before sexual activity begins.)

NEJM November 17, 2005; 353: 2101-04 “Perspective”, editorial first author Mark Schiffman, National Cancer Institute, National Institute of Health, Bethesda MD.

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*“No Single Element Of Chest Pain History Is A Powerful Enough Predictor Of Non-ACS To Allow the Clinician To Make Decisions According To It Alone.”*

#### **11-6 VALUE AND LIMITATIONS OF CHEST PAIN HISTORY IN THE EVALUATION OF PATIENTS WITH SUSPECTED ACUTE CORONARY SYNDROMES**

Despite diagnostic advances, missed acute coronary syndromes (ACS) and acute myocardial infarctions (AMI) remain problematic. The diagnosis is missed in 2% to 10% of patients.

Conversely, a large proportion of patients with chest pain who are admitted do *not* turn out to have an ACS. This has enormous economic implications.

Distinguishing ACS from non-ACS is at best difficult.

The differential diagnosis of chest pain is broad and includes many systems (pulmonary, musculoskeletal, gastrointestinal, psychiatric, and cardiovascular). In addition to ACS, the differential includes other immediately life-threatening diseases (pulmonary embolism, tension pneumothorax, aortic dissection) necessitating rapid diagnosis and treatments that differ markedly from those of ACS.

The chest pain history is a readily available tool to help guide disposition of patients with chest pain. It must be used in conjunction with other markers to determine disposition. (This also recognizes that AMI and ACS may present with non-pain symptoms, or may truly be silent.)

This study, a literature review, attempts to identify components of the chest-pain history which may be helpful.

Conclusion: Although certain elements of the chest-pain history are associated with increased (or decreased) likelihood of a diagnosis of ACS or AMI, none alone, or in combination, can be entirely reliable.

## STUDY

1. A search of MEDLINE and OVID 1970 to 2005 used a large number of specific key words and medical subject headings.
2. Reviewed prospective and retrospective observational studies as well as systematic reviews.
3. Included studies if they described the characteristics of pain, and if the diagnosis of AMI and ACS was made (or ruled out) with appropriate diagnostic tests.
4. Determined the likelihood that the symptom would be associated with ACS. (The ratio of patients with ACS who have a characteristic of pain to patients without ACS who have the same type of pain—true positive tests/false positive test—the positive likelihood ratio)

## RESULTS

### 1. Chest pain characteristics related to likelihood of ACS:

#### A. Quality of pain:

- 1) Pressure and aching descriptions have yielded conflicting findings. These descriptors predict ACS weakly or not at all.
- 2) Sharp and stabbing more powerfully differentiates non-ischemic from ischemic pain.
- 3) Pain that is worse than previous angina or MI is likely to be associated with recurrence.  
(Note that there are cultural differences in describing quality and severity of pain.)

#### B. Location of pain:

- 1) One study concluded that central or midchest pain has little value for predicting AMI.  
Pain arising in the esophagus is typically retrosternal.
- 2) The same authors found that pain in the inframammary region was more common in patients without AMI, although differences may be too small to be useful.
- 3) Many studies have reported that the myocardial region of an AMI is not associated with differences in location of pain. However, inferior AMI more often is associated with abdominal pain and GI symptoms.

#### C. Radiation:

- 1) Classically, pain of AMI radiates from the chest to shoulders and arms.
- 2) One study reported that of every 5 patients with such pain, one did not have an AMI.

#### D. Size of area of chest pain:

- 1) In one study, 7% of patients with AMI localized their pain to a point or the size of a coin.

#### E Severity of pain:

- 1) Several studies of severity of pain of consecutive patients admitted with chest pain found no statistical difference between severity in those without AMI as in those with AMI.

#### F. Time variables:

- 1) Classically, AMI pain is described as having a crescendo pattern, reaching maximal intensity only after several minutes.

- 2) One authority stated that pain that is maximal in intensity at onset is *not* likely to be due to cardiac ischemia.
- 3) In contrast, pain of aortic dissection is most often abrupt and “severe” from onset.
- 4) Classically, the pain of angina lasts 2 to 10 minutes. Over 10 to 30 minutes suggests unstable angina. Pain over 30 minutes indicates either AMI or non-ischemic pain (especially gastroesophageal pain).

G. Precipitation and aggravating factors. (The 3 p’s):

- 1) Pleuritic: (associated with cough or deep breathing) is often associated with non-ACS diseases (pulmonary embolism; costochondritis)
- 2) Positional: pain exacerbated by changes in position is more indicative of non-ACS causes. Pericarditis is often alleviated by leaning forward. Musculoskeletal pain is typically reproduced by movement.
- 3) Palpable chest pain: Tenderness suggests non-cardiac pain.

F. Exercise:

- 1) The relation between exertion and angina is classical. The relation with AMI is less clear. Among AMI patients, heavy exertion before onset has been reported frequently.

2. Relieving factors:

- A. Nitroglycerin relieves anginal pain, but also may relieve esophageal spasm and pain.
- B. “GI Cocktail” administration (usually a mixture of lidocaine, a liquid antacid, and anticholinergics-sedative such as *Donnatal*) has been common practice to differentiate esophageal from cardiac pain. Recent studies have not supported this effect.
- C. Rest characteristically relieves stable angina pain within 5 minutes. Pain continuing longer than 10 minutes after rest has traditionally been considered to be associated with ACS. It may also occur in patients with non-cardiac pain.
- D. One study reported that 50% of patients with esophageal pain experienced relief by rest.

3. Combinations of characteristics of chest pain history to formulate low-risk groups.

- A. “No single element of chest pain history is a powerful enough predictor of non-ACS or non-AMI to allow the clinician to make decisions according to it alone.” Protocols combining various elements of pain to improve triage decisions have either not been validated or have demonstrated mixed results.
- B. One study identified variables that defined a very low risk for AMI: sharp, stabbing; positional; pleuritic; reproducible with palpation.
- C. Combination protocols have yet to prove successful when implemented in the clinical setting.

4. Despite limitations, the chest pain history, when interpreted in the light of the existing literature, allows the clinician to establish approximate probabilities for acute cardiac ischemia.

5. Overall, the likelihood ratios of positive tests (the presence of an individual descriptor of pain) varies from 0.2 to 4.7. That is, the discomfort described can be present in 2 out of 12 patients with AMI. Or can be present in 5

out of 6, not robust enough to be independently useful in establishing a diagnosis. There will always be patients without ACS who have discomfort similar to that of patients with ACS..

## Conclusion

“No single element of the chest pain history conveys a powerful enough likelihood ratio to allow the clinician to safely discharge a patient without some additional testing.”

JAMA November 23/30 2005; 294: 2623-29 “Clinical Review”, systematic review, first author Clifford J Swap, Massachusetts General Hospital, Boston Mass.

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**“Overall The Inhaled Insulin Approach Seems Effective And Safe.”**

### **11-7 INHALED INSULIN IMPROVES GLYCEMIC CONTROL WHEN SUBSTITUTED FOR OR ADDED TO ORAL COMBINATION THERAPY IN TYPE 2 DIABETES.**

Traditional treatment of type 2 diabetes (**DM2**) generally involves initiation of oral hypoglycemic therapy if lifestyle measures are not effective. Once insulin secretory capacity becomes insufficient, good control with oral agents will not be achieved. These patients then must receive insulin to reduce the risk of complications. This usually involves addition of basal insulin (24-hour) therapy to oral agents.

The optimum strategy for insulin add-on therapy is yet to be determined. Both patients and physicians are reluctant to initiate subcutaneous insulin.

This study examined the effect of a preparation of inhaled, dry-powdered human insulin (*Exubera*) which is currently in development. Does inhaled insulin improve glycemic control when taken alone, or when added to oral agents?

Conclusion; Inhaled insulin improved glycemic control and hemoglobin A1c levels when added to, or substituted for oral agents.

## STUDY

1. Open label parallel-group followed over 300 patients with DM2 (mean age 57; mean BMI = 30).

All were receiving two oral antidiabetes medications (predominantly a sulfonylurea and metformin).

All had a HbA1c of 8% or greater (mean = 9.5%). All were considered to have failed on dual oral therapy.

None had significant respiratory disease. None were smokers.

2. Randomized to:

A. Inhaled insulin alone given 3 times daily before meals.

B. Inhaled insulin + continued oral agents

C. Oral agents alone.

3. The inhaled insulin delivers aerosolized powdered insulin to the small airways and alveoli. This enables rapid absorption. Its effect lasts 4 to 6 hours.

(An illustration of the insulin delivery system is on page 551.)



3. Blood glucose levels were monitored before each meal and at bedtime. Doses of insulin were adjusted accordingly.
4. Primary efficacy endpoint = change in HbA1c. Secondary efficacy endpoints = changes in fasting blood glucose and 2-hour postprandial glucose, and % of patients achieving HbA1c below 8%.
5. Follow-up = 3 months.

## RESULTS

1. HbA1c reduction compared with oral agents alone:
  - A. Inhaled insulin alone = -1.18 %
  - B. Inhaled insulin + continued oral agents = - 1.67 %
2. HbA1c levels less than 7%:
  - A. Inhaled insulin + continued oral agents = 32%
  - B. Oral agents alone = 1%.
3. In the insulin groups, fasting glucose and 2-hour postprandial glucose mean levels improved by up to 50 mg/dL and 75 mg/dL. Triglyceride levels improved by 40 to 54 mg/dL
4. Adverse effects:

Hypoglycemia occurred at a rate of 1.3 to 1.7 episodes per month in the insulin groups; 0.1 in the oral agents-alone group. One severe episode in the insulin-alone group. No patient discontinued insulin due to hypoglycemia.

Cough was more common in the insulin groups. It was generally mild and decreased in incidence and prevalence during the trial. No patients discontinued for this cause.

Pulmonary function tests remained similar in all 3 groups.

Insulin antibodies increased in the insulin groups There were no associated allergic events. Glycemic control was not affected.

Weight: Mean body weight increased in the insulin groups over 3 months ( + 6 pounds); did not change in the oral-alone group.

Withdrawals were similar in all 3 groups (about 6%--none due to adverse events).

## DISCUSSION

1. Previous investigations reported that inhaled insulin can be used to maintain glycemic control for at least 4 years.
2. "Inhaled insulin is an effective agent to improve glycemic control on the basis of hemoglobin A1c level, fasting and postprandial glucose levels and triglyceride levels." "Premeal inhaled insulin therapy provides better glycemic control and more frequently achieves target hemoglobin A1c levels, and is well-tolerated over 3 months."
3. Its value seems greater when combined with oral agents.

4. Inhaled insulin was available in 1-mg and 3-mg blister packs. (One mg = about 3 U of a standard subcutaneous insulin dose.) Patients can attain a relatively stable insulin dose by week 4. Titration should proceed cautiously.
5. Previous studies reported that inhaled insulin is associated with greater patient satisfaction compared with subcutaneous insulin.

## CONCLUSION

Inhaled insulin improved glycemic control when added to, or substituted for, oral therapy.  
Hypoglycemia and weight gain occurred.  
Pulmonary function was not affected.

Annals Int Med October 18, 2005; 143: 549-58 Original investigation, first author Julia Rosenstock, Dallas Diabetes and Endocrine Center, Dallas TX

An editorial in this issue of the Annals (pp 609-10 ) by Richard J Comi, Dartmouth Hitchcock Medical Center, comments and expands:

Successful treatment of the central issues in therapy of DM2—hyperglycemia and obesity—is difficult, elusive and enigmatic. Lifestyle change is difficult. Increasing exercise and reducing weight remain the cornerstones of management. Most pharmaceutical agents cause weight gain. Faced with obese patients with failing glucose control, clinicians must decide whether a further reduction in glucose of 10 to 20 mg/dL is worth another 10 pounds of weight gain.

Poor lifestyle choices continue to undo the benefits of our treatments. “Sustaining the changes in behavior that are required to improve diet and exercise is exceedingly difficult for patients

The choice of the study treatments surprised the editorialist. Given the pharmacokinetic properties of inhaled insulin, physicians would seldom choose it for patients whose oral therapy is failing. Few clinicians add a rapid acting insulin under these circumstances. Most would add a long-acting (24-hour) insulin. Few clinicians would prescribe insulin that targets postprandial glycemia without also prescribing a long-acting insulin.

Inhaled insulin appears to be more potent than injected insulin. The dose was equivalent to 3 to 9 units per meal. Obese patients (as in the study) often require much larger doses of injected insulin.

“Overall the inhaled insulin approach seems effective and safe.”

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*No Difference in Cardiovascular and All-Cause Mortality.*

## **11-8 HIGH-DOSE ATORVASTATIN VS USUAL-DOSE SIMVASTATIN FOR SECONDARY PREVENTION AFTER MYOCARDIAL INFARCTION The IDEAL Study**

Statins are part of the standard treatment regimen after myocardial infarction (MI). Incremental benefits have been demonstrated with intensive lowering of LDL-cholesterol (LDL-c) among patients with the acute coronary syndrome (ACS). The National Cholesterol Education Program now recommends a LDL-c level less than 70 for patients at very high risk of ACS.

The IDEAL study hypothesized that intensive lowering of LDL-c with atorvastatin (*Lipitor*) at the highest recommended dose would yield incremental benefits compared with the usual recommended dose of simvastatin (*Zocor*).

Conclusion: Intensive lowering of LDL-c with atorvastatin did *not* result in a significant reduction in the primary outcome of major coronary events. It did reduce risk of other secondary outcomes and non-fatal MI. There was no difference in cardiovascular and all-cause mortality.

## STUDY

1. Prospective, randomized, open label, multicenter trial enrolled over 8500 patients (mean age = 61).

All had a history of acute MI. (*This is a secondary preventions study.*)

2. Randomized to 1) atorvastatin 80 mg daily, or 2) simvastatin 20 mg daily. The dose of simvastatin could be increased if the total cholesterol remained over 190 mg/dL. The dose of atorvastatin could be decreased to 40 mg if any adverse events occurred, or if the LDL-c decreased below 39 mg/dL.

All subjects received dietary counseling.

3. Main outcome = occurrence of a major coronary event (coronary death, non-fatal MI, or cardiac arrest with resuscitation).

4. Follow-up = mean of 4.8 years.

## RESULTS

1. During treatment, mean LDL-c levels were 104 mg/dL in the simvastatin group and 81 mg/dL in the atorvastatin group.

2. Over 4.8 years:	Atorvastatin (n = 4439)	Simvastatin (n = 4449)	Absolute difference	NNT*
Major cardiac event	9.3%	10.4%	1.1%	90**
Non-fatal acute MI	6.0 %	7.2%	1.2%	

(\* Number needed to treat for 5 years to benefit one patient.)

(\*\* not statistically significant)

Major cardiovascular events	12%	13.6%	1.6	62
Any coronary event	20%	23.8%	3.8	26
Non-cardiovascular death	3.2%	3.5%		
Death from any cause	8.2%	8.4%		

3. Adverse effects: Adverse event resulting in permanent discontinuation were more common in the atorvastatin group (9.6% vs 4.2%). Transaminase elevation in 1% vs 0.1%. Serious myopathy and rhabdomyolysis were rare in both groups.

## DISCUSSION

1. There was no significant difference between groups in the prespecified primary endpoint. There were statistically significant reductions in the atorvastatin group in non-fatal MI, and any cardiovascular event.

2. No difference in all-cause or cardiovascular mortality.
3. “More intensive lowering of LDL-c than usual in patients with previous myocardial infarction might prevent 68 first cardiovascular events per 1000 patients over 5 years.”

## CONCLUSION

When standard vs intensive LDL-c lowering was compared in patients with past MI (high risk) there was no statistical difference in cardiovascular and all-cause mortality. There was a reduction in other composite secondary endpoints and non-fatal MI.

JAMA November 4, 2005; 294: 2437-45 Original investigation by the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study group, first author Terje R Pedersen, Ulleval University Hospital, Oslo, Norway.

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### *A Public Health Intervention Producing Remarkable Benefits.*

#### **11-9 LEGISLATION FOR SMOKE-FREE WORKPLACES AND HEALTH OF BAR WORKERS IN IRELAND: Before And After Study**

In March 2004, The Republic of Ireland introduced a comprehensive smoke-free law covering all indoor workplaces. This created a natural experiment for identifying effects of the ban.

This study compared exposure to secondhand smoke and respiratory health in bar staffs before and after the law was passed.

Conclusion: The smoke-free law protected non-smoking bar workers from exposure to secondhand smoke and reduced respiratory symptoms.

## STUDY

1. Enrolled staff working in pubs in the Republic (n = 111) six months before the smoking ban went into effect.  
The study considered non-smokers only.
2. Followed the cohort for one year after to assess changes in exposure to secondhand smoke and symptoms.
3. Measured saliva cotinine (a metabolite of nicotine).
4. Also recorded self-reported exposure to secondhand smoke at work.
5. Used a questionnaire to get information on symptoms of respiratory and sensory irritation.

## RESULTS

1. Cotinine concentrations fell by 71%. Levels fell in 106 of 111 subjects
2. Self reported exposure to secondhand smoke was high before the ban, with smoke at work accounting for by far the greatest exposure. Exposure fell from 40 hours a week to zero.
3. Exposures outside of work also fell.

4. At baseline, 65% reported one or more respiratory symptoms. This dropped to 49% on follow-up. Fewer reported cough and production of phlegm, red eyes, and sore throat.

## CONCLUSION

The ban in smoking protected non-smoking bar workers from exposure to secondhand smoke. It reduced cotinine levels and reduced respiratory symptoms.

BMJ November 12, 2005; 331: 1117-20 Original investigation, first author Shane Allwright, University of Dublin, Republic of Ireland.

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### *The Basic DASH Diet Modified By Increased Protein and Monounsaturated Fat Improved BP and Lipid Levels*

#### **11-10 MORE NOVEL EFFECTS OF DIET ON BLOOD PRESSURE AND LIPIDS:**

#### **Results of the OmniHeart Randomized Trial “Effects of Protein, Monounsaturated fat, and Carbohydrate Intake on Blood Pressure and Serum Lipids”**

Dietary Approaches to Stop Hypertension (**DASH**) study<sup>1</sup> demonstrated that, in patients with prehypertension and stage 1 hypertension, a diet modestly reduced in salt content coupled with fresh fruits, vegetables, and low-fat dairy products could lower BP. Subsequent DASH diet studies comparing varying salt intakes (usual, modestly reduced, and greatly reduced) provided evidence of a graded influence of dietary salt restriction on BP.

This issue of JAMA presents the OmniHeart randomized trial<sup>2</sup> which represents the latest effort by members of the DASH Trials group to examine the effect of varying protein, monounsaturated fat, and carbohydrate intakes on BP.

The Trial recruited subjects with BP 120-159/80-99. It used a complex crossover design which continued the basic DASH diet and modified it to contain:

- A. 58% of kcal as carbohydrate, or
- B. 25% of kcal as protein, or
- C. 37% of kcal as monounsaturated fat (olive oil, canola oil, safflower oil).

The total calorie content was designed to avoid weight loss.

## RESULTS

1. The high carbohydrate diet was associated with the least reduction in BP and the smallest improvements in lipids.
2. Compared with the carbohydrate diet, the high protein decreased systolic by 3.5 in those with hypertension, decreased LDL-c by 3.3 mg/dL and decreased triglycerides by 15.7 mg/dL, but *decreased* HDL-c by 1.3 mg/dL

3. Compared with the carbohydrate diet, the high monounsaturated fat diet decreased systolic in those with hypertension by 2.9; had no significant effect on LDL-c; *increased* HDL-c by 1.1 mg/dL, and lowered triglycerides by 9.6 mg  
(Overall the high monounsaturated diet seemed to produce the greatest benefit with the least adverse effects.)
4. Adverse effects: The protein diet was associated with poor appetite, bloating and fullness to a greater extent than the other 2 diets.
5. The authors suggest that a basic DASH diet modified by increased protein and monounsaturated fat content improved BP and lipid levels and reduced risk of estimated cardiovascular disease.

JAMA November 16, 2005; 294: 2497-98 Editorial by Myron H Weinberger, Indiana University Medical Center, Indianapolis.

- 1 “Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet NEJM 2001; 336: 344-10
  - 2 “Effects of Protein, Monounsaturated Fat, and Carbohydrate Intake on Blood Pressure and Serum Lipids JAMA November 16, 2005; 294: 2455-64 The OmniHeart Randomized Trial
- A “News” commentary in BMJ December 17, 2005; 331: 1425 comments: “Smoke from Cigarette Tip is More Toxic Than Main Inhaled Smoke”

Unpublished research from studies by the cigarette industry as far back as 1980 indicated that inhaled “sidestream” smoke (the smoke that rises from the burning tip of the cigarette between puffs) is more toxic than “mainstream” smoke (smoke inhaled by the smoker). Inhaled sidestream smoke makes up about 85% of secondhand smoke.

The journal *Tobacco Control* (2005; 14: 396-404) described research conducted by *Phillip Morris Tobacco*. The research was done in Germany at the secret *Institut fur Biologische Forschung*. The research showed that sidestream smoke caused 2 to 6 times more tumors in animals than mainstream. Sidestream smoke was about 4 times more toxic per gram when painted on the skin of mice. It inhibited weight gain in developing animals, and at low levels caused damage to their respiratory epithelium.

Sidestream from filtered “light” cigarettes was significantly more toxic than that from full flavored cigarettes.

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***Coffee Lovers—Be Reassured. Cola Drinkers—Some Reason For Concern***

### **11-11 HABITUAL CAFFEINE INTAKE AND THE RISK OF HYPERTENSION IN WOMEN**

Much clinical lore about the possible association between caffeine intake and the risk of hypertension is available. Some have reported an increased risk. But studies have been limited by short observation periods. Information about prolonged, regular intake is not available.

If indeed there were a relationship, the public health implications would be considerable.

This study prospectively examined the association between caffeine intake and incident hypertension in a large cohort of women over many years.

Conclusion: Habitual caffeine consumption was *not* related to incident hypertension. Consumption of sugared and diet cola was associated with development of incident hypertension.

## STUDY

1. The Nurses' Health Study (I and II), which began in 1976 and 1989, entered over 155 000 middle-aged women and followed them for a mean of 12 years. All were free from physician-diagnosed hypertension at baseline.
2. Ascertained caffeine intake by regularly administered food frequency questionnaires which included the types of caffeinated beverages. Calculated the total caffeine intake from US Department of Agriculture food composition sources. It assumed the caffeine content;

One cup of coffee            137 mg

One cup of tea                47 mg

Can of cola                    46 mg

3. Main outcome measure = incident physician-diagnosed hypertension.

## RESULTS

1. During follow-up, over 33 000 cases of hypertension were reported.
2. No linear association between caffeine intake and hypertension was observed.
3. Adjusted relative-risk of hypertension:
  - A. Caffeine consumption: Those in the third quintile had a 13 % increased risk of hypertension. Interestingly, those in the 4<sup>th</sup> and 5<sup>th</sup> quintiles were not at increased risk –an *inverse U-shaped* curve.) Trend was non-linear.
  - B. Caffeinated coffee consumption: No increase in the risk between quintiles. Actually, those in the 4<sup>th</sup> and 5<sup>th</sup> quintile had a lower risk than those in the 1<sup>st</sup> quintile.
  - C. Decaffeinated coffee: Similar to caffeinated.
  - D. Sugared caffeinated cola: There was a definite linear increase in incidence of hypertension with increasing intake between quartiles—highest quartiles had 28% to 44% higher risk.
  - E. Diet caffeinated cola: also a linear trend with increasing intake—highest quartiles had 16% to 19% greater risk.

## DISCUSSION

1. In two large cohorts of women, caffeine intake was associated with a modest inverse U-shaped association with hypertension. The magnitude of the highest relative risk was 1.13. Risk fell as consumption rose. (I.e, a non-linear trend.)
2. Neither caffeinated nor decaffeinated coffee demonstrated a positive association with incident hypertension. “We found strong evidence to refute speculation that coffee consumption is associated with increased risk of hypertension in women. “

3. There was, however, a highly significant and consistent association between cola intake (sugared and non-sugared) and incident hypertension. (Both containing caffeine.) “Hence, we speculate that it is not caffeine, but perhaps some other compound contained in soda-type soft drinks that may be responsible for the increased risk in hypertension.” If these associations are causal, they may have considerable impact on public health.

## CONCLUSION

Caffeine consumption does not appear to increase risk of incident hypertension.

Consumption of coffee (caffeinated and decaffeinated) does not appear to increase risk of developing hypertension.

Caffeinated soft drink (sugared and diet) appear to be associated with increased risk of hypertension. Whether the association is causal will require further study.

JAMA November 9, 2005; 2330-35 Original investigation from the Nurses’ Health Study, first author Wolfgang C Winkelmayr, Brigham and Women’s Hospital, Boston Mass.

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