

PRACTICAL POINTERS

FOR PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JULY 2002

THE NEW DEFINITION OF MYOCARDIAL INFARCTION

HEART PROTECTION OF CHOLESTEROL LOWERING WITH SIMVASTATIN

RISKS AND BENEFITS OF ESTROGEN PLUS PROGESTIN IN HEALTHY POSTMENOPAUSAL WOMEN

CARDIOVASCULAR DISEASE OUTCOMES DURING 6.8 YEARS OF HORMONE THERAPY

NON-CARDIAC OUTCOMES DURING 6.8 YEARS OF HORMONE THERAPY

ASSOCIATION OF HEALTH LITERACY WITH DIABETES OUTCOMES.

METFORMIN: An Update

RAPID MEASUREMENT OF B-TYPE NATRIURETIC PEPTIDE IN THE DIAGNOSIS OF HEART FAILURE.

B-TYPE NATRIURETIC PEPTIDE – A Window to the Heart

EXERCISE IN PEOPLE WITH FIBROMYALGIA

DEBRIDEMENT AND LAVAGE FOR OSTEOARTHRITIS OF THE KNEE

IS PLACEBO SURGERY UNETHICAL?

POLYMYALGIA RHEUMATICA AND GIANT-CELL ARTERITIS

BETA-BLOCKER THERAPY AND SYMPTOMS OF DEPRESSION, FATIGUE, AND SEXUAL DYSFUNCTION

THE VALUE OF INFLAMMATION FOR PREDICTING UNSTABLE ANGINA

CONTACTS WITH VARICELLA AND PROTECTION AGAINST HERPES ZOSTER IN ADULTS

COMPARATIVE EFFICACY OF INSECT REPELLENTS AGAINST MOSQUITO BITES

JAMA, NEJM, BMJ, LANCET

ARCHIVES INTERNAL MEDICINE

ANNALS INTERNAL MEDICINE

www.practicalpointers.org

PUBLISHED BY PRACTICAL POINTERS, INC.

EDITED BY RICHARD T. JAMES JR. MD

400 AVINGER LANE, SUITE 203

DAVIDSON NC 28036 USA

rjames6556@aol.com

HIGHLIGHTS JULY 2002

7-1 THE NEW DEFINITION OF MYOCARDIAL INFARCTION

In 2000, the European and American Cardiology Societies published a new definition of AMI which for the first time included troponins. According to the definition, 1) elevated levels of enzymes (CK-MB or troponin I or T), with 2) either symptoms or ECG changes suggestive of ischemia constitute an AMI.

Application of new criteria for diagnosis of AMI resulted in a substantial increase in the number of patients diagnosed with AMI.

7-2 MRC/BHF HEART PROTECTION STUDY OF CHOLESTEROL LOWERING WITH SIMVASTATIN IN 20 536 HIGH-RISK INDIVIDUALS.

Lowering LDL with simvastatin produced substantial benefits in reduction of cardiovascular events in a wide range of high-risk patients, irrespective of their initial cholesterol levels.

Benefits appeared to be largely independent of, and hence additional to, those of all other treatments being used by participants.

The benefits in reducing risk of stroke should resolve any uncertainty about the effects of statins on the risk of stroke.

It has been suggested that there might be a threshold of LDL below which lowering would not further reduce risk. This study demonstrated unequivocally that there is no threshold. Lowering LDL from 116 to 78 reduced vascular events over 5 years, similar to the reduction in events following lowering from 134 to 96. "If a threshold exists it is a LDL lower than 77 mg/dL and a total cholesterol below 135."

7-3 RISKS AND BENEFITS OF ESTROGEN PLUS PROGESTIN IN HEALTHY POSTMENOPAUSAL WOMEN

Among a large cohort of healthy postmenopausal women, overall health risks slightly exceeded benefits from use of combined estrogen/progestin for an average of 5 years. (Overall, 19 more adverse effects per 10 000 persons per year.)

Combined HRT should not be used for primary prevention of chronic diseases.

7-4 CARDIOVASCULAR DISEASE OUTCOMES DURING 6.8 YEARS OF HORMONE THERAPY (Heart and Estrogen/progestin Replacement Study Follow-up (HERS II)

HRT did not reduce risk of cardiovascular events in a group of women with established coronary heart disease. Neither was there an *increase* in risk

7-5 NON-CARDIAC OUTCOMES DURING 6.8 YEARS OF HORMONE THERAPY (The HERS II Follow-up Study)

Treatment with estrogen plus progestin in older women with coronary disease was associated with an increase in rates of venous thromboembolism and biliary tract surgery.

7-6 ASSOCIATION OF HEALTH LITERACY WITH DIABETES OUTCOMES.

Two thirds of patients in this sample who had a high school education or less, had inadequate health literacy.

Among primary care patients with type 2 diabetes, inadequate health literacy was independently associated with poorer glycemic control and higher rates of retinopathy. Inadequate health literacy contributes to the disproportionate burden of diabetes-related problems among disadvantaged populations. (*This large subset of patients is not included in randomized, controlled trials. Therefore primary care clinicians must treat these individuals empirically. RTJ*)

7-7 METFORMIN: AN UPDATE

In treatment of type 2 diabetes, metformin has an excellent safety profile. It is effective as monotherapy and in combination with other drugs. It does not promote weight gain and may even cause weight reduction. It appears to have substantial benefit on lipid metabolism, clotting factors, and platelet function. It improves vascular relaxation and probably reduces BP. These cardio-protective benefits are in addition to its anti-hyperglycemic effect

7-8 RAPID MEASUREMENT OF B-TYPE NATRIURETIC PEPTIDE IN THE EMERGENCY DIAGNOSIS OF HEART FAILURE.

B-TNP is included in the European guidelines for diagnosis of chronic HF. It offers valuable predictive information and assessment of severity of the disease. It will improve the ability of clinicians to differentiate patients with dyspnea due the HF from dyspnea due to other causes in the acute care setting. The diagnostic information can be immediately available.

7-9 B-TYPE NATRIURETIC PEPTIDE – A Window to the Heart

Measurement of B-type natriuretic peptide is valuable in the diagnosis of congestive heart failure. It parallels the severity of the congestive heart failure. It can be measured rapidly and accurately at the point of care. It can be used to confirm the diagnosis of congestive heart failure; to measure the severity of left ventricular compromise; to quantify the functional class; to estimate the prognosis and predict future cardiac events, including sudden death in patients with cardiomyopathy; and to evaluate efficacy of treatment.

7-10 PRESCRIBED EXERCISE IN PEOPLE WITH FIBROMYALGIA

Prescribed, graded aerobic exercise was effective in improving symptoms of fibromyalgia. It is simple, cheap, and potentially widely available. Compliance with the protocol was poor.

7-11 DEBRIDEMENT AND LAVAGE FOR OSTEOARTHRITIS OF THE KNEE

“Numerous uncontrolled, retrospective case series have reported substantial pain relief after arthroscopic lavage or arthroscopic debridement for osteoarthritis of the knee.” “This study provides strong evidence that arthroscopic lavage with and without debridement is *not* better than, and appears to be equivalent to a placebo procedure in improving knee pain and self-reported function.” The study has also shown the great potential for a placebo effect of surgery.

7-12 IS PLACEBO SURGERY UNETHICAL?

The editorialist states that we should not confound the ethics of clinical research with the ethics of clinical care. The randomized, controlled trial is not a form of individualized medical therapy. It is a scientific tool for evaluating treatments in groups of research participants with the aim of improving the care of patients in the future. Clinical trials are *not* designed to promote the medical best interests of enrolled patients. Indeed, they often expose them to risks that are not outweighed by known potential medical benefits. “The use of placebo surgery must be evaluated in terms of the ethical principles appropriate to clinical research, which are not identical to the ethical principles of clinical practice.”

7-13 ”POLYMYALGIA RHEUMATICA AND GIANT-CELL ARTERITIS”

Recognizable and treatable. Devastating if neglected. A review of points of interest, both old and new.

7-14 BETA-BLOCKER THERAPY AND SYMPTOMS OF DEPRESSION, FATIGUE, AND SEXUAL DYSFUNCTION

Beta-blocker therapy, compared with placebo, was *not* associated with substantial risk of depression, fatigue and sexual dysfunction. These small risks should be put in the context of the documented benefits of beta-blockers.

7-15 THE VALUE OF INFLAMMATION FOR PREDICTING UNSTABLE ANGINA

Morphologically, atherosclerosis is an inflammatory disease.

“Active” coronary disease is clearly associated with evidence of inflammation, both systemically and at the level of the arterial wall. Elevated levels of fibrinogen (an acute-phase reactant) were independently associated with future coronary events. Increased levels of markers of inflammation (eg, cytokines, adhesion molecules, and C-reactive protein) predict future cardiovascular events.

Statin drugs, which reduce risk of coronary events, also reduce circulating inflammatory markers independently of their cholesterol-lowering effect.

Coronary angiography is not particularly useful in identifying the inflamed atherosclerotic plaques that are prone to produce clinical events. Acute myocardial infarction is often a consequence of coronary stenosis which is mild on angiography. Persons with an increased risk of acute coronary events are likely to have many vulnerable plaques throughout the coronary circulation. Plaque modification may be best modulated by systemic means (eg, statins; diet).

“The current challenge remains the identification of persons with vulnerable atherosclerotic plaques”

7-16 CONTACTS WITH VARICELLA OR WITH CHILDREN AND PROTECTION AGAINST HERPES ZOSTER IN ADULTS

Re-exposure to varicella-zoster virus via contact with children seemed to protect latently infected adults against HZ.

This suggests that vaccination of the elderly might protect against HZ.

7-17 COMPARATIVE EFFICACY OF INSECT REPELLENTS AGAINST MOSQUITO BITES

Only DEET products offered long-lasting protection after a single application. Currently available non-DEET repellants cannot be relied on to provide prolonged protection in environments where mosquito-borne diseases are a substantial threat. DEET has a remarkable safety record

Troponin determinations extend the diagnosis to many more patients

7-1 THE NEW DEFINITION OF MYOCARDIAL INFARCTION

Acute myocardial infarction (**AMI**) has been variously defined by means of clinical, electrocardiographic, and laboratory criteria. The old WHO definition required 2 of 3 criteria: 1) ischemic symptoms, 2) ECG changes consistent with ischemia, and 3) enzyme elevations (usually CK-MB).

In 2000, the European and American Cardiology Societies published a new definition of AMI which for the first time included troponins. According to the definition, 1) elevated levels of enzymes (CK-MB or troponin I or T), with 2) either symptoms or ECG changes suggestive of ischemia constitute an AMI.

The inclusion of troponins was based on a large body of evidence showing that an elevated troponin correlates with pathologically proved myocardial necrosis.

This objectives of this study were to address issues: 1) Does the new definition influence the number of patients diagnosed as AMI? 2) Is there a difference in prognosis between patients diagnosed by the two criteria?

Conclusion: Yes to both. .

STUDY

1. Followed over 450 consecutive patients (mean age 65) admitted with suspected AMI.
2. Patients with suggestive symptoms and elevated cardiac enzymes were divided into 2 groups:
 - 1) Group A: symptoms of ischemia, and/or new ECG changes (ST-elevation or left bundle branch block), and elevated peak CK-MB, and
 - 2) Group B: symptoms of ischemia, and an elevated troponin with a normal peak CK-MB, and without ECG changes. Group B would not have been diagnosed as AMI by the old criteria. They constitute additionally diagnosed patients.

RESULTS

1. Fifty one additional patients were diagnosed as AMI by the new criteria. (Additional 11%)
2. Patients in group B were older women with increased co-morbidities.
2. In-hospital events (reinfarction, heart failure, shock, and mortality) were similar between groups.
3. At 6 months, mortality was higher in group B (16.3% vs 5.9%).

DISCUSSION

1. The new criteria detected about 10% additional patients with AMI. The old criteria would have missed 51 of 450 individuals who had an AMI. The new criteria can identify patients with AMI who are likely to be missed by the previous diagnostic criteria or, at best, were labeled as unstable angina.
2. The new criteria did not miss the diagnosis of any patient who was diagnosed as AMI by the old criteria.
3. The new criteria identified patients with more co-morbid conditions leading to a higher 6-month mortality.
4. The new criteria will allow physicians to tailor specific treatments that may decrease mortality.
It is likely that the new criteria will lead to more aggressive therapy

CONCLUSION

Application of new criteria for diagnosis of AMI resulted in a substantial increase in the diagnosis of AMI.

Comment:

Troponins have been termed “perfect biomarkers”.

=====

“There is no definite “threshold” below which a lower concentration is not associated with lower risk.”

Simvastatin benefited regardless of presenting lipid levels.

7-2 MRC/BHF HEART PROTECTION STUDY OF CHOLESTEROL LOWERING WITH SIMVASTATIN IN 20 536 HIGH-RISK INDIVIDUALS.

A positive relationship exists between risk of coronary disease and LDL-cholesterol levels. The relationship extends well beyond the range currently seen in Western populations. “There is no definite “threshold” below which a lower concentration is not associated with lower risk.”

The absolute size of the risk reduction produced by lowering LDL-cholesterol may be determined more by individuals’ overall risk of cardiovascular disease than by their initial blood lipid concentrations. Thus, the benefits of treatment may be greatest in those, who as a consequence of their previous medical history (occlusive arterial disease or diabetes) or other factors such as age, are at greatest risk. (*Eg, two groups patients have the same initial LDL levels, say 140 mg/dL. One has diabetes, the other does not. Lowering LDL to 100 in both will reduce risk of future cardiovascular events to a greater extent in the individuals with diabetes.*)

This study assessed the long-term effects of cholesterol-lowering therapy on mortality and major morbidity in a wide range of patients. It included large numbers of persons at high risk and involved a substantial LDL-reduction maintained for several years.

Conclusion: Lowering LDL with simvastatin produced substantial benefits in reduction of cardiovascular events in a wide range of high-risk patients, irrespective of their initial LDL levels.

STUDY

1. Followed over 20 000 adults (age 40-80).
2. All had non-fasting total cholesterols of over 135 mg/dL. All were considered to be at substantial 5-year risk of death from coronary disease because of past history of CHD, occlusive disease of non-coronary arteries, or diabetes. Males over age 65 with treated hypertension were also included. (*Ie, a secondary prevention trial.*)
3. Randomized to 1) 40 mg simvastatin daily, or 2) placebo.
4. Primary outcomes = overall mortality, and fatal or non-fatal cardiovascular events.
5. Follow-up = mean of 5 years.

RESULTS

1. Total cholesterol levels fell by 46 mg/dL and LDL-cholesterol fell by 38 mg/dL compared with placebo.

2. Outcomes at 5 years:	Simvastatin	Placebo	Absolute difference	NNT(over 5 y to benefit 1)
All cause mortality	12.9%	14.7%	1.8%	55
Coronary deaths	5.7%	6.9%	1.2%	83
Non-fatal MI or coronary death	8.7%	11.8%	3.1%	32
Stroke	4.3%	5.7%	1.4%	71
First occurrence of any event	19.8%	25.2%	5.4%	18

3. Proportional reductions in risk did not appear to be materially influenced by the pretreatment lipid levels:

First major vascular event associated with presenting lipid levels:

	Absolute reduction in events	NNT(over 5 years to benefit 1)
Total cholesterol (mg/dL)		
Presenting level 230		
Treatment level 184	5.2%	19
Presenting level 192		
Treatment level 146	5.4%	18
<i>(This assumes a 46 mg/dL reduction.)</i>		
LDL-cholesterol		
Presenting level 134		
Treatment level 96	5.2%	19
Presenting level 116		
Treatment level 78	4.6%	21

(This assumes a 38 mg/dL reduction.)

(Ie, simvastatin just as beneficial when it lowered total cholesterol from 192 to 146 as when it was lowered from 230 to 184. Reducing LDL-cholesterol was just as beneficial when lowered from 134 to 96 as when lowered from 116 to 78. Ie, benefit was similar regardless of the initial cholesterol levels. This surprised me. I would have believed that there would be greater benefit when the levels were initially high, simply because the risks are higher at the higher levels. RTJ)

4. Benefits were evident in smokers, those with hypertension, and in those not taking aspirin, beta-blockers or ACE inhibitors. Benefits were also evident in older persons and women.

5. Benefits of simvastatin were additional to other cardioprotective treatments.

6. During the first year the reduction in major vascular events was not significant. Subsequently, it was highly significant. *(Ie, the lag period has been reported in several studies. RTJ)*

7. Adverse effects: Levels of alanine aminotransferases were measured at each follow-up. Few were found elevated. Those allocated to simvastatin showing no significant risk of liver enzyme elevations compared with placebo patients. Annual excess risk of myopathy was about 1 in 10 000.

(Simvastatin was very safe. RTJ)

DISCUSSION

1. Lowering LDL-cholesterol with a statin produced a substantial reduction in the incidence of major vascular events in a much wider range of high-risk individuals than previously shown.
2. Benefits appeared to be largely independent of, and hence additional to, those of all other treatments being used by participants.
3. The benefits in reducing risk of stroke should resolve any uncertainty about the effects of statins on the risk of stroke.
4. It has been suggested that there might be a threshold of LDL below which lowering would not further reduce risk. This study demonstrated unequivocally that there is no threshold, Lowering LDL from 116 to 77 reduced vascular events by about one quarter, similar to the reduction in events following lowering from 134 to 96. If a threshold exists it is a LDL lower than 77 mg/dL and a total cholesterol below 135.
5. Present guidelines may mislead by suggesting target levels which are too high.
6. Benefits extend to prevention of ischemic stroke and peripheral revascularizations as well as coronary revascularizations.
7. The substantial benefits were not much influenced by the initial concentrations of lipids.
8. Lowering cholesterol to these levels by simvastatin was safe.
9. Given the large numbers of subjects, it was inevitable that some in the active treatment group discontinued the drug, and some in the placebo group began taking the drug. This would dilute the reported benefits. (Ie, statins likely produce greater benefits than reported by the study.)
10. Statin treatment would, over a 5-year period, prevent up to 100 major vascular events per 1000 individuals. More prolonged treatment would likely produce additional benefits.

CONCLUSION

Lowering lipids with statin therapy produced substantial reductions in vascular events among a wide range of high-risk individuals, irrespective of their initial cholesterol levels.

Benefits were in addition to those of aspirin, beta-blockers, and ACE inhibitors.

Statin therapy is safe and thus applicable to a very wide range of patients.

Lancet July 6, 2002, 360: 7-22 Original multicenter investigation by the Heart Protective Study Collaboration Group reported by the Radcliffe Infirmary, Oxford, UK www.thelancet.com

Comment:

Are we to become a nation of statin takers? RTJ

=====

Neither Clinically Significant Harms Nor Benefits In Preventing Chronic Disease

7-3 RISKS AND BENEFITS OF ESTROGEN PLUS PROGESTIN IN HEALTHY POSTMENOPAUSAL WOMEN

Despite decades of accumulated observational evidence, the balance of risks and benefits of hormone use in healthy postmenopausal women remains uncertain.

This subset of the Women's Health Initiative assessed the benefits and risks of estrogen + progestin, one of the most commonly used preparations for hormone replacement therapy (**HRT**).

Conclusion: Over 5 years, use of this HRT (vs placebo) slightly *increased* risk of invasive breast cancer, stroke, coronary heart disease events, and pulmonary embolism. And slightly *reduced* colorectal cancer and hip fractures. Overall, there was no benefit.

STUDY

1. Randomized over 16 500 postmenopausal women, age 50-79 (mean = 63) at baseline, to:
 - A. Conjugated equine estrogen (*Premarin*; 0.625 mg) + medroxyprogesterone (*Provera*; 2.5 mg) or
 - B. Placebo
2. All had an intact uterus. The great majority was healthy and free of cardiovascular disease; only 8% reported prior CVD. (*Ie, this was essentially a primary prevention trial.*)
3. Primary outcome = coronary heart disease (CHD death and non-fatal myocardial infarct), invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

RESULTS

1. The trial was terminated early (at 5 years) because risks of invasive breast cancer exceeded the stopping boundary.

2. Outcomes (harm annualized):	E + P (%) (n = 8506)	Placebo (%) (n = 8102)	Absolute difference %	NNT (harm one over 1 year)
CHD death	33 (0.07)	26 (0.06)	0.01	10 000
Non-fatal MI	133 (0.30)	96 (0.23)	0.07	1428
Stroke	127 (0.29)	85 (0.21)	0.08	1250
Venous thromboembolic disease	151 (0.34)	67 (0.16)	0.18	555
Invasive breast cancer	166 (0.38)	124 (0.30)	0.08	1250

3. Outcomes (benefit annualized)	NNT (benefit one over 1 year)			
Fractures	650 (1.47)	788 (1.91)	+0.44	227
Colorectal cancer	45 (0.10)	67 (0.16)	+0.06	1616
Death due to other causes	165	166	--	--

4. Global index considering both benefits and harms	751 (1.70)	623 (1.51)	-0.19	526 (harm one over 1 year)
---	------------	------------	-------	----------------------------

(I calculated these NNT from the table on page 326. I do not believe many clinicians would

consider these high NNTs to be clinically significant. RTJ)

5. No difference between groups in risk of all-cause mortality.
6. The investigators presented the absolute risks and benefits as number of events for ten thousand women per year:

CHD events	+7 (harm)
Stroke	+8 (harm)
Pulmonary embolism	+8 (harm)
Invasive breast cancer	+8 (harm)
Colorectal cancer	-6 (benefit)
Hip fractures	-5 (benefit)
Global index	+19 (harm)

DISCUSSION

1. This study addressed the question as to whether HRT with estrogen/progestin prevents *chronic disease* in a large cohort of healthy postmenopausal women. It does not.
2. The number of harms exceeded benefits.
3. The authors caution that the study does not relate to women taking only estrogen. The progestin content of the present study may be the factor leading to increased risk of breast cancer and CHD and stroke. A study considering only estrogen continues.
4. “The risk-benefit is not consistent with the requirements for a viable intervention for the primary prevention of chronic diseases.”
5. The trial did not address the short-term risks and the significant benefits of hormones given for treatment of menopausal symptoms.

CONCLUSION

Among a large cohort of healthy postmenopausal women, overall health risks exceeded benefits from use of combined estrogen/progestin for an average of 5 years.

Combined HRT should not be used for primary prevention of chronic diseases.

JAMA July 17, 2002; 288: 321-33 Original investigation by the Women’s Health Initiative Investigation Group, National Heart, Lung, and Blood Institute, Bethesda MD. Correspondence to Jacques E Rossouw.

www.jama.com

An editorial in this issue (pp 366-68), first author Suzanne W Fletcher, Harvard Medical School, Boston Mass, comments:

Combined estrogen/progestin may act differently than estrogen alone. Addition of progestins may increase risk of breast cancer. Mitotic activity in the breast during the normal menstrual cycles is greatest when progesterone levels are highest.)

Recent evidence for secondary prevention trials using combined therapy showed increased risk of coronary heart disease during the first year of use. This may reflect the pro-thrombotic and pro-inflammatory effects of progestins.

Comment:

As noted above, the absolute risk is very small and the NNT over 5 years to harm one person is very large. If interventional study benefited only 5 persons per 10 000 per year, it would not be considered *clinically* relevant. Similarly, the very low risk of harms reported in the study can not be considered *clinically* relevant. The message is – there is no benefit.

The main message of the study is the demonstration of the lack of benefit in prevention of chronic diseases.

I believe it should not deter women who are experiencing menopausal symptoms for taking HRT – at least short-term as long as hot flashes persist.

A large volume of observational studies in the past suggested a 40%-50% reduction in risk of CHD among users of either estrogen alone or combined estrogen/progestin. This demonstrates how faulty and misleading observational studies can be. RTJ

=====

No Benefit From HRT In Reducing Risk Of CHD

7-4 CARDIOVASCULAR DISEASE OUTCOMES DURING 6.8 YEARS OF HORMONE THERAPY (Heart and Estrogen/progestin Replacement Study Follow-up (HERS II))

The original HERS study (*JAMA 1998; 280: 605-13*) found no overall reduction in risk of coronary heart disease events among postmenopausal women who had established coronary heart disease at baseline. (A high-risk group)

The study suggested a higher risk of recurrent CHD during the first year, and a decreased risk during years 3 to 5. This study (HERS II) extended the study for an additional 2.7 years.

There was no significant reduction in rates of CHD events over 6.8 years. The relative hazard for events (treated vs placebo group) was 1.00.

The lower rates of CHD events among women taking hormone replacement therapy did not persist after 6.8 years.

HRT did not reduce risk of cardiovascular events in a group of women with established coronary heart disease.

JAMA July 3, 2002; 288: 49-57 Original investigation, first author Deborah Grady, University of California, San Francisco.

Comment:

Neither was there an *increase* in risk.

This leaves us with only one indication for HRT (an important one) – amelioration of menopausal symptoms. I believe a good case can be made for all women who choose to take HRT to also take preventive low-dose aspirin. Some will decide to use statin drugs regardless of their baseline lipid concentrations. Anti-osteoporosis treatment will be indicated for almost all. RTJ

=====

Increased Risk Of Venous Thrombosis And Gall Bladder Disease. No Increase In Cardiovascular Disease

7-5 NON-CARDIAC OUTCOMES DURING 6.8 YEARS OF HORMONE THERAPY

(The HERS II Follow-up Study)

The Heart and Estrogen/progestin study (**HERS I**) was a randomized, blinded trial to determine the effects of estrogen plus progestin (compared with placebo) in older post-menopausal women who had a history of coronary disease. (*A secondary prevention trial.*) During 6.8 years of observation, no overall effect of hormone replacement therapy (**HRT**) on cardiovascular disease event rates was detected. (The study also did not report any increase or decrease in cardiovascular events. Relative hazard for CHD events was 1.00.)

This study examined the effect of long-term postmenopausal hormone therapy on common non-cardiac disease outcomes.

Conclusion; HRT was associated with increased rates of thromboembolism, and biliary tract surgery.

STUDY

1. Randomized placebo-controlled trial of 4.1 years (HERS I) was followed by 2.7 years of open-label observation. (HERS II)
2. Over 2700 postmenopausal women had coronary disease at baseline. Average age = 67.
3. Randomized to: 1) 0.625 mg conjugated estrogen plus 2.5 mg medroxyprogesterone, or 2) placebo during the first 4.1 years. This was followed by open-label hormone therapy prescribed by personal physicians. By the end of the study, adherence to HRT declined from about 80% to about 45% in the HRT group, and use of HRT increased to about 8% in the placebo group.
4. Main outcome measures – thromboembolic events, biliary tract surgery, cancer, fracture, and total mortality.

RESULTS

1. Events per <u>1000 persons</u> per year	HRT	Placebo	Absolute difference	NNT(over 1y to harm 1)
Venous thromboembolism	4.5	2.2	0.23 %	434
Pulmonary embolism	2.0	0.7	0.13 %	767
Total thromboembolic events	5.9	2.8	0.31 %	322
Biliary tract surgery	19.1	12.9	0.62 %	161
Breast cancer	5.9	4.7	0.12 %	833
Any cancer	19.7	16.5	0.32 %	312

Any fracture 29.7 28.4 0.13 % 769

(I calculated these NNT from table 2 p 61. All indicate small harms for HRT, even for cancer and fractures. The NNT indicate the number of patients needed to treat for one year to harm one patient.

I believe the numbers needed to treat are so large as to be clinically irrelevant. RTJ)

2. Deaths were more common in the HRT groups – 22.5% vs 20.5%.

DISCUSSION

1. Over 6 years, treatment with combined HRT was associated with a statistically significant increase in venous thromboembolism and biliary tract surgery.

2. That hormone therapy increases risk of venous thromboembolism is well documented.

Estrogen is the likely cause since estrogen without progestin is associated with venous thromboembolism, and selective estrogen receptor modulators also increase risk. Use of aspirin or statins appears to be protective.

3. This study represents a population with a relatively high absolute risk of deep vein thrombosis and pulmonary embolism.

4. The higher rate of fracture (including hip fracture) and the higher rate of colon cancer in the HRT group was surprising, given past reports of increase in bone mass density and fewer fractures in HRT-treated women.. The finding may be due to chance.¹

CONCLUSION

Treatment with estrogen plus progestin in older women with coronary disease was associated with an increase in rates of venous thromboembolism and biliary tract surgery.

JAMA July 3, 2002; 288: 58-66 Original investigation by the Heart and Estrogen/progestin Replacement Study Follow-up (HERS II) First author Stephen Hulley, University of California, San Francisco www.jama.com

www.jama.com

Comment:

1 Other studies have reported benefit from HRT in reducing risk of fracture.. This study reported a slight *increase* in the HRT group which the investigators attributed to chance. Since the NNTs to harm are large (NNT to treat 1 year to be associated with 1 fracture = 769). Could not the other harms reported be due to chance as well?

Do the large numbers needed to treat to harm represent any *clinically* meaningful outcomes? Even a slight benefit from HRT would outweigh these harms.

Use of low-dose aspirin for prevention of venous thromboembolism when women take HRT is an important preventive measure. RTJ

=====
Illiteracy Leads To Poor Control

7-6 ASSOCIATION OF HEALTH LITERACY WITH DIABETES OUTCOMES.

Poor health literacy is most prevalent in public hospitals, but is also common among the elderly in private sectors. A recent study reported that more than 1/3 of Medicare enrollees had poor health literacy. Health literacy is a measure of patients' ability to read, comprehend, and act on medical instructions.

Poor health literacy is independently associated with poor self-rated health and higher use of services. Poor health literacy may directly contribute to poor outcomes. Patients with poor health literacy have greater difficulties naming their medications and describing their indications, more frequently hold health beliefs that interfere with adherence, and are more likely to have poor understanding of their condition and its management.

This study examined the association between health literacy and type-2 diabetes outcomes.

Conclusion: Poor health literacy was independently associated with worse glycemic control.

STUDY

1. Cross-sectional study of over 400 English- and Spanish-speaking patients (mean age =58) with type-2 diabetes. All attended primary care health clinics.
2. Patients completed questionnaires assessing literacy by a short-form test of functional health literacy in adults in English and Spanish.
3. Main outcome measure = most recent HbA1c related to health literacy. Classified patients as having good glycemic control if their HbA1c was in the lowest quartile; poor control if in the highest quartile.

RESULTS

1. 66% of patients in this sample who had a high school education or less, had inadequate health literacy.
2. After adjusting for multiple possible confounding factors, for each 1-point decrement in test score, the HbA1c value increased by 0.02.
3. Patients with inadequate health literacy were less likely than patients with adequate health literacy to achieve tight glycemic control (HbA1c < 7.2%); and were more likely to have poor control (HbA1c > 9.5%).
4. More in the poor health literacy group reported retinopathy.

DISCUSSION

1. "Our study demonstrates that, among patients who have type 2 diabetes and access to primary care physicians in public hospital clinics, health literacy was independently associated with glycemic control.
2. Poor health literacy was an independent predictor of poor glycemic control and was associated with a lower likelihood of achieving tight control and a higher rate of retinopathy.
3. It is possible that patients with inadequate health literacy are less likely to recognize signs and symptoms of diabetes and present to care late.

4. Poor health literacy probably impedes successful communication across many levels.

CONCLUSION

Among primary care patients with type 2 diabetes, inadequate health literacy was independently associated with poorer glycemic control and higher rates of retinopathy. Inadequate health literacy contributes to the disproportionate burden of diabetes-related problems among disadvantaged populations.

JAMA July 24/31 2002; 288; 475-82 Original investigation, first author Dean Schllinger, University of California, San Francisco. www.jama.com

Comment:

Large numbers poor health literacy patients consult primary care clinicians. This eliminates any application of “evidence-based” medicine (EBM) to this large group. Evidence-based medicine relates to select patients. EBM simply does not apply to a host of patients seen by primary care clinicians. Providers then do the best they can.

RTJ

Cardio-protective Benefit in Addition to Anti-hyperglycemic Effect

7-7 METFORMIN: AN UPDATE

(I enjoy update and review articles. I abstract points which are of general interest to primary care. This refreshes my memory and presents some information I never knew. RTJ)

Metformin (*Glucophage*) is an insulin-sensitizing biguanide agent. It may correct several of the primary pathophysiologic abnormalities of the metabolic syndrome. In diabetic patients it appears to provide cardiovascular protection that cannot be attributed only to its antihyperglycemic effects.

Clinical role:

Metformin is as effective as insulin and sulfonylureas when used as monotherapy. In conjunction with diet, it reduces HbA1c levels by 1.3% to 2.0%. It may have special benefits in overweight patients with type 2 diabetes. Unlike insulin, sulfonylureas and thiazolidinediones (which often are related to weight gain) metformin does not increase body mass index in obese diabetic patients. Significant reductions in total body fat and visceral fat have been observed in women with abdominal obesity when treated with metformin. (Excessive fat in the para-intestinal area is a major contributor to the pathogenesis of the cardiovascular metabolic syndrome.) Weight loss with metformin has been attributed to decreased net caloric intake probably through appetite suppression, an effect largely independent of any gastrointestinal side effect. Reduction in hyperinsulinemia related to reduced insulin resistance may have additive effects on producing weight reduction in obese, insulin-resistant persons.

Metformin as part of combination therapy:

It is effective in combination with insulin, sulfonylureas, and thiazolidinediones. This is important because single drugs often fail to maintain normoglycemia. (As time progresses, diabetes progresses, and treatment with sulfonylureas fails.) Metformin then adds significant improvement.

Practical considerations in therapy:

The ideal patient to consider for metformin is an obese person with type 2 diabetes and normal kidney function. Heart failure, hypoxic respiratory disease, liver failure, alcoholism, and moderate to severe infections also predispose to lactic acidosis. Age over 80 per se may predispose to lactic acidosis because lean body mass may lead to misleadingly low creatinine concentrations that fails to reflect the true degree of decrease in kidney function. .

The histamine₂ blocker cimetidine (*Tagamet*; generic) competitively inhibits renal tubular secretion of metformin, significantly reducing clearance and increasing bioavailability.

Therapy should be started with a single dose of 500 mg taken with the largest meal (to prevent GI symptoms). GI symptoms generally disappear within 2 weeks. Dose may be increased by 500 mg increments every 1 to 2 weeks until a desirable blood glucose is obtained or the maximal dose is achieved (2550 mg). The hypoglycemic benefit is dose related.

Development of hypoglycemia is rare because the drug only partially suppresses gluconeogenesis in the liver, and does not stimulate insulin production.

Mechanisms of action:

Metformin reduces hepatic glucose output through inhibition of gluconeogenesis, and to a lesser extent, glycogenolysis. It also increases glucose uptake in muscle and adipocytes. It depends on the presence of insulin for its peripheral action. It has no direct effect on beta-cells. It may also improve hyperglycemia by decreasing intestinal absorption of glucose. This contributes to decreased postprandial glucose levels.

Effect of treatment on cardiovascular morbidity and mortality:

Compared with a conventionally diet-treated group of patients with type 2 diabetes, patients had a 39% reduction in risk for myocardial infarction; a 42% decrease in diabetes-related death; and 36% reduction in all cause mortality. These results are likely due to improved glycemic control. Each 1% reduction in HbA_{1c} was related to, a reduction of 21% in diabetes-related deaths; a 14% reduction in myocardial infarction; 12% reduction in stroke; and 16% reduction in heart failure. Metformin was more effective in producing these benefits than either sulfonylureas or insulin.

Mechanism of cardiovascular protection:

Metformin has major effects on lipid metabolism in patients with insulin resistance. It decreases plasma free acid levels, decreases triglycerides and low-density lipoprotein, decreases LDL-cholesterol while maintaining or increasing HDL-cholesterol.

It also lessens hypercoagulation and increases fibrinolysis in insulin-resistant states. And decreases platelet aggregation.

Hypertension is associated with diabetes. Defective insulin signaling may contribute to increased vascular resistance which is the hallmark of hypertension in diabetes. Even the small reduction in BP associated with metformin may benefit.

Conclusion:

Metformin has an excellent safety profile. It is effective as monotherapy and in combination with other drugs. It does not promote weight gain and may even cause weight reduction. It appears to have substantial benefit on lipid metabolism, clotting factors, and platelet function. It improves vascular relaxation and probably reduces BP.

Annals Int Med July 2, 2002; 137: 25-33 Review article, first author Dmitri Kirpichnikov, State University of New York Health Sciences Center at Brooklyn, NY

=====

Useful in establishing and excluding heart failure

7-8 RAPID MEASUREMENT OF B-TYPE NATRIURETIC PEPTIDE IN THE EMERGENCY DIAGNOSIS OF HEART FAILURE.

Rapid and accurate differentiation of heart failure (**HF**) from other causes of dyspnea is often difficult in the urgent care setting. Symptoms may be nonspecific and physical findings insensitive. Echocardiography (considered the gold standard for diagnosis) is expensive and not always accessible.

Misdiagnosis of HF can be life-threatening. Treatments may be hazardous to patients with other conditions (eg, COPD) that have similar symptoms at presentation. In the urgent care setting, there is no gold standard for either the diagnosis or prognosis of HF.

B-type natriuretic peptide (**B-TNP**) is released from the ventricles in response to increased wall tension. It is elevated in patients with left ventricular dysfunction and correlates well with the severity of HF and the prognosis.

This study evaluated a bedside assay of B-TNP in patients presenting to the emergency department with acute dyspnea.

Conclusion: B-TNP was useful in establishing and excluding the diagnosis of HF.

STUDY

1. Prospectively followed over 1500 patients (mean age 64) presenting to the ED with acute dyspnea.
2. Performed rapid B-TNP in the ED. (A rapid quantitative assay is available by a kit using a fluorescent immunoassay method.)
3. Two cardiologists determined the actual diagnosis of HF or no-HF independently using clinical criteria.
4. Correlated levels of B-TNP with the clinical diagnosis confirmed by other tests.

RESULTS

1. Final diagnosis: HF confirmed (47%); dyspnea due to non-cardiac causes in persons with a history of left ventricular dysfunction (5%); no HF (49%).
2. B-TNP by itself was more accurate than any historical or physical finding or other laboratory finding in identifying HF as a cause of the dyspnea.
3. Mean B-TNP in patients with acute HF = 675 pg/mL; in those without HF = 110 pg/mL. In the 72 patients with baseline left ventricular dysfunction without an acute exacerbation of HF mean B-TNP = 346 pg/mL.
4. Diagnostic accuracy at a cutoff point of 100 pg/mL was 83%. Predictive value of a negative test (< 50 pg/mL) was 96%.¹
5. Median B-TNP levels increased as severity of HF increased.
6. B-TNP added independent predictive power to other clinical variables assessing HF.
7. The authors judged the optimal cutoff point for making the diagnosis was 100 pg/mL

DISCUSSION

1. B-TNP levels by themselves were more accurate than any other finding in the history, physical examination, or laboratory value in delineating the cause of dyspnea.
2. The B-TNP levels correspond with the severity of the HF.
3. B-TNP is included in the European guidelines for diagnosis of chronic HF. It offers valuable predictive information and assessment of severity of the disease. It will improve the ability of clinicians to differentiate dyspnea due the HF from dyspnea due to other causes in the acute care setting. The diagnostic information can be immediately available.

CONCLUSION

Used in conjunction with other clinical information, rapid measurement of B-TNP is useful in establishing or excluding the diagnosis of HF in patients with acute dyspnea.

NEJM July 18, 2002; 347: 161-67 Original investigation, first author Alan S Maisel, University of California, San Diego. www.nejm.org

Comment:

- 1 The predictive value of a negative test the ratio of true negative tests to the sum of all negative tests. Other studies have considered B-TNP more accurate in ruling out HF than ruling it in. (Ie, if the B-TNP is low, HF is unlikely.)

=====

A Valuable Aid In Diagnosis Of Heart Failure

7-9 B-TYPE NATRIURETIC PEPTIDE – A Window to the Heart

Natriuretic peptides represent a favorable side of neurohumoral activation. They are produced by the heart and the vasculature. They improve the loading conditions of the failing heart through their diuretic, natriuretic, and vasodilator properties.

A-type natriuretic peptide is secreted primarily by the atrial myocardium. B-type natriuretic peptide (initially called brain natriuretic peptide) is released almost exclusively by the ventricular myocardium in response to elevations of end-diastolic pressure and volume. C-type natriuretic peptide was discovered recently. It is released by endothelial cells in response to shear stress.

These peptides are not normally produced by these cells. In each of the anatomical areas, the higher the stress, the greater the level of natriuretic peptide produced and released.

There is some evidence that they also inhibit the renin-angiotensin system and the endothelin pathway.

Diagnosis of heart failure: Measurement of B-type natriuretic peptide is valuable in the diagnosis of congestive heart failure. It parallels the severity of the congestive heart failure. It can be measured rapidly and accurately at the point of care. It can be used to confirm the diagnosis of congestive heart failure; to measure the severity of left ventricular compromise; to quantify the functional class; to estimate the prognosis and predict future cardiac events, including sudden death in patients with cardiomyopathy; and to evaluate efficacy of treatment.

A tool is now available to determine whether a patient has CHF, and to measure its severity. It appears most helpful in confirming the diagnosis of CHF in whom the diagnosis is uncertain. It appears to be more helpful than standard diagnostic studies, including ECG, and chest radiography. It may be more cost-effective than echocardiography.

Treatment: Nesiritide is a synthetic recombinant human B-type natriuretic peptide. It was recently approved by the FDA for short-term infusion in patients with congestive heart failure. It improves signs and symptoms of volume overload and cardiac decompensation. It is a novel approach to the “physiologic” management of heart failure.

The boundaries of usefulness will likely expand.

NEJM July 18, 2002; 347: 158-59 “Perspective”, review article by Kenneth L Baughman, Johns Hopkins Hospital, Baltimore MD.

Comment:

The diagnosis of HF is aided by determination of B-TNP along with other clinical data. It does not stand alone.

May Benefit, but Compliance is Poor

7-10 PRESCRIBED EXERCISE IN PEOPLE WITH FIBROMYALGIA

Chronic widespread musculoskeletal pain has a community prevalence of up to 13% in the UK. The cause is often unexplained. Fibromyalgia, the severe end of the spectrum, comprises chronic musculoskeletal pain in association with multiple tender points. Its community prevalence is about 1%. Treatment with analgesics, NSAIDs, and antidepressants is relatively ineffective.

This randomized, controlled study evaluated the effect of cardiovascular fitness exercise in patients with fibromyalgia.

Conclusion: Prescribed, graded exercise was effective, but compliance was disappointing.

STUDY

1. Followed 132 patients with fibromyalgia. (median age = 45.) Participants had low self-rated scores indicating high levels of disability. Most were unemployed and came from ethnic minorities.
2. Randomized to: 1) community-based graded, aerobic exercise, or 2) relaxation and flexibility therapy.
3. Therapy comprised individualized aerobic exercise, mostly walking on treadmills and cycling on exercise bicycles. Participants were encouraged to increase the amount of exercise steadily from 6 minutes twice weekly to 25 minutes as tolerated at an intensity that made them sweat slightly.
4. Patients self-assessed any degree of improvement, tender point counts, and impact on condition.
5. Primary outcome measure = change in self rated global impression. Follow-up = 12 weeks.

RESULTS

1. Compared with relaxation, exercise led to significantly more participants rating themselves as much or very much better at 3 months [35% vs 18%; NNT(benefit one person over 3 months) = 6.]
2. Tender point counts were reduced from 4.2 to 2.0.
3. Benefits were maintained or improved at one year at which time fewer in the exercise group fulfilled the criteria for fibromyalgia. (45% vs 66%; NNT = 5)
4. But compliance was poor. Only slightly over half attended 1/3 or more of the classes. Twelve in each group (18%) withdrew.

DISCUSSION

1. A three month program of prescribed, graded exercise significantly benefited patients' global self rating of fibromyalgia.
2. Tender point counts were reduced and scores on fibromyalgia impact also improved.
3. Prescribed exercise can be undertaken effectively in the community by personal trainers previously inexperienced in management of ill persons.
4. Compliance with a program may be a problem. Patients may experience initial increases in pain and stiffness immediately after exercise, and believe that exercise worsens their condition.

CONCLUSION

Prescribed, graded aerobic exercise was effective in improving symptoms of fibromyalgia. It is simple, cheap, and potentially widely available.

Probably not efficacious

7-11 DEBRIDEMENT AND LAVAGE FOR OSTEOARTHRITIS OF THE KNEE

Lavage of the knee joint through a large needle, or lavage plus debridement, is often performed for patients suffering from osteoarthritis of the knee. In theory, lavage removes debris that may induce synovitis, a likely source of pain. It also removes calcium phosphate crystals that are detectable in most severely osteoarthritic joints.

Debridement consists of smoothing rough, fibrillated articular and meniscal surfaces, shaving tibial-spine osteophytes that interfere with motion, and removing inflamed synovium. The procedure is assumed to decrease stress on the cartilage, lessen cartilage loss, and prevent release of more fragments, thus interrupting a vicious circle of joint damage.

Do these interventions alleviate knee pain and disability? To establish effectiveness of the procedure, studies are required using a sham arthroscopy procedure as a control.

This issue of NEJM¹ reports a randomized, blinded, placebo (sham surgery)-controlled trial of arthroscopic surgery for osteoarthritis of the knee. Patients were assigned to: 1) lavage, 2) lavage + debridement, or 3) sham arthroscopy. At no point over 2 years did either of the intervention groups report less pain or better function than the sham arthroscopy group. “If anything, the group that underwent the sham procedure did slightly better in terms of major outcomes.” In any case, small treatment effects may not be sufficient to justify this type of surgical treatment.

Despite current popularity, lavage and debridement are probably not efficacious as treatments for most persons with osteoarthritis of the knee. However, for the subgroup of knees with loose bodies or flaps of meniscus or cartilage that are causing mechanical symptoms, especially locking, catching, or giving way of the joint, there is a consensus that arthroscopic removal of these unstable tissues improves joint function and alleviates symptoms.

Although the debris in osteoarthritic joints may be related to synovitis, the results of this trial suggest that the effects of this debris on clinical symptoms are negligible. Larger forces within and outside the joint, such as malalignment, muscle weakness, instability, and obesity, which are not addressed by this surgery, may have greater effects on clinical outcomes. Debridement and lavage may simply remove some of the evidence while the destructive forces of osteoarthritis continue to work.

NEJM July 11, 2002; 347: 132-33 Editorial, first author David T Felson, Boston University, Mass. www.nejm.org

1 “A Controlled Trial Of Arthroscopic Surgery For Osteoarthritis Of The Knee” NEJM July 11, 2002; 347: 81-88

Original investigation, first author, J Bruce Mosley, Houston Veterans Affairs Medical Center, Texas

The ethics of clinical research differ from the ethics of clinical care

7-12 IS PLACEBO SURGERY UNETHICAL?

(This editorial comments on the preceding study.)

All subjects in the preceding study provided informed consent. They were advised that there was one chance in 3 that they would receive a sham procedure; and two chances out of 3 that they would receive lavage or lavage + debridement. They were told the sham procedure would not benefit the arthritis. About 40% of the originally selected cohort refused to accept this probability.

The sham procedure consisted of prepping and draping the knee, making three 1-cm incisions in the skin. The surgeon asked for all instruments and manipulated the knee as if arthroscopy were being performed. Saline was splashed to simulate the sounds of lavage. No instrument was entered. The patients were kept in the operating room for the same amount of time required for a debridement. They were kept in the hospital overnight. Their nurses were not aware of the treatment-group assignment.

Sham surgery subjects received a short-acting intravenous tranquilizer and an opioid, and spontaneously breathed oxygen-enriched air.

Is this ethical? The editorial comments:

Clinical trials of surgery have seldom included placebo surgery as a control, owing to ethical concerns. The idea is apt to elicit an immediate negative judgment, because it appears to violate the fundamental ethical principles of beneficence and non-maleficence. Doctors should not expose patients to risks if there is no prospect of possible benefits. Surgeons should not invade the body except for the purpose of cure or amelioration.

The editorialist states that this stance confounds the ethics of clinical research with the ethics of clinical care. The randomized, controlled trial is not a form of individualized medical therapy. It is a scientific tool for evaluating treatments in groups of research participants with the aim of improving the care of patients in the future. Clinical trials are *not* designed to promote the medical best interests of enrolled patients. Indeed, they often expose them to risks that are not outweighed by known potential medical benefits. "The use of placebo surgery must be evaluated in terms of the ethical principles appropriate to clinical research, which are not identical to the ethical principles of clinical practice."

To avoid exploiting research subjects, clinical trials must satisfy several ethical requirements: 1) must be designed to answer valuable scientific questions with the use of valid research methods; 2) must present a favorable risk-benefit ratio; 3) risks must be minimized and justifiable by the benefits from them; 4) informed consent must be obtained.

Placebo surgery in clinical trials must be compatible with the requirement to minimize risk; the risks must be justifiable in relation to the potential value of the scientific knowledge gained; valid informed consent must be obtained.

The invasiveness of surgery is associated with a pronounced placebo effect. Thus, placebo-controlled trials are required for a rigorous scientific evaluation of surgery when the primary outcome is a subjective phenomenon such as pain or quality of life.

But, even if the risks of a valid clinical trial have been minimized, it does not follow that they are justified. It is clearly unethical to severely jeopardize the health and well-being of research subjects only for the good of future patients. In the arthroscopic trial, the risks of the sham surgery did not substantially exceed the risks of other generally accepted research interventions such as muscle biopsy, bronchoscopy, and phase 1 testing of experimental drugs in healthy volunteers.

Many persons would refuse to participate in a placebo-controlled surgical trial. Indeed, in the arthroscopic trial many did indeed refuse to be included after they had been fully informed about the probability of being a placebo-control. Some vulnerable individuals must be excluded: those who may be susceptible to “undue inducement”, those who have limited capacity to give informed consent, and those who do not fully understand the nature of the trial. There is also concern about deception in that the placebo-recipients, as described above, were “deceived” into believing they received the full surgical procedure.

“Reasonable people are bound to differ.”

NEJM July 11, 2002; 347: 137-139 “Sounding Board” editorial, first author Sam Horng, National Institutes of Health, Bethesda, MD

Comment:

Any sham surgical trial must be based on the question of clinical equipoise. It is not known whether the procedure is more beneficial than that of a placebo or another established drug or procedure. Many surgical procedures are so established that a randomized trial was never required. The investigators apparently were not convinced that the arthroscopic procedure was truly beneficial. If they were, they would not have considered the trial.

I believe much of the ethical concern would be alleviated if the persons entering the trial were termed “volunteers” rather than subjects. Volunteers would then be considered as offering to undergo an experiment to benefit mankind rather than to benefit themselves. Walter Reed was a volunteer, not a subject.

Common and treatable. Devastating if neglected

7-13 POLYMYALGIA RHEUMATICA AND GIANT-CELL ARTERITIS: Review article

(I enjoy abstracting review articles. They present important points of interest which I had forgotten or never knew. RTJ)

Polymyalgia rheumatica (**PMR**) and giant-cell arteritis (**GCA**) are closely related. They affect middle aged and older persons. They frequently occur together. Some authorities consider them to be different phases of the same disease. GCA and PMR are probably polygenic diseases in which multiple genetic and environmental factors influence susceptibility. Some suggest a relationship to viral infections.

Polymyalgia rheumatica is an inflammatory condition of unknown cause characterized by aching and morning stiffness in the cervical region and shoulder and pelvic girdles. It is common. A prevalence of 1 case for every 133 people over age 50 has been reported. Incidence peaks at ages 70-80.

It usually responds rapidly to low doses of corticosteroids. It has a favorable prognosis.

Criteria for diagnosis: (All findings must be present for diagnosis.)

Age 50 or older

Bilateral aching and stiffness for one month or more involving two of 3 areas (neck, shoulders, pelvic girdle (most commonly in the shoulders)).

Rapid response to prednisone 20 mg/d or less.

Sedimentation rate over 40 mm/hour

Exclusion of all diagnoses other than giant cell arteritis.

The discomfort is bilateral. It worsens with movement and interferes with usual daily activities. Pain limits movement. Pain usually radiates to the elbows and knees.

Systemic symptoms and signs are present in about 1/3 of patients – fever, malaise, anorexia, and weight loss.

Physical examination reveals little evidence of swelling or tenderness. This is in contrast to the patient's marked symptoms. Distal manifestations are present in about half the patients – non-erosive, self-limited asymmetric peripheral arthritis (especially knees and wrists) carpal tunnel syndrome, and swelling and pitting edema of dorsum of the hands and wrists, ankles and feet.

Some studies have reported a minority of patients have a normal sed rate at the time of diagnosis. A normal sed rate is not incompatible with a diagnosis of active PMR.

Giant cell arteritis is present in about 20% of patients. The two may begin at the same time. One may begin before the other.

Pathological findings include: a mild synovitis in proximal joints and periarticular structures. MRI may identify subdeltoid and subacromial bursitis.

Giant cell arteritis:

GCA is a chronic vasculitis of large and medium-sized vessels. Symptomatic inflammation usually involves the cranial branches of the arteries originating from the aortic arch. Its onset tends to be gradual, but it can be abrupt. Systemic symptoms are present in about half the patients. Headache is the most frequent symptom and occurs in about 2/3 of patients. Scalp tenderness is usually confined to the temporal areas.

The frontal or parietal branches of the superficial temporal arteries may be thickened, nodular, tender and erythematous. Pulses may be decreased or absent. Nearly half suffer from jaw claudication. Occasionally intermittent claudication occurs in the tongue or muscles involved in swallowing.

Permanent partial or complete loss of vision in one or both eyes occurs in up to 20% of patients. It is often an early manifestation of GCA. If one eye is involved, the other is likely to be involved within weeks. "Amaurosis fugax is an important visual symptom that precedes permanent visual loss in 44% of patients."

About 30% have neurological manifestations – mononeuropathies and peripheral polyneuropathies in the extremities. Transient ischemic attacks or stroke may occur.

In about 10% of patients the branches of the aortic arch, especially the subclavian and axillary arteries become narrowed and result in claudication of the arms. Thoracic aortic aneurysm is much more likely to occur in patients with GCA than in patients without.

A markedly elevated sed rate is the hallmark of GCA. However, it may be normal in some before treatment. A normal sed rate is not incompatible with a diagnosis of GCA.

The C-reactive protein is a more sensitive indicator of disease activity than the sed rate.

Most patients have a mild to moderate anemia of chronic disease. About 1/3 have mildly abnormal liver function tests.

Criteria for diagnosis:

Age of onset 50 or over
New headache
Temporal artery abnormality (tenderness, decreased pulsation)
Elevated sedimentation rate. (Over 50 mm/h)
Abnormal biopsy of temporal artery.

(At least 3 of the criteria must be met)

The arteritis is often intermittent rather than continuous.

Symptoms of PMR occur in up to 60% of those with GCA.

Pathological findings in arteries originating from the aortic arch include disruption of the internal elastic lamina. Granulomatous inflammation includes giant cells at the junction between intima and media.

Treatment:

Corticosteroids are the drugs of choice. For PMR, a dose of 10 to 20 mg prednisone daily is adequate in most cases of PMR. GSA requires an initial dose of 40 to 60 mg. Initial high-dose pulsed methylprednisolone may be given to patients with recent or impending visual loss. Corticosteroids may prevent but usually do not reverse visual loss.

The response is rapid with resolution of many symptoms after a few days. A lack of improvement should question the diagnosis. The initial course is usually given for 3 to 4 weeks and then gradually reduced by a maximum of 10% each week. If withdrawn too quickly, relapse or recurrence usually occurs.

Regular assessment of symptoms, the sed rate and c-reactive protein are the most useful ways of monitoring progress. A treatment course of one to two years is often required. Low dose steroids may be required for several years.

Corticosteroid-related adverse effects are common. Preventive treatment for diabetes and osteoporosis should be undertaken.

NEJM July 25, 2002; 347: 261-78 "Medical Progress, review article, first author Carlo Salvarani, Arcispedale S. Maria Nuova, Reggio Emilia, Italy. www.nejm.org

Comment:

Primary care clinicians, if they practice long enough, will encounter patients with PMR and GSA. Recognition and treatment at an early stage is most rewarding to patient and clinician alike. RTJ

=====
Adverse Effects have been Overblown

7-14 BETA-BLOCKER THERAPY AND SYMPTOMS OF DEPRESSION, FATIGUE, AND SEXUAL DYSFUNCTION

Beta-blocker therapy lowers mortality in patients with heart failure as well as in patients after an acute myocardial infarction. They are potent anti-hypertension drugs. Despite their importance, they are underused. The reluctance of some physicians to use these agents may be in part due to fear of adverse effects.

This study asked – What is the likelihood of fatigue, depression, and sexual dysfunction due to beta-blockers?

Conclusion: No significant increase in depression; small increases in fatigue and sexual dysfunction.

STUDY

1. Search for randomized trials testing beta-blockers in treatment of myocardial infarction, heart failure, and hypertension found 15 studies (over 35 000 subjects) meeting authors' inclusion criteria. All reported on depressive symptoms, fatigue, or sexual dysfunction in beta-blocker groups compared with placebo.
2. All had a follow-up of at least 6 months.

RESULTS

1. Adverse effects (compared with placebo)	per 1000 patients/y	NNT (harm one patient/y)
Depressive symptoms	6	166
Fatigue	18	57
Sexual dysfunction	5	199

(Symptoms were compared with frequency in placebo groups. Symptoms of fatigue, depression and sexual dysfunction were common among the placebo groups.)

2. Adverse effects did not result in an increased number of patients withdrawing from therapy.
(13 patients withdrew from both active treatment and placebo groups; 4 per 1000/y for fatigue and 2 per 1000/y for sexual dysfunction.)
3. None of the risks of adverse effects differed significantly by degree of beta-blocker lipid solubility. Reported risk of fatigue was less for late-generation beta-blockers than for the early-generation (eg, propranolol; timolol).

DISCUSSION

1. This quantitative review combined all available data from randomized trials concerning symptoms of fatigue, depression and sexual dysfunction related to beta-blocker therapy.
2. The study found no increased risk of depression, and only small risks for fatigue and sexual dysfunction.
3. Patients rarely withdrew from therapy due to these adverse effects.
4. Concerns about these adverse effects may have contributed to the relatively slow adoption of beta-blocker therapy. "Our findings should alleviate concerns that long-term treatment with beta-blockers causes substantial increases in these symptoms that may compromise quality-of-life, and should encourage the implementation of this life-saving therapy. "

5. Symptoms of fatigue, depression and sexual dysfunction were common among the placebo groups.

CONCLUSION

Beta-blocker therapy, compared with placebo, was *not* associated with substantial risk of depression, fatigue and sexual dysfunction. These small risks should be put in the context of the documented benefits of beta-blockers.

JAMA July 17, 2002; 288: 351-57 Original investigation, first author Dennis T Ko, Yale University School of Medicine New Haven Conn.

=====
“Active” coronary disease is clearly associated with inflammation, both systemically and at the level of the arterial wall

7-15 THE VALUE OF INFLAMMATION FOR PREDICTING UNSTABLE ANGINA

Morphologically, atherosclerosis is an inflammatory disease. In animals, early after initiation of an atherosclerotic diet, monocytes adhere to vascular endothelium and accumulate in lesion-prone arterial sites. Adherent monocytes enter the arterial intima and differentiate into macrophages with the help of inflammation-modulators which are produced locally by smooth muscle cells. Resident macrophages then accumulate lipids to become foam cells. Sites of rupture of atherosclerotic plaques are characterized by collections of activated macrophages and smooth muscle cells, indicating an ongoing inflammatory response.

Inflammation is also involved in later clinical manifestations of atherosclerosis. C-reactive protein levels are higher in patients with unstable coronary disease than in those with stable coronary disease. Persistent elevations of C-reactive protein are predictive of future myocardial ischemia and infarction.

“Active” coronary disease is clearly associated with evidence of inflammation, both systemically and at the level of the arterial wall. In the Framingham study, elevated levels of fibrinogen (an acute-phase reactant) were independently associated with future coronary events. Increased levels of markers of inflammation (eg, cytokines, adhesion molecules, and C-reactive protein) predict future cardiovascular events.

Statin drugs, which reduce risk of coronary events, also reduce circulating inflammatory markers, independently of their cholesterol-lowering effect.

In this issue of NEJM¹ a study of unstable angina reported evidence of inflammation in the venous drainage of the left coronary artery. They also found evidence of inflammation in the left coronary circulation when the culprit lesion was in the right coronary artery, and the left coronary circulation was substantially free of atherosclerosis. Patients with chronic stable angina did not have much evidence of inflammation despite angiographic evidence of atherosclerotic disease. “Thus, myocardial ischemia alone was not sufficient to induce the inflammatory state found in patients with unstable angina.”

The study implies that coronary angiography is not particularly useful in identifying the inflamed atherosclerotic plaques that are prone to produce clinical events. Acute myocardial infarction is often a consequence of coronary stenosis which is mild on angiography. Persons with an increased risk of acute coronary events are likely to have many vulnerable plaques throughout the coronary circulation. Plaque modification may be best modulated by systemic means (eg, statins; diet).

“The current challenge remains the identification of persons with vulnerable atherosclerotic plaques.”

NEJM July 4, 2002; 347: 55-57 Editorial, first author John F Keaney, Boston University School of Medicine
www.nejm.org

1 “Widespread Coronary Inflammation in Unstable Angina” NEJM July 4, 2002;347: 5-12
first author Antonino Buffon, Catholic University, Rome, Italy

Hope for Prevention of Herpes Zoster

7-16 CONTACTS WITH VARICELLA OR WITH CHILDREN AND PROTECTION AGAINST HERPES ZOSTER IN ADULTS

Primary infection with varicella-zoster virus causes varicella (chicken pox). After the acute infection, the virus establishes latency in the dorsal root ganglia. Reactivation of the latent infection (associated with age-related decline in specific cell-mediated immunity) leads to herpes zoster. (HZ)

HZ and its sequelae, especially post-herpetic neuralgia, are common and disabling in the elderly.

There has been speculation that contact with children with varicella might boost immunity in latently-infected older persons.

This study tested this hypothesis.

Conclusion: Re-exposure to varicella virus via contact with children seemed to protect against development of HZ in adults.

STUDY

1. Case-control study selected 244 adult patients with HZ; and 485 matched controls who had no history of HZ. Median age =57.
2. Asked participants about contacts over the past 10 years with people who had active varicella or zoster. And also with social and occupational contacts with children as proxies for varicella contacts.

RESULTS

1. Social contacts by adults with many children outside the household and occupational contact with ill children were associated with graded protection against HZ. Compared with the group least exposed to children, the group most heavily exposed experienced 80% less risk of developing HZ.
2. Protection increased with longer duration of occupational exposure to many ill children,

and exposure to children not living in the household.

3. Contact with persons with HZ was not associated with protection.

DISCUSSION

1. The findings suggest that continuous exogenous exposure to varicella protects against HZ in latently infected adults.
2. Dose-response effects were associated with a range of occupational and social exposures to children and exposures to varicella.
3. Living with children seems to protect against HZ by increasing access to a range of other children outside the household.
4. Protection against HZ was strongest when contacts were in groups of changing membership in occupational or social settings (increasing the likelihood of contacting a case of varicella).
5. Contact with HZ patients was not protective.
6. Children who are vaccinated against varicella might be at a lower risk of later developing HZ. Widespread varicella vaccination programs might eventually *decrease* the incidence of HZ. However, this may lead to a temporary *increase* in HZ in latently infected adults because they will be less exposed to children carrying the virus, and thus not re-immunized by contacts.
7. We should consider whether varicella vaccination in adults will protect against HZ. Studies are underway.

CONCLUSION

Re-exposure to varicella-zoster virus via contact with children seemed to protect latently infected adults against HZ.

This suggests that vaccination of the elderly might protect against HZ.

Lancet published on line July 2, 2002 First author Sara L Thomas, London School of Hygiene and Tropical Medicine, UK. www.thelancet.com

<http://image.thelancet.com/extras/01art6088web.pdf> ¹

Comment:

Although not a definitive study, it does add to the hope that immunization of elders against varicella-zoster will protect against HZ.

“Shingles” is a heavy burden for those elders who contract it. Living in a retirement complex, I observe first hand how common and disabling the disease is. Prevention would be a great blessing.

1 Journals are now publishing articles presenting new and important information on a timely basis, either by advancing the publication date in the journal itself, or by the internet.

“DEET” is by Far the Best

7-17 COMPARATIVE EFFICACY OF INSECT REPELLENTS AGAINST MOSQUITO BITES

Mosquito-transmitted diseases affect more than 700 million persons each year. Many are fatal. In many countries, applying repellants to the skin may be the only feasible way to protect against bites.

Many different repellants are marketed to consumers.

This study sought to determine which products available in the USA provide reliable and prolonged protection from mosquito bites.

Conclusion: DEET-based products are superior by far.

STUDY

1. Recruited 15 volunteers to test relative efficacy of 7 different insect repellants. Four contained DEET (N,N diethyl-3methylbenxamide). Others included repellant-impregnated wristbands and a moisturizer commonly claimed to have repellant effects. (*See text*)
2. Tested them in a controlled environment in which the species of the mosquitoes, their age and degree of hunger were kept constant; and the humidity, temperature and the light-dark cycle of a cage were kept constant.
3. Volunteers covered their forearm and hand with the products or wore the wristband while inserting their forearm into a cage containing the mosquitoes.

RESULTS

1. DEET-based products provided complete protection for the longest duration. Higher concentrations of DEET provided longer-lasting protection. A product containing 24% DEET had a mean complete-protection of 5 hours.
2. A soy bean-oil-based product protected for 1 ½ hours; others protected for less than ½ hour.
3. Repellant-impregnated wrist bands (impregnated with either DEET or citronella) offered no protection.

DISCUSSION

1. After the study was completed, two new repellants were introduced into the USA – 1) Repel Lemon Eucalyptus Insect Repellant, and 2) Fite Bite Plant-Based Insect Repellant. In one study a localized cutaneous reaction occurred after the first test and the subject discontinued the study. All others completed 3 tests. The mean complete protection time was 2 hours.
2. A commonly used preparation of DEET is termed “OFF”. “OFF Deep Woods” contains 24% DEET.
3. DEET has been used worldwide since 1957. It has is a broad spectrum of activity -- effective

against chiggers, biting flies, fleas, and ticks, as well as many species of mosquitoes.

4. No oral compound (including garlic and thiamine) has been found capable of repelling biting arthropods.
5. DEET is not a perfect repellent. It may be washed off by perspiration. Its efficacy decreases dramatically with rising outdoor temperatures. It is also a plasticizer and can dissolve watch crystals, frames of glasses, and some synthetic fabrics.
6. DEET has a remarkable safety record. After millions of users, fewer than 50 cases of serious toxicity have been reported, and most resolved without sequelae. "Normal use of DEET does not present a health concern to the general US population. DEET remains the gold standard."

CONCLUSION

Only DEET products offered long-lasting protection after a single application. Currently available non-DEET repellants cannot be relied on to provide prolonged protection in environments where mosquito-borne diseases are a substantial threat.

NEJM July 4, 2002; 347: 13-18 Original investigation, first author Mark S Fradin, Chapel Hill Dermatology, Chapel Hill NC. www.nejm.org

=====
