PRACTICAL POINTERS

FOR
PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JANUARY 2007

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE
www.practicalpointers.org

PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA
Rjames6556@aol.com

This document is divided into two parts

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

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

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

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

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

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

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

Requests for "subscription" to rjames6556@aol.com

Distribution of Practical Pointers January 2007:

Successful requests	11,831
Successful requests for pages	6,748
Distinct hosts served	3,259
Sent directly to "subscribers" by e-mail attachment	236

HIGHLIGHTS AND *EDITORIAL COMMENTS* JANUARY 2007

"Should Now Be Considered A Part Of Routine Care Of Suitable Stroke Patients."

1-1 THROMBOLYSIS WITH ALTEPLASE FOR ACUTE ISCHAEMIC STROKE

Alteplase (recombinant tissue plasminogen activator) is currently the only approved therapy for patients with acute ischemic stroke. Most stroke associations recommend it as first-line treatment.

Randomized, controlled trials (**RCTs**) have shown that administration within 3 hours of onset of ischemic stroke symptoms is safe and effective.

This study assessed the benefits and harms of alteplase when incorporated into clinical practice across a wide range of centers. (Ie, a pragmatic study.) When it is applied to the community, is it as safe and effective as in RCTs?

Prospective, open, observational study recruited over 6400 patients (age 18 to 80; mean = 68) with stroke from 285 different centers in 14 countries. All received intravenous alteplase (0.9 mg/kg) within 3 hours of stroke onset. The patients had considerable co-morbidity.

Primary outcomes:

A. Symptomatic intracerebral hemorrhage:

At 24 hours	1.7%	(Symptomatic intracerebral hemorrhage was defined as a parenchymal hematoma on CT scan combined with 4 or more points worsening on the NIHSS.
At 7 days	7.3%	(Any degree of hemorrhage on CT combined with any neurological worsening. This compared with 8.6% in pooled RCTs)

B. Mortality within 3 months = 11%. (Compared with 17% in pooled RCTs.)

Deaths considered to be related to alteplase = 1.5% (96 patients)

C. Complete recovery at 3 months (Rankin score of 0 to 1 = 39% compared with 42% in RCTs).

Outcomes at centers with little experience in administering alteplase within 3 hours compared favorably with outcomes in centers with more experience.

Conclusion: Intravenous alteplase is safe and effective in routine clinical use in the community when used within 3 hours of stroke onset, even in centers with little experience.

RCTs ask the question: Can it work? (Efficacy)

Observational studies ask: Does it work for routine use in the community? (Effectiveness)

Cost-effective studies ask: How much does it cost? Is it worth it? (Efficiency)

This pragmatic study extends an important application to primary care (Effectiveness). I believe it will lead to greater interest in application of alteplase therapy in the community.

Substantial logistic problems connect with this application in the community:

1) Making community dwellers aware of the symptoms of stroke and encouraging them to request immediate assistance.

2) A coordinated and prompt emergency transportation system.

3) Provision of trained personnel in emergency departments.

4) Making prompt scanning facilities available 24-hours a day.

I congratulate the communities, the institutions, and the investigators on completion of a difficult and important study.

Thrombolytic therapy for stroke poses a dilemma—sort of a "Catch 22". There is no way one can determine if an individual patient will be harmed or benefited.

A. If the patient has little or no residual effects from the stroke, it is not possible to determine if the benefit was due to the thrombolysis. The stroke symptoms may have regressed spontaneously. Although the clinician and the patient may attribute improvement to the therapy, it actually may not have been due to the therapy.

B. If, on the other hand, the patient develops severe disability or dies from a hemorrhage, the clinician and the patient (and the family) will likely blame the thrombolysis for the disaster even if the outcome was due to the natural progression of the stroke.

I believe there are also ethical considerations. Is it ethical to administer a possibly lethal treatment to a patient without first fully informing the patient about risks and benefits, allowing him to make an informed choice? Will taking the time to discuss pros and cons with the patient extend the time to treatment beyond 3 hours?

Age; Blood pressure; Clinical Attributes; Duration

1-2 VALIDATION AND REFINEMENT OF SCORES TO PREDICT VERY EARLY STROKE RISK AFTER TRANSIENT ISCHEMIC ATTACK

This study aimed to validate two existing scores for early risk of stroke after a TIA, and to derive and validate a unified score for prediction of 2-day stroke risk. Patients at high risk need immediate evaluation to optimize stroke prevention. The 2-day risk of stroke after a TIA is most relevant for decisions about urgent evaluation and observation.

This study evaluated over 4800 individuals with TIA. Most patients presented within 24 hours. (Patients who present after 2 days may have an entirely different prognosis.)

Overall, stroke occurred in 442 patients: 4% within 2 days; 5.5% within 7 days; 7.5% within 30 days; 9% within 90 days

The new score (ABCD2) consisted of 5 factors:	Points	
Age 60 or over	1	
BP > 140/90	1	
Unilateral weakness	2	
Speech impairment without weakness	1	
Duration > 60 minutes	2	
Duration 10-59 minutes	1	(A total of 7 to 8 points possible)

(No mention of visual defects. RTJ)

	ABCD2		Risk of stroke (%)		
	Points	% of patients	2-day	7-day	90 day risk
High risk	6-7	21	8	12	18
Moderate risk	4-5	45	4	6	10
Low risk	0-3	34	1	1.2	3.1

Risks of stroke after a TIA are similar to risk of a myocardial infarction after presentation with chest pain. The investigators suggest that stroke has as devastating consequences as myocardial infarction. Patients presenting with chest pain are often treated urgently and observed for 24 hours in the hospital. Patients with TIA should receive the same consideration.

The ABC2 score might be useful in determining which patients are admitted and which need assessment within 24 hours. Based on a previous cost-utility analysis, and ABCD2 score of 4 or greater might justify a 24-hour admission solely on the basis of a greater opportunity to administer thrombolysis early if a subsequent stroke occurs in the hospital as opposed to at home.

The presence of new ischemic lesions on MRI or CT in patients with transient symptoms can portend an increased short-term risk of stroke. Clinical risk scores and imaging studies can be combined to predict risk.

"Brain and vascular imaging is recommended for all patients with TIA to identify causes and target efforts to prevent stroke."

Conclusion: The ABCD2 score is likely to be more predictive of stroke, especially within 2 days. Patients at high risk need immediate evaluation to optimize stroke prevention.

With the advent of thrombolytic therapy, close observation is required for patients with TIA to determine if stroke will occur, and to make preparations for prompt thrombolytic therapy if it does occur. This would be much easier in hospitalized patients.

I believe this guide would help primary care clinicians to quickly triage patients.

"Physicians Have Become More Comfortable About Using These Drugs"

1-3 OPIOID PRESCRIPTIONS SOAR

Increase in Legitimate Use as Well as Abuse

According to a recent survey—"Pain is a serious, undertreated health problem in the United States—19% of US adults reported chronic pain; 34% reported recurrent pain. Some 63% of patients with pain had spoken to their physician about their pain, but only 31% reported complete relief, and 21% reported little or no relief."

Campaigns to make pain control a priority have succeeded in raising patient and physician awareness of the need for analgesics. Opioids are now among the most prescribed drugs.

By far, the most commonly used prescription analgesic in the US is hydrocodone/acetaminophen (eg. *Vicodin*), with over 100 million prescriptions in 2005.

"Physicians have become more comfortable about using these drugs as they have learned more about them." Physical dependence on a drug, which develops in most patients who use opioids for prolonged periods, can be treated by tapered withdrawal. This differs from addiction and its associated damaging behaviors.

State and national organizations are emphasizing the importance of managing pain. "These policies provide reassurance to physicians that appropriate prescribing will not lead to punitive action."

The positive trend in legitimate use in improving pain control in patients has been shadowed by growing abuse of opioids. There is a growing trend of abuse of prescription pain medications.

In the US, the abuse of prescription pain medications is widespread and is not concentrated in urban areas. In addition to pharmacy theft and stealing or sharing the prescriptions of friends and relatives, "doctor shopping" is another possible source of abuse.

The article presents a guideline from the Federation Of State Medical Boards outlining physicians' responsibilities regarding their oversight of prescription narcotics.

Pain-control is one of the most important functions of primary care.

I believe most primary care clinicians know their patients well, and can and do monitor prescription drug use carefully to avoid misuse.

The Epidemiology Is Changing. Adolescents And Adults Need Immunization

1-4 THE CONTROL OF PERTUSSIS—2007 AND BEYOND

During the past 2 decades, there has been a slow, steady resurgence of pertussis, although rates have not approached the levels of the pre-vaccine era. The shift from the whole-cell vaccine in the 1990s to the acellular vaccine was associated with reduced rates of adverse effects. But the incidence of pertussis continued to increase.

The epidemiological shift is probably multifactorial:

Limited duration of immunity from both the natural infecting and vaccination.

Increasing incidence of infection in adolescents and adults who previously received a less-effective whole-cell vaccine.

Improved laboratory methods for diagnosis..

The changing picture probably represents both a real epidemic and a pseudo-epidemic. The "marching cohort" of infected preadolescents and adolescents indicates that the shift in epidemiology is not just a consequence of changing patterns of laboratory testing.

Pertussis remains underdiagnosed and underreported. Practitioners will need to carefully evaluate patients in whom they suspect pertussis.

The Advisory Committee on Immunization Practices recommends that all adolescents and adults receive acellular vaccine combined with diphtheria and tetanus toxoid (Tdap).

The Johns Hopkins web site to guide therapy for infectious disease (http://hopkins-abxguide.org/):

Advises clarithromycin or erythromycin as first choice therapy for pertussis

Second choice—trimethoprim-sulfamethoxizole

"There Is No One Division Of Medicine By Which We Know And Another By Which We Act. "

1-5 WHAT STAYS CONSTANT AT THE HEART OF MEDICINE

To identify the art of medicine with "artfulness" is to fall into a set of modern confusions. The art of medicine is not about appearance at the expense of substance, but rather the way in which knowledge is related to advice and treatment.

The problem might be reformulated in this way: medicine requires knowledge of universals, and of the application of them to particular instances as embodied in individual patients.

Medical art may be a form of knowledge that is more probabilistic than the demonstrative certainty of science, but it is crucially important knowledge nevertheless. Its exercise requires not only knowledge of content, but something called "judgment". Judgment requires attending to a patient.

For thousands of years, the question of how best to associate the universal and the particular has been the real doctor's dilemma. No formulae, however good, can ever obscure the second part of medical knowledge, which comes from clinical judgment.

Few, if any, primary care clinicians completely master melding the "art" with the "science". But keep on trying.

"Outcomes Of RCTs Should Always Be Extrapolated With Caution To Real-Life Patients."

1-6 EXTERNAL VALIDITY OF CLINICAL TRIALS IN ACUTE MYOCARDIAL INFARCTION

The relevance of randomized controlled trials (**RCTs**) to clinical practice may be hampered by doubts regarding their external validity. RCTs tend to recruit highly selected populations that may not represent patients encountered in everyday practice.

This study compared: 1) patients with acute myocardial infarction (**AMI**) enrolled in RCTs of reperfusion therapy with 2) patients with AMI who were eligible for enrollment but who were not enrolled and with 3) patients with AMI who were not eligible for enrollment.

Based on baseline characteristics, patients included in the RTCs differed from those not included (but eligible) and from those considered ineligible. Patients included had the lowest baseline risk of death: lower age; fewer women; and less frequent past history of myocardial infarction, diabetes, hypertension, TIA and stroke, and peripheral arterial disease.

Patients in the group eligible of inclusion in the RCT (but not included) had higher baseline risks of death. Ineligible patients had still higher risks. Actual hospital mortality showed a similar gradient (3.6%; 7.1%; 11.4%)

.It is usually accepted that, while RCTs enroll a highly selected population, the outcomes can be extrapolated to real-life patients who fulfill the main inclusion and exclusion criteria, but are not enrolled.

There are important concerns about the external validity of RTCs

Conclusion: Patients with AMI enrolled in RCTs differed markedly in terms of their baseline characteristics, hospital treatment, and outcomes from patients who would have been eligible for inclusion, but were not included.

Caution is necessary when extending the findings obtained in RTCs to the general population.

Although primary care clinicians would not likely care for many patients with AMI in hospitals, I abstracted this article to again point out the pitfalls of too strict application of results of RCTs to individual patients seen in every day primary care practice.

We must always ask "Do the results of this RTC apply to my next patient?" There are many reasons why they may not apply, and may cause more harm than benefit.

Many times social constraints prevent application of the RCT treatment: very old age, lack of insurance, medical illiteracy, and patient non-compliance and preference.

Keen clinical judgment must be applied to all patients. The "art" of medicine is indeed a long and difficult.

Read the following abstract.

H Pylori Is Likely To Cause About 9% Of Dyspepsia Cases Where No Ulcers Are Detected.

1-7 DYSPEPSIA AND HELICOBACTER PYLORI

Dyspepsia is not a diagnosis. It is a term used to describe a range of symptoms, from upper abdominal pain to heartburn, nausea, bloating, and retrosternal pain. It occurs in up to 40% of adults in the UK. A general practitioner will see on average 210 patients with dyspepsia each year.

Most dyspepsia is "functional"—ie, no abnormalities are found on endoscopy.

The Cochran review of initial management strategies for dyspepsia:

Proton pump inhibitors **(PPIs**) are more effective than histamine receptors and antacids.

Initial endoscopy is associated with a small reduction in risk of recurrent dyspepsia symptoms compared with test and treat. But, it is not cost-effective.

Test and treat for H pylori may be more effective than acid suppression alone.

Infection with H pylori is likely to cause about 9% of dyspepsia cases where no ulcers are detected.

You should urgently refer patients older than age 55 with dyspepsia of recent onset that is persistent (lasting 4 to 6 weeks), or unexplained (not related to NSAIDs) even in the absence of alarm symptoms.

Do not underestimate the risks associated with NSAIDs. About 10% to 20% of people who use these drugs regularly will develop peptic ulcer that is detectable with endoscopy. 1% develop perforation or bleeding. Offer protection with a PPI to those who require NSAIDs regularly.

Screening: "Would screening the general population for H pylori be cost effective?" Probably not.

Diagnosis: The urea breath test is the most accurate way to detect H pylori.

In dyspeptic patients positive for H pylori, eradication treatment has been reported to relieve symptoms in 3% to 14% of patients.

Which eradication treatment?

Seven day full dose PPI + either

1) Metronoidazole 400 mg + clarithromycin 250 mg, or

2) Amoxicillin 1 g + clarithromycin 250 mg

No mention of the possible connection between H pylori and gastric cancer.

Read the full abstract. for details

"A Mere Leap Of Faith." ?

1-8 THE PREVENTIVE POLYPILL—Much Promise, Insufficient Evidence

Dr. K S Reddy of the All India Institute of Medical Sciences discusses the pros and cons of the "Polypill" The pill, was proposed in 2003 by Wald and Law for *universal* use by persons over age 55 to reduce the risk of acute coronary events and stroke. It contained a statin drug, a thiazide, an ACE-inhibitor, a beta-blocker, low-dose aspirin, and folic acid, aimed at reducing LDL-cholesterol, blood pressure, platelet adhesiveness, and homocysteine.

Wald and Law suggested the pill could reduce cardiovascular disease in the population by more than 80%.

The pill would be more readily accepted for *secondary* prevention of cardiovascular disease. For *primary* prevention, the benefit/harm-cost ratio is uncertain.

Read the full abstract.

When I first read the article I thought the authors were presenting the "pill" tongue in cheek. Not so. The staying power of this suggestion has been remarkable.

Many people in the USA are already taking one, two, three, or four of the components. Aspirin, folic acid (in a daily vitamin supplement) and simvastatin (in the UK) are now available over-the-counter.

This goes against the traditional approach to risk reduction by drugs. But, I suspect that many people would take the pill if offered.

At present, outrageous and toxic nostrums and "herbal" medications (for which there is certainly "insufficient evidence") are widely advertised and freely available over-the-counter.

Why not the "polypill"?

Are Popular, Are Safe, But Are They Effective?

1-9 EFFICACY OF GLUCOSAMINE AND CHONDROITIN AS SUPPLEMENTS TO TREAT OSTEOARTHRITIS

Glucosamine and chondroitin sulfate are popular over-the-counter drugs. Glucosamine is an amino sugar that may play a role in cartilage formation. Chondroitin is one of the proteoglycans that give cartilage elasticity. They are considered to be "supplements" and are not regulated by the FDA. An estimated 1 million people in the US take them. Their effectiveness in easing joint pain and preventing disease progression is unproven.

Results from clinical trials are interpreted differently.

The largest study to date, funded by the National Institutes of Health, compared: glucosamine-alone; chondroitin-alone; both combined; celecoxib; and placebo. The study concluded that glucosamine-chondroitin in combination may be effective in the subgroup of patients with moderate or severe knee pain. But, "The outcome of GAIT was not straight forward, so it was difficult to give a distinct and clear message." There was an unusually high response rate (60%) in the placebo group. "This and other trials with glucosamine and chondroitin have faced challenges in design, implementation, and analysis."

Stakeholders are remarkably polarized on these issues.

Since supplements are not regulated by the FDA, a lack of standardization and quality control can make it difficult to accurately interpret and compare studies.

While disagreement persists about efficacy, almost all agree that these supplements are safe.

It is remarkable and somewhat discouraging that, after all these years, the benefit/harm-cost ratio of these supplements is not clarified The numerator is in doubt. The denominator is clearer. Harm is nil. Cost …..…

How should the primary care clinician act on this information? There must be a large placebo effect in reducing discomfort from osteoarthritis. If my patient finds the drug(s) helpful, I would not dissuade her from taking them. Alternative drugs, including acetaminophen and NSAIDs may or may not be more helpful. But they may be more harmful, and may not cost less.

I could suggest a N = 1 trial for an individual. I doubt if many would implement and conclude it.

I do believe the supplements do have some beneficial effect (beyond the placebo effect), based mainly on the fact that they continue to be used by so many persons over so many years.

Benefits Were Mediated By Drug Effects; They Did Not Reflect "Healthy Behavior".

1-10 RELATIONSHIP BETWEEN ADHERENCE TO EVIDENCE-BASED PHARMACOTHERAPY AND LONG-TERM MORTALITY AFTER ACUTE MYOCARDIAL INFARCTION.

This study asks: Are the benefits of drugs attributable to a drug's biological responsiveness (drug effect), or to the adoption of healthier lifestyles that often accompany adherence behaviors (healthy user effect)? Are mortality differences after an acute myocardial infarction (**AMI**) attributable to the "healthy adherer" effect, or due to the pharmacological action of drugs?

The population-based observational study followed over 31 000 elderly survivors of AMI (mean age 75). All patients had filled at least one of 3 possible drug prescriptions: statins, beta-blockers, or calcium blockers. Statins and beta-blockers are recommended for secondary prevention after an AMI. Calcium blockers were considered a control, given the absence of any clinical trial-proven post AMI survival benefit.

Divided patient adherence into 3 categories:

1) High adherence (80% or over of days covered).

2) Intermediate (40% to 79% of days covered)

3) Low (less the 40% of days covered)

Follow-up = a median of 2.4 years. Main outcome measure = long-term survival.

Results:

Deaths (%)	High adherers	Intermediate adherers	Low adherers
Statins	16	20	24
Beta-blockers	21	23	25
Calcium blockers	30	31	27

(No statistically significant association between calcium blocker use and mortality.)

There was a positive and graded relation between mortality and adherence to drugs known to be effective in secondary prevention in patients with a history of AMI. There was no relationship between mortality and adherence to a drug known to be ineffective in secondary prevention.

Conclusion: The mortality benefits associated with adherence to drugs known to be effective in secondary prevention of mortality after an AMI were mediated by drug effects more so than by generic healthy-adherer behavioral attributes.

This underscores the need to optimize patient behavior patterns which will increase adherence to taking effective drugs prescribed for secondary prevention. This will maximize survival gains of drug therapies in real-world populations.

I believe the "healthy user" effect could be applied to all drugs, effective as well as ineffective. The healthy user benefit would be due to more favorable lifestyles adopted by persons who are conscientiously concerned about their health.

Lifestyle interventions take a long-time to become evident. The effect would not be evident in high-risk patients in whom adverse outcomes occur over a short time (as following AMI). This may be the reason no benefit was evident in the calcium blocker group—no time to occur.

Part of the reason statins and beta-blockers demonstrate benefit may have been due to the healthy user effect, but it would be more evident long-term in patients not at high risk.

"Significantly Improved Domains Of Cognitive Function"

1-11 EFFECT OF 3-YEAR FOLIC ACID SUPPLEMENTATION ON COGNITIVE FUNCTION IN OLDER ADULTS: The FACIT Trial

Poor folate status is a suspected risk factor for age-related cognitive decline.

This trial considered the effect of folic acid supplementation on cognitive function in older adults in the Netherlands who had higher homocysteine levels. (A possible indicator of folic acid deficiency.)

On the assumption that a high concentration of plasma homocysteine is a risk factor for vascular disease, the trial selected subjects expected to benefit from folic acid's homocysteine-lowering effect. It excluded participants with normal plasma homocysteine concentrations (less than 13 umol/L; 73% of those screened)

Changes (mean) in cognitive performance over 3 years: (Z scores)

	Folic acid	Placebo	
Global cognitive function	+ 0.067	-0.031	
Memory	+0.480	+0.142	
Information processing speed	-0.072	-0.159	(All statistically significant)

By the investigators calculation, the 3-year folic acid supplementation (mean age 60 to 63) conferred to an individual the performance of someone 4.7 years younger for memory, 2.1 years younger for information processing speed, and 1.5 years younger for global cognitive functioning.

Memory—specifically delayed memory—is the most clinically relevant test. Supplementation improved

performance on the delayed recall sub-test of the 15 word-learning test by 0.47 words, similar to a performance of an individual 6.9 years younger.

"Given the general scarcity of positive findings from other trials . . . our results need to be confirmed by other investigators."

Conclusion: In patients with raised serum homocysteine levels, 3-year folic acid supplementation improved performance on tests that measure information processing speed and memory domains that are known to decline with age.

The effect of folic acid on atherosclerosis has been controversial and continues to be hotly debated.

Although doubt persists, there is provocative evidence that low folic acid levels (and high homocysteine levels) are related to increased risk of atherosclerotic disease—and now, cognitive function.

The benefit/harm-cost ratio of folic acid supplementation may be high in those with higher homocysteine levels. Although the benefit is still not established, the denominator of the ratio (harm and cost) is extremely low. Thus, the ratio may be high.

How should the primary care clinician act on this information about higher doses of folic acid?

I would not advise patients to purchase a separate supplement of 800 ug of folic acid. I would advise them that the folic acid content of the daily multivitamin supplement (usually containing 400 ug) they may be taking may be beneficial.

More effective, however, are the well-established means of retarding the atherosclerotic process, thus preventing the adverse effects of atherosclerosis on the brain (vascular dementia).

I congratulate the investigators on completion of a detailed and difficult study. They are understandably enthusiastic about the benefits of folic acid. However, they caution that confirmation is required. The study does not establish any clinically significant benefit in delaying onset of dementia.

Benefits of Combined Therapy Are Questionable. There Is An Increased Risk Of Major Bleeding.

1-12 COMBINED ASPIRIN-ORAL ANTICOAGULANT THERAPY COMPARED WITH ORAL ANTICOAGULANT THERAPY ALONE AMONG PATIENTS AT RISK FOR CARDIOVASCULAR DISEASE

Combination therapy [**CT**]—oral anticoagulants [**OAC**] + low-dose aspirin—is recommended by the American College of Chest Physicians *only* for patients with a mechanical prosthetic heart valve. Despite this recommendation, a considerable number of patients with chronic atrial fibrillation (**AF**) receive combined therapy.

Despite a lack of evidence for the efficacy of CT, some experts have suggested that adding aspirin to OAC therapy might be useful because patients using OAC frequently have concomitant coronary artery disease, or are at high risk for stroke.

This systematic review and meta-analysis of randomized controlled trials (**RCTs**) compared OAC-alone with OAC + aspirin to assess benefits and risks.

Risk of arterial thromboembolism was lower in the OAC + aspirin groups, but *only* in studies of mechanical valves. (Odds ratio OAC + aspirin vs OAC alone = 0.27)

There was no difference in outcomes (OAC + aspirin vs OAC-alone) in risk of arterial thromboembolism in patients with atrial fibrillation or coronary disease.

The risk of major bleeding was higher in patients receiving combined therapy:

Combined therapy 3.8%

OAC-alone 2.8%

NNT to harm = 100.

Conclusion: Benefits from combined OAC + aspirin in reducing thromboembolic events are questionable. There is an increased risk of major bleeding.

I believe primary care clinicians should be very wary of prescribing combined therapy.

"Extensive Periaortic Inflammation" "It Is Not Uncommon"

1-13 INFLAMMATORY ABDOMINAL AORTIC ANEURYSM

This article describes an important variant AAA, inflammatory AAA (**I-AAA**), the symptoms of which are so protean that patients may present to a wide range of physicians. Like classical atherosclerotic A-AAA, it most commonly affects the infrarenal portion of the aorta.

I-AAA was not described before 1972. Few physicians are familiar with it.

It differs from classical A-AAA in many ways:

The risk of rupture in less than 5%.

Patients are usually younger, male and smokers.

The great majority of patients with I-AAA are symptomatic at presentation (in contrast to A-AAA). Pain in the back and abdomen is common. Abdominal tenderness (with or without a pulsating mass) occurs in about one third of patients. Systemic symptoms (fever, malaise, weight loss) may be associated. Symptoms are so protean that patients may present to a wide range of physicians.

CT and MRI imaging show a characteristic cuff of soft tissue inflammation surrounding the aneurysm. There is an extraordinary expansion of the adventitia due to inflammation.

It may be an autoimmune disorder. Sed rate, C-reactive protein and other inflammatory cytokines may be elevated.

Corticosteroids and corticosteroid-sparing drugs (eg, methotrexate). relieve symptoms and reduce the inflammation.

Smoking cessation is critical.

This was my introduction to inflammatory abdominal aortic aneurysm. (I-AAA)

I spent a lot of time abstracting details about I-AAA. I believe it was worthwhile. I-AAA patients may present with obscure symptoms, especially back and abdominal pain. Abdominal scan may reveal the diagnosis and lead to effective symptomatic treatment.

Although the condition is rare, primary care clinicians should know about it.

Read the full abstract for a description of an individual case.

ABSTRACTS JANUARY 2007

"Should Now Be Considered A Part Of Routine Care Of Suitable Stroke Patients."

1-1 THROMBOLYSIS WITH ALTEPLASE FOR ACUTE ISCHAEMIC STROKE

The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST)

Concern has focused on the speed of emergency response, since the time taken to initiate thrombolytic treatment after the onset of stroke symptoms affects the extent of tissue damage and the possibility of recovery without impairment.

Alteplase (recombinant tissue plasminogen activator) is currently the only approved therapy for patients with acute ischemic stroke. Most stroke associations recommend it as first-line treatment.

Randomized, controlled trials (**RCTs**) have shown that administration within 3 hours of onset of ischemic stroke symptoms is safe and effective.

There are concerns about the applicability of alteplase in routine practice, especially considering the short time within which treatment must be given, and the potential risks of intracerebral hemorrhage from the thrombolysis.

This study assessed the benefits and harms of alteplase given within 3 hours of stroke onset when incorporated into clinical practice across a wide range of centers. (Ie, a pragmatic study.) When it is applied to the community, is it as safe and effective as in RCTs?

Conclusion: Alteplase was effective and safe in routine practice when used within 3 hours.

STUDY

1. Prospective, open, observational study recruited over 6400 patients (age 18 to 80; mean = 68) with stroke from 285 different centers in 14 countries. All received intravenous alteplase (0.9 mg/kg) within 3 hours of stroke onset. The patients had considerable co-morbidity.
2. About half of the centers had little previous experience with thrombolysis in stroke patients.
3. All centers fulfilled the eligibility criteria for inclusion in the study: national recognition as a stroke unit; routine monitoring of patients during and after thrombolysis; a policy of early mobilization and rehabilitation of stroke patients; holding a neurologist or stroke specialist with considerable experience responsible for clinical oversight.
4. Exclusion criteria:

   Age over 80

   Severe neurological deficits (NIHSS[1] score > 25)

   BP > 180/110

   Treatment initiation over 3 hours after symptom onset

. Previous stoke within 3 months

   Previous stroke with residual dysfunction in combination with treated diabetes

   Taking anticoagulants

4. Primary outcomes = symptomatic intracerebral hemorrhage and death within 3 months.

RESULTS

1. Baseline characteristics:

Mean age = 68

Degree of neurological severity

Mild	23%	NIHSS 1-7
Moderate	37%	NIHSS 8-14
Severe	40%	NIHSS = or > 15

Causes of stroke included large vessel disease with substantial carotid stenosis; large vessel disease other than substantial carotid stenosis; cardiac origin; and lacunar stroke.

Signs of current infarction on baseline imaging in 20%

Stroke onset to treatment time = mean of 140 minutes.

Treated within 90 minutes	11%
Treated within 90 to 120 minutes	23%
Treated within 120 to 180 minutes	66%

Door to needle time (mean) = 68 minutes.

2. Primary outcomes:

A. Symptomatic intracerebral hemorrhage:

At 24 hours 1.7% (Symptomatic intracerebral hemorrhage was defined as a parenchymal hematoma on CT scan combined with 4 or more points worsening on the NIHSS.

At 7 days 7.3% (Any degree of hemorrhage on CT combined with any neurological worsening. This compared with 8.6% in pooled RCTs)

B. Mortality within 3 months = 11%. (Compared with 17% in pooled RCTs.)

Cause of death

Fatal intracerebral hemorrhage within 24 hours = 0.28% (18 patients)

Fatal intracerebral hemorrhage within 7 days = 2.2% (144 patients)

Deaths considered to be related to alteplase = 1.5% (96 patients)

3. Complete recovery at 3 months (Rankin score[2] of 0 to 1 = 39%, compared with 42% in RCTs).

4. Outcomes at centers with little experience in administering alteplase within 3 hours compared favorably with outcomes in centers with more experience.

DISCUSSION

1. RCTs (alteplase vs placebo) have shown that about 10% more patients who receive alteplase achieve functional independence (Rankin score 0 to 1) within 3 months than those who receive placebo.

2. Compared to RTCs, alteplase given in this observations study, was about as effective treatment, even in centers with little previous experience.

3. Alteplase, when used in routine practice, has a safety profile at least as good as that seen in RCTs. The proportion of patients who developed symptomatic intracerebral hemorrhage was much the same as in RCTs.

4. There was a greater reduction in mortality within the first 3 months in SITS-MOST compared with RCTs (11% vs 17%). (This may have been due in part because of more exclusion criteria in SITS-MOST.)
5. By the end of the study, about 50% more centers had been recruited. This shows broad implementation, increased awareness, and growing practical ability to provide thrombolysis within 3 hours. Neither the proportion of patients with symptomatic intracerebral hemorrhage nor the degree of independence at 3 months differed between experienced and new centers.
6. "Our data suggest that thrombolysis should now be considered a part of routine care of suitable stroke patients."

CONCLUSION

Intravenous alteplase is safe and effective in routine clinical use in the community when used within 3 hours of stroke onset, even in centers with little experience.

Lancet January 27, 2007; 369: 275-82 Original investigation, first author Nils Wahlgren, Karolinska Institute, Stockholm, Sweden

Study funded by Boehringer Ingelheim

Both the Rankin stroke score and the National Institutes of Health Stroke scale are available at GOOGLE

1 The National Institutes of Health Stroke Severity Score. (NIHSS)

Consists of 11 functional categories (from level of consciousness to extinction or inattention) with 0 to 2, 3, or 4 subdivisions which add up to 32 points. It is presented in Lancet January 27, 2007;369:321

2 The Rankin stroke score

The score ranges from 0 to 5 and 6. 0 = no symptoms at all; 1 = no significant disability; 2, 3,and 4 indicate increasing disability, 5 = severe disability and need for assistance; 6 = death

==========

Age; Blood pressure; Clinical Attributes; Duration

1-2 VALIDATION AND REFINEMENT OF SCORES TO PREDICT VERY EARLY STROKE RISK AFTER TRANSIENT ISCHEMIC ATTACK

The overall incidence of transient ischemic attacks (**TIA**) approaches that of stroke. Patients with TIA are generally unstable: 4% to 20% will have a stroke within 90 days, half of these within the first 2 days. Most, however, will have a benign short-term course.

Identification of those at highest and lowest risk in the first days would allow appropriate use of costly secondary prevention strategies, including hospital admission.

Two prognostic scores for short-term risk of stroke have been proposed.[1,2] Both rely on summation of points associated with clinical factors independently predictive of stroke risk. The California score predicts risk within 90 days; the ABCD score predicts risk within 7 days. They have several factors in common.

The 2-day risk of stroke after a TIA is often most relevant for decisions about urgent evaluation and observation. (Complete diagnostic evaluation would be difficult to implement within 48 hours in the outpatient setting.)

This study aimed to validate the two existing scores for early risk of stroke and to derive and validate a unified score for prediction of 2-day stroke risk. Patients at high risk need immediate evaluation to optimize stroke prevention.

Conclusion: The new score (ABCD2) predicted 2-day risk of stroke.

STUDY

1. This study evaluated over 4800 individuals with TIA. Most patients presented within 24 hours. (Patients who present after 2 days may have an entirely different prognosis.)
2. The California and the ABCD scores were validated in 4 independent groups of patients diagnosed with TIA in defined populations in the USA and UK. The two groups were used to derive a new unified score.
3. The diagnosis of TIA was based entirely on the opinion of the initial treating doctor so that the results would be generalisable to patients not diagnosed by stroke specialists.
4. Stroke was defined as a rapidly developing clinical symptom of local (or occasionally global) disturbance of cerebral function lasting more than 24 hours or until death, with no apparent non-vascular cause, that was clearly distinguishable from the event leading to the initial diagnosis of TIA.

RESULTS

1. Overall, stroke occurred in 442 patients: 4% within 2 days; 5.5% within 7 days; 7.5% within 30 days; 9% within 90 days.
2. Only 5 of 442 were hemorrhagic strokes. All others were ischemic.
3. Death within 90 days = 20%.
4. Since both previous prognostic scores validated well across a wide range of populations and contained similar components, the investigators generated a unified prognostic score for optimum prediction of 2-day risk.
5. The new score (ABCD2) consisted of 5 factors:

	Points
Age 60 or over	1
BP > 140/90	1
Unilateral weakness	2
Speech impairment without weakness	1
Duration > 60 minutes	2
Duration 10-59 minutes	1 (A total of 7 to 8 points possible)

(No mention of visual defects. RTJ)

6.:

	ABCD2		Risk of stroke (%)		
	Points	% of patients	2-day	7-day	90 day risk
High risk	6-7	21	8	12	18
Moderate risk	4-5	45	4	6	10
Low risk	0-3	34	1	1.2	3.1

7. Scores were grouped to create strata for low, moderate, and high risk, with the goal of identifying patients who could be managed non-urgently and those who need priority evaluation.
8. A policy dictating admission for all those with moderate or high risk would have resulted in 66% of patients being admitted.

DISCUSSION

1. This study created a unified score (ABCD2) for predicting 2-day risk of stroke after a TIA.
2. The new score also predicted stroke risks at time points varying from 7 days to 90 days.
3. Overall, the risks of stroke after a TIA are considerable. Risks of stroke after a TIA are similar to risk of a myocardial infarction after presentation with chest pain. The investigators suggest that stroke has as devastating consequences as myocardial infarction. Patients presenting with chest pain are often treated urgently and observed for 24 hours in the hospital. Patients with TIA should receive the same consideration.
4. Recommended acute approaches to patients with TIA include: brain imaging; carotid imaging; antiplatelet therapy; and statin drugs. Urgent carotid imaging may be especially pertinent because endarterectomy for patients with substantial symptomatic carotid stenosis is more effective if done early.
5. The ABC2 score might be useful in determining which patients need urgent assessment, and should be admitted. Based on a previous cost-utility analysis, and ABCD2 score of 4 or greater might justify 24-hour admission solely on the basis of a greater opportunity to administer thrombolysis early if a subsequent stroke occurs in the hospital as opposed to at home.
6. The 21% of patients classified as high risk (score 6 or more) are likely to benefit from urgent evaluation, observation, and treatment. Conversely, most patients with a score of 3 or less will not need hospital observation. For those with a score of 4 or 5 the risk is substantial. Constraints of the health-care system are likely to be more important in determining the necessity of observation for this group.
7. The ABCD2 score might predict risk of stroke partly because it identifies patients more likely to have had a true TIA.
8. The diagnosis of TIA, however, is not reliable. Transient neurological symptoms may be indistinguishable from those due to focal brain or retinal ischemia. Spells of longer duration and those accompanied by focal weakness might be more likely to represent a true TIA. Imaging studies show a higher prevalence of new ischemic brain lesions in patients with clinical TIA who have these characteristics.
9. Incidence of cerebral ischemia increases with age and with diabetes.
10. Frequency of acute ischemic lesions on MRI in patients with TIA increased with the original ABCD score.
11. The presence of new ischemic lesions on MRI or CT in patients with transient symptoms can portend an increased short-term risk of stroke. Clinical risk scores and imaging studies can be combined to predict risk.
12. “Brain and vascular imaging is recommended for all patients with TIA to identify causes and target efforts to prevent stroke.”
13. The ABCD2 score might be useful for educating the public.

CONCLUSION

The ABCD2 score is likely to be more predictive of stroke after TIA, especially for risk of stroke within 2 days. Patients at high risk need immediate evaluation to optimize stroke prevention.

Lancet January 27, 2007; 36(: 283-92 Original investigation, first author S Claiborne Johnston, University of California, San Francisco.

1 "Short-term prognosis after emergency department diagnosis of transient ischemic attack" JAMA 2000; 284: 2901-06 (The California Risk score)

2 A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischemic attack" Lancet 2005; 366: 29-36

The "ABCD" is a mnemonic:

A age (over and under age 60)

B blood pressure (over 140/90)

C clinical features (the ABCD2 score includes 2 clinical characteristics: unilateral weakness and impaired speech)

D duration (The ABCD2 score contains 2 durations—10 to 59 minutes and over 59 minutes.)

An editorial in this issue of Lancet (p 247) comments: "Implementation of interventions that reduce hypertension, poor diet, and tobacco use will save more lives than all the thrombolytics, antiplatelets, and neuroprotectants combined. There is little doubt that for stroke, prevention really is better than cure."

Another article in this issue (pp 293-98) first author Julio A Chalela, Medical University of South Carolina, Charleston, concludes that MRI is better than CT for detection of acute ischemia. It should be preferred for accurate diagnosis of patients with suspected acute stroke.

==========

"Physicians Have Become More Comfortable About Using These Drugs"

1-3 OPIOID PRESCRIPTIONS SOAR

Increase in Legitimate Use as Well as Abuse

Campaigns to make pain control a priority have succeeded in raising patient and physician awareness of the need for analgesics. Opioids are now among the most prescribed drugs.

According to a recent survey—"Pain is a serious, undertreated health problem in the United States—19% of US adults reported chronic pain; 34% reported recurrent pain, Some 63% of patients with pain had spoken to their physician about their pain, but only 31% reported complete relief, and 21% reported little or no relief."

The problem may worsen as the population ages.

Recognizing these needs, physicians have been treating pain more aggressively, including use of opioids. Between 1999 and 2002, oxycodone prescriptions increased by 50%; fentanyl by 150%; morphine by 60%.

In addition to increased awareness of the importance of pain control, pain experts attribute the overall increases in prescription pain medication to support and requirements for appropriate pain control from state medical boards, and advances in the science of pain control.

By far, the most commonly used prescription analgesic in the US is hydrocodone/acetaminophen (eg. *Vicodin*), with over 100 million prescriptions in 2005.

Physicians are likely to chose a short-acting opioid combination such as hydrocodone/acetaminophen for treating chronic intermittent pain. It is easier for physicians to prescribe schedule III drugs such as hydrocodone/acetaminophen because, under current federal law, they can provide a prescription which may be refilled up to 5 times in 6 months.

"Physicians have become more comfortable about using these drugs as they have learned more about them." Physical dependence on a drug, which develops in most patients who use opioids for prolonged periods, can be treated by tapered withdrawal. This differs from addiction and its associated damaging behaviors.

State and national organizations are emphasizing the importance of managing pain. "These policies provide reassurance to physicians that appropriate prescribing will not lead to punitive action."

The positive trend in legitimate use in improving pain control in patients has been shadowed by growing abuse of opioids. There is a growing trend of abuse of prescription pain medications. A study in Canada (2006) reported that use of prescription opioid drugs has become "the predominant form of illicit opioid use". Most individuals abusing prescription opioids reportedly obtained them directly from the medical system or indirectly through friends of partners.

In the US, the abuse of prescription pain medications is widespread and is not concentrated in urban areas. In addition to pharmacy theft and stealing or sharing the prescriptions of friends and relatives, "doctor shopping" is another possible source of abuse.

Physicians' responsibilities: (Guideline from the Federation of State Medical Boards):

- Obtain and document a physical examination and thorough medical history, including the patient's history of drug use and the effect of pain on the patient's function.
- Develop a written treatment plan, including objectives to determine whether treatment has been successful. Keep accurate and complete medical records.
- Obtain a patient's informed consent and possibly ask patients at high risk of abuse to sign an agreement outlining their responsibilities.
- Conduct periodic reviews during the patient's course of treatment, possibly including information from family members or caregivers.
- Be willing to refer patients to specialists when appropriate.
- Comply with controlled substances laws and regulations.

JAMA January 17, 2007; 297: 249-51 "Medical News and Perspectives" commentary by Bridgit M Kuehn, JAMA staff.

The Epidemiology Is Changing. Adolescents And Adults Need Immunization

1-4 THE CONTROL OF PERTUSSIS—2007 AND BEYOND

In November 2006, an outbreak of whooping cough affected one patient and 15 staff members of The Boston Children's Hospital.

In Dartmouth Medical Center in 2006, more than 4500 hospital employees were given acellular pertussis vaccine in response to cases of pertussis among health care workers.

In 2005 in Texas, more than 2000 cases of pertussis were reported; nine patients died, eight of them infants.

Outbreaks were also reported in Wisconsin in 2003, and in New York in 1999.

What is happening? To understand these events, one must understand the history of the epidemiology of pertussis, the nature of immunity against it, and the characteristics of the laboratory tests used to diagnose it.

In the pre-vaccine era, pertussis was one of the most common childhood bacterial infections. More than half of children became infected before beginning school. Although it causes a prolonged cough illness in older children, and may merely be a nuisance among some of them, its presence in the community inevitably results in infections in infants. Indeed, whooping cough was one of the leading causes of infant death in the 19th century.

With the widespread use of the whole-cell vaccine (introduced in the 1940s), rates of whooping cough dropped dramatically. But the vaccine was associated with frequent local reactions and occasionally severe systemic symptoms.

During the past 2 decades, there has been a slow, steady resurgence of pertussis, although rates have not approached the levels of the pre-vaccine era. The shift from the whole-cell vaccine in the 1990s to the acellular vaccine was associated with reduced rates of adverse effects. But the incidence of pertussis continued to increase.

There was a change in age-related epidemiology, with more cases reported in adolescents and adults. This uncovered a susceptible cohort that had in the past received a less effective whole-cell vaccine.

Recently, programs of universal immunization of adolescents with the acellular vaccine have been implemented to address this change in epidemiology.

The epidemiological shift is probably multifactorial. After vaccination, immunity is of limited duration. With whole-cell vaccine it begins to diminish after 3 to 5 years. There is no demonstrable protection by 10 to 12 years. The duration of protection after acellular vaccine is not yet established, but immunity begins to decline after 4 to 5 years. A 10-year dose interval may be appropriate.

Immunity to natural pertussis is not lifelong, and may not greatly exceed that achieved by immunization. Control of pertussis in the past may have been due to continued circulation of the bacterium resulting in subclinical or mild infections which boosted immunity.

The changing epidemiology is complicated by the changing methods used for laboratory diagnosis. Culture of *Bordetella pertussis* has been the gold standard. In patients who do indeed have the infection, culture is positive in relatively few (low sensitivity), especially in adolescents and adults. And in persons who have received anti-microbial therapy; and those who have been coughing for 3 weeks or longer. Amplification by polymerase chain reaction dramatically increases diagnostic sensitivity. Serology with an enzyme immunoassay detects antibodies against pertussis toxin and may provide confirmation particularly in patients who present late. The increasing

availability of these tests has probably contributed to the increase in reported cases. But pertussis remains underdiagnosed and underreported.

The changing picture probably represents both a real epidemic and a pseudo-epidemic. The “marching cohort” of infected preadolescents and adolescents indicates that the shift in epidemiology is not just a consequence of changing patterns of laboratory testing.

Practitioners will need to carefully evaluate patients in whom they suspect pertussis.

The Advisory Committee on Immunization Practices recommends that all adolescents and adults be given a dose of acellular vaccine combined with diphtheria and tetanus toxoid (Tdap).

NEJM January 11, 2007; 356: 110-113 Commentary by Scott A Halperin, Dalhousie University, Halifax, NS, Canada.

==========

“There Is No One Division Of Medicine By Which We Know And Another By Which We Act. “

1-5 WHAT STAYS CONSTANT AT THE HEART OF MEDICINE

The expression “the science and the art of medicine” is much misunderstood. Too often, the parts of medicine termed as its “art” seem to amount to no more than good communication skills, or to what was once called a good bedside manner.

No doubt patients feel better, and perhaps even do better, when they think their doctor cares about them. But stories also abound about well dressed doctors who with smooth manners, but little knowledge, who have gained—and sometimes abused—the trust of their patients.

To identify the art of medicine with ”artfulness” is to fall into a set of modern confusions. The art of medicine is not about appearance at the expense of substance, but rather the way in which knowledge is related to advice and treatment.

The problem might be reformulated in this way: medicine requires knowledge of universals, and of the application of them to particular instances as embodied in individual patients.

A millennium ago, Avicenna[1] put it so: “When we say that practice proceeds from theory, we do not mean that there is one division of medicine by which we know, and another distinct there from, by which we act. We mean instead that these two aspects are both sciences—but one dealing with the basic problems of knowledge, the other with the mode of operation of these principles.”

The first aspect was called science proper, the second art.

Medical art may be a form of knowledge that is more probabilistic than the demonstrative certainty of science, but it is crucially important knowledge nevertheless. Its exercise requires not only knowledge of content, but something called “judgment”. Judgment requires attending to a patient.

While the science of medicine continues to be advanced, the parts of it termed “the art” are developing too.

For thousands of years, the question of how best to associate the universal and the particular has been the real doctor’s dilemma.

No formulae, however good, can ever obscure the second part of medical knowledge, which comes from clinical judgment.

BMJ December 23-30 2006; 333: 1281-82 Editorial by Harold J Cook, Wellcome Trust Centre for the History of Medicine, at UCL, London UK

1. I expose my ignorance. I do not recall hearing about Avicenna before.

Google and Wikipedia present details about his life:

Avicenna (Ibn Sina) was a Persian polymath—physician, philosopher, scientist and poet. He lived around 1000 CE. He authored 400 books including "The Book of Healing" and The Canon of Medicine". The latter was used as a text book for over 600 years.

He was greatly influenced by Aristotle.

He has been called "The most famous scientist of Islam, and one of the most famous of all races, places, and times."

He remains a national icon in Iran.

==========

"Outcomes Of RCTs Should Always Be Extrapolated With Caution To Real-Life Patients."

1-6 EXTERNAL VALIDITY OF CLINICAL TRIALS IN ACUTE MYOCARDIAL INFARCTION

The relevance of randomized controlled trials (**RCTs**) to clinical practice may be hampered by doubts regarding their external validity. RCTs tend to recruit highly selected populations that may not represent patients encountered in everyday practice.

Enrollment of very large numbers of patients in "megatrials" would hopefully result in less selection bias and increased representativeness. However, even large RCTs may select non-generalisable populations.

This study compared: 1) patients with acute myocardial infarction (**AMI**) enrolled in RCTs of reperfusion therapy with 2) patients with AMI who were eligible for enrollment but who were not enrolled and with 3) patients with AMI who were not eligible for enrollment.

Conclusion: Patients enrolled in these RCTs differed from patients eligible, but not included in the trials, and from patients who were not eligible for randomization. Randomized patients had lower baseline risks and experienced lower mortality than non-enrolled patients.

STUDY

1. This study was designed to determine if patients enrolled in RTCs differed from those not included in the RCTs.
2. Divided consecutive patients hospitalized with AMI enrolled in the GRACE[1] registry into 3 groups:

   1) patients enrolled in RCTs [n = 950]; 2) patients eligible but not enrolled in RCTs [n = 4700]; and 3) ineligible patients [n = 2800].
2. All patients had a confirmed diagnosis of ST-elevation AMI.
3. Main outcome measure = hospital mortality.

RESULTS

1. Based on baseline characteristics, patients included in the RTCs had the lowest baseline risk of death: Lower age; fewer women; and less frequent past history of myocardial infarction, diabetes, hypertension, TIA and stroke, and peripheral arterial disease.
2. Patients in the group eligible of inclusion the RCT (but not included) had higher baseline risks of death.
3. Ineligible patients had still higher risks.
4. Actual hospital mortality showed a similar gradient (3.6%; 7.1%; 11.4%)
5. RCT participants were far more likely to undergo angiography and percutaneous coronary intervention than patients not enrolled. They were also more likely to receive aspirin, beta-blockers, and fibrinolytic therapy.

DISCUSSION

1. Important concerns have been raised about the external validity of RTCs. It is usually accepted that, while RCTs enroll a highly selected population, the outcomes can be extrapolated to real-life patients who fulfill the main inclusion and exclusion criteria, but are not enrolled.
2. Current trends toward the performance of ever-larger mega-trials stem not only from the need for larger sample size to demonstrate benefits, but also from the desire to enroll patients who would be more representative of those treated in practice.
3. Even in pragmatic trials (trials reflecting daily clinical practice) there remain important differences in baseline characteristics, baseline risk, and outcomes between eligible patients and participants.
4. Improved outcomes in patients entered into RTCs may also be due to the beneficial impact of experimental interventions and therapies tested in the RTC, and might also result from the closer medical attention and overall better care provided for the RTC patients.
5. “Outcomes of RCTs should always be extrapolated with caution to real-life patients.”

CONCLUSION

Patients with AMI enrolled in RCTs differed markedly in terms of their baseline characteristics, hospital treatment, and outcomes from patients who would have been eligible for inclusion, but were not included.

Caution is necessary when extending the findings obtained in RTCs to the general population.

Archives Int Med January 8, 2007; 167: 68-73 Original investigation by The GRACE (Global Registry of Acute Coronary Events) investigators, first author Philippe Gabriel Steg, Hopital Bichat, Paris France. A multinational contemporary cohort study.

==========

H Pylori Is Likely To Cause About 9% Of Dyspepsia Cases Where No Ulcers Are Detected.

1-7 DYSPEPSIA AND HELICOBACTER PYLORI

Dyspepsia is not a diagnosis. It is a term used to describe a range of symptoms, from upper abdominal pain to heartburn, nausea, bloating, and retrosternal pain. It occurs in up to 40% of adults in the UK. A general practitioner will see on average 210 patients with dyspepsia each year.

Most dyspepsia is “functional”—ie, no abnormalities are found on endoscopy.

The Cochran review of initial management strategies for dyspepsia:

Proton pump inhibitors **(PPIs**) are more effective than histamine receptors and antacids.

Initial endoscopy is associated with a small reduction in risk of recurrent dyspepsia symptoms compared with test and treat. It is not cost-effective.

Test and treat for H pylori may be more effective than acid suppression alone.

Endoscopy for dyspepsia:

Most patients with dyspepsia do not need referral. Of patients referred for endoscopy, about 30% have normal findings. Only 2% reveal malignancy.

The most common findings on endoscopy are:

Gastritis, duodenitis, and hiatus hernia (30%)

Esophagitis (10%-17%)

Duodenal ulcer (10% - 15%)

Patients with alarm symptoms should be referred for endoscopy.

You should also urgently refer patients older than age 55 with dyspepsia of recent onset that is persistent (lasting 4 to 6 weeks), or unexplained (not related to NSAIDs) even in the absence of alarm symptoms.

The H pylori connection

Prevalence:

In a sample of people from Bristol UK, about 15% tested positive for H pylori. *(I believe prevalence of H pylori infection varies greatly over the world, depending on the area studied. It is related to the hygienic conditions of the community. RTJ)*

Screening:

“Would screening the general population for H pylori be cost effective?” Probably not.

Diagnosis:

The urea breath test is the most accurate way to detect H pylori— in patients who have H pylori infection, a positive test is present in 95%; in patients who do not have H pylori infection, a negative test is present in 95%.

The ulcer connection:

Infection with H pylori causes most duodenal ulcers (95%) and gastric ulcers (70%) . It is also likely to cause about 9% of dyspepsia cases where no ulcers are detected.

Treatment of H [pylori:

Treating patients with H pylori infection is more likely to benefit those whose main symptom is gastritis than those whose main symptom is acid reflux.

A study in Bristol UK[1] randomized patients who tested positive to: eradication treatment, or to placebo.

Of those randomized to eradication, 7% consulted for dyspepsia over the next 2 years; 10% of placebo patients consulted. (NNT = 33)

Another randomized controlled trial[2] looked at the efficacy of the "test and treat" strategy for anyone presenting with moderate or severe dyspepsia. Patients who were positive were randomized. The treatment group received one week of eradication; control group received PPIs-alone. Results: 50% of eradication treated patients were symptom-free at one year vs 36% of controls given PPI alone. "Test and treat" is likely to be more effective than treating dyspeptic patients with proton pump inhibitors alone.

Patients with dyspepsia without ulcer disease on endoscopy: initial treatment of H pylori, followed by management of symptoms.

Patients with a peptic ulcer on endoscopy: stop NSAIDS, start full dose PPI for 2 months, and offer eradication treatment for H pylori. Patients with gastric ulcer on endoscopy: at least one month of full PPI treatment in addition to H pylori eradication. Repeat endoscopy should be performed to rule out the small risk (2%) of cancer.

In patients with symptoms of heartburn or reflux who are positive for H pylori, eradication does not improve symptoms. Neither do symptoms worsen.

Which eradication treatment?

Seven day full dose PPI + either

1) Metronoidazole 400 mg + clarithromycin 250 mg, or

2) Amoxicillin 1 g + clarithromycin 250 mg

The NSAID connection

Do not underestimate the risks associated with NSAIDs. About 10% to 20% of people who use these drugs regularly will develop peptic ulcer that is detectable with endoscopy. 1% develop perforation or bleeding. Offer protection with a PPI to those who require NSAIDs regularly.

BMJ January 6, 2007; 334: 41-43 "Practice" "BMJ Master Classes for GPs" authored by Rupal Shah

1 BMJ 2006; 332: 199-204

2 BMJ 2002; 324: 1012

==========

"A Mere Leap Of Faith." ?

1-8 THE PREVENTIVE POLYPILL—Much Promise, Insufficient Evidence

"The rapidly increasing global burdens of cardiovascular disease (**CVD)** and diabetes call for interventions that have a population-wide effect, as well as interventions that identify and protect individual patients who have a high risk of major adverse effects."

Such actions are especially needed in low-income and middle-income countries which can ill afford the huge losses in human and financial resources that will result from unchecked development of clinical disease.

Many drugs are effective in the primary and secondary prevention of CVD, including aspirin, ACE-inhibitors, statins, beta-blockers, and calcium channel blockers. These drugs have not been used optimally even in developed countries. Poor adherence and costs are common barriers to their use.

The "Polypill", suggested in 2003 by Wald and Law,.[1] is a single pill that includes six key drugs. There is no trial evidence to suggest a benefit from addition of folic acid and a diuretic (proposed for inclusion in the original 'polypill") to a regimen that already includes two BP-lowering drugs. Recent trial evidence supports *primary* prevention regimens that include a calcium-channel blocker. *Secondary* prevention regimens must include a beta-blocker. Aspirin, an ACE inhibitor and a statin would be incorporated into both types of regimens.

The availability of most of these drugs in generic forms may help to reduce cost, especially in countries such as India, with an active generic drug industry.

Modeling economic analyses suggest that such multidrug regimens would be cost-effective in reducing the burden of CVD even in low-income countries.

A combination pill would probably be accepted for *secondary* prevention. For *primary* prevention the value of such a pill would have to be clearly demonstrated, rather than simply assumed.

The World Heart Federation recently announced that it would support the development and evaluation of a polypill consisting of aspirin, an ACE-inhibitor, and a statin. Two Indian drug manufacturers have already developed a four-drug combination (the 4th drug being a beta-blocker). Clinical trials will begin soon to determine if the polypill is miracle or mirage. "Without such evidence, advocacy for the polypill would be a mere leap of faith."

NEJM January 18, 2007; 356: 212 "Perspective" by K Srinath Reddy, All India Institute of Medical Sciences, New Delhi.

1 "A Strategy to Reduce Cardiovascular Disease by More than 80%" BMJ June 28, 2003; 326: 1419-24
N J Wald and M R Law

The daily pill was aimed at reducing LDL-cholesterol, blood pressure, platelet adhesiveness, and homocysteine. They suggested inclusion of 6 drugs (all generics):

A statin (eg, simvastatin 40 mg)
A thiazide (eg, hydrochlorothiazide)*
A beta-blocker (eg, atenolol)*
An ACE-inhibitor (eg, enalapril)*
Folic acid 0.8 mg
Aspirin 75 mg
(* At half standard dose)

Each component has been used in medical practice for years with substantial evidence of safety and efficacy. Of all the components, low-dose aspirin has the most serious adverse effects, mainly due to bleeding.

The authors calculate that one third of people taking the pill, beginning at age 55, would benefit, gaining on average 11 years of life free of heart disease events or stroke.

Adverse effects would cause symptoms in about 15%.

Wald and Law admit the strategy is radical. They state: "It is time to discard the view that risk factors need to be measured and treated individually if found to be "abnormal". There is no need to measure the 4 risk factors before starting treatment, because intervention is effective whatever the initial levels of the risk factors. Instead, it should be recognized that, in Western society, the risk factors are high in us all, so everyone is at risk; that the diseases that they cause are common and often fatal; and that there is much to gain and little to lose by the widespread use of these drugs. "No other preventive method would have so great an impact on public health in the Western world."

==========

Are Popular, Are Safe, But Are They Effective?

1-9 EFFICACY OF GLUCOSAMINE AND CHONDROITIN AS SUPPLEMENTS TO TREAT OSTEOARTHRITIS

Glucosamine and chondroitin sulfate are popular over-the-counter drugs. Glucosamine is an amino sugar that may play a role in cartilage formation. Chondroitin is one of the proteoglycans that give cartilage elasticity. They are considered to be "supplements" and are not regulated by the FDA. An estimated 1 million people in the US take them. Their effectiveness in easing joint pain and preventing disease progression is unproven.

Results from clinical trials are interpreted differently.

Several studies have found positive results for glucosamine compared with NSAIDs in management of osteoarthritis. "A number of double-blind, controlled, randomized trials and meta-analyses support the efficacy to these agents." However, there are differences in opinion concerning interpretation of the studies.

Research has also generated conflicting results regarding the extent to which these supplements are absorbed from the gastrointestinal tract and make their way into the joints. Information is limited.

A meta-analysis of 15 trials conducted before 2000 assessing the drugs in patients with knee and hip osteoarthritis found the evidence suggests that they do have moderate to large effects, But quality issues and likely publication bias (eg, studies sponsored by manufacturers) suggest that these effects are exaggerated.

More recently, clinical trials have reported results ranging from no effect, to significant decrease in pain and cartilage loss. A recent Cochrane review of 20 studies with over 2500 patients found that glucosamine improved pain more then placebo when measured by one type of scale, but was similar to placebo when measured by another scale.

The largest study to date,[1] funded by the National Institutes of Health, compared: glucosamine-alone; chondroitin-alone; both combined; celecoxib; and placebo. The study concluded that glucosamine-chondroitin in combination may be effective in the subgroup of patients with moderate or severe knee pain. But, "The outcome of GAIT was not straight forward, so it was difficult to give a distinct and clear message." There was an unusually high response rate (60%) in the placebo group. "This and other trials with glucosamine and chondroitin have faced challenges in design, implementation, and analysis."

Stakeholders are remarkably polarized on these issues.

Since supplements are not regulated by the FDA, a lack of standardization and quality control can make it difficult to accurately interpret and compare studies.

While disagreement persists about efficacy, almost all agree that these supplements are safe.

JAMA January 24/31, 2007; 297: 351-52 "Medical News and Perspective" authored by Tracy Hampton. JAMA staff.

1 Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) NEJM 2006; 354: 795-808

==========

Benefits Were Mediated By Drug Effects; They Did Not Reflect "Healthy Behavior".

1-10 RELATIONSHIP BETWEEN ADHERENCE TO EVIDENCE-BASED PHARMACOTHERAPY AND LONG-TERM MORTALITY AFTER ACUTE MYOCARDIAL INFARCTION.

Clinical trials have demonstrated that select drugs reduce cardiovascular mortality. However, their projected survival impact in the real world is less known, in part because of variations in drug adherence.

This study asks: Are the benefits of drugs attributable to a drug's biological responsiveness (drug effect), or to the adoption of healthier lifestyles that often accompany adherence behaviors (healthy user effect)? Are mortality differences after an acute myocardial infarction (**AMI**) attributable to the "healthy adherer" effect, or due to the pharmacological action of drugs?

If mortality gains are directly attributable to the biological effect of a drug, one might hypothesize that outcome benefits correlate with adherence intensity, and that survival-adherence gains follow a "dose response" type gradient. Interventions that selectively target and improve drug-taking behaviors should translate into important mortality advantages when applied to the real world.

This study examined the relationship between drug adherence (of drugs known to have protective effects vs a drug which has no known protective effects) and mortality in survivors of acute myocardial infarction (**AMI**).

Conclusion: In these patients with AMI, benefits were mediated by drug effects, and did not merely reflect "healthy behavior".

STUDY

1. Population-based, observational study followed over 31 000 elderly survivors of AMI (mean age 75).
2. All patients had filled at least one of 3 possible drug prescriptions: statins, beta-blockers, or calcium blockers. Statins and beta-blockers are recommended for secondary prevention after an AMI. Calcium blockers were considered a control, given the absence of any clinical trial-proven post AMI survival benefit.
3. Determined quantity dispensed, and number of days supplied to calculate the proportion of days on which a patient had pills available in the year following the first filled prescription after discharge.
4. Divided patient adherence into 3 categories:
   1) High adherence (80% or over of days covered).
   2) Intermediate (40% to 79% of days covered)
   3) Low (less the 40% of days covered)
5. Follow-up = a median of 2.4 years. Main outcome measure = long-term survival.

RESULTS

1. Deaths (%)	High adherers	Intermediate adherers	Low adherers
Statins	16	20	24
Beta-blockers	21	23	25
Calcium blockers	30	31	27

(No statistically significant association between calcium blocker use and mortality.)

2. The differences in mortality between statins and beta-blockers vs calcium blockers were more evident in the sub-class of patients considered at higher risk for mortality.

DISCUSSION

1. The mortality benefits associated with high placebo-adherence in randomized controlled trials raise questions about whether the benefits in reducing mortality demonstrated in this trial are predominantly (or partially) attributable to the healthy adherer effects rather than to drug effects.
2. There was a positive and graded relation between mortality and adherence to drugs known to be effective in secondary prevention in patients with a history of AMI. There was no relationship between mortality and adherence to a drug known to be ineffective in secondary prevention.
3. Specifically, for statins and beta-blockers, adherence correlated with survival in a graded, dose-response manner. Conversely, no such adherence-mortality relationship existed for calcium channel blockers (a drug class with no proven post-AMI survival advantages).
4. This study, of real world patients, demonstrated that patients taking effective drugs after an AMI benefited in a dose-gradient way. (Ie, patients taking the drug conscientiously benefited more than patients taking it intermittently.) This is consistent with the biological effects related to the drugs themselves.
5. Patients with a history of AMI taking a drug without known efficacy did not benefit even if they took the drug conscientiously.
6. “Our study has important clinical and policy implications. The graded dose response-type relationship underscores the importance of drug adherence when projecting the survival benefits of evidence-based therapies in the population.”

CONCLUSION

The mortality benefits associated with adherence to drugs known to be effective in secondary prevention of mortality after an AMI were mediated by drug effects more so than by generic healthy-adherer behavioral attributes.

This underscores the need to optimize patient behavior patterns which will increase adherence to taking effective drugs prescribed for secondary prevention. This will maximize survival gains of drug therapies in real-world populations.

JAMA January 10, 2007; 297: 177-86 Original investigation, first author Jeppe N Rasmussen, Institute of Clinical Evaluative Sciences, Toronto, Canada.

"Significantly Improved Domains Of Cognitive Function"

1-11 EFFECT OF 3-YEAR FOLIC ACID SUPPLEMENTATION ON COGNITIVE FUNCTION IN OLDER ADULTS: The FACIT Trial

This investigation is part of the "Folic Acid and Carotid Intima-media Thickness" FACIT trial, (not yet published.) This part of the trial considered the effect of folic acid supplementation on cognitive function in older adults who had higher homocysteine levels. (A possible indicator of folic acid deficiency.)

Cognitive function declines with aging, especially in domains related to memory and information processing. Changes in cognitive performance, especially memory function, have been linked to risk of dementia.

Poor folate status is a suspected risk factor for age-related cognitive decline. However, a systematic review of supplementation with folic acid showed no beneficial effect. Many of the trials included in the review were of small study populations, of supplementation for short periods, and used the Mini-Mental State Examination to gauge results. The M-MSE is not able to detect subtle changes in cognitive function.

This study investigated whether a supplement of 800 ug daily of folic acid for 3 years would improve cognitive performance (determined by detailed cognitive tests).

Conclusion: Folic acid supplementation for 3 years significantly improved domains of cognitive function.

STUDY

1. Randomized, double-blind, placebo-controlled trial assigned 818 participants (mean age 60) to: 1) 800 ug folic acid daily, or 2) placebo for 3 years.
2. On the assumption that a high concentration of plasma homocysteine is a risk factor for vascular disease, the trial selected subjects expected to benefit from folic acid's homocysteine-lowering effect. It excluded participants with normal plasma homocysteine concentrations (less than 13 umol/L; 73% of those screened) *(Ie, the trial included only about one quarter of those screened, perhaps an indication of the frequency of folic acid deficiency in their communities. RTJ)*
3. Measured effect on cognitive performance as the difference between the groups in the 3-year change in 5 factors: memory, sensorimotor speed, complex speed, information processing speed, and word fluency.[1]
4. Outcome = difference in performance of the 5 factors between the folic acid group and the placebo group over 3 years.
5. Analysis by intention-to-treat.

RESULTS

1. In the folic acid group, serum folate concentrations increased by 576%, and plasma homocysteine decreased by 26%.
2. Changes (mean) in cognitive performance over 3 years: (Z scores) [2]

	Folic acid	Placebo
Global cognitive function	+ 0.067	-0.031
Memory	+0.480	+0.142

Information processing speed -0.072 -0.159 (All statistically significant)

3. Memory tests improved in both groups (probably due to procedural learning effects). The improvement in the folic acid group was greater.
4. Folic acid did not affect sensorimotor speed, complex speed, or word fluency.
5. Performance in the Mini-Mental state Examination was not affected by folic acid.
6. By the investigators calculation, the 3-year folic acid supplementation (mean age 60 to 63) conferred to an individual the performance of someone 4.7 years younger for memory, 2.1 years younger for information processing speed, and 1.5 years younger for global cognitive functioning.
7. Memory—specifically delayed memory—is the most clinically relevant test. Supplementation improved performance on the delayed recall sub-test of the 15 word-learning test by 0.47 words, similar to a performance of an individual 6.9 years younger.

DISCUSSION

1. In older adults, daily folic acid supplementation for 3 years beneficially affected global cognitive function, memory, and information processing speed—functions that are sensitive to aging.
2. High serum concentrations of homocysteine have been associated with atrophy of the hippocampus, an area of the brain important in memory consolidation.
3. Folic acid may be ineffective (too late) in patients who already experience mild cognitive impairment.
4. Sensitive tests such as used in this study are needed to detect subtle effects of cognitive aging.
5. "Given the general scarcity of positive findings from other trials . . . our results need to be confirmed by other investigators."
6. Additional research is needed to determine whether folic acid supplementation can reduce the risk of mild cognitive impairment or Alzheimer's disease.
7. These results may not apply in countries where food is fortified with folic acid.

CONCLUSION

In patients with raised serum homocysteine levels, 3-year folic acid supplementation improved performance on tests that measure information processing speed and memory domains that are known to decline with age. Lancet January 20, 2007; 369: 208-16 Original investigation, first author Jane Durga, Wageningen University, Netherlands.

1 The tests were detailed and complex. (See panel 1 p 211)

2 Z score indicates the distance from the population mean expressed as units of the standard deviation. An improvement of +0.1 of a standard deviation must be small in absolute terms.

Benefits Are Questionable. There Is An Increased Risk Of Major Bleeding.

1-12 COMBINED ASPIRIN-ORAL ANTICOAGULANT THERAPY COMPARED WITH ORAL ANTICOAGULANT THERAPY ALONE AMONG PATIENTS AT RISK FOR CARDIOVASCULAR DISEASE

Combination therapy [**CT**]—oral anticoagulants [**OAC**] + low-dose aspirin—is recommended by the American College of Chest Physicians *only* for patients with a mechanical prosthetic heart valve. Despite this recommendation, a considerable number of patients with chronic atrial fibrillation (**AF**) receive combined therapy.

Despite a lack of evidence for the efficacy of CT, some experts have suggested that adding aspirin to OAC therapy might be useful because patients using OAC frequently have concomitant coronary artery disease, or are at high risk for stroke.

This systematic review and meta-analysis of randomized controlled trials (**RCTs**) compared OAC-alone with OAC + aspirin to assess benefits and risks.

Conclusion: Benefits in reducing thromboembolic events are questionable. There is an increased risk of major bleeding.

STUDY

1. Selected RTCs with at least 3 months of follow-up that compared OAC + aspirin with OAC-alone. OAC was administered to achieve the same international normalized ratio, or was given at the same fixed dose in both treatment arms. OAC therapy was considered necessary in all patients.
2. Included 10 studies (4180 patients) assessing a broad spectrum of patients irrespective of the clinical indication for anticoagulation:
   - Mechanical valve
   - Unstable angina
   - Non-Q wave infarction
   - Primary prevention of high risk patients
   - Chronic non-valvular atrial fibrillation
   - Secondary prevention in patients with acute coronary syndrome or CABG
   - Patients with a previous thromboembolic event.
   - *(There was considerable heterogeneity between studies. RTJ)*
3. Low-dose aspirin (100 mg or less) was used in 6 studies. The others used up to 1000 mg daily.
4. All patients were followed for at least 3 months. There was at least one prespecified outcome (arterial thromboembolism, mortality, or major bleeding).

RESULTS

1. Risk of arterial thromboembolism was lower in the OAC + aspirin groups, but *only* in studies of mechanical valves. (Odds ratio OAC + aspirin vs OAC-alone = 0.27)
2. There was no difference in outcomes (OAC + aspirin vs OAC-alone) in risk of arterial thromboembolism in patients with atrial fibrillation or coronary disease.

3. There was no difference between groups in all-cause mortality or fatal thromboembolism.
4. The risk of major bleeding was higher in patients receiving combined therapy vs OAC therapy-alone.

Combined therapy	3.8%
OAC alone	2.8%

NNT to harm = 100.

DISCUSSION

1. There is little support in the published literature for the common clinical practice of adding aspirin to OAC, except in patients with mechanical heart valves.
2. The reported benefit of combined therapy appears to be driven by results of 3 trials in patients with mechanical valves, and one trial assessing primary prevention of cardiovascular disease in high-risk patients.
3. There was no difference in mortality between OAC + aspirin vs OAC-alone
4. Only 2 small RCTs addressed OAC + aspirin vs OAC-alone in patients with atrial fibrillation. They provided conflicting results.
5. A recent study of over 3500 patients with chronic AF who were receiving warfarin (aimed at an INR of 2.0 to 3.0) reported that patients who were receiving concomitant low-dose aspirin had a two-fold increased risk of major bleeding.
6. "Our findings question the current practice of using combined aspirin-OAC therapy in patients with atrial fibrillation and concomitant CAD, or in patient at high risk of stroke."

CONCLUSION

The current practice of using combined OAC + aspirin (except in patients with mechanical valves) should be questioned, given the doubtful benefits of added aspirin in reducing thromboembolic events, and the increased risk of major bleeding.

Archives Int Med January 22, 2007; 167: 117-24 Review article, first author Francesco Dentali, McMaster University, Hamilton, Ontario, Canada

==========

"Extensive Periaortic Inflammation" "It Is Not Uncommon"

1-13 INFLAMMATORY ABDOMINAL AORTIC ANEURYSM

Atherosclerotic abdominal aortic aneurysm (**A-AAA**) occurs in 4% to 10% of people over age 60. Currently it accounts for 15 000 deaths per year. Published guidelines call for performing ultrasound to screen for A-AAA in men age 65-75 who have ever smoked.

This article describes an important variant of AAA, inflammatory AAA (**I-AAA**), the symptoms of which are so protean that patients may present to a wide range of physicians. Like classical A-AAA, it most commonly affects the infrarenal portion of the aorta. I-AAA accounts for 5% to 10% of all cases of AAA.

I-AAA was not described before 1972. Few physicians are familiar with it.

It differs from classical A-AAA in many ways:

Patients are usually younger, male and smokers. They are usually symptomatic.

Back and abdominal pain may be presenting symptoms. Systemic symptoms may be associated (fever, malaise, weight loss)

CT and MRI imaging show a characteristic cuff of soft tissue inflammation surrounding the aneurysm. In contrast to classical A-AAA, it is characterized by marked thickening of the aneurysm wall, fibrosis of the adjacent retroperitoneum, and rigid adherence of the adjacent structures.

There is an extraordinary expansion of the adventitia due to inflammation.

The pathogenesis in the inflammation appears to involve an immune response localized to the vessel wall. It is almost never associated with inflammation of other arteries.

Male sex and smoking are the main risk factors for classical A-AAA, and even stronger risk factors for I-AAA.

I-AAA may coexist with A-AAA. The intima of the aorta may reveal atherosclerosis much as seen in A-AAA.

The author presents a case of I-AAA:

A 42 year old man who had smoked heavily for over 20 years.

He had been treated for familial hyper-cholesterolemia.

Started to develop mild back and flank pain which went away in a few weeks

A second episode of flank pain accompanied by dysuria (no bleeding). This also went away

A third episode of pain in the low back and over the kidneys was a “killer”. It was severe enough to cause him to miss work. No fever.

After a few weeks the pain subsided

A few weeks later the pain recurred.

Physical examination was normal. Blood count, urinalysis and blood chemistry panel were normal

Sed rate was 16.

A CT scan of the abdomen demonstrated an infrarenal aortic aneurysm with extensive inflammatory soft tissue surrounding the aorta extending into the peri-aneurysmal fat. This made the diagnosis of I-AAA.

No leak or rupture was evident.

He was started on prednisone 40 mg daily. This led to complete relief. The prednisone was tapered to 20 mg, and methotrexate 15 mg weekly was added.

A CT scan several months later showed a marked decrease in retroperitoneal inflammation. Sed rate declined to 3.

I-AAA is one member of a family of disorders referred to as “chronic periaortitis”. The family consists of 3 members: 1) I-AAA 2) idiopathic retroperitoneal fibrosis [in the absence of I-AAA] , and 3) a combination

of the 2. In I-AAA, the inflammation surrounds the aorta, usually without obstructing the bowel or ureters. The extraordinary expansion of the adventitia due to inflammation is the major feature that distinguishes I-AAA from A-AAA.

The etiology is not known. The immuno-histopathological findings suggest an immune response to an antigen located in the adventitia.

There is some, but less compelling, evidence that I-AAA is a systematic autoimmune disease. Some patients have associated auto-immune disease.

The great majority of patients with I-AAA are symptomatic at presentation (in contrast to A-AAA). Pain in the back and abdomen is common. Abdominal tenderness (with or without a pulsating mass) occurs in about one third of patients. Systemic symptoms (fever, malaise, weight loss) may be associated.

The risk of rupture is less than 5%

On imaging, most patients with I-AAA have aortic calcification. This does not distinguish I-AAA from atherosclerotic AAA. The thickened adventitial wall distinguishes one from the other.

Ultrasound is inferior to CT and MRI in demonstrating the thickening of the aortic wall.

Treatment

Medical:

Corticosteroids and corticosteroid-sparing drugs (eg, methotrexate).

Since atherosclerotic lipids may be associated with the local inflammation, attention should be paid to dyslipidemia and other risk factors.

Smoking cessation is critical.

Surgical:

The aim is to prevent rupture (which is much less likely than with A-AAA). Surgical intervention appears prudent once the diameter exceeds 5.5 cm.

The dense adhesions surrounding the aneurysm make surgery difficult. Adhesions may involve the duodenum, inferior vena cave, and ureters. Surgical mortality is higher than for A-AAA.

JAMA January 24/31 2007; 297: 395-400 “Grand Rounds” “Clinician’s Corner”, first author David B Hellmann, Johns Hopkins University school of Medicine, Baltimore MD

==========