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HIGHLIGHTS SEPTEMBER 2002

9-1 EVIDENCE FROM RANDOMIZED TRIALS ON THE LONG-TERM EFFECTS OF HORMONE REPLACEMENT THERAPY

Over 5 years of use by 1000 healthy post-menopausal women HRT was estimated to cause:

In women age 50-59: 6 extra strokes, 6 breast cancers, and 6 extra pulmonary emboli.

Prevent 2 colorectal cancers and 2 fractured femurs.

In women age 60-69: 12 extra strokes, breast cancers, and pulmonary emboli.

Prevent 5 colorectal cancers and 5 fractured femurs.

The increased risk of harms is greater than the benefits. Excess risk over 5 years:

Women age 50-59: 1 per 230 users

Women age 60-69: 1 per 150 users

9-2 HORMONE REPLACEMENT THERAPY AND ASSOCIATED RISK OF STROKE IN POSTMENOPAUSAL WOMEN.

Cardiovascular risks may be greater in the first year of HRT use.

Lower doses of estrogen may be safer.

9-3 A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY WITH WATCHFUL WAITING IN EARLY PROSTATE CANCER

In a select group of generally healthy men mean age 65 with moderately-well, or well-differentiated PC, the study found a statistically significant difference in the risk of death over 6 years due to PC after radical prostatectomy as compared with watchful waiting (surgery – 5%; waiting – 9%).

Local progression and distant metastases were much less common in the surgery group.

No difference in overall mortality.

9-4 QUALITY OF LIFE AFTER RADICAL PROSTATECTOMY OR WATCHFUL WAITING

Assignment of patients to watchful waiting or radical prostatectomy entails different risks, but on average, the choice has little if any influence on well-being and or subjective quality of life after 4 years.

9-5 SURGERY AND THE REDUCTION OF MORTALITY FROM PROSTATE CANCER.

Should all undergo radical prostatectomy? The answer is a categorical “no”.

Should no one be followed by watchful waiting? The answer is a categorical “no”.

In a young man with localized mild- to moderate-PC who is otherwise in good health, surgery performed by an experienced surgeon, is an excellent option. And his subsequent quality of life should be more satisfactory.

9-6 MANAGING ACUTE APPENDICITIS

The simple expedient of close observation and repeated re-evaluation has been shown to reduce the unnecessary exploration rate. The single greatest change in surgical practice has been the widespread introduction of laparoscopy. It has been quickly applied to the problem of acute appendicitis. A systematic review reported that laparoscopic appendectomy halves the number of wound infections, reduces pain,

and shortens hospital stay and time to return to work. This is at a cost of a three-fold increase in the number of postoperative intra-abdominal abscesses.

9-7 WALKING COMPARED WITH VIGOROUS EXERCISE FOR THE PREVENTION OF CARDIOVASCULAR EVENTS IN WOMEN

Walking and vigorous exercise were associated with similar risk reductions.

Both walking and vigorous exercise were associated with substantial reductions in incidence of cardiovascular events among postmenopausal women, irrespective of race, ethnic group, age and body mass index. Prolonged sitting increased risk.

9-8 SPLINTING VS SURGERY IN THE TREATMENT OF CARPAL TUNNEL SYNDROME

Treatment with open carpal tunnel release surgery resulted in better outcomes than treatment with wrist splinting for patients with CTS.

9-8 EFFICACY, TOLERABILITY AND UPPER GASTROINTESTINAL SAFETY OF CELECOXIB FOR TREATMENT OF OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS: Systematic Review

Celecoxib was as effective as other NSAIDS for relief of symptoms of arthritis, and had significantly improved gastrointestinal safety and tolerability even when aspirin was co-administered.

9-10 OBSERVATIONAL STUDY OF UPPER GASTROINTESTINAL HAEMORRHAGE IN ELDERLY PATIENTS GIVEN SELECTIVE CYCLO-OXYGFENASE-2 INHIBITORS OR CONVENTIONAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS.

This population-based observational study found a lower short-term risk of upper gastrointestinal hemorrhage associated with selective COX-2 inhibitors compared with non-selective.

But, risk of hemorrhage in those taking celecoxib was *not* increased compared with non-takers.

9-11 EFFICACY AND SAFETY OF COX-2 INHIBITORS

"At present, it is still difficult to give patients an honest, accurate, and understandable account of the balance between relief of pain and improved function on one hand and the likelihood of serious adverse effects on the other."

More information is required for prescribers to be able to make rational decisions about the use of these agents, particularly in older people in whom co-morbidity is common.

They may be safer, but they are not safe.

9-12 SPONTANEOUS TALKING TIME AT START OF CONSULTATION IN OUTPATIENT CLINIC.

The average patient visiting a doctor in the USA gets 22 seconds for his initial statement, then the doctor takes the lead. Doctors may assume that patients will mess up the time schedule if allowed to talk as long as they wish.

This study asked – How long will patients actually talk, at least initially, if they are not interrupted? How long would it take outpatients to indicate they have completed their story?

Mean talking time was 92 seconds. About 3 out of 4 patients completed their statement within 2 minutes. Few patients talked more than 5 minutes.

9-13 PATIENTS' PERCEPTIONS OF ENTITLEMENT TO TIME IN GENERAL PRACTICE FOR DEPRESSION.

Patients' self-imposed restraint in taking up doctors' time. This has important consequences for the recognition and treatment of depression. Doctors need to have a greater awareness of patients' anxieties about time and should move to allay such anxieties by preemptive reassurance and reinforcing patients' sense of entitlement to time.

9-14 PATIENT'S VIEWS OF THE GOOD DOCTOR

"Technical Skill, Humaneness, Competence, Time For Care, Listening, Involving Patients In Decisions, Communication, Trust, Support, Reassurance" Quite An Order. Nevertheless, "Most doctors are good doctors in the eyes of most patients."

9-15 EFFECTS OF LOSARTAN ON CARDIOVASCULAR MORBIDITY AND MORTALITY IN PATIENTS WITH ISOLATED SYSTOLIC HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY

Therapy based on the angiotensin II blocker, losartan, was more effective than a beta-blocker-based therapy with atenolol in preventing CV morbidity and mortality (especially stroke) in patients with isolated systolic BP and left ventricular hypertrophy.

However, the NNT for one year is over 100. Additional cost is over $400 a year.

9-16 PLASMA NATRIURETIC PEPTIDES FOR COMMUNITY SCREENING FOR LEFT VENTRICULAR HYPERTROPHY AND SYSTOLIC DYSFUNCTION: The Framingham Heart Study

In a large community-based sample, the performance of BNP and ANP for detection of elevated LV mass and LVSD was suboptimal. Natriuretic peptides are of limited usefulness as mass screening tests.

9-17 PEGINTERFERON ALFA-2a PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C VIRUS INFECTION

In patients with chronic hepatitis C, peginterferon alfa-2a once weekly + ribavirin daily offered significantly enhanced sustained virologic responses in all patients regardless of HCV genotype and viral load. The combination was tolerated as well as other regimens.

9-18 FONDAPARINUX VS ENOXAPARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN MAJOR ORTHOPEDIC SURGERY.

In patients undergoing orthopedic surgery, fondaparinux (a factor Xa inhibitor) once daily, starting 6 hours post surgery, showed major benefit over enoxaparin (a low-molecular weight heparin) in reducing DVT at the expense of a slightly increased risk of bleeding.

Fondaparinux may be a valuable addition to anticoagulant therapy.

9-19 PEPTIC-ULCER DISEASE

A review of the remarkable progress in our understanding over the past 20 years.

Many questions answered; more questions arise.

Excess harms over 5 years = one in 230 to one in 150

9-1 EVIDENCE FROM RANDOMIZED TRIALS ON THE LONG-TERM EFFECTS OF HORMONE REPLACEMENT THERAPY

(*This brief article summarizes the risks and benefits of HRT, putting harms and benefits into perspective. This overview may help primary care clinicians advise, and women decide*.)

Four randomized trials included over 20 000 women followed for 5 years. They report the effect of HRT on major, potentially fatal, conditions. Three trials recruited women with previous cardiovascular disease (a high-risk group) and one recruited healthy women. Combined estrogen/progestin was used in 3 trials and estrogen alone in one. Several estrogen-alone trials are pending.

Overall, HRT users had significantly increased incidence of :

Breast cancer, stroke, and pulmonary embolism

And a significantly reduced incidence of:

Colorectal cancer and fracture of neck of femur

No significant change in:

Endometrial cancer or coronary heart disease

There was no significant variation across the trials in the results for any condition.

Over 5 years of use by 1000 healthy post-menopausal women HRT was estimated to cause:

In women age 50-59:

6 extra strokes, 6 breast cancers, and 6 extra pulmonary emboli.

Prevent 2 colorectal cancers and 2 fractured femurs.

In women age 60-69:

12 extra strokes, breast cancers, and pulmonary emboli.

Prevent 5 colorectal cancers and 5 fractured femurs.

The increased risk of harms is greater than the benefits. Excess risk over 5 years:

Women age 50-59:

1 per 230 users

Women age 60-69:

1 per 150 users

Results of randomized trials broadly agree with observational trials regarding risks of breast cancer, colorectal cancer, pulmonary embolism, and fracture.

The risk of venous thromboembolism was greater soon after starting HRT.

Results from older observational trials which suggested a substantially reduced risk of coronary heart disease must now be regarded as severely biased.

The increased risk of stroke is a new finding.

The trials found no change in all-cause mortality. HRT does not have an immediate, substantial, and non-specific effect on mortality.

"These estimates of excess risk provide, at best, a rough guide to the likely change in incidence for these conditions over a 5-year period for typical HRT users in western countries. Individuals who have varying background risks for each disease may assign different weights to their importance, as well as to the relief of menopausal symptoms."

The largest trials to date suggest that HRT does not slow progress of Alzheimer's disease, and has little effect on quality-of-life other than reducing menopausal symptoms. **1**

Lancet September 21, 2002; 360: 942-44 "Rapid review" first author Valerie Beral, Radcliffe Infirmary, Oxford, UK **www.thelancet.com**

Comment:

1 There is no reliable substitute for HRT to prevent menopausal symptoms. They can be very disturbing to some women and no doubt substantially decrease quality-of-life. I believe the data should not discourage primary care clinicians from prescribing HRT to select women who are adequately informed about the risks, which after all, occur in few out of every 1000 patients over 5 years. I believe, further that some of the risks can be substantially lowered by low-dose aspirin and statin drugs as well as by use of lower doses of estrogen. (eg, 0.3 mg *Premarin*)

Women at increased risk of breast cancer, or more fearful of it, may wish to increase surveillance for it. RTJ

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Increased risk only in the first 6 months. Less Common With Lower Doses Of Estrogen.

9-2 HORMONE REPLACEMENT THERAPY AND ASSOCIATED RISK OF STROKE IN POSTMENOPAUSAL WOMEN.

Recent reports suggest that initiation of hormone replacement therapy (**HRT**) has adverse effects on incidence of cardiovascular events, including stroke.

This study assessed the possible relation between HRT and stroke.

Conclusion: There was a transitory increase of stroke in the first 6 months use of HRT.

STUDY

1. Population-based case-control study assessed whether HRT was associated with incidence of stroke.

2. A. Cases: All post-menopausal women enrolled in a health maintenance organization (~ 570 000 enrollees; mean age = 69) who sustained an incident ischemic (n = 726) or hemorrhagic (n = 213) stroke. (Total = 949)

   B. Controls: Randomly selected matched patients without a stroke. (n= 2525)

3. Determined HRT use in both groups. Follow-up = 10 years.

RESULTS

1. Over the follow-up period, after risk factor adjustment, ischemic and hemorrhagic stroke were *not* associated with current use of estrogen with progestin or with estrogen alone, compared with never-use:

   Adjusted odds ratio of ischemic stroke

Never-use	1.00 (Reference)
Current use estrogen + progestin	0.97
Current use estrogen only	0.94
Past use estrogen + progestin	0.90

2. However, the risks of stroke were increased 2-fold during the first 6 months of hormone use.

   Incidence of stroke in the first 6 months of HRT use: Compared with never-users, adjusted odds ratio of stroke in the first six months of HRT use was 1.7.

   (*Note these are small numbers of stroke. Suggestive, not definitive evidence RTJ* .)

3. Over a mean of 7 years use, stroke was *less* common in those taking estrogen equivalent to 0.3 mg conjugated estrogen compared with those taking 0.625 or more:

   Adjusted odds ratio of ischemic stroke.

0.3 mg	1.00 (referent)
0.625	1.44
> 0.625	2.41

DISCUSSION

1. Overall, in this case-control study, ever use of estrogen, past use of estrogen, current use of estrogen, and current use of estrogen/progestin were *not* associated with risk of stroke after adjustment for cardiovascular risk factors.

2. But, incidence of both ischemic and hemorrhagic stroke appeared to increase transiently in the first 6 months of use.

3. Use of lower doses of estrogen (0.3 mg) appeared to be safer regarding incidence of stroke than higher doses. This is in agreement with previous studies.

4. The authors admit the small numbers of subjects was a weakness of the study.

CONCLUSION

The transitory increase in risks of stroke associated with initiation of HRT merits further investigation.

Archives Int Med September 23, 2002; 162: 1954-60 Original Investigation, first author Rozenn N Lemaitre, University of Washington, Seattle. **www.archinternmed.com**

Comment:

I do not consider this article as being definitive in any way. I abstracted it for 2 reasons:

1) Because of the suggestions that cardiovascular risks may be greater in the first year of HRT use.

2) Lower doses of estrogen may be safer.

Many women are now fearful of using HRT because of the recent adverse publicity. HRT is still the only really effective remedy for menopausal symptoms. I believe primary care clinicians will do their menopausal patients great service by prescribing it. It may be prudent to recommend low-dose aspirin to prevent cardiovascular events at least in the 1st year of use. And to use lower than the usually recommended doses of estrogen. I believe many postmenopausal women will benefit as much from 0.3 mg as from 0.625 mg. RTJ

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In Support Of Surgery In A Select Group

9-3 A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY WITH WATCHFUL WAITING IN EARLY PROSTATE CANCER

Radical prostatectomy has become widely used for early prostate cancer (**PC**). Benefit has not been adequately documented. Systematic overviews of observational studies lack reliable data to support any specific recommendations.

This 6-year randomized trial compared outcomes from watchful waiting with radical prostatectomy.

Conclusion: Surgery was associated with fewer deaths from PC. No difference in overall survival

STUDY

1. Followed over 650 men (mean age = 65; all under age 75) with clinical stage T1b, T1c, and T2.

All had newly diagnosed adenocarcinoma of the prostate. All were in a generally good physical condition and mental status expected to permit a radical prostatectomy and a follow-up of at least 10 years.

All cancers were in early stages, either clinically inapparent, or confined to the prostate.

Some were diagnosed by needle biopsy performed because of an elevated prostate-specific antigen. (Had to be less than 50 ug/mL)

The tumor had to be well differentiated or moderately well differentiated. Men with poorly differentiated PC were excluded.

Those diagnosed by an extended biopsy protocol were accepted if less than 25% of the tumor was Gleason grade 4, and less than 5% was Gleason grade 5.

None had metastasis seen on bone scan. None had evidence of upper urinary tract obstruction.

2. Randomized to: 1) watchful waiting, or 2) radical prostatectomy.

3. Primary end point = death due to PC. Secondary endpoints = overall mortality, metastasis-free survival, and local progression.

4. Follow-up a median of 6 years.

RESULTS

1. Outcomes over a median of 6 years:

	Surgery (n=348)	Watchful waiting (n = 347)	Absolute Difference	NNT(to benefit one over 6 y)
Death (all causes)	53 (15%)	62 (18%) [2]	3%	33
Death due to PC	16 (5%)	31 (9%)	4%	25

2. Outcomes at 8 years

Death due to PC	7%	14%	7%	14
Local progression	19%	61%	42%	2.4
Distant metastases	13%	27%	14%	7
Overall mortality	28%	22%	6%	16 *

(* *Favors ww; not statistically significant. The differences in favor of surgery in PC death, local progression, and distant metastases are impressive. RTJ*)

3. Overall, 116 in the watchful waiting group (25%) and 80 (17%) in the surgery group received hormonal treatment.

4. The cumulative hazard for death from PC increased over time with a difference favoring surgery. Absolute difference at 5 years = 2%; at 8 years = 6%.

DISCUSSION

1. The study found a statistically significant difference in the risk of death over 6 years due to PC after radical prostatectomy as compared with watchful waiting (surgery – 5%; waiting – 9%)

2. All who died of PC had clinically verified metastases, and all received palliative hormonal therapy. There was no significant difference in overall mortality.

3. The authors stress that results were obtained in a group of men with well-differentiated or moderately well differentiated PC.

4 Surgical removal of the primary tumors will prevent spread and provide cure only in men with localized disease at diagnosis. This effect will be tangible beyond 5 years after surgery.

5 Any benefit from surgery must be weighed against the side effects of surgery – erectile

dysfunction and urinary leakage (*and surgical mortality*). And the side effects of watchful waiting – obstructed voiding and possibly fecal leakage. The level of distress varies considerably among subjects. Men give different priorities to survival and to avoidance of therapy-induced distress.

6. The choice in early PC is complex. Patients need complete information about alternatives. Physicians need to know about individual patients' concerns.

8. Outcomes may differ with elapse of more time.

CONCLUSION

Radical prostatectomy significantly reduced disease-specific mortality. There was no significant difference between watchful waiting and surgery in terms of overall survival.

NEJM September 12, 2002; 347: 781-89 Original investigation by the Scandinavian Prostate Cancer Group Study Number 4, First author Lars Holmberg, University Hospital, Uppsala, Sweden **www.nejm.org**

Comment:

1 Note this was a select group of men with PC – localized, lower grade tumors; relatively healthy men.

"Choice of therapy had little if any influence on well-being and or subjective quality of life."

9-4 QUALITY OF LIFE AFTER RADICAL PROSTATECTOMY OR WATCHFUL WAITING

(*This study examined outcomes in a subset of patients entered in the preceding trial)*

A man with newly diagnosed localized prostate cancer (**PC**) faces a frustrating choice. He can defer treatment until symptoms appear, or undergo major surgery (or radiotherapy). He may also receive hormonal therapy or undergo castration. The choice may influence survival and risk of adverse effects.

This study compared symptoms and self-assessment of quality of life between watchful waiting and radical prostatectomy in men with localized PC. (*See previous articles.)*

Conclusion: On average, the choice had little, if any, influence on well being after a mean follow-up of 4 years.

STUDY

1. Randomly assigned and followed 326 men (mean age = 64) with localized PC.
2. Detailed questionnaire obtained information about various physical and psychological changes in quality of life.

RESULTS

1. Outcomes at mean of 4 years:	Surgery (%)	Waiting (%)
Erectile dysfunction	80	45
Urinary leakage	49	21
Urinary obstruction	28	44

2. Bowel function, anxiety, depression, well-being, and subjective quality of life were similar in the 2 groups.

DISCUSSION

1. Men who underwent surgery had a higher prevalence of erectile dysfunction, and urinary leakage, but a lower prevalence of obstructive voiding problems.
2. The data were consistent with no difference between the 2 groups regarding psychological symptoms, well-being, subjective quality of life.
3. There was no data concerning the extent to which surgeons attempted to preserve erectile nerves.
4. The study leaves little doubt that bladder emptying function is improved by radical prostatectomy.
5. There was no evidence of disturbance in bowel function. Radiotherapy is undoubtedly associated with this risk.
6. "We cannot say that radical prostatectomy is better than watchful waiting for all men with localized prostate cancer." "Each man must judge for himself."

CONCLUSION

Assignment of patients to watchful waiting or radical prostatectomy entails different risks, but on average, the choice has little if any influence on well-being and or subjective quality of life after 4 years.

NEJM September 12, 2002; 347: 790-96 Original investigation, first author Gunnar Steineck, Karolinska Institute, Stockholm, Sweden. **www.nejm.org**

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"Clear evidence that surgical treatment reduces the risk of death from prostate cancer"

9-5 SURGERY AND THE REDUCTION OF MORTALITY FROM PROSTATE CANCER.

(*This editorial comments and expands on the preceding articles*.)

More than ever, it is important to establish definitively whether aggressive management of localized PC reduces rate of death from PC. "Is cure necessary in those in whom it may be possible, and is cure possible in those in whom it is necessary."

The preceding landmark study provides the first concrete answer. After 8 years, radical prostatectomy reduced PC-specific deaths by about 7% (NNT = 14) "For the first time, and after a surprisingly short follow-up period, we have clear evidence that surgical treatment reduces the risk of death from prostate cancer"

The frequency of distant metastases was reduced by 14%. (NNT = 7)

There was no statistically significant difference in overall mortality at 8 years. However, an excess risk of death from PC persists for up to 25 years after diagnosis. Another study from Sweden reported that about 2/3 of

conservatively treated men who lived longer than 10 years eventually died of PC. The editorialist believes that with longer follow-up the difference in mortality between conservative treatment and surgery will increase.

Over recent years surgical techniques have improved. The incidence of surgery-related impotence and incontinence has declined markedly in the hands of expert surgeons.

Nevertheless, a man evaluating treatment strategies for localized PC must recognize that all options can jeopardize his quality of life.

How should we now advise patients?

Should all undergo radical prostatectomy? The answer is a categorical "no".

Should no one be followed by watchful waiting? The answer is a categorical "no".

There have always been and always will be many men who are best served by watchful waiting. (Eg, those who are too aged or too ill.) If the cancer progresses to the point where it causes symptoms, there are many ways to palliate. Furthermore, in the era of prostate specific antigen screening, up to 20% of men with non-palpable disease have small tumors and may be candidates of watchful waiting. For patients with larger tumors, definitive treatments should be considered.

In a young man with localized PC who is otherwise in good health, surgery performed by an experienced surgeon, is an excellent option. And his subsequent quality of life should be more satisfactory. In an older patient with coexisting conditions, radiation therapy is the best option and has the fewest side effects. Radiation technology has improved in the past decade. No trial has yet determined if radiation reduces rate of death from PC.

Physicians must fully inform men with PC about their options and help them select the best specialist for the treatment they choose.

NEJM September 12, 2002; 347: 839-40 Editorial by Patrick C Walsh, Johns Hopkins Hospital, Baltimore MD.
www.nejm.org

Comment:

Primary care clinicians must know the track record of their surgical consultants in order to advise patients regarding surgery. RTJ

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"Clinical Judgment Still Has A Place" Laparoscopy Comes To The Forefront.

9-6 MANAGING ACUTE APPENDICITIS

Despite more than 100 years experience, accurate diagnosis is still evasive. Avoiding perforation and subsequent complications must be weighed against removal of a normal appendix in patients with other causes of abdominal pain. "Negative" appendectomies have a rate as high as 20%. "This is not a trivial problem."

The simple expedient of close observation and repeated re-evaluation has been shown to reduce the unnecessary exploration rate.

What about ultrasound? One study reported the only difference was a slightly earlier operation. The negative appendectomy rate remained high. Ultrasound is highly dependent on the clinician who performs the examination. It will be of value only when performed regularly by the same clinician, and in the context of careful, frequent clinical evaluation. Ultrasound has no place as a screening tool, but may be helpful in some patients where the diagnosis is doubtful.

What about helical computer tomography? This has a greater potential to show alternative pathology, and may reduce the rate of negative appendectomies. Availability is a problem. It should be reserved for patients in whom there is a suspicion of an alternative diagnosis.

The single greatest change in surgical practice has been the widespread introduction of laparoscopy. It has been quickly applied to the problem of acute appendicitis. A systematic review reported that laparoscopic appendectomy halves the number of wound infections, reduces pain, and shortens hospital stay and time to return to work. This is at a cost of a three-fold increase in the number of postoperative intra-abdominal abscesses. This risk may be reduced as the experience of the laparoscopist grows. Laparoscopy comes into its own when there is diagnostic doubt. A special case is that of young women in whom the diagnostic dilemma is often greatest and in whom endoscopic surgery can be performed if tubo-ovarian pathology is found. The rate of removal of a normal appendix may approach zero.

Laparoscopy has a definite place in women, and in others where there is diagnostic uncertainty. It is best avoided when suspicion of perforation is strong.

Clinical judgment still has a place. The experienced clinician must be prepared to re-evaluate doubtful cases at regular intervals. There is no case for rushing to operate in marginal cases.

BMJ September 7, 2002; 325: 505-06 Editorial, first author Irving S Benjamin, Kings College, London, UK.
www.bmj.com/cgi/content/full/7363/505

Comment:

I believe the advice to perform repeated evaluations in doubtful cases will be most helpful to primary care clinicians and their patients. This means every few hours, not the next day. RTJ

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Keep Walking As Briskly And As Long As You Can

9-7 WALKING COMPARED WITH VIGOROUS EXERCISE FOR THE PREVENTION OF CARDIOVASCULAR EVENTS IN WOMEN

Data on the association of physical activity among women and minority racial and ethnic groups are sparse. Newer guidelines suggest at least 30 minutes of moderate-intensity physical activity for most or all days of the week. Older guidelines suggested vigorous endurance exercise.

Most Americans perform neither.

The role of time spent in sedentary behavior, such as sitting, in predicting risk remains relatively unexplored.

This study compared the roles of walking and vigorous exercise in the prevention of cardiovascular events in a large diverse cohort of postmenopausal women.

Conclusion: Both walking and vigorous exercise were associated with reductions in incidence of cardiovascular events. Prolonged sitting increased risk.

STUDY

1. Prospectively examined: walking, vigorous exercise, total physical-activity score. and hours spent sitting as predictors of total cardiovascular events among over 73 000 postmenopausal women age 50 to 79.
2. All were free of diagnosed cardiovascular disease and cancer at baseline.
3. Questionnaire asked for detailed data about physical activity. Divided participants into quintiles of total metabolic equivalent hour (MET-Hr per week) categories of walking and vigorous activity.
4. Follow-up = 6 years.

RESULTS

1. Documented 345 newly diagnosed cases of coronary heart disease (**CHD**), and 1551 total cardiovascular disease (**CVD**) events.
2. An increasing physical-activity score had a strong, graded inverse association with risk of both CHD and CVD.
3. Results were similar between white and black women.
4. Age-adjusted relative risk according to quintiles of increasing energy expenditure:

Coronary heart disease	1.00, 0.73, 0.69, 0.68, 0.47
Total cardiovascular disease	1.00, 0.89, 0.81, 0.78, 0.72

5. Risks of cardiovascular disease over 6 years according to quintiles of MET-hours per week:

Quintile	1	2	3	4	5
Total exercise					
Total MET-hr/wk (median)	0	4.2	10	17	33
CHD (No. of cases)	92	70	68	70	45
Total CVD (No. of cases)	396	342	304	281	228
Walking					
Total MET-hr/wk (median)	0	1.5	4	8	17
CHD (No. of cases)	133	64	52	47	48
Total CVD (No. of cases)	550	322	249	236	194
Vigorous exercise					
Total min strenuous exercise /wk	0	30	90	140	210
CHD (No. of cases)	269	35	13	14	14
Total CVD (No. of cases)	1220	125	78	61	67

6. Walking and vigorous exercise were associated with similar risk reductions.

7. Results did not substantially vary according to race, age, and body mass index.
8. A brisker walking and fewer hours spent sitting predicted lower risk. As walking speed increased – casual, brisk, very brisk – risk was reduced.
9. Relative risk of CVD between hours sitting and lying down increased as the time increased. Among women who spent 12 to 15 hours per day lying down or sleeping relative risk was 1.4 compared with more active women. Among women who spent at lest 16 hours per day sitting, relative risk of CVD was 1.7 compared with women who spent less than 4 hours per day sitting.

DISCUSSION

1. In this cohort of post-menopausal women, both walking and vigorous exercise were associated with substantial reeducations in cardiovascular events.
2. Prolonged time spent sitting or lying down predicted increased risk.
3. Results were similar among white and black women, among different age groups, and categories of body mass index.
4. This study lends support to the current federal guidelines that endorse moderate-intensity exercise for at least 30 minutes daily.
5. "Evidence of the applicability of these guidelines to non-white women is of particular importance because of the high prevalence of sedentary lifestyles, obesity and related conditions minority populations."
6. The strong dose-response gradient observed between physical activity and reduced risk and the consistency of the findings across strata of age, race, and body-mass index lend credence to a causal relationship in women.
7. Physical activity has also been linked to improvement in emotional well being.

CONCLUSION

Both walking and vigorous exercise were associated with substantial reductions in incidence of cardiovascular events among postmenopausal women, irrespective of race, ethnic group, age and body mass index. Prolonged sitting increased risk.

NEJM September 5, 2002; 716-25 Original investigation by the Women's Health Initiative Observational Study, first author JoAnn E Manson, Harvard Medical School, Boston Mass. **www.nejm.org**

An editorial in this issue by Paul D Thompson, Hartford Hospital Hartford CT comments:

The highest quintile of energy expenditure in the study (24 MET-hours per week) is roughly equivalent to walking at 3 miles per hour for an hour each day.

As compared with the least active women (45 minutes walking per week), the most active (7 hours per week) had 4 to 8 fewer cardiovascular events for 1000 women over 3 years. This is comparable to the benefit observed when healthy women are treated with statin drugs over 5 years.

Comment:

Practical Pointers has abstracted many articles which send this same message. It is worth repeating.

Keep walking as long as you can!

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Surgery Better

9-8 SPLINTING VS SURGERY IN THE TREATMENT OF CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome (**CTS**) is the most common entrapment neuropathy. It is caused by compression of the median nerve at the wrist. It can be treated by wrist splints and corticosteroid injections, or both. Open carpal tunnel release is the preferred surgical treatment.

There is no consensus on the most effective treatment.

Study compared short-term and long-term efficacy of splinting vs surgery for relieving symptoms of CTS.

Conclusion: Surgery was more effective.

STUDY

1. Randomized, controlled trial followed 147 outpatients. All had clinical CTS confirmed electrophysiologically.
2. Randomized to: wrist splinting during the night for at least 6 weeks, or 2) open release surgery.

   The splint was custom made. It immobilized the wrist in a neutral position. (*Both extension and flexion of the wrist can increase pressure on the nerve*. *RTJ*) Surgery consisted of release of the transverse carpal ligament
3. Main outcome (intention to treat) = general improvement and number of nights waking up due to symptoms.
4. Final follow-up assessment = 18 months.

RESULTS

1. Surgery was more effective:

   General improvement at 3 months 80% vs 54% (Absolute difference = 26%; NNT one patient = 4)

   At 18 months, success rates increased to 90% in the surgery group vs 75% in the

   splinting group. However, by that time, 41% of the splint group had also received surgery.
2. Adverse effects in both groups were generally mild and of short duration. One patient

   who underwent surgery developed reflex sympathetic dystrophy.

DISCUSSION

1. Surgery was more effective than splinting at 3, 6, 12, and 18 months.
2. A large number of patients originally assigned to splinting crossed over to surgery.
3. The least severe and the most severe cases were probably not included in this trial.

   These patients and their physicians typically have a strong preference for splinting or surgery.
4. The American Academy of Neurology recommends treatment of CTS with non-invasive

options (eg, splinting) first and surgery only if the non-invasive approach fails. A splint might be used while a patient waits for surgery.

5. A recent randomized controlled trial reported that splinting offered more relief than no treatment.

CONCLCUSION Treatment with open carpal tunnel release surgery resulted in better outcomes than treatment with wrist splinting for patients with CTS.

JAMA September 11, 2002; 288: 1245-51 Original investigation, first author Annette A M Gerritsen, Vrije University Medical Center, Amsterdam, Netherlands. **www.jama.com**

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Safer Than Other NSAIDs; But Not Safe!

9-9 EFFICACY, TOLERABILITY AND UPPER GASTROINTESTINAL SAFETY OF CELECOXIB FOR TREATMENT OF OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS: Systematic Review

About 2500 deaths occur each year in the UK each year as a result of use of NSAIDs.

Will use of COX-2 inhibiting, COX-1 sparing drugs increase safety?

This study determined efficacy, safety and tolerability of celecoxib (*Celebrex*)

Conclusion: Celecoxib is as effective as other NSAIDs, and has improved safety and tolerability.

STUDY

1. Systematic review of 9 randomized trials comparing use of celecoxib with other NSAIDs in over 15 000 patients. Use was continued for at least 12 weeks.
2. Compared effectiveness, tolerability safety, and withdrawal rates.
3. Compared safety of celecoxib alone with celecoxib + aspirin.

RESULTS

1. Celecoxib was equally effective as other NSAIDs for relief of symptoms.
2. Tolerability at 12 weeks:

Celecoxib vs placebo:	Celecoxib	Placebo	Absolute diff	NNT (To withdraw one patient)
Withdrawal due to any adverse effect	9%	6%	3%	33
Withdrawal due to any GI adverse effect	3%	2%	1%	100
(Withdrawals more common than with placebo.)				
Celecoxib vs other NSAIDs				
Withdrawals due to any adverse effect	8%	10%	2%	50
Withdrawals due to any GI adverse effect	3%	6%	3%	33
(Withdrawals less common than with other NSAIDs.)				

3. Tolerability at 24 weeks:

Withdrawals due to bleeding, symptomatic	Celecoxib	NSAIDs	Absolute difference
ulcers, perforation, and obstruction	0.76%	1.23%	0.47%
(Celecoxib is safer, but far from safe!)			

4. What is the impact of celecoxib added to prophylactic aspirin?

Ulcers detected by routine endoscopy at 12 weeks:	Celecoxib	NSAIDs	Absolute difference
No prophylactic aspirin	6%	23%	17%
Prophylactic aspirin	12%	26%	14%

(Celecoxib + aspirin safer than NSAIDs + aspirin; but not safe!)

CONCLUSION

Celecoxib was as effective as other NSAIDS for relief of symptoms of arthritis, and had significantly improved gastrointestinal safety and tolerability even when aspirin was co-administered.

BMJ September 21, 2002; 325: 619-23 First author Jonathan J Deeks, Institute of Health Sciences, Headington, Oxford, UK. **www.bmj.com/cgi/content/full/7365/619**

Comment:

The article states that the National Institute for Clinical Excellence (UK) recommends that celecoxib should be withheld from aspirin users. Concomitant use of aspirin is safer in those taking celecoxib than in patients taking other types of NSAIDs. However, it is not safe! The combination led to ulceration in 12% of patients taking the combination for 12 weeks vs 6% when used alone.

Is this is a significant clinical observation for the many elders with arthritis who will be taking low-dose prophylactic aspirin? RTJ

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Short-Term Use Of Celecoxib Just As Safe As Placebo In Causing Hemorrhage?

9-10 OBSERVATIONAL STUDY OF UPPER GASTROINTESTINAL HAEMORRHAGE IN ELDERLY PATIENTS GIVEN SELECTIVE CYCLO-OXYGFENASE-2 INHIBITORS OR CONVENTIONAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS.

This observations study compared rate of upper gastrointestinal hemorrhage among elderly patients taking selective NSAIDs (COX-2) with those taking non-selective NSAIDs.

Conclusion: COX-2 were associated with lower short-term risk of hemorrhage.

STUDY

1. Observational cohort study identified over 43 000 patients over age 65 who were taking a variety of NSAIDs: [non-selective NSAIDS; diclofenac (*Generic*) plus misoprostol (*Cytotec*); rofecoxib (*Vioxx*); celecoxib (*Celebrex*) and a randomly selected cohort of over 100 000 subjects not taking NSAIDs.]
2. All patients were NSAID-naïve and had started NSAID use in the years 2000 and 2001.
3. Main outcome = rates of hospital admissions for upper gastrointestinal hemorrhage, as adjusted for potential confounders.

RESULTS

1. Relative to controls, there was an increased short-term risk of hemorrhage for users of:

Non-selective NSAIDs	Rate ratio =	4
Diclofenac plus misoprostol		3
Rofecoxib		1.9
Celecoxib		1.0

2. The NNT to cause hemorrhage = 403 for non-selective NSAIDs; 592 for diclofenac-misoprostol; 1389 for rofecoxib. (Users of rofecoxib had a significantly reduced risk of hemorrhage compared with the other 2 groups.)
3. But, risk of hemorrhage in those taking celecoxib was not increased compared with non-takers. (Rate ratio = 1.0) (The risk of rofecoxib was higher that that for celecoxib.).
4. "The differences in unobserved covariates between rofecoxib and celecoxib groups are probably minimal and would not explain the difference in upper gastrointestinal hemorrhage between the two drugs."

CONCLUSION

This population-based observational study found a lower short-term risk of upper gastrointestinal hemorrhage for selective COX-2 inhibitors compared with non-selective.

BMJ September 21, 2002; 325: 624-27 Original investigation, first author Muhammad Mamdani, Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada. **www.bmj.com/cgi/content/full/7365/624**

Comment:

Studies vary in reporting adverse effects. I doubt that celecoxib is just as safe as placebo or non-takers. Others report that combined misoprostol-NSAID is just as safe as COX-2 inhibitors.

None is completely safe. RTJ

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Numerous Questions Remain.

9-11 EFFICACY AND SAFETY OF COX-2 INHIBITORS

(*This editorial comments and expands on the preceding articles*.)

In addition to the adverse upper gastrointestinal effects NSAIDs can also have adverse effects on the lower bowel, lungs, kidneys, and cardiovascular system.

Previous large trials have been reported. One large trial was criticized on the grounds of design of the study. Another study comparing rofecoxib with naproxin reported an excess of cardiovascular events among the rofecoxib group. (*Subsequent studies blamed the increase in thrombotic effects on naproxin. RTJ*)

Numerous questions remain: Are the costs of these new drugs justified? Are they really safe? Are they appropriate for patients with a history of upper gastrointestinal symptoms? Are they better than co-prescription of a proton pump inhibitor with the traditional NSAIDs?

The preceding articles answer some questions. The newer COX-2 were safer regarding upper gastrointestinal adverse effects. But there was no information on long term sequelae of death, and cardiovascular events. The follow-up period was short. Data on benefits and harms on non-gastrointestinal effects was lacking and remains controversial.

"At present, it is still difficult to give patients an honest, accurate, and understandable account of the balance between relief of pain and improved function on one hand and the likelihood of serious adverse effects on the other."

More information is required for prescribers to be able to make rational decisions about the use of these agents, particularly in older people in whom co-morbidity is common.

BMJ September 21, 2002; 325: 607-08 Editorial by Roger Jones, Guy's, King's and St Thomas's School of Medicine, London, UK **www.bmj.com/cgi/content/full/7365/607**

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Usually Less Than 2 Minutes.

9-12 SPONTANEOUS TALKING TIME AT START OF CONSULTATION IN OUTPATIENT CLINIC.

The average patient visiting a doctor in the USA gets 22 seconds for his initial statement, then the doctor takes the lead. Doctors may assume that patients will mess up the time schedule if allowed to talk as long as they wish.

This study asked – How long will patients actually talk, at least initially, if they are not interrupted? How long would it take outpatients to indicate they have completed their story?

The study entered a sequential cohort of outpatients at a department of internal medicine. Over 300 patients visiting 14 doctors were included. Doctors were asked to time the patient's uninterrupted first statement from beginning until they indicated they had completed the statement. Doctors facilitated listening by nodding, echoing, or other indicators of attention. They were advised to interrupt the patient only if she talked more than 5 minutes.

Mean talking time was 92 seconds. About 3 out of 4 patients completed their statement within 2 minutes. Only 7 patients talked more than 5 minutes. In all these cases, the doctor felt the patients were continuing to give important information and should not be interrupted.

No other socio-demographic variable (education, income, civil status, type of employment and sex) had a significant influence on spontaneous talking time. Age was an exception. Older patients talked somewhat longer.

Doctors do not risk being swamped by their patients' complaints if they listen until the patient indicates the list of complaints is complete. Two minutes of listening time should be possible even in a busy practice. This will be sufficient for nearly 80% of patients, even for difficult patients. Select groups might need even less time.

BMJ September 28, 2002; 325: 682-83 Original investigation, first author Wolf Langewitz, University Hospital, Basle, Switzerland**. www.bmj.com/cgi/content/full/7366/682**

Comment:

A proper introduction to the consultation is "What are your health concerns today?" Then sit back and listen. When the patient stops, ask "Anything else?"

Non-verbal clues during the period of doctor-silence will be helpful. RTJ

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Patients Self-Imposed Limits in Their Consultation Time

9-13 PATIENTS' PERCEPTIONS OF ENTITLEMENT TO TIME IN GENERAL PRACTICE FOR DEPRESSION.

Shortage of time in primary care practice consultations is widely acknowledged to constrain the quality of care. (*An average slot of 5-8 minutes per patient is allotted in the UK. It may be somewhat longer in the USA. RTJ*) Shortage of time is a major obstacle to the realization of a more patient-oriented practice.

Little is known about patients' perceptions of the adequacy or quality of time spent with their primary care clinicians.

This study investigated patients' perceptions of their entitlement to time in consultations.

Conclusion: Patients themselves self-imposed restraints in taking up the doctors' time.

STUDY

1. Recruited a sample of 32 general practice patients with recently diagnosed mild to moderate depression.
2. Interviewed them to assess their perceptions of entitlement to time in the consultation.

RESULTS

1. An intense sense of time pressure and a *self-imposed* rationing of time in consultations were key concerns among the patients.
2. Anxiety about time affected their freedom to talk about their problems.
3. Patients took upon themselves part of the responsibility for managing time in the consultation to relieve the burden they perceived their doctors to be working under.
4. There was often a mismatch between patients own sense of time entitlement and the doctors' capacity to respond flexibly and constructively in offering extended consultation time when this was necessary. There was often a disparity between patients' sense of time shortage and the amount of time their doctors were willing to and able to provide.
5. Patients valued time to talk and would often have liked more, but they did not necessarily associate length of time with quality.
6. The impression the doctor gave in handling time in the consultation sent strong messages

about legitimizing the patients' illness and their decision to consult.

DISCUSSION

1. "It is the patients rather than doctors who take the initiative in rationing consultation time."
   In effect, the patients in this study often failed to capitalize on the resource that was on offer, feeling unable to use the time their doctors were willing to provide. Consequently, they left with questions unasked and issues unexplored.
2. This inhibits the development of more patient-centered and concordant consultations. Paradoxically, it may be patients' concern to keep within their perceived time entitlement that causes time to be "wasted" in ineffective and superficial consultations from which they derive little benefit. Patients with depression feel under such acute pressure of time that they are often inhibited from fully disclosing their problems.
3. Despite their anxieties about time, patients quite commonly reported receiving more time than they expected, especially during the first consultation for depression. When patients presented with severe distress, some doctors managed to find up to an hour or more to extend the consultation. Patients were deeply appreciative of this kind of response.
4. The scope for flexible and creative use of time still obtains (though doubtless reinforcing the stress of other patients in the waiting room). There is a wide range of consultation times.
5. The quality of patients' relationships with their doctors is fashioned over a series of consultations, it is important to take account of the extension of time across these consultations as well as what happens in discrete episodes. "Perhaps the preoccupation the average length of consultation is misplaced. Doctors' ability to allocate time flexibly and according to individual need is what is really critical."
6. Doctors should be more aware of patients' anxieties about time and allay these anxieties by providing pre-emptive reassurance as a means of reinforcing patients' sense of entitlement to consultation time.

CONCLUSION

Patients' self-imposed restraint in taking up doctors' time has important consequences for the recognition and treatment of depression. Doctors need to have a greater awareness of patients' anxieties about time and should move to allay such anxieties by preemptive reassurance and reinforcing patients' sense of entitlement to time.

BMJ September 28, 2002; 325: 687-90 Original investigation, first author Kristian Pollock, Keele University, Keele, UK. **www.bmj.com/cgi/content/full/7366/687**

Comment:

I had not thought of this aspect of time allocation before. Primary care clinicians can improve the patient-oriented relationship by recognizing the patients' concerns about consultation time. Reaching an understanding about time is important to patient and clinician alike. I believe most primary care clinicians and their patients can and should reach a mutually satisfactory of allocation of time to be devoted to subsequent consultations, not necessarily to the first. RTJ

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"Technical Skill, Humaneness, Competence, Time For Care, Listening, Involving Patients In Decisions, Communication, Trust, Support, Reassurance" Quite An Order.

9-14 PATIENT'S VIEWS OF THE GOOD DOCTOR

(BMJ devoted this issue to commentary on "What's a good doctor and how do you make one"?)

"Most doctors are good doctors in the eyes of most patients." Despite media's fixation with medical errors, doctors come high in the popularity stakes in almost any poll Furthermore, familiarity tends to breed contentment, not contempt. Patients who have recent experience of medical care tend to give higher, less critical ratings than patients whose experience is less current.

The profession does, however, attract criticism from patients—sometimes deservedly so.

For years, patient groups have drawn attention to the deficiencies of the traditional model and its tendency to demean and disempower patients. Early anti-paternalists emphasized self education and self help as a way of redressing the power imbalance between doctors and patients. But, "It is often forgotten that most health care is self care". Too often the manner of health care delivery serves to increase dependency and undermine coping skills.

What do patients want?

Both interpersonal relations and technical skill are rated high. One systematic review reported the most highly rated aspect of primary care was "humaneness". This was followed by "competence/accuracy", "patients involvement in decisions", and "time for care", "having a doctor who listens and does not hurry me". Provision for information and opportunities for participation feature highly in most studies of patient satisfaction. "Patients increasingly expect to participate in decisions about their care. Failures in communication and incorrect assumptions about patients' preferences are surprisingly common."

The patient wants to be an informed and empowered consumer. The doctor may prefer a long-term relationship with a docile patient.

Patients' ratings of doctors' interpersonal skills are strongly related to trust. Trust is very important, but it does not equate to blind faith. Sick patients need empathy, support, and reassurance. They also need honest information about their condition, options for treatment, and clinicians who listen to their concerns and preferences.

Doctors who are concerned that more patient-empowerment might mean greater burdens of their time should consider ways of sharing the load. Giving information, helping patients to think through their preferences, or training them in active self-management can be done by nurses, counselors,
and fellow patients. [1]

Doctor's lack of inclination, or time, or both, means that patients' desire for information, education, and empowerment is inadequately provided for in modern medical practice. Patients want to trust their doctors, but trust has to be earned. Treat patients as grown ups, answer questions clearly and honestly, listen to their views, and involve them in decisions.

BMJ September 28, 2002; 325: 668-69 Editorial by Angela Coulter, Picker Institute Europe, Oxford UK.
www.bmj.com/cgi/content/full/7366/668

Comment:

This theme has been repeatedly addressed in different ways in the primary care literature.
Patients feel differently about the medical profession and their personal physicians. A paradox exists. They may criticize the profession, but when asked about their personal physician they express satisfaction and confidence. Since all medical care is one-on-one, I can't explain the contradiction.

1 As the editorialist mentions, primary care doctors need to spread their burdens, many of which can be assumed and actually performed more efficiently by non-MD professionals. I believe primary care practice will more and more evolve into a team effort rather than solo. We need help. RTJ

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One Patient In One Hundred Benefited From Losartan Each Year. Extra cost = $420

9-15 EFFECTS OF LOSARTAN ON CARDIOVASCULAR MORBIDITY AND MORTALITY IN PATIENTS WITH ISOLATED SYSTOLIC HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY. A Losartan Intervention for Endpoint Reduction (LIFE) Substudy

Left ventricular hypertrophy (**LVH**) is a manifestation of preclinical cardiovascular disease (**CVD**) and a strong, independent risk factor for CVD complications in patients with hypertension. Reversal of LVH may improve prognosis. Angiotensin II is associated with development of LVH.

This study tested the hypothesis that, in patients with isolated systolic BP and LVH, the angiotensin II blocker losartan (*Cozaar*) would improve outcomes better than the beta-blocker atenolol (*Tenormin*). Losartan may be especially effective in reversing LVH in patients with isolated systolic hypertension.
It may confer protective benefits over and above BP lowering.

Conclusion: Losartan-based therapy was superior to atenolol-based therapy.

STUDY

1. Double-blind, randomized, parallel-group study entered over 1300 patients (mean age = 70).

2. All had systolic hypertension (160-200 mmHg), and diastolic pressure < 90. (Mean = 174/83)
3. All had LVH by ECG criteria based on QRS duration and voltage. (*See p 1492*) This subset of hypertensive patients is at higher risk of cardiovascular complications than those without LVH.
4. Randomized to: 1) losartan (50 mg) or atenolol (50 mg) . Used hydrochlorothiazide as a secondary agent in both arms. Losartan and atenolol were increased to 100 mg, and a third drug was added if needed to reduce systolic BP to < 140
5. Main outcome = composite endpoint of cardiovascular death, stroke, or myocardial infarction.
6. Follow-up – 4.7 years.

RESULTS

1. Fewer than 10% of patients were controlled by the original dose of 50 mg. Most required an increase in dose of losartan or atenolol, and addition of hydrochlorothiazide. . About 20% required three drugs.
2. Over 25% in both groups discontinued therapy. Drug-related withdrawals – 7% for losartan; 13% for atenolol.
3. BP was reduced equally in both groups. (- 28/9)
4. Outcomes per 100 patient years:

	Losartan (%)	Atenolol (%)	Absolute difference	NNT(losartan to benefit one/y)
Main composite outcome	2.5	3.5	1%	100
Cardiovascular mortality	0. 87	1.69	0.82%	122
Stroke	1.06	1.89	0.83%	120
New onset diabetes	1.26	2.02	0.75%	133
Total mortality	2.12	3.02	0.90%	111

5. No difference in reduction of myocardial infarction.
6. Losartan regimen was associated with a greater decrease in LVH. Voltage reduction of 3.9 mm vs 2.3 mm
8. And was better tolerated. Drug related withdrawals – losartan = 15%; Atenolol = 22%

DISCUSSION

1. This confirms the hypothesis that losartan is more effective than atenolol in reversing LVH.
2. This study "showed that losartan treatment resulted in a 25% reduction in the main outcome, the predefined primary composite endpoint of CV death, stroke, and myocardial infarction vs atenolol." **1**
3. This occurred without any difference in the degree of BP reduction.
4. "A further reduction in stroke with losartan-based therapy, as demonstrated in this study, is an important finding because stroke is a major cause of death and disability." **1**
5. Losartan regimen was better tolerated and resulted in fewer withdrawals.
7. It is not known if losartan is superior to diuretic or calcium-blocker regimens.

CONCLUSION

Losartan-based antihypertensive therapy was more effective than an atenolol-based therapy in preventing CV morbidity and mortality (especially stroke) in patients with isolated systolic BP and left ventricular hypertrophy.

JAMA September 25, 2002; 288: 1491-98 Original investigation by the Losartan Intervention for Endpoint Reduction (LIFE) Substudy, First author Sverre E Kjeldsen, University of Michigan, An Arbor.
www.jama.com

Comment:

Study supported by Merck.

1 Authors and journal publishers continue to cite relative risks in both the their abstracts and discussions. There is a good bit of "spin" placed on the results by the authors "The main outcome was reduced by 25% with losartan compared with atenolol." " A further 40% reduction in stroke with losartan-based therapy . . . is an important finding." This is misleading.. Likely the 25% reduction and the 40% reductions will be quoted by drug advertisements.

In absolute terms, 100 patients needed to be treated for one year to prevent one main-outcome event. And 133 NNT for one year to prevent one stroke.

The withdrawal rate over 5 years was 25% to 33%. Withdrawals by patients in primary care would be much higher.

Costs over 5 years; Cozaar ~ $500; Atenolol (generic) ! $80.

Is inconvenience and costs of this long-term treatment in primary care justified? Some fully informed concerned patients may wish to use the losartan regimen despite the inconvenience and cost.

Cardiovascular morbidity and mortality could be further reduced by adding aspirin and statin drug therapy. This would further reduce benefits of losartan vs atenolol. RTJ.

JAMA September 25, 2002; 288: 1491-98 Original investigation by the Losartan Intervention for Endpoint Reduction (LIFE) Substudy, First author Sverre E Kjeldsen, University of Michigan, An Arbor.
www.jama.com

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Not a Good Screening Test for LVH and LVSD

9-16 PLASMA NATRIURETIC PEPTIDES FOR COMMUNITY SCREENING FOR LEFT VENTRICULAR HYPERTROPHY AND SYSTOLIC DYSFUNCTION: The Framingham Heart Study

Asymptomatic left ventricular systolic dysfunction (**LVSD**) is a treatable precursor of congestive heart failure (**HF**). Left ventricular hypertrophy (**LVH**) also may be a risk factor. Screening tools for early detection may be clinically helpful.

Brain natriuretic peptide (**BNP**) and the N-terminal component of pro-atrial natriuretic peptide (**ANP**) have been reported useful in determining symptomatic LVSD and LVH.

This study examined usefulness of these peptides as screening tools.

Conclusion: The peptides were of limited usefulness in screening for LVH and LVSD.

STUDY

1. Community-based prospective cohort study entered over 3100 participants from the Framingham Heart Study who attended routine examinations 1995-98. Patients with a history of heart failure were excluded.
2. All underwent echocardiography:
   - Determined left ventricular internal dimensions, thickness of LV walls, and calculated left ventricular mass.
   - Estimated left ventricular ejection fraction. [Defined as normal >55%; borderline 51%-55%; mildly reduced 41% -50%; moderately diminished 31% - 40%; severely impaired < 30%]
   - Elevated let ventricular mass was defined as greater than or equal to the sex-specific 90th percentile for the entire sample.
   - LVSD defined as a fractional shortening of less than 29%.
3. Measured natriuretic peptides by an immuno-radiometric assay.
4. Used a statistical analysis to compare various levels of BNP and ANP with echocardographic LSVD. (*Those more expert in statistical analysis than I am, see the text. RTJ*)

RESULTS

1. Overall, 70 (2%) subjects had moderate to severe LVSD.
2. BNP levels were in general higher in individuals with elevated LV mass and in subjects with LVSD.
3. But, various determinations of BNP and ANP concentrations identified less than 1/3 of subjects who had elevated LV mass and LVSD.

DISCUSSION

1. BNP discrimination limits (cutpoints) have limitations. They vary considerably. This is in part related to referral bias (inclusion of symptomatic and asymptomatic subjects, post-myocardial infarction patients, varying definitions of LVSD, and different NP assays.
2. In the case on NP screening for asymptomatic LVSD or elevated LV mass, because of the size of the screened population and the low prevalence of the condition, the false-positive rate of the screening test must be low to reduce the burden of expensive follow-up tests.
3. The performance of NPs for detection of LV mass and LVSD in the community was only fair

in men and poor in women. The low sensitivity combined with the low prevalence of LVD may offset any potential usefulness of screening.

CONCLUSION

In a large community-based sample, the performance of BNP and ANP for detection of elevated LV mass and LVSD was suboptimal. Natriuretic peptides are of limited usefulness as mass screening tests.

JAMA September 11, 2002; 288: 1252-59 Original investigation, first author Ramachandran S Vasan, National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham Mass.

www.jama.com

Comment:

I believe NPs are useful in patients with clinically suspected congestive heart failure. If the NP is within normal range, CHF is unlikely. If high, CHF is more likely. RTJ

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Making Progress in Treating Hepatitis C

9-17 PEGINTERFERON ALFA-2a PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C VIRUS INFECTION

The current standard treatment for chronic hepatitis C is ribavirin plus an interferon. The mechanism of action of ribavirin is speculative. Many patients, especially those with more resistant genotypes do not respond to these agents.

Two types of pegylated interferon (interferons combined with polyethylene glycol; alfa-1a and alfa-2a) have been developed. They have different pharmokinetic and chemical properties. Both have demonstrated superior efficacy to non-pegylated interferons. Alfa-1a has an extended serum half life and provides constant viral suppression for seven days. This allows once-a-week dosing and enhanced clinical efficacy. Alfa-1 is given three times weekly.

This study asked: Which interferon is best treatment when combined with ribavirin? Is peginterferon alfa-2a alone effective?

Conclusion: Combined pegylated interferon alfa-2a + ribavirin was more effective.

STUDY

1. Followed over 1100 patients with chronic hepatitis C. All had at least 2000 copies of HCV-RNA per milliliter of serum by polymerase chain reaction, elevated alanine aminotransferase levels, and a liver biopsy consistent with chronic hepatitis.
2. Randomized to: 1) peginterferon alfa-2a once weekly + ribavirin once daily, 2) pegylated interferon alfa-2b + daily ribavirin, and 3) weekly pegylated interferon alfa-2a alone.

3. Defined sustained virological response as absence of detectable HCV RNA at 24 weeks after cessation of therapy.
4. Drugs were administered for 48 weeks.

Results

1. Significantly more patients who received peginterferon alfa-2a + ribavirin had a sustained virologic response: 1) 56%; vs 2) 44%: vs 3) 29%.
2. More patients with a high viral load and those with HCV genotype 1 (more likely to be resistant) responded to peginterferon alfa-2a + ribavirin
3. Overall safety and withdrawals were similar between groups. Incidence of influenza-like symptoms and depression was higher in the peginterferon alfa-2a + ribavirin group.
4. If there was no virologic response at 12 weeks, there was almost no chance of a sustained response.

DISCUSSION

1. Peginterferon alfa-2a + ribavirin was more effective than the other 2 regimens.
2. Ability to predict response after 12 weeks of therapy is a useful clinical tool.

CONCLUSION

In patients with chronic hepatitis C, peginterferon alfa-2a once weekly + ribavirin daily offered significantly enhanced sustained virologic responses in all patients regardless of HCV genotype and viral load. The combination was tolerated as well as other regimens.

NEJM September 26, 2002; September 26, 2002; 347: 975-82 Original investigation, first author Michael W Fried, University of North Carolina, Chapel Hill. **www.nejm.org**

Comment:

How long does the response last and what is the effect on long-term prognosis? How do primary care clinicians decide which patients should be treated? Who should be referred to a hepatologist for treatment?

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A Possible Improvement in Anticoagulant Therapy.

9-18 FONDAPARINUX VS ENOXAPARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN MAJOR ORTHOPEDIC SURGERY.

Fondaparinux is the first of a new class of synthetic antithrombotic agents that act through specific inhibition of activated factor X (Xa). It is devoid of any direct inhibition of thrombin generation (factor IIa). Inactivation of factor Xa results in effective inhibition of thrombin generation.

Fondaparinux is 100% bioavailable when administered subcutaneously. It does not undergo metabolism. It exhibits a linear pharmokinetic profile with little variability between subjects. The half maximum plasma concentration is reached within 25 minutes, and the dose-independent elimination half-life is 15 hours. This allows once-daily administration.

Orthopedic surgery remains a high-risk condition for venous thromboembolism (**VTE**). How does fondaparinux compare with low-molecular-weight heparin (**LMWH**) in reducing risk in orthopedic surgery patients? This meta-analysis compared the two for efficacy and safety.

Conclusion: Fondaparinux provided a major benefit over enoxaparin.

STUDY

1. Meta-analysis of 4 double-blind trials in over 5200 patients (mean age = 68) undergoing elective knee surgery and surgery for hip fracture.
2. Compared fondaparinux (2.5 mg subcutaneously daily) with the LMWH enoxaparin (*3 different preparations*) 30 mg twice daily or 40 mg once daily. Fondaparinux was started 6 hours after surgery.
3. Primary efficacy outcome defined as VTE up to day 11 detected by bilateral venography, documented symptomatic deep vein thrombosis, or pulmonary embolism.

RESULTS

1. Fondaparinux was superior in preventing VTE:

Outcome at day 11:	Fondaparinux	Enoxaparin	Absolute difference	NNT (benefit one patients)
Incidence of VTE	7%	14%	7%	14
Proximal deep vein thrombosis	1.3%	2.9%	1.6%	62

2. Benefit was consistent across all types of surgery and all subgroups.
3. Incidence of major bleeding was higher in the fondaparinux group (2.7% vs 1.7%) NNT (harm one patient = 100)
4. Incidence of bleeding (fondaparinux vs enoxaparin) leading to death (0 vs 1 patient), reoperation (12 vs 8 patients) or occurring in a critical organ (0 vs 1) did not differ statistically between groups.

CONCLUSION

In patients undergoing orthopedic surgery, fondaparinux once daily, starting 6 hours post surgery, showed major benefit over enoxaparin in reducing DVT at the expense of a slightly increased risk of bleeding.

Archives Int Med September 9, 2002; 1833-40 Meta-analysis, first author Alexander G G Turpie, Hamilton Health Sciences corporation, Hamilton, Ontario, Canada. **www.archinternmed.com**

Comment:

I abstracted this article to acquaint myself with this new anticoagulant. More experience is needed before admitting into treatment of medical conditions in primary care. Watch for developments. RTJ

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H Pylori, NSAIDs, Both, and Neither. Clearer Understanding; More Questions Raised.

9-19 PEPTIC-ULCER DISEASE

(*This review article presents points to refresh memory, as well as some new observations.)*

Pathophysiology of *H pylori* ulcers:

***Duodenal ulcers* (DU)**

DU can be effectively treated by acid suppression. This strongly suggests that DU is largely a disease of acid hyper-secretion. But this is only a part of the equation. It is the imbalance between acid load and the buffering capacity of the duodenum that leads to DU formation.

Evidence implicates *H pylori* in the development of **DU**. The mechanism is not clear. Increased basal and stimulated acid output has been associated with *H pylori*-associated DU. The net effect is an increase in acid production and duodenal acid load. But there is a substantial overlap in acid production between patients with DU and controls.

Patients with DU have impaired bicarbonate secretion in the proximal duodenum in response to acidification of the duodenum. This impairment seems specific for DU patients. Eradication of *H pylori* returns bicarbonate secretion to normal.

Gastric metaplasia of the duodenal bulb develops in response to increased acid load. It is a prerequisite for the *H pylori* colonization which leads to duodenitis and DU.

***Gastric ulcers* (GU)**

Long before discovery of *H pylori*, patterns of gastritis associated with duodenal ulcers were known to be different from those associated with gastric ulcers. DU is associated with an antrum-predominant gastritis; GU with a corpus-predominant gastritis. The latter is associated with low acid output, gastric atrophy, and adenocarcinoma.

Gastric acid has a role in the distribution of *H pylori* colonization. Acid suppression with a proton pump inhibitor results in a proximal shift of *H pylori* in the stomach. Colonization of *H pylori* is increased in the corpus. This leads to inflammation and further reduction in acid secretion.

H pylori-associated GU has a predilection for the antrum-corpus junction (the transitional zone). This is where the antral-type mucosa abuts the acid-secreting mucosa of the corpus. It is a region of dense colonization of *H pylori.* This results in maximum atrophy and intestinal metaplasia, especially in

patients with low acid output. Intense inflammation in this region disrupts mucosal defense, and might account for the preferential location of GU at this junction.

The pendulum seems to swing from enthusiasm for the idea that peptic ulcer is an infectious disease to a more cautious view that *H pylori* has a causative role in peptic ulcer disease.

Treatment of *H pylori* ulcers:

Treatments have evolved substantially. The early bismuth-metronidazole-tetracycine regimen led to side effects which impaired compliance. Effective first-line regimens of proven efficacy now consist of a proton-pump inhibitor (or ranitidine bismuth citrate) plus 2 antibiotics (eg, amoxicillin and metronidazole).given twice daily for 7 to14 days. [*List on table 1 p 935. A new 4-drug regimen is listed on p 936*]

The rapid emergence of resistance has now substantially reduced efficacy (especially for clarithromycin and metronidazole). Post-treatment testing for cure has been recommended – eg, stool antigen test. A positive test 7 days after treatment indicates failure.

NSAID-induced gastric injury:

The widespread use of NSAIDs and aspirin has led to an epidemic of ulcer complications. In the USA, NSAIDs account for about 25% of all reported adverse drug effects. Thousands of patients with arthritis die each year from GI toxicity. Although there is evidence that highly selective COX-2 inhibitors reduce GI toxicity, whether this translates into clinical benefits is unclear. Whether *H pylori* infection modifies the risk of NSAID ulcers has generated conflicting data.

***Topical injury*:**

Acidic NSAIDs can directly damage the gastric epithelium due to the intracellular accumulation of the drugs in an ionized state (ion trapping). However, enteric-coated preparations, pro-drugs, and systemic administration do not reduce frequency of GI ulcerations. This implies a minor role for topical injury. **(***I still choose enteric-coated aspirin for long-term prophylaxis. If there is, as the article states, local toxicity from NSAIDs, it would make sense to avoid this aspect of toxicity. RTJ)*

NSAIDs act by inhibiting prostaglandin synthesis. There is substantial evidence that the ulcerogenic effect of NSAIDs correlates with their ability to suppress prostaglandins.. Endogenous prostaglandins regulate mucosal blood flow, epithelial cell proliferation, epithelial restitution, and mucus and bicarbonate secretion. Inhibition of prostaglandin synthesis probably weakens gastric mucosal defenses. But, inhibition of prostaglandin synthesis is not the only mechanism for the ulcerogenic effects of NSAIDs. They may adversely affect nitric oxide synthesis. Recent attention has focused on nitric oxide (NO) in increasing gastric mucosal blood flow, stimulating mucus secretion, and inhibiting neutrophil adherence.

Role of acid:

Gastric acid exacerbates NSAID injury by disrupting the basement membrane, producing deep injury, affecting platelet aggregation, and impairing ulcer healing.

One important research issue is whether the combination of misoprostol and an acid suppressor would provide better gastric protection than either drug alone.

Current issues in prevention of NSAID ulcers:

Strategies to reduce gastric toxicity of NSAIDs have been investigated: 1) concurrent treatment with histmine-2 receptor antagonist s (**H2RAs**), misoprostol, and proton pump inhibitors (**PPIs**) , and 2) substitution of conventional NSAIDs with selective COX-2 inhibitors. PPIs are better than standard H2RAs, but no better than misoprostol in prevention of gastric ulcer. High dose H2RAs afford only a slight reduction in risk of gastric ulcer.

The gastric-sparing effect of COX-2 inhibitors is (*partially*) offset by concomitant low-dose aspirin.

Prophylactic antiulcer agents:

Misoprostol, proton pump inhibitors, and histamine blockers:

All doses of misoprostol significantly reduce risk of endoscopic ulcers. High-dose (800 ug daily) is the only prophylactic agent documented to reduce ulcer complications.

Standard doses of H2RAs reduce risk of duodenal ulcer but not gastric ulcer.

Both PPIs and double-dose H2RAs are effective in reducing risk of duodenal and gastric ulcers, and are better tolerated than misoprostol. However, there are inconsistencies in reports about efficacy of PPIs and high dose H2RAs in prevention of NSAID-associated ulcers. The efficacy of PPIs is affected by *H pylori* status. Acid suppression by PPIs may be augmented by presence of *H pylori.* (Ie, a protective effect.)

COX-2 inhibitors:

These agents have been marketed as effective anti-inflammatory agents with no gastric toxicity. Two large studies have shown that highly selective COX-2 reduce risk of ulcer complications compared with non-selective NSAIDs. Acid suppression would still be needed for patients with arthritis who need aspirin prophylaxis for cardiovascular disease. "Whether selective inhibition of COX-2 has any clinical impact on ulcer healing remains unknown."

***H pylori.* and NSAIDs:**

Is there interaction between *H pylori* and NSAIDs? Controversy remains. Several findings suggest that suggest that *H pylori* and NSAIDs are largely independent risk factors. Pathogenesis of the two differs. Some studies suggest that *H pylori* infection might alleviate NSAID injury. However, a meta-analysis of studies of *H pylori*-NSAID association reported that the infection increased risk of NSAID ulcer and increased risk of bleeding compared with non-infected NSAID-users. Eradication of *H pylori* before starting chronic NSAID use in NSAID-naïve patients substantially reduces risk of risk of ulcer. Conversely, curing the infection in NSAID users does not reduce risk of ulcer. Thus many issues remain unsolved.

Non- NSAID, non-H pylori ulcers:

Prevalence of *H pylori* infections has declined in the USA, Among ulcer patients up to 25%-47% of patients have been free of the infection. Recurrences are common in duodenal ulcer patients after cure. It is proposed that the increased prevalence of non- NSAIDs, non-*H pylori* ulcers is apparent because the numbers of *H pylori* associated ulcers is falling due to the decreasing prevalence of the infection. Thus the *H pylori* test-and-treat strategy for dyspepsia might no longer be cost effective because the predictive value of serologic testing will fall. An increasing number of patients might require acid-suppressive therapy to prevent ulcer recurrence.

Unsolved issues:

Why do only a few patients with *H pylori* antral gastritis develop duodenal ulcers?

Is *H pylori* infection relevant in the era of COX-2 inhibitors?

Will eradication of the infection confer long-term protection against aspirin-related ulcer complications?

The ideal treatment for *H pylori* has yet to be identified. Resistance to antimicrobials is increasing. Ulcer complications associated with NSAID use continue to increase in elderly patients.

Aspirin-related ulcer complications are expected to rise since low-dose use is increasing. Non- NSAIDs, non-*H pylori* ulcer might determine our approach to peptic ulcer disease in the future.

Lancet September 21, 2002; 360: 933-41 "Seminar", review article, first author Francis K L Chan, Chinese University of Hong Kong, China. **www.thelancet.com**

Comment:

I abstracted this article in detail to understand the remarkable advances made in knowledge about peptic ulcer disease in the past 20 years. . Our understanding of the pathogenesis has undergone a sea-change. However, with more understanding come more unanswered questions. RTJ

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