

PRACTICAL POINTERS
FOR
PRIMARY CARE
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IMMEDIATE INITIATION OF EXISTING TREATMENTS FOR TIA AND MINOR STROKE REDUCES RISK OF STROKE

THE LOWERED RISK OF CHD FROM STATIN THERAPY CARRIES FORWARD FOR YEARS

HEALTHY LIFESTYLE BEHAVIORS + A HEALTHY DIET REDUCES RISK OF MYOCARDIAL INFARCTION BY 92%

**INFLUENZA VACCINE REDUCES RISK OF DEATH AND HOSPITALIZATION EVEN IN YEARS WHEN THE VACCINE-
FLU MATCH IS POOR**

EARLY PREDNISOLONE THERAPY IMPROVES OUTCOMES OF BELL'S PALSY

INVASIVE MRSA HAS BECOME A MAJOR PUBLIC HEALTH PROBLEM

BENEFIT OF ADDING INSULIN TO ORAL THERAPY FOR TYPE-2 DIABETES

ALLOW PATIENTS TO MAKE INFORMED DECISIONS ABOUT CANCER SCREENING

**WOMEN SHOULD BE INFORMED ABOUT RISKS AS WELL AS BENEFITS OF SCREENING MAMMOGRAPHY, AND
SHOULD DECIDE FOR THEMSELVES**

HUMAN PAPILLOMA VIRUS TESTING + PAP TEST TO SCREEN FOR CERVICAL CANCER PRECURSORS

NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY—AN EPIC REVOLUTION IN SURGERY?

CT-COLONOGRAPHY VS COLONOSCOPY SCREENING FOR ADVANCED NEOPLASIA

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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 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.

Editor/Publisher.

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HIGHLIGHTS AND EDITORIAL COMMENTS OCTOBER 2007

“A Short Window Of Opportunity For Prevention.” “Long Delays To Assessment In TIA Clinics Are No Longer Acceptable.”

10-1 EFFECT OF URGENT TREATMENT OF TRANSIENT ISCHEMIC ATTACK AND MINOR STROKE ON EARLY RECURRENT STROKE

The risk of recurrent stroke in the week after a transient ischemic attack (TIA) or a minor stroke is up to 10%. “These warning events provide a short window of opportunity for prevention.”

Several treatments are effective in preventing stroke in the long term after TIA or minor stroke: aspirin and other antiplatelet agents; BP lowering drugs; statins; anticoagulation for atrial fibrillation; and endarterectomy for symptomatic carotid stenosis. Assuming that benefits from these interventions are independent, use of *all* the interventions in appropriate patients would be predicted to substantially reduce the long-term risk of recurrent stroke.

This study aimed to determine the effect of rapid treatment after TIA or minor stroke in patients who are not admitted directly to the hospital.

This rigorous observational study, in a population of 91 000 individuals served by 63 primary care physicians, was divided into 2 phases:

Phase 1: non-urgent care (within one week) after a TIA or minor stroke.

Phase 2: Urgent immediate care. Aspirin, simvastatin, BP control, brain imaging.

The primary care physician initiated aspirin in 71 (11%) of patients in phase 1 and 2 combined before the clinic visit.

For those presenting with TIA, the 90-day risk of stroke in phase 1 = 16/156 (10%), and in phase 2 = 1/160 (<1%) number needed to treat to benefit one patient (NNT) = 10; and for those presenting with minor stroke the 90-day risk of recurrent stroke = 16/154 (10%) vs 5/121 (4%) NNT = 17.

Overall, within 90 days, the risk of stroke during the second phase was (*clinically and statistically*) lower than the risk in the first phase: 10.3% vs 2.1%; absolute difference = 8.2%; (NNT) = 12.

Conclusion: After onset of a TIA or minor stroke, early initiation of existing treatments can prevent about 80% of early recurrent strokes.

I believe we often forget the remarkable protective value of aspirin in lowering risk of death in patients with MI and stroke. If aspirin were an expensive proprietary drug, it would be highly advertised by the drug company. I carry a couple of aspirin tablets in my wallet. It is good insurance for myself and for others I may encounter with suspected acute MI and TIA. In such cases, every minute counts. Aspirin should be in the blood stream as soon as possible.

Evidence Of A “Carry-Over” Benefit After 5-Years Of Statin Therapy.

10-2 LONG-TERM FOLLOW-UP OF THE WEST OF SCOTLAND CORONARY PREVENTION STUDY

The WOSCP study was a *primary-prevention*, randomized, clinical trial comparing the statin drug pravastatin (*Pravachol*; Bristol-Myers-Squibb; 40 mg daily) with placebo. Subjects were men (n = over 6500; mean age = 55 at baseline) with elevated cholesterol. None of the subjects had a history of myocardial infarction (**MI**). The duration of the original study was 5 years. During the trial (1990-1995) the combined outcome of death from CHD + non-fatal MI was reduced from 7.9% to 5.5%. [Absolute difference = 2.4%; NNT for 5 years = 42.]

This article reports the planned follow-up for an additional 10 years after the end of the original study.

Five years after the trial ended, 39% of subjects who had been taking pravastatin, and 35% of those who had been taking placebo were taking a statin drug.

This post-trial study compared outcomes from the two original study groups regardless of the subsequent use of lipid-lowering therapy.

	Trial period (%)		Post-trial period (%)		Total follow-up period (%)	
Adjusted CHD-related death or non-fatal MI	P	S	P	S	P	S
	6.0	3.7	10.3	8.6	15.5	11.8

(P = placebo S = pravastatin)

During the 10-year follow-up period, over half of the original pravastatin group discontinued the drug. There was evidence of ongoing reduction in risk of major coronary events among participants treated with pravastatin during the 5-years of the trial, regardless of whether they continued to take the statin.

Benefits may have been greater if all had continued the drug for the following 10 years.

Conclusion: 5 years of treatment with pravastatin was associated with reduction in coronary events over a subsequent 10 years. (A carry-over effect.)

I believe this evidence of a “carry-over” benefit is clinically important.

Patients should be encouraged to continue taking the drug, but even if they discontinue after a period of compliance, benefits may continue.

The men in this study began taking the statin at a mean age of 55. Statin therapy in high-risk patients should be started at an early age to prevent development of atherosclerosis.

“Much Of The Burden Of CHD Might Be Reduced By Changes In Modifiable Lifestyle Behaviors”

10-3 COMBINED EFFECT OF LOW-RISK DIETARY AND LIFESTYLE BEHAVIORS IN PRIMARY PREVENTION OF MYOCARDIAL INFARCTION IN WOMEN

The percentage of sudden deaths from CHD in women without previous symptoms is higher than in men. Diet and lifestyle largely influence morbidity and mortality from CHD.

This prospective study examined the benefit of a combined healthy diet + 3 major lifestyle factors on risk of *primary* myocardial infarction (MI) in over 24 000 postmenopausal women (age 48 to 83; mean age 59). All were free of diagnosed cancer, cardiovascular disease, and diabetes at baseline (1997).

The final comprehensive low-risk-factor category (healthy diet, no current smoking, being physically active, low waist/hip ratio, and alcohol intake > 5 g on average daily) was associated with a 92% lower risk of MI compared with the high-risk group (unhealthy diet, smoking, abdominal adiposity, less physically active, and low alcohol consumption).

But, only 5% of the cohort of women fit the low-risk factor category.

The strength of association of the 5-low-risk behaviors is compatible with a clinical definition of a low-risk profile based on favorable levels of blood pressure and serum cholesterol, and absence of diabetes.

Conclusion: Most MIs in women may be preventable by consuming a healthy diet, and moderate amounts of alcohol, being physically active, not smoking, and maintaining a healthy weight.

These associations are repeated frequently in journal articles. I believe they bear repeating. It should be a constant reminder to patients.

The epidemiological evidence of a benefit from modest alcohol intake seems well established.

Protection May Be Substantial, Although Lower, During Years With A Poor Match.

10-4 EFFECTIVENESS OF INFLUENZA VACCINE IN THE COMMUNITY-DWELLING ELDERLY

Most studies assessing effectiveness of the vaccine in the elderly have included only one or only a few seasons. Because of the variability of severity of flu from season to season, short term studies might provide incomplete or misleading pictures about benefits of the vaccine.

This study analyzed effectiveness of the vaccine among 18 cohorts of community-dwelling elderly members of a health maintenance organization during 10 seasons.

The study compared outcomes between vaccinated (n = 415 000) and unvaccinated (n = 299 000) subjects, and estimated effectiveness of the vaccine for prevention of hospitalizations for pneumonia and influenza, and all-cause death.

“Influenza vaccination was associated on average with substantial reductions in hospitalizations for pneumonia or influenza (vaccine effectiveness = 27%) and in all cause death (vaccine effectiveness = 48%).”

In the two seasons with a poor match between the vaccine and the virus strain, effectiveness was lower for reducing death (37%). In seasons with a good match, vaccine was effective for reducing death, but not for reducing hospitalization.

Protection may be substantial, although lower, during years with a poor match.

Conclusion: During 10 seasons, influenza vaccine was associated with significant reductions in risk of hospitalizations for pneumonia or influenza, and in the risk of all-cause death among community-dwelling elderly persons.

The observation that the vaccine appeared to remain somewhat effective, even when the match was not good, strengthens the advice for all persons to be immunized every year.

Elderly persons in retirement centers are exposed to many outsiders in addition to health care workers (many different staff members including young food service workers) and visitors and family members as well.

Why not try to vaccinate everyone? Herd immunity is a powerful preventive measure. Healthy younger adults who do not feel personally threatened by flu, and may not be anxious to be immunized, may consider immunization a public service.

Prednisone Yes; Acyclovir No; Valcyclovir + Prednisone Maybe.

10-5 EARLY TREATMENT WITH PREDNISOLONE OR ACYCLOVIR IN BELL'S PALSY

This study examined effects of prednisolone, acyclovir, and both combined, on recovery of facial function.

Randomized double-blind to: 1) prednisolone 25 mg twice daily for 10 days; 2) acyclovir 400 mg 5 times daily for 10 days; 3) both together, or 4) placebo.

Complete recovery*	At 3 months (%)	At 9 months (%)
Prednisolone + placebo	87	95
Acyclovir + placebo	64	79
Placebo	65	85

(* My calculation from figure 2 page 1605)

There was no benefit from acyclovir compared with placebo.

There was no additional benefit when acyclovir was added to prednisolone.

The absolute difference in complete recovery at 3 months between the two groups that received prednisolone vs no prednisolone = 19% [NNT = 5]; and = 12% at 9 months [NNT = 12].

This study confirmed the generally favorable prognosis of Bell's palsy. Without treatment, about 65% of patients recover completely at 3 months, and about 85% completely recover at 9 months.

Early treatment with prednisolone for 10 days increased these rates to 87% and 95%.

No benefit from acyclovir given alone, or when added to prednisolone.

Conclusion: In patients with Bell's palsy, early treatment with prednisolone alone significantly improved the chances of complete recovery at 3 and at 9 months.

An accompanying editorial comments: The lack of benefit from acyclovir conflicts with a recent randomized study from Japan which compared a combination of valacyclovir + prednisolone vs prednisolone alone. It reported absolute recovery was 7% greater in the group treated with both drugs vs prednisolone alone. (NNT = 15) The benefit of valacyclovir + prednisolone vs prednisolone alone appeared to correlate with the severity of the palsy—those with more severe disease responded more favorably. There was no benefit in patients with moderate palsy. Despite the Japanese study being somewhat flawed methodologically, the editorialist would treat severe or complete paralysis with valacyclovir in addition to prednisone. (Prednisone is favored in the US; prednisolone in the UK.)

“What Happens In The Hospital Does Not Stay In The Hospital.”

10-6 INVASIVE METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS INFECTIONS IN THE UNITED STATES

Community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) has become the most common cause of skin and soft tissue infections presenting to emergency departments in the U.S.

Although outbreaks of MRSA in diverse populations in the community usually involve skin disease, MRSA can also cause severe, sometimes fatal invasive disease.

The epidemiology *invasive* MRSA disease has been changing. The distinction between community-acquired MRSA and hospital-acquired MRSA is becoming blurred. The strains of MRSA which were in the past confined mainly to hospitals are appearing in the community. And strains usually confined to the community are now appearing in hospitals.

The majority of cases have a health-care association (presence of an invasive device, or a hospitalization, surgery, or residence in a long-term health care facility within the past 12 months). Most of these cases start outside the hospital. About ¼ of cases begin in the hospital. About 10% of cases begin in the community, occur in otherwise healthy persons, and have no obvious connection with health care.

The incidence of invasive MRSA has increased in the past 7 years, both in the community and in health care facilities. Incidence rates were highest among persons over age 65; among blacks; and among males. In 2005, the standardized incidence rate of *invasive* MRSA (30 per 100 000 persons) was higher than the incidence of other important invasive pathogens (*S pneumoniae* or *H influenzae*).

Conclusion: Invasive MRSA disease is a major public health problem. It affects certain populations disproportionately. It is primarily related to health care, but is no longer confined to intensive care units, or acute care hospitals, and may occur in the community without any exposure to a health care institution.

An accompanying editorial comments:

Strategies to prevent MRSA infections in hospitals (handwashing, surveillance, cultures, judicious antibiotic use, limiting invasive devices, environmental cleansing) are well known, but imperfectly practiced. Strategies to prevent sporadic community-associated infections are not as well described, although handwashing, not sharing personal items, and keeping wounds clean, dry and covered are commonly mentioned.

“Deciding Among The Various Strategies For Insulin Initiation Is Probably Less Important Than Taking Steps To Start Insulin In Patients Who Need It.”

10-7 ADDITION OF BIPHASIC, PRANDIAL, OR BASAL INSULIN TO ORAL THERAPY IN TYPE 2 DIABETES.

Type 2 diabetes (**DM2**) is a progressive disease in which the glycated hemoglobin level rises inexorably over time as the function of beta-cells declines. Most patients eventually require insulin to maintain good control.

This study followed over 700 patients with DM2 (mean age = 62). All had suboptimal glycated hemoglobin levels. (7.0% to 10.0%; mean = 8.5%) while receiving maximally tolerated doses of metformin and sulfonylurea.

Subjects were randomized to 1) long acting insulin detemir at bedtime, or 2) short acting insulin aspart given 3 times daily before meals, or 3) intermediate-acting insulin (70% insulin aspart-protamine; 30% soluble insulin aspart) given twice daily.

Overall, target levels were achieved in a minority of patients, with 16% having a level of 6.5% or less, and 39% having a level of 7% or less.

Glucose lowering was achieved at the expense of weight gain and an increased risk of hypoglycemia. The long-acting bedtime insulin detemir (*Levemir*) was associated with less hypoglycemia and less weight gain. It was not as effective in reducing HbA1c levels.

The three insulin regimens did not differ in glycemic efficacy for patients with a baseline glycated hemoglobin level of less than 8.5%, but differed significantly for patients with values above this level.

This was a substitute end-point. Clinical benefits (if any) were assumed, not determined.

Note that many subjects were smokers, hypertensive, had increased body-mass-index and abdominal girth, and had elevated LDL-cholesterol levels. I believe lowering these risk factors would be more beneficial in reducing macro-vascular complications than normalizing HbA1c.

Giving one dose of insulin glargine at bedtime is a good starting point. Patients may then self-titrate fasting glucose levels.

A target level of 6.5% is an arbitrary endpoint. Would not patients benefit from lowering HbA1c from 9% to 7.5%?

Allowing Patients To Make An Informed Decision To Decline Screening Should Also Be Considered A Marker Of Good Quality Care.

10-8 MAXIMIZING INFORMED CANCER SCREENING DECISIONS

Most quality-improvement initiatives have focused on maximizing cancer-screening rates rather than maximizing *informed* cancer-screening decisions. Public service announcements promoting some form of cancer screening are widespread. Few of these announcements provide accurate information about the pros and cons of screening. Most communicate a one-sided message that screening is always the right thing to do.

There are few meaningful discussions about risks and benefits of screening persons in whom screening efficacy is less clear (eg, patients with advanced age and multiple co-morbidities). Performance measures that equate ordering a screening test with high-quality health care discourage physicians from discussing the risks of screening with patients, and minimize the importance of informed cancer screening decisions.

Interest in informed decision-making for cancer screening is growing, catalyzed by public controversy about the effectiveness of certain cancer-screening tests, such as prostate specific antigen (PSA), and at what age to start and to stop screening. There is an increased call for patients to understand the risks and benefits of screening, to clarify personal values about them, and to make informed decisions about whether to undergo, and to continue screening.

Currently, we classify patients who receive screening as having received good quality care. Allowing patients to make an informed decision to decline screening should also be considered a marker of good quality care.

To screen or not to screen is a recurring topic. I believe it bears repeating.

Women Should Be Encouraged To Decide What Is Right For Themselves, Rather Than Being Told What To Do

10-9 PARTICIPATION IN MAMMOGRAPHY SCREENING

In April 2007, the American College of Physicians issued new guidelines on screening mammography for women age 40-49. Rather than calling for universal screening, the guidelines recommend that women in this age group make an informed decision after learning about the harms as well as the benefits of screening.

The public and the profession increasingly accept that cancer screening has harms as well as benefits. “Perhaps we are finally moving beyond the debate about what women should do, and are ready to focus on how to help women make the best decision for themselves.”

I believe this approach to screening should be applied to all screening methods. I believe many screening tests are applied too frequently to patients who will be harmed rather than benefited. And to many patients who will not be benefited at all.

There comes a time when the burdens of screening outweigh any benefits. When to stop (as well as when to start) screening requires keen clinical judgment. It depends on our ability to inform the patient accurately about risks vs benefits, and to ascertain the patient’s preference.

How long:

Should we continue to recommend cholesterol determinations?

Should we continue to recommend PSA determinations?

Should we continue to measure the body mass index?

Should we continue periodic Pap tests; colonoscopy?

Should we continue routine chemistry profiles and periodic physical “check ups”?

Should we continue to prescribe the array of drugs older patients often receive?

We should know when to stop as well as when to start. Stopping depends on age, co-morbidity and the informed-patient’s preferences.

“A Shift From Cellular To Viral Tests, Coupled With Education And Vaccination, Will Contribute To A More Efficient Control Of Cervical Cancer.”

10-10 HUMAN PAPILLOMAVIRUS DNA VERSUS PAPANICOLAOU SCREENING TESTS FOR CERVICAL CANCER.

This study was designed to compare HPV testing vs Pap testing to identify high-grade cervical intraepithelial neoplasia (CIN).

Randomized over 10 000 community-dwelling women age 30 to 69 to: 1) Pap test or 2) HPV test to identify CIN. Referred patients with either a positive Pap test or a positive HPV test to colposcopy and biopsy. (Biopsy was the gold standard.)

. Determined the sensitivity, specificity, and predictive values for each test, and for the tests combined.

Screening approach	Sensitivity	Specificity	PPV ¹	NPV ²
Pap test	55	97	7	99.8
HPV test	95	94	6	100

1 Positive predictive value 2 Negative predictive value.

The HPV test yielded many more true positive tests (was more sensitive) than Pap test in screening for CIN (95% - 55% = 40% difference).

When a positive HPV test was followed by a Pap test, and the Pap test was also positive, the sensitivity of the tests was 54%, the specificity remained about 99%, and the positive predictive value rose to 21%

Co-testing (HPV test followed by a Pap test) is an acceptable option for cervical screening in the United States.

“Triage algorithms that identify women with positive HPV tests who are at higher risk for cervical intraepithelial neoplasia, such as ‘HPV followed by Pap’ strategy, are essential.”

“We believe that a shift from cellular to viral tests, coupled with education and vaccination, will contribute to a more efficient control of cervical cancer.”

Conclusion: As compared with Pap testing, HPV testing had greater sensitivity for detection of cervical intraepithelial neoplasia.

I struggled to abstract this article accurately and concisely.

I abstracted the article because I believe HPV testing offers a clinical advantage. HPV testing may become a standard screening test. And will be used in conjunction with cytology.

In addition, I welcomed the opportunity to review and refresh my memory about sensitivity, specificity, and predictive values. If I do not do so periodically, I forget how to determine them.

They are essential for primary care clinicians' understanding the current literature.

(See the full abstract.)

HPV infections are the cause of cervical cancer. The infections are necessary, but not sufficient. HPV infections in young women often regress spontaneously (an immune effect). Thus, most screening programs will likely begin at age 30.

The period between HPV testing may be extended because the HPV infection precedes development of cytological changes in the cervix. Consequently there is a longer latent period (a longer lead time) between HPV infection and CIN compared with the latent period associated with abnormalities of the Pap test. This could add to cost effectiveness of HPV.

If the HPV test is negative, even if the Pap test is positive, the likelihood that the Pap represents an important pre-cancerous state is nil.

HPV DNA tests are highly reproducible. Pap tests are highly subjective.

“An Epic Revolution In Surgery” ?

10-11 NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY

What if a surgeon could enter the abdominal cavity without making an incision in the abdominal wall? What if that surgeon could use a fiberoptic scope, pass it into the vagina, then make an incision through the vaginal wall, examine the abdominal cavity, remove the gall bladder through the vagina, then repair the vaginal incision? There would be no visible scars.

See the full abstract for a short description of this technique, which has been described as “an epic revolution in surgery”.

Holy-moly—what next? This was my introduction to this technique. It startled me when I first read about it. Of course, it has no connection to primary care at this time. I abstracted the article because of its general interest.

Is This The Most Effective Approach To Colon-Cancer Prevention.?

10-12 CT-COLONOGRAPHY VERSUS COLONOSCOPY FOR THE DETECTION OF ADVANCED NEOPLASIA

This study compared computed tomography of the colon (CT-C) with the traditional optical colonoscopy (OC) as screening strategies when applied to the same general screening population. CT-C could provide a selective filter for therapeutic OC in the detection of advanced neoplasia.

Compared results from over 6200 consecutive patients (mean age 58) referred by a physician to

undergo first-time screening for colorectal cancer. The majority was asymptomatic and at average risk for cancer. Half received CT-C; half OC

For all polyps of at least 6 mm, the patient was offered same-day therapeutic OC. Patients with one or two small polyps (6 to 9 mm) were also offered the option of CT-C surveillance. Diminutive polyps 5 mm or less were not reported.

All polyps, including diminutive lesions, were removed in patients receiving OC, either at primary or at secondary screening.

Outcomes	CT-C (n = 3120)	OC (n = 3163)
A. Advanced neoplasms	3.2%	3.4%
(This did not include 158 patients with 6 to 9 mm polyps detected by CT-C that were not resected. (They were referred for surveillance). Of the 158 patients, 54 had returned for follow-up.)		
B Total number of polyps removed	561	2434
(Of these, 14 in the CT-C group were cancer; 4 in the OC group.)		
C. Advanced lesions in diminutive polyps		0.2%

Conclusion: Primary CT-C and OC screening strategies resulted in similar detection rates for advanced neoplasia. The number of polyps removed in the OC group was over four times as great as in the CT-C group.

I believe there are good reasons why primary care clinicians should not refer patients for this screening procedure:

- 1. CT-C screening ignored the small (5 mm and smaller) polyps. They were removed in the primary OC group. I believe removal of small adenomas is a cancer-prevention strategy. Some will enlarge over time, become dysplastic, and go on to malignancy. I believe it is advantageous to remove them when first discovered. (Note that the investigators reported a small % of these small polyps were “advanced”.)*
- 2. Patients with polyps 6 to 9 cm were offered surveillance. (Not stated how often.) If no subsequent enlargement is noted, they will have to return. Many did not return for follow-up.*
- 3. A two procedure protocol, CT-C followed by OC, is costly and inconvenient*
- 4. Continuing surveillance in the CT-C group with polyps 6 to 9 mm would add to anxiety, expense and inconvenience.*
- 5. I believe the carcinogenic risk of radiation is higher than is usually considered. The bad news may not appear for decades.*

ABSTRACTS OCTOBER 2007

“Simply Giving Aspirin 300 Mg More Quickly After the Presenting Event Probably Accounted For A Proportion Of The Benefit.”

10-1 EFFECT OF URGENT TREATMENT OF TRANSIENT ISCHEMIC ATTACK AND MINOR STROKE ON EARLY RECURRENT STROKE

The risk of recurrent stroke in the week after a transient ischemic attack (TIA) or a minor stroke is up to 10%. “These warning events provide a short window of opportunity for prevention.”

Several treatments are effective in preventing stroke in the long term after TIA or minor stroke: aspirin and other antiplatelet agents; BP lowering drugs; statins; anticoagulation for atrial fibrillation; and endarterectomy for symptomatic carotid stenosis. Assuming that benefits from these interventions are independent, use of *all* the interventions in appropriate patients would be predicted to substantially reduce the long-term risk of recurrent stroke.

This study aimed to determine the effect of rapid treatment after TIA or minor stroke in patients who are not admitted directly to the hospital.

Conclusion: Early initiation of existing treatments for TIA or minor stroke was associated with a reduction in risk of early recurrent stroke.

STUDY

1. This rigorous observational study, in a population of 91 000 individuals served by 63 primary care physicians, was divided into 2 phases:

A) Phase 1: 2002-2004 (n = 323 patients). A stroke clinic asked primary-care physicians to refer all patients with a TIA or minor stroke for whom immediate hospitalization was not considered necessary. The clinic was appointment-based with inherent delays in receiving referrals. Treatment was not initiated by the clinic, and no prescription was issued. The clinic made recommendations to referring physician. Studies, arranged, within the week, included ECG, carotid ultrasound imaging (all patients), and trans-thoracic or trans-esophageal echocardiography (when clinically indicated). The treatment protocol recommended:

- 1) Aspirin 75 mg daily
- 2) Clopidogrel (*Plavix*; Bristol-Myers-Squib) 75 mg daily (to be stopped in 30 days) in addition to aspirin, for those thought to be at particularly high risk, or if aspirin was contraindicated
- 3) Simvastatin (*Generic*; 40 mg daily)

4) BP lowering (unless systolic was below 130) either by increasing medications or by initiating perindopril (*Aceon*; Solway—an ACE inhibitor 4 mg daily) with or without indapamide (*Generic*—a diuretic; 1.25 mg daily)

5) Brain imaging was required before starting combination antiplatelet therapy, or anticoagulation after a minor stroke.

B) Phase 2: 2004-2007 (n = 297 patients). Protocol was changed. No appointment was necessary. Primary care physicians were requested to send all patients considered to have a TIA or minor stroke directly to the study clinic. Treatment was initiated immediately if the diagnosis was confirmed. Patients were assessed as in phase 1. All those considered to have a TIA or stroke were given 300 mg aspirin immediately¹, and started on the other study medications the same day. A loading dose of 300 mg clopidogrel was also given to cases in which it was indicated. A CT brain scan was obtained immediately for patients with incomplete resolution of symptoms to exclude intracerebral hemorrhage before giving aspirin, clopidogrel or anti-coagulants.

2. Outcomes in phase 1 and phase 2 were compared. Primary outcome = proportion of patients with recurrence of stroke within 90 days.

RESULTS

1. Roughly half of patients referred to the clinic were not confirmed as having TIA or stroke.

(Ie, clinics such as this can act as diagnostic centers and are able to reassure or refer patients. RTJ)

2. Of 620 patients in both phases combined, about half had TIA and half had minor stroke. Most had co-morbidities. About 1/3 were over age 80; 10% over 90. There were 6 intracerebral hemorrhages; 15% had atrial fibrillation¹

3. For those presenting with TIA, the 90-day risk of stroke in phase 1 = 16/156 (10%), and in phase 2 = 1/160 (<1%) number needed to treat (NNT) = 10; and for those presenting with minor stroke the 90-day risk of recurrent stroke = 16/154 (10%) vs 5/121 (4%) NNT = 17. Overall, within 90 days, the risk of stroke during the second phase was (*clinically and statistically*) lower than the risk in the first phase: 10.3% vs 2.1%; absolute difference = 8.2%; (NNT) to benefit one patient = 12

4. The reduction in risk was independent of age and sex. Early treatment did not increase risk of intracranial bleeding or other bleeding.

5. There were three myocardial infarctions in phase 1 and one in phase 2. Overall risk of non-fatal stroke, myocardial infarction, or death at 90 days in phase 1 = 11.9%; in phase 2 = 3.6%. Absolute difference = 8.3%; NNT = 12.

6. The primary care physician initiated aspirin in 71 (11%) of patients in phase 1 and 2 combined before

the clinic visit.

7. There were 3 episodes of g.i. bleeding in phase 1 and 4 in phase 2.
8. Carotid endarterectomy was performed in 17 (5%) patients in phase 1, and 15 (5%) in phase 2. But was done earlier in phase 2.
9. A beneficial effect in phase 2 was noted immediately after its introduction.

DISCUSSION

1. Urgent assessment and early initiation of a combination of existing preventive treatments can reduce the risk of early recurrent stroke after TIA or minor stroke by about 80%.
2. The low risk of stroke in phase 2 in patients with TIA is consistent with data now emerging from other studies in which patients with TIA are treated urgently and intensively. The high rate in phase 1 is consistent with similar studies in which patients were not treated urgently.
3. Simply giving aspirin 300 mg more quickly after the presenting event probably accounted for a proportion of the benefit. Other studies have reported a relative reduction in the 14-day risk of recurrent ischemic stroke due to aspirin given to patients with acute ischemic stroke is about 30%. The benefit could be larger in patients with TIA.
4. In patients with unstable angina or non-Q-wave myocardial infarction, initiation of a statin within 24-96 hours reduced the early risk of ischemic stroke by about 50% compared with placebo.
5. There are some data from randomized trials to suggest that the combination of aspirin + clopidogrel might be more effective in the acute phase of TIA and stroke than either given alone. (Brain imaging should be done first)
6. "Long delays to assessment in TIA clinics are no longer acceptable."
7. The public needs to be educated about symptoms of TIA and minor stroke, and the need to seek medical attention urgently. Most do not think of TIA as an emergency.

CONCLUSION

After onset of a TIA or minor stroke, early initiation of existing treatments can prevent about 80% of early recurrent strokes.

"These results have immediate implications for service provision and public education about TIA and minor stroke."

Lancet October 20, 2007; 370: 1432-42 original investigation by the Early use of Existing Preventive Strategies for Stroke (EXPRESS) study, first author Peter M Rothwell, Radcliffe Infirmary, Oxford UK.

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Evidence Of A “Carry-Over” Benefit After 5-Years Of Statin Therapy.

10-2 LONG-TERM FOLLOW-UP OF THE WEST OF SCOTLAND CORONARY PREVENTION STUDY

The WOSCP study was a *primary-prevention*, randomized, clinical trial comparing the statin drug pravastatin (*Pravachol*; Bristol-Myers-Squibb; 40 mg daily) with placebo. Subjects were men (n = over 6500; mean age = 55 at baseline) with elevated cholesterol. None of the subjects had a history of myocardial infarction (**MI**). The duration of the original study was 5 years. During the trial (1990-1995) the combined outcome of death from CHD + non-fatal MI was reduced from 7.9% to 5.5%. [Absolute difference = 2.4%; NNT for 5 years = 42.]

After the final scheduled visit, both study drugs were withdrawn. Patients were returned to the care of their primary care physicians.

This article reports the planned follow-up for an additional 10 years after the end of the study.

Conclusion: 5 years of treatment with pravastatin was associated with reduction in coronary events over a subsequent 10 years. (A carry-over effect.)

STUDY

1. At baseline and randomization, these subjects were at high risk for cardiovascular disease.
Mean LDL-cholesterol = 193 mg / dL; almost half were current smokers.
2. Tracked all deaths, hospitalizations, and deaths from coronary events, incident cancers, and deaths from cancer for an additional 10 years (1995-2005). [The full period of study was 15 years. The first 5 years of the study drugs was reported originally in 1995, and now another 10 years of follow-up.]
3. Five years after the trial ended, 39% of subjects who had been taking pravastatin, and 35% of those who had been taking placebo were taking a statin drug.
4. This post-trial study compared outcomes from the two original study groups regardless of the subsequent use of lipid-lowering therapy.

RESULTS

1. Deaths from any cause over the entire 15-year follow-up:
Original pravastatin group 619 of 3302 (18.7%)

Original placebo group 674 of 3293 (20.5%)

Absolute difference = 1.8%; NNT = 55 (*Statistically and clinically significant.*)

2. Deaths from any cause during the 10-year post trial period

Original pravastatin group 513 of 3196 (16.1)

Original placebo group 539 of 3158 (17.1)

Absolute difference = 1.0%; NNT = 100 (Not statistically significant)

3. For the composite cardiovascular endpoints:

	Trial period (%)		Post-trial period(%)		Total follow-up period (%)	
	P	S	P	S	P	S
CHD-related death or non-fatal MI	6.0	3.7	10.3	8.6	15.5	11.8
CHD-related death or hospitalization	9.0	6.1	19.0	15.6	25.3	20.5
Fatal or non-fatal stroke	1.4	1.0	5.6	5.1	6.8	5.9

(P = placebo S = pravastatin)

There was a trend for reduction in stroke (not statistically significant). CHD results were highly significant.

4. No significant differences between groups in rates of death from non-cardiovascular causes or cancer at any time.

DISCUSSION

1. During the first 5 years of the trial, there was a clinically significant reduction in risk of coronary events associated with the use of pravastatin vs placebo.
2. During an extended 10-year follow-up after the end of the trial, there was evidence of ongoing reduction in risk of major coronary events among participants treated with pravastatin during the 5-years of the trial, regardless of whether they continued to take the statin. (Ie, a carry-over benefit)
3. The benefits may have been due to stabilization of existing plaques in the coronary arteries, and a slowing of the progression of coronary artery disease.
4. During follow-up, many subjects in the original placebo group began to take a statin drug. This may have attenuated the difference between the two groups. (Ie, if none of the placebo group took a statin, the benefits noted above in the placebo group would not have been as great.)
5. During the 10-year follow-up period, over half of the original pravastatin group discontinued the drug. Benefits may have been greater if all had continued the drug for the following 10 years.

6. A strong trend toward a reduction in non-fatal stroke was offset in part by an increase in fatal stroke.
7. There was no evidence of increase in risk of cancer related to long-term pravastatin.

CONCLUSION

In men with hypercholesterolemia who did not have a history of myocardial infarction (primary prevention), statin treatment for 5 years provided an ongoing reduction in risk of coronary events for an additional period of up to 10 years. (A carry-over benefit.)

NEJM October 11, 2007; 357: 1477-86 Original investigation by the West of Scotland Coronary Preventions Study Group, first author Ian Ford, University of Glasgow, Scotland

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“Much Of The Burden Of CHD Might Be Reduced By Changes In Modifiable Lifestyle Behaviors”

10-3 COMBINED EFFECT OF LOW-RISK DIETARY AND LIFESTYLE BEHAVIORS IN PRIMARY PREVENTION OF MYOCARDIAL INFARCTION IN WOMEN

“Coronary heart disease (CHD) is the most important cause of death and disability in women.” The percentage of sudden deaths from CHD in women without previous symptoms is higher than in men.

Regardless of predisposing factors or proved benefits from pharmacological therapies, diet and lifestyle largely influence morbidity and mortality from CHD.

This prospective study examined the benefit of a combined healthy diet and 3 major lifestyle risk factors on risk of primary myocardial infarction (MI) in a large population-based cohort of Swedish women.

Conclusion: Almost all MIs in women may be preventable by consuming a healthy diet with moderate amounts of alcohol, with being physically active, not smoking, and maintaining a healthy weight.

STUDY

1. Prospective study followed over 24 000 postmenopausal women (age 48 to 83; mean age 59). All were free of diagnosed cancer, cardiovascular disease, and diabetes at baseline (1997).
2. Determined dietary patterns by questionnaire. A low-risk diet was defined as a high intake of vegetables, fruits, whole grains, fish, and legumes in combination with moderate alcohol intake (on average 5 g or less of alcohol daily).

3. Divided healthy diet scores into quintiles. Compared with women in the highest quintile of a healthy diet, women in the lowest quintile had low intakes of vegetables fruits, legumes, fish, whole grains, and higher intake of saturated fat, and lower intake of mono-unsaturated fat, poly-unsaturated fat, and fiber. Women in the top quintile of a healthy-diet pattern had almost a 4-fold higher weekly consumption of vegetables, 3-fold higher consumption of legumes, 70% higher consumption of fish, 50% higher intake of dietary fiber, and more vitamin C and folate compared with those in the lowest quintile.
4. Also determined frequency of 3 low-risk lifestyle factors: non-smoking, waist/hip ratio less than 85/100, and being physically active (at least 40 minutes of walking or bicycling daily).
5. Determined risk of MI over 6 years of follow-up, and compared low-risk groups with high-risk groups.

RESULTS

1. Over the 6 years of follow-up, 308 incident cases of MI occurred. (Fifty-one fatal.)
2. Effect of combined low-risk behaviors in relation to risk of MI:

	No of events	Rate per 100 000
A. Healthy diet + alcohol > 5 g daily	42	95
B. Healthy diet + alcohol >5 g + no current smoking	27	84
C. Healthy diet + alcohol 5 g + no current smoking + being physically active	7	66
D. Healthy diet + alcohol > 5 g + no current smoking + being physically active + waist / hip ratio < 85 /100	3	40

(Only 5% of women fit category. D.)

3. The final comprehensive low-risk-factor category (D.) was associated with a 92% lower risk of MI compared with the high-risk group (unhealthy diet, smoking, abdominal adiposity, less physical activity, and low alcohol consumption).

DISCUSSION

1. In this study, the combined benefit of diet, lifestyle, and healthy body weight was associated with

prevention of more than 3 of 4 cases of MI.

2. "Our results of alcohol . . . agreed with previous findings of alcohol and CHD incidence."
3. Much of the burden of CHD might be reduced by changes in modifiable lifestyle behaviors.
4. The strength of association of the 5-low-risk behaviors is compatible with a clinical definition of a low-risk profile based on favorable levels of blood pressure and serum cholesterol, and absence of diabetes.

CONCLUSION

Most MIs in women may be preventable by consuming a healthy diet, and moderate amounts of alcohol, being physically active, not smoking, and maintaining a healthy weight.

Archives Int Med October 22, 2007; 167: 2122-27 Original investigation, first author Agneta Akesson, Karolinska Institutet, Stockholm, Sweden

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Protection May Be Substantial, Although Lower, During Years With A Poor Match.

10-4 EFFECTIVENESS OF INFLUENZA VACCINE IN THE COMMUNITY-DWELLING ELDERLY

Each year flu and its complications are responsible for about 186 000 excess hospitalizations, and 44 000 excess all-cause deaths in the elderly in the U.S.

The elderly are included among high risk persons for whom the vaccine is recommended.

Most studies assessing effectiveness of the vaccine in the elderly have included only one, or only a few seasons. Because of the variability of severity of flu from season to season, short term studies might provide incomplete or misleading pictures about benefits of the vaccine.

This study analyzed effectiveness of the vaccine among 18 cohorts of community-dwelling elderly members of a health maintenance organization during 10 seasons.

Conclusion: Among the elderly, during 10 seasons, the vaccine was associated with significant reductions in the risk of hospitalization for pneumonia or influenza, and in the risk of all-cause death.

STUDY

1. Observational study pooled subjects from 18 cohorts of elderly members of an HMO (mean age 73).
About half of the individuals had one or more high-risk medical conditions.
2. Each cohort provided retrospective data for more than 20 000 person-seasons for a total of over

713 000 person-seasons.

3. Compared outcomes between vaccinated (n = 415 000) and unvaccinated (n = 299 000) subjects. Estimated effectiveness of the vaccine for prevention of hospitalizations for pneumonia and influenza, and all-cause death, after adjustment for important covariates.

RESULTS

1. Vaccinated subjects were slightly older and had higher prevalence of baseline medical conditions (diabetes, heart disease, lung disease, etc.).
2. The vaccine-circulating virus antigenic match was good to excellent except for 2 of the 10 seasons.
3. During the 10 seasons, there were 4600 hospitalizations for pneumonia or influenza.
4. In both the vaccinated and unvaccinated groups, hospitalizations and deaths increased as age increased and as comorbidity increased.
5. Outcomes per season (average):

	Vaccinated (%)	Unvaccinated(%)	Absolute diff (%)	NNT*
Hospitalizations	0.6%	0.7%	0.1%	1000
Deaths (all causes)	1.0 %	1.6%	0.6%	166

(* NNT – number of persons needed to treat to benefit one person.)

6. “Influenza vaccination was associated on average with substantial reductions in hospitalizations for pneumonia or influenza (vaccine effectiveness = 27%) and in all cause death (vaccine effectiveness = 48%).”
7. In the two seasons with a poor match between the vaccine and the virus strain, effectiveness was lower for reducing death (37%). In seasons with a good match vaccine effectiveness for reducing death (52%), but not for reducing hospitalization.

DISCUSSION

1. “Influenza vaccine of community-dwelling elderly patients during 10 seasons was associated with substantial reductions in hospitalizations for pneumonia or influenza, and in death.”
2. “Benefits probably extend to a broad spectrum of elderly persons.”
3. This study was not designed to evaluate levels of vaccine effectiveness among the frailest elderly, such as those living in nursing homes, who may have impaired immune responses.
4. Protection may be substantial, although lower, during years with a poor match.
5. Achieving optimal success in preventing and controlling influenza among the elderly may require

strategies that induce more herd immunity and thereby interrupt influenza transmission in communities. (Eg, increasing vaccinating rates in children.)

CONCLUSION

During 10 seasons, influenza vaccine was associated with significant reductions in risk of hospitalizations for pneumonia or influenza, and in the risk of all cause death among community-dwelling elderly persons.

NEJM October 4, 2007; 357: 1373-81 Original investigation, first author Kristen L Nichol, University of Minnesota, Minneapolis.

An editorial in this issue of NEJM (pages 1439-41 by John D Treanor, University of Rochester Medical Center, Rochester, NY comments and expands on this study:

Surprisingly, flu vaccination was associated with reductions in deaths from any cause, and in reduction of deaths from stroke and heart attack. This implies that the vaccine is effective, and also that influenza must account, either directly or indirectly, for a substantial proportion of all wintertime deaths in the elderly.

It is clear that inactivated flu vaccine is not a perfect solution to the problem. About half of wintertime hospitalizations and deaths in this study occurred in the vaccinated population. Some deaths may have been due to other viruses that can mimic influenza. Many likely represent vaccine failure. The vaccine is less immunogenic and probably less effective in the elderly than in young adults.

But, influenza cannot develop in elderly persons if they are not exposed to the virus from others. The elderly have frequent contact with health care workers and others in the health care system. Some of these workers often report to work when they are not feeling well and can easily serve as vehicles of doom for their unsuspecting patients. "This is why the extraordinary low rates of vaccination of health care workers in the United States are so appalling."

High vaccination rates among the general population, particularly among children, might interrupt transmission, and provide secondary protection for those who cannot be protected directly by vaccination.

"Ultimately, the key to effective control of the devastating effects of influenza in elderly people may be found in the ability to effectively vaccinate the youngest members of the population."

Prednisone Yes; Acyclovir No; Valcyclovir + Prednisone Maybe.

10-5 EARLY TREATMENT WITH PREDNISOLONE OR ACYCLOVIR IN BELL'S PALSY

Vascular, inflammatory, and viral (eg, herpes infection) causes of Bell's palsy have been suggested based on paired serological analyses and studies of cerebral ganglia.

Although most patients recover well, up to 30% have a poor recovery, with continuing facial disfigurement, psychological difficulties, and facial pain.

Treatment remains controversial and variable. Prednisolone (or prednisone) and acyclovir are commonly prescribed. Recent Cochrane reviews concluded that there is insufficient evidence to support treatment with either corticosteroids or antivirals, or both combined.

This study examined effects of prednisolone, acyclovir, and both combined, on recovery of facial function.

Conclusion: Early treatment with prednisolone improved chances of complete recovery. No evidence of a benefit from acyclovir alone, or in addition to prednisolone.

STUDY

1. Multicenter study recruited over 550 adults over age 16 (mean age = 44) with unilateral facial nerve weakness of no identifiable cause (idiopathic). All entered the study within 72 hours of onset. In the great majority treatment was started within 48 hours.
2. Randomized double-blind to: 1) prednisolone 25 mg twice daily for 10 days; 2) acyclovir 400 mg 5 times daily for 10 days; 3) both together, or 4) placebo.
3. Primary outcome (analysis by intention-to-treat) = facial nerve function graded by a function test which measures recovery of the paralysis caused by damage to the lower motor neurons.
4. Follow-up at 3 and 9 months.

RESULTS

1. Complete recovery*	At 3 months (%)	At 9 months (%)
Prednisolone + placebo	87	95
Acyclovir + placebo	64	79
Placebo	65	83

(* My estimates from figure 2 page 1605)

2. There was no benefit from acyclovir compared with placebo.
3. There was no benefit from acyclovir when added to prednisolone.
4. The absolute difference in complete recovery at 3 months between the two groups that received prednisolone vs no prednisolone = 19% [NNT = 5]; and = 12% at 9 months [NNT = 12].
5. Adverse events: No serious events.

DISCUSSION

1. This study confirmed the generally favorable prognosis of Bells palsy. Without treatment, about 65% of patients recover completely at 3 months, and about 85% completely recover at 9 months.
2. Early treatment with prednisolone for 10 days increased these rates to 83% and 94%.
3. No benefit from acyclovir given alone, or when added to prednisone.

CONCLUSION

In patients with Bell's palsy, early treatment with prednisolone alone significantly improved the chances of complete recovery at 3 and at 9 months.

There was no evidence of benefit from acyclovir alone, or when added to prednisolone.

NEJM October 18, 2007; 357: 1598-607 Original investigation. First author Frank M Sullivan, Scottish School of Primary Care, University of Dundee, Scotland.

Given the prior lack of firm evidence about treatment of Bell's palsy, The Health Technology Assessment Program of the National Institute of Health of Scotland commissioned this independent study.

An editorial in this issue of NEJM, first author Donald H Gilden, University of Colorado, comments and expands on this article:

About 1/3 of cases of acute peripheral facial weakness are caused by trauma, diabetes, hypertension, eclampsia, the Ramsay Hunt syndrome (facial palsy with zoster oticus caused by the varicella-zoster virus), Lyme disease, sarcoidosis, Sjogren's syndrome, parotid gland tumors, and amyloidosis. It may also be a complication of intranasal influenza vaccine. The remaining 2/3 of cases are idiopathic. Beside the facial asymmetry, there may be other permanent sequelae (synkinesia, ¹ hyperacusis, loss of taste, and inability to produce tears).

Surgeons have long reported the presence of facial nerve swelling during decompression operations for Bells palsy. The edema may be due to ischemia or inflammation, as evidenced by MRI of the facial nerve.

Glucocorticosteroids have been used for years to treat Bell's palsy. Detection of herpes simplex virus in the endoneural fluid has led to use of antiviral drugs in addition to corticosteroids, although the exact role of the virus in the pathogenesis of the disease is not known.

The lack of benefit from acyclovir conflicts with a recent randomized study from Japan which compared a combination of valacyclovir + prednisolone vs prednisolone alone. It reported absolute recovery was 7% greater in the group treated with both drugs vs prednisolone alone. (NNT = 15) The benefit of valacyclovir + prednisolone vs prednisolone alone appeared to correlate with the severity of the palsy—those with more severe disease responded more favorably. There was no benefit in patients with moderate palsy.

How should we apply these results? We should advise corticosteroids within 72 hours. In the U.S., prednisone is usually prescribed—1 mg per kg daily for 7 to 10 days. Cost is relatively low², and the NNT is also low. Valcyclovir 500 mg twice daily costs about \$70 for 10 days. It has substantially increased bioavailability compared with acyclovir. Despite the Japanese study being somewhat flawed methodologically, the editorialist would treat severe or complete paralysis with valcyclovir in addition to prednisone.

- 1 Synkinesia Unintended (involuntary) movement accompanying a volitional movement.
- 2 Go to *\$4 prescriptions* on Google. Some pharmacies sell 20 mg prednisone #30 for \$4.

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“*What Happens In The Hospital Does Not Stay In The Hospital.*”

10-6 INVASIVE METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTIONS IN THE UNITED STATES

Community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) has become the most common cause of skin and soft tissue infections presenting in the U.S.¹

Although outbreaks of MRSA in diverse populations in the community usually involve skin disease, MRSA can also cause severe, sometimes fatal invasive disease.

Studies of the emergence of MRSA disease over the past decades determined that isolates causing community-associated MRSA and hospital-associated MRSA were distinct. The bacterial strains were different. The strain most often isolated in community outbreaks was type USA300. In contrast, the strain most frequently associated with invasive MRSA in health care settings was USA100.

Isolates from the community were susceptible to most non-beta-lactam antimicrobial agents. Invasive MRSA (isolated from a normally sterile site) associated with health care settings were traditionally multidrug resistant.

The epidemiology of MRSA disease has been changing. The distinction between community-acquired MRSA and hospital-acquired MRSA is becoming blurred.

This report describes the incidence and distribution of *invasive* MRSA disease in 9 communities in the U.S. in 2005.

Conclusion: MRSA is a major public health problem.

STUDY

1. A population-based surveillance for *invasive* MRSA, conducted in 9 U.S. communities in 2005, investigated reports of invasive MRSA and classified them as either 1) health-care associated, or 2) community associated.

2. Investigated each potential case of invasive MRSA infection isolated from normally sterile sites to confirm presence of infection, and the demographic characteristics of the patients.
3. Arbitrarily divided the invasive infections into two mutually-exclusive groups:
 - A. Health-care associated cases:
 - a. Community-onset, health-care associated hospital infections: Cases in the hospital with a health-care risk factor (presence of an invasive device on admission, or a hospitalization, surgery, or residence in a long-term health care facility within the past 12 months), but with culture obtained less than 48 hours after hospital admission. *(This assumed the infection began in the community before the patient was hospitalized. And that the infection had been acquired from a health-care source.)*
 - b. Hospital-onset infections: Cases with culture obtained more than 48 hours after admission. *(This assumed the infection was acquired in the hospital.)*
 - B. Community-associated infections: Patients without a documented connection with health-care.

RESULTS

1. There were over 8900 cases of invasive MRSA in the 9 communities in 2005.
 - A. Health-care associated infections
 - a. Community-onset health-care associated 58%
(Note that most cases apparently acquired their infection in the community from a source connected to health-care.)
 - b. Hospital-onset 27%
(Acquired the infection while in the hospital)
 - B. Community-associated infections 14%
(These infections occurred in otherwise healthy persons in the community who had no obvious connection with health care.)
2. The standardized incidence rate of invasive MRSA = 32 per 100 000. The investigators estimated that over 94 000 persons in the U.S. had invasive MRSA infections in 2005, and there were over 18 000 deaths.
3. Incidence rates were highest among persons over age 65; among blacks; and among males.
4. Almost all cases were hospitalized; 18% died during hospitalization; 13% developed recurrent invasive infections.
5. Over 1550 in-hospital deaths occurred. The standardized mortality rate = 6 per 100 000 overall;

and 35 per 100 000 in persons over age 65.

6. In health-care associated infections, molecular testing identified some strains historically associated with community-associated disease outbreaks (USA300). And in community-associated MRSA, molecular testing identified some strains historically associated with hospital-associated disease outbreaks (USA100)

Typing of isolates:	USA100 (%)	USA300 (%)
Hospital onset	74	16
Community onset health-care associated	62	22
Community onset not health-care associated	23	67

7. Clinical syndromes associated with invasive MRSA were primarily bacteremia (75%); also pneumonia (13%); less frequently, cellulitis, osteomyelitis, and endocarditis and septic shock.

8 . Empirical therapy was documented in 64%, primarily vancomycin.¹ The majority of cases received multi-anti-microbial therapy.

DISCUSSION

1. The incidence of invasive MRSA has increased in the past 7 years, both in the community and in health care facilities.
2. The standardized incidence rate of *invasive* MRSA in 2005 (30 per 100 000 persons) was higher than rates of other important invasive pathogens *S pneumoniae* or *H influenzae* (between 14 per 100 000 to 1 per 100 000). This is due largely to the success of vaccination.
3. Of the estimated 95 000 MRSA infections in 2005, 75% were bacteremias.
4. In the community, non-invasive MRSA greatly outnumber invasive infections.²
5. Invasive MRSA infections do occur in persons in the community without any apparent connection to a health-care facility. The strains of MRSA causing these community infections are also found in hospitals.
6. The difference associated with race (blacks vs white) is striking. Little progress has been made in understanding why.
7. Persons in the community who develop invasive MRSA likely acquired the pathogen from their health care contacts, such as those with recent hospitalizations, surgery, or nursing home residence. Molecular analysis suggests that most of these infections are caused by MRSA strains of hospital origin. (USA100)

CONCLUSION

The epidemiology of MRSA is changing. Invasive MRSA disease is a major public health problem. It affects certain populations disproportionately. It is primarily related to health care, but is no longer confined to intensive care units, or acute care hospitals. It may occur without any exposure to a health care institution.

JAMA October 17, 2007; 298: 1763-71 Original investigation by The Active Bacterial Core surveillance (ABCs) MRSA Investigators, first author R Monina Klevens, CDC, Atlanta GA.

- 1 The Johns Hopkins Antibiotic Guide (<http://hopkins.abx.guide.org>) still recommends vancomycin as first-line therapy. Daptomycin (*Cubicin*; Cubist pharmaceuticals) is second-line therapy.
- 2 Compared with *invasive* MRSA, skin and soft tissue infections are a different problem. These infections are very common in the general population.. They are not invasive, but may become invasive. They are treated primarily by incision and drainage. Simple hygienic measures can prevent transmission. Culture and appropriate antibiotic therapy may be indicated. .

An editorial in this issue of JAMA (pp 1803-04) by Elizabeth A Bancroft, Los Angeles Department of Public Health, comments and expands on this article:

Patients with MRSA infections have worse outcomes than those with methicillin-sensitive *S aureus*.

More than 10% of bloodstream infections are due to invasive MRSA.

Deaths likely exceed that related to HIV-AIDS.

In recent years, identification of MRSA in otherwise healthy individuals has become increasingly common.

Health-care associated MRSA is typified by type USA100 strain. The strain in most community-associated MRSA is USA300. But, either strain can appear in both locations. The majority of invasive MRSA was among patients who had health-care risk factors, but community onset of the disease. The majority was USA100, suggesting health-care origin. "What happens in the hospital does not stay in the hospital." Patients are discharged from health-care facilities with MRSA colonization that is not identified, and only later develop invasive disease.

Strategies to prevent MRSA infections in hospitals (handwashing, surveillance, cultures, judicious antibiotic use, limiting invasive devices, environmental cleansing) are well known, but imperfectly practiced. Strategies to prevent sporadic community-associated infections are not as well described, although handwashing, not sharing personal items, and keeping wounds clean, dry and covered are commonly mentioned.

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“Deciding Among The Various Strategies For Insulin Initiation Is Probably Less Important Than Taking Steps To Start Insulin In Patients Who Need It.”

10-7 ADDITION OF BIPHASIC, PRANDIAL, OR BASAL INSULIN TO ORAL THERAPY IN TYPE 2 DIABETES.

Type 2 diabetes (**DM2**) is a progressive disease in which the glycosylated hemoglobin level rises inexorably over time as the function of beta-cells declines. Most patients eventually require insulin to maintain good control.

Maintenance of normal, or nearly normal, glycemic levels reduces risk of complications of diabetes, but is difficult to achieve despite escalating doses of oral anti-diabetes medications. Many patients do not reach targets for glycosylated hemoglobin with conventional insulin regimens. Large-scale direct comparisons of various regimens are lacking.

This study compared efficacy of each of 3 different insulin regimens added to patients who had suboptimal glycemic control while receiving “maximum tolerated doses” of metformin and sulfonylureas. (*Maximum tolerated doses were not defined in the article.*)

Conclusion: Target glycosylated hemoglobin levels (6.5% or less) were obtained in a minority of patients.

STUDY

1. Recruited and followed over 700 patients with DM2 (mean age = 62). All had suboptimal glycosylated hemoglobin levels. (7.0% to 10.0%; mean = 8.5%) while receiving maximally tolerated doses of metformin and sulfonylurea. None were taking thiazolidinediones.
2. Randomized to:
 - 1) Biphasic insulin aspart 30 injected twice daily
(*Novolog Mix 70/30; Novo Nordisk; 70% insulin aspart-protamine; and 30% soluble insulin aspart. Peaks at 2 hours and lasts 6 hours.*)
 - 2) Prandial insulin aspart injected 3 times daily immediately before meals
(*Novo Log; Novo Nordisk; insulin aspart peaks at 1 hour and lasts 2-3 hours*)
 - 3) Basal insulin detemir once daily at bedtime (or twice daily if required).
(*Levemir; Novo Nordisk; long acting insulin peaks at about 8 hours, and lasts up to 14 hours. Action is longer than NPH insulin and shorter than insulin Glargine. Detemir is often given twice daily. Many patients in this study received 2 doses.*)
3. Starting doses of insulin were determined by a formula including body weight, height, and fasting plasma glucose. (*Page 1717-18*). Mean starting dose = 16 U/day

4. Aimed for glucose values of 72 to 99 mg/dL before meals, and 90 to 126 mg/dL 2-hours after meals.
5. If glycated hemoglobin levels remained above 10%, or if two consecutive levels were above 8.0%, a second type of insulin was added and the sulfonylurea was discontinued.
6. Primary outcome = glycated hemoglobin level at one year.

RESULTS

1. Mean glycated hemoglobin levels at one year:

1) Biphasic insulin	7.3%
2) Prandial insulin aspart	7.2%
3) Basal insulin detemir	7.6%

2. Reductions in mean glycated hemoglobin at one year (%):

1) Biphasic insulin	1.3
2) Prandial insulin aspart	1.4
3) Basal insulin detemir	0.8

4. Patients with glycated hemoglobin:

	6.5% or less (%)	7.0% or less (%)
1) Biphasic insulin	17	42
2) Prandial insulin aspart	24	49
3) Basal insulin detemir	8	28

5. Mean number of hypoglycemic events per patient per year:

1) Biphasic insulin	6
2) Prandial insulin aspart	12
3) Basal insulin detemir	2

(None was serious enough to require third party assistance.)

6. Mean weight gain (kg)

1) Biphasic insulin	5
2) Prandial insulin aspart	6
3) Basal insulin detemir	2

5. Maximum reductions in glycated hemoglobin occurred at 24 weeks, and then remained stable.
6. Self-measured capillary glucose profiles improved on all regimens.

DISCUSSION

1. This trial “showed that three different analogue insulin regimens, when added to metformin and sulfonylurea therapy in patients with type 2 diabetes mellitus were associated with clinically relevant and sustainable reductions in glycated hemoglobin levels.”
2. However, target levels were achieved in a minority of patients overall, with 16% having a level of 6.5% or less, and 39% having a level of 7% or less.
3. Glucose lowering was achieved at the expense of weight gain and an increased risk of hypoglycemia.
4. The three insulin regimens did not differ in glycemic efficacy for patients with a baseline glycated hemoglobin level of less than 8.5%, but differed significantly for patients with values above this level.
5. Most patients are likely to need more than one type of insulin to achieve target glucose levels.
6. The study will continue for another 2 years.

NEJM October 25, 2007; 357: 1716-30 Original investigation by the Treating to Target in Type-2 Diabetes (4-T) Study Group, first author Rury R. Holman, University of Oxford, Oxford, UK

Study supported by Novo Nordisk.

An editorial in this issue of NEJM (pp 1759-61), first author Graham T McMahon, Deputy Editor of NEJM comments and expands on this article:

Many diabetologists recommend that insulin be added when the HbA1c remains above 7% after having received maximum doses of two oral agents for more than a few months.

For patients with a HbA1c constantly above 7% while on two oral agents, the best approach is to continue metformin, add a basal insulin, and stop the sulfonylurea.

The editorialist recommends insulin glargine (*Lantus*) as a once-daily basal insulin because of its longer duration. Glargine is relatively peak free. Basal insulin is usually sufficient to bring most patients close to the HbA1c target. Attaining normal glucose levels usually necessitates use of additional short-acting prandial insulin.

The dose of bedtime long-acting insulin should be titrated to a fasting glucose level of no more than 100 mg/dL. Patients can usually self-titrate to this level.

Once insulin is added, sulfonylureas should be discontinued. They do not add any benefit in addition to insulin. And may add to risk of hypoglycemia.

Prandial and biphasic insulin formulations are suboptimal choices for insulin initiation. They may expose patients to unnecessary high risk of hypoglycemia without clinically important benefit.

“Deciding among the various strategies for insulin initiation is probably less important than taking steps to start insulin in patients who need it.”

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Allowing Patients To Make An Informed Decision To Decline Screening Should Also Be Considered A Marker Of Good Quality Care.

10-8 MAXIMIZING INFORMED CANCER SCREENING DECISIONS

A study in this issue of Archives¹ discusses promotion of screening mammography in 70-year old women. The authors developed a visual decision aid to help patients to understand the risks and benefits of continuing mammography, and to help them make a choice consistent with their values and preferences. The decision aid presents clear information about the potential risks of mammography screening, and includes the possibility of overdiagnosis and overtreatment of breast cancer (BC) that may occur as a result of screening. The objective is to maximize informed decisions, rather than maximizing screening rates.

Is the high enthusiasm for mammography screening appropriate for 70-year old women? There is no evidence that the potential benefits suddenly cease at age 70. Older women have a higher absolute risk of dying from BC. Mammograms in older women are more accurate for diagnosing cancer than for younger women. Most guidelines recommend continuing screening mammography until co-morbid conditions limit life expectancy to 5 years or less. Approximately 90% of women age 70 will live for 5 years or more.

What about a 70-year old in poor health? An 80-year old? A 90 year old?

We need decision aids to help older patients make informed decisions about screening—aids that provide individualized information about potential risks as well as benefits of screening tailored to the patient's health status and prognosis rather than basing decisions solely on age. Detecting BC at an early stage does not improve survival in elderly women with multiple co-morbidities.

Explaining how the consequences of screening depend on health status and life expectancy will become increasingly important.

Currently, we classify patients who receive screening as having received good quality care. Allowing patients to make an informed decision to decline screening should also be considered a marker of good quality care.

Archives Int Med October 22, 2007; 167: 2027-28 Editorial, first author Louise C Walter, VA Medical Center, San Francisco

1 "Informed Choice in Mammography Screening" Archives Int Med October 22,2007; 167: 2039-46, first author Erin Mathieu, University of Sydney, Australia

The article presents a decision aid in pictorial form representing outcomes from continued screening and from discontinuing screening.

The visual aid presented a small rectangle containing 1000 small brown dots representing 1000 70-year old women who stop screening mammography. Another represented 1000 who continue screening.

Eight small green spots represent women who stop screening who would die of BC over the next 10 years. Six green spots illustrate the number of women who continue screening every 2 years who will die of BC over the next 10 years despite screening. This illustrates that 2 lives per 1000 will be “saved” by screening between ages 70 and 80.

The aid also illustrates what else happens to 1000 70-year old women who stop screening, and what else happens to 70-year olds who continue screening every 2 years.

In summary, mammography screening for 1000 70-year olds will result in:

2 less women dying from BC.

15 more women diagnosed with BC. Without screening, some of these cancers would never be found.

135 women have extra tests after an abnormal mammogram, but do not have BC.

824 women are correctly reassured that they do not have BC.

The aid increased knowledge, and helped more women make a better-informed choice about screening mammography. It did not increase anxiety about breast cancer.

Interestingly, after the investigation clearly presented potential risks and benefits of mammography screening to 70-year old women who had been regularly screened, their intention to continue screening was not reduced. But they felt more confident that they made the correct choice.

Women Should Be Encouraged To Decide What Is Right For Themselves, Rather Than Being Told What To Do

10-9 PARTICIPATION IN MAMMOGRAPHY SCREENING

(This article continues the theme presented in the preceding article.)

In April 2007, the American College of Physicians issued new guidelines on screening mammography for women age 40-49.¹ Rather than calling for universal screening, the guidelines recommend that women in this age group make an informed decision after learning about the harms as well as the benefits of screening.

The public and the profession increasingly accept that cancer screening has harms as well as benefits. “Perhaps we are finally moving beyond the debate about what women should do, and are ready to focus on how to help women make the best decision for themselves.”

No right choice exists. Screening has mixed effects—some women will benefit (by avoiding death due to breast cancer); others will be harmed.

The editorialists present a table which estimates benefits and harms from screening women at different ages every 1 to 2 years for 10 years:

	Age 40-49	Age 50-69
Benefits		
10-year risk of death from BC		
No screening	3.3 / 1000	8.9 / 1000
Screening	2.5 / 1000	6.0 / 1000
Avoidance of death from BC	0.8 / 1000	3 / 1000
(Screening women who are 50 or older improves the chance of <i>not</i> dying from BC in the next 10 years from about 991/1000 to 994/1000)		
Harms		
At least one false positive test		
resulting in additional testing	100-500 / 1000	100-500 / 1000
At least one false positive that		
resulting in unnecessary		
diagnosis and treatments	2.5 / 1000	3.0 / 1000

The table is not the final word. The numbers are still controversial. They are based on averages, so risks will be different for women at high risk (strong family history).

BMJ October 13 2007; 335: 731-32 Editorial, first author Lisa M Schwartz, Department of Veterans Affairs Medical Center, White River Junction, VT

1 See Practical Pointers April 2007

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“A Shift From Cellular To Viral Tests, Coupled With Education And Vaccination, Will Contribute To A More Efficient Control Of Cervical Cancer.”

10-10 HUMAN PAPILOMAVIRUS DNA VERSUS PAPANICOLAOU SCREENING TESTS FOR CERVICAL CANCER.

Testing for the DNA of oncogenic (high risk) types of human papilloma virus (**HPV**) is now used mainly to triage for colposcopy those women with Pap smear labeled as “atypical squamous cells of undetermined significance” (**ASCUS**). Population-based, nonrandomized studies indicate that HPV testing is more sensitive than Pap testing for identifying cervical cancer and its precursors.

This study was designed to compare HPV testing vs Pap testing to identify cervical intraepithelial neoplasia (CIN)

Conclusion: HPV testing is a much more sensitive test. (More true positive tests.)

STUDY ¹

1. Randomized over 10 000 community-dwelling women age 30 to 69 to: 1) Pap test or 2) HPV test ² to identify high-grade cervical intraepithelial neoplasia
2. Referred patients with either a positive Pap test or a positive HPV test to colposcopy and biopsy. (Biopsy was the gold standard.)
3. Determined the sensitivity, specificity, and predictive values for each test, and for the tests combined.

RESULTS

1. Comparison of Pap and HPV testing to identify high-grade cervical intraepithelial neoplasia (CIN) (table 2 page 1585)

Screening approach	Sensitivity ^a	Specificity ^b	+ PV ^c	- PV ^d
Pap test	55	97	7	99.8
HPV test	95	94	6	100

2. When a positive HPV test was followed by a Pap test, and the Pap test was also positive, the sensitivity of the tests was 54%, the specificity remained about 99%, and the positive predictive value rose to 21%.

DISCUSSION

1. The HPV test yielded many more true positive tests (was more sensitive) than Pap test in screening for CIN (95% - 55% = 40% difference).
2. HPV test yielded a few more false positive tests than Pap test (was slightly less specific) (6% vs 3% = 3 more false positives out of 100 tests.)
3. Co-testing (HPV test followed by a Pap test) is an acceptable option for cervical screening in the United States
4. The success of HPV vaccines opens a new era of cervical-cancer prevention. Vaccination will not, however, eliminate screening. Not all women will be vaccinated. Women who have already been exposed to oncogenic HPV will not benefit.³ The present vaccines target only two of the cancer-

causing types. For vaccinated women, continued HPV screening provides the added benefit of HPV surveillance.

5. The higher sensitivity and the more “upstream” focus on cervical carcinogenesis conferred by HPV testing relative to Pap testing should safely permit prolongation of screening intervals.
6. “Triage algorithms that identify women with positive HPV tests who are at higher risk for cervical intraepithelial neoplasia, such as ‘HPV followed by Pap’ strategy, are essential.”
7. “We believe that a shift from cellular to viral tests, coupled with education and vaccination, will contribute to a more efficient control of cervical cancer.”

CONCLUSION

As compared with Pap testing, HPV testing had greater sensitivity for detection of cervical intraepithelial neoplasia.

NEJM October 18,2007; 357: 1579-88 original investigation by the Canadian Cervical Cancer Screening Trial (CCCaST), first author Marie-Helene Mayrand, McGill University, Montreal, Canada.

- 1 The investigation was much more detailed and sophisticated than I have indicated. I believe I have captured the essence of the study.
- 2 The investigators described 2 different tests for the HPV. The ideal test is not yet decided upon.
- 3 Immunization with HPV does not eliminate infections that are already present. It is not a treatment; it is strictly prophylactic.

An editorial in this issue of NEJM (pages 1650-52) by Carolyn D Runowicz, University of Connecticut, Farmington, comments and expands on this article:

In 1943, Papanicolaou published the vaginal cytology screening method. The test has become the most commonly used method to screen for cervical neoplasia. It is the best screening tool ever introduced for any cancer. It led to a remarkable improvement in prevention of cervical cancer. However, the test, even in high quality laboratories, had limited sensitivity (high % of false negative tests). Consequently, repeat tests were required at regular intervals. In the US, of the women who develop cervical cancer, 60% have never been screened, or have not been screened within the 5 years before diagnosis.

Now, because oncogenic HPVs have been identified as the underlying cause of cervical cancer, there is interest in using HPV testing as a primary screening test. The overall prevalence of HPV among cervical cancers has been reported to be more than 99%, the highest attributable fraction ever identified for a specific cause of cancer. HPV DNA testing is highly reproducible, more sensitive than cytology, is easily monitored, and provides an objective outcome. HPV infection is necessary for cervical cancer to develop, but it is not sufficient.

Most HPV infections resolve spontaneously. Thus, there are many positive HPV tests in younger women that do not have clinical importance. Screening is not usually started until age 30. If the positive tests persist, progression to cervical cancer may occur.

The investigators suggest that the higher sensitivity of the HPV test and the more “upstream” focus on cervical carcinogenesis conferred by the HPV DNA test relative to the Pap test, should safely permit prolongation of the screening intervals.

Because in most women over age 30, the HPV test, if positive, is a false positive test, the referral rate for colposcopy may be high. If the HPV test is positive, it should be checked by a Pap test. If the Pap test is also positive, colposcopy may be indicated.

The editorialist states that the optimal approach to screening will depend on the prevalence of the disease, access to screening, and available resources. “We are not there yet.”

a. Sensitivity of a test applies to the subjects in a trial in whom the disease is present. It deals with only the subjects in a trial who actually have the disease. For the cohort in the study, sensitivity answered the question: What proportion (percentage) of subjects with CIN (determined by biopsy) had a positive Pap test? A positive HPV test? A “true positive” test?

To calculate sensitivity:

1) First, determine the total number of subjects in the cohort who actually have the disease (in this study, CIN) as diagnosed by biopsy, the “gold standard”.

2) Determine the number of these subjects who have a positive test. A “true positive” test.

3) Calculate the ratio: $2) / 1)$. Number of true positive tests / total number of subjects in the cohort who actually had the disease (CIN).

I.e., the ratio of the number of subjects with the disease who had a positive test to the total number of subjects who had the disease. .

4) For the Pap test in this trial, the sensitivity was 55%. For the HPV test, it was 95%.

For the Pap test, 55% of subjects who actually had the disease (CIN) had a “true positive” test; and 95% who actually had the disease had a “true positive” HPV test.. The HPV test was much more “sensitive”.

Sensitivity is a property of a “true positive” test.

Sensitivity of a test differs from the positive predictive value in that it does not depend on the prevalence of the disease in the population to which the test is applied. It is the same whether the prevalence of the disease in a trial is 1% or 10%.

b. Specificity of a test applies to the subjects in the trial in whom the disease is absent. It deals with only the subjects in the trial who do not have the disease. For this cohort, specificity answered the question: What proportion (percentage) of subjects without CIN had a negative Pap test? A negative HPV test?

To calculate specificity:

- 1) First, determine the total number of subjects in the trial who did not have the disease
- 2) Determine the number of these subjects who have a negative test. A “true negative” test.
- 3) Calculate the ratio between 2) and 1)

Ie, the ratio of negative tests in the cohort of subjects who did not have the disease to the total number of subjects who did not have the disease.

- 4) For the Pap test in this trial, the specificity was 97%. For the HPV test, it was 95%.

For the Pap test, 97% of all subjects who did not have CIN had a “true negative” test, and 3% had a “false positive” test. For the HPV test, 94% had a “true negative” test, and 6% had a “false positive” test. The HPV test is slightly less “specific” than the Pap test.

Specificity is a property of a “true negative” test.

Specificity of a test differs from the negative predictive value. It does not depend on the prevalence of the disease in the population to which the test is applied.

c. The positive predictive value (PPV) of a test deals only with the subjects in the trial who have a positive test. [I believe a more descriptive term would be: “The predictive value of a positive test”] In this study, the positive PPV answers the question: How many women with a positive Pap test had CIN? How many women with a positive HPV test had CIN?

To calculate the positive predictive value of the test:

- 1) First, determine the total number of subjects in the trial who have a positive test.
- 2) Then, determine the number of subjects with a positive test who actually have the disease.
Ie, the number with a “true positive” test.
- 3) Calculate the ratio between 2) and 1). Ie, the ratio of true positive tests to the total number of positive tests. .
- 4) For the Pap test in this trial of 10 000 subjects, the PPV was 7%. (Ie, 7% subjects with a positive test actually had CIN. And 93% did not have CIN.) For the HPV test in this trial, the PPV was 6%. (Ie, 6% of all subjects who had a positive test actually had CIN. And 94% with a positive test did not have CIN.)

A positive predictive value deals with 1) all subjects in the trial who have a positive test, and with 2) subjects with a positive test who actually have the disease.

The positive predictive value depends on the prevalence of the disease in the cohort. In this study, the absolute number of subjects who had a “true positive” test for CIN was very small. The absolute number of

subjects who had a “ false positive” test was large. The great majority of subjects with a positive test did not have CIN. Thus the ratio of true positive to false positive was small. And the PPV of the test was low.

Positive predictive values are more clinically meaningful than sensitivity.

d. The negative predictive value of a test is similar. It deals with the ratio of the number of subjects who have a negative test who do not have the disease to the total number of subjects who have a negative test.

In this study, if both tests were negative, the likelihood of CIN was nil.

“An Epic Revolution In Surgery” ?

10-11 NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY

What if a surgeon could enter the abdominal cavity without making an incision in the abdominal wall? What if that surgeon could use a fiberoptic scope, pass it through a natural orifice such as the mouth, then make an incision through the stomach wall, examine the abdominal cavity, perform biopsies, perhaps remove an organ or repair a defect, then close the incision in the stomach? There would be no visible scars.

Natural orifice transluminal endoscopic surgery is a developing field of surgery. The endoscope is inserted into preexisting orifices (mouth, anus, or vagina) to access the peritoneal cavity. Incisions in the abdominal wall and the pain and disfigurement that accompany them are eliminated.

This article in the JAMA describes a case reported in the *Archives of Surgery*¹ in which a cholecystectomy was performed through an endoscope inserted into the abdominal cavity through the vagina. The report comes from France.

The postoperative course was uneventful. The patient had no postoperative pain, and no scars. She was discharged on the second postoperative day.

The article describes this as an “epic revolution in surgery” which is feasible, and is enormously advantageous to the patient.

JAMA October 3, 2002; 298: 1560-61 Commentary by Jo Buyske, University of Pennsylvania School of Medicine, Philadelphia.

1 The original article was published in the *Arch Surgery* 2007; 142: 823-27 by The Institute of Digestive Cancer Research-European Institute of TeleSurgery. This group has been actively involved in the development of this technique since 2004.

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Is This The Most Effective Approach To Colon-Cancer Prevention.?

10-12 CT-COLONOGRAPHY VERSUS COLONOSCOPY FOR THE DETECTION OF ADVANCED NEOPLASIA

Advanced neoplasia of the large intestine consists of both adenocarcinoma and a subgroup of benign neoplasms referred to as advanced adenomas. “The advanced adenoma represents the optimal target lesion for strategies to prevent colorectal cancer.” “This benign lesion is associated with a high risk of progression to cancer.”

The advanced adenoma is specifically defined as an adenoma that meets one or more of the following: 1) a size of at least 1 cm, or 2) presence of a substantial villous component, or 3) presence of high-grade dysplasia.

“Removal of advanced adenomas effectively disrupts the potential pathway to development of cancer.”

“Most subcentimeter polyps are not adenomas, and only a small fraction of adenomas are advanced suggesting a need for more selective alternatives to the practice of universal polypectomy.”

This study compared computed tomography of the colon (**CT-C**) with the traditional optical colonoscopy (**OC**) as screening strategies when applied to the same general screening population. CT-C could provide a selective filter for therapeutic OC in the detection of advanced neoplasia.

Conclusion: Both screens resulted in similar detection rates for advanced neoplasia. The number of polypectomies was smaller in the CT-C group.

STUDY

1. Compared results from over 6200 consecutive patients (mean age 58) referred by a physician to undergo first-time screening for colorectal cancer. The majority was asymptomatic and at average risk for cancer. Half received CT-C; half OC
2. Preparation for CT-C involved both a cathartic agent and oral contrast-tagging agents. No sedating or spasmolytic agents were given. Colonic distention was achieved by automated low-pressure delivery of carbon dioxide. A multi-detector 8-channel or 16-channel CT scanner was used. The CT-C examinations were immediately interpreted by gastrointestinal radiologists.
3. The OC was performed in the usual manner.
4. Identified all pathologically proven neoplasms detected by each screening method. Classified polyps by size: 1) large 10 mm or larger, 2) small 6 to 9 mm, 3) diminutive 5 mm or less.
5. Also classified adenomas as tubular, tubulo-villous, or villous. Invasive cancer was defined as

malignant spread beyond the muscularis mucosa.

6. For all polyps of at least 6 mm, the patient was offered same-day therapeutic OC. Patients with one or two small polyps (6 to 9 mm) were also offered the option of CT-C surveillance. Diminutive polyps 5 mm or less were not reported.
7. All polyps, including diminutive lesions, were removed in patients receiving OC, either at primary or at secondary screening.

RESULTS

1. Eight % of patients undergoing CT-C were referred for OC:

2. Outcomes	CT-C (n = 3120)	OC (n = 3163)
A. Advanced neoplasms	3.2%	3.4%

(This did not include 158 patients with CT-C-detected 6 to 9 mm polyps that were not resected (and referred for surveillance). Of the 158 patients, 54 had returned for follow-up.)

B Total number of polyps removed	561	2434
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(Of these, 14 in the CT-C group were cancer; 4 in the OC group.)

C. Advanced lesions in diminutive polyps		0.2%
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DISCUSSION

- 1.. “Targeted detection and removal of advanced adenomas may be the most effective approach to cancer prevention.”
2. “Our results suggest that primary CT-C with selective OC also deserves consideration as a preferred screening strategy.”
3. “The diagnostic yield for advanced neoplasia was similar in the two groups, despite the fact that small lesions (5 mm or smaller) were not reported during CT-C.”
4. “These observations suggest that a 10-mm threshold for polypectomy at screening would probably capture the vast majority of clinically relevant lesions.”
5. “These findings support the use of CT-C as a primary screening test before therapeutic OC”

CONCLUSION

Primary CT-C and OC screening strategies resulted in similar detection rates for advanced neoplasia. The number of polyps removed in the OC group was over four times as great as in the CT-C group

NEJM October 4, 2007; 357: 1403-12 Original investigation, first author David H Kim, University of Wisconsin Medical School, Madison.

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