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FOR

PRIMARY CARE MEDICINE

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26th YEAR OF PUBLICATION

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 reviews of the current literature and his 26-year publication of Practical Pointers.

2) The **FULL 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 10 years can be accessed at www.practicalpointers.org

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* FEBRUARY 2012

Supports The Hypothesis That Colonoscopic Removal Of Adenomas Prevents Death From CRC.

2-1 COLONOSCOPY, POLYPECTOMY AND LONG-TERM PREVENTION OF COLORECTAL CANCER

Screening for colorectal cancer (**CRC**) affects mortality in 2 ways: 1) Detecting cancer at an early, curable stage, and 2) More commonly, detecting and removing precancerous adenomas.

This study is a continuation of the National Polyp Study (**NPS**; 1980-1990), which examined whether polypectomy would reduce the incidence of death from CRC. It is a long-term follow-up study (up to 23 years) to determine the mortality from CRC in the general population vs the observed rate of CRC deaths among patients with adenomatous polyps that had been removed.

The NPS was a multicenter post-polypectomy surveillance study of patients who had one or more newly diagnosed adenomas removed. It involved 7 clinical centers that represented a wide range of endoscopic practices.

The long term follow-up analysis entered 2602 individuals in whom adenomas had been removed. Individuals were followed to determine the incidence of death from CRC.

Used the National Death Index to identify deaths and to determine the death rate and the cause of death in the general population.

Mortality from CRC among patients who had adenomas removed was compared with the expected mortality from CRC in the general population with similar age, sex, race and calendar year.

The end point was a comparison of death from CRC in both groups,

Baseline characteristics of 2602 individuals who had adenomas removed: Mean age 62; 66% male; advanced adenoma 57% (diameter over 10 mm; tubulovillous or villous; high grade dysplasia).

The median follow-up was 16 years with a maximum of 23 years.

There were 12 deaths from CRC in the adenoma cohort. And 25 estimated deaths in the general population over 20 years. Mortality rose after the first 4 years.

The cumulative 20-year mortality in the adenoma cohort was 0.8% vs an estimated 1.5% in the general population.

Conclusion: The findings support the hypothesis that colonoscopic removal of adenomas prevents death from CRC.

(See the full abstract for details and the citation,. Ed.)

This is not a strong study. No direct comparison was made between the 2 groups. Nevertheless, I believe most clinicians would accept the conclusion of the study, knowing the long observed adenoma-carcinoma sequence.

By my rough calculation from their data, about 200 patients would undergo polypectomy to prevent one death from CRC.

The study also considered a group of patients who had non-adenomatous polyps removed. I omitted these data.

Both Have Advantages And Disadvantages

2-2 COLONOSCOPY VERSUS FECAL IMMUNOCHEMICAL TESTING IN COLORECTAL CANCER SCREENING

Several studies have shown that CRC screening is effective and cost-effective in the average risk population. There are two recommended strategies for screening: 1) Stool testing—occult blood [eg, fecal immunochemical testing **FIT**] and 2) Structural examination (flexible sigmoidoscopy, computed tomography, and colonoscopy).

Recent evidence suggests that, in patients in whom one normal colonoscopy is reported, risk of CRC is markedly reduced.

Comparative studies have shown that semi-quantitative FIT is more accurate than guaiac in detecting CRC and advanced adenomas. This test is now recommended as a first-choice stool screening examination.

Although FIT is less effective for detection of neoplasms than colonoscopy, it may be better accepted by the public. Higher acceptance may counteract its lower detection capacity. FIT may be more effective and less costly than other screening strategies.

This randomized, controlled trial compared FIT with colonoscopy. The investigators hypothesized that FIT screening every 2 years would be non-inferior to one-time colonoscopy in reducing mortality from CRC among average risk patients.

This is a preliminary report of a proposed 10-year trial.

Randomized to: 1) one-time colonoscopy or 2) FIT stool examination to be done every 2 years. The study was based on the hypothesis that screening average-risk subjects with biennial FIT would not be inferior to one-time colonoscopy in respect to the rate of death from CRC at 10 years.

Those with a positive FIT were referred for colonoscopy.

Over 57 000 subjects underwent randomization. (Average age 59; 53% women.) Only about

18% of those randomized to colonoscopy underwent colonoscopy; 37% of those assigned to FIT received FIT.

Among subjects screened by FIT, 7% tested positive. All were referred for colonoscopy; 86% actually underwent colonoscopy.

As screened analysis after exclusions and refusals, and some cross-overs:

	Colonoscopy	FIT
Number	5059	10 507
Cancer (%)	27 (0.5)	36 (0.3)
Advanced adenoma	493 (9.7)	252 (2.4)
Non-advanced adenoma	1116 (22)	112 (1.1)
Any neoplasm	1636 (32)	400 (4)

The most relevant result of this interim analysis was that one-time screening with FIT was very similar to one-time colonoscopy with respect to rate of detection of CRC. (0.5% vs 0.3%) There was no significant difference in the stage of cancers detected.

Conclusion: In this interim analysis, patients randomized to the FIT group were more likely to participate in screening. The number of CRCs detected was similar in the 2 groups. More adenoma were detected in the colonoscopic group.

(See the full abstract for details and the citation. Ed.)

The article reports the intention-to-treat results at length. I omit these because I believe primary care clinicians are much more interested in results based on subjects who actually receive the test.

The FIT stool screening test is based on specific antibodies to globulin. It is more effective in outcomes and costs than guaiac testing. It reports quantitative results, detecting down to 0.3 mL of blood. It does not detect bleeding from the upper GI tract and thus is more specific to colo-rectal bleeding. Source: Wikpedia

The FIT test in this study was done on the automated semi-quantitative OC-Sensor machine (Eiken Chemical)

The trial analyzed stool samples with the use of an automated semi-quantitative OC-Sensor (Eiken Chemical) without specific dietary restriction or medication use.

Stool testing for exfoliated DNA is being developed. I believe further experience is required.

The investigators argue that biannual FIT exams are made more acceptable than colonoscopy simply because many more patients will accept FIT. (Better a less sensitive test than no test at all.) If repeated every 2 years, more adenomas and CRCs will be detected.

The authors stated that about 1 in 3 subjects had a neoplasm (cancer, advanced adenoma, non-advanced adenoma). This seems high to me.

They also state that detection of CRC (0.5 by colonoscopy vs 0.3 by FIT were clinically similar, I disagree. This amounts for 2 cancers per 1000 which remained undetected by FIT.

Perhaps a one-time normal colonoscopy followed by biennial FIT exam will turn out to be an acceptable, cost-saving approach.

The most effective and cost-effective screening strategy for CRC is to be determined.

2-3 HORMONE REPLACEMENT THERAPY

Hormone replacement therapy (**HRT**) contains estrogen-alone (**E**) for relief of menopausal symptoms (in women who have had a hysterectomy) and estrogen combined with progesterone (**E +P**) in those with an intact uterus—to protect against endometrial cancer.

Vasomotor symptoms are normal and affect about 80% of women during the menopause transition. Symptoms are severe in 20%. Median duration is 4 years, but symptoms may persist for years. HRT is indicated when symptoms adversely affect quality-of-life.

HRT is the most effective treatment for vasomotor symptoms. It also reduces fracture risk; improves vaginal dryness and sexual function; and may also improve muscle aches and pains.

Adverse effects of HRT:

Breast cancer: E + P increases risk. It also increases breast density and the likelihood of having a difficult-to-read mammogram. For E-alone data are conflicting. The Women's Health Study and the Million Women Study reported increased risk for use for 5 to 7 years. Most observational studies report no increased risk. Studies show the greatest risk is related to E + P.

Venous Thromboembolism: Both E-alone and E +P increase risk of VTE and pulmonary embolism. The risk increases with age and other risk factors such as obesity, previous VTE, smoking and immobility. Previous VTE is a contraindication. Compared with oral HRT, transdermal HRT may lessen risk of VTE. In low-risk patients, low dose estrogen may not increase risk.

Stroke: HRT (both E-alone and E + P) increases risk of stroke. Risk rises with age, and duration of HRT use. Risk is lowered by use of transdermal preparations.

Cholecystitis: Large trials have shown increased risk of cholecystitis.

Coronary heart disease: Relationship between HRT and CHD is controversial. Risk increases with age, duration of use of HRT, and pre-existing CHD. In women under age 60, there is no statistically significant risk. In older women, HRT is generally avoided. Because they are more likely to have CHD.

Endometrial cancer: E-alone may lead to endometrial hyperplasia and increased risk of cancer. E + P does not increase risk. E-alone should not be used in patients who retain their uterus,

Avoid or discontinue HRT:

Uncontrolled hypertension

History of breast cancer. (Check mammography results before starting)

Known or high risk of VTE, stroke, CHD,

Abnormal liver function. (HRT are metabolized by the liver)

Abnormal vaginal bleeding

History of endometrial or ovarian cancer

History or high risk of gallbladder disease

Other considerations:

Start with a low dose and gradually increase dose as needed to control symptoms. Use HRT at the lowest dose for the shortest time. Care in starting long after menopause. .

Background disease and risks of HRT increase with age.

Consider HRT in patients at high risk of fracture.

Consider associated depression and anxiety in women with severe menopausal symptoms.

Transdermal HRT is safer then oral .

Gabapentin (*Neurontin*; Pfizer; originally a drug to treat epilepsy—later used for neuropathic pain) is the only non-hormonal product to be equally effective as low dose estrogen for vasomotor symptoms.

(See the full abstract for details and the citation. Ed.)

Treatment of menopausal symptoms is an important application for primary care. It benefits many women.

In general, estrogen-alone is safer than combined estrogen-progesterone. I believe progesterone is the major contributor to the risk of breast cancer. Progesterone protects against endometrial cancer (when estrogen is used), but an important question is—Does the increase in breast cancer outweigh the reduction in endometrial cancer?

The term "hormone replacement therapy" is entrenched in medical terminology. But it is imprecise and confusing, and, I believe, obsolete. The term applies to estrogen-alone, progesterone-alone and the combination. They are completely different drugs. It also could be applied to other hormone replacements such as insulin, thyroxin, and cortisol. I believe the term should be abandoned and replaced by more specific hormonal drugs.

If used cautiously, E and E +P treatment of menopausal symptoms is safe.

"Offered Little Clinical Benefit For Most Patients"

2-4 AMOXICILLIN FOR ACUTE RHINO-SINUSITIS: A Randomized Controlled Trial.

Acute rhino-sinusitis (**R-S**) accounts for 1 in 5 prescriptions for antibiotics in adults in the US.

Evidence of efficacy is conflicting. This trial evaluated the incremental effect of amoxicillin treatment over symptomatic treatment in adult community dwellers on disease-specific quality-of-life in patients with clinically diagnosed acute R-S.

This randomized, placebo-controlled trial was conducted in 10 primary care offices. (2006-2009). Patients were adults age 18-70 (median age 32). All met the CDC's diagnostic criteria for acute bacterial R-S. All had moderate, severe, or very severe symptoms.

Randomized (n = 166) to: 1) A 10-day course of amoxicillin 500 mg three times a day, or 2) Matching placebo three times a day. All reported purulent nasal discharge and maxillary pain or tenderness.

All patients received a 5 to 7 day supply of symptomatic treatments to be used as needed.

Primary outcome = effect of treatment on disease-specific quality-of-life at day 3.

The primary outcome was measured using the modified Sino-nasal Outcome Test -16. (SNOT-16), which considers both the severity and frequency of symptoms. Each participant scored how much each of 16 R-S related symptoms bothered them in the past few days—0 for no problem to 3 for severe problem.

Mean SNOT-16 scores

Day 0		Day 3		Day 7		Day 10		
A	C	A	C	A	C	A	C	
1.71	1.70	1.12	1.14	0.65	0.84	0.48	0.49	(A = amoxicillin; C = control)

(For the SNOT-16 score, a difference of 0.5 is the minimal difference representing a clinically significant effect.)

The mean improvements in the SNOT-16 score was similar between groups except for day 7, when A was favored.

Eight patients stopped treatment at day 3; 13 at day 7; and 32 more by day 10. Reasons were failure to improve (2 in A; 6 in C); worsening symptoms (3 and 4); improved symptoms (4 in A); and adverse effects (1 in A). Sixteen were treated with another antibiotic. (5 in A; 11 in C)

Adverse effects: No serious adverse effect was reported in either group. Nausea, diarrhea, abdominal pain, and vaginitis occurred equally (5% to 9%).

These findings support the recommendation to avoid routine antibiotic treatment for patients with uncomplicated acute rhino-sinusitis.

It is important to note that patients with symptoms indicative of serious complications were excluded from this trial, and likely to need a different strategy.

Conclusion: Treatment with amoxicillin for 10 days offered little clinical benefit for most patients with clinically diagnosed uncomplicated acute rhino-sinusitis

(For details and the citation, see the full abstract Ed.)

I was unable to access the snot-16 score on Google. Apparently, it has been replaced by the SNOT-22. Both scores contain symptoms relating to the upper respiratory tract as well as systemic symptoms. They assess functional limitations, physical problems, and emotional consequences of rhino-sinusitis.

Patients request antibiotics to cure the infection. By "cure" they mean relief of symptoms. Symptomatic treatment, as applied in this study, relieves symptoms while the infection is cured by natural immunity. Many will improve in a few days. .

I believe treatment tilts slightly in favor of A. The greater improvement in the A group at day 7 may indicate some beneficial effect. In addition, a few more patients failed to improve in the C group and were given antibiotics. Some in the A groups discontinued treatment because of improved symptoms.

There will be some patients for whom antibiotics are required at the first visit because of the severity of the illness and the likelihood of complications from the sinusitis. Clinical judgment is required to distinguish this smaller group. Primary care clinicians may more readily prescribe antibiotics for this reason.

I believe the "if" or "delayed " prescription is a useful approach to treatment by primary care clinicians. A prescription is written for the antibiotic, but the patient is admonished not to fill it unless symptoms get worse or do not improve over a few days. Most of the time, the prescription will not be filled.

There was no need for sinus X-rays.

Identifies Higher Risk

2-5 EFFECT OF ADDING SYSTEMATIC FAMILY HISTORY ENQUIRY TO CARDIOVASCULAR DISEASE RISK ASSESSMENT IN PRIMARY CARE

Family history (**FH**) is a recognized risk factor for many chronic diseases. It is traditionally a part of history-taking in practice.

Guidelines for risk assessment of CHD are based on the Framingham risk-factor assessment and are widely used in the UK. It incorporates age, sex, smoking, systolic BP, and the ratio of total to HDL-cholesterol.

The trial asked: If such information is collected and used systematically, how many more persons at high risk would be identified?

This trial compared 1) an intervention in which FH of premature CHD was systematically collected and incorporated into risk assessment [intervention group] with 2) risk assessment based on usual practice [control group]. Included 24 matched family practices in England (2007-2000; total of 748 patients; age 30-65).

Patients in 12 practices (control group) received the Framingham-based cardiovascular risk assessment using existing FH information in their electronic medical record.

Patients in 12 practices (intervention group) in addition completed a more detailed questionnaire to systematically collect the FH, which included a FH of premature CHD. Identified 105 (15%) patients as having high risk based on FH.

For participants in the intervention group, the percentage of those at high risk increased by 5.1%. In the control group (which considered only the FH initially incorporated in the electronic health record) risk increased by 0.5%. (Difference = 4.6%)

The number of participants at high risk in the intervention group increased from 49 to 69 (40%) after the FH from the questionnaire was incorporated.

About 5% in both groups had a positive FH of CHD in the original electronic record. This increased to 29% in the intervention group.

(See the full abstract for details and the citation,.

The venerable FH has largely been neglected in favor of other markers of risk. I am delighted to see it resurrected. FH is important.

FH is easily ascertained by self-reporting for inclusion in the electronic record.

After obtaining the FH and including it in the risk profile, what next? It should lead patients to better their lifestyles and take appropriate drugs as needed. This may be surprisingly unsuccessful.

The Surgeon General's Family History Portrait tool is available on line. It helps patients to complete a detailed FH for personal use and for the medical record.

FULL ABSTRACTS FEBRUARY 2012

Supports The Hypothesis That Colonoscopic Removal Of Adenomas Prevents Death From CRC.

2-1 COLONOSCOPY, POLYPECTOMY AND LONG-TERM PREVENTION OF COLORECTAL CANCER

Screening for colorectal cancer (**CRC**) affects mortality in 2 ways: 1) Detecting cancer at an early, curable stage, and 2) More commonly, detecting and removing precancerous adenomas.

This study is a continuation of the National Polyp Study (**NPS**; 1980-1990), which examined whether polypectomy would reduce the incidence of death from CRC. It is a long-term follow-up study (up to 23 years) to determine the mortality from CRC in the general population vs the observed rate of CRC deaths among patients with adenomatous polyps that had been removed.

STUDY

1. The NPS was a multicenter post-polypectomy surveillance study (1980-1990) of patients who had one or more newly diagnosed adenomas removed. It involved 7 clinical centers that represented a wide range of endoscopic practices.
2. Patients referred from the initial polypectomy group were enrollment in this follow-up study.
3. The long term follow-up analysis entered 2602 individuals in whom adenomas had been removed. Individuals were followed to determine the incidence of death from CRC.
4. Used the National Death Index to identify deaths and to determine the death rate and the cause of death in the general population.
5. Mortality from CRC among patients who had adenomas removed was compared with the expected mortality from CRC in the general population with similar age, sex, race and calendar year.
6. The end point was a comparison of death from CRC in both groups,

RESULTS

1. Baseline characteristics of 2602 individuals who had adenomas removed: Mean age 62; 66% male; advanced adenoma 57% (diameter over 10 mm; tubulovillous or villous; high grade dysplasia).
2. The median follow-up was 16 years with a maximum of 23 years.
3. There were 1246 all-cause deaths among the 2602 participants. Mortality was lower in the adenoma group than in the general population.
4. There were 12 deaths from CRC in the adenoma cohort. And 25 estimated deaths in the general population over 20 years. Mortality rose after the first 4 years.

5. The cumulative 20-year mortality in the adenoma cohort was 0.8% vs an estimated 1.5% in the general population.

DISCUSSION

1. This study suggests that adenoma removal significantly reduces death from CRC.
2. Because 57% of the adenomas removed were advanced adenomas, this group may be considered to be at higher risk.
3. A comparison of a large group of patients with adenomas, half undergoing polypectomy and half with long-term observation only, would be more meaningful in determining any mortality reduction from polypectomy. But such a study would be unethical.
4. "Our findings provide an indirect estimate of the effect of removing adenomas, which is the primary intervention measure in screening colonoscopy."
5. Comparisons with mortality from CRC were limited by inability to adjust between the 2 cohorts in risk factors, behaviors, access to health care, or quality of health care.
6. Most patients in the adenoma cohort underwent surveillance colonoscopies after polypectomy. Consequently, any benefit for these patients would include the effect of surveillance colonoscopies as well.

CONCLUSION

The findings support the hypothesis that colonoscopic removal of adenomas prevents death from CRC.

JAM February 23, 2012l 366: 687-96 Original investigation, first author Ann G Zauber, Memorial Sloan-Kettering Cancer Center, New York.

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2-2 COLONOSCOPY VERSUS FECAL IMMUNOCHEMICAL TESTING IN COLORECTAL CANCER SCREENING

Several studies have shown that CRC screening is effective and cost-effective in the average risk population. There are two recommended strategies for screening: 1) Stool testing—occult blood [eg, fecal immunochemical testing **FIT**] and 2) Structural examination (flexible sigmoidoscopy, computed tomography, and colonoscopy).

Stool testing primarily detects cancer. Structural examination detects both cancer and

pre-malignant lesions.

Recent evidence suggests that, in patients in whom one normal colonoscopy is reported, risk of CRC is markedly reduced.

FIT testing is used more commonly in Europe; colonoscopy in the US. Colonoscopy is considered the most accurate test for early detection and prevention of CRC. Although data from randomized studies are lacking, colonoscopy is recommended for first-line screening on the basis of indirect data and observational studies.

Comparative studies have shown that semi-quantitative FIT is more accurate than guaiac in detecting CRC and advanced adenomas. This test is now recommended as a first-choice stool screening examination.

Although FIT is less effective for detection of neoplasms than colonoscopy, it may be better accepted by the public. Higher acceptance may counteract its lower detection capacity. FIT may be more effective and less costly than other screening strategies.

This randomized, controlled trial compared FIT with colonoscopy. The investigators hypothesized that FIT screening every 2 years would be non-inferior to one-time colonoscopy in reducing mortality from CRC among average risk patients over 10 years.

This is a preliminary report of a proposed 10-year trial.

STUDY

1. Conducted a randomized, controlled non-inferiority trial in 8 regions in Spain. The study was designed to assess the efficacy of one-time colonoscopy and biennial FIT for reducing the rate of death from CRC over 10 years. The first round of testing finished in 2011. Ten-year follow-up will be completed in 2021.
2. Asymptomatic men and women age 50-69 were eligible. Exclusions included: personal history of CRC, adenoma, inflammatory bowel disease; positive family history for CRC; previous colonoscopy.
3. Randomized to: 1) one-time colonoscopy or 2) FIT stool examination to be done every 2 years.
4.. Those with a positive FIT were referred for colonoscopy.

RESULTS

1. Over 57 000 subjects underwent randomization. (Average age 59; 53% women.) Only about 18% of those randomized to colonoscopy underwent colonoscopy; 37% of those assigned to FIT received FIT.

2. Among subjects screened by FIT, 7% tested positive. All were referred for colonoscopy; 86% actually underwent colonoscopy.

4. As screened analysis after exclusions and refusals, and some cross-overs:

	Colonoscopy	FIT
Number	5059	10 507
Cancer (%)	27 (0.5)	36 (0.3)
Advanced adenoma	493 (9.7)	252 (2.4)
Non-advanced adenoma	1116 (22)	112 (1.1)
Any neoplasm	1636 (32)	400 (4)

[Advanced adenoma: 10 mm or more n diameter; villous architecture; high grade dysplasia; intra-mucosal carcinoma.]

5. The numbers needed to be screened:

	Colonoscopy	FIT
To find one cancer	191	281
To find one advanced neoplasm	10	36

6. Major complications of colonoscopy:

Total 34 individuals (0.7%): bleeding; hypotension; bradycardia; perforation.

DISCUSSION

1. Participation rate was low in both groups. Subjects randomized to FIT were more likely to participate.
2. Colonoscopy performed much better than FIT in diagnosis of adenomas.
3. The most relevant result of this interim analysis was that one-time screening with FIT was very similar to one-time colonoscopy with respect to rate of detection of CRC. (0.5% vs 0.3%) There was no significant difference in the stage of cancers detected.
5. Additional cases of CRC might be detected by the proposed 2-yearly FIT screenings.
6. More cancers might have been prevented in the colonoscopy group due to the removal of adenomas. However, the advantage of colonoscopy was diminished by the lower uptake relative to FIT.

CONCLUSION

In this interim analysis, patients randomized to the FIT group were more likely to participate in screening.

The number of CRCs detected was similar in the 2 groups.

More adenoma were detected in the colonoscopic group.

NEJM February 23, 2012; 366: 692-706 Original investigation by the COLONPREV Study, first author, Enrique Quintero, Hospital Universitsrio, Tenerife, Spain.

2-3 HORMONE REPLACEMENT THERAPY

Hormone replacement therapy (**HRT**) contains estrogen-alone (**E**) for relief of menopausal symptoms (in women who have had a hysterectomy) and estrogen combined with progesterone (**E +P**) in those with an intact uterus (to protect against endometrial cancer).

Vasomotor symptoms are normal and affect about 80% of women during the menopause transition. Symptoms are severe in 20%. Median duration is 4 years, but symptoms may persist for years. HRT is indicated when symptoms adversely affect quality-of-life.

HRT is the most effective treatment for vasomotor symptoms. It also reduces fracture risk; improves vaginal dryness and sexual function; and may also improve muscle aches and pains.

Estimated absolute harms and benefits for HRT use in postmenopausal American women age 50-59 in addition to the background risks:

NUMBER OF WOMEN PER 1000 PER 5 YEARS

BENEFITS		HARMS	
ESTROGEN-alone		ESTROGEN-alone	
Breast cancer	2	Venous thromboembolism	2
Coronary heart disease	4	Stroke	1
Fractures	5	Cholecystitis	14
Diabetes	11		
Overall mortality	5		
E + P		E + P	
Coronary heart disease	1	Breast cancer	8
Endometrial cancer	1	Venous thromboembolism	6
Fracture	5	Stroke	1
Diabetes	11	Cholecystitis	9
Overall mortality	5		

(Data from subgroup analyses of the Women's Health Imitative Study and the Nurse's Halt Study)

The principal harms of HRT are breast cancer, venous thromboembolic disease, stroke, and gallbladder disease.

Breast cancer: E + P increases risk. It also increases breast density and the likelihood of having a difficult-to-read mammogram. For E-alone data are conflicting. The Women's Health Study and the Million Women Study reported increased risk for use for 5 to 7 years. Most observational studies report no increased risk. Studies show the greatest risk is related to E + P.

Venous Thromboembolism: Both E-alone and E +P increase risk of VTE and pulmonary embolism. The risk increases with age and other risk factors such as obesity, previous VTE, smoking and immobility. Previous VTE is a contraindication. Compared with oral HRT, transdermal HRT may lessen risk of VTE. In low-risk patients, low dose estrogen may not increase risk.

Stroke: HRT (both E-alone and E + P) increases risk of stroke. Risk rises with age, and duration of use. Risk is lowered by use of transdermal preparations.

Cholecystitis: Large trials have shown increased risk of cholecystitis.

Coronary heart disease: Relationship between HRT and CHD is controversial. Risk increases with age, duration of use, and pre-existing CHD. In women under age 60, there is no statistically significant risk. In older women, HRT is generally avoided because they are more likely to have CHD.

Endometrial cancer: E-alone may lead to endometrial hyperplasia and increased risk of cancer. E + P does not increase risk. E-alone should not be used in patients who retain their uterus,

Fracture: HRT reduces risks of fracture.

(The authors did not comment further on diabetes and overall mortality Ed.))

The risk of most adverse events linked with HRT increases with duration of use, and with age of the patient, and with change in current health status. The benefits and harms noted above will change with aging and baseline risks.

Precautions:

Avoid or discontinue HRT:

Uncontrolled hypertension

History of breast cancer. (Check mammography results before starting)

Known or high risk of VTE, stroke, CHD,

Abnormal liver function. (HRT are metabolized by the liver)

Abnormal vaginal bleeding

History of endometrial or ovarian cancer

History or high risk of gallbladder disease

Other considerations:

Start with a low dose and gradually increase dose as needed to control symptoms. Use HRT at the lowest dose for the shortest time. Care in starting long after menopause.

Background disease and risks of HRT increase with age.

Consider HRT in patients at high risk of fracture.

Consider associated depression and anxiety in women with severe menopausal symptoms.

Transdermal HRT is safer then oral

Gabapentin (*Neurontin*; Pfizer; originally a drug to treat epilepsy—later used for neuropathic pain) is the only non-hormonal product to be equally effective as low dose estrogen for vasomotor symptoms.

BMJ February 25, 2012; 344: 44-49 (doi.101136/bmj.e763) "Practice', review article, first author Marin Hickey, University of Melbourne, Australia.

"Offered Little Clinical Benefit For Most Patients"

2-4 - AMOXICILLIN FOR ACUTE RHINO-SINUSITIS: A Randomized Controlled Trial.

Acute rhino-sinusitis (**R-S**) accounts for 1 in 5 prescriptions for antibiotics in adults in the US.

Considering the public health threat posed by increasing antibiotic resistance, strong evidence of symptom relief of R-S is needed to justify prescribing antibiotics for this usually self-limited disease. The rate of spontaneous improvement is high.

Evidence of efficacy is conflicting. This trial evaluated the incremental effect of amoxicillin treatment over symptomatic treatment in adult community dwellers on disease-specific quality-of-life in patients with clinically diagnosed acute R-S.

STUDY

1. Conducted a randomized, placebo-controlled trial in 10 primary care offices. (2006-2009).

Patients were adults age 18-70 (median age 32). All met the CDC's diagnostic criteria for acute bacterial R-S. All had moderate, severe, or very severe symptoms.

2. Diagnosis required history of maxillary pain or tenderness in the face or teeth; purulent nasal secretions; and R-S symptoms for 7 days or more and 28 days or less that were not improving or were worsening.
3. None had allergy to penicillin or amoxicillin; prior antibiotic treatment within 4 weeks; complications of sinusitis; impaired immune response; or cystic fibrosis. None rated their symptoms as very mild or mild.
4. Randomized to: 1) A 10-day course of amoxicillin 500 mg three times a day, or 2) Matching placebo three times a day.
5. All patients received a 5 to 7 day supply of symptomatic treatments to be used as needed:
   Acetaminophen 500 mg every 6 hours for pain
   Guaifenesin 600 mg every 12 hours to thin secretions
   Dextromethorphan 10 mg per 5 mL—guaifenesin 100 mg/5 mL given at 10 mL every 4 hours for cough
   Pseudoeephedrin-sustained action 120 mg every 12 hours for nasal congestion.
   Saline spray 0.65% 2 puffs as needed.
6. Primary outcome = effect of treatment on disease-specific quality-of-life at day 3. (The investigators expected benefit from amoxicillin to be evident at this time.) Day 10 was not chosen as the primary outcome due to the high rate of spontaneous resolution of the disease.
7. The primary outcome was measured using the modified Sino-nasal Outcome Test -16 (SNOT-16), which considers both the severity and frequency of symptoms. Each participant scored how much each of 16 R-S related symptoms bothered them in the past few days—0 for no problem to 3 for severe problem.
8. Improvement in disease-specific quality-of-life was assessed by reductions in the SNOT-16 scores from day 0 to day 3 and to day 7.
9. Analysis was by intention-to-treat. (All who were randomized.)

RESULTS

1. Randomized 166 patient; 155 completed the trial. All reported purulent nasal discharge and maxillary pain or tenderness.
2. Mean SNOT-16 scores

Day 0		Day 3		Day 7		Day 10		
A	C	A	C	A	C	A	C	
1.71	1.70	1.12	1.14	0.65	0.84	0.48	0.49	(A = amoxicillin; C = control)

(For the SNOT-16 score, a difference of 0.5 is the difference which represents a clinically significant effect.)

3. The mean improvements in the SNOT-16 score was similar between groups except for day 7, when A was favored. (74% in A reported improvement vs 56% of C; number needed to treat = 6) .)
4. For those that completed 10 days of treatment (per protocol analysis; n = 143) findings were consistent with the intention-to-treat analysis.
5. Duration of use and self-reported adherence did not differ between groups.
6. Eight patients stopped treatment at day 3; 13 at day 7; and 32 more by day 10. Reasons were failure to improve (2 in A; 6 in C); worsening symptoms (3 and 4); improved symptoms (4 in A); and adverse effects (1 in A).
7. Sixteen were treated with another antibiotic. (5 in A; 11 in C).
8. Concomitant use of symptomatic treatment was high and did not vary with group.
9. Other secondary outcomes were similar between groups. Days missed from work; unable to perform usual duties; rates of relapse and recurrence by day 28; additional health care use; and satisfaction with treatment did not differ between groups. Only one patient had a sinus X-ray.
10. Adverse effects: No serious adverse effect was reported in either group. Nausea, diarrhea, abdominal pain, and vaginitis occurred equally (5% to 9%).
11. Nasal obstruction was the only symptom that predicted benefit from A at day 7. There was no benefit in those without nasal obstruction.

DISCUSSION

1. These findings support the recommendation to avoid routine antibiotic treatment for patients with uncomplicated acute rhino-sinusitis.
2. The patients in this study were representative of patients for whom antibiotics might be prescribed. In both groups, disease-specific quality-of-life and sinus symptoms improved over time. With no significant difference at 10 days.
3. In this study, retrospective assessment of change in sinus symptoms suggested that antibiotic treatment may provide more rapid resolution of symptoms for some patients by day 7. However, when improvement was assessed as the difference in mean SNOT-16 scores, the statistical significance of benefit at day 7 was too small to represent any clinically important change.
4. The study population is representative of patients for whom antibiotics are prescribed.
5. There is now a considerable body of evidence from clinical trials conducted in primary care that

antibiotics provide little if any benefits for patients with clinically diagnosed rhino-sinusitis. Yet, antibiotic treatment is often both expected by patients and proscribed by physicians.

6. Guidelines suggest watchful waiting, which delays and may preclude antibiotic treatment while providing symptomatic treatment and an explanation of the natural history of the disease.
7. Intranasal steroids are not as effective as first hoped, but may reduce symptoms in some patients with mild disease.
8. It is important to note that patients with symptoms indicative of serious complications were excluded from this trial, and likely need a different strategy.

CONCLUSION

Treatment with amoxicillin for 10 days offered little clinical benefit for most patients with clinically diagnosed uncomplicated acute rhino-sinusitis

JAMA February 15, 2012; 307: 685-93 Original investigation, first author Jane M Garbutt, Washington University, St. Louis, MO

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2-5 EFFECT OF ADDING SYSTEMATIC FAMILY HISTORY ENQUIRY TO CARDIOVASCULAR DISEASE RISK ASSESSMENT IN PRIMARY CARE

Family history (**FH**) is a recognized risk factor for many chronic diseases. It is traditionally a part of history-taking in practice. There is a need for evidence from controlled trials to assess the value of systematically collecting the FH in primary care.

FH is rarely used in isolation. It is part of a multifactorial risk assessment for such conditions as coronary heart disuse (**CHD**).

Guidelines for risk assessment of CHD are based on the Framingham risk-factor assessment and are widely used in the UK. It incorporates age, sex, smoking, systolic BP, and the ratio of total to HDL-cholesterol.

Guidelines define a significant FH as CHD in male first-degree relatives younger than age 55. or female first-degree relatives younger than age 65.

Epidemiological studies suggest that adding FH might identify patients at greater risk for CHD who might benefit from preventive care. However, pragmatic randomized trials are required to evaluate the effect of FH on risk assessment.

FH is poorly recorded in electronic records in primary care practice. A more systematic approach to collecting FH is needed. Self-administered questionnaires may provide a solution.

The trial asked: If such information is collected and used systematically, how many more persons at high risk would be identified?

STUDY

1. This trial compared 1) an intervention in which FH of premature CHD was systematically collected and incorporated into risk assessment [intervention group] with 2) risk assessment based on usual practice [control group]. Included 24 matched family practices in England (2007-2000; total of 748 patients; age 30-65).
2. Patients in 12 practices (control group) received the Framingham-based cardiovascular risk assessment using existing FH information in their electronic medical record.
3. Patients in 12 practices (intervention group) in addition completed a more detailed questionnaire to systematically collect the FH, which included a FH of premature CHD.
4. No patient had previously diagnosed diabetes, CHD, stroke or peripheral vascular disease.
5. Used the JBS2 risk assessment tool [1] to assess cardiovascular risk.
6. The primary outcome measure was the difference between groups in the proportion of participants classified as having a high risk for cardiovascular disease (20% or more over 10 years).

RESULTS

1. Identified 105 (15%) patients as having high risk based on FH.
2. For participants in the intervention group, the percentage of those at high risk increased by 5.1%. In the control group (which considered only the FH initially incorporated in the electronic health record) risk increased by 0.5%. (Difference = 4.6%)
3. The number of participants at high risk in the intervention group increased from 49 to 69 (40%) after the FH from the questionnaire incorporated.
4. About 5% in both groups had a positive FH of CHD in the original electronic record. This increased to 29% in the intervention group.
5. About 50% of participants in each group had no FH of CHD recorded in the original electronic record.
6. Study groups did not differ in any level of anxiety or other secondary outcome measures.
7. Ten smokers in the intervention group quit at 6 months.

DISCUSSION

1. In primary care, adding a self-completed, structured questionnaire to the usual FH increased the number of persons considered to be at high risk for CHD.
2. Being identified as having high risk would justify intensive lifestyle changes and preventive medication.
3. Identifying those at high risk did not increase anxiety.
4. Recording FH in usual primary care practice is limited. Many records do not contain any FH data. And primary care clinicians may not use the FH information available in the usual medical record.

CONCLUSION

Systematically collecting FH increased the proportion of persons identified as having a high cardiovascular risk for further targeted prevention.

Annals Internal Medicine February 21, 2012; 156: 253-62 "Improving Patient Care" Original investigation by the Added Value of Family History in CVD Risk Assessment Study Group (ADDFAM) first author Nadeem Qureshi, University of Nottingham, UK

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1 Go to Google to assess information about the Joint British Societies (JBS2 assessment tool):

The Framingham focuses on atherosclerotic coronary heart disease (**a-CHD**). The JBS2 enlarges the focus to include the whole of atherosclerotic cardiovascular diseases (**a-CVD**) rather than limiting it to a-CHD. JBS2 assesses acute coronary syndromes; stable angina; cerebra-vascular disease (non-hemorrhagic atherosclerotic and hemorrhagic stroke); and transient cerebral ischemia rather than highlighting a-CHD alone.

Updated JBS2 includes risk factors: age; sex; smoking; systolic BP; diastolic BP; ratio of total cholesterol to HDL-cholesterol; blood glucose; left ventricular hypertrophy (on ECG); central obesity; south Asian origin; serum triglycerides. The trial adds FH.

Risk of developing a-CVD over the next 10 years is calculated as 0-9); 10-19% and 20% or over. (Ie, 20% of patients in this category likely will develop the disease within 10 years.)

There are patients who should not have their risk calculated. They are already at high risk:

Known a-CVD; diabetes; hypertension (160/100 and over); smoking; obesity; renal dysfunction; familial hypercholesterolemia; left ventricular hypertrophy.

Patients age 75 and over should be considered at high risk of a-CVD particularly if hypertensive and if they smoke.

Healthy lifestyles should be emphasized for all regardless of risk. The UK guidelines advise drug therapy (eg, aspirin and statins) for those with risks of 20% and over.

Conclusion: Systematically collecting FH increased the proportion of persons identified as having a high cardiovascular risk for further targeted prevention.