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DELAYED PRESCRIPTIONS—IMPORTANT IN PRIMARY CARE TO REDUCE ANTIBIOTIC USE

ISOLATED SYSTOLIC HYPERTENSION—IMPORTANCE OF CONTROL

OVERCOME CLINICAL INERTIA TO CONTROL SYSTOLIC BP

DOXAZOCIN, FINASTERIDE, AND COMBINATION TO DELAY PROGRESSION OF BPH

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SCREENING VIRTUAL COLONOSCOPY—NOT READY FOR PRIME TIME

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HIGHLIGHTS AND EDITORIAL COMMENTS

12-1 DELAYED PRESCRIPTIONS

Best evidence indicates that antibiotics are of minimal or no benefit for sore throat, acute bronchitis, the common cold, and otitis media. Antibiotics continue to be commonly used for these conditions. This is potentially inappropriate prescribing.

This has prompted the use of delayed (or “as needed”, or “if”) prescriptions. These prescriptions are written with the proviso that they are not to be used immediately—only later if symptoms do not improve in a few days. Use of a delayed prescription should be restricted to patients who request antibiotics or for whom the doctor thinks one is not immediately indicated.

A randomized trial in 1997 gave prescriptions for antibiotics for respiratory infections: 1) to be filled immediately, or 2) to be filled after 3 days, or 3) no antibiotic prescription.

The immediate group filled 99%.

The delayed group filled 31%.

In the no-prescription group, 13% filled an antibiotic prescription after a return visit to the physician.

The reduction in use of antibiotics for upper respiratory infections through using delayed prescriptions is as effective, and in many cases, more effective than educational projects.

12-2 EXTENT OF CARDIOVASCULAR RISK REDUCTION ASSOCIATED WITH TREATMENT OF ISOLATED SYSTOLIC HYPERTENSION

A great many older adults remain at high risk of heart disease and stroke from untreated isolated systolic hypertension (**ISH**; systolic > 140, diastolic < 90). Treatment of ISH is associated with clear benefits. The Systolic Hypertension in the Elderly Program (*JAMA 1991*) demonstrated a 36% reduction in stroke among participants assigned to active BP treatment. The Systolic Hypertension in Europe trial (*Lancet 1998*) reported that active treatment of ISH significantly reduced the incidence of dementia. And also exerted a strong effect in preventing heart failure.

This subset of the SHEP study was begun after closure of the original study. It compared risk of death and cardiovascular event rates in actively treated patients with ISH, vs placebo controls, and normotensive controls. Follow up was up to 14 years. Event rates were decreased by 21% in the actively treated group.

Early treatment, before advanced atherosclerosis develops, results in the best long-term outcomes. The prevalence of subclinical atherosclerosis in individuals with ISH is high compared with normotensive controls. Active treatment of ISH is associated with slower progression of subclinical atherosclerosis. The development of atherosclerosis with ISH likely adds to the acceleration of vascular stiffening, which is the underlying cause of ISH. Thus, early treatment may slow not only the progression of atherosclerosis, but progression of ISH as well.

Severe ISH may be difficult to control, requiring multiple drugs.

12-3 OVERCOME CLINICAL INERTIA TO CONTROL SYSTOLIC BP

It is clear that in individuals younger than age 50, diastolic BP (**DBP**) is a better predictor of future complications of hypertension than in older individuals. For those older than 50, systolic BP (**SBP**) is a better predictor. Most persons with hypertension are older than 50. For these patients control of SBP is a high priority, even in the face of a normal DBP.

“Systolic blood pressure alone correctly classifies hypertensive status in about 98% of adults.”

Most patients with elevated SBP need aggressive treatment to reach the evidence-based goal of less than 140. We are beginning to see that 130 and even 120 is some groups such as those with diabetes, congestive heart failure, and chronic kidney disease is a beneficial goal. SBP in these mostly older patients is the variable that indicates the need for more intensive therapy.

12-4 THE LONG-TERM EFFECT OF DOXAZOCIN, FINASTERIDE, AND COMBINATION THERAPY ON THE CLINICAL PROGRESSION OF BENIGN PROSTATIC HYPERPLASIA

This study assessed the long-term effects of diazoxide (an alpha blocker) alone, finasteride (a reductase inhibitor) alone, and the combination on clinical progression of BPH. It concluded that long-term therapy with combined drugs reduced the risk of clinical progression significantly more than either drug alone.

The number needed to treat by combined therapy over 5 years was 8, vs 14 to 15 for the drugs used alone.

Risk of acute retention and need for invasive therapy were reduced by finasteride but not by doxazocin.

The risk of overall clinical progression increased with increasing baseline PSA levels and prostate volume in the doxazocin group, but *not* in the finasteride or combination group. No alpha blocker stops the progression of prostate size.

Finasteride reduces circulating dihydro-testosterone levels by about 80%; PSA levels by 50%; and prostate size by 20%. Reductase inhibitors do not act rapidly, and often require 6 months to reduce prostate size.

Current initial therapy in most cases consists of an alpha blocker given alone. It acts rapidly to relieve symptoms. In the current study, clinical progression occurred in only 17% of men in the placebo group. In men with a low PSA and modest prostate size, progression of BPH may be slow and use of a reductase inhibitor may be delayed. The study does support dual use in men whose symptoms progress during monotherapy, or in men at high risk of progression. (PSA over 4 mg/mL or prostate volume more 40 mL on ultrasound).

12-5 CLINICAL IMPACT OF BLEEDING IN PATIENTS TAKING ORAL ANTICOAGULANT THERAPY FOR VENOUS THROMBOEMBOLISM

In patients with venous thromboembolism (**VTE**), there is a perception that the clinical impact of preventing recurrent VTE and possible fatal pulmonary embolism outweighs the risk of bleeding associated with long-term anticoagulation..

The subgroup of patients with idiopathic (unprovoked) VTE, and VTE associated with factor V Leiden, prothrombin mutations, and deficiencies of protein C and protein S make up about half of the thousands of patients in whom symptomatic VTE is diagnosed each year in the USA.

The optimal duration of anticoagulation is still unclear.

This systematic review of randomized, controlled trials and prospective cohort studies (10 757 patients; 4373 patient-years) investigated patients with confirmed idiopathic VTE. All received oral anticoagulant therapy (target INR--2.0 to 3.0) for at least 3 months. Nine of 33 studies reported use for over 3 months (6 to 24 months).

The chances of a major bleed *per year of anticoagulation* were 7 in 100 patients with 1 in 1000 chance of fatality, and about 1 chance in 100 of an intracranial bleed.

The primary care clinician must make some attempt to balance the risk of bleeding vs the benefits of anticoagulation in each individual patient. (*I know of no means of doing this beyond “clinical judgment”. RTJ*)

12-6 INTRA-ARTICULAR HYALURONIC ACID IN TREATMENT OF KNEE ARTHRITIS

“Based on the findings of this meta-analysis, intra-articular hyaluronic acid has, at best, modest efficacy in the treatment of knee osteoarthritis. This effect . . . “is equivalent to the effect of NSAIDs over that of acetaminophen, an effect that itself remains controversial.” .” “Our findings suggest the controversy surrounding the efficacy of intra-articular hyaluronic acid is justified and the best evidence does not support its efficacy.”

At least 17 of the 22 trials were industry sponsored. Others have suggested that findings from industry-sponsored trials compared with those that were otherwise funded showed that research funded by pharmaceutical companies was more likely to have outcomes favoring the sponsor.

All 22 studies reported improvement of pain in the intra-articular placebo groups. Placebo injections may have efficacy for treating knee OA. The investigators calculated that intra-articular placebo accounted for 79% of the efficacy of intra-articular hyaluronic acid.

“This supports our hypothesis that the majority of the effect of intra-articular hyaluronic acid is an intra-articular placebo effect.”

Publication bias may overestimate the effect. Compared with lower-molecular-weight hyaluronic acid, the higher-molecular weight hyaluronic acid may be more efficacious, but heterogeneity of studies limits definitive conclusions.

I doubt this study will deter enthusiasts from using HA. Individual patients who have apparently obtained relief may insist on continuing.

The only way an individual’s response can be accurately determined is by an N-of-one trial. I doubt this would be feasible considering the ethical issues involved.

12-7 SCREENING FOR DEPRESSION IN PRIMARY CARE WITH TWO VERBALLY ASKED QUESTIONS

The US Preventive Services Task Force endorsed screening for depression, but did not recommend a specific tool. Many primary care clinicians find screening questionnaires for depression too cumbersome and time consuming for routine use.

This study used a simple screening tool of two questions. If one or two were answered positively, the screen was considered positive, and further questions were asked to determine if major depression was present. (A composite interview--the “Gold Standard”)

The screening questions:

- 1) During the past month have you often been bothered by feeling down, depressed, or hopeless?
- 2) During the past month have you often been bothered by little interest or pleasure in doing things?

In the community setting, the two verbally asked questions have a good sensitivity (97%) and reasonable specificity (67%) for screening for depression. If the screen was negative (both questions answered negatively) major depression is almost surely absent.

About 5 false positives would occur for every true positive when asking the questions alone. This is common in screening studies which are in essence a diagnostic test performed in a low prevalence setting. Further questions will be required to clarify presence or absence of depression.

12-8 REVIEW OF SENSITIVITY, SPECIFICITY, PREDICTIVE VALUES AND LIKELIHOOD RATIOS

Calculate sensitivity from the left column; specificity from the right column; positive predictive value from the top row; negative prediction value from the bottom row; the likelihood ratios from both columns.

See text.

12-9 EFFICACY AND SAFETY OF ECHINACEA IN TREATING UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN

Echinacea is a herbal remedy widely used for prevention and treatment of upper respiratory infections (**URIs**). It is one of the most commonly used herbal remedies in the USA . Three species of echinacea are used. Beneficial effects are thought to be due to its “immunomodulating” activity, most notably macrophage activation and enhanced neutrophil phagocytosis.

This study postulated that treatment with *E purpurea* would result in at least a 1.5- to 2-day reduction in duration of URIs in children, and that symptoms would be less severe than in patients receiving placebo.

The preparation used in this study was *not* effective in treating URIs in children. After the trial was completed, parents could *not* guess correctly whether their child had taken echinacea or placebo. “Our results do *not* support the use of echinacea for treatment of URIs in children.” Its use was associated with an increased risk of rash.

This study was supported by a grant from the National Center for Complementary and Alternative Medicine, Bastyr University (an alternative medicine institution) and National College of Naturopathic Medicine, Portland Oregon.

It continues to amaze me that so many persons take unstandardized and unproven nostrums and give them to their children. I am sure devotees will fault this study. They will remain convinced that echinacea is beneficial.

12-10 SCREENING VIRTUAL COLONOSCOPY—READY FOR PRIME TIME?

A new virtual colonoscopy (VC) used a multidirectional CT scanner providing a primary 3-dimensional endoluminal display. It permitted faster, higher-resolution imaging than previously obtainable. Residual fluid and stool was tagged by contrast material. The imaging software digitally removed all opacified fluid and stool from the colon by a process called “electronic cleansing”.

The study subjects received the VC followed by conventional colonoscopy for comparison:

Sensitivity of VC for detection of adenomas vs traditional colonoscopy:

10 mm or larger was 92% vs 88%

8 mm or larger was 92% vs 89%

6 mm or larger was 86% vs 90%

The study suggests that VC can detect polyps of 6 mm or larger as accurately as conventional colonoscopy in a population with a low prevalence of colorectal neoplasia.

Decisions regarding the use of VC as a first-line screening test will require more information about cost and insurance coverage. “The performance of VC in this asymptomatic population is impressive, with detection rates similar to those achieved by conventional colonoscopy.” Only if the important questions about the appropriate size threshold and the surveillance of smaller polyps can be resolved will VC be ready for prime time.

The bugaboo is the need for follow-up conventional colonoscopy to remove suspicious polyps.

Patients will be asking about this. Application in the local community is likely to be far-off.

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Reduces Antibiotic Use By 2/3

12-1 DELAYED PRESCRIPTIONS

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This has prompted the use of delayed (or “as needed”, or “if”) prescriptions. These prescriptions are written with the proviso that they are not to be used immediately—only later if symptoms do not improve in a few days.

A randomized trial in 1997 gave prescriptions for antibiotics for respiratory infections: 1) to be filled immediately, or 2) to be filled after 3 days, or 3) no antibiotic prescription.

The immediate group filled 99%.

The delayed group filled 31%.

In the no-prescription group, 13% filled an antibiotic prescription after a return visit to the physician.

Five controlled trials of delayed prescriptions have been published: otitis media, sore throat, cough lasting over a week, and the common cold. In three trials the patients in the delayed prescription arm had more symptoms during the trial, implying that patients are willing to tolerate some symptoms to avoid antibiotics.

An additional benefit of delayed prescriptions may be a reduction in repeat visits, at least for sore throat.

The reduction in use of antibiotics for upper respiratory infections through using delayed prescriptions is as effective, and in many cases, more effective than educational projects.

The positive aspects of delayed prescriptions include avoiding side effects, reducing the drug bill, educating patients, and involving patients in decision-making. Although reducing antibiotic resistance is a major concern for physicians, it is not a concern for patients.

Use of a delayed prescription should be restricted to patients who request antibiotics or for whom the doctor thinks one is not immediately indicated.

BMJ December 13, 2003; 327; 1361-62 Editorial, first author Bruce Arroll, University of Auckland, New Zealand

Comment:

I have had some experience with delayed prescribing. I believe it is a useful method to reduce unnecessary antibiotic use. As the article mentioned, patients are not so concerned about resistance developing in the population. They will respond to doctor’s advice about adverse effects to themselves as well as costs of the drug. RTJ

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12-2 EXTENT OF CARDIOVASCULAR RISK REDUCTION ASSOCIATED WITH TREATMENT OF ISOLATED SYSTOLIC HYPERTENSION

A great many older adults remain at high risk of heart disease and stroke from untreated isolated systolic hypertension (**ISH**). Treatment of ISH is associated with clear benefits.

The Systolic Hypertension in the Elderly Program (SHEP; *JAMA 1991*) demonstrated a 36% reduction in stroke among participants assigned to active BP treatment. Treatment of ISH also reduces risk of dementia and heart failure.

This study of a subset of the SHEP patients was begun after closure of the original study. It compared risk of death and cardiovascular event rates in actively treated patients with ISH, vs placebo controls, and normotensive controls. Follow up was up to 14 years. Cardiovascular events were reduced by 21% treated patients as compared with controls.

If treatment is begun before development of advanced atherosclerosis, the associated risks of ISH are reduced to a level close to the baseline risk experienced by a control group without ISH.

STUDY

1. Long-term prospective study followed a cohort (subset) of the original SHEP study. It included 268 SHEP participants; 135 received active treatment (SHEP Active) and 133 placebo controls (SHEP Placebo) and 187 normotensive controls. All were over age 60 at baseline.
2. At entry, systolic BP (SBP) was between 160 and 219 mm Hg in the SHEP patients; mean = 171. Mean BP in non-hypertensive controls = 127. All had a diastolic BP under 90.
3. Treated patients received chlorthalidone 12.5 and then 25 mg. If BP goal not reached, they received, in addition, 25 mg atenolol.
4. After the initial SHEP trial ended, the patients were followed:
 - A. Those who had received active treatment were given a 4-month supply of medication and were told to visit their physician for continued treatment
 - B. The placebo controls (all with systolic > 160) were asked to visit their physician within 4 months so antihypertension medication could be initiated.
 - C. Control group (no ISH) was followed annually for development of ISH.
5. All groups were followed for up to 15 years for development of cardiovascular events.

RESULTS

1. Numbers taking antihypertension drugs

	After one year	After 5 years
Group A (N = 135; SHEP active)	81%	72%
Group B (N = 133; SHEP placebo)	55%	65%
2. Of the controls (N = 187) who had normal BP at end of the initial trial, 31% developed ISH during follow-up.
3. In group A, a lower event rate (compared with placebo group B) was observed beginning at year one.
4. Event rates at 14 years:

Group A	58%
Group B	79% (21% reduction: NNT = 5)

At 11 years,

Group A	47%
Group B	65%
Group C	35%

5. Among those with no clinical or subclinical cardiovascular disease at baseline, the ISH group assigned to active treatment (Group A) had a 10-year event rate similar to those in the control group. (Group C).

DISCUSSION

1. Long-term treatment of ISH is effective in reducing cardiovascular events including cardiovascular death.
2. If treatment is begun before development of advanced atherosclerosis, the associated risks of ISH are reduced to a level close to the baseline risk experienced by a control group without ISH.
3. The prevalence of subclinical atherosclerosis in individuals with ISH is high compared with normotensive controls. Active treatment of ISH is associated with slower progression of subclinical atherosclerosis. The development of atherosclerosis with ISH likely adds to the acceleration of vascular stiffening, which is the underlying cause of ISH. Thus, early treatment may slow not only the progression of atherosclerosis, but progression of ISH as well. Severe ISH may be difficult to control, requiring multiple drugs.
4. There is a common perception that ISH, particularly in older individuals, does not require treatment. Despite efforts to educate clinicians in the importance of treatment, about 30% of clinicians in the geographical area of this study either failed to initiate antihypertension treatment or discontinued treatment. Undertreatment of ISH is pervasive.
5. ISH is the most frequent subtype of uncontrolled hypertension. Of the untreated hypertensive individuals over age 50, 82% had an elevated systolic and only 17 had an elevated diastolic.
6. Uncontrolled hypertension occurs most often among adults, most of whom have good access to health care and frequent physician visits.
7. The Systolic Hypertension in Europe trial (*Lancet 1998; 352: 1347-51*) reported that active treatment of ISH significantly reduced the incidence of dementia. Active also exerts a strong protective effect in preventing heart failure.

CONCLUSION

Long-term treatment of ISH in older adults is associated with a dramatic reduction of death and cardiovascular events. Early treatment, before advanced atherosclerosis develops, results in the best long-term outcomes.

Archives Int Med December 8/22; 163: 2728-31 Original investigation, first author Kim Sutton-Tyrrell, University of Pittsburgh, PA.

Comment:

Control of ISH is one of the greatest challenges and opportunities in primary care medicine. As the article stresses, early treatment is most rewarding.

I believe, low-dose, gradual and careful titration with generic diuretic + generic beta-blocker + generic angiotensin II blocker is effective, relatively inexpensive, and well tolerated treatment for ISH RTJ

“Physicians Need To Do A Better Job Of Conveying To Patients The Seriousness Of Elevated BP.”

12-3 OVERCOME CLINICAL INERTIA TO CONTROL SYSTOLIC BP

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

It is clear that in individuals younger than age 50, diastolic BP (**DBP**) is a better predictor of future complications of hypertension than in older individuals. For those older than 50, systolic BP (**SBP**) is a better predictor. Most persons with hypertension are older than 50. For these patients control of SBP is a high priority, even in the face of a normal DBP.

“Systolic blood pressure alone correctly classifies hypertensive status in about 98% of adults.”

The preceding study found that long-term (14 years) control of SBP in older individuals resulted in a 21% reduction in cardiovascular events. Thus, only 5 patients need to have SBP controlled to prevent one major complication. Moreover, early initiation of SBP control increases the benefit.

Concern remains that pursuit of SBP goals may lead to excessively low DBP. The long-standing debate about potential disadvantages of DBP less than 55 mm Hg continues. Prudence suggests DBP be maintained at approximately 55 as *a minimum* in most patients. However, the problem of excessively low DBP is dwarfed by the much more common problem of uncontrolled SBP.

Most patients with elevated SBP need aggressive treatment to reach the evidence-based goal of less than 140. We are beginning to see that 130 and even 120 in some groups such as those with diabetes, congestive heart failure, and chronic kidney disease is a beneficial goal. SBP in these mostly older patients is the variable that indicates the need for more intensive therapy.

Diuretics and angiotensin-enzyme-inhibitors (ACE-I) are excellent choices for initial therapy. Most patients will eventually require more than one drug to reach desired levels of SBP. The potential of weight loss, physical activity, and sodium restriction to improve BP should not substantially delay initiation and titration of drug therapy.

“Physicians need to do a better job of conveying to patients the seriousness of elevated BP.” Primary care physicians are experts at individualizing care, and our knowledge of the particulars of a patient’s case must also enter into the selection of optimal therapy.

“If the SBP is 140 mm Hg or greater, we ought to do something. Maybe we need not wait for the next visit. Maybe we should do something now.”

Archives Int Med December 8/22 2003; 163: 2677-78 Editorial by Patrick J O’Conner, Health Partners Research Foundation, Minneapolis, MN.

Comment

The bugaboo of white coat hypertension always enters the consideration to start treatment. Multiple BP readings should be taken to ensure that the SBP is indeed elevated. Home BP readings and ambulatory BP readings are preferable. But, in all likelihood, if a clinic SBP is elevated in an elderly person, it will be a true elevation. RTJ

In Select Patients The Combination Is Better Than Either Alone

12-4 THE LONG-TERM EFFECT OF DOXAZOCIN, FINASTERIDE, AND COMBINATION THERAPY ON THE CLINICAL PROGRESSION OF BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (**BPH**) is commonly treated with alpha-blockers (eg, doxazocin; *Cardura*; *Generic*) or reductase inhibitors (eg, finasteride; *Proscar*).

Alpha-adrenergic-receptor blockers reduce smooth-muscle tone in the prostate and bladder neck. In the short-to-moderate term they effectively relieve symptoms and improve urinary flow.

An enzyme (reductase) converts testosterone (inactive) to the active male hormone dihydro-testosterone. Finasteride, a reductase inhibitor, prevents conversion of testosterone to dihydro-testosterone, thereby inducing epithelial atrophy and reducing prostate volume. Finasteride reduces rate of progression and lessens risk of urinary retention and need for surgery in men with symptomatic BPH.

This study assessed the long-term effects of diazoxide alone, finasteride alone, and the combination on clinical progression of BPH.

Conclusion: Long-term therapy with combined drugs reduced the risk of clinical progression significantly more than either drug alone.

STUDY

1. Double blind, placebo-controlled trial involved over 3000 men over age 50 with symptomatic BPH. All had American Urological Association (AUA) symptom scores of 8 to 35. (Scores can range from 0 to 35.)
2. Randomized to: 1) doxazocin alone, 2) finasteride alone, 3) both together, or 4) placebo.
Doxazocin was given at a gradually increasing dose of 1 mg to 8 mg; finasteride given 5 mg daily.
3. Primary outcome = risk of clinical progression defined as: an increase of 4 points over baseline in the AUA symptom score, acute urinary retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence.
4. Mean follow-up = 4.5 years.

RESULTS

1. Compared with placebo, the rate of clinical progression, was significantly *reduced* by doxazocin alone (39%); finasteride alone (34%); both (66%).

2. Clinical progression (Rate per 100 person-years):

Event	Placebo (N=737)	Doxazocin (N=756)	Finasteride (N=768)	Both (N=786)
Overall progression	4.5	2.7	2.9	1.5
> 4 point AUA increase	3.6	1.9	2.5	1.3
Retention	0.6	0.4	0.2	0.1
Incontinence	0.3	0.3	0.3	0.1
Invasive therapy	1.3	1.3	0.5	0.4

3. The number needed to treat by combined therapy over 5 years was 8, vs 14 to 15 for the drugs used alone.

4. Doxazocin alone did not reduce risk of acute retention and need for invasive therapy. Finasteride alone and in combined therapy reduced these risks.

5. The risk of overall clinical progression increased with increasing baseline PSA levels and prostate volume in the doxazocin group, but *not* in the finasteride or combination group.

6. Adverse events:

Doxazocin—dizziness, postural hypotension, and asthenia.

Finasteride—erectile dysfunction, decreased libido, abnormal ejaculation.

Up to 27% discontinued mainly because of adverse effects.

DISCUSSION

1. Treatment with finasteride alone, or doxazocin alone, ameliorated symptoms and improved urinary flow rates. Finasteride alone substantially reduced risk of acute retention and need for surgery.

2. Combination therapy was more effective than either drug alone in decreasing risk of clinical progression.

3. Continued growth of the prostate in the doxazocin alone group eventually overcame the reduction in prostatic urethral obstruction achieved by relaxation of smooth-muscle tone.

4. Progression in men with a low PSA tended to be low even in the placebo group. Benefit of combination therapy was greater in men with higher PSA levels and larger prostate size.

CONCLUSION

Long-term combined finasteride plus doxazocin was safe and reduced risk of overall clinical progression of BPH significantly more than either drug alone. Risk of urinary retention and need for surgery were also reduced.

NEJM December 18, 2003; 349: 2387-98 Original investigation, by the Medical Therapy of Prostatic Symptoms (MTOPS) Research Group, first author John D McConnell, University of Texas Southwestern Medical Center, Dallas, Texas

An editorial in this issue of NEJM by E Darracott Vaughn Jr comments and expands on the study:

A number of alpha blockers are available for prescription. At present, tamsulosin (*Flomax*; a *specific alpha blocker*) is favored over doxazocin. The daily dose (5 mg) does not have to be titrated. The incidence of side effects is lower than for non-specific alpha blockers. However, no alpha blocker stops the progression of prostate size. Finasteride reduces circulating

dihydro-testosterone levels by about 80%; PSA levels by 50%; and prostate size by 20%. Reductase inhibitors do not act rapidly, and often require 6 months to reduce prostate size.

Current initial therapy in most cases consists of an alpha blocker given alone. It acts rapidly to relieve symptoms. In men with a low PSA, progression of BPH may be slow and use of a reductase inhibitor may be delayed. In the current study, clinical progression occurred in only 17% of men in the placebo group. The study does support dual use in men whose symptoms progress during monotherapy, or men at high risk of progression. (ie, PSA over 4 mg/mL or prostate volume more 40 mL on ultrasound).

The Prostate Cancer Prevention Trial (See *Practical Pointers* July 2003) reported that finasteride reduced prevalence of prostate cancer by 25%, but increased the likelihood of development of high grade cancers (Gleason grade 7 to 10). Caution is warranted for long-term use until this point is clarified. Men should be advised of this possible complication.

Note that about ¼ of men withdrew from the study. I believe *Flomax* would be better tolerated and reduce numbers of withdrawals.

Cost of long-term medication is critical in determining compliance. *Flomax + Proscar* would cost over \$7500.00 for 5 years. RTJ

Risk Is Considerable And Dangerous

12-5 CLINICAL IMPACT OF BLEEDING IN PATIENTS TAKING ORAL ANTICOAGULANT THERAPY FOR VENOUS THROMBOEMBOLISM

In patients with venous thromboembolism (VTE), there is a perception that the clinical impact of preventing recurrent VTE and possible fatal pulmonary embolism outweighs the risk of bleeding associated with long-term anticoagulation.

The subgroup of patient with idiopathic (unprovoked) VTE, and VTE associated with factor V Leiden, prothrombin mutations, and deficiencies of protein C and protein S make up about half of the thousands of patients in whom symptomatic VTE is diagnosed each year in the USA.

The optimal duration of anticoagulation is still unclear.

The objective of this meta-analysis was to obtain reliable estimates of the clinical impact of anticoagulant-related bleeding in patients with unprovoked VTE.

Conclusion: The clinical impact of major bleeding in patients given anticoagulant therapy in patients with unprovoked VTE is considerable.

STUDY

1. Conducted a systematic review of randomized, controlled trials and prospective cohort studies (10 757 patients; 4373 patient-years) that investigated patients with confirmed VTE. All received oral anticoagulant therapy (target INR--2.0 to 3.0) for at least 3 months. Nine of 33 studies reported use for over 3 months (6 to 24 months).
2. All studies reported major bleeding and death as primary outcomes. Defined a major bleeding episode as one which involved a major organ or body cavity, or required transfusion, or hospitalization, or was fatal.

3. Patients receiving anticoagulation for atrial fibrillation and other cardiac conditions were *not* included in this study.

RESULTS

1. 10 757 patients received anticoagulation; 8335 for 3 months only; 2433 over 3 months for up to 24 months.

2. Overall incidence of major bleeding and death (N = 10 757):

Major bleeding episodes 2.6% (276 patients)

Died from the bleeding 13% of the 276 (36 patients)

(The risk of major bleeding overall was 2 to 3 per 100 patients treated for up to 24 months.

Risk of death from bleeding was about 3 to 4 per 1000 patients treated.

3. Incidence of intracranial bleeding = about 2 per 1000 (24 patients) Died of intracranial bleeding 11 of 24 (about 1 in 1000 patients treated) Intracranial bleeding was associated with greater risk of death. Almost half died of the bleeding.

4. Nine studies involved 2422 patients (606 patient-years) who received anticoagulation for more than 3 months:

	First 3 months (N = 2422)	3 to 24 months (N = 2422)
Major bleeding	54 patients	44 patients
Rate per 100 treated	2.2%	1.8%

5. Calculated on a *patient-year* basis: (Per 100 patient-years):

Major bleeding	7
Fatal bleeding	0.3
Intracranial bleeding	1.2

(The chances of a major bleed *per year of anticoagulation for at least 2 years* were 7 in 100 patients with 1 in 1000 chance of fatality, and about 1 chance in 100 of an intracranial bleed.)

DISCUSSION

1. Calculated on a *patient-year* basis, over a 2-year period, major bleeding occurred in 7 of 100 patients; fatal bleeding in 3 of 1000; and intracranial bleeding in 1 to 2 per 100

2. About 1 in 7 major bleeding episodes was fatal or intracranial.

3. There appears to be a front-loading of major bleeding episode shortly after initiation of therapy.

As many major bleeding episodes occurred during the initial 3 months of anticoagulation as during the entire year thereafter. (*I believe, as time of anticoagulation is extended and patients age, the incidence of major bleeding will increase, and far exceed the incidence in the first 3 months. RTJ*)

Other studies have noted that patients are more likely to bleed soon after start of therapy. Many major bleeds occur in the initial 3 weeks of treatment, consistent with an underlying predisposition to bleeding. (*I believe also in part due to the initial difficulty of regulating INR.*)

4. The primary care clinician must make some attempt to balance the risk of bleeding vs the benefits of anticoagulation in each individual patient. (*I know of no means of doing this beyond “clinical judgment”.* RTJ)

CONCLUSION

The clinical impact of anticoagulant-related major bleeding in patients treated for VTE is considerable. Calculated on a patient-year basis, over a 2-year period, major bleeding occurred in 7 of 100 patients; fatal bleeding in 3 of 1000; and intracranial bleeding in 1 to 2 per 100

Annals Int Med December 2, 2003; 139: 893-900 Original investigation, first author Lori-Ann Linkins, McMaster University, Hamilton, Ontario, Canada.

Comment:

The investigators comment that their estimates of bleeding in this study are consistent with the bleeding rates of patients in the “real world”. I disagree. I believe the risk of major bleeding occurring in primary care will be higher than the risk in these well-conducted trials in which control of INR was likely be more stringent. Most randomized, controlled trials appearing in the journals tend to report relatively low rates of major bleeding in part because of more careful and expert monitoring, and usually a shorter period of observation. Control is inevitably less strict in primary care. And duration of therapy may be much longer.

The difficulty of maintaining an INR of 2.0 to 3.0 is well known. Risk continues and adds up the longer the anticoagulation is continued. A host of variables may interfere with control. Indeed, I believe some degree of bleeding is inevitable in patients receiving long-term anticoagulation.

Note that this study did *not* consider patients with atrial fibrillation who were receiving anticoagulation. These individuals require long-term therapy. Their risk of major bleeding increases continuously with time and as the patients age. The risk of bleeding from anticoagulation must be balanced against the increased severity and fatality of stroke from emboli arising in the heart in patients with AF.

Not all patients with a history of VTE need long-term anticoagulation. Some who are judged at lower risk for recurrence may be treated with aspirin or with warfarin aimed an INR of 1.5 TO 2.0. The advent of the direct thrombin inhibitor, ximelagatran may lead to a lower risk of bleeding. RTJ

At Best, A Small Benefit. The Placebo Effect Predominated

12-6 INTRA-ARTICULAR HYALURONIC ACID IN TREATMENT OF KNEE ARTHRITIS

Hyaluronic acid (**HA**) is a large molecule composed of repeating disaccharides of glucuronic acid and acetylglucosamine. It is naturally present in synovial fluid. The FDA has approved it for treatment of osteoarthritis (**OA**). Despite FDA approval, the efficacy of HA remains controversial. There is insufficient evidence to allow a statement more definitive than that it is “probably effective in knee OA”. The American College of Rheumatology has recommended intra-articular HA as an alternative for use in patients at increased risk of gastrointestinal tract adverse events from oral agents.

There has been an absence of data supporting treatment efficacy. Many of the clinical trials had design flaws including problems with patient selection, inadequate blinding, and an inappropriate focus on analyses of subjects that completed the trials in preference to intention-to-treat analyses.

This study evaluated whether intra-articular HA, compared with placebo injections is efficacious.

Conclusion: HA has a small effect when compared with an intra-articular placebo. The placebo effect may be the main reason for pain relief.

STUDY

1. Meta-analysis of 22 single- or double-blind randomized controlled trials compared intra-articular HA with intra-articular placebo for treatment of knee arthritis. HA was injected at least every week for 3 weeks (as recommended by the manufacturers) and compared with placebo injections. All trials had data on pain reported by outcome measures recommended by the Osteoarthritis Society.
2. For each trial these investigators calculated an effect size: small-effect sizes--0.2 to 0.5; and large effect sizes--1.0 to 1.8 (equivalent to a total knee replacement).

RESULTS

1. The overall dropout rate was 12%.
2. At least 17 of the 22 trials were industry sponsored .
3. There was significant heterogeneity among studies.
4. Including all studies, the pooled effect size was 0.32, consistent with a small effect. No trials had an effect size less than zero
5. Two outlier trials evaluating the highest-molecular-weight HA had effect in excess of 1.5.
(The investigators suggest that effect sizes comparable to knee replacement do not seem realistic.)
A third trial of the same compound showed a nearly null effect. When these 3 trials were removed, heterogeneity was no longer significant, and the pooled effect size of HA decreased to 0.19.
6. There was evidence of publication bias. The pooled effect size of the unpublished studies was 0.07. (Close to zero.)

DISCUSSION

1. “Based on the findings of this meta-analysis, intra-articular hyaluronic acid has, at best, modest efficacy in the treatment of knee OA.” “Our findings suggest the controversy surrounding the efficacy of intra-articular hyaluronic acid is justified and the best evidence does not support its efficacy.”
2. This effect . . . “is equivalent to the effect of NSAIDs over that of acetaminophen, an effect that itself remains controversial.”
3. The effect size of most trials had 95% confidence intervals that included an effect size of zero, consistent with no effect.
4. Multiple trials used analysis of only those who completed the trials and not intention-to-treat. They

had substantial dropout rates. Thus, the assumptions of these studies no longer hold and the validity of treatment comparisons is threatened.

5. At least 17 of the 22 trials were industry sponsored. Others have suggested that findings from industry-sponsored trials compared with those that were otherwise funded showed that research funded by pharmaceutical companies was more likely to have outcomes favoring the sponsor.
6. All 22 studies reported improvement of pain in the intra-articular placebo groups. Placebo injections may have efficacy for treating knee OA. The investigators calculated that intra-articular placebo accounted for 79% of the efficacy of intra-articular hyaluronic acid.
7. “This supports our hypothesis that the majority of the effect of intra-articular hyaluronic acid is an intra-articular placebo effect.”

CONCLUSION

Intra-articular hyaluronic acid has a small effect when compared with intra-articular placebo. Publication bias may overestimate the effect. Compared with lower-molecular-weight hyaluronic acid, the higher-molecular weight hyaluronic acid may be more efficacious, but heterogeneity of studies limits definitive conclusions.

JAMA December 1, 2003; 290: 3115-21 Original meta-analysis, first author Grace H Lo, Boston University School of Medicine, Boston, Mass.

Comment:

This article presents some interesting points:

1. Enthusiasm of early trials usually is blunted by later on-going trials. (Partly due to reduction toward the mean?)
2. Industry-sponsored trials unfortunately are suspect. This is a shame, I believe that many trials so sponsored do not include bias promoted by manufacturers. However, enthusiastic independent investigators may subconsciously be biased toward the sponsored drug.
3. Industry-sponsored trial drugs showing little or no benefit over placebo or over a previously effective similar drug are less likely to be published.

I doubt this study will deter enthusiasts for using HA. Individual patients who have apparently obtained relief may insist on continuing.

The only way an individual's response can be accurately determined is by an N-of-one trial.

I doubt this would be feasible considering the ethical issues involved. RTJ

12-7 SCREENING FOR DEPRESSION IN PRIMARY CARE WITH TWO VERBALLY ASKED QUESTIONS

The US Preventive Services Task Force endorsed screening for depression, but did not recommend a specific screening tool. Many primary care clinicians find screening questionnaires for depression too cumbersome and time consuming for routine use. This study used a simple screening tool of two questions. If one or two were

answered positively, further questions were asked to determine if major depression was present. (A composite interview--the "Gold Standard")

The screening questions:

- 1) During the past month have you often been bothered by feeling down, depressed, or hopeless?
- 2) During the past month have you often been bothered by little interest or pleasure in doing things?

The objective of this study was to determine the diagnostic accuracy of these questions when asked verbally.

Conclusion: The questions would detect almost all cases of depression in primary care. Many false positives occurred and would require further investigation. If the questions were answered negatively, depression was ruled out.

STUDY

1. Cross sectional study of 15 general practices asked the questions of 421 consecutive patients.
None were taking psychotropic drugs.
2. Practitioners asked the questions at any time during the consultation. If either was answered positively, the test was considered positive.
3. The gold standard for depression was a composite interview.

RESULTS

1. The sensitivity of the two screening questions was 97% (few false positives).
2. The specificity of the two questions was 67%. (many false positives)
3. True and false positives: true and false negatives:

Positive screen		Negative screen	
True positive	False positive	True negative	False negative
28	129	263	1

4. The high sensitivity was accompanied by a high number of false positive results. This would require follow-up investigation to determine if depression was truly present.
If both questions were answered negatively, it was highly unlikely that depression was present.

DISCUSSION

1. In the community setting, the two verbally asked questions have a good sensitivity (97%) and reasonable specificity (67%) for screening for depression.
2. About 5 false positives would occur for every true positive when asking the questions alone.
This is common in screening studies which are in essence a diagnostic test performed in a low prevalence setting. Further questions can clarify presence or absence of depression.
3. The two questions are considerably shorter than the shortest (7 questions) screening questionnaire (Beck depression inventory). They are a good compromise between the time

required to administer the screen and the likelihood ratio.

CONCLUSION

Two verbally asked questions for screening for depression would detect most cases of depression in primary care. Many false positive tests occur, necessitating further questioning in subjects with a positive 2-question screen.

BMJ November 15, 2003; 327: 1144-46 Original investigation, first author Bruce Arroll, University of Auckland, New Zealand.

Comment:

The investigators stress that the questions should be asked verbally. They did not go into detail about their reasons. I assume the verbal response would be more revealing (body language) than responses to written questions. The gist to the screen is that if it is negative, depression is very unlikely. If the screen is positive, doubt remains, and further investigation is warranted.

12-8 REVIEW OF SENSITIVITY, SPECIFICITY, PREDICTIVE VALUES AND LIKELIHOOD RATIOS

I abstracted the preceding article in part because it gave me the opportunity to review various applications of “evidence-based medicine” which are so often included in studies I abstract. If I do not review them periodically, I will forget how to calculate them. RTJ

1. Sensitivity and specificity of the test:

	Truly depressed*	Not depressed*	Total
Test positive	27 (a; true positive)	129 (b; false positive)	156 (g)
Test negative	1 (c; false negative)	263 (d; true negative)	264 (h)
Total	28 (e)	392 (f)	

(*By composite interview—the “gold standard”)

A. *Sensitivity* of test = % of subjects *with* depression who had a *positive* test = $a/e = 27/28 = 97\%$

(When a test has a high sensitivity (few false negatives), a negative result makes the diagnosis highly unlikely (ruled out). In this example, only 3% of truly depressed persons replied negatively to both questions.)

(Note—this calculation is made from the first column.)

B. *Specificity* of test = % of subjects *without* depression who had a *negative* test = $d/f = 263/392 = 67\%$

(When a test has a high sensitivity (few false positives) most subjects with a positive test will be true positives. And the disease is ruled in. In this study, the specificity was moderate, and no definite conclusions can be drawn.) (Note—this calculation is made from the 2nd column.)

2. Predictive values:

A. *Positive* predictive value (+PV) = the proportion of subjects with positive tests who have depression = True + / total + = $27/156 = a/g = 0.17 = 17\%$

In the study the test does not have a very high +PV (only 17%). Thus a positive test does not indicate a high probability that the subject has depression. (too many false + tests.)

(Note—the +PV is calculated from the top row.)

B. *Negative* predictive value (-PV) = the proportion of subjects with a negative who do not have depression = true negative/total negative = $d/h = 263/264 = 0.99 = 99\%$.

In this study a negative test has a high probability (99%) or ruling out depression. (Very few false negatives.) At a population prevalence of 6% of major depression, a negative test would almost always rule out depression. (Note that the -PV calculated from the bottom row.)

3. Likelihood ratios

A. *Positive* likelihood ratio (+LR)

Ratio between positive tests:

1) The % of subjects *with* depression who have a *positive* test (true + percent) and

2) The % of subjects *without* depression who have a *positive* test.(false + percent)

In this study 1) = $a/e = 27/28 = 97\%$

2) = $d/f = 129/392 = 33\%$

The positive likelihood ratio = $97/33 = 2.9$

(Note that the + LR = sensitivity of the test/100 – specificity of the test. The calculation is made from both columns..)

Likelihood ratios of greater than one produce a post-test probability that is higher than the pre-test probability. 2.9 is a modest +LR and indicates the probability that depression is present by a small degree. A +LR of 10 or 20 would indicate a strong possibility that depression is present.

B. *Negative* likelihood ratio (-LR):

The ratio between negative tests:

1) The % of subjects *with* depression who had a *negative* test and

2) The % of subjects *without* depression who had a *negative* test.

In this study: 1) = $a/e = 1/28 = 3.5\%$ (false positive percent)

2) = $d/f = 263/392 = 75\%$ (false negative %)

1) / 2) = $3.5/75 = 0.05$

Likelihood ratios of less than one produce a post-test probability that is lower than the pre-test probability. 0.05 virtually rules out the probability that the patients have depression.

Go to www.cebm.net for more explanations.

I still struggle with these calculations. And when I complete them I am not certain they are correct. The more often I calculate them, the more certain I become. Readers, have I calculated them correctly? RTJ

This Preparation Was Not Effective

12-9 EFFICACY AND SAFETY OF ECHINACEA IN TREATING UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN

Echinacea is a herbal remedy widely used for prevention and treatment of upper respiratory infections (URIs). It is one of the most commonly used herbal remedies in the USA . Three species of echinacea are used for medical purposes. Beneficial effects are thought to be due to its “immunomodulating” activity, most notably macrophage activation and enhanced neutrophil phagocytosis.

A number of clinical trials of echinacea have concerned adults. Results have been mixed. Most investigations have concluded that the evidence suggests that it may be an efficacious treatment for URIs. This conclusion is limited by methodological flaws in many of the studies. There are limited data in pediatric patients.

This study postulated that treatment with *E purpurea* would result in at least a 1.5- to 2-day reduction in duration of URIs in children, and that symptoms would be less severe than in patients receiving placebo.

Conclusion: The preparation used in this study was *not* effective in treating URIs in children.

STUDY

1. Randomized, double-blind, placebo-controlled trial entered over 400 healthy children age 2 to 11. (Mean age 5)
2. Randomized to: 1) echinacea, or 2) placebo. Study medication was begun at the onset of URI symptoms and continued throughout the URI, for a maximum of 10 days.
3. The preparation used was made from juice pressed from flowering *E purpurea* which was then dried. and combined with syrup. Plain syrup was used as the placebo. This extract has been used extensively. The dosing instructions were based on the recommendations of the manufacturer. The study medication was begun at the start of the URI and continued until all symptoms had resolved.
4. Parents were asked to monitor their child’s symptoms daily and record severity of symptoms (sneezing, coughing, nasal congestion, and runny nose) on a 4-point scale. The overall severity was computed by summing daily scores.
5. Main outcome measures: duration and severity of symptoms, and adverse events
6. “Other symptoms” were classified as an adverse event.

RESULTS

1. Data on 707 URIs in 407 children:

Outcomes	Echinacea (n =200)	Placebo (N = 207)
Duration of symptoms (days)	9	9
Severity of symptoms (median)	33	33 (sum of daily scores)
Days of fever	0.81	0.64
Peak severity of symptoms	6.0	6.1
No. of days of peak severity	1.6	1.6
Parental assessment of severity (%)		
Mild	46	46

Moderate	40	43
Severe	4	11

2. Adverse events:

Rash	24 (7.1%)	10 (2.7%) (P value .008)
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(At least one adverse event was reported during 43% of URIs, with no significant difference between groups except for rash.)

Two children (both in the echinacea group) had an adverse event (sudden onset of stridor) severe enough to necessitate a visit to the emergency department.

3. Parents were asked to guess which medication their child had taken.

	Echinacea group	Placebo group
Correct guess	35%	34%
Thought taken placebo	23%	
Thought taken echinacea		34%
Didn't know	42%	41%

DISCUSSION

1. Echinacea as given in this study was not effective in shortening duration or decreasing severity of URIs in children. In no group of children studied did echinacea appear to have a positive effect.
2. Rash was more common in those taking echinacea. Severe reactions to echinacea, including anaphylaxis have been reported.
3. Because the active ingredients in echinacea have not been standardized, it is difficult to determine the optimal dosing regimen in children.
4. The effect of echinacea in *prevention* of URIs deserves additional study.

CONCLUSION

“Our results do not support the use of echinacea for treatment of URIs in children.” Its use was associated with an increased risk of rash.

JAMA December 3, 2003; 290: 2824-30 Original study first author James A Taylor, University of Washington, Seattle, with additional authors from Bastyr University, Kenmore, Washington. and Helfgott Research Institute, National College of Naturopathic Medicine, Portland Oregon.

Comment:

This study was supported by a grant from the National Center for Complementary and Alternative Medicine. Bastyr University is an alternative medicine institution.

It continues to amaze me that so many persons take unstandardized and unproven nostrums and give them to their children. I am sure devotees will fault this study. They will remain convinced that echinacea is beneficial.

Several “alternative and complementary” interventions have recently fared poorly when examined scientifically:

St John's wort: Significantly induces cytochrome P450 in the liver. This hastens the metabolism of at least half of all marketed medications thus diminishing their clinical effectiveness. Recent randomized, placebo controlled studies do not support its effectiveness for moderate or severe depression. (*JAMA September 17, 2003; 290: 1500-04*)

Evening primrose: Gamma linolenic acid, the presumed active ingredient in Evening Primrose oil ("Borage oil") has been used extensively for treatment of atopic dermatitis. A randomized, double-blind, placebo-controlled trial GLA failed to find any benefit. (*BMJ December 13, 2003; 327: 1385-87 and Editorial in the same issue pp 1358-59*) The UK's Medicines Control Agency has withdrawn the product license.

Magnets for plantar heel pain: A randomized, double-blind, placebo controlled trial reported no benefit. (*JAMA September 17, 2003; 290: 1474-78*)

Ephedra: The FDA recently ordered its removal from over-the-counter distribution due to reports of a number of deaths.
RTJ

Interesting, But Far-Off

12-10 SCREENING VIRTUAL COLONOSCOPY—READY FOR PRIME TIME?

Screening for colo-rectal cancer (CRC) is recommended for asymptomatic, average-risk adults, beginning at age 50. Screening detects early-stage non-metastatic cancers that are surgically curable, and permits removal of benign adenomas, the precursor lesions of nearly all adenocarcinomas.

Several approaches to screening are available. Each test has inherent strengths and weaknesses.

Fiberoptic colonoscopy is the current gold standard for screening against which all other tests are compared. It provides high sensitivity with a false-negative rate of about 6% for adenomas 10 cm or more in diameter. Its drawbacks include need for insertion of an intravenous catheter for administration of sedatives, a recovery time of 30- to 60-minutes, and the requirement for a driver to accompany the patient home. Total time is about 2 hours. It carries some risk of perforation and bleeding, effects of sedatives, and other complications. Most consider the risks to be acceptable.

Virtual colonoscopy (computed tomographic colonography) was first described in 1994. It requires the same bowel-cleansing preparation as conventional colonoscopy. And insertion of a rectal tube, and insufflation of air or carbon dioxide to distend the colon. Time required is about 10 to 15 minutes, with an additional 30 minutes for interpretation.

A study reported in this issue of NEJM describes a new technique for virtual colonoscopy. The new VC used a multidirectional CT scanner providing a primary 3-dimensional endoluminal display which permitted faster, higher-resolution imaging than previously obtainable. Residual fluid and stool was tagged by contrast material. The imaging software digitally removed all opacified fluid and stool from the colon by a process called "electronic cleansing".

Subjects received the new virtual colonoscopy (VC) followed by conventional colonoscopy for comparison:

Sensitivity of VC for detection of adenomas vs traditional colonoscopy:

10 mm or larger was 92% vs 88%

8 mm or larger was 92% vs 89%

6 mm or larger was 86% vs 90%

The study suggests that VC can detect polyps of 6 mm or larger as accurately as conventional colonoscopy in a population with a low prevalence of colorectal neoplasia.

A critical issue remains—what is the choice of polyp size for VC that should trigger referral for conventional colonoscopy? “The referral of all patients who were found on VC to have a polyp 10 mm or larger would probably result in the detection of nearly all cancers and eliminate the need for a large number of colonoscopies.”

At the close of the study patients were asked to state their preference, VC or traditional. Only 50% chose VC; 41% chose conventional. A substantial proportion may still opt for conventional because it allows suspicious lesions to be removed

Decisions regarding the use of VC as a first-line screening test will require more information about cost and insurance coverage. “The performance of VC in this asymptomatic population is impressive, with detection rates similar to those achieved by conventional colonoscopy.” Only if the important questions about the appropriate size threshold and the surveillance of smaller polyps can be resolved will VC be ready for prime time.

NEJM December 4, 2003; 349: 226-64 Editorial, first author Martina M Morrin, Harvard Medical School, Boston, Mass

Comment

1 “Computed Tomographic Virtual Colonoscopy to Screen for Colorectal Neoplasia in Asymptomatic Adults” NEJM December 4, 2003; 349: 2191-200, original investigation, first author Perry J Pichhardt, Uniformed Services University of the Health Sciences, Bethesda, MD

The investigators commented that VC also detected 5 asymptomatic cancers outside the colon as well as aortic aneurysms, and renal and gall bladder calculi.

I abstracted this editorial as a look into the future. Patients may be asking about it. Much more training, experience and local availability will be needed for this new VC to reach primary screening status. One large bugaboo is the need for a follow-up conventional colonoscopy for removal of polyps of a certain size. And repeated follow up scans in those with polyps under a stated size. This size is not yet determined. RTJ