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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

Richard T. James Jr. M.D.

Editor/Publisher.

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It Is Time To Move Beyond The Binary Diagnostic Thinking That Has Dominated Medicine For So Long

8-1 AGAINST DIAGNOSIS

The concept of diagnosis is essentially binary. You either have a certain disease, or you do not.

Consider cardiovascular disease, type 2 diabetes, depression, obesity, autism, back pain, arthritis, cancer, and HIV. The authors contend that all except HIV are continuous, reflecting a range of severity. Categorizing patients as having, or not having, the disease depends on choosing a somewhat arbitrary cut point of severity. The definition of hypertension currently includes a systolic pressure of 140 or higher. But there is no particular biological relevance of 140 such that individuals with a BP of 141 differ qualitatively from those with a BP of 139.

The authors propose that thinking about disease in terms of risk prediction is often superior to thinking about disease in terms of diagnosis. The risk prediction alternative uses a statistical model to estimate the probability that a patient will have a clinically important event within a certain period.

Prediction models have 2 particular advantages over our standard way of thinking about diagnosis:

1) They take into account patient preferences
2) They can incorporate multiple patient characteristics

The risk prediction model is not new. Physicians have traditionally called on multiple variables to risk-stratify patients, usually weighing each variable on the basis of clinical judgment and experience. Many diseases include some measure of risk stratification. The use of prediction models adds a quantitative estimate to group patients according to risk, and to aid physicians’ process of risk adjustment. Prediction models give physicians explicit information to use in shared decision making with patients.

Despite the provocative title of this perspective, the authors are not against diagnosis. There are many diseases which are either present or absent. A patient has syphilis or does not. The harms of untreated syphilis cannot seriously be compared with those of penicillin.

Prediction modeling may be more difficult to implement than the diagnostic approach. It is easier to classify patients as having hypertension or not, and to prescribe treatment accordingly, than to enter BP into a calculation of a predicted risk, explain to the patient what this risk means, and then make a shared decision about treatment.

Prediction depends on the availability of a good model. Most models have been evaluated only with regard to their accuracy. Whether use of a model, even a relatively accurate one, would improve an outcome is not entirely clear.

Nonetheless, an approach based on risk prediction can be of great value for many diseases of greatest concern in industrialized countries. Many disorders are best suited for a risk prediction approach. Classification of these complex disorders exists on a continuum perhaps best understood in terms of risk for associated outcomes.

It is time for us to move beyond the binary diagnostic thinking that has dominated medicine for so long and embrace a quantitative approach.
I enjoyed this article.

I believe most primary care clinicians do consider risk prediction. During a consultation, however, primary care clinicians may concentrate on one risk factor and neglect others.

Most patients do not understand the concept. Patients tend to concentrate on one factor (e.g., cholesterol, BP).

It takes more time to approach patient care from the aspect of risk prevention. In this medical era, prevention and lowering risk of chronic disease predominates. Patients must understand that their health depends on consideration of many risk factors, and respond by treating all of them.

Reducing all risk factors as much as possible, even if the cutpoint is not reached, will likely reduce risk more than treating one factor and reaching its cutpoint.

One of the greatest challenges for primary care is to get patients to take charge of their own health. by reducing lifestyle risk factors. Patients need not improve their lifestyles to a cutpoint. I believe small improvements in diet, BMI, physical activity and adherence to medications when added, will improve prognosis despite not reaching target levels. The exception is smoking. It is either a yes or no risk.

During each consultation, in addition to attention to the primary complaint, primary care clinicians will benefit the patient by briefly listing their lifestyle risk factors as time and the situation permit.

Is spiritual care always an important part of medical care? If yes, who should assess the need for it?

Because spirituality is not usually based on human-made laws of reason or logic, it is often described as the non-logical or non-rational part of being human that connects to the sacred—God, the Ultimate, or Universal Principle. The spiritual transcends ordinary human experience. Spirituality is part of what it means to be human.

The healing art of medicine includes, and goes beyond, the science and takes into account what gives a person meaning—his or her loves, priorities, beliefs, fears, dreams, and questions.

The practice of medicine, at its finest, involves far more than knowing the right science; it involves working with the whole person and not just a diseased body part.

For many patients, faith in the supernatural (i.e., spirituality) is important—in health and especially in illness. Faith gives meaning to their lives. It provides comfort when their lives are not going well, and it remains when other resources are spent. Faith can support when support is most needed.

At times of vulnerability because of illness many patients want their physician to know what gives them meaning, comfort, and support. Spirituality is an important part of medical care, especially when patients are very ill or dying.
Each physician has his or her own spirituality that gives meaning to life. Although physicians might not believe in a personal God, they might believe in something. It is good for physicians to be cognizant of their own spirituality,

Although physicians do not need to deliver spiritual care, asking questions to discern the spiritual needs of their patients might be in the best interest of both.

Addressing spiritual matters with patients offers a meaningful opportunity to primary care clinicians. Many physicians, especially younger ones, have difficulty in discussing spiritual matters with their patients. Maturity makes it easier. A simple leading question or statement (Are you at peace?) may broach the subject and make it possible for patients to express their inner thoughts, and bring comfort.

Low Concentrations Were Associated With Higher Risk Of Hip Fracture.

8-3 SERUM 25-HYDROXY VITAMIN D CONCENTRATIONS AND RISK FOR HIP FRACTURE

This study tested whether low serum levels of 25-hydroxy vitamin D \(25(\text{OH})\text{D}\) are associated with higher risk of hip fracture.

The study population came from the large Women’s Health Initiative Study (1994-98), which was limited to women age 50 to 79 at baseline. All were postmenopausal. All were community dwelling.

Measured total \(25(\text{OH})\text{D}\) in all subjects. \((D2 + D3)\)

Followed all for a median of 7 years for incident hip fracture. Of the over 39 000 eligible women, 404 developed a hip fracture during follow-up.

Cases = 400 women randomly selected from the 404 who sustained a hip fracture during follow-up.

Controls = 400 women without hip fracture randomly selected and carefully matched.

(Mean age = 71. None had taken estrogen or other bone-active therapies at baseline.)

Compared \(25(\text{OH})\text{D}\) levels in cases and controls.

Mean serum \(25-\text{OH-D}\) levels were lower in cases than in controls \((56 \text{ nmol/L vs } 60 \text{ nmol/L})\)

Divided \(25(\text{OH})\text{D}\) levels into quartiles and determined odds ratio of hip fracture of the lowest quartile vs the highest:

<table>
<thead>
<tr>
<th>(25(\text{OH})\text{D})</th>
<th>Lowest Q</th>
<th>Highest Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-48 nmol/L</td>
<td>71-122 nmol/L</td>
<td></td>
</tr>
</tbody>
</table>

Odds ratio of hip fracture 1.72 1.00 (reference)

The increased risk for hip fracture was primarily confined to women with the lowest \(25(\text{OH})\text{D}\) concentration.

Conclusion: Low \(25(\text{OH})\text{D}\) levels were associated with an increased risk for hip fracture in elderly community dwelling women. Lower serum levels might help identify women at high risk for hip fracture.

This is particularly applicable to primary care because so many patients are deficient.
Recent reports of adverse effects of vitamin D deficiency have been astounding. Practical Pointers has abstracted a number of articles related to vitamin D deficiency over the past few years.

Some authors have linked deficiency to a variety of conditions: breast cancer, colon cancer, rheumatoid arthritis, cardiovascular disease, diabetes, hypertension, multiple sclerosis, muscle weakness, falls, mortality, and premenstrual syndrome, as well as osteoarthritis, osteoporosis, osteopenia. Almost all are speculative and require follow-up and confirmation.

See Practical Pointers:
- 2008 January [1-7]
- 2007 July [7-1]; February [2-4]
- 2006 February [2-4]
- 2005 March [3-8]; May [5-3]; June [6-14]; November [11-3];

Vitamin D supplementation must have one of the highest benefit/harm-cost ratios of any medication. The cost is very low and the harm nil.

Primary care clinicians are increasingly obtaining vitamin D serum levels in their patients. I believe an alternative for many patients would be to assume the level is low and empirically prescribe supplementation. Dose should be at least 800 IU daily with added calcium.


This study was based on the National Health and Nutrition Examination (1988-94), a nationally representative group of adults 20 years of age and older. Serum vitamin D levels were determined at baseline.

During followed for mortality for a median of 9 years, there were 1806 deaths.

Compared with the highest quartile of vitamin D, the lowest quartile (< 18 ng/mL) experienced a 26% increase in death compared with the highest quartile.

Does Not Increase Risk Of Diverticulitis And Diverticular Bleeding

8-4 NUT, CORN, AND POPCORN CONSUMPTION AND THE INCIDENCE OF DIVERTICULAR DISEASE

Historically, physicians have advised individuals with diverticulosis to avoid nuts, seeds, popcorn, corn and other high-residue foods. The recommendation comes from the theory that luminal trauma is a causal mechanism for both diverticulitis and bleeding. Stool may lodge within a diverticulum, obstruct the neck, or abrade the mucosa, and precipitate inflammation or bleeding. Nuts and the other foods are presumed to be particularly likely to abrade the mucosa or to lodge within small diverticula.

This study determined whether consumption of nuts, corn, of popcorn is associated with complications of diverticulosis. It included over 47 000 men aged 40 to 75 who were free of diverticulosis or its complications at
baseline. All returned a food-frequency questionnaire which included average frequency of consumption of nuts, corn, and popcorn.

Frequency categories for total consumption of these foods were collapsed into 4 categories: 1) less than once a month, 2) 1 to 3 times a month, 3) once a week, and 4) 2 or more times per week. (27% of participants reported eating nuts at least twice a week.)

During 18 years of follow-up, there were 801 incident cases of diverticulitis, and 383 incident cases of diverticular bleeding.

Nut, corn, and popcorn consumption was not associated with an increased risk of complicated diverticular disease. Instead, an inverse relationship was observed. After adjustment of other known and potential risk factors for diverticular complications, the hazard ratios (HRs) of men with the highest consumption compared with the lowest consumption were 80/100 for nuts, and 72/100 for popcorn.

No associations were seen between corn consumption and diverticulitis, or between nut, corn, or popcorn consumption and diverticular bleeding.

Although the study was unable to assess the total seed intake, it did examine the relationship between combined strawberry and blueberry consumption. (The small seeds found in berries have been implicated in diverticular complications.) The HRs of consumption at least twice per week vs less than once a month were 87/100 for diverticulitis, and 86/100 for diverticular bleeding. (Again, a possible protective effect.)

A recent survey reported that about half of colorectal surgeons felt that patients with diverticular disease should avoid these foods. Foods with poorly digested particles are presumed to be particularly abrasive, and apt to lodge within diverticula.

Although fecal matter is commonly found within wide-necked diverticula, the relationship between the ingestion of a particular food and subsequent trauma to a diverticulum is largely speculative.

The exact mechanisms leading to diverticular complications are not known.

Conclusion: These results suggest that consumption of nuts, corn, and popcorn is not associated with an increased risk of diverticulitis or diverticular bleeding.

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In the mind of the American public, nuts and seeds are associated with risk of diverticulitis.

How should primary care clinicians respond to this new information, given that nuts are part of the healthy diet?

I would not tell patients who fear diverticulitis or a recurrence of diverticulitis, especially those who have been advised to eliminate them from their diet that they should begin to eat nuts and seeds. Should symptoms recur, even though “scientifically” not associated with ingestion of these foods, blame would fall on the food and clinician alike.
Individualize Decision-Making To The Specific Patient Or Situation.

8-5 SCREENING FOR PROSTATE CANCER: U.S. Preventive Services Task Force Recommendation

Statement

The USPTF makes recommendations about preventive care services for patients without recognized signs and symptoms of the target condition.

The USPTF recognizes that decisions involve more consideration than this body of evidence alone. Clinicians should understand the evidence, but individualize decision-making to the specific patient or situation.

Clinical summary of the USPTF recommendations for prostate cancer (PC) screening:

A. Men age 75 and older:

Do not screen. The USPTF recommends against screening. There is moderate or high certainty that screening has no net benefit, or that harms outweigh the benefits. For men age 75 and older, and for those whose life expectancy is 10 years or fewer, the incremental benefit from treatment of PC detected by screening is small to none.

B. Men younger than age 75:

No recommendation.

Current evidence is insufficient to assess the balance of benefits over harms. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

The prostate specific antigen (PSA) is more sensitive than digital rectal examination (DRE). The conventional cut-point (4.0 ug/L) misses some early PC. Lowering the cut-point would increase the rate of false positives. Variations of PSA screening have not yet been demonstrated to improve health outcomes.

Suggestions for practice: Clinicians should discuss the potential benefits and know harms of PSA screening with their patients younger than age 75. They should be informed of the gaps in the evidence, and their personal preference should guide the decision of whether to order the test.

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This is a good example of how fashions in medicine change. In the early days of PSA screening, almost everyone climbed on the bandwagon, and screening became routine—often without any discussion with the patient. As a result, many men became obsessed with their “PSA”.

Does this end the discussion? I believe not. Large screening studies are still progressing.

In primary care practice, younger men should be fully informed before a PSA test is ordered.

Do the recommendations apply to digital rectal examinations? I believe not. DRE is not really a screening test for PC. It is included in a routine examination to evaluate benign prostate enlargement as well as rectal carcinoma. If a nodule suggestive of PC is found, further tests and treatment should follow.
Migraine with Aura is A Risk Factor for Myocardial Infarction and Stroke. Younger Women with MwA who Have No Cardiovascular Risk Factors May Be at Increased Risk of Ischemic Stroke

8-6 MIGRAINE, VASCULAR RISK, AND CARDIOVASCULAR EVENTS IN WOMEN.

Migraine with aura (MwA) is associated with an increased risk of ischemic stroke, migraine angina, myocardial infarction, and other ischemic vascular events.

This prospective cohort study was based on data from over 27,000 women in the Women’s Health Study. It evaluated whether the association between MwA and cardiovascular disease differs according to vascular risk status as measured by the Framingham risk score.

Categorized women as having migraine and not having migraine, classified as to having aura and not having aura.

Five % of women had MwA.

Women with active MwA had increased incidence of cardiovascular events:

Compared with women without migraine, the age-adjusted hazard ratios in women with active MwA:

<table>
<thead>
<tr>
<th></th>
<th>Major cardiovascular disease</th>
<th>Ischemic stroke</th>
<th>Myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.93</td>
<td>1.80</td>
<td>1.94</td>
</tr>
</tbody>
</table>

There was a strikingly different pattern of association for the outcomes of ischemic stroke and myocardial infarction according to their Framingham risk scores:

A. Ischemic stroke:

When women with active MwA were classified according to their Framingham risk scores, those who developed ischemic stroke were more likely to have a low score (ie, were younger and had lower BP and total cholesterol levels).

The age adjusted hazard ratio of these women, compared with women without migraine:

<table>
<thead>
<tr>
<th>Framingham score</th>
<th>Age-adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>3.88</td>
</tr>
<tr>
<td>≥ 10</td>
<td>1.00</td>
</tr>
</tbody>
</table>

B. Myocardial infarction:

When women with MwA were classified according to their Framingham risk scores, those who developed myocardial infarction were more likely to have a high score (ie, were older and had a higher total cholesterol levels).

The age adjusted hazard ratio of these women, compared with women without migraine:

<table>
<thead>
<tr>
<th>Framingham score</th>
<th>Age-adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1.29</td>
</tr>
<tr>
<td>≥ 10</td>
<td>3.34</td>
</tr>
</tbody>
</table>

6. Women with migraine without aura were not at increased risk for ischemic stroke or myocardial infarction in any of the Framingham risk score groups.
This diametric pattern of association was driven particularly by the increased risk of ischemic stroke among young women (age 45-49) with active MwA who had a low total cholesterol.

In contrast, the association with MI was high among those with high total cholesterol.

The data add to the growing evidence that MwA is associated with increased risk of vascular events. And imply that cardiovascular risk factors should be more carefully sought and controlled.

Conclusion:

Migraine with aura is associated with increased risk of cardiovascular events.

The association between MwA and cardiovascular disease varies by vascular risk status:

A. Risk of MI rose as the Framingham risk score rose.
B. Risk of ischemic stroke was actually lower in those with a high score, and higher in those with a low score. (Ie, in younger women with few risk factors.)

Overall, the risk of a major cardiovascular event in women with MwA was 3.3%; in those without migraine it was 2.5%. Risk for an individual is low. On a population basis, risk is likely high.

To me, the most important message is the risk of stroke in younger women.

What are the implications for primary care?

1) Consider migraine with aura to be a significant risk factor for vascular complications.
2) These patients should be told that they are at increased risk.
3) They should be treated to reduce incidence of migraine with aura.
4) All risk factors should be reduced as much as possible.

“There Was No Evidence Of A Renal Benefit With Combination Therapy.”

8-7 RENAL OUTCOMES WITH TELMISARTAN, RAMIPRIL, OR BOTH, IN PEOPLE AT HIGH VASCULAR RISK

Angiotensin converting enzyme inhibitors (ACE-i; eg, ramipril; Altace; King), and angiotensin II receptor blockers (ARB; eg, telmisartan; Micardis; Boehringer Ingelheim) have been reported to reduce albuminuria as well as renal risk (ie, decrease of glomerular filtration rate, and need for dialysis) in patients with advanced renal disease. Combination therapy has been associated with greater adverse effects than monotherapy (eg, acute renal failure and hyperkalemia).

Inhibition of the renin-angiotensin-aldosterone system by ACE-i or ARB has been reported to preserve renal function better than other antihypertension drugs.

This trial asks—Are the effects of the two drugs equivalent? Does the combination further reduce renal risk? This large multicenter, randomized, double-blind controlled trial (2001-2007) entered over 25 000 patients. All were over age 55; all had established atherosclerotic vascular disease, or diabetes with end-organ damage.

Randomized to:

1) Ramipril 10 mg daily
2) Telmisartan 80 mg daily. or
3) Both drugs combined.

Primary renal outcome was a composite of dialysis, renal transplantation, doubling of serum creatinine, and death. Secondary renal outcome was dialysis or doubling of serum creatinine.

Also determined changes in surrogate markers such as estimated glomerular filtration rate and proteinuria.

Median follow-up = 56 months.

The number of events for the composite primary outcome was similar for telmisartan (13.4%) and ramipril (13.5%), but was increased with the combination (14.5%). The secondary renal outcome was similar for telmisartan (2.21%) and ramipril (2.03%), and most frequent with combination therapy (2.49%).

Estimated glomerular filtration declined in all 3 groups, least in the ramipril group, most in the combination group.

Serum creatinine showed greater increase with combination therapy than with ramipril. Urinary albumin secretion increased in all 3 groups, most in the ramipril group, least in the combination group.

“There was no evidence of a renal benefit with combination therapy.” “The observation that combination therapy was associated with more renal outcomes and a faster decrease in GFR than on ramipril alone is of concern.”

Conclusion: In patients at high risk, effects of telmisartan and ramipril on major renal outcomes were similar. Combination therapy (compared with either drug alone) worsened renal outcomes.

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Since neither ACE-i nor ARB completely block the renin-angiotensin, aldosterone system, the hope was that combined therapy would be more effective. The investigators must have been disappointed.

Unfortunately, there was no placebo group in this trial. The benefits and harms of therapy with these drugs, as compared to placebo, were not determined.

“PCI Is Not Always Essential For The Relief Of Symptoms In Patients With Stable Angina.”

8-8 EFFECT OF PCI ON QUALITY OF LIFE IN PATIENTS WITH STABLE CORONARY DISEASE.

This study (2008), derived from the COURAGE trial (2007), reports outcomes based on an angina questionnaire score.

Randomized over 2200 patients with stable CAD to:

1) Percutaneous coronary intervention (PCI) + optimal medical therapy, or
2) Optimal medical therapy alone.

Optimal medical therapy (OMT-alone) included:

1) Aspirin (added clopidogrel for those undergoing PCI)
2) Anti-ischemic therapy: long-acting metoprolol, amlodipine, and isosorbide, alone or in combination
3) Statin drug: simvastatin
4) Either lisinopril (an ACE-inhibitor) or losartan (an angiotensin II blocker)
Assessed angina-specific health status with the use of the Seattle Angina Questionnaire (SAQ) and overall physical and mental function with use of the RAND 36-item health survey.

Patients who were free of angina (%):

<table>
<thead>
<tr>
<th></th>
<th>PCI + OMT</th>
<th>OMT-alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>One month</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td>6 months</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>One year</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Two years</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>Three years</td>
<td>59</td>
<td>56</td>
</tr>
</tbody>
</table>

Scores on the SAQ were similar between groups at baseline. In both groups, the percentage of patients who became angina-free increased substantially by one month, and continued to improve thereafter.

During follow-up, the percentage of angina-free patients was significantly higher in the PCI + OMT group than in the OMT-alone group. The difference was not statistically significant at 36 months.

On the RAND-36, a greater proportion of patients who received PCI + OMT had clinically significant improvements in physical function, anginal frequency, and quality of life for the first 6 months. These differences were no longer significant at 12 months.

At 3 months, among patients with the SAQ scores at baseline which indicated the most severe angina, there was a greater benefit from PCI + OMT vs OMT-alone. There was also a clinically significant improvement related to PCI + OMT in those with less severe angina. Among those with the least angina or no angina, there was no difference in improvement between groups.

Unexpectedly, during the first 6 months, there was a significant and rapid improvement in the SAQ among patients in the OMT-alone group,

“This finding with respect to the benefit of optimal medical therapy alone shows that PCI is not always essential for the relief of symptoms in patients with stable angina.”

Throughout the follow-up period, the mean differences between treatment groups on the SAQ scales were small. However, likelihood of clinically significant improvement from baseline was greater in the PCI + OMT group during the first six months (though not thereafter).

Conclusion: Patients with chronic coronary disease may expect relief from angina whether they are treated with PCI + OMT or with OMT-alone. An initial strategy of PCI + OMT relieved angina and improved self-assessed health status to a greater extent than an initial strategy of OMT-alone for approximately 24 months, but not thereafter.

A greater benefit from PCI + OMT was observed in patients with more severe and frequent angina.

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*OMT is required for all patients with angina*
Primary care clinicians will see patients with angina. This study will help them to classify and advise the patient accordingly. Clinical judgment by the primary care clinician, and a fully informed patient are essential. If the angina is severe, immediate consultation for PCI is advisable. Those with less severe angina can be given a choice. (I believe many patients will resist intervention.) Borderline patients may be started on a strict OMT program and rechecked for improvement within 1 and 3 months.

Note that almost ½ of patients in both groups still experienced angina at 3 years. The study did not concern these patients.

“This Should Serve As Encouraging News To Patients With Coronary Disease.”

8-9 FINDING THE COURAGE TO RECONSIDER MEDICAL THERAPY FOR STABLE ANGINA

(This editorial comments and expands on the preceding article.)

Coronary stents have revolutionized percutaneous coronary intervention (PCI) and have reduced the rate of complications and the need for repeat interventions. Clinician’s thresholds for PCI intervention have been markedly altered. Now, the presence of any angina can precipitate coronary angiography to detect amenable lesions, followed by PCI. Symptoms are no longer a prerequisite. Aggressive strategies for screening may reveal lesions that can be treated with PCI.

The therapeutic paradigm has reversed, with medical therapy generally reserved for those who have exhausted revascularization options.

The trial showed that, with contemporary medical treatment, the majority of patients had substantial improvements in health status that were sustained for several years. The rapid improvement with optimal medical therapy alone suggests that anginal medications are underused.

This underscores a major challenge to clinicians—how to successfully execute a strategy of optimal medical therapy in a health care system that provides strong financial rewards for PCI but few rewards for careful management of medications.

A very reasonable take home message from the trial is to pursue optimal medical therapy initially, and if it is ineffective, turn to PCI. Executing such a strategy will require “courage” to reconsider the algorithms of current care and the changes in policy that are necessary to give appropriate value to the effort that is required to manage medications optimally, and to monitor the health status of patients.

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The study reported that benefits of PCI were much greater in patients with severe angina. It included few patients who received stents. If stents had been used more frequently, outcomes might be more favorable in the PCI group.

I believe primary care clinicians should generally advise patients with severe and frequent angina to start optimal medical therapy immediately and to consult a cardiologist.

The primary care clinician’s approach to patients with angina requires keen clinical judgment in order to advise patients, and to work with the patient to determine his personal informed decision.
According To This Study Of Low-Risk Patients, The Risks Of Seizure Relapse Are In Fact Small.

8-10 ANTIEPILEPTIC DRUG WITHDRAWAL IN SEIZURE-FREE PATIENTS

The ultimate goal of epilepsy treatment is to become seizure free and have a healthy life without the need to take antiepileptic drugs.

A benchmark study (the Akershus study) was published in *Epilepsia* in 2008:

Randomized 160 adult patients who were taking a single antiepileptic drug and who were seizure free for more than 2 years to:

1) Withdrawal
2) No withdrawal

Follow-up for 12 months or until seizure relapse:

<table>
<thead>
<tr>
<th>Seizure recurrence:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Withdrawal</td>
<td>15%*</td>
</tr>
<tr>
<td>2) No withdrawal</td>
<td>7% *</td>
</tr>
<tr>
<td>3) After a median of 41 months off medication</td>
<td>27%</td>
</tr>
</tbody>
</table>

(*Difference not statistically significant)

A normal result to all 15 neuropsychological tests improved from 11% to 28% in those withdrawing from treatment. By contrast, the proportion of normal tests decreased from 11% to 9% in those remaining on treatment.

Withdrawal did not affect quality of life and the EEG.

“We now have class 1 evidence about the benefits and risks of withdrawing antiepileptics in seizure-free adults that we did not have before.”

“It is reassuring, and very valuable that, according to this study of low-risk patients, the risks of seizure relapse are in fact small.”

“Patients and physicians are now better equipped to make the difficult decision to withdraw the drug, after taking into account important other factors, such as the preference of the patient, and the sometimes grave social consequences of seizure relapse.”

Primary care clinicians will encounter this problem.

Although the study was small and had limitations, I believe it provides some guidance.

As noted, many patients did not meet the indications for withdrawal. There is no evidence on outcomes for these patients.

Attempting withdrawal is a personal decision. Primary care clinicians and patients now have some basis for their advice and informed decision.
It Is Time To Move Beyond The Binary Diagnostic Thinking That Has Dominated Medicine For So Long

8-1 AGAINST DIAGNOSIS

The concept of diagnosis is essentially binary. You either have a certain disease, or you do not. Differential diagnosis, often considered to be the highest expression of a physician’s art, is a matter of considering a list of possible diseases and then deciding that the patient has disease A, but not B, C, D, or E.

Consider cardiovascular disease, type 2 diabetes, depression, obesity, autism, back pain, arthritis, cancer, and HIV. The authors contend that all except HIV are continuous, reflecting a range of severity. Categorizing patients as having, or not having, the disease depends on choosing a somewhat arbitrary cut point of severity.

The definition of hypertension currently includes a systolic pressure of 140 or higher. But there is no particular biological relevance of 140 such that individuals with a BP of 141 differ qualitatively from those with a BP of 139. Similarly, there is no particular cut point for obesity (BMI of 30 kg/m²) such that everyone above the cut point is in one homogenous risk category and everyone below it is in another.

Even atherosclerosis is a matter of degree. Most adults have some level of endothelial dysfunction.

Type 2 diabetes is a good example of how a continuous end point is turned into a binary disease state. A fasting blood glucose above 125 mg/dL is diabetes. A level of 124 is not. A level of 126 might be considered a serious problem, while 124 is not a serious problem.

Psychological and developmental disorders are also a matter of degree. The diagnosis of depression is made by comparing symptoms or behaviors against a checklist. For a diagnosis of depression, patients must have at least 5 symptoms of at least 2 weeks. But what about 4 symptoms for 3 weeks?

The diagnosis of “cancer” is also a judgment call. Many cancers are diagnosed long before they cause symptoms. A large proportion of men with prostate cancer will die of causes other than their cancer. Yet many men with low risk prostate cancer, when told their risk of death from the cancer is low, will say that if they have “cancer” they want it removed. If such tumors were called something other than “cancer”, the rates of unnecessary surgery and radiation therapy would decrease.

Risk prediction as an alternative:

The authors propose that thinking about disease in terms of risk prediction is often superior to thinking about disease in terms of diagnosis. The diagnostic approach for BP is divided into 2 populations—those who have hypertension and those who do not. The risk prediction alternative uses a statistical model to estimate the probability that a patient will have a clinically important event within a certain period. For prediction of a cardiovascular event, BP is only one predictor. Others include cholesterol, smoking, age, and sex. At a given BP level, the risk of a future event differs between a young man with no other risk factors and an older man with high cholesterol who smokes. Treatment approach is different.

Prediction models have 2 particular advantages over our standard way of thinking about diagnosis:

1) Traditional cutpoints do not take into account patient preferences. A higher cut point might be
set for patients who have a troublesome adverse effect from medications. A prediction model provides probabilities of events. Patients can weigh these according to their preferences. It makes more sense to ask patients whether they would accept treatment for a 2% vs a 4% absolute reduction in the risk for a cardiovascular event than to ask whether a systolic BP of 150 is a more appropriate treatment threshold than 160.

2) Prediction models can incorporate multiple patient characteristics. A person with BP of 160 benefits more from reduction in cholesterol than does a patient with a BP of 130. For prostate cancer, the patient at high risk for cardiovascular death would be less likely to benefit from prostatectomy because he is more likely to die before his cancer progresses sufficiently to affect his quality of life or survival.

The risk prediction model is not new. Physicians have traditionally called on multiple variables to risk-stratify patients, usually weighing each variable on the basis of clinical judgment and experience. Many diseases include some measure of risk stratification. The use of prediction models adds a quantitative estimate to group patients according to risk, and to aid physicians’ process of risk adjustment. Prediction models give physicians explicit information to use in shared decision making with patients.

Why diagnosis?

Despite the provocative title of this perspective, the authors are not against diagnosis.

There are many diseases which are either present or absent. A patient has syphilis or does not; a ruptured aorta or not. Here, patient preference plays no important role. The harms of untreated syphilis or a torn aorta cannot seriously be compared with those of penicillin or surgery.

Challenges for the risk prediction approach:

Prediction modeling may be more difficult to implement than the diagnostic approach. It is easier to classify patients as having hypertension or not, and to prescribe treatment accordingly, than to enter BP into a calculation of a predicted risk, explain to the patient what this risk means, and then make a shared decision about treatment.

Prediction depends on the availability of a good model. Most models have been evaluated only with regard to their accuracy. Whether use of a model, even a relatively accurate one, would improve an outcome is not entirely clear.

Nonetheless, an approach based on risk prediction can be of great value for many diseases of greatest concern in industrialized countries. Many disorders are best suited for a risk prediction approach. Classification of these complex disorders exists on a continuum perhaps best understood in terms of risk for associated outcomes.

It is time for us to move beyond the binary diagnostic thinking that has dominated medicine for so long and embrace a quantitative approach.

Annals Int Med August 5, 2008; 149: 200-203 “Perspective” first author Andrew J Vickers, Memorial Sloan-Kettering Cancer Center, New York, NY


**Spirituality Is Part Of What It Means To Be Human. Spirituality Is An Important Part Of Medical Care**

**8-2 MEDICINE, SPIRITUALITY, AND PATIENT CARE.**

Is spiritual care always an important part of medical care? If yes, who should assess the need for it?

Religion is defined as “the service and worship of God or the supernatural; a personal set or institutionalized system of religious attitudes, beliefs, and practices”. Spirituality is defined as “the quality or state of being “spiritual” (with “spiritual” meaning of, or related to, sacred matters”). The spiritual transcends ordinary human experience.

Religion tends to be associated with formal practices and rules that connect a person to the sacred.

Because spirituality is not usually based on human-made laws of reason or logic, it is often described as the non-logical or non-rational part of being human that connects the sacred—God, the Ultimate, or Universal Principle.

For many people, religion and spirituality are one and the same, as one’s spiritual practices frequently flow from the religion espoused by the person.

The science of medicine is highly rational—concerned with causes, diagnoses, and cures. The healing art of medicine includes, and goes beyond, the science and takes into account what gives a person meaning—his or her loves, priorities, beliefs, fears, dreams, and questions.

Some physicians believe that spirituality is part of the human condition and, as such, is part of the healing art practiced by physicians.

The practice of medicine, at its finest, involves far more than knowing the right science; it involves working with the whole person and not just a diseased body part.

Some physicians believe that because medicine is rational, and spiritual care is non-rational—their union is incompatible.

Hippocrates understood that “It is more important to know what sort of a person has a disease than to know what sort of disease the person has.”

Osler said “Care more particularly for the individual patient than for the special features of the disease”. He understood the importance of faith broadly—faith in the physician, faith in medications or procedures, and faith in a supernatural force.

For many patients, faith in the supernatural (ie, spirituality) is important—in health and especially in illness. Faith gives meaning to their lives. It provides comfort when their lives are not going well, and it remains when other resources are spent. Faith can support when support is most needed.

Multiple studies have revealed that a majority of patients not only would not mind, but would even want, their physician to ask about their religious beliefs. At times of vulnerability because of illness, many patients want their
physician to know what gives meaning, comfort, and support. This does not imply that physicians must agree with patient’s beliefs. Physicians must listen respectfully, and may inquire whether the patient has spoken to, or wants to speak to a member of the clergy.

The Joint Commission requires that a spiritual history is obtained from every patient admitted to an acute care hospital or nursing home, or observed by a home health care agency, and that spiritual history is documented in the medical record. The best tools use open-ended questions designed to give a patient the opportunity to provide a full answer rather than a perfunctory “yes” or “no”.

Two questions may be asked in a compassionate, non-proselytizing way: 1) Do you have spiritual beliefs than might influence your medical decisions? 2) How would you like me to address these issues in your health care?

Although many physicians appreciate the importance of spirituality for patients, many doubt that they must be the ones to ask these questions, convinced that others are better suited to this task. But, many physicians will respond if the patient raises the subject.

Each physician has his or her own spirituality that gives meaning to life. Although physicians might not believe in a personal God, they might believe in something. Although a person’s spirituality is usually rooted in a religious tradition, that is not always the case. It is good for physicians to be cognizant of their own spirituality, especially when it is at odds with a given patient’s spirituality. Perspectives may evaluate a moral situation differently. A physician may believe in God but also may believe the extraordinary means are unwarranted when a patient nears death. The patient (or more likely) a family member may believe that all measures should be continued indefinitely because only God can end a life.

Spirituality is an important part of medical care, especially when patients are very ill or dying.

Spirituality is part of what it means to be human.

It is important for physicians to understand not only their own spirituality, but also that of their patients. For that reason, although physicians do not need to deliver spiritual care, asking questions to discern the spiritual needs of their patients might be in the best interest of both.

JAMA August 20, 2008; 399: 836-38 “Commentary” by Pat Fosarelle, Ecumenical Institute of Theology, Baltimore, MD

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Low Concentrations Were Associated With Higher Risk Of Hip Fracture.

8-3 SERUM 25-HYDROXY VITAMIN D CONCENTRATIONS AND RISK FOR HIP FRACTURE

Vitamin D deficiency is common in older adults, especially during the winter and in homebound populations, general medical inpatients, and community-dwelling women admitted to the hospital with hip fracture.
This study tested whether low serum levels of 25-hydroxy vitamin D $25(OH)D$ are associated with higher risk of hip fracture.

Conclusion: Low $25(OH)D$ concentrations were associated with higher risk of hip fracture.

STUDY
1. The study population came from the large Women’s Health Initiative (WHI) Study (1994-98), which was limited to women age 50 to 79 at baseline. All were postmenopausal. All were community-dwelling.
2. Measured total $25(OH)D$ in all subjects. (D2 + D3).
3. Followed all for a median of 7 years for incident hip fracture. Of the over 39,000 eligible women, 404 developed a hip fracture during follow-up.
4. Cases = 400 women randomly selected from the 404 who sustained a hip fracture during follow-up.
   Controls = 400 women without hip fracture randomly selected and carefully matched.
   (Mean age = 71. None had taken estrogen or other bone-active therapies at baseline.)
5. Compared $25(OH)D$ levels in cases and controls.
6. Divided $25(OH)D$ levels into quartiles and determined odds ratio of hip fracture of the lowest quartile vs the highest.

RESULTS
1. Mean serum $25-OH-D$ levels were lower in cases than in controls (56 nmol/L vs 60 nmol/L).
2. Serum $25(OH)D$ quartiles
   - Lowest Q: 9-48 nmol/L
   - Highest Q: 71-122 nmol/L
   Odds ratio of hip fracture: 1.72 vs 1.00 (reference)
   (Adjusted for many possible confounders: including age, falls, BMI, physical function, previous corticosteroid use, smoking, alcohol use, frailty, renal function, geographic location, and sex-steroid hormone levels.)
3. The increased risk for hip fracture was primarily confined to women with the lowest $25(OH)D$ concentration.

DISCUSSION
1. Women with the lowest $25(OH)D$ concentration (<48 nmol/L) at study entry had a significantly greater increased risk for subsequent hip fracture during the next 7 years than did women in the highest concentration (>70 nmol/L).
2. These results are consistent with a recent National Health and Nutrition Examination Survey which reported a lower relative risk (0.64) of hip fracture among participants with $25(OH)D$ concentrations greater than 60 nmol/L, compared with those with lower concentrations.
3. A recent Swedish study reported that those with $25(OH)D$ levels less than 54 nmol/L had a 2-fold increased risk of fracture.
4. Randomized trials of vitamin D supplementation (with and without calcium) that brought serum 25(OH)D up to 75 nmol/L reported significantly lower fracture rates.

5. The optimal serum 25(OH)D level has not been established.

6. The mechanism for the protective effect of 25(OH)D is not clear. It may be partially mediated by less bone resorption.

**CONCLUSION**

Low 25(OH)D levels were associated with an increased risk for hip fracture in elderly community dwelling women. Lower serum levels might help identify women at high risk for hip fracture.

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**Does Not Increase Risk Of Diverticulitis And Diverticular Bleeding**

**8-4 NUT, CORN, AND POPCORN CONSUMPTION AND THE INCIDENCE OF DIVERTICULAR DISEASE**

One third of the US population will develop diverticulosis by age 60; 2/3 by age 85. Complications, including diverticulitis and bleeding, occur in an estimated 10% to 35% of persons with diverticulosis.

Historically, physicians have advised individuals with diverticulosis to avoid nuts, seeds, popcorn, corn and other high-residue foods. The recommendation comes from the theory that luminal trauma is a causal mechanism for both diverticulitis and bleeding. Stool may lodge within a diverticulum, obstruct the neck, or abrade the mucosa, and precipitate inflammation or bleeding. Nuts and the other foods are presumed to be particularly likely to abrade the mucosa or to lodge within small diverticula.

The biological mechanisms responsible for diverticular complications remains poorly understood. “To our knowledge, there is no evidence to support consumption of nuts, corn, popcorn, or seeds as a risk factor.”

This study determined whether consumption of nuts, corn, or popcorn is associated with complications of diverticulosis. .

Conclusion: Consumption of nuts and the other foods did *not* increase risk of diverticulitis and diverticular bleeding.

**STUDY**

1. The Health Professionals Follow-up Study is a cohort of US professional men followed prospectively from 1986 to 2004 via self-administered questionnaires about medical and dietary information.

2. The study included over 47 000 men aged 40 to 75 who were free of diverticulosis or its complications at
baseline. All returned a food-frequency questionnaire which included average frequency of consumption of nuts, corn, and popcorn. Men reporting newly diagnosed diverticulosis or diverticulitis were mailed supplemental questionnaires.

3. Frequency categories for total consumption of these foods were collapsed into 4 categories: 1) less than once a month, 2) 1 to 3 times a month, 3) once a week, and 4) 2 or more times per week. (27% of participants reported eating nuts at least twice a week.)

4. Primary endpoints were diverticulitis and diverticular bleeding. Determined relation between frequency of consumption of these foods and incidence of end-points.

RESULTS

1. During 18 years of follow-up, there were 801 incident cases of diverticulitis, and 383 incident cases of diverticular bleeding.

2. Nut, corn and popcorn consumption was not associated with an increased risk of complicated diverticular disease. Instead, an inverse relationship was observed.

3. After adjustment of other known and potential risk factors for diverticular complications, the hazard ratios (HRs) of men with the highest consumption compared with the lowest consumption were 80/100 for nuts, and 72/100 for popcorn.

4. No associations were seen between corn consumption and diverticulitis, or between nuts, corn, or popcorn consumption and diverticular bleeding.

5. Although the study was unable to assess the total seed intake, it did examine the relationship between combined strawberry and blueberry consumption. (The small seeds found in berries have been implicated in diverticular complications.) The HRs of consumption at least twice per week vs less than once a month were 87/100 for diverticulitis, and 86/100 for diverticular bleeding. (Again, a possible protective effect.)

DISCUSSION

1. In this large study with a follow-up of 18 years, frequent consumption of nuts, corn, and popcorn was not associated with an increased risk of diverticular complications. Indeed, there appeared to be an inverse relationship.

2. A recent survey reported that about half of colorectal surgeons felt that patients with diverticular disease should avoid these foods. Foods with poorly digested particles are presumed to be particularly abrasive, and apt to lodge within diverticula.

3. Although fecal matter is commonly found within wide-necked diverticula, the relationship between the ingestion of a particular food and subsequent trauma to a diverticulum is largely speculative.

4. The exact mechanisms leading to diverticular complications are not known.

5. This study suggests that the recommendations to avoid these foods in diverticular disease should be reconsidered.
6. Given the observational nature of this study, residual confounding cannot be ruled out.

CONCLUSION
These results suggest that consumption of nuts, corn, and popcorn is not associated with an increased risk of incident diverticulitis or diverticular bleeding.

JAMA August 27, 2008; 300: 907-14  Original investigation, first author Lisa L Strate, University of Washington School of Medicine, Seattle.

1 The authors suggest some theoretical reasons for the apparent protective effects of nuts, corn, seeds and popcorn—none particularly convincing. If there is indeed a protective effect, the reason is not known.

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**Individualize Decision-Making To The Specific Patient Or Situation.**

8-5  **SCREENING FOR PROSTATE CANCER: U.S. Preventive Services Task Force Recommendation Statement**

The USPTF makes recommendations about preventive care services for patients without recognized signs and symptoms of the target condition. It bases recommendations on a systematic review of the evidence of the benefits and harms and an assessment of net benefit of the service.

The USPTF recognizes that decisions involve more consideration than this body of evidence alone. Clinicians should understand the evidence, but individualize decision-making to the specific patient or situation.

1. Clinical summary of the USPTF recommendations for prostate cancer (PC) screening:
   A. Men age 75 and older:
      1) Do not screen.
      2) The USPTF recommends against screening. There is moderate or high certainty that screening has no net benefit, or that harms outweigh the benefits. For men age 75 and older, and for those whose life expectancy is 10 years or fewer, the incremental benefit from treatment of PC detected by screening is small to none.
   B. Men younger than age 75:
      1) No recommendation.
      2) Current evidence is insufficient to assess the balance of benefits over harms. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

2. PC is more common in older men, African Americans, and men with a family history of PC.
   The same uncertainties about the effects of screening apply to these higher-risk men.

3. The prostate specific antigen (PSA) is more sensitive than digital rectal examination (DRE).
The conventional cut-point (4.0 ug/L) misses some early PC. Lowering the cut-point would increase the rate of false positives. Variations of PSA screening have not yet been demonstrated to improve health outcomes.

4. Management strategies for localized PC include watchful waiting, active surveillance, surgery, and radiation. There is no consensus regarding optimal treatment.

5. The harms of screening include the discomfort of prostate biopsy, and the psychological harm of a false-positive test. Harms of treatment include erectile dysfunction, urinary incontinence, bowel dysfunction, and death. A proportion of those treated, and possibly harmed, would never have developed cancer symptoms in their lifetime.

6. Suggestions for practice: Clinicians should discuss the potential benefits and know harm of PSA screening with their patients younger than age 75. They should be informed of the gaps in the evidence, and their personal preference should guide the decision of whether to order the test.

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**Migraine With Aura is A Risk Factor for Myocardial Infarction and Stroke. Younger Women With MwA who Have No Cardiovascular Risk Factors May Be at Increased Risk of Ischemic Stroke**

**8-6 MIGRAINE, VASCULAR RISK, AND CARDIOVASCULAR EVENTS IN WOMEN.**

Migraine with aura (MwA) is associated with an increased risk of ischemic stroke, migraine angina, myocardial infarction (MI), and other ischemic vascular events.

It is not clear what mechanisms link migraine with vascular events or whether the biological mechanisms leading to ischemic stroke differ from mechanisms leading to MI.

Underlying risk status might be related to the association between migraine and cardiovascular disease and might help to identify individuals at increased risk.

This study evaluated whether the association between MwA and cardiovascular disease differs according to vascular risk status as measured by the Framingham risk score.¹

Conclusion: The association varies by vascular risk status. In women with active MwA, higher Framingham risk scores were associated with increased risk of MI; lower scores were associated with increased risk of ischemic stroke.

**STUDY**

1. This prospective cohort study was based on data from over 27 000 women in the Women’s Health Study. All were free of cardiovascular disease at baseline (1992-95). None had a history of cardiovascular disease, cancer, or other major illnesses.

2. Information was self-reported and collected by periodic questionnaires.

3. Categorized women as having active migraine with aura, active migraine with no aura, and migraine without
aura. (Active defined as having migraine continuing within the preceding year.)
4. Used the Framingham risk score to classify the women into vascular risk categories.
5. Follow-up to 2007. Main outcome measure was the occurrence of a major ischemic vascular event—a combined endpoint of non-fatal myocardial infarction, non-fatal ischemic stroke, and death from ischemic cardiovascular disease.
6. Calculated the hazard ratios for the combined endpoint associated with active MwA, and active migraine without aura, compared with persons without migraine.
7. Also determined hazard ratios of MI and stroke according to the Framingham risk scores.

RESULTS
1. At baseline, of the 27 519 participants who remained in the study, 18 % reported any history of migraine; 13% reported active migraine, and 5% reported active MwA.
2. During 12 years of follow-up, there were 697 major ischemic cardiovascular disease events.
3. Women with active MwA had increased incidence of cardiovascular events:
   Compared with women without migraine, the age-adjusted hazard ratios in women with active MwA:
   
<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
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<tbody>
<tr>
<td>Major cardiovascular disease</td>
<td>1.93</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.80</td>
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<tr>
<td>Myocardial infarction</td>
<td>1.94</td>
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</table>
4. There was a strikingly different pattern of association for the outcomes of ischemic stroke and myocardial infarction according to their Framingham risk scores:
   A. Ischemic stroke:
      When women with active MwA were classified according to their Framingham risk scores, those who developed ischemic stroke were more likely to have a low score (ie, were younger and had lower BP and total cholesterol levels).
      The age adjusted hazard ratio of these women, compared with women without migraine:
      
      | Framingham score | Age-adjusted hazard ratio |
      |------------------|---------------------------|
      | 0-1              | 3.88                      |
      | ≥ 10             | 1.00                      |
   B. Myocardial infarction:
      When women with MwA were classified according to their Framingham risk scores, those who developed myocardial infarction were more likely to have a high score (ie, were older and had a higher total cholesterol levels).
      The age adjusted hazard ratio of these women compared with women without migraine:
      
      | Framingham score | Age-adjusted hazard ratio |
      |------------------|---------------------------|
      | 0-1              | 1.29                      |
      | ≥ 10             | 3.34                      |
6. Women with migraine without aura were not at increased risk for ischemic stroke or myocardial infarction in any of the Framingham risk score groups.

DISCUSSION
1. In women with active MwA, there was a strikingly different pattern of association for risk of MI and risk of ischemic stroke according to their Framingham risk score. The HR of ischemic stroke was highest in the group with the lowest score (younger age and lower cholesterol). The HR of MI was highest in those with the highest score.
2. This diametric pattern of association was driven particularly by the increased risk of ischemic stroke among young women (age 45-49) with active MwA who had a low total cholesterol. In contrast, the association with MI was high among those with high total cholesterol.
3. The data add to the growing evidence that active MwA is associated with increased risk of vascular events. And imply that cardiovascular risk factors should be more carefully sought and controlled.
4. Potential biological mechanisms:
   Migraine can be viewed as a systemic disorder that affects the vasculature.
   Migraineurs might have reduced number and function of endothelial progenitor cells, a surrogate for impaired vascular function.
   Even in the absence of vascular risk factors, people with migraine have decreased cerebral and peripheral vascular resistance, increased likelihood of retinal microvascular signs, hyper-coagulability, and inflammation.
   Altered vascular reactivity is already present among young patients with recent onset of migraine.
   It is plausible that MwA results in ischemic vascular events in the brain not altered by atherosclerotic changes.
   The effect of MwA on the coronary arteries might involve two mechanisms:
   1) One involving a vasculature not altered by atherosclerosis which leads to angina
   2) One involving a vasculature impaired by atherosclerosis leading to MI

CONCLUSION:
Migraine with aura is associated with increased risk of cardiovascular events.

The association between MwA and cardiovascular disease varied by vascular risk status:
A. Risk of MI rose as the Framingham risk score rose.
B. Risk of ischemic stroke was actually lower in those with a high score, and higher in those with a low score. (Ie, in younger women with few risk factors.)

BMJ August 16, 2008; 337: 383-87 Original investigation, first author Tobias Kurth, Brigham and Women’s Hospital and Harvard Medical School, Boston Mass
The Framingham score, based on age, total cholesterol, smoking, high density lipoprotein cholesterol, systolic BP, estimates 10-year risk of coronary heart disease.

An editorial in this issue of BMJ, first author Richard B Lipton, Albert Einstein College of Medicine, Bronx, NY comments:

In women, MwA is a risk factor for several ischemic outcomes including all-cause death, stroke, myocardial infarction, angina, coronary revascularization, and claudication.

The findings of the study raise questions regarding the mechanistic links between MwA, stroke, and myocardial infarction, and have implications for clinical practice and preventive interventions.

Cerebral blood rises and then falls during the process of migraine in response to metabolic changes in the brain, through the mechanism of auto-regulation. Although blood flow rarely falls below the ischemic threshold during the aura, a cascade of mediators is released, some of which may damage blood vessels and the brain parenchyma.

Even in the absence of vascular risk factors, aura may contribute to an immediate or delayed stroke. In people with low risk scores, competing risk factors for stroke are few and MwA is a major determinant of stroke. The study’s findings suggest that, as risk scores increase, the influence of aura on stroke is offset by other cardiovascular risk factors.

As the Framingham score rises, the editorialists predict that the absolute risk of stroke will increase in people with migraine with aura.

Although MwA has profound effects on the brain, its influence may be less pronounced on the coronary circulation. The study found that MwA increased the risk of myocardial infarction only in those with high risk scores.

The study has implications for clinical practice and public health interventions. Because MwA occurs in about 7% of the US population, it is a potential risk factor for stroke and myocardial infarction. It is not clear whether treating migraine modifies vascular risk. Preventive drugs and behavioral modifications reduce the frequency of migraine. Reducing frequency may reduce the risk of vascular complications.

It may be important to modify traditional risk factors for myocardial infarction in people with MwA. Reducing cardiovascular risk should diminish both the relative and absolute risk of myocardial infarction. Reducing the risk is unlikely to influence the relative risk of stroke, although it may reduce absolute risk.

“There Was No Evidence Of A Renal Benefit With Combination Therapy.”

8-7 RENAL OUTCOMES WITH TELMISARTAN, RAMIPRIL, OR BOTH, IN PEOPLE AT HIGH VASCULAR RISK

Angiotensin converting enzyme inhibitors (ACE-i; eg, ramipril; Altace; King), and angiotensin II receptor blockers (ARB; eg, telmisartan; Micardis; Boehringer Ingelheim) have been reported to reduce albuminuria as well as renal risk (ie, decrease in glomerular filtration rate, and need for dialysis) in patients with advanced renal disease. Combination therapy has been associated with greater adverse effects than monotherapy (eg, acute renal failure and hyperkalemia).

Inhibition of the renin-angiotensin-aldosterone system by ACE-i or ARB has been reported to preserve renal function better than other antihypertension drugs.

This trial asks—Are the effects of the two drugs equivalent? Does the combination further reduce renal risk?
Conclusion: In patients at high risk, effects of telmisartan and ramipril on major real outcomes were similar. Combination therapy (compared with either drug alone) worsened renal outcomes.

STUDY
1. Multicenter, randomized, double-blind controlled trial (2001-2007) entered over 25 000 patients. All were over age 55; all had established atherosclerotic vascular disease, or diabetes with end-organ damage.
2. Randomized to:
   1) Ramipril 10 mg daily
   2) Telmisartan 80 mg daily. or
   3) Both drugs combined.
3. Primary renal outcome was a composite of dialysis, renal transplantation, doubling of serum creatinine, and death.
4. Secondary renal outcome was dialysis or doubling of serum creatinine.
5. Also determined changes in surrogate markers such as estimated glomerular filtration rate and proteinuria.
6. Median follow-up = 56 months.

RESULTS
1. The number of events for the composite primary outcome was similar for telmisartan (13.4%) and ramipril (13.5%), but was increased with the combination (14.5%).
2. The secondary renal outcomes was similar for telmisartan (2.21%) and ramipril (2.03%), and most frequent with combination therapy (2.49%).
3. Estimated glomerular filtration declined in all 3 groups, least in the ramipril group, most in the combination group.
4. Serum creatinine showed greater increase with combination therapy than with ramipril.
5. Urinary albumin secretion increased in all 3 groups, most in the ramipril group, least in the combination group.
6. Over 750 patients permanently discontinued therapy because of symptoms of hypotension (Fewest on ramipril; more on telmisartan, most on combination).

DISCUSSION
1. The primary renal outcome was similar for telmisartan and ramipril; was more frequent in the combination group.
2. Dialysis and increase in serum creatinine were also greater in the combination group.
3. “There was no evidence of a renal benefit with combination therapy.” “The observation that combination therapy was associated with more renal outcomes and a faster decrease in GFR than on ramipril alone is of concern.”
CONCLUSION

In patients at high risk, effects of telmisartan and ramipril on major real outcomes were similar. Combination therapy was associated with worsening renal outcomes compared with either drug used alone.

Lancet August 16, 2008; 372: 547-53 Original investigation by the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), First author Johannes F E Mann, Maximillans University, Munchen, Germany.

A noble effort. The investigators must have been disappointed in these results. There was, unfortunately, no placebo group.

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“PCI Is Not Always Essential For The Relief Of Symptoms In Patients With Stable Angina.”

8-8 EFFECT OF PCI ON QUALITY OF LIFE IN PATIENTS WITH STABLE CORONARY DISEASE.

Among patients with stable coronary artery disease (CAD), percutaneous coronary intervention (PCI) is indicated for the relief of angina.

Clinical trials involving patients with chronic (stable) CAD, in contrast to those involving acute coronary syndromes, have not shown that PCI prevents major cardiovascular events.

The initial COURAGE trial\(^1\) (2007) compared a strategy of PCI + optimal medical therapy (PCI + OMT) with optimal therapy alone (OMT-alone). It reported no significant difference in death or myocardial infarction (MI) during a median follow-up of 5 years.

This study (2008), based on data from the COURAGE trial, reports outcomes based on an angina questionnaire score.

Conclusion: Generally, among patients with stable angina, both those treated with PCI + OMT and those treated with OMT-alone had marked improvements in health status during follow-up. PCI + OMT did not benefit patients with the least severe angina.

STUDY

1. Randomized over 2200 patients with stable CAD to:
   1) PCI + optimal medical therapy, or
   2) Optimal medical therapy alone.
2. At baseline, all had stenosis of more than 70% in at least one major coronary artery with objective evidence of myocardial ischemia, or stenosis of at least 80% in at least one coronary artery with classic angina without provocative testing.
3. At baseline, 22% were free of angina.
4. Optimal medical therapy (OMT-alone) included:
   1) Aspirin (added clopidogrel for those undergoing PCI)
   2) Anti-ischemic therapy: long-acting metoprolol, amlodipine, and isosorbide, alone or in combination
   3) Statin drug: simvastatin
   4) Either lisinopril (an ACE-inhibitor) or losartan (an angiotensin II blocker)
5. Assessed angina-specific health status with the use of the Seattle Angina Questionnaire (SAQ) and overall physical and mental function with use of the RAND 36-item health survey.
6. The baseline frequency of angina in the cohort was divided into thirds: 1) multiple bouts of angina per week; 2) angina about once a week; 3) angina rarely or not at all.
7. Follow-up a minimum of 30 months.

RESULTS
1. During a median follow-up of 4.6 years, there was no significant difference in death or MI. (19% vs 18.5%)
2. Patients who were free of angina (%):
<table>
<thead>
<tr>
<th></th>
<th>PCI + OMT</th>
<th>OMT-alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>One month</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td>6 months</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>One year</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Two years</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>Three years</td>
<td>59</td>
<td>56</td>
</tr>
</tbody>
</table>
3. Scores on the SAQ were similar between groups at baseline.
4. In both groups, the percentage of patients who became angina-free increased substantially by one month, and continued to improve thereafter.
5. During follow-up, the percentage of angina-free patients was significantly higher in the PCI + OMT group than in the OMT-alone group. The difference was not statistically significant at 36 months.
6. On the RAND-36, a greater proportion of patients who received PCI + OMT had clinically significant improvements in physical function, anginal frequency, and quality of life for the first 6 months. These differences were no longer significant at 12 months.
7. Of the OMT-alone patients, 68 required coronary revascularization within 3 months. Baseline values for these patients indicated more severe angina.
8. At 3 months, among patients with the SAQ scores at baseline which indicated the most severe angina, there was a greater benefit from PCI + OMT vs OMT-alone. There was also a clinically significant improvement related to PCI + OMT in those with less severe angina. Among those with the least angina or no angina, there was no difference in improvement between groups.
DISCUSSION
1. The primary results of the original COURAGE trial (2007) showed that in patients with stable CAD and inducible ischemia who were treated with optimal medical therapy, the addition of PCI did not significantly reduce the risk of death or MI over 5 years.
2. However, PCI is performed not only to prevent events, but to improve health status.
3. Overall, on the basis of the SAQ, patients with stable angina had an incremental benefit from PCI for the first 12 to 24 months in physical limitations, frequency of angina, and quality of life.
4. Unexpectedly, during the first 6 months, there was a significant and rapid improvement in angina among patients in the OMT-alone group.
5. “This finding with respect to the benefit of optimal medical therapy alone shows that PCI is not always essential for the relief of symptoms in patients with stable angina.”
6. Throughout the follow-up period, the mean differences between treatment groups on the SAQ scales were small. However, likelihood of clinically significant improvement from baseline was greater in the PCI + OMT group during the first six months (though not thereafter).
7. On the basis of these data, the number needed to treat (NNT) with PCI + OMT to benefit one patient compared with OMT-alone was:
   - 17 to have significantly greater angina relief
   - 11 to have a significant benefit in physical function
   - 13 to have significant improvement in quality of life.
8. Patients with angina several times per week had the greatest improvement from PCI + OMT. Those with angina about once a week had less improvement, and those who had angina rarely or not at all had no improvement.
9. The subset of patients with the most severe anginal symptoms at baseline had dramatic improvement. Some patients do have an especially marked benefit from PCI + OMT.
10. The investigators note that stents were used rarely in patients receiving PCI. Whether the use of stents would improve outcomes is not known.

CONCLUSION
Patients with chronic coronary disease may expect relief from angina whether they are treated with PCI + OMT or with OMT-alone. An initial strategy of PCI + OMT relieved angina and improved self-assessed health status to a greater extent than an initial strategy of OMT-alone for approximately 24 months, but not thereafter.

A greater benefit from PCI + OMT was observed in patients with more severe and frequent angina.

NEJM August 12, 2008; 359: 677-87 Original investigation, by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial Group, first author William S Weintraub, Christiana Care Health System, Newark, DEL
“This Should Serve As Encouraging News To Patients With Coronary Disease.”

8-9 FINDING THE COURAGE TO RECONSIDER MEDICAL THERAPY FOR STABLE ANGINA

(This editorial comments and expands on the preceding article.)

Twenty-five years ago, care for patients with symptomatic coronary artery disease centered on the selection and titration of antianginal medications. Percutaneous coronary intervention (PCI), which was limited at that time to balloon angioplasty, was an alternative. However, the risks associated and the rate of restenosis largely relegated the procedure to second-line therapy for patients who did not respond to best medical therapy.

Coronary stents have revolutionized PCI and have reduced the rate of complications and the need for repeat interventions. Clinician’s thresholds for PCI intervention have been markedly altered. Now, the presence of any angina can precipitate coronary angiography to detect amenable lesions, followed by PCI. Symptoms are no longer a prerequisite. Aggressive strategies for screening may reveal lesions that can be treated with PCI.

The therapeutic paradigm has reversed, with medical therapy generally reserved for those who have exhausted revascularization options.

A remarkable finding of the study was the rapidity of improvement in health status in both treatment groups. Both treatment strategies can have a profoundly positive effect on patient’s health status.

This left open the question of whether a PCI-first strategy is justified.

Patients with angina can become depressed because they believe that their well-being may decline in parallel with their narrowing coronary arteries. The trial showed that, with contemporary treatment, the majority of patients had substantial improvements in health status that were sustained for several years. The rapid improvement with optimal medical therapy alone suggests that anginal medications are underused. At present, 40% of patients in practice are not taking beta-blockers or statin drugs. There is a long way to go to realize the potential gains of optimal medical therapy before undertaking PCI.

This underscores a major challenge to clinicians—how to successfully execute a strategy of optimal medical therapy in a health care system that provides strong financial rewards for PCI but few rewards for careful management of medications.

From a cost-effectiveness point of view, it is difficult to assert that a PCI-first strategy should be adopted routinely in patients with stable angina.

A very reasonable take home message from the trial is to pursue optimal medical therapy initially, and if it is ineffective, turn to PCI. Executing such a strategy will require “courage” to reconsider the algorithms of current care and the changes in policy that are necessary to give appropriate value to the effort that is required to manage medications optimally, and to monitor the health status of patients.

NEJM August 14, 2008; 359: 751-53 Editorial, first author Eric D Peterson, Duke University Medical center, Durham NC

1 The study included few patients who received stents. The new approach may increase benefits of PCI + OMT.
I believe PCI + OMT in patients with severe angina should be first choice. While awaiting interventions, strict OMT should be applied.

“According To This Study Of Low-Risk Patients, The Risks Of Seizure Relapse Are In Fact Small.”

**8-10 ANTIEPILEPTIC DRUG WITHDRAWAL IN SEIZURE-FREE PATIENTS**

The ultimate goal of epilepsy treatment is to become seizure free and have a healthy life without the need to take antiepileptic drugs.

“The consequences of withdrawal of an antiepileptic in seizure-free patients has now been discussed for over 120 years, after bromides were introduced for the management of epilepsy by Locock in 1857.”

Although about 70% of patients with newly diagnosed epilepsy become seizure free with such drugs, many seizure free patients (and their physicians) prefer to continue medication, mainly for fear of relapse.

Withdrawal is controversial because evidence to guide it is lacking. Heretofore, there has been no class 1 evidence, based on randomized, double blind trials, for withdrawal in adults who become seizure free while taking antiepileptic drugs.

A benchmark study (the Akershus study) was published in *Epilepsia* in 2008:

Randomized 160 adult patients who were taking a single antiepileptic drug and who were seizure free for more than 2 years to:

1) Withdrawal
2) No withdrawal

Follow-up for 12 months or until seizure relapse:

Seizure recurrence:

1) Withdrawal 15% *
2) No withdrawal 7% *
3) After a median of 41 months off medication 27%

(*Difference not statistically significant)

A normal result to all 15 neuropsychological tests improved from 11% to 28% in those withdrawing from treatment. By contrast, the proportion of normal tests decreased from 11% to 9% in those remaining on treatment. (But still the difference was not statistically significant.)

Withdrawal did not affect quality of life and the EEG.

Predictors for remaining seizure free over 1 year:

Normal neurological examination

Use of carbamazepine (Generic; *Tegretol; Carbatrol*; Shire US) before withdrawal (perhaps due to selection bias).
Limitations:

The study was small.

The study excluded patients with a high risk of relapse after withdrawal: idiopathic generalized epilepsy; epileptiform discharges; juvenile myoclonic epilepsy; seizure free on use of polypharmacy; history of two previous withdrawal attempts; inability to assess the long-term prognosis of patients randomized to no-withdrawal.

Implications of the study:

Withdrawal was associated with an average of twice the risk of seizure relapse compared to those remaining on the drug. (However, the effect size was small and not statistically significant.) Neuropsychological outcomes improved somewhat in the withdrawal group. (But not statistically significant.)

Quality of life did not improve after withdrawal.

“We now have class 1 evidence about the benefits and risks of withdrawing antiepileptics in seizure-free adults that we did not have before.”

“It is reassuring, and very valuable that, according to this study of low-risk patients, the risks of seizure relapse are in fact small.”

“Patients and physicians are now better equipped to make the difficult decision to withdraw the drug, after taking into account important other factors, such as the preference of the patient, and the sometimes grave social consequences of seizure relapse.”
