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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS*

JANUARY 2009

A Higher Sodium/Potassium Excretion Ratio Was Associated With Increased Risk Of CVD.

1-1 JOINT EFFECTS OF SODIUM AND POTASSIUM INTAKE ON SUBSEQUENT CARDIOVASCULAR DISEASE: *The Trials of Hypertension Prevention Follow-up Study (TOHP)*

Lower levels of sodium intake and higher levels of potassium intake are associated with reduced risk of hypertension. Long-term interventions aimed at sodium reduction and potassium substitution may lead to a reduced risk of CVD.

This follow-up study was based on intermittent measurements of 24-hour urinary electrolyte excretion. It assessed the relation of 24-h urinary excretion of sodium and potassium and their ratio with subsequent CVD (stroke, myocardial infarction, coronary revascularization, or CVD mortality) through 10 to 15 years of post trial follow-up.

Excretion of sodium increased with increasing BMI,

For potassium excretion, there was a statistically significant *inverse* trend across quartiles, with a 45% reduction in risk of CVD among participants in the highest quartile vs the lowest quartile.

For the sodium to potassium ratio, the trend across quartiles was statistically significant:

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Na/K excretion ratio	<2.2			>3.4
Relative Risk of CVD	1.00	1.06	1.35	1.77
Cardiovascular events (%)	7.7	7.4	8.4	10.1

Absolute difference Q4 – Q1 = 2.4%; NNT = 41 (*My calculations RTJ*)

The sodium to potassium excretion ratio displayed the strongest association with risk of CVD. For each unit of increase in the ratio, there was a 24% increase in risk of CHD and stroke.

Conclusion: The totality of evidence suggests that lowering dietary sodium intake, while increasing potassium consumption at the population level might reduce incidence of CVD.

Of interest—sodium intake increased as BMI increased.

See Practical Pointers May 2007 [5-1] for an excellent discussion of sodium and potassium in the pathogenesis of hypertension abstracted from NEJM May 10, 2007; 359: 1966-78. It stresses the need for a higher potassium intake as well as a lower sodium intake.

I believe control of potassium and sodium intake is essential for a reduction in population prevalence of hypertension and CVD. On a population basis, this intervention could have a beneficial effect matching any other intervention.

"Ancillary Testing Adds Little To The Prediction Of Individual Cardiovascular Risk. It Does Not Affect Care, Lifestyle, Adherence, or Clinical Outcomes"

1-2 EVALUATING CARDIOVASCULAR RISK ASSESSMENT FOR ASYMPTOMATIC PEOPLE

Formal risk prediction tools increase accuracy of clinical assessment of future risk of cardiovascular disease in asymptomatic patients. Prediction tools that are easy to use and that integrate the Framingham criteria into one global risk score have evolved to aid risk assessment.

New putative clinical risk factors have been described: Chronic kidney disease, metabolic syndrome, and numerous laboratory markers.

Do ancillary tests in asymptomatic patients improve accuracy of predicting cardiovascular risk? What effect might they have on patient care, behavior, and clinical outcomes?

Indiscriminant testing of asymptomatic patients could waste resources, increase anxiety, and lead to interventions that have not been proved.

A positive or abnormal value for a *new* risk factor will be more useful if:

- The more abnormal the test, the greater the risk of an event.
- The strong association persists after the contribution of traditional risk factors has been taken into account.
- The test discriminates well between individuals who have an event in the future and those who will not.
- The testing method is reliable and standardized.
- The test value leads to a change in risk estimates, which are large enough to justify altering the intended management.
- Results of clinical trials predict that the altered management plan will improve outcomes.

The article considers laboratory tests; coronary artery imaging (both for carotid calcification and obstructive disease); carotid and peripheral artery screening; metabolic syndrome; resting and exercise EKG.

Implications for clinical practice.

According to the available evidence, ancillary testing in most asymptomatic patients adds little to the prediction of individual cardiovascular risk. It does not affect care, lifestyle, adherence, or clinical outcome.

Ancillary testing in most middle age people is premature and potentially wasteful of resources.

An alternative strategy, which needs to be studied, is to ensure that all adult patients (and their doctors) are aware of their cardiovascular risk by using simple, accessible clinical risk calculators, and adopt a management plan appropriate to their level of risk.

"No randomized evidence to date has shown that informing clinicians and patients of the absolute risk of cardiovascular events leads to changes in care or improvement in outcomes."

In primary care, we have little use for additional risk markers. Our problem is to apply the ones we already have.

"NSAIDs Should Be Avoided In All Patients With HF."

1-3 INCREASED MORTALITY AND CARDIOVASCULAR MORTALITY ASSOCIATED WITH USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN CHRONIC HEART FAILURE

Accumulating evidence indicates there is an increased cardiovascular risk associated with NSAID use, particularly in patients with established cardiovascular disease (**CVD**).

NSAIDs are available OTC and are used by many elderly patients. The widespread use of NSAIDs and the general perception that they are low-risk drugs prompted this study.

Entered (in 1993-2004) and followed over 107 000 patients (mean age 75) who had survived their first hospitalization for heart failure (HF). Determined subsequent use of NSAIDs from the nationwide registry of Denmark. A total of over 36 000 patients claimed at least one prescription for NSAIDs after discharge. Determined total deaths, and hospitalizations from HF and myocardial infarction over a 10 year period.

A total of 60 974 patients died during the study. The hazard ratio for death in those taking a NSAID (compared with taking no NSAID) was: diclofenac 2.08; celecoxib 1.75; rofecoxib 1.70; ibuprophen 1.31; naproxin 1.22.

There was an increased risk of death associated with most NSAIDs. Risk highest for rofecoxib, celecoxib, and diclofenac.

There was a clear dose-dependent increase in risk. Low doses of ibuprofen (under 1200 mg/d) and

naproxin (under 500 mg/d) were not associated with increased mortality. Higher doses were associated with increased risk.

Hospitalizations because of MI (9%) and HF (37%) increased in a dose-dependent manner with use of both selective and non-selective NSAIDs Hazard ratios were similar for all types except for rofecoxib, which was associated with the highest risk in a dose-dependent manner.

"We found increased mortality and increased risk of hospitalization for MI or HF related to use in an unselected cohort of patients discharged alive after their first hospitalization because of HF."

Conclusion: Treatment with NSAIDs, both selective and non-selective, in patients with chronic HF is associated with increased mortality and cardiovascular morbidity in a dose-dependent manner.

HF patients who persist in using NSAIDs should be advised to use ibuprophen or naproxin in low doses.

Diclofenac, naproxin, and ibuprophen are much cheaper (compared with OTC price) when purchased by prescription at several pharmacies offering prescriptions at $4.00 for a 30-day supply and $10.00 for a 90-day supply.

Weight Reduction Was Associated With A Decrease In Incontinence

1-4 WEIGHT LOSS TO TREAT URINARY INCONTINENCE IN OVERWEIGHT AND OBESE WOMEN

Obesity is an established and modifiable risk factor for urinary incontinence (**UI**) Conclusive evidence for a beneficial effect of weight loss is lacking.

This study asked if a behavioral weight–reduction intervention would reduce incontinence.

A randomized trial of overweight and obese women assigned: 1) patients (n = 220) to an intensive six-month weight-loss program (diet, exercise, and behavioral modification), or 2) to a structured education program (n = 112).

All had at least 10 UI episodes per day.

Participants were given a reduced-calorie diet (1200 to 1500 kcal) providing no more than 30% of calories from fat. They were encouraged to gradually increase exercise (brisk walking) to at least 200 minutes a week.

Baseline (means and %) : Age 53; BMI 36; postmenopausal 56%; 24-h involuntary urine loss 33g; urge predominant 32%; stress predominant 17%; mixed 33%

At 6 months (% change)	Weight-loss group	Control
Body weight	-8	-2

UI	-47	-28
Stress incontinence	-58	-33
Urge incontinence	-42	-26

(Overall, more women with stress incontinence improved than those with urge incontinence.)

A higher number of women in the weight-loss group had a reduction of at least 70% in total number of incontinence episodes per week. (41% vs 22%). A few had 100% reduction (7% vs 4%)

Conclusion: A 6-month behavioral weight loss intervention reduced the frequency of self-reported UI episodes among overweight and obese women.

I congratulate these patients for losing 8% of body weight in 6 months. It will be interesting to know if they maintained weight loss and if their incontinence remained less frequent over then next few years.

I believe primary care clinicians can, with assurance, advise obese patients that reduction in UI is another benefit of weight loss.

Combined Agents Are Clearly The Wiser Choice

1-5 FDA PANEL ADVISES BANNING 2 POPULAR ASTHMA DRUGS

The panel, which advises the FDA on safety issues, recommends that the FDA ban marketing of 2 popular drugs—the long acting beta-agonists formoterol and salmeterol. These inhaled drugs, when used alone, are associated with increased risk of rare, but serious, adverse effects—in some cases death.

The committee advises banning the drugs when used alone—not when combined with a corticosteroid.

NIH guidelines recommend asthma patients first receive low-dose inhaled corticosteroid. Then, if symptoms remain uncontrolled, they could receive additional medications.

“Our recommendation is that the combined agent is clearly the wiser choice.”

The FDA typically follows the panel’s recommendations.

The FDA may or may not follow the advice of the panel.

Formoterol and salmeterol already have black box warnings. This article emphasizes caution for primary care.

Antidepressants Were Associated With Improvement.

1-6 TREATMENT OF FIBROMYALGIA SYNDROME WITH ANTIDEPRESSANTS: *A Meta-analysis*

FMS is described as chronic widespread pain with a minimum of 11 of 18 defined tender points. Fatigue and non-restorative sleep are common. Most patients report additional somatic and psychological symptoms.

This systematic review determined efficacy of antidepression drugs in the treatment of FMS. The goals of the study were: 1) to evaluate effects of treatment of FMS-related symptoms; 2) to determine internal validity (methodological quality); and 3) external validity (generalizability). It included 18 randomized, controlled trials of antidepressants prescribed for outpatients. (Mean duration = 8 weeks; mean age = 47; mostly female) None had severe somatic disease.

"We found strong evidence for the efficacy of antidepressants in reducing pain, sleep disturbances, depressed mood, and for improving HRQOL."

This meta-analysis does not allow a definitive conclusion regarding superiority of one class of antidepressant over another. However, duloxetine is the only one the FDA approves for treating FMS. Only duloxetine has demonstrated efficacy for FMS patients with, as well as without, major depressive disorder.

The internal and external validity of the RCTs analyzed was limited.

Short-term use of amitriptyline and duloxetine can be considered for the treatment of pain and sleep disturbance in patients with FMS—based on the number of patients studied (duloxetine) and the effects size (amitriptyline).

Goals of treatment should be defined (no cure, but possible symptom reduction). Evidence of long-term effects is lacking.

Conclusion: In patients with FMS, antidepressants are associated with improvements in pain, depression, fatigue, sleep, and HRQOL.

This meta-analysis provides primary care clinicians with nebulous data and nebulous guidance.

Primary care clinicians and their patients must rely on trial and error when applying antidepressant therapy for FMS. Individual patients should be informed about risks and benefits in order to make an informed choice about whether they wish to start drug therapy. They should be informed at outset that therapy will not cure—it may improve symptoms.

With so many drugs available—where to start? I believe a reasonable choice would be amitriptyline, given in low dose at bedtime.

Is This A Reasonable Recommendation For Primary Care?

1-7 CLINICIANS ADVISED TO STEP UP HIV TESTS

An estimated one million individuals in the US have human immunodeficiency virus (**HIV**) infection. Of these, about 20% are not aware of their status.

Experts on HIV/AIDs care have called upon health care professionals to follow federal recommendations (issued more than 2 years ago by the CDC) that call for routine HIV testing *all* patients age 13 to 64. (*Patients are given an opportunity to opt out of the test. RTJ)*

Rapid screening saliva test is highly sensitive and specific. "The test is cheap, and easy. It's almost perfect in terms of getting positive or negative results. If positive, it requires confirmatory testing.

"Testing for HIV should be as routine as the flu shot".

HIV infection can be approached as a chronic, rather than a fatal illness. Routine testing could help tens of thousands receive lifesaving treatment while preventing new infections. These individuals are more likely to transmit their infection to others.

Lack of reimbursement by insurers is a barrier to testing. Medicare and Medicaid do not routinely reimburse.

The recommendation has not been widely implemented by clinicians.

JAMA January 28, 2009; 301: 366 "Medical News and Perspectives" by Rebecca Voelker, JAMA staff.

The State of North Carolina has changed the rules for testing: eliminating the requirement for pre-test counseling, and post-test counseling for those with a negative test. HIV test can be included in a panel of tests using a general consent for treatment. Ie, the patients must be notified that they will be tested, but a specific consent for testing is not required.

I can think of reasons why testing is not implemented in primary care.

1) *Time: Explaining the reason for the procedure, as well as performing it, requires time primary care clinicians can ill afford*
2) *If one million patients in the US have HIV, and 20% are not aware of it, then only 200 000 individuals have unknown HIV. To discover them, about 200 million individuals need be tested at a considerable cost. I believe a more reasonable course would be to test selected patients—those who would be more likely to harbor HIV. Testing select patients in emergency departments would be reasonable*
3) *How much does the test cost? Who pays? Would a 60 year old lady be offended when she is billed for a HIV test?*
4) *Is one-time testing the recommendation? How about the many individuals who might*

acquire the infection after the first test?

5) False positives: No matter how high the specificity of the test, when a large number of individuals are tested, some false-positives will occur. This leads to confirmatory testing with added time spent, added expense, and a high degree of anxiety.

This 6-Year Trial Reports No Benefits From Intensive Control

1-8 GLUCOSE CONTROL AND VASCULAR COMPLICATIONS IN VETERANS WITH TYPE-2 DIABETES

The effects of intensive glucose control on cardiovascular (**CV**) events in patients with long-standing type-2 diabetes (**DM-2**) remain uncertain. Two recent large studies of intensive control reported no significant decrease in cardiovascular events..

This VA study compared the effects of intensive control vs standard glucose control on CV events. It randomized 1791 military veterans with DM-2 (mean age 60; 40% with previous CV disease) to 1) Intensive control, or 2) Standard control. Follow-up = 6 years.

The goal was an absolute HbA1c reduction of 1.5% in the intensive group as compared with the control group.

At 6 months, mean HbA1c decreased to 8.4% in the standard group, and to 6.9% in the intensive group, and remained at these levels throughout 6 years. The prespecified goal of an absolute difference of 1.5% between groups was met.

At 6 years, the observed CV event rate was 33.5% in the standard group and 29.5% in the intensive group—a relative reduction of 12% (Hazard ratio = 0.88; CI = 0.74 to 1.05)

No significant differences between groups in time to death from CV disease.

"For now, appropriate management of hypertension, dyslipidemia, and other cardiovascular risk factors appears to be the most effective approach to preventions of cardiovascular morbidity and mortality."

Conclusion: Over 6 years, intensive glucose control did not significantly reduce cardiovascular events in patients with previously diagnosed type-2 diabetes.

I would agree that lipid, weight, and BP control are the most effective approaches to reducing cardiovascular events in patients with DM-2, as well as in those without.

I would not agree that glucose control lacks benefit on long-term reduction of cardiovascular events:

1) Six years of intensive control is insufficient time to judge benefits. Beginning better control at

an earlier age and continuing for many years may lower CV complications. The classical link between DM-2 and peripheral atherosclerosis may take many years to develop.

2) Note that the observed event rate in the intensive group was 12% lower than in the standard group (confidence interval 0.74 to 1.05). Although this did not reach the standard criterion for statistical significance, a longer period of intensive control may have resulted in statistical significance.

3) The subjects had a high rate of established CV disease. They were at high risk. If intensive therapy was started before this risk was established, and continued for a longer time, the benefit may have been greater. Intensive control in patients with established CV disease may not be as beneficial as beginning control before CV is established.

4) Good control lessens microvascular complications. The study showed no benefit in reducing microvascular complications except for albuminuria. This, again, may have been due to insufficient time to observe a benefit.

5) Do these studies negate the classical link between diabetes and peripheral arteriosclerosis? I believe not.

6) DM-2 has for many years been considered a risk factor for CHD, equal to that of established CHD. Do these studies negate the classical link between diabetes and cardiovascular disease? I believe not.

7) Rosiglitazone in retrospect, may have been a poor therapeutic choice.

Intensive control, especially with insulin, leads to frequent hypoglycemia, weight gain, and probably an increase in death, especially in the elderly. We should be cautious in attempting intensive control in the elderly—not lowering HbA1c below 7%.

1-9 CDC PANEL RECOMMENDS PNEUMONIA VACCINE FOR SMOKERS.

The CDC Advisory Committee on Immunizations advises: "All smokers (*age 19-64*) should receive the 23-valent pneumococcal vaccine." This is the first time smokers have been targeted for vaccination.

Smokers are at increased risk of developing pneumococcal disease. More than half of adults with pneumococcal disease are current or former smokers.

Smoking can cause structural changes in the respiratory tract that may make individuals more vulnerable to respiratory infections (bacterial and viral). It can also dampen immune response systemically and locally within the lungs. *S pneumoniae* may adhere more readily to the epithelial cells of smokers.

There is evidence that cessation can reduce risk of respiratory infections.

All individuals over age 65, as well as those with asthma and COPD, should receive the vaccine. Many smokers may have been covered by previous recommendations.

JAMA December 17, 2008; 300: 2713 “Medical News and Perspectives” by Bridget M Kuehn, JAMA staff.

ABSTRACTS JANUARY2009

A Higher Sodium/Potassium Excretion Ratio Was Associated With Increased Risk Of CVD.

1-1 JOINT EFFECTS OF SODIUM AND POTASSIUM INTAKE ON SUBSEQUENT CARDIOVASCULAR DISEASE: *The Trials of Hypertension Prevention Follow-up Study (TOHP)*

Lower levels of sodium intake and higher levels of potassium intake are associated with reduced risk of hypertension. Long-term interventions aimed at sodium reduction and potassium substitution may lead to a reduced risk of CVD.

This follow-up study was based on intermittent measurements of 24-hour urinary electrolyte excretion. It assessed the effect of 24h urinary sodium and potassium excretion, as well as the sodium to potassium excretion ratio on long-term risk of CVD.

Conclusion: A higher sodium/potassium excretion ratio was associated with increased risk of CVD.

STUDY

1. The original TOHP studies[1] intermittently collected 24-hour urinary sodium and potassium excretion and calculated their ratio during; 1) an 18 month period, and 2) a subsequent 4 year period (1987-1990 and 1990-1995).
2. The present observational study for incidence of CVD began in 2000.
3. All subjects (n = 2275) were age 30 to 54 at baseline. All had prehypertension. None was on a sodium reduction intervention.
4. Assessed the relation of 24-h urinary excretion of sodium and potassium and their ratio with subsequent CVD (stroke, myocardial infarction, coronary revascularization, or CVD mortality) through 10 to 15 years of post trial follow-up.

RESULTS

1. Among the 2275 subjects, 193 (8.5%) experienced a study end point.
2. Analysis of usual intake:

   Overall median urinary sodium 158 mmol/24 h (9.2 g/24h of NaCl)*

   Men = 171; women = 134

   Overall median urinary potassium 60 mmol/24 h (3.2 g /24h of KCl) *

   Median sodium to potassium ratio 2.8

   (* *my calculation. RTJ*)
3. Excretion of sodium increased with increasing BMI, from 145 mmol/24h in men with BMI < 25

to 196 mmol/24h in men with BMI > 30. (Similar increases in women.)

4. For sodium excretion, there was a trend toward increased risk with increasing excretion, but the trend was not statistically significant.
5. For potassium excretion, there was a statistically significant *inverse* trend across quartiles, with a 45% reduction in risk of CVD among participants in the highest quartile vs the lowest quartile.
6. For the sodium to potassium ratio, the trend across quartiles was statistically significant:

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Na/K excretion ratio	<2.2			>3.4
Relative Risk of CVD	1.00	1.06	1.35	1.77
Cardiovascular events (%)	7.7	7.4	8.4	10.1

Absolute difference Q4 – Q1 = 2.4%; NNT = 41 (*My calculations RTJ*)

DISCUSSION

1. The sodium to potassium excretion ratio displayed the strongest association with risk of CVD. For each unit of increase in the ratio, there was a 24% increase in risk of CHD and stroke.
2. Strength of this study was increased because sodium and potassium excretion were measured. The study did not depend on recall of dietary intake, which is less precise than urinary measurements.
3. "The joint activity of these 2 electrolytes may have an important biological role."
4. A recent study from Taiwan compared the effects of a potassium-enriched salt containing less sodium. Compared with a control group, there was a 41% reduction in CVD mortality.
5. The 2005 US dietary guidelines recommend consumption of potassium-risk foods such as fruits and vegetables, as well as consumption of little salt.

CONCLUSION

The totality of evidence suggests that lowering dietary sodium intake, while increasing potassium consumption at the population level might reduce incidence of CVD.

Archives Int Med January 12, 2009; 169: 32-40 Original investigation, first author Nancy R Cook, Brigham and Women's Hospital, Harvard Medical School, Boston Mass.

1 The Trials Of Hypertension Prevention (TOHP I and TOHP II)

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"Ancillary Testing Adds Little To The Prediction Of Individual Cardiovascular Risk. It Does Not Affect Care, Lifestyle, Adherence, or Clinical Outcomes"

1-2 EVALUATING CARDIOVASCULAR RISK ASSESSMENT FOR ASYMPTOMATIC PEOPLE

Formal risk prediction tools increase accuracy of clinical assessment of future risk of cardiovascular disease in asymptomatic patients. Prediction tools that are easy to use and that integrate the Framingham criteria[1] into one global risk score have evolved to aid risk assessment.

New putative clinical risk factors have been described: Chronic kidney disease, metabolic syndrome, and numerous laboratory markers.

Do ancillary tests in asymptomatic patients improve accuracy of predicting cardiovascular risk? What effect might they have on patient care, behavior, and clinical outcomes?

Indiscriminant testing of asymptomatic patients could waste resources, increase anxiety, and lead to interventions that have not been proved. In the 35% of adults deemed to be at low risk (<5% in 10 years), further tests, even with abnormal results, may not justify further investigation and treatment. In the 25% of patients at high risk (>20% in 10 years) normal results from newer tests should not necessarily prompt discontinuation of aggressive prevention strategies. Patients in between might benefit from further testing.

A positive or abnormal value for a *new* risk factor will be more useful if:

- The more abnormal the test, the greater the risk of an event.
- The strong association persists after the contribution of traditional risk factors has been taken into account.
- The test discriminates well between individuals who have an event in the future and those who will not.
- The testing method is reliable and standardized.
- The test value leads to a change in risk estimates, which are large enough to justify altering the intended management.
- Results of clinical trials predict that the altered management plan will improve outcomes.

Laboratory tests: (*The article lists 29 new proposed CVD risk markers*.)

In general, tests are clinically useful if they correctly predict an event in 70% or more of cases. Thus far, however, studies that have assessed the predictive value of new single biomarkers in individual patients have shown no incremental value beyond traditional risk factors.

Coronary artery imaging:

1) CT scanning for coronary artery calcium: The largest study to date reported that scores above 10 were independently predicative of all-cause mortality after adjustment for traditional risk factors. When scores were compared with age alone as a continuous variable, the discrimination difference was attenuated. This implies that age is the single most important predictor of death and extent of coronary artery calcification.

2) Tomography is also used to identify substantial obstructive coronary disease (>50% luminal obstruction) including non-calcified plaque. Current expert consensus recommends avoiding CT in risk assessment for asymptomatic people at low risk because of carcinogenic risk associated with radiation and the possibility of iatrogenic morbidity incurred by imaging. Pulmonary lesions are identified in up to 20% of people who undergo screening. Most are benign.

Carotid and peripheral artery screening:

Thickening of the carotid media and a low ankle/brachial index are associated with increased risk of CHD after adjustment for traditional risk factors. However, no recommendations exist for routine use of vascular ultrasound in risk prediction.

Metabolic syndrome:

Is reported to increase risk by 50% after adjustment after traditional risk factors. Most studies note little or no added improvement in risk prediction. Its value remains unclear.

Electrocardiography resting and exercise:

Major abnormalities of resting EKG are associated with increased risk. But outcomes are incorrectly classified in a third of the cases.

Exercise tests reporting ST segment deviations are little better than the Framingham score.

More sophisticated stress EKG scores (based on exercise time, extent of ST deviation, and provocation of chest pain) show more promise.

Implications for clinical practice.

According to the available evidence, ancillary testing in most asymptomatic patients adds little to the prediction of individual cardiovascular risk. It does not affect care, lifestyle, adherence, or clinical outcome.

To guide interpretation of results, we need information on the potential harms and cost-effectiveness of additional testing; generalizability of results to populations with different ethnicities and comorbidities; standardization of test assays; and validation of population norms.

Ancillary testing in most middle age people is premature and potentially wasteful of resources.

An alternative strategy, which needs to be studied, is to ensure that all adult patients (and their doctors) are aware of their cardiovascular risk by using simple, accessible clinical risk calculators such as QRISK[2] and adopt a management plan appropriate to their level of risk.

"No randomized evidence to date has shown that informing clinicians and patients of the absolute risk of cardiovascular events leads to changes in care or improvement in outcomes."

BMJ January 17, 2008; 338: 164-68 "Clinical Review" by Ian A Scott, Princess Alexandria Hospital, Brisbane, Australia.

1 Age, sex, total cholesterol, HDL-cholesterol, systolic BP, smoking, diabetes, and left ventricular hypertrophy. Recent additions include existing treatment for hypertension, and a family history of premature CHD.

2 www.qr2.dyndns,org This risk calculator is more extensive than the Framingham. It includes age; sex; diabetes; history of CVD; smoking; atrial fibrillation; chronic kidney disease; treatment for high BP; rheumatoid arthritis; cholesterol/HDL ratio; BMI, systolic BP, and especially ethnicity.

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"NSAIDs Should Be Avoided In All Patients With A History of HF."

1-3 INCREASED MORTALITY AND CARDIOVASCULAR MORTALITY ASSOCIATED WITH USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN CHRONIC HEART FAILURE

Accumulating evidence indicates there is an increased cardiovascular risk associated with NSAID use, particularly in patients with established cardiovascular disease (**CVD**).

Recently the AHA recommended that selective COX-2 inhibitors should be avoided in patients with established CVD and in those at high risk for CVD.

NSAIDs are available OTC and are used by many elderly patients. The widespread use of NSAIDs and the general perception that they are low-risk drugs prompted this study.

Conclusion: NSAIDs are associated with increased risk of death in patients with a history of HF

STUDY

1. Entered (in 1993-2004) and followed over 107 000 patients (mean age 75) who had survived their first hospitalization for heart failure (HF).
2. Determined subsequent use of NSAIDs from the nationwide registry of Denmark. A total of over 36 000 patients claimed at least one prescription for NSAIDs after discharge.

3. Determined total deaths, and hospitalizations from HF and myocardial infarction over a 10 year period.

RESULTS

1. A total of 60 974 patients died during the study. The hazard ratio for death in those taking a NSAID (compared with taking no NSAID) was: diclofenac 2.08; celecoxib 1.75; rofecoxib 1.70; ibuprophen 1.31; naproxin 1.22.

2.

	Deaths per 1000 person years	Absolute risk increase (%)	NNH*
Rofecoxib	329	11	9
Celecoxib	288	7	14
Diclofenac	308	9	11
Ibuprophen	236	2	53
Naproxen	237	2	51
No NSAID	218		

(* = number needed to treat to harm one patient per year.)

4. There was an increased risk of death associated with most NSAIDs. Risk highest for rofecoxib, celecoxib, and diclofenac.

5. There was a clear dose-dependent increase in risk. Low doses of ibuprofen (under 1200 mg/d) and naproxin (under 500 mg/d) were not associated with increased mortality. Higher doses were associated with increased risk.

	Dose (mg/d)	Hazard ratio for death
Rofecoxib	<25	1.4
	> 25	3.5
Celecoxib	< 200	1.3
	> 200	2.7
Diclofenac	< 100	1.3
	> 100	5.5
Ibuprophen	<1200	1.0
	>1200	2.8
Naproxen	<500	0.8
	>500	2.0

5. Hospitalizations because of MI (9%) and HF (37%) increased in a dose-dependent manner with

use of both selective and non-selective NSAIDs Hazard ratios were similar for all types except for rofecoxib, which was associated with the highest risk in a dose-dependent manner.

DISCUSSION

1. “We found increased mortality and increased risk of hospitalization for MI or HF related to use in an unselected cohort of patients discharged alive after their first hospitalization because of HF.”
2. The absolute risk increase of adverse effects (11% for rofecoxib, 7% for celecoxib, and 9% for diclofenac), and the low number needed to harm are worrisome because 34% of patients with HF received a prescription for an NSAID. “Apparently, awareness is low among physicians concerning international clinical recommendations that discourage use of NSAIDs in patients with HF.”
3. NSAIDs influence renal function and the regulation of fluid balance, causing fluid retention and worsening HF. They also increase risk of hypertension. Animal studies have reported that COX-2 inhibition can induce structural changes in the myocardium and impair systolic function. “A causative relationship between NSAID use and cardiovascular risk in patients with established HF is therefore highly probable.”
4. It is generally agreed that rofecoxib is associated with increased risk. The association with celecoxib has been debated. Now, “It seems that celecoxib may be particularly harmful in patients with established cardiovascular disease.”
5. In this study, naproxin at high doses was associated with increased risk. “Physicians must exert caution in using naproxin in patients with HF.”
6. Diclofenac, whose COX-2 selectivity is similar to that of celecoxib, is the NSAID associated with highest risk. (It is dispensed OTC in many countries.)
7. Most patients in the study used NSAIDs for a short time. This indicates relatively acute cardiotoxic effects.
8. “NSAIDs should be avoided in all patients with HF.”

CONCLUSION

Treatment with NSAIDs, both selective and non-selective, in patients with chronic HF is associated with increased mortality and cardiovascular morbidity in a dose-dependent manner.

The balance between risk and benefit requires careful consideration when any NSAID is given to patients with HF.

Archives Int Med January 26, 2009 Original investigation, first author Gunnar H Gislason, Genlotte University Hospital, Hellerup, Denmark

Generic name	Brand name	OTC
Rofecoxib	*Vioxx* (Removed from market)	
Celecoxib	*Celebrex* (Searle)	
Diclofenac	*Arthrotec* (Searle) (Combined with a prostaglandin) *Voltarin* (Novartis) (Enteric coasted)	Diclofenac
Ibuprophen		Ibuprophen Motrin Advil
Naproxin	*Naproxin* (Roche) *Anaprox* (Roche)	Naproxin Naprosyn Aleve

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Weight Reduction Was Associated With A Decrease In Incontinence

1-4 WEIGHT LOSS TO TREAT URINARY INCONTINENCE IN OVERWEIGHT AND OBESE WOMEN

Urinary incontinence (**UI**) affects millions of women in the US. It has adverse effects on quality of life. Obesity is an established and modifiable risk factor for UI. Conclusive evidence for a beneficial effect of weight loss is lacking.

This randomized trial determined whether a behavioral weight–reduction intervention would reduce incontinence.

Conclusion: Weight reduction was associated with a decrease in UI.

STUDY

1. Randomized trial of overweight and obese women assigned: 1) patients (n = 220) to an intensive six-month weight-loss program (diet, exercise, and behavioral modification), or 2) to a structured education program (n = 112).
2. All had at least 10 UI episodes per day.
3. Participants were trained to complete a 7-day diary of voiding.

4. They identified each episode of UI as:
   1) Stress incontinence (involuntary loss of urine with coughing, sneezing, straining, or exercise, or
   2) Urge incontinence (loss of urine associated with a strong need or urge to void).
5. The weight loss program was designed to produce an average loss of 7% to 9% of body weight within 6 months. Participants were given a reduced-calorie diet (1200 to 1500 kcal) providing no more than 30% of calories from fat. They were encouraged to gradually increase exercise (brisk walking) to at least 200 minutes a week.
6. 24-h involuntary urine loss was determined by weighing urinary-incontinence pads.
7. Primary outcome = change in the number of incontinence episodes reported in a 7-day diary.

RESULTS

1. Baseline (means and %) : Age 53; BMI 36; postmenopausal 56%; 24-h involuntary urine loss 33g; urge predominant 32%; stress predominant 17%; mixed 33%
2. At 6 months (% change)

	Weight-loss group	Control
Body weight	-8	-2
UI	-47	-28
Stress incontinence	-58	-33
Urge incontinence	-42	-26

   (Overall, more women with stress incontinence improved than those with urge incontinence.)
3. A higher number of women in the weight-loss group had a reduction of at least 70% in total number of incontinence episodes per week. (41% vs 22%)
4. A few had 100% reduction (7% vs 4%)
5. Women in the weight-loss group perceived a lower volume of urine loss, and regarded incontinence as less of a problem.
6. The investigators observed no evidence of a benefit from pelvic floor exercises.

DISCUSSION

1. A higher proportion of women in the weight-loss group than in the control group reported clinically meaningful reduction in UI. They were also more satisfied with the outcome.
2. “This result suggests that overweight or obese women with stress, urge, or mixed incontinence may benefit from weight loss.”
3. A possible mechanism: lower intraabdominal pressure due to loss of central adiposity leading to decrease in bladder pressure.

CONCLUSION

A 6-month behavioral weight loss intervention reduced the frequency of self-reported UI episodes among overweight and obese women.

NEJM January 29, 2009; 360; 481-90 Original investigation, first author Leslee L Subak, University of California, San Francisco.

The "Program to Reduce Incontinence by Diet and Exercise" (PRIDE)

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Combined Agents Are Clearly The Wiser Choice

1-5 FDA PANEL ADVISES BANNING 2 POPULAR ASTHMA DRUGS

The panel, which advises the FDA on safety issues, recommends banning marketing of 2 popular drugs—the long acting beta-agonists formoterol and a salmeterol. These inhaled drugs, when used alone, are associated with increased risk of rare, but serious, adverse effects—in some cases death.

The committee advises banning the drugs when used alone—not when combined with a corticosteroid.

NIH guidelines recommend asthma patients first receive low-dose inhaled corticosteroid. Then, if symptoms remain uncontrolled, they could receive additional medications.

"Our recommendation is that the combined agent is clearly the wiser choice."

The FDA typically follows the panel's recommendations.

JAMA January 28, 2009; 301: 365-66 "Medical News and Perspectives" by Bridget M Kuehn, JAMA staff**.**

Formoterol (*Foradil*; Schering)

Salmeterol (*Serevent*; GSK)

Budesonide + formoterol (*Symbicort*; AZ) Salmeterol + fluticasone (*Advair*; GSK)

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Antidepressants Were Associated With Improvement.

1-6 TREATMENT OF FIBROMYALGIA SYNDROME WITH ANTIDEPRESSANTS: *A Meta-analysis*

FMS is described as chronic widespread pain with a minimum of 11 of 18 defined tender points. Fatigue and non-restorative sleep are common. Most patients report additional somatic and psychological symptoms.

Patients with FBS experience disability and reduced health-related quality-of-life (**HRQOL**).

Whether FMS is a distinct disorder or a manifestation of an underlying disorder (eg, inflammatory arthritis; depression) is controversial. Some classify FMS as a functional somatic syndrome.

This systematic review determined efficacy of antidepression drugs in the treatment of FMS. The goals of the study were: 1) to evaluate effects of treatment of FMS-related symptoms; 2) to determine internal validity (methodological quality); and 3) external validity (generalizability).

Conclusion: Antidepressants were associated with improvement.

STUDY

1. Systematic review included 18 randomized, controlled trials of antidepressants prescribed for outpatients. (Mean duration = 8 weeks; mean age = 47; mostly female) None had severe somatic disease. A total of 1423 patients completed treatment; 916 were on antidepressants.
2. Allowed patients to take acetaminophen, aspirin, and NSAIDS.
3. Summarized effects on pain; fatigue; sleep; depressed mood; and HRQOL. Measured outcomes at end of treatment.
3. Attempted to determine effects of various classes of antidepressants.

RESULTS

1. Antidepressants were strongly associated with improvements in:

	Standard mean difference
Pain	-0.43
Fatigue	-0.13
Depressed mood	-0.26
Sleep	-0.32
HRQOL	-0.31

2. Effect sizes of different classes of drugs:

	TCAs[1]	SSRIs[2]	SSNRIs[3]
Reducing pain	-1.64	-0.39	-0.36
Reducing fatigue	-1.12	-0.17	-0.08
Improving sleep	-1.84	-0.23	-0.31
Improved HRQOL	-0.31	-0.41	-0.31
Improved mood	NS	-0.37	-0.26

3. Adverse effects:

Median rates of reported adverse effects: Antidepressants 76%; Placebo 63%

Dropout due to adverse effects: Antidepressants 16%%; Placebo 8%

DISCUSSION

1. "We found strong evidence for the efficacy of antidepressants in reducing pain, sleep disturbances, depressed mood, and for improving HRQOL."
2. This meta-analysis does not allow a definitive conclusion regarding superiority of one class of antidepressant over another, However, duloxetine is the only drug the FDA approves for treating FMS. Only duloxetine has demonstrated efficacy for FMS patients with, as well as without, major depressive disorder.
3. The internal validity of the RCTs analyzed was limited. Adherence was not measured. No study controlled for consumption, dose, adverse effects, or effects of concomitant analgesics.
4. The external validity was limited. Studies were of short duration. Optimum treatment duration not determined. No definitive information on treatment of men and patients over age 65. No information about treatment of patients with concomitant severe somatic disease. Evidence of long-term effects is lacking.
5. Short-term use of amitriptyline and duloxetine can be considered for the treatment of pain and sleep disturbance in patients with FMS—based on the number of patients studied (duloxetine) and the effects size (amitriptyline).
6. Goals of treatment should be defined (no cure, but possible symptom reduction).
7. "Our findings are mainly consistent with published literature."

CONCLUSION

In patients with FMS, antidepressants are associated with improvements in pain, depression, fatigue, sleep, and HRQOL.

JAMA January 14, 2008; 301: 198-209 "Clinical Review", first author Winifred Hauser, Klinikum Saarbrucken, Saarbrucken, Germany.

1 Tricyclic Antidepressants

Amitriptyline (*Elavil*)

Nortriptyline (*Pamelor*)

2 Selective Serotonin Reuptake Inhibitors

Fluoxetine (*Prozac*) .

Paroxetine (*Paxil*)

Citalopram (*Celexa*)

3 Selective Serotonin and Norepinephrine Reuptake Inhibitors

Duloxetine (*Cymbalta*; Lilly)

Most of these drugs are available as generics by prescription—several for $4 for a month's supply

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Is This A Reasonable Recommendation For Primary Care?

1-7 CLINICIANS ADVISED TO STEP UP HIV TESTS

An estimated one million individuals in the US have human immunodeficiency virus (**HIV**) infection. Of the estimated 1 million individuals in the US with HIV infection, about 20% are not aware of their status.

Experts on HIV/AIDs care have called upon health care professionals to follow federal recommendations (issued more than 2 years ago by the CDC) that call for *routine* HIV testing *all* patients age 13 to 64. (*Patients are given an opportunity to opt out of the test. RTJ)*

Rapid screening saliva test is highly sensitive and specific. "The test is cheap, and easy. It's almost perfect in terms of getting positive or negative results. If positive, it requires confirmatory testing.

"Testing for HIV should be as routine as the flu shot".

HIV infection can be approached as a chronic, rather than a fatal illness. Routine testing could help tens of thousands receive lifesaving treatment while preventing new infections. These individuals are more likely to transmit their infection to others.

Lack of reimbursement by insurers is a barrier to testing. Medicare and Medicaid do not routinely reimburse.

The recommendation has not been widely implemented by clinicians.

JAMA January 28, 2009; 301: 366 "Medical News and Perspectives" by Rebecca Voelker, JAMA staff.

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This 6-Year Trial Reports No Benefits From Intensive Control

1-8 GLUCOSE CONTROL AND VASCULAR COMPLICATIONS IN VETERANS WITH TYPE-2 DIABETES

Intensive control of type-2 diabetes (**DM-2**) reduces the progression on micro-vascular disease.

The effects of intensive glucose control on cardiovascular events in patients with long-standing type-2 diabetes (**DM-2**) remain uncertain. Epidemiologic studies have not been consistent on this point.

Two recent large studies [1,2] reported no significant decrease in cardiovascular events with intensive glucose control.

This VA study compared the effects of intensive control vs standard glucose control on CV events.

Conclusion: Intensive control over 6 years had no statistically significant benefits.

STUDY

1. Randomized 1791 military veterans with DM-2 (mean age 60) to: 1) Intensive control, or
   2) Standard control. The goal was an absolute reduction of 1.5% HbA1c in the intensive group as compared with the control group.
2. Previously, all had suboptimal response to therapy; 40% had a previous cardiovascular event.
3. Intervention:
   1) Intensive Control
      A. For patients with a BMI 27 and over—metformin + rosiglitazone
      B. Patients with BMI under 27—glimepiride + rosiglitazone
         (All started on maximal doses.)
      C. Insulin was added for those who did not achieve HbA1c less than 6%
   2) Standard Control
      A. For patients with a BMI 27 and over—metformin + rosiglitazone
      B. Patients with BMI under 27—glimepiride + rosiglitazone
         (All started on half maximal doses)
      C. Insulin was added for those who did not achieve HbA1c less than 9%
   3) All received a statin drug and aspirin.
   4) Other cardiovascular risk factors were treated uniformly.
4. Primary outcome = time from randomization to the first occurrence of a major cardiovascular

event (a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene).

5. Subjects were also checked annually for neuropathic and microvascular outcomes.
6. Follow-up = 6 years; 85% completed the study or reached an endpoint.

RESULTS

1. Means and % at baseline: Age 60; sex chiefly male; HbA1c 9.4%; BMI 31; time since diagnosis of diabetes 12 years; previous cardiovascular event 40%; current smoking 16%; receiving insulin 52%; history of microvascular events 62%; history of hypertension 72% (BP > 140/90 or current treatment).
2. Lipid levels improved. BP was lowered in both groups.
3. Mean weight and BMI *increased* in both groups. More in the intensive group (+ 18 pounds; and + 2.6)
4. At 6 months, mean HbA1c decreased to 8.4% in the standard group, and to 6.9% in the intensive group, and remained at these levels throughout 6 years. The prespecified goal of an absolute difference of 1.5% between groups was met.
5. At 6 years, the observed event rate was 33.5% in the standard group and 29.5% in the intensive group—a relative reduction of 12% (Hazard ratio = 0.88; CI = 0.74 to 1.05)
6. No significant differences between groups in time to death from CV disease.
7. Sudden deaths; 11 in the intensive group; 4 in the standard group
8. Hypoglycemia occurred more frequently in the intensive group.
9. *Micro*vascular events: No significant differences between groups in number of new eye procedures; in progression of diabetic retinopathy or clinically important macular edema; or in decline in GFR. Worsening of albuminuria was greater in the standard group.

DISCUSSION

1. Lifestyle changes and control of BP and lipids can reduce development, progression, and complications associated with DM-2.
2. The study suggests that glucose control may reduce microvascular complications but not cardiovascular complications. In this study, microvascular complications were minimally controlled by intensive therapy over 6 years.
3. The UKPDS provided *contrary* evidence. One year after the end of this trial, there were no

significant differences in HbA1c. Despite this finding, over the next 10 years, in the previous intensive therapy group there was a reduction in risk of microvascular complications, myocardial infarction, and death from any cause. This delayed effect may have been associated with the cumulative effects of the previous better control of glycemia in the intensive group.

4. "For now, appropriate management of hypertension, dyslipidemia, and other cardiovascular risk factors appears to be the most effective approach to preventions of cardiovascular morbidity and mortality."

CONCLUSION

Intensive glucose control for 6 years did not reduce cardiovascular events in patients with previously diagnosed type-2 diabetes.

NEJM January 8, 2009; 360: 129-39 Original investigation by the Veterans Administration Diabetes Trial (VADT), first author William Duckworth, Phoenix VA Health Care Center, Phoenix, AZ

1 "Action in Diabetes and Vascular Disease to Control Cardiovascular Risk in Diabetes" (ADVANCE) NEJM 2008; 358: 2560-72

2. "Action to Control Cardiovascular Risk in Diabetes (ACCORD) NEJM 2008; 358: 2545-59

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