PRACTICAL POINTERS

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PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

DECEMBER 1999

LIPID CONTROL WITH SIMVASTATIN BENEFITS PATIENTS WITH IMPAIRED FASTING GLUCOSE

CAREGIVING AS A RISK FACTOR FOR MORTALITY

ALENDRONATE VS ESTROGEN FOR LONG-TERM BONE MASS PROTECTION

BETA-BLOCKADE WITH BISOPROLOL FOR HIGH RISK PATIENTS UNDERGOING SURGERY

REDUCING CARDIAC RISK IN SURGERY

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ANTI-IGE ANTIBODY FOR ASTHMA

USPHS/IDSA GUIDELINEDS FOR HIV INFECTED INDIVIDUALS.

JAMA, NEJM, LANCET
BRITISH MEDICAL JOURNAL
ARCHIVES OF INTERNAL MEDICINE
ANNALS OF INTERNAL MEDICINE

PUBLISHED BY PRACTICAL POINTERS, INC
EDITED BY RICHARD T. JAMES JR., M.D.
FIRST CHARLOTFE PHYSICIANS
300 BILLINGSLEY ROAD
CHARLOTTE NC 28211 USA

A public service publication. Copies on file in Charlotte AHEC library.

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HIGHLIGHTS (*AND COMMENTARY*) DECEMBER 1999

12-1 REDUCED CORONARY EVENTS IN SIMVASTATIN-TREATED PATIENTS WITH CORONARY HEART DISEASE AND DIABETES OF IMPAIRED FASTING GLUCOSE LEVELS.

In patients with established CHD, lowering cholesterol with simvastatin benefited patients with impaired fasting blood glucose (110 to 125) as well as patients with diabetes (FBG ≥ 126). Total and coronary mortality and major coronary events were reduced in both groups. (*This practical point stresses the importance of considering fasting blood glucose levels below the usual cut point for "diabetes".)* Archives Int Med December 13/27 1999; 2661-67

12-2 CAREGIVING AS A RISK FACTOR FOR MORTALITY

Elderly spouses acting as caregivers to their spouse were at increased risk for death. (*Primary care clinicians should care for the stressed spouse even if that spouse is not a patient.*) JAMA December 15, 1999; 282: 2215-19

12-3 ALENDRONATE AND ESTROGEN-PROGESTIN IN THE LONG-TERM PREVENTION OF BONE LOSS: Four-year Results from the Early Postmenopausal Intervention Cohort Study.

Four years of alendronate or estrogen-progestin was more effective than placebo in preserving bone mass in early postmenopausal women. (Primary prevention.) Two years after discontinuation, there was a residual, although waning, benefit of alendronate.

Estrogen-progestin was equally effective as alendronate in maintaining hip and total BMD, and more effective in maintaining spine and wrist BMD

Alendronate was well tolerated and can be used as an alternative to estrogen-progestin for prevention of osteoporosis.

All women at the menopause should adopt a program of osteoporosis prevention. (*Added drug treatment will benefit all, including those with a favorable lifestyle including adequate diet [calcium and vitamin D] and exercise.*) Annals Int Med December 21, 1999; 131: 935-43

12-4 THE EFFECT OF BISOPROLOL ON PERIOPERATIVE MORTALITY AND MYOCARDIAL INFARCTION IN HIGH-RISK PATIENTS UNDERGOING VASCULAR SURGERY

Bisoprolol (*Zebeta*) was associated with a marked reduction of perioperative death from cardiac causes and non-fatal MI in high-risk patients undergoing major vascular surgery. (*This is an important clinical application. Primary care clinicians should use beta-blockers more liberally)* NEJM December 9, 1999; 1789-94

12-5 REDUCING CARDIAC RISK IN NONCARDIAC SURGERY

In summary, the preceding study suggests that perioperative care will be characterized by fewer tests, fewer coronary revascularization procedures, more use of beta-blockers – and fewer complications. NEJM December 9, 1999; 1838-40

12-6 IS SIMPLE CLINICAL ASSESSMENT ADEQUATE FOR CARDIAC RISK STRATIFICATION BEFORE ELECTIVE NON-CARDIAC SURGERY?

"For most patients cardiac risk stratification before elective non-cardiac surgery requires only a knowledge of the risk associated with the procedure and simple clinical assessment." Patients undergoing high-risk abdominal and thoracic surgery and who have a history of ischemic heart disease, heart failure, insulin-treated diabetes and/or elevated plasma creatinine have increased risks of major cardiovascular complications. (*They will benefit from beta-blocker protection.*) Lancet November 27, 1999; 354: 1837-38

12-7 LOW RISK-FACTOR PROFILE AND LONG-TERM CARDIOVASCULAR AND NON-CARDIOVASCULAR MORTALITY AND LIFE EXPECTANCY

In this very large cohort study, individuals with total cholesterol < 200, BP ≤ 120/80, and who did not smoke, experienced lower long-term mortality and longer life expectancy than those with any one of these risk factors.
(*These are important goals to set for middle-aged and older patients.*) JAMA December 1, 1999; 282: 2012-18

12-8 NEW RECOMMENDATIONS FOR ADULT IMMUNIZATION

The Advisory Committee on Immunization Practices recommends the age for receiving flu vaccine be lowered from 65 to 50, in part because morbidity and mortality for influenza start to rise at age 50. JAMA December 15, 1999; 282: 2199

12-9 A PROSPECTIVE STUDY OF WEIGHT CHANGE AND HEALTH-RELATED QUALITY OF LIFE IN WOMEN

These longitudinal data indicated a strong association between weight change and change in health related quality of life among normal weight and overweight middle-aged women. Weight loss in overweight women can substantially improve physical functioning, vitality and bodily pain. Weight gain is associated with the declines.
(*Even young women can be assured that their quality of life will be enhanced if they do not gain weight. RTJ*)
JAMA December 8, 1999; 282: 2136-42

12-10 DIETARY SODIUM INTAKE AND SUBSEQUENT RISK OF CARDIOVASCULAR DISEASE IN OVERWEIGHT ADULTS

High sodium intake was strongly and independently associated with an increased risk of cardiovascular disease and all-cause mortality in overweight persons. Moderate reductions in sodium intake are recommended.

(*This does not lead to the conclusion that salt restriction would reduce risk. However, it seems a reasonable biologically-based conclusion. Compliance would be difficult, but overweight patients should be informed of the possible benefit since the harm-cost would be nil.*) JAMA December 1, 1999; 282: 2027-34

12-11 SMOKING AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN MEN WITH LOW LEVELS OF CHOLESTEROL

Current cigarette smoking was a major, independent risk factor for ASCVD in Korea despite the relatively low levels of cholesterol in the population. A low cholesterol conferred no protection against risks of smoking.
(*Smoking presents its own increased risk by its adverse effects on the endothelium.*) JAMA December 8, 1999; 282: 2149-55

12-12 NONINVASIVE GLUCOSE MONITORING

An automatic, non-invasive glucose-monitoring machine (Glucowatch) which makes frequent measurements demonstrated close agreement with blood glucose measurements obtained by finger stick. The machine provided more information about glucose levels than the current standard of care.
(*The FDA has given the machine a conditional approval.)* JAMA November 17, 1999; 282: 1839-44

12-13 QUINUPRISTIN/DALFOPRISTIN, A NEW ADDITION TO THE ANTIMICROBIAL ARSENAL

A new drug, quinupristin/dalfopristin (*Synercid*), is now licensed in the US. It is active against gram-positive bacteria, including difficult organisms such as methicillin-resistant *Staphylococcus aureus* , and vancomycin-resistant *Enterococcus faecium*, and penicillin-resistant and macrolide-resistant pneumococci. Its activity is exclusively against gram-positive pathogens.

The drug is specifically indicated when no other antibacterial agents are suitable. When mixed infections are suspected, quinupristin/dalfopristin should be used in combination with one or more agents active against nosocomial gram-negative bacteria. Lancet December 11, 1999; 354: 2012-13

12-14 THE ENERGY EXPENDED IN CHEWING GUM

Chewing led to a mean increase in energy expenditure of 11 kcal per hour, a 19% increase over baseline. In the same subjects, standing was associated with a mean increase of 11%, and walking 1 mile per hour with a mean increase of 106% above baseline.

If a person chewed gum during waking hours and changed no other component of energy balance, a yearly loss of over 10 pounds of body fat might be anticipated. (*This emphasizes the importance of small intermittent expenditures of energy [eg, walking up stairs instead of taking the elevator] in maintaining fitness.)* NEJM December 30, 1999; 341: 2100

12-15 THE YEAR IN REVIEW: THE THYROID

Review of some pointers about screening, thyroid eye disease, antithyroid drug therapy, and treatment of hypothyroidism and thyroid nodules. Annals Int Med December 21, 1999; 131: 959-962

12-16 RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR (ALTEPLASE) FOR ISCHEMIC STROKE 3 TO 5 HOURS AFTER SYMPTOM ONSET.

There was no significant benefit from t-PA given within 3 to 5 hours after symptom onset. The study does not support use beyond 3 hours. (*Thrombolysis for acute stroke should be used only in protocol studies*.) JAMA December 1, 1999; 282: 2019-26

12-17 TREATMENT OF ALLERGIC ASTHMA WITH MONOCLONAL ANTI-IGE ANTIBODY

A recombinant humanized monoclonal antibody directed against IgE has potential as a treatment for patients with asthma. (*Interesting new approach. Not a practical application now — possibly for the future.)* NEJM December 23, 1999; 341: 1966-73

12-18 1999 USPHS/IDSA GUIDELINES FOR THE PREVENTION OF OPPORTUNISTIC INFECTIONS IN PERSONS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

In August 1999, the US Public Health Service and the Infectious Disease Society of America published these updated guidelines. They are intended primarily for health care providers who care for HIV-infected persons. The document is long and inclusive. Annals Int Med December 7, 1999; 131: 873-908

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The editor welcomes feedback: content?; formatting?; errors?; corrections?; clarifications?. The aim is to make the publication as helpful, interesting, and as accurate as possible

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The editor thanks Lois M. James for proofreading and secretarial services.

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12-1 REDUCED CORONARY EVENTS IN SIMVASTATIN-TREATED PATIENTS WITH CORONARY HEART DISEASE AND DIABETES OF IMPAIRED FASTING GLUCOSE LEVELS.

Patients with type 2 diabetes (**DM**) experience at least a 2-fold increased risk of coronary heart disease (**CHD**). When they do develop clinical CHD their prognosis is worse than in non-diabetic patients.

In addition, impaired fasting glucose (**IFG**), even in the non-diabetic range, may also be significantly related to mortality. Indeed, analysis of previous studies suggests continuous increases in risk of CHD across the spectrum of non-diabetic glucose tolerance.

This subgroup analysis of the "Scandinavian Simvastatin Survival Study"[1] examined the effect of the statin drug, simvastatin (*Zocor*) in lowering cholesterol levels in patients with DM and IFG.

Conclusion: Cholesterol lowering was associated with a reduced risk of recurrent CHD events in patients with DM and IFG who had established CHD. (Secondary prevention)

STUDY

1. Used the 1997 American Diabetes Society diagnostic criteria for DM (fasting glucose ≥ 126 mg/dL = DM; fasting glucose 110 to 125 =IFG).
2. The post-hoc study assessed effect of simvastatin on CHD in patients with DM and IFG. (This was a study of secondary prevention.)
3. Followed over 3000 patients with normal fasting glucose; 678 with IFG; and 483 with DM. (Mean ages = 59)

4. Follow-up = 5.4 years.

RESULTS

1. Relative risks of patients treated with simvastatin (compared with placebo):

	Patients with DM	Patients with IFG
Major coronary events	0.58	0.62
Revascularizations	0.52	0.57
Total mortality	0.79	0.57
Coronary mortality	0.72	0.45

2. Absolute benefit of simvastatin therapy (number of patients needed to treat over 5 years to benefit one):

	Normal fasting glucose	IFG	DM
NNT(benefit –5 years)	12	8	7

DISCUSSION

1. Based on the ADA criteria, in patients with DM, simvastatin was associated with a 42% reduction in major coronary events, and in patients with IFG, a reduction by 38%.
2. The current expanded group of patients might be more representative of impaired glucose tolerance in the general population.
3. The dyslipidemia of diabetes is likely a major contributor to the excess risk – increased triglycerides, decreased HDL-cholesterol, increased levels of small, dense LDL-cholesterol particles. However, most did not have total LDL-c levels that meet the criteria for treatment set by the National Cholesterol Education Program.
4. The mean LDL-cholesterol level was 187mg/dL. The beneficial effect of simvastatin was evident in those below the mean level (45% reduction in major coronary events) as well as in those above the level (40% reduction).
5. The ADA recommends that the LDL-c goal for all adults *with* DM (including those without CHD) should be ≤ 100 mg/dL. (Ie, the same level recommended for patients *without* DM who have established CHD.) This is because of the high risk of CHD in patients with DM and their poor prognosis after CHD is present.
6. "Aggressive management of cardiovascular risk factors in patients with DM . . . should precede the onset of clinical coronary disease."

CONCLUSION

In patients with established CHD, cholesterol lowering with simvastatin benefited patients with impaired fasting blood glucose (110 to 125) as well as patients with diabetes (FBG ≥ 126). Total and coronary mortality and major coronary events were reduced in both groups.

Archives Int Med December 13/27 1999; 2661-67 Original subgroup investigation by The Scandinavian Simvastatin Survival Study, first author Steven M Haffner, University of Texas Health Sciences Center, San Antonio.

1 *Lancet* 1994; 344: 1383-89

Comment:

A larger question concerns individuals with IFG and DM who do *not* have established CHD. (Primary prevention) As usual, effectiveness of primary prevention will be much less than of secondary prevention. Participants in this study had 2 major risk factors (impaired glucose tolerance and established CHD).

It seems evident that we should pay more attention to cholesterol levels in individuals as their fasting glucose levels rise above 110 (and even to above 100). Would not lipid control be more beneficial in patients with slightly elevated fasting glucose than in individuals with lower glucose levels even though their LDL-cholesterol levels are the same? I believe so.

The important point is to seek out those whose glucose levels put them at increased risk. Not to rule in or out "diabetes".

The study concerned only patients with established CHD. Note that the NNT to prevent one event is most favorable in those with both CHD and DM (NNT=7); somewhat less favorable in those with both CHD and IFG (NNT = 8); still less favorable (NNT = 12) in those with normal fasting blood glucose. This is a general principle. The benefits of a useful intervention are greatest in those at highest risk. RTJ

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12-2 CAREGIVING AS A RISK FACTOR FOR MORTALITY

In the US about 15 million adults currently provide care to relatives. The majority of the care givers are middle-aged adult children and older spouses. They give care at considerable cost to themselves. Caring for an elderly, disabled person is burdensome and stressful – and contributes to psychiatric morbidity, especially depression. Caregivers are less likely to engage in preventive health, exhibit greater cardiovascular reactivity, and experience slow wound healing and impaired immune function. Thus, caring may increase risk for physical health problems and lead to increased mortality.

This study examined the relationship between caregiving demands among older spousal caregivers and 4-year mortality.

Conclusion: Being a caregiver was an independent risk factor for mortality.

STUDY

1. Prospective population-based cohort study followed almost 400 spousal caregivers and over 400 spousal non- caregivers age 66 to 96 (mean = 80; equally men and women)
2. All were living with their spouses.
3. Calculated 4-year mortality based on level of caregiving.

RESULTS

1. At 4 years 13% of caregivers had died.
2. After adjustment for socio-demographic factors, caregivers who were providing care and experiencing caregiver strain had mortality risks 63% higher than non-caregiver controls. (RR = 1.63)
3. About one out of three strained caregivers with prevalent disease died within the 4 years.
4. Participants who were giving care, but not experiencing strain, had a RR of 1.08; those with a disabled spouse who were not giving care did not have an elevated adjusted mortality rate.

DISCUSSION

1. Caregiving by elderly spouses living with their sick spouse was an independent risk factor for mortality. Mortality was highest among caregivers with prevalent disease.
2. Participants with a disabled spouse who provided no care and reported no strain did not have a significant increase in mortality.
3. Strained caregivers had higher levels of depression, anxiety, and lower levels of perceived health. They were less likely to get enough rest, to rest when they are sick, and to have time for exercise.
4. Primary care MDs who care for community-residing older adults may be in the best position to identify caregivers at risk. Older married couples should be evaluated as a unit. Treatment approaches should focus on the needs of *both* individuals simultaneously.
5. Interventions that reduce caregiving demands and give respite may be needed. Some may need permanent respite.

CONCLUSION

Elderly spouses acting as caregivers to their spouse were at increased risk for death.

JAMA December 15, 1999; 282: 2215-19 Original investigation by The Caregiver Health Effects Study, first author Richard Schultz, University of Pittsburgh, PA

Comment:

I believe primary care clinicians should care for the strained spouse even if that spouse is not a patient. This article presents a valid and important clinical point. RTJ

12-3 ALENDRONATE AND ESTROGEN-PROGESTIN IN THE LONG-TERM PREVENTION OF BONE LOSS: Four-year Results from the Early Postmenopausal Intervention Cohort Study.

Alendronate (*Fosamax*) , a bisphosphonate, inhibits bone resorption (but not mineralization), prevents bone loss and increases bone mineral density **(BMD).** It is associated with a clinically significant decrease in incidence of hip and spine fractures. It can be used as an alternative to estrogen-progestin in prevention of postmenopausal osteoporosis.

How long should alendronate be continued? Is it more effective than hormone replacement therapy?

This primary prevention study compared 1) 4 years of alendronate treatment vs 2) 2 years of alendronate followed by 2 years of placebo vs 3) placebo for 4 years. A group of participants receiving estrogen-progestin was included for comparison.

Conclusion: Continuous 4-year treatment was more effective than 2-years followed by 2 years of placebo. Estrogen-progestin was more effective than alendronate on maintaining spine BMD.

STUDY

1. Entered over 1600 healthy postmenopausal women age 45 to 59 (mean = 55) . All were at least 6 months past
   the menopause. The great majority (90%) were not classified as osteoporotic. (This was a primary prevention trial.)
2. Randomized to: 1) alendronate 5 mg daily; 2) placebo, or 3) open-label estrogen-progestin.[1]
3. All women in the alendronate groups received it for 2 years. Over the following 2 years, half received placebo, and half continued alendronate. Estrogen-progestin was given daily for 4 years.

RESULTS

1. At year 4 (mean change);	5 mg (4 years)	5 mg (2-y on 2-y off)	Estrogen-progestin[2]	Placebo
BMD				
Spine	+4%	+1%	+5%	-2.5%
Hip	+ 3%	+1%	+3%	-1.5%

2. At 4 years, after receiving alendronate for 2 years, than placebo for 2 years, BMD was greater than in those receiving placebo for 4 years.
3. Estrogen-progestin: Compared with 4 years of 5 mg alendronate, estrogen-medroxyprogesterone resulted in greater increases in BMD at the spine and wrist, and similar increases in the hip and total body.
4. During the 4 years, alendronate was as safe and as tolerable as placebo. The number of upper GI adverse effects was similar.

DISCUSSION

1. Continuous alendronate over 4 years more effectively increased and maintained BMD than placebo and intermittent alendronate.
2. Continuous estrogen-progestin increased BMD at the spine more than continuous alendronate. And more fully

   maintained BMD at the forearm.
3. "Our results are consistent with recent reports of a modest residual effect observed up to 3 years after withdrawal of therapy with various doses of alendronate."
4. Alendronate 10 mg daily has been shown to reduce the incidence of vertebral and hip fractures by approximately 50% in women with established osteoporosis. Because of the association between BMD and susceptibility to fractures, treatments that effectively maintain bone mass probably provide long-term protection against fracture.

CONCLUSION

Four years of alendronate or estrogen-progestin was more effective than placebo in preserving bone mass in early postmenopausal women. (Primary prevention.) Two years after discontinuation, there was a residual, although waning, benefit of alendronate.

Estrogen-progestin was equally effective as alendronate in maintaining hip and total BMD, and more effective in maintaining spine and wrist BMD

Alendronate was well tolerated and can be used as an alternative to estrogen-progestin for prevention of osteoporosis.

Annals Int Med December 21, 1999; 131: 935-43 Original investigation by the Early Postmenopausal Intervention Cohort Study, first author Pernille Ravn, Center for Clinical and Basic Research, Ballerup, Denmark.

1 Continuous daily conjugated estrogen 0.625 mg (*Premarin*) + medroxyprogesterone 5 mg (*Provera*) in the U.S. A different schedule was used in Europe (*See text*).

2 My estimates figure 1 p 937. RTJ

Comment:

1. In this study, alendronate was associated with no more adverse upper GI effects than placebo. The article does not mention any particular precautions about timing of administration. The usual precautions must have been applied. Fosamax is a nuisance to take. It requires high compliance to avoid esophageal irritation – taking it on an empty stomach at least 30 minutes before breakfast with a full glass of water and remaining upright for at least 30 minutes after breakfast.
2. Alendronate 5 mg daily is recommended for prophylaxis of osteoporosis (primary prevention); 10 mg for treatment. One aspect of the study (which I did not include in the abstract) used 2.5 mg daily. Results were favorable, although not as marked as with the 5 mg dose. If the original dose of 5 mg is not well tolerated, it can be titrated downward.
3. Estrogen-progestin was at least as effective as alendronate; actually more effective in increasing BMD of the spine. I have not seen any studies which included patients receiving combined alendronate-estrogen.
4. The cost of alendronate 5 mg daily for a year would exceed $800. RTJ
5. I believe a reasonable argument can be made to advise *essentially all* menopausal and postmenopausal women to adopt a program of osteoporosis prevention. Indeed, prevention begins in adolescence with an adequate intake of calcium and vitamin D. I believe estrogen-progestin is the favored anti-osteoporosis intervention in menopausal women. It has benefits extending beyond osteoporosis prevention, is easier to take, and is perhaps less costly. RTJ

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12-4 THE EFFECT OF BISOPROLOL ON PERIOPERATIVE MORTALITY AND MYOCARDIAL INFARCTION IN HIGH-RISK PATIENTS UNDERGOING VASCULAR SURGERY

Patients undergoing major vascular surgery are at risk for serious perioperative complications such as myocardial infarction (**MI**) and death.

Beta-blockers prevent cardiac complications in patients with acute MI, silent ischemia, and heart failure.

This study hypothesized that perioperative beta-blockade with bisoprolol (*Zebeta*) would reduce incidence of non-fatal MI and death from cardiac causes in high-risk patients undergoing major surgery.

Conclusion: Bisoprolol reduced perioperative complications.

STUDY

1. Randomized trial assessed the effect of perioperative beta-blockade on incidence of non-fatal MI and death from cardiac causes within 30 days of major vascular surgery.
2. Followed 112 high-risk patients. Risk was determined by presence of clinical risk factors *and* positive

results on dobutamine echocardiography.

3. Clinical factors for "high risk": Age > 70; angina; prior MI; compensated heart failure; current treatment for ventricular arrhythmias; diabetes; inability to perform most normal daily activities.
4. A dobutamine echocardiography test was positive if wall motion in any ventricular segment decreased by one or more grades.
5. Randomized to: 1) standard care, or 2) standard care + perioperative bisoprolol.
6. Bisoprolol was started at 5 mg daily by mouth, and titrated to 10 mg if the pulse rate remained above 60. The same dose was continued postoperatively. If patients were unable to take the oral preparation, the pulse rate was monitored closely and intravenous bisoprolol was administered in sufficient dose to keep pulse below 80. The drug was withheld if the pulse rate was under 50 or the systolic BP under 100.
7. Follow-up = 30 days

RESULTS

1. Died of cardiovascular causes: bisoprolol – 2 patients; control – 9.
2. Non-fatal MI: bisoprolol – none; control – 9
3. The combined endpoint death or non-fatal MI – 3.4% vs 34%.

DISCUSSION

1. The marked difference in cardiac events or death caused the safety committee to interrupt the study after the first planned interim analysis.
2. The causes of perioperative deaths remained undefined. However, such events occur almost exclusively among patients with a positive dobutamine test. This suggests significant coronary artery stenosis and increasing vulnerability to ischemia.
3. Beta-blockade may decrease the heart rate, improve myocardial contractility, prevent ischemia, decrease myocardial oxygen demand, and increase the threshold for ventricular fibrillation.
4. A previous study of atenolol in patients undergoing major surgery reported a reduction in myocardial ischemia

   (as detected by Holter monitoring) by 50% in the first 48 hours, and an absolute 10% decrease in mortality during 2 years of follow-up. However, atenolol did not significantly reduce death from cardiac causes during the hospitalization, or reduce perioperative MI. (In this study the incidence of perioperative events was only 3%.)
5. The present study limited use of bisoprolol to high-risk patients with an anticipated event rate of 28%.
6. Patients with no clinical risk factors and without stress-induced ischemia have a rate of serious perioperative cardiac events that is close to zero.

7. “We recommend that high risk surgical patients receive beta-blockade perioperatively, beginning one to two weeks before surgery. The goal should be to reduce the heart rate to less than 70 beats per minute preoperatively, and to less than 80 beats per minute in the immediate postoperative period. Therapy should continue for at least two weeks postoperatively.”

CONCLUSION

Bisoprolol (*Zebeta*) was associated with a reduction of perioperative death from cardiac causes and non-fatal MI in high-risk patients undergoing major vascular surgery.

NEJM December 9, 1999; 341: 1789-94 Original investigation from The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group, first author Don Poldermans, Erasmus Medical Centre, Rotterdam, the Netherlands.

Comment:

Beta-blockers are one of the most important clinical advances in recent years – both for prevention and treatment. Primary care physicians should use them more liberally. RTJ

12-5 REDUCING CARDIAC RISK IN NONCARDIAC SURGERY

(This editorial comments and expands on the preceding)

“Avoid hypotension” has been a not-so-helpful recommendation appearing at the end of many preoperative consultation notes. It has been the extent of the science of operative risk reduction.

Now there is strong evidence that beta-blockers reduce the perioperative risks of patients undergoing major surgery, especially in those with highest risk. This justifies rethinking about strategies of perioperative care for patients undergoing major non-cardiac procedures.

The extraordinary 91% reduction in risk reported by the study may be “too good to be true”, but it was sufficient to lead to the recommendation to end the trial prematurely.

The authors noted a previous trial of atenolol resulted in a 50% lowering of mortality over 2 years, but no advantage early post-operatively. Why the difference? Likely because the two treatment groups differed. The bisoprolol study selected only extremely high risk patients.

“The findings of this study have profound implications for the evaluation and treatment of patients undergoing major non-cardiac surgery.” Current guidelines urge the use of non-invasive tests for ischemia in patients considered to have an intermediate risk of complications on a clinical basis. Coronary catheterization and revascularization are commonly performed in patients who have abnormal test results, despite the lack of

data demonstrating efficacy of this approach. “It seems likely that the cumulative morbidity resulting from 3 sequential procedures (coronary angiography, revascularization, and then a major vascular procedure) would be higher than the 3.4 percent rate of major cardiac complications in this study among patients given bisoprolol. Why not simply give a beta-blocker and reduce the frequency of preoperative testing in some patients?

A simple validated index for prediction of cardiac risk of major non-cardiac surgery includes 6 clinical factors: a high-risk surgical procedure; history of ischemic heart disease; history of heart failure; history of cerebrovascular disease; preoperative treatment with insulin; serum creatinine > 2.0 mg/dL. (normal = 0.6 to 1.2) One point is given for each. This has identified a larger number of patient with moderate or high risk.[1]

Coronary revascularization before non-cardiac surgery should be recommended only for patients with unstable angina or when non-invasive tests for ischemia indicate a high risk. ”There are no data showing that coronary revascularization reduces complications among patients undergoing elective surgery; hence, coronary revascularization should be reserved for patients in whom it would be considered appropriate as part of their routine long-term care.”

In the absence of major contraindications, therapeutic doses of beta-adrenergic antagonists should be given to patients with intermediate or high risk of cardiac complications. The side effects of these drugs can be tolerated during the perioperative period.

In summary, the preceding study suggests that perioperative care will be characterized by fewer tests, fewer coronary revascularization procedures, more use of beta-blockers – and fewer complications.

NEJM December 9, 1999; 1838-40 Editorial by Thomas H Lee, Partners Community HealthCare, Boston, Mass.

1 For additional commentary see the following abstract.

Note that bisoprolol is a *cardio-selective* beta1 adrenergic-receptor blocker.

What about emergency surgery? I suspect an intravenous beta-blocker can be used with care to select high-risk patients before and during surgery just as with a patient with an acute myocardial infarction presenting to the emergency department.

What about patients with heart failure? This would be difficult due to the requirement of slow upward titration of dose. Low doses combined with careful monitoring might be given prior to surgery. RTJ

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12-6 IS SIMPLE CLINICAL ASSESSMENT ADEQUATE FOR CARDIAC RISK STRATIFICATION BEFORE ELECTIVE NON-CARDIAC SURGERY?

A recent study[1] reported that simple clinical assessment can be used as the *only* risk-stratifying measure required for most patients being considered for major non-cardiac surgery.

Risk factors include:

1. High-risk surgery (thoracic, abdominal, abdominal aortic aneurysm repair)
2. Ischemic heart disease (myocardial infarction, Q waves on ECG, angina, use of nitrates, positive exercise test.)
3. Heart failure (history, examination, chest X-ray)
4. Insulin-treated diabetes
5. Creatinine > 177 umol/L (2 mg/dL)

Number of risk factors	Proportion of population	Major cardiac complications
0	36%	0.4%
1	39%	1%
2	18%	5%
≥3	7%	10%

(*Note that high-risk surgery automatically places a patient at one risk factor.)*

Patients undergoing *minor* surgery do not require elaborate cardiac investigation. Identification of obstructive coronary disease will not alter how they are managed.

For patients undergoing *major* surgery, this clinical approach contrasts with the prevailing trend in many centers where clinicians rely on objective risk-stratification with significant resource implications.

"Patients undergoing more major surgery (eg, abdominal or thoracic) but who are at intrinsically low clinical risk will not benefit from further investigation, since no non-invasive test will have a positive predictive accuracy sufficient to stratify further a group already known to be at less than 1% risk."

Patients with angina need stratification with invasive tests whether or not non-cardiac surgery is planned. Their risk of a perioperative event when undergoing major surgery is over 5%. Successful by-pass surgery will reduce the risk to 2.5%. If elective non-cardiac surgery is planned for patients with angina, cardiac investigation and treatment should be completed before the surgery.

The most difficult patients to assess are those without symptoms of coronary disease who are nevertheless at high risk because of obstructive coronary disease. "It is in these symptom-free but high-risk patients for whom further risk stratification with non-invasive stress-based imaging investigations is most useful." The dipyridamole thallium perfusion scintigraphy or the dobutamine stress ECG (as in the preceding study) are widely used in the preoperative setting. Those with positive tests are assessed by coronary angiography for possible revascularization. Although this strategy provides reassurance for the clinician, . . ."Coronary bypass surgery in symptom-free patients has never been shown to reduce the risk of subsequent non-cardiac surgery". "Percutaneous intervention is unlikely to improve prognosis because it cannot protect against plaque rupture over most of the length of the coronary artery."

Revascularizaiton would mean treatment of many patients in an attempt to prevent a few adverse outcomes. "In any event, the modest survival benefit is unlikely to exceed the additional risk of a by-pass operation that would not ordinarily have been done. These risk/benefit considerations apply particularly to patients with peripheral vascular disease, in whom coronary bypass carries an especially high risk."

Although myocardial infarction might be expected to occur during the stress of the operation, it is commonest on the second or third postoperative day, and is strongly predicted by episodes of ischemia on Holter monitoring. This is usually preceded by a peak in tachycardia seen on days 1 and 2. (*Simply observing the pulse rate can still be a most valuable clinical observation. RTJ*) The stress response to surgery (high catecholamines, prothrombotic tendency) results in increased myocardial oxygen demand and increased shear stress on atherosclerotic plaques leading to plaque rupture.

The emphasis on perioperative management of high risk patients should be directed away from mechanical revascularization toward improved control of myocardial oxygen demand and protection of vulnerable atherosclerotic plaques. Perioperative hemodynamic monitoring, meticulous pain control, and careful use of beta-blockers are crucial.

"For most patients cardiac risk stratification before elective non-cardiac surgery requires only a knowledge of the risk associated with the procedure and simple clinical assessment."

Lancet November 27, 1999; 354: 1837-38 Editorial by Andrew D Kelion and Adrian P Banning, John Radcliffe Hospital, Oxford UK

1 *Circulation* 1999; 100: 1043-49

Comment:

Age was not considered a risk factor.

Clinical decision-making before elective major surgery regarding interventions in persons with CHD, or those who are likely to have CHD, is difficult. Individualism, as usual, is the key.

Does not the decision to proceed with a cardiac intervention stand on the cardiac status alone? Ie, if the decision to intervene heart-wise would be made even if no surgery was contemplated, would it not be prudent to advise this intervention before the elective surgery? Conversely, if the patient's condition would not call for a cardiac intervention in the short-term, the elective surgery might proceed (with beta-blocker protection) in those at high-risk.

Patients who would be strongly considered for invasive cardiac procedures (regardless of the need for elective non-cardiac surgery) should be considered candidates for the procedure regardless of whether they are symptomatic or non-symptomatic. RTJ

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12-7 LOW RISK-FACTOR PROFILE AND LONG-TERM CARDIOVASCULAR AND NON-CARDIOVASCULAR MORTALITY AND LIFE EXPECTANCY

Three major coronary risk factors – serum cholesterol, high blood pressure, and smoking – increase incidence of coronary heart disease (**CHD**).

This study measured long-term mortality rates for individuals with favorable levels of all 3 risk factors compared with individuals with one or more unfavorable factors.

Conclusion: Individuals with favorable levels of the risk factors experienced much lower mortality.

STUDY

1. Retrieved data from several large studies of over 350 000 individuals (mainly men; age 35-59).
2. Defined favorable risk factors: total cholesterol < 200 mg/dL; and BP ≤ 120/80; and non-smoking.
3. Individuals with diabetes; history of myocardial infarction, and ECG abnormalities were excluded from the study.

RESULTS:

1. Fewer than 10% of the cohort had all 3 favorable risk factors
2. Those in the favorable group (compared with persons with one or more unfavorable factors) experienced significantly and markedly lower cardiovascular disease mortality. The adjusted relative risk below age 40 was 0.08; age 40-59 = 0.23
3. All cause mortality was decreased by 40% to 58%. Estimated longevity was greater by 6 to 10 years.

DISCUSSION

1. "These findings are relevant for the national effort to end the CHD-CVD epidemic."
2. Absence of 3 factors: diabetes, history of MI, and ECG abnormalities also favorably influences prognosis.

CONCLUSION

In this very large cohort study, individuals with total cholesterol < 200, BP ≤ 120/80, and who did not smoke, experienced lower long-term mortality and longer life expectancy than those with any one of these risk factors.

JAMA December 1, 1999; 282: 2012-18 Original investigation, first author Jeremiah Stamler, Northwestern University Medical School, Chicago, Ill.

Comment:

Fewer than 10% of relatively young males in this investigation had all 3 favorable risk factors The findings are no surprise. They may be set as a goal for interested individuals.

Would it not be likely for those with 2 or 3 unfavorable factors, as well as those with diabetes, to have a greater mortality than those with only one unfavorable factor? The study did not make this distinction.

Primary care clinicians should congratulate patients who have all 3 favorable factors. RTJ

12-8 NEW RECOMMENDATIONS FOR ADULT IMMUNIZATION

The Advisory Committee on Immunization Practices (ACIP) of the CDC noted that 24% of the US population between ages 50 to 65 have a high risk condition, but only 38% of these are being vaccinated against influenza. They recommend the age for receiving flu vaccine be lowered from 65 to 50, in part because morbidity and mortality for influenza start to rise at age 50.

Influenza vaccination of healthy younger working persons has also been shown to reduce morbidity and absenteeism, and to be cost saving.

Physicians caring for adults don't think of immunizations the way that pediatricians do. Immunizations (including influenza and pneumococcal disease) have to be routinely incorporated into their practice and worked into their schedules.

JAMA December 15, 1999; 282: 2199 "Medical News and Perspectives", a note form Charles Marwick, JAMA staff.

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12-9 A PROSPECTIVE STUDY OF WEIGHT CHANGE AND HEALTH-RELATED QUALITY OF LIFE IN WOMEN

Although approximately 40% of adult women in the US are trying to lose weight at any given time, most appear to be gaining.

Weight loss has been associated with improvement in many risk factors for cardiovascular disease. Other studies reported that BMI was the most important predictor of physical function and impaired ability to work, and the second important predictor of vitality (after physical activity). But, few studies are available to indicate the impact of weight change on functional health status.

This study assessed the association between weight change and health-related quality of life.

Conclusion: In overweight women, weight loss was beneficial for physical functioning, vitality, and bodily pain.

STUDY

1. Subset of the Nurses' Health Study entered over 40 000 women (age 46 to 71) in 1992-96.
2. Prospectively observed outcomes using a 36-item self-administered Health Status Survey to measure quality of life.
3. Followed 3 patterns of weight change over 4 years: weight stable (within 5 pounds of baseline); weight loss (loss of 5 pounds or more); and weight gain (gain of 5 pounds or more).
4. Determined changes in scores of health-related qualities-of-life: physical functioning; vitality; bodily pain; limitations in role functioning due to emotional or physical problems; social functioning; and mental health.

RESULTS

1. Thirty nine percent maintained their weight; 38% gained; 17% lost between 5 and 20 pounds.
2. Weight gain was associated with decreased physical function and vitality, and increased bodily pain.
3. The leanest women at baseline who gained 20 pounds developed role limitations due to physical problems (Odds ratio = 2)
4. Weight loss in overweight women was associated with improved physical functioning and vitality as well as decreased bodily pain.

DISCUSSION

1. Weight gain was consistently associated with declines in physical functioning and vitality, and increased levels of pain among women of all ages (old and young) and all baseline BMI levels. This included women of normal weight.
2. Weight loss was associated with improved physical functioning and decreased bodily pain.
3. Weight change was associated more strongly with physical than with mental components of health-related quality of life.
4. The average decline in physical function of 7 points in women who gained 20 pounds or more over 4 years (compared with women who maintained their weight) was nearly 3 times the decline in physical functioning associated with cigarette smoking over the same period.
5. The possibility that weight loss was not intentional and due to depression or other illness might be a limitation to the study. However, the number of women in this category was small.

CONCLUSION

These longitudinal data indicated a strong association between weight change and change in health related quality of life among normal weight and overweight middle-aged women. Weight loss in overweight women can substantially improve physical functioning, vitality and bodily pain. Weight gain is associated with the declines.

JAMA December 8, 1999; 282: 2136-42 Original investigation, first author Jennifer T Fine, Harvard School of Public Health, Boston Mass.

Comment:

The conclusions would seem self-evident. It may be helpful to show patients documentation of the benefits of weight control. Even women who gained but still remained within "normal" weight boundaries experienced some decrease in quality-of –life.

The study was short-term (4 years). Even young and middle aged women who gain over a period of 3 to 4 years are likely to experience adverse effects. RTJ

12-10 DIETARY SODIUM INTAKE AND SUBSEQUENT RISK OF CARDIOVASCULAR DISEASE IN OVERWEIGHT ADULTS

Epidemiologic studies have repeatedly identified an independent, positive relationship between dietary sodium intake and blood pressure, both across and within populations.

Randomized, controlled trials also demonstrated that reduced sodium intake leads to a reduction in BP. A high dietary intake could predict an increased risk of cardiovascular disease.

Other studies suggest that obese persons are more sensitive to the effect of sodium on BP than non-obese persons.

This study examined the risk of cardiovascular disease associated with dietary sodium intake in overweight persons and non-overweight persons.

Conclusion: High sodium intake was associated with increased risk in overweight persons.

STUDY

1. The National Health and Nutrition Examination Survey entered over participants age 25 to 74 in 1971-75.
   Over 2500 were overweight (mean BMI = 31) ; over 6500 non-overweight (mean BMI = 23).
2. Estimated dietary sodium intake and energy intake by a 24-hour dietary recall.
3. Followed periodically through 1992 (average = 19 years).
4. Recorded incidence of mortality for cardiovascular diseases over the years.

RESULTS

1. Among overweight persons with an average energy intake of 7500 kJ/d (1800 kcal/d), a 100 mmol higher

sodium intake (comparing the highest quintile of intake with the lowest) was associated with a 32% increase in incidence of stroke. (Relative risk compared with non-overweight = 1.3.)

2. Other outcomes (highest quintile vs lowest) Relative risk

Stroke mortality	1.9
Coronary heart disease mortality	1.4
Cardiovascular disease mortality	1.6
Mortality from all causes	1.4

3. Mean BP was not different between lowest and highest quintile of sodium intake (142/89 vs 144/89).

4. Dietary sodium intake was not significantly associated with cardiovascular disease in non-overweight persons.

DISCUSSSION

1. The study documents the presence of a positive and independent relationship between sodium intake and cardiovascular disease risk in overweight adults
2. This suggests that reduced sodium intake may be especially efficacious in overweight persons.
3. Obesity activates the sympathetic nervous and renin-angiotensin systems, causes insulin resistance and hyperinsulinism, and alters intrarenal tubular reabsorption and sodium retention.
4. Dietary sodium intake was related to cardiovascular disease risk and mortality independently of baseline BP. The relative risk increases associated with a 100 mmol greater sodium intake were much larger than would be expected based on the corresponding influences on BP.

CONCLUSION

High sodium intake was strongly and independently associated with an increased risk of cardiovascular disease and all-cause mortality in overweight persons. Moderate reductions in sodium intake are recommended.

JAMA December 1, 1999; 282: 2027-34 Original investigation, first author Jiang He, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA.

Comment:

By my calculations from their data, the high intake group ingested about 15 g of NaCl vs about 3 g in the low group. Three gram intake is difficult to achieve given the high NaCl content of prepared foods in the US.

Observational studies can not prove causality. This study does not prove that reducing salt intake at middle age in an obese person will improve prognosis.

Is there any clinical application of these findings? By my calculations, the excess total mortality in the high NaCl intake group was about 5 per 1000 person-years compared with the low intake group. Adding salt

restriction to a difficult regimen of calorie restriction and increased physical activity (which few obese persons maintain over time) would likely decrease compliance. Nevertheless, I believe individual patients should be informed of the potential benefit of salt restriction. The putative benefit/harm-cost ratio may be high because the harm and cost are nil. RTJ

12-11 SMOKING AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN MEN WITH LOW LEVELS OF CHOLESTEROL

In Korea and other East Asian countries, the prevalence of smoking is among the highest in the world. In the early 1990s, atherosclerotic cardiovascular disease (**ASCVD**) became the leading cause of death in South Korea. But, cholesterol levels in Korea are relatively low.

This study examined the interactive effects of smoking and serum cholesterol levels on morbidity and mortality from CVD.

Conclusion: A low level of total cholesterol conferred no protection.

STUDY

1. Prospective cohort study followed over 106 000 Korean men age 35 to 59 at baseline.
2. Determined smoking history and hospital admissions and deaths from ASCVD.
3. Follow-up = 6 years.

RESULTS

1. At baseline, 58% were current cigarette smokers.
2. Of these, 60% had a total cholesterol less than 200 mg/dL; 31% 200 to 239; and 9% over 239. There was no evidence of an interaction between smoking and cholesterol levels.
3. Over 6 years — Events per 100 000 person-years

Ischemic heart disease (**IHD**)	176
Cerebrovascular disease (**CVD**)	238
Other **ASCVD**	125

4. After controlling for multiple other risk factors, the relative risk (RR) in current smokers for IHD = 2.2; CVD = 1.6; total ASCVD = 1.6 (compared with non-smokers).
5. For each outcome there were significant dose-response relationships with the duration and amount of smoking throughout the range of cholesterol levels. In the lowest quartile of cholesterol (< 171 mg/dL), the RR from current smoking was 3.3 for IHD; and 1.6 for CVD.

DISCUSSION

1. Populations in Asian countries tend to be leaner and have lower cholesterol levels and perhaps less atherosclerosis than in the West. This has led to the belief that smoking is less of a risk factor.
2. The study found that current cigarette smoking was a strong, independent risk factor for ASCVD events.
3. The risk relationship was present throughout the entire range of total cholesterol, including those with total cholesterol levels < 171 mg/dL.
4. The authors calculate that smoking accounted for over 40% of ASCVD events.
5. The same study demonstrated that smoking was a significant risk factor for stroke, both ischemic and hemorrhagic.

CONCLUSION

Current cigarette smoking was a major, independent risk factor for ASCVD in Korea despite the relatively low levels of cholesterol in the population. A low cholesterol conferred no protection against risks of smoking.

JAMA December 8, 1999; 282: 2149-55 Original investigation by The Korea Medical Insurance Corporation Study, first author Sun Ha Jee, Yonsei University, Seoul, Republic of Korea.

Comment:

The article seems to equate the endovascular damage caused by smoking with atherosclerotic disease. Smoking may increase the likelihood of cholesterol plaque infiltration in the endothelium, but is it the only pathogenic factor caused by smoking? Does not smoking independently cause endothelial damage in addition to atherosclerosis? RTJ

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12-12 NONINVASIVE GLUCOSE MONITORING

Comprehensive Clinical Results

The Glucowatch automatic glucose biographer (*illustration p 1840*) provides a means to obtain painless, automatic, and noninvasive blood glucose (**BG**) measurements. It provides up to 3 readings per hour for as long as 12 hours after a single calibration. This might provide improvement in glucose control. The machine also provides the opportunity to be sounded in response to values below an alert level or as a result of too rapid declines in BG.

The method extracts glucose through the skin using an applied constant, low level electrical current (iontophoresis). This transports glucose across the skin, then measures the glucose using an electrochemical-enzymatic sensor. (*See p 1840 for details about workings of the machine*.)

This study determined accuracy of the machine compared with serial glucose measurements by blood glucose monitoring.

Conclusion: There was close agreement.

STUDY

1. Multicenter study entered 92 subjects with diabetes. Compared the Glucowatch with HemoCue (a blood glucose monitor).
2. Participants wore 2 Glucowatch biographers during 15 hours. And performed 2 finger sticks per hour.
3. Diet and insulin were manipulated to produce a broad glycemic range.

RESULTS

1. Tracking was close between the 2 methods throughout the study.
2. The machine determinations lagged behind the BG determinations by a mean of 18 minutes.
3. The 2 Glucowatch machines worn at the same time closely correlated with each other.
4. The variation of the difference between the methods ranged from a high of 8% at glucose levels below 100mg/dL, and 5% for values above 200 mg/dL. The machine closely tracked changes in glucose.
5. Mild skin irritation was noted at the site. It resolved within 7 days.

DISCUSSION

1. One of the greatest potential advantages of the machine is the ability to determine glucose patterns and trends.
2. During a 10 minute period, the BG may change as much as 27 mg/dL

CONCLUSION

An automatic, non-invasive glucose-monitoring machine which makes frequent measurements demonstrated close agreement with blood glucose measurements obtained by finger stick. The machine provided more information about glucose levels than the current standard of care.

JAMA November 17, 1999; 282: 1839-44 Original study, first author Janet A Tamada, Cygnus Inc, Redwood City, CA.

Comment: Study funded by Cygnus.

This type of machine may indeed lead to better glucose monitoring and control. I believe automated non-invasive techniques such as this will be an important clinical advance in the near future. Primary care clinicians

will await reports of further experience and marketing. The FDA has given the machine a conditional approval. RTJ

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12-13 QUINUPRISTIN/DALFOPRISTIN, A NEW ADDITION TO THE ANTIMICROBIAL ARSENAL

Antibiotic resistance, especially that of gram-positive bacteria, is a huge problem. Millions of patients each year develop nosocomial infections, many of which involve resistant organisms.

A new drug, quinupristin/dalfopristin (*Synercid*), is now licensed in the US. It is active against gram-positive bacteria, including difficult organisms such as methicillin-resistant *Staphylococcus aureus* , and vancomycin-resistant *Enterococcus faecium*, and penicillin-resistant and macrolide-resistant pneumococci. Its activity is exclusively against gram-positive pathogens.

The drug is specifically indicated when no other antibacterial agents are suitable. When mixed infections are suspected, quinupristin/dalfopristin should be used in combination with one or more agents active against nosocomial gram-negative bacteria.

Recent studies indicate a high rate of clinical and bacteriological success in a wide variety of infections in seriously ill patients with bacteremia and co-morbidity.

One drawback is the lack of activity against *Enterococcus faecalis*, which makes up the great majority of isolates of enterococci. *E faecalis* generally remains sensitive to ampicillin, and is much less frequently vancomycin resistant.

Availability of the drug is good news, giving clinicians an additional agent against serious gram-positive infections.

Resistance to quinupristin/dalfopristin has already been reported.

Lancet December 11, 1999; 354: 2012-13 Editorial by Alan P Johnson and David M Livermore, Central Public Health Laboratory, London, UK

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12-14 THE ENERGY EXPENDED IN CHEWING GUM

Gum chewing may have greater metabolic effects than has been appreciated. In cows, chewing increases energy expenditure by about 20%.

These correspondents used an indirect calorimeter to measure how energy expenditure changed with gum chewing in humans. Measurements were performed in seven non-obese subjects with stable weight while they were at rest for 30 minutes. Then they were provided by an 8 gm stick of calorie free gum and instructed to

chew at a frequency of 100 Hz (a value approximating the gum-chewing frequency) for 12 minutes. Subjects continued at rest except for the chewing.

Mean energy expenditure increased in all subjects from 58 kcal per hour at baseline to 70 kcal per hour while chewing, returning to baseline within 12 minutes after chewing stopped.

Chewing led to a mean increase in energy expenditure of 11 kcal per hour, a 19% increase over baseline. In the same subjects, standing was associated with a mean increase of 11%, and walking 1 mile per hour with a mean increase of 106% above baseline.

If a person chewed gum during waking hours and changed no other component of energy balance, a yearly loss of over 10 pounds of body fat might be anticipated. The metabolic effect of chewing calorie-free gum should not be discounted.

NEJM December 30, 1999; 341: 2100 Letter to the editor, original investigation, first author James Levine, Mayo Clinic, Rochester MN

Comment:

Small intermittent increases in activity are recommended for achieving and maintaining fitness – eg, walking up steps instead of taking the elevator; parking the car at a distance and walking the rest of the way. Small increments performed daily can result in measurable benefits in weight control over the year. RTJ

REFERENCE ARTICLE

12-15 THE YEAR IN REVIEW: THE THYROID

Several recently published studies have important implications for the management of patients with thyroid disease:

Screening for thyroid disease:

The American College of Physicians in 1998 published guidelines for screening patients seen in primary care for non-thyroid-related reasons. Screening can identify: overt hypo-thyroidism, overt hyper-thyroidism, subclinical hypo-thyroidism, and subclinical hyper-thyroidism. A sensitive TSH test is followed by a free thyroxine test when the TSH is abnormal. When the TSH is high and the thyroxine normal, subclinical hypo-thyroidism is present. When the TSH is low and the thyroxine normal, subclinical hyper-thyroidism is present. When TSH is high (> 10 mU/L) and free thyroxine is low, overt hypo-thyroidism is present. When TSH is low (< 0.4 mU/L) and free thyroxine is high, overt hyper-thyroidism is present. Abnormalities occur in 1% to 2% of women over age 50, justifying screening in this population. Screening for younger women and men is not recommended because of low prevalence in these groups.

Subclinical hypo- and subclinical hyper-thyroidism (abnormal TSH with normal thyroxine) warrant follow-up and consideration for treatment.

Thyroid eye disease:

Smoking increases risk of progression of thyroid eye disease.

^{131}I treatment can be associated with progression of eye disease. It should be avoided in patients with active eye disease who are smokers. If no other option is available, a fully ablative dose should be given followed by a 3-month course of prednisone. (Prednisone is not given routinely to non-smokers even if they have mild eye disease because of increased bone loss.)

Antithyroid drug treatment:

A 1991 study of Grave's disease reported that adding thyroxine to long-term methimazole or propylthiouracil reduced the likelihood of recurrence of the disease after the anti-thyroid drug was discontinued. Several later studies failed to confirm this. It is difficult to justify this combined therapy.

Anti-thyroid drugs are often used to render a Grave's disease patient euthyroid before ^{131}I therapy to forestall an exacerbation of hyper-thyroidism by radiation thyroiditis. This is especially important in patients with cardiac disease. Methimazole is preferred over propylthiouracil because, following methimazole, one dose ^{131}I cure rates are higher. In addition, methimazole is less likely to be associated with agranulocytosis, and has the convenience of a less frequent dosing schedule.

Treatment of hypothyroidism:

A recent study reported that, in some patients, adding low-dose triiodotyronine (T3) to partially substitute for some of the thyroxine (T4) was associated with improved neuropsychological functioning. However, the present combined preparations contain an excess of T3, and thyroid extracts vary in potency. These findings should be confirmed before routine use. For patients who do not achieve optimal state of well being, it is reasonable to replace 50 ug of T4 with 5 ug of T3 given twice daily.

Thyroid nodules:

Non-palpable nodules (incidentalomas) are frequent – similar to that of palpable nodules (@ 5%). Ultrasound guided needle biopsy should be done if the patient has a history of radiation therapy to the head or neck, or a family history of thyroid cancer; or the diameter is over 1.0 cm; or if suspicious ultrasound findings are present. In the absence of any of these features, a 6- to 12-month follow-up without biopsy is recommended because most occult carcinomas are papillary and rarely aggressive.

What about TSH suppressive therapy with thyroxine for benign solitary nodules? The latest meta-analysis reported that volume decreased by more than 50% in 25% of treated patients — compared with 8% of control patients. The number of patients in whom the nodule increased in size was greater in the controls. The reviewer recommends a 1-year course in younger patients to be continued only if the nodule size decreases. For older

patients, the risk of adverse effects of the T4 (increased bone resorption and atrial fibrillation) may offset the benefit.

Annals Int Med December 21, 1999; 131: 959-962 Review by Kenneth A Woeber, University of California, San Francisco.

Comment:

Although most of these studies have been reported in *Practical Pointers*, I enjoy a concise refresher which I file in my reference folder. RTJ

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12-16 RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR (ALTEPLASE) FOR ISCHEMIC STROKE 3 TO 5 HOURS AFTER SYMPTOM ONSET.

Current approved use of t-PA is for up to 3 hours after onset of ischemic stroke.

Will use after 3 hours be effective?

Conclusion: No.

STUDY

1. Randomized, controlled trial followed 500 patients with acute ischemic stroke – all seen within 3 to 5 hours of onset of symptoms.
2. Randomized to intravenous t-PA, or placebo.

RESULTS

1. One third of both groups had excellent recovery at 90 days.[1]
2. No difference at 90 days in functional outcome measures.
3. Within the first 10 days, symptomatic intracerebral hemorrhage was 7% for t-PA vs 1% for placebo.
4. Mortality was 11% in the t-PA group vs 7% in the placebo group. (Not significant.)

CONCLUSION

There was no significant benefit from t-PA given within 3 to 5 hours after symptom onset. The study does not support use beyond 3 hours.

JAMA December 1, 1999; 282: 2019-26 Original investigation by the ATLANTIS study, first author Wayne M Clark, Oregon Stroke Center, Portland.

Comment:

1 Many patients presenting with a "stroke" which fits the protocol for treatment with tPA will recover spontaneously. It is difficult within 3 hours to differentiate this group from those who go on to experience neurological damage. However, entering them in the protocol would expose them needlessly to the considerable adverse effects of tPA. Again, a disappointment; t-PA is not for primary care. Use should be restricted to controlled trials. RTJ

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12-17 TREATMENT OF ALLERGIC ASTHMA WITH MONOCLONAL ANTI-IGE ANTIBODY

Recombinant humanized monoclonal antibody **(RHMA)** is produced by immunizing mice with human IgE. The antibody recognizes IgE at the same site as the cellular receptor for IgE. It complexes with free (unbound) IgE (but not with IgG or IgA). RHMA removes IgE from the circulation. It blocks the binding of IgE to cell membrane receptors in mast cells and basophiles, thereby inhibiting the release of mediators. It does not bind to cell-bound IgE. The antibody (an immunoglobulin protein) is more than 95% human.

When given to humans, the antibody dramatically reduces serum concentrations of free IgE. After a course of therapy both the early and late-phase reactions to inhaled allergens are attenuated. The ability of the antibody to suppress the late-phase reaction (which is associated with bronchial inflammation and bronchoconstriction) is postulated to produce a beneficial effect on the pathogenesis of asthma.

This study assessed the efficacy of the antibody as a treatment for moderate and severe asthma.

Conclusion: The humanized antibody directed against IgE has potential as a treatment.

STUDY

1. Entered over 300 patients age 11 to 50 with moderate to severe persistent perennial asthma. All were positive to skin testing to two or more perennial allergens. All had reversible airways obstruction.
2. All required inhaled or oral corticosteroids; had FEV1 < 71% of predicted; a mean daily symptom score of 4.0 or less on a 7-point scale (1 = no symptoms, 7 the most severe); and daily use of rescue beta-agonist inhaler.
3. Randomized double-blind to: 1) RHMA given IV every 2 weeks (in microgram doses), or 2) placebo.
4. Follow-up = 20 weeks during which attempts were made to taper the corticosteroids. The best of conventional treatment was continued in both groups.

RESULTS

1.	RHMA	Placebo
Mean asthma symptom score		
Baseline	4.0	4.0
12 weeks	2.8	3.1

20 weeks	2.7	2.9
Reduction in inhaled beta-agonist	-1.2	-0.8 puffs daily
Improvement in FEV1	+1.9%	+1.0%
Peak expiratory flow increase	+31	+11 liters/min
Quality of life (asthma specific)	+1.4	+0.8 overall score
Reduction in oral corticosteroids	51%	38% of patients
Discontinued corticosteroids	18%	12%

2. No significant difference in incidence of adverse events between groups. No antibodies to the antibody occurred.

DISCUSSION

1. Allergic diseases are characterized by biphasic reactions mediated by IgE:
   A. Immediate reaction appears within minutes after exposure to the antigen.
   B. Late-phase reaction occurs 2 to 8 hours later. The late-phase reaction is the model for allergic disease. In patients with asthma the presence of inflammation seen on lung biopsy is consistent with the late-phase reaction. Pulmonary function tests show hyper-responsiveness of the airways proportional to the late-phase response.
2. IgE binds to high-affinity receptors on mast cells and basophiles.
3. Effective immunotherapy attenuates the late phase reaction. However, the basis of therapy remains the consistent use of anti-inflammatory agents.
4. All subjects tolerated the RHMA therapy well. Few withdrew.
5. Improvements in the placebo group were attributed to the excellent conventional care given.

CONCLUSION

A recombinant humanized monoclonal antibody directed against IgE has potential as a treatment for patients with asthma.

NEJM December 23, 1999; 341: 1966-73 Original investigation, first author Henry Milgrom, National Jewish Medical and Research Center, Denver, CO

Comment:

I took the time to abstract details of this study because of the potential of RHMA as an entirely new treatment.

I will look forward for additional studies.

The study was supported by Genentech. RTJ

REFERENCE ARTICLE

12-18 1999 USPHS/IDSA GUIDELINES FOR THE PREVENTION OF OPPORTUNISTIC INFECTIONS IN PERSONS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

In August 1999, the US Public Health Service and the Infectious Disease Society of America published these updated guidelines. They are intended primarily for health care providers who care for HIV-infected persons. The document is long and inclusive. *Annals Int Med* December 7, 1999; 131: 873-908