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HIGHLIGHTS MARCH 2003

3-1 INFLUENZA VACCINATION AND REDUCTION IN HOSPITALIZATIONS FOR CARDIAC DISEASE AND STROKE AMONG THE ELDERLY

In the elderly, vaccination against influenza was associated with large reductions in numbers of hospitalizations from heart disease, cerebrovascular disease, as well as pneumonia and influenza. Risk of death was reduced by about 50%.

Flu vaccination is one of the most cost-effective health interventions. Primary care clinicians bear responsibility for increasing uptake by the general population.

3-2 LONG-TERM, LOW-INTENSITY WARFARIN THERAPY FOR THE PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM.

Long-term, low-intensity warfarin therapy with a target INR of 1.5 to 2.0 was highly effective in preventing recurrent VTE in patients with a history of *idiopathic* VTE, including patients with thrombophilia due to factor V Leiden and prothrombin mutations.

For patients with acute VTE, low-dose warfarin is appropriate after a 3-month course of conventional-dose warfarin. How long should therapy be continued? No definite answer, but probably long-term.

3-3 CEREAL, FRUIT, AND VEGETABLE FIBER INTAKE AND THE RISK OF CARDIOVASCULAR DISEASE IN ELDERLY INDIVIDUALS.

Cereal fiber consumption (equivalent to 2 slices of whole grain bread) in later life was associated with lower risk of incident CVD.

3-4 EFFECT OF FOUR MONTHLY ORAL VITAMIN D_3 (CHOLECALCIFEROL) SUPPLEMENTATION ON FRACTURES AND MORTALITY IN MAN AND WOMEN LIVING IN COMMUNITY.

Vitamin D supplements of 100 000 IU given orally every 4 months for *primary* prevention was associated with a lower risk of fractures (and without adverse effects) in older men and women living in the community.

This is equivalent to our usual dose of 800 IU daily. Calcium supplements would have lowered ris even more.

3-5 SILENT BRAIN INFARCTS AND THE RISK OF DEMENTIA AND COGNITIVE DECLINE

Silent brain infarcts are common in the elderly. Persons with silent brain infarcts had an increased risk of dementia, and a steeper decline in cognitive function than persons without such lesions.

In clinical practice—How can we intervene to benefit the patient? The hope is that treatment directed at vascular disease will reduce the burden of dementia. We should optimize cardiovascular health by established means: control of hypertension; lipid control; weight control; exercise; smoking-avoidance.

Other possible beneficial interventions: low-dose aspirin; one alcoholic drink daily; and folic acid supplementation to reduce homocysteine levels.

3-6 SUDDEN ACUTE RESPIRATORY SYNDROME (SARS)

"Plagues are as certain as death and taxes. The optimism of the 1960s and 1970s has given way to a mature realism that relationship between human beings and microbes is neither completely predictable nor biased in favor of humans." Is SARS a rehearsal for the next pandemic of influenza.?

The disease represents a sudden jump from animal species to humans. The virus probably evolved in animals for eons and for some reason suddenly became able to infect humans.

The SARS story has been astounding! In a short period of 2 months, the world-wide epidemiology has been described, the virus identified, its genetic code determined, and control measures instituted and found effective. As of the end of April 2003, the epidemic has been declared to be controlled in Vietnam and in Toronto Canada because no new cases were reported over a 3 week period. How would the history of the 20th century have changed if we had the technology, control measures, and world-wide instantaneous communication available during the 1918 influenza epidemic?

The ability of the virus to spread and cause serious illness and death in healthy persons increases the alarm.
Is SARS a rehearsal for the next pandemic of influenza.?

3-7 MOVING BEYOND SINGLE AND DUAL DIAGNOSIS IN GENERAL PRACTICE.

"The awkward phrase 'multiple morbidity' describes the common predicament of the many patients who have more than one health problem." Poor health is inextricably linked to low income, unemployment, poor housing, and inadequate social support as well as old age.

The trend towards more specialization tends to disadvantage people with multiple morbidity. The effective management of such patients depends heavily on primary care practice.

"As general practitioners it is our job to manage all of a patient's health problems by drawing on help for specialists where we can."

3-8 EARLY INTERVENTION WITH BUDESONIDE IN MILD PERSISTENT ASTHMA

Long-term, once-daily low-dose inhaled budesonide decreased the risk of severe exacerbations and the need for systemic corticosteroids and improved asthma control in patients with mild, persistent asthma of recent onset.

3-9 INHALED GLUCOCORTICOIDS VERSUS LEUKOTRIENE RECEPTOR ANTAGONIST AS SINGLE AGENT ASTHMA TREATMENT

Anti-leukotrienes as single agents were *less* effective than inhaled corticosteroids in the treatment of adults with mild to moderate asthma.

3- 10 ACCESSIBILITY, ACCEPTABILITY, AND EFFECTIVENESS OF ROUTINE TELEPHONE REVIEW OF ASTHMA: Pragmatic, Randomized, Trial

Telephone consultations enabled more patients with asthma to be reviewed. There was no apparent clinical disadvantage or loss of satisfaction. They may be an efficient option for primary care practice.

3-11 A RANDOMIZED TRIAL OF ASPIRIN TO PREVENT COLORECTAL ADENOMAS IN PATIENTS WITH PREVIOUS COLORECTAL CANCER

Compared with placebo, a daily dose of 325 mg aspirin reduced risk of adenoma development in patients with a history of surgery for CRC. (High risk patients.)

3-12 A RANDOMIZED TRIAL OF ASPIRIN TO PREVENT COLORECTAL ADENOMAS

Low-dose aspirin had a moderate chemoprotective effect on adenoma formation.

3-13 ASPIRIN AND PREVENTION OF COLORECTAL CANCER

Among persons with a history of adenomas or CRC the number of recurrences of adenomas prevented by aspirin (*secondary prevention*) would be higher than the number of episodes of bleeding. However, the cumulative clinical importance of bleeding probably exceeds that of surrogate neoplasm-related outcomes, especially when the effect of colonoscopic surveillance is taken into account.

If aspirin is used for *primary* prevention of CRC, it would have to be given for 10 to 20 years, the time it takes for CRC to develop. The cumulative adverse effects of aspirin over this time outweigh any benefit in prevention of CRC, particularly when prevention by screening for CRC is considered. Long-term use of aspirin for primary prevention of CRC is not cost-effective. It does not obviate the need for screening and surveillance.

Aspirin does reduce risk of recurrent colorectal neoplasia. Whether aspirin has a role in preventing colorectal cancer and whether it can be used to decrease the required frequency of screening or surveillance must await results of clinical trials.

3-14 PLASMA HOMOCYSTEINE AND RISK FOR CONGESTIVE HEART FAILURE IN ADULTS WITHOUT PRIOR MYOCARDIAL INFARCTION

An increased plasma homocysteine level independently predicted risk of development of CHF in adults without prior myocardial infarction. Another indication for supplementation with folate?

3-15 OUTCOME OF ELDERLY PATIENTS WITH CHRONIC SYMPTOMATIC CORONARY ARTERY DISEASE WITH INVASIVE VS OPTIMIZED MEDICAL TREATMENT STRATEGY.

After one year, there was no difference in quality-of-life between optimized medical therapy vs early invasive therapy. However, about half of the medical group needed hospitalization and later revascularization during the year. Death and non-fatal MI occurred at similar rates.

Elderly patients with severe angina have a difficult choice.

3-16 PROGNOSTIC IMPORTANCE OF WEIGHT LOSS IN CHRONIC HEART FAILURE AND THE EFFECT OF TREATMENT WITH ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS

Cardiac cachexia is common in chronic HF. It independently predicts a poor outcome. This may assist decisions for Hospice care.

3- 17 APOLIPOPROTEINS VERSUS LIPIDS AS INDICES OF CORONARY RISK AND AS TARGETS FOR STATIN TREATMENT.

Apo-lipo-protein B **(APO-B)** is a measure of the total number of atherogenic particles. APO-B is a *risk* factor, as is LDL-cholesterol. The *higher* the ABO-B, the *higher* the risk. In contrast, **APO-A1** is a *protective* factor, as is HDL-c. The *higher* the APO-A1, the *lower* the risk. Many studies show that APO-B is a better marker of risk of vascular disease and a better guide to the adequacy of statin treatment than any cholesterol index.

We are still pursuing the search for the best, most accurate, most reproducible, least costly risk factor for cardiovascular disease. LDL-cholesterol remains the choice at present. Other candidates are forthcoming, including C-reactive protein and APO-B. It will be interesting to follow the search. RTJ

Remarkable Reductions In Complications And Death. Give More Flu Shots !

3-1 INFLUENZA VACCINATION AND REDUCTION IN HOSPITALIZATIONS FOR CARDIAC DISEASE AND STROKE AMONG THE ELDERLY

Among the elderly, serious complications of influenza include exacerbations of co-existing conditions as well as pneumonia. Acute infections, including upper respiratory infections, may increase the risk of ischemic heart disease and stroke. During influenza epidemics, hospitalizations for cerebrovascular and cardiovascular events increase.

This observational study followed large cohorts of patients during two influenza seasons to determine if vaccination was associated with reduced rates of cardiovascular and cerebrovascular events.

Conclusion; Vaccination against influenza was associated with large reductions in hospitalizations for heart disease, cerebrovascular disease, and death.

STUDY

1. Observational study included over 140 000 subjects from three large, managed-care organizations in each of two influenza seasons (1998-1999 and 1999-2000). All were over age 65 (mean age = 74) and were living in the community. Many had co-existing conditions (heart disease, lung disease, cancer, hypertension, diabetes).
2. Between 56% and 60% were immunized for influenza. Patients in the vaccinated group were, on average, sicker and had higher rates of care than those in the non-vaccinated group.
3. Determined hospitalizations and deaths from cardiac disease, and cerebrovascular disease as well as from pneumonia.

RESULTS

1. As expected, vaccination was associated with a reduction in hospitalization for pneumonia and influenza by about 30%.
2. Risk of death was reduced by about 50%
3. Vaccination was also associated with a reduction in hospitalization for cardiac disease (-19%) in both seasons; and cerebrovascular disease (-16% and -23%).
4. Outcomes 1998-1999 season:

	Odds ratio (Vaccinated vs non-vaccinated)	NNT (To prevent one outcome in one season)
Cardiac disease	0.81	329
Ischemic heart disease	0.80	556
Congestive heart failure	0.81	585
Cerebrovascular disease	0.84	893
Pneumonia or influenza	0.68	347
Death	0.52	95

5. Outcomes were similar in all age groups, co-existing risks, and site of study.

DISCUSSION

1. Possible mechanisms for increased risk of cardiovascular and cerebrovascular disease associated with influenza include: alterations in clotting factors, platelet aggregation, concentrations of inflammatory response proteins, and alterations in cytokine concentrations. Thrombotic tendencies, impaired vasodilation, and endothelial injury may result.
2. Influenza vaccination of elderly persons was associated with substantial reductions in risk of hospitalizations for cardiac and cerebrovascular disease. This was even though the vaccinated group was, on average, sicker and were receiving higher rates of care than the non-vaccinated. As expected, risk of hospitalization for pneumonia and influenza was also reduced.
3. The reduction in risk of death was remarkable.
4. The authors believe that these results can be generalized.
5. Vaccination protects the many elderly persons with high-risk co-existing conditions as well as healthy elderly. Many high-risk patients receive care from subspecialty physicians. Subspecialists are less likely than primary care clinicians to recommend vaccination.

CONCLUSION

In the elderly, vaccination against influenza was associated with large reductions in numbers of hospitalizations from heart disease, cerebrovascular disease, as well as pneumonia and influenza. Risk of death was reduced by about half.

NEJM April 3, 2002; 348: 1322-32 Original investigation, first author Kristen L Nichol, University of Minnesota, Minneapolis. www.nejm.org

Comment:

The benefits of flu vaccinations are much greater than we previously had assumed. On a public health basis, benefits are huge. Flu shots must be one of the most cost-effective interventions. Primary care clinicians bear responsibility for increasing uptake. RTJ

Making Life Simpler For Patients And Clinicians

3-2 LONG-TERM, LOW-INTENSITY WARFARIN THERAPY FOR THE PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM.

Standard therapy for *idiopathic* venous thromboembolism **(VTE)** typically includes a 5 to 10 day course of heparin followed by 3 to 12 months treatment with full-dose warfarin with a target INR to between 2.0 to 3.0. After cessation of anticoagulation, recurrent VTE is a major problem, with an estimated annual rate up to 9%. Extended full dose warfarin is associated with substantial risk of major hemorrhage.

By contrast, low-intensity warfarin carries a lower risk of bleeding when used long-term. Such therapy requires less frequent monitoring.

This trial tested the hypothesis that long-term, low-intensity warfarin might provide a safe and effective method of reducing recurrence among patients with previous *idiopathic* VTE. It also tested whether this regimen

would be effective in preventing recurrent VTE in patients with thrombophilic mutations (factor V Leiden and prothrombin mutations).

Conclusion: Long-term, low-intensity warfarin was highly effective preventive therapy.

STUDY

1. Randomized, double-blind, placebo-controlled trial followed over 500 patients (mean age = 53). All patients had a history of one or more episodes of previous idiopathic VTE. All patients had been on full-dose warfarin for a median of 6.5 months. (At least 3 months)
2. About 1/3 had a positive family history of VTE, about 25% had Factor V Leiden present, 5% had prothrombin mutation. Patients with cancer were excluded.
3. All participated in a 30-day open-label run-in phase during which their dose of warfarin was titrated to a stable level that achieved an INR between 1.5 and 2.0.
4. Randomized to: 1) low-intensity warfarin, or 2) matching placebo.
5. Checked prothrombin time every 2 months and adjusted warfarin dose if necessary.
6. End point = confirmed recurrent VTE (positive venographic study or clear evidence of pulmonary embolism).

RESULTS

1. The trial was terminated early at a mean of 2 years therapy because effectiveness and safety were considered established.
2, Median dose of warfarin = 4 mg (range 0.5 to 10 mg daily). Median INR was 1.7 in the warfarin group.
3. Outcomes

Outcomes	Warfarin (n = 255)	Placebo (n = 253)
Recurrent VTE (per 100 person years)	2.6	7.2
Major hemorrhage	5 patients	2 patients
Death	4 patients	8 patients

NNT (to prevent one recurrence in one year) = 46

4. Outcomes were more favorable in women than in men. Hazard ratio of recurrent VTE: women = 0.20; men = 0.47
5. Recurrent events per 100 person-years of the 77 patients with either factor V Leiden, or prothrombin mutations:

   Placebo -- 8.6; Low-dose warfarin – 2.2 NNT(to prevent one event per year) = 16
6. Bleeding episodes necessitating hospitalization per 100 person-years:

   Placebo—0.4; Warfarin—0.9 [NNT(harm) = 200]
7. Minor bleeding or bruising occurred about twice as often in the warfarin group.
8. The rate of the composite end-point (recurrent VTE, major hemorrhage, or death from any cause) favored warfarin. (Hazard ratio = 0.52)

DISCUSSION

1. "Long-term low-intensity warfarin therapy given with a target INR of 1.5 to 2.0 results in a large and significant reduction in the risk of recurrent venous thrombosis."
2. Benefit was achieved with little evidence of any increase in the risk of hemorrhage or stroke, despite the infrequency of monitoring anticoagulant therapy. (Every 2 months)
3. Low-dose long-term therapy can be implemented easily in primary care practice.
4. Importantly, this therapy was equally effective in patients with idiopathic DVT associated with thrombophilia (factor V Leiden and prothrombin mutations). Patients with anti-phospholipid antibody syndrome were not studied.

CONCLUSION

Long-term, low-intensity warfarin therapy with a target INR of 1.5 to 2.0 was highly effective in preventing recurrent VTE in patients with a history of idiopathic VTE, including patients with thrombophilia due to factor V Leiden and prothrombin mutations.

NEJM April 10, 2003; 348: 1425-34 Original investigation, first author Paul M Ridker, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass. www.nejm.org

Comment:

An accompanying editorial (pp 1478-80 by Andrew I Shafer, University of Pennsylvania, Philadelphia comments and reminds us of several important points:

"Venous thromboembolism encompasses deep venous thrombosis and pulmonary embolism, which represent different manifestations of the same disease process. Indeed, most patients in whom symptoms of either condition develop will simultaneously have overt or subclinical evidence of the other."

VTE is a chronic disease. Almost one third of patients have a recurrence within 8 years after the initial event. VTE is at least in part a systemic disease. Most (and perhaps all) affected patients have an underlying hereditary hypercoagulable state, compounded by an acquired thrombogenic insult that triggers the acute thromboembolic event. The observation that the recurrences of deep venous thrombosis in the legs involve the contralateral leg in almost half the cases underscores the critical role of systemic hyper-coagulability in the pathogenesis of venous thromboembolism.

The study convincingly demonstrates that low-intensity warfarin prophylaxis is superior to placebo in preventing recurrence. It is reasonable now to adopt this regimen for secondary prophylaxis in patients who require more than 3 months of anticoagulation. However, a three-way comparison of placebo, low-dose warfarin and conventional-dose warfarin for secondary prophylaxis is necessary to determine risk/benefit after at least 3 months of conventional-dose therapy.

There is a rationale for the efficacy of low-intensity or even very-low-intensity in prevention of thrombosis. Several studies have reported that low dose regimens have ability to suppress coagulation in vivo.

Comment:

This makes life much simpler for primary care clinicians as well as for patients.

I was particularly pleased to note the benefit in patients with some types of thrombophilia. Indeed, thrombophilia was present in about 1/3 of these patients.

Should patients with acute VTE continue to be treated for 3 months with conventional-dose warfarin? I believe so. Low-dose may take over after 3 months.

The study did not consider how long anticoagulation should be continued. I believe many will require life-long anticoagulant therapy. Idiopathic VTE is a chronic disease.

Could low-dose therapy be effective as well in patients with VTE secondary to surgery, trauma, and immobilization? It would be reasonable to assume that it is after 3 months. RTJ

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Two Slices Of Whole Wheat Bread A Day Make A Difference!

3-3 CEREAL, FRUIT, AND VEGETABLE FIBER INTAKE AND THE RISK OF CARDIOVASCULAR DISEASE IN ELDERLY INDIVIDUALS.

Dietary fiber, comprising non-digestible polysaccharides, naturally occurring starch, and oligosaccharides in plants, has been associated with reduced incidence of heart disease and stroke.

Biologically plausible explanations for the benefit of fiber include effects on lipids, blood pressure, insulin sensitivity, fibrinolysis, coagulation, and endothelial function.

This study assessed the effects of fiber on risk of cardiovascular disease **(CVD)** in a cohort of elderly persons.

Conclusion: Increased intake of dietary *cereal* fiber was associated with reduced risk. Fruit and vegetable fibers were not.

STUDY

1. Population-based multicenter study followed over 3500 men and women--all over age 65 (mean age = 72). All were free of known CVD at baseline.
2. At baseline, determined usual dietary fiber consumption by a food frequency questionnaire. Average consumption of cereal fiber was 4.2 grams per day; fruit fiber – 5.2 grams/day; and vegetable Fiber--6.9 grams/ day.
3. The main foods contributing to the cereal fiber were dark breads and bran cereals. The intake of persons in the highest quintile of cereal fiber was 8 grams per day; the lowest quintile was 0.8 grams. (One slice of whole grain bread contains about 4 grams of fiber. Two slices would contain the 8 grams consumed by the highest quintile.)
4. Determined incident CVD over a 9 year period as related to quintiles of intake of fiber.

RESULTS

1. Over follow-up there were 811 incident CVD events.
2. After adjustment for multiple other risk factors, incidence of CVD was 21% lower in the highest quintile vs the lowest quintile of cereal fiber intake. Associations of cereal fiber consumption with CVD risk appeared to be graded and continuous.
3. Benefit was not evident for intake of vegetable or fruit fiber, only in relation to cereal fiber.
4. When CVD events were separately evaluated, higher cereal fiber intake was associated with

lower incidence of stroke. Hazard ratio for ischemic stoke = 0.76. There was also a trend toward lower incidence of ischemic heart disease.

5. The lower risk appeared predominantly related to fiber intake from dark breads (whole wheat, rye, pumpernickel), rather than to fiber from bran or granola cereals and other cold or cooked cereals.

DISCUSSION

1. Consumption of cereal fiber (approximately equal to 2 slices of whole grain bread daily) was inversely associated with risk of incident CVD (especially stroke) in elderly people.
2. The difference in risk was modest[1], but the benefit/harm-cost ratio is high. Benefits on a population or public health level may be substantial
4. Cereal fiber consumption may also reduce risk by a substitution effect, replacing intake of other foods having potential detrimental effects.
5. No benefits from fruit and vegetable fiber were noted. This is consistent with prior observations.

CONCLUSION

Cereal fiber consumption (equivalent to 2 slices of whole grain bread) in later life was associated with lower risk of incident CVD.

JAMA April 2, 2003; 289: 1659-6 Original investigation, first author Daniel Mozaffarian, University of Washington, Seattle www.jama.com

Comment:

1 By my calculation NNT for one year to benefit one person = 118

This is not to say that fruit and vegetable intake is not beneficial, only that their fiber content does not benefit. Even persons over age 65 may benefit from this dietary modification. RTJ

"Isolated Vitamin D Supplementation Prevents Fractures."

3-4 EFFECT OF FOUR MONTHLY ORAL VITAMIN D_3 (CHOLECALCIFEROL) SUPPLEMENTATION ON FRACTURES AND MORTALITY IN MAN AND WOMEN LIVING IN COMMUNITY.

Osteoporotic fractures are projected to increase exponentially worldwide. Most fracture prevention trials have focused on clinically defined groups such as persons with osteoporosis or previous fractures, mainly in women. Safe, effective, *primary* prevention measures are needed in older men as well as women.

This trial determined the effect of 4-times yearly high-dose vitamin D supplementation in older community dwelling men and women.

Conclusion: Supplementation prevented fractures without adverse effects.

STUDY

1. Randomized, double-blind controlled trial followed over 2600 persons (over 2000 men and over 600 women) living in the general community in the UK. All were between ages 65 and 85.
2. Randomized to: 1) 100 000 IU oral cholecalciferol every 4 months, or 2) placebo. (Fifteen doses total)
3. Mean calcium intake at 4 years = 742 mg/d.
4. Observed for fracture incidence.
5. Follow-up = 5 years.

RESULTS

1. After 5 years, 268 men and women had incident fractures—147 in common osteoporotic sites (hip, wrist, forearm, of vertebra).

2. Incidence of fractures 5 years	Vitamin D	Placebo	Absolute difference
Overall--hip wrist, forearm, vertebra	60/1345 (4.5%)	87/1341 (6.5%)	2.0%
Men – hip wrist, forearm, vertebra	36/1019 (3.5%)	50/1018 (4.9%)	1.4%
Women – hip wrist, forearm, vertebra	24/326 (7.4%)	37/323 (11.5%)	4.1%

3. Number needed to treat with vitamin D for 5 years to prevent one fracture:
   Men = 71; women = 24

4. Relative risks (intention to treat)	Vitamin D	Placebo
Any first fracture	0.78	1.00
First fracture at osteoporotic sites	0.67 (~ a 30% reduction)	
Mortality	0.88 (not significant statistically)	

5. Differences in fracture rate were evident at one year into the study.
6. No difference between groups on mortality, or incidence of cancer or cardiovascular disease.

DISCUSSION

1. The 100 00 IU dose every 4 months is equivalent to 800 IU daily.
2. No calcium supplements were prescribed.
3. This pragmatic ("real world") primary prevention trial maximized generalizability. Subjects were similar to the general practice population in the UK and in the USA. Most fractures do not occur in persons with severe osteoporosis, but in the large numbers at moderately increased risk.[1] Indeed, population-wide preventive interventions have been proposed for all elderly people. "The clinical dilemma for primary prevention is that whereas the population-attributable risk is large, the absolute individual risk is still low." The risk-benefit balance for community based prevention (*and overall costs)* differs from that for intervention in clinically defined groups. Safety, feasibility, and cost effectiveness are crucial. Side effects are less acceptable in a healthy group in which the risk of fracture is not high."
4. Cost of vitamin D is low. The investigators quote a price of less than $2 for a year of treatment.
   (*In the USA, supplements of calcium + vitamin D given daily cost less than $10 per year. RTJ*)
5. "The results indicate that isolated vitamin D supplementation prevents fractures."

CONCLUSION

Vitamin D supplements of 100 000 IU given orally ever 4 months for primary prevention was associated with a lower risk of fractures (and without adverse effects) in older men and women living in the community.

BMJ March 1, 2003; 326: 469-72 Original investigation, first author Daksha P Trivedi, University of Cambridge School of Clinical Medicine, Cambridge, UK www.bmj.com/cgi/content/full/326/7387/469

Comment:

1 This depends on what segment of the population one is considering. In the elderly, the incidence of osteoporosis-related fractures is very high. Consider all the old women with "dowager's hump" and hip fracture.

The dosage of vitamin D3 used in the study would be unusual in the USA. Indeed, I could not find any reference to a 100 000 IU capsule in the PDR. As the article indicated, the 4-monthly dose is equivalent to our usual 800 IU daily dose. The study was confined to effects of vitamin D only. Clinically, for prevention and therapy, calcium is added.

Is vitamin D3, especially in large doses, toxic in any way? The article did not mention any. I was unable to find any reference to toxicity or side effects in the PDR or in a textbook of pharmacology. (Certainly, no toxicity is related to an 800 IU daily dose.)

I enjoyed this article. It suggests several important, potentially clinically applicable applications:

1) Vitamin D is a useful and effective preventive therapy. Its benefit/harm-cost ratio is very high.

2) It brings potential benefit to men as well as women. Prevention and treatment of osteoporosis has been a neglected subject in men. It is important.

3) Primary prevention can be effective even in old age. The age group in the study was 65 to 85. (The mean age was not mentioned. It must have been greater than 65.)

4) The absolute risk of osteoporosis is very high, almost universal as we age. Prophylaxis should be started at an early age (in the teen years). If not started early in life, it may be started much later with considerable benefit. Osteoporosis in older age brings great disability. We should prevent it as much as possible. RTJ

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Protect Your Brain As Well As Your Heart !

3-5 SILENT BRAIN INFARCTS AND THE RISK OF DEMENTIA AND COGNITIVE DECLINE

Silent brain infarcts **(SBI)** are frequently seen on magnetic resonance imaging **(MRI)** in healthy elderly people. Vascular abnormalities have a role in the development of dementia. Patients with a stroke are at increased risk for both vascular dementia and Alzheimer's disease. People found at autopsy to have had lacunar infarcts are more likely to have had dementia. Fewer pathological findings of Alzheimer's disease are needed in persons with such infarcts for clinical symptoms of dementia to be present. Patients with Alzheimer's disease more frequently have silent (asymptomatic) brain infarcts on MRI than control subjects without dementia.

This study examined the relation between SBI and risk of dementia and cognitive decline in the elderly in the general population.

Conclusion: Elderly people with SBI had an increased risk of dementia and a steeper decline in cognitive function.

STUDY

1. A prospective population-based cohort study (The Rotterdam Scan Study) was designed to study the causes and consequences of brain changes in the elderly.
2. In 1995-1996, randomly selected over 1000 participants (mean age = 71; range 60 to 90). All were free of dementia and stroke at baseline.
3. Conducted neuropsychologic testing and cerebral MRI at baseline and again in 3 to 4 years; 619 of the cohort underwent the second MRI for SBI. SBI was defined as one or more areas of focal hyperintensity at least 3 mm in diameter without a history of a corresponding stroke or TIA Infarcts on both the baseline and second MRI were graded with respect to location and size.
4. Monitored all for development of dementia throughout the study and any history of stroke or transient ischemic attacks **(TIA).**
5. Also analyzed for the presence or absence of subcortical atrophy and white-matter lesions.
7. Follow-up = mean of 3.6 years.

RESULTS

1. Baseline characteristics all participants (n = 1015)

Mean age	72 years	
Hypertension	51%	
Diabetes	7%	
Use of aspirin	11%	
Silent brain infarcts	21%	(The great majority lacunar)

(*Note that at mean age 72, in this study, about 1/5 of all asymptomatic individuals had already experienced a SBI. This requires confirmation. RTJ)*

2. Presence of SBI at baseline more than doubled the risk of dementia during follow-up of 3.6 years. Of 798 subjects without SBI at baseline, 16 (2%) developed dementia; of 217 with SBI at baseline, 14 (6%) developed dementia. (*My calculation, RTJ*)
3. Greater severity of periventricular white-matter lesions was associated with greater risk.
4. Greater subcortical atrophy of the brain was also associated with greater risk.
5. Nineteen of the 30 patients who developed dementia underwent a second MRI. Of these 3 (16%) experienced a symptomatic infarct, and a new SBI was found in 4 (21%). Of the 618 without dementia at follow-up, 1% had a symptomatic infarct and 11% had a new SBI. Global cognitive function declined more in those with SBI at baseline who developed an additional infarct during follow-up.
6. Subjects with SBI at baseline experienced steeper decline in cognitive function over 3.6 years. This was especially evident in those with multiple SBI.

DISCUSSION

1. The presence of SBI on MRI in elderly persons without dementia at baseline, more than doubled the risk of developing dementia (majority of the Alzheimer's type) over the next 3.6 years

2. There is increasing evidence that vascular factors may contribute to the development of Alzheimer's disease. After a symptomatic stroke, dementia (including Alzheimer's disease) develops in approximately 30% of patients. .

4. A greater severity of periventricular white-matter lesions (thought to result from small-vessel disease) was associated with increased risk of dementia.

5. Persons with SBI are at greater risk for additional infarcts, both symptomatic and silent.

CONCLUSION

Elderly people with silent brain infarcts had an increased risk of dementia, and a steeper decline in cognitive function than persons without such lesions.

NEJM March 27, 2003; 348: 1215-22 Original investigation, first author Sarah E Vermeer, Erasmus Medical Center, Rotterdam, the Netherlands. www.nejm.org

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"SILENT" STROKES AND DEMENTIA

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

The observations in the previous study are intuitively attractive. Stroke can impair brain function, including cognition. Previous stroke is a major risk factor for subsequent stroke. But, large neuroanatomical defects can exist without detection of functional abnormalities on standard neurological examinations or without recognition of defects by family. Although strokes frequently cause cognitive impairment, by themselves they tend not to lead to full-blown dementia.

The relation between stroke and dementia is complex. Until the 1970s (70 years after Alzheimer's description) mainstream opinion attributed senile dementia to cerebral arteriosclerosis. Thereafter the term "multi-infarct dementia" was used. Alzheimer's disease can certainly occur in people with no independent evidence of cerebrovascular disease, although meticulous studies have shown that vascular disease, especially of the white matter, commonly accompanies the neuropathologic lesions of Alzheimer's disease Risk factors for cardiovascular disease and those for dementia tend to overlap. Vascular disease can be one of the factors contributing to the development of neuropathologic Alzheimer's lesions and clinical Alzheimer's dementia.

In clinical practice—How can we intervene to benefit the patient? The hope is that treatment directed at vascular disease will reduce the burden of dementia. We should optimize cardiovascular health by established means: control of hypertension; lipid control; weight control; exercise; smoking-avoidance.
Other possible beneficial interventions: low-dose aspirin; one alcoholic drink daily; folic acid supplementation to reduce homocysteine levels.

NEJM March 27, 2003; 348: 1277-78 Editorial, first author John P Blass, Weill Medical College of Cornell University, White Plains, NY. www.nejm.org

A Rehearsal For The Next Pandemic Of Influenza.?

3-6 SUDDEN ACUTE RESPIRATORY SYNDROME (SARS)

"Plagues are as certain as death and taxes. The optimism of the 1960s and 1970s has given way to a mature realism that relationship between human beings and microbes is neither completely predictable nor biased in favor of humans."

Over the past few decades, several important human viruses have emerged—HIV, Ebola, Hantaan, Nipah, human metapneumovirus. Against this background, emergence of new viral diseases is not surprising.

The severe acute respiratory syndrome **(SARS)** emerged at the end of February in Hanoi, Vietnam. (Some evidence that the disease originated in South-east China, but was not reported until later.) It is highly contagious with attack rates over 50% among health care workers caring for patients with the syndrome. The incubation period is about one week. Early systemic symptoms include fever, malaise, myalgia, headache, and dizziness. Sore throat and rhinorrhea occur early in only about ¼ of cases, and cough occurs early in about 40%. Because of the non-specific early manifestations, SARS will be overlooked unless clinicians have a high index of suspicion and seek a history of travel or contact with the syndrome.

After a few days of fever, a lower respiratory phase begins with a non-productive cough, which may be accompanied by dyspnea and chest pain. Dyspnea requiring oxygen occurs in many cases after about 5 days, and may progress to hypoxemia requiring ventilatory support in about 15%.

Early chest X-rays typically show small focal unilateral diffuse interstitial infiltrates which may be overlooked initially. The appearance evolves rapidly, often becoming more generalized and affecting both lung fields. Chest radiographs may, however, be normal during the febrile prodrome and throughout the illness.

Clinically, SARS varies. It ranges from mild illness to death. It is speculated that the most severe illnesses occur among the first level contacts of an index case. If real, this may reflect repeated exposure of unsuspecting healthcare workers to the index case, or an attenuation of the pathogen during subsequent waves of infection.

Management: Antibiotics targeted at known bacterial pathogens causing atypical pneumonia are without apparent benefit. Oseltamivir, the influenza neuraminidase inhibitor is not effective. Steroids and the antiviral agent, ribavirin, given IV have been used. Their efficacy is not proved, although some clinical improvement was seen in critically ill patients in Hong Kong. Fortunately, many cases of probable SARS improve steadily over 7 to 10 days without complications or a need for supplemental oxygen. The case fatality rate is about 3%.

Many epidemiologic and clinical issues remain. SARS may be transmitted by droplets, although transmission in some cases is not explained. Control measures should include airborne precautions (including a negative pressure room, isolation room, full respiratory protection, and eye protection), and contact precautions (gowns, gloves, hand hygiene).

The speed of travel favors intercontinental spread of disease. "The rapid dissemination of sudden acute respiratory syndrome around the world should be considered a rehearsal for the next pandemic of influenza." BMJ March 29,2003; 326: 669-70 Editorial, first author Maria Zambon, Public Health Laboratory Service, London, UK www.bmj.com/cgi/content/full/326/7391/669

BMJ March 29; 326: 669-70 Editorial, first author Maria Zambon, Public Health Laboratory Service, London, UK. www.bmj.com/cgi/cotent.full/326/7391/669

Comment:

Researchers have cultured a new coronavirus, in the same family as viruses that cause colds and upper respiratory tract infections. The CDC considers this the cause. The disease represents a sudden jump from animal species to humans. The virus probably evolved in animals for eons and for some reason suddenly became able to infect humans.

The SARS story has been astounding! In a short period of 2 months, the world-wide epidemiology has been described, the virus identified, its genetic code determined, and control measures instituted and found effective. As of the end of April 2003, the epidemic has been declared to be controlled in Vietnam and in Toronto Canada because no new cases were reported over a 3 week period. I wonder how the history of the 20th century would have changed if we had the technology, control measures, and the world-wide instantaneous communication available during the 1918 influenza epidemic.

Interest in the disease has been enormous. Numerous descriptive articles have been published in the lay press and in medical journals. Authorities have appeared on TV, commenting on various aspects of the disease.

SARS is spread by close contact—droplets, hand contact, by fomites, and possibly by aerosol over short distances. In no other infectious disease is hand-washing more important. More recent studies report that the virus can survive for days on fomites, especially in the cold.

The virus grows readily on culture. The fact that over 95% of subjects recover suggests an immune response and that an effective vaccine may be developed. Recent studies report the possibility that the virus can mutate. Hopefully not too drastic or too frequent a mutation.

The ability of the virus to spread and cause serious illness and death in healthy persons causes the high degree of alarm. The acute and deadly disease progression may be in part due to an enhanced local immune reaction in the lungs. Some recent reports suggest that relapse may occur. RTJ

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Primary Care Clinicians are Integrators.

3-7 MOVING BEYOND SINGLE AND DUAL DIAGNOSIS IN GENERAL PRACTICE.

"The awkward phrase 'multiple morbidity' describes the common predicament of the many patients who have more than one health problem." Such patients are disproportionately represented among the elderly, and among populations that are socioeconomically deprived. Individuals and families that are socioeconomically disadvantaged are at risk of a compounding multiplicity of health and social problems. Poor health is inextricably linked to low income, unemployment, poor housing, and inadequate social support.

This multiple morbidity, coupled with the aging of the population, challenges the delivery of effective health care. Primary care clinicians have an important role in ensuring adequate care for patients with "multiple morbidity". (*This includes oversight of the adverse effects of the multiple drugs prescribed by consultants, and their multiple adverse effects. A high percentage of elderly patients taking multiple drugs will experience adverse effects. RTJ*)

Practice has become increasingly specialized. It is not uncommon for patients to receive care from several specialists. The extraordinary advances in medical knowledge and the overwhelming volume of relevant scientific literature mean that specialization is a requirement for some diseases. Patients with multiple problems will still

require multiple referrals. But an immense depth of knowledge of a disease runs the risk of overlooking the complexities of clinical management of multiple morbidity.

The trend towards more specialization tends to disadvantage people with multiple morbidity. The effective management of such patients depends heavily on primary care practice.

The requirement to contain costs compounds the problem.

"As general practitioners it is our job to manage all of a patient's health problems by drawing on help from specialists where we can, and by using whatever research evidence exists to guide practice."

Multiple morbidity is a major component of health inequalities, particularly in an aging population..

BMJ March 8, 2003; 326: 512-14 Editorial, by Liam Smeeth, London School of Hygiene and Tropical Health and Iona Heath, Royal College of General Practioners, London UK www.bmj.com/cgi/content/full/326/7388/512

Comment:

This is the British view. I believe it applies equally to the USA.

Some authorities have predicted the death of primary care in America. I believe this is premature. Certainly increasing co-operation between specialists and primary care clinicians needs to be developed. But the primary care physician is the only clinician with the opportunity of coordinating therapy and trying to deal long-term with "dual diagnoses" and the multiple social and personal problems patients present. The primary care clinician can continue care outlined by the specialist consultants who do not have the opportunity of knowing what other specialists may be prescribing. Primary care clinicians are integrators. Primary care, well done, is the most difficult of specialties.

Primary care clinicians who follow specialist-prescribed care must know and be able to identify the adverse effects of multiple medications. I believe the primary care clinician in the USA will increasingly evolve into a community-based "primary care team" The advantages of co-ordination of care of multiple problems at one facility are obvious: increasing convenience, lower costs, increased opportunity to apply the principles of "patient-oriented" care. RTJ

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Decreased Risk Of Exacerbations, but at High Cost

3-8 EARLY INTERVENTION WITH BUDESONIDE IN MILD PERSISTENT ASTHMA

Chronic airway inflammation is a major cause of symptoms and abnormal airway physiology in asthma, even in mild disease.

Inhaled glucocorticosteroids benefit patients with chronic persistent asthma by decreasing airway inflammation, improving lung function, lessening symptoms and airways hyper-responsiveness, and reducing mortality.

This study assessed the effectiveness of *long-term low-dose* inhaled glucocorticosteroids in patients with mild asthma of relatively recent origin.

Conclusion: Long-term once-daily low-dose budesonide (*Pulmicort*) decreased the risk of exacerbations and improved asthma control.

STUDY

1. World-wide, randomized, double-blind trial followed over 7000 patients (age 5 to 66; mean = 24)

to completion of a 3-year trial.

2. All had mild persistent asthma of less than 2-years duration. All had symptoms in the 3 months before entry. None had previous regular treatment with corticosteroids.

3. Mild persistent asthma defined as wheezing, cough, dyspnea, or chest tightness at least once a week , but not as often as daily. All had reversible airway obstruction (increase in FEV1 of more than 12% after a short-acting bronchodilator, a fall in FEV1 of more than 15% on exercise testing, or a variation of more than 15% between the two highest and two lowest peak expiratory flow rates during 14 days.)

4. Randomized to: 1) once daily inhaled budesonide (400 micrograms [two inhalations]for adults; 200 ug for children under age 11), or 2) inhaled lactose. [In the USA, *Pulmicort* turbohaler delivers 200 mcg of budesonide with each activation.]

5. The primary outcome was time to first severe asthma-related event, defined as one which required admission or emergency treatment for worsening asthma, or as death due to asthma.

6. Other asthma treatments were continued as before.

RESULTS

1. Outcomes over 3 years:	Budesonide (n = 3568)	Placebo (n = 3597)
At least one severe exacerbation	117 (3.3%)	198 (5.5%)

[*Absolute difference = 2.2%; NNT (to benefit one patient over 3 years) = 45*]

Treated patients had fewer courses of systemic corticosteroids and more symptom free days.

Treatment benefited all age groups.

Compared with placebo, post-bronchodilator FEV1 increased by 1.5% after one year and by 0.9% after three years (expressed as percent of the predicted value).

2. In younger children, 3-year growth was reduced by 1.3 cm; the greatest reduction in the first year.

3. "Both treatment regimens were well tolerated with a similar rate of non-asthma related adverse effects."

DISCUSSION

1. Substantial morbidity is associated with mild asthma.

2. Early once-daily inhalations of low-dose budesonide reduced risk of having a severe asthma exacerbation "*by almost half*"[1] and even more so for life-threatening exacerbations.

3. Treatment also resulted in more symptom-free days, and a reduced need for systemic corticosteroids.

4. The effectiveness of budesonide was independent of lung function or medications at baseline.

5. The small change in growth noted in children was expected. Despite the reported initial effect on growth, other studies reported children attained normal adult height while continuing treatment with budesonide for 10 years.

CONCLUSION

Long-term, once-daily low-dose inhaled budesonide decreased the risk of severe exacerbations and the need for systemic corticosteroids and improved asthma control in patients with mild, persistent asthma of recent onset.

Lancet March 29, 2003; 361: 1071-76 Original investigation from the inhaled Steroid Treatment As Regular Therapy in early asthma (START) study, first author Romain A Pauwles, Ghent University Hospital, Belgium. www.thelancet.com

Comment:

1 Journal editors continue to permit the misleading relative risk reductions--"by almost half" in this study means an absolute risk reduction of 2.2%; NNT for 3 years = 45.

My pharmacy quotes a price of $150 for each *Pulmicort* inhaler containing 200 inhalations of 200 ug (enough for 100-days therapy). Daily cost = $1.50. By my calculation, cost to prevent one or more exacerbations over 3 years in this group of patients would be over $1600. Patients will ask—is the benefit/harm-cost ratio high enough?

Compliance with this daily regimen may be difficult. About 25% of subjects randomized to the inhalations did not complete the 3-year study. Compliance will be less in primary care practice. RTJ

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Inhaled Beclomethasone Wins !

3-9 INHALED GLUCOCORTICOIDS VERSUS LEUKOTRIENE RECEPTOR ANTAGONIST AS SINGLE AGENT ASTHMA TREATMENT

Anti-leukotrienes are a new class of anti-inflammatory drugs, They interfere directly with leukotriene production or with leukotriene receptors. They are administered orally, and seem to lack the adverse effects associated with long-term glucocorticoids.

Several guidelines advocate their use as adjunct therapy to inhaled glucocorticoids for moderate-severe persistent asthma, or as alternative single-agent therapy. In 2001, sales in the USA almost equaled those of inhaled corticosteroids.

This study compared the safety and efficacy of anti-leukotrienes with inhaled glucocorticoids as *monotherapy* in asthma.

Conclusion: Inhaled glucocorticoids are more effective.

STUDY

1. Systematic review of randomized-controlled trials found 13 trials (12 in adults; 1 in children) meeting inclusion criteria. All were in patients with mild to moderate asthma.
2. Compared anti-leukotriene receptor antagonists montelukast (*Singulair*) 10 mg once daily; and zafirlukast 20 mg twice daily) with inhaled glucocorticoids equivalent to beclomethasone (*Beclovent; Vanceril*) 400-450 micrograms daily.
3. Main outcome = rate of exacerbations requiring treatment with systemic glucocorticoids.
4. Follow-up = as long as 37 weeks.

RESULTS

1. Leukotriene receptor antagonists were more likely to suffer an exacerbation requiring systemic glucocorticoids; 11.6% vs 6.1%. (NNT = 18)
2. Inhaled glucocorticoids provided greater improvement in FEV1, in morning peak expiratory flow rate, nocturnal awakenings, use of rescue beta-agonists, and days without symptoms.
3. Side effects did not differ between groups according to a priori definition of equivalence. However, treatment period was limited and adverse effects typical of inhaled corticosteroids were not measured.
4. Anti-leukotrienes were associated with more withdrawals due to poor control of asthma.

DISCUSSION

1. In patients with mild to moderate asthma, use of anti-leukotrienes was more likely to require systemic glucocorticoid therapy.
2. The effect was not influenced by the type of anti-leukotriene or the inhaled corticosteroid used, by disease severity, or intention to treat analysis.
3. There was a higher rate of withdrawals of anti-leukotrienes due to lack of efficacy.
4. The superiority of inhaled glucocorticosteroids was evident within 4 to 6 weeks, and persisted for up to 37 weeks.

CONCLUSION

Anti-leukotrienes as single agents were less effective than inhaled corticosteroids in the treatment of adults with mild to moderate asthma.

BMJ March 22, 2003; 326: 621-23 Original investigation by Francine M Ducharme, McGill University Health Centre, Quebec, Canada. www.bmj.com/cgi/content/full/326/7390/621

Comment:

What about anti-leukotrienes as add-on therapy with inhaled corticosteroids? The same author reports in BMJ 2002;324:1545 that any improvement in response is modest. Add-on cannot be recommended as a substitute for increasing dose of inhaled glucocorticosteroids.

Costs of drugs: My pharmacy quotes:

Montelukast (*Singulair*) 10 mg $3.00 each; $93 per month

Beclomethasone (*Beclovent*) 200 puffs 42 micrograms each puff costs $45 each inhaler. By my calculation, at 400 micrograms daily, this = 20 days therapy RTJ

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Periodic Telephone Consultations May Have Significant Clinical Advantages.

3- 10 ACCESSIBILITY, ACCEPTABILITY, AND EFFECTIVENESS OF ROUTINE TELEPHONE REVIEW OF ASTHMA: Pragmatic, Randomized, Trial

Regular review of patients with asthma reduces morbidity, and is endorsed as good practice. A large USA trial showed that telephone review has the potential to reduce morbidity, medication use, and use of health services in patients with a range of chronic disorders.

The authors of this study hypothesized that telephone consultations would improve access of patients to care and are an acceptable and effective alternative to face-to-face consultations for the routine care of asthma.

Conclusion: Compared with face-to-face consultations, telephone consultations enabled more people with asthma to be reviewed, without clinical disadvantage or loss of satisfaction.

STUDY

1. Pragmatic (real world), randomized controlled trial in 4 general practices in the UK followed 278 adults (mean age 55) with asthma. None had received a routine asthma review in the past 11 months.
2. Randomized to: 1) telephone reviews with a specialist nurse trained in asthma treatment., or 2) office consultations
3. Patients randomized to telephone were sent a letter informing them that they would receive a telephone review and that they should expect a call from an asthma nurse within the month.
4. Nurses followed their normal practice made appropriate to each patient's individual clinical need.
5. Nurses arranged any follow-up office consultations they felt necessary. Patients were free to arrange any consultations they wished.
6. Patients in the control group were sent a written invitation to make an appointment to see the asthma nurse within a month.
7. Outcomes—change in asthma symptoms and related quality-of-life determined by questionnaire.

RESULTS

1. Telephone consultations were shorter than office visits (mean duration 11 min vs 22 min).
2. The 2 types of consultation addressed similar aspects of asthma care. Peak flow measurements were more likely to be discussed in the office.
3. Quality-of-life scores and symptom scores measured within 3 months of randomization were similar in the two groups.
4. The number of acute asthma exacerbations and use of health resources did not differ.

DISCUSSION

1. Telephone consultations enabled 26% more people with asthma to be reviewed as compared with office visits, without any apparent clinical disadvantage or loss of satisfaction.
2. Because of their shorter duration, telephone consultations may be an efficient option in primary care for routine review of patients with asthma.
3. All practices were "asthma interested"—they all had specialist nurses experienced in providing asthma care.
4. Content of the telephone consultations was similar to office consultations, apart from peak

flow measurements.

5. Telephone reviews can take as long or as short a time as necessary. The time limits imposed on office visits do not apply. However, nurses observed that telephone consultations were more "focused". This may reflect the tendency of telephone consultations to be more goal oriented, with fewer digressions.
6. Despite the shorter time, there was no evidence of dissatisfaction with the time spent.
7. There may be some cost advantages to patients.

CONCLUSION

Telephone consultations enabled more patients with asthma to be reviewed. There was no apparent clinical disadvantage or loss of satisfaction. They may be an efficient option for primary care practice.

BMJ March 1 2003; 326; 477-79 Original investigation, first author Hilary Pinnock, University of Aberdeen, UK
www.bmj.com/cgi/content/full/326/7387/477

Comment:

I believe this approach may be applicable to many patients with chronic conditions in the USA. It will require continued evolution from the "primary care physician" to a "primary care team".

Admittedly, some of the advantages of face-to-face consultations will be lost—eg, expressions of other concerns, non-verbal (body language) communication, visual appraisal of patient's well being and mood.

Some patients may wish to contract for a periodic telephone visit interspersed with office visits. This would be more efficient, much less costly, and would avoid the considerable inconvenience of travel to the office.

Some of the doctor-patient relationship may be lost. However, this may be preserved by interspersing office visits with telephone visits.

Some financial considerations must be agreed upon. RTJ

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One-a Day Aspirin Reduced Recurrence of Adenomas in High-risk Patients

3-11 A RANDOMIZED TRIAL OF ASPIRIN TO PREVENT COLORECTAL ADENOMAS IN PATIENTS WITH PREVIOUS COLORECTAL CANCER

Adenomas are precursors of most colorectal carcinomas **(CRC).** Observational studies have suggested that regular aspirin and other NSAID use may decrease the risk of adenomas.

This study assessed the effect of aspirin on incidence of adenomas in patients with previous colorectal cancer—a high-risk group.

Conclusion: Daily aspirin was associated with a significant reduction in incidence of recurrent adenomas.

STUDY

1. Randomized, double-blind trial assessed the effect of aspirin on incidence of adenomas in 635 persons. All had a history of previous CRC. All had undergone surgery aimed at cure.
2. Participants were considered at relatively low risk for recurrence of cancer. Most had Dukes' stage

A or B1 and had no metastatic spread. Some patients with higher grades of CRC were entered if they had received surgery aimed at cure and had been free of disease for more than 5 years.

3. Before study entry, all received colonoscopy within 4 months, with removal of all polyps.
4. Randomized to: 1) enteric-coated aspirin 365 mg daily, or 2) placebo.
5. During follow-up, (median of 31 months) repeat colonoscopy determined the proportion of patients with adenomas, the number of recurrent adenomas, and the time of development of adenomas between randomization and subsequent colonoscopic examinations.

RESULTS

1. A total of 517 patients had at least one colonoscopy after randomization.
2. Outcomes

Outcomes	Aspirin (n = 259)	Placebo (n = 258)
One or more new adenomas found	43 (17%)	70 (27%)

(Absolute difference = 10%; NNT(to benefit one patient) = 10.)

3. Median size of adenomas and proportion of subjects with advanced adenomas was the same in both groups.
4. Incidence and type of adverse effects were similar in the two groups.

DISCUSSION

1. Previous trials have reported that patients with familial adenomatous polyposis treated with celecoxib (*Celebrex*) and sulindac (Generic; *Clinoril*) developed fewer adenomas.
2. It is difficult, however, to show that NSAIDs prevent CRC because of the long latency period of progression from benign adenoma to CRC. Because most CRCs develop from adenomas, adenomas have been used as surrogate endpoints in prevention trials.
3. The present trial was based on the premise that patients with a history of CRC might constitute a group at higher risk for adenomas and thus be particularly suitable for a study of chemopreventive effects of NSAIDs.
4. Support for the hypothesis that aspirin protects against colorectal neoplasia comes from other studies that have used either cancer or adenomas as endpoints. “These studies have had remarkably consistent results, with benefits irrespective of age, race, sex, location of the study centers, and location of the tumor in the colon or rectum, and have generally shown a 40 to 50 percent reduction in the risk of colorectal neoplasia.”
5. This present study is important because it demonstrates a protective effect of aspirin in a population at higher risk.
6. A recent study that used rectal mucosal prostaglandin E2 levels as a biologic marker found that, as compared with placebo, an *81-mg dose* of aspirin significantly suppressed prostaglandin levels to an extent equivalent to that of higher doses.
7. Aspirin cannot be viewed as a replacement for surveillance colonoscopy.

CONCLUSION

Compared with placebo, a daily dose of 325 mg aspirin reduced risk of adenoma development in patients with a history of surgery for CRC.

NEJM March 6, 2003; 348: 883-90 Original investigation, first author Robert S Sandler, University of North Carolina, Chapel Hill. www.nejm.org

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Low-dose Aspirin Better than Standard Dose?

3-12 A RANDOMIZED TRIAL OF ASPIRIN TO PREVENT COLORECTAL ADENOMAS

This trial randomized over 1100 patients (mean age = 57) to aspirin or placebo. All had a recent history of colorectal adenomas.

Half of the aspirin group received 81 mg daily; half received 325 mg daily.

Follow-up colonoscopy was to be performed approximately 3 years after the qualifying colonoscopy.

Incidence of recurrent adenomas:	Aspirin 81 mg	Aspirin 325 mg	Placebo
	38% (statistically significant)	45% (not significant)	47%

Advanced neoplasms (adenomas over 1 cm, with tubulovillous features, severe dysplasia, or invasive cancer.

Relative risks:	Aspirin 81 mg	Aspirin 325 mg	Placebo
	0.59	0.83 (not significant)	1.00

The authors suggest that a few years of aspirin use can reduce adenoma recurrence. The effect is moderate, and significant only in those receiving 81 mg daily, not in those receiving 325 mg.

DISCUSSION

"Our finding that aspirin was associated with more substantial reductions in the risk of advanced lesions than that of non-advanced lesions suggests that effects of aspirin may be greater in later stages of the adenoma-carcinoma sequence.

At the low doses of aspirin used in this study -- "risk of bleeding was not a substantial problem".

It is not clear why the dose of 81 mg, but not the 325 mg dose, reduced risk. Both doses suppress colorectal prostaglandin levels to a similar extent. The difference many have been due to chance.

Broad recommendations for aspirin as a chemoprotective agent are premature, and must be considered in the context of possible toxic effects was well as the potential benefits already provided by periodic surveillance colonoscopy. Nonetheless, the findings provide a basis for optimism regarding development of NSAIDs as effective chemopreventive therapy against colorectal cancer.

CONCLUSION

Low-dose aspirin had a moderate chemoprotective effect on adenoma formation.

NEJM March 6, 2003; 348: 891-89, first author John A Baron, Dartmouth Medical School, Hanover, N.H. www.nejm.org

Not for Primary Prevention. Possibly for Secondary Prevention. Seek Patient Preferences

3-13 ASPIRIN AND PREVENTION OF COLORECTAL CANCER

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

A protective effect of aspirin is biologically plausible. It works in part through the inhibition of cyclo-oxygenase which is found in colorectal cancer tissue.

Aspirin delayed development of adenomas. It reduces risk of recurrent adenomas among persons with history of CRC or adenomas. Should it be recommended for *primary* prevention in those over age 50 considered at average risk for CRC? Should it now be recommended for *secondary* prevention? The editorialist calculated the numbers needed to treat for some benefits and risks of aspirin:

Outcome	NNT	Estimated duration of treatment
Secondary prevention		
Recurrence of adenoma	10	31 months
Recurrence of advanced adenoma	19	33 months
Primary prevention		
Any coronary heart disease event	50- 250	5 years
Colorectal cancer	471-962	> 5 years
Death from colorectal cancer	1250	10-20+ years
Adverse events		
GI hemorrhage	100	24 months
Major GI hemorrhage	300-800	4-6 years
Hemorrhagic stroke	800	4-6 years.

The fact that most adenomas do not progress to cancer makes surrogate outcomes less important in terms of prevention. Given that endoscopic surveillance for recurrent neoplasia would result in detection and removal of most neoplasms anyway, the true clinical benefit—avoidance or delay of polypectomy for 1 of every 10 or 19 persons treated with aspirin—would seem to be small.

Among persons with a history of adenomas or CRC the number of recurrences of adenomas prevented by aspirin (*secondary prevention*) would be higher than the number of episodes of bleeding. However, the cumulative clinical importance of bleeding probably exceeds that of surrogate neoplasm-related outcomes, especially when the effect of colonoscopic surveillance is taken into account.

If aspirin is used for *primary* prevention of CRC, it would have to be given for 10 to 20 years, the time it takes for CRC to develop. The cumulative adverse effects of aspirin over this time outweigh any benefit in prevention of CRC, particularly when prevention by screening for CRC is considered. Long-term use of aspirin for primary prevention of CRC is not cost-effective. It does not obviate the need for screening and surveillance.

Aspirin does reduce risk of recurrent colorectal neoplasia. Whether aspirin has a role in preventing colorectal cancer and whether it can be used to decrease the required frequency of screening or surveillance must await results of clinical trials.

NEJM March 6, 2003; 348: 879-80 “Perspective”, editorial comment by Thomas F Imperiale, Indiana University School of Medicine, Indianapolis. www.nejm.org

Comment:

I believe it is likely that long-term (low-dose) aspirin and other NSAIDs do retard adenoma development.

Is the effect clinically beneficial? For *primary* prevention, harms likely outweigh benefits over a long term. For *secondary* prevention, some fully informed patients may choose to take aspirin, especially if it is also of possible benefit for prevention of cardiovascular disease. Aspirin or no-aspirin, colonoscopic surveillance is still required. RTJ

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Raised Levels Independently Predict Risk Of CHF

3-14 PLASMA HOMOCYSTEINE AND RISK FOR CONGESTIVE HEART FAILURE IN ADULTS WITHOUT PRIOR MYOCARDIAL INFARCTION

Plasma homocysteine (an amino acid) has emerged as a major vascular disease risk factor. Elevated levels have been related to greater risk of atherosclerotic sequelae, including cardiovascular mortality, coronary heart disease, and stroke.

Experimental evidence suggests that the myocardium may be uniquely susceptible to homocysteine-induced injury.

This study hypothesized that elevated levels of homocysteine would increase the risk of congestive heart failure (**CHF**).

Conclusion: An increased homocysteine level independently predicted risk of CHF.

STUDY

1. Community-based prospective cohort study entered over 2400 adults (mean age 72) who participated in the Framingham Heart Study. All were free of CHF and prior myocardial infarction at baseline.
2. Divided homocysteine levels into quartiles for women (in umol/L) 1) 3.5 to 8.9; 2) 9.0 to 11.0; 3) 11.1 to 13.6; 4) 13.7 to 65. Mean = 12.0. In men levels were slightly higher.
3. Main outcome = incidence of a first episode of CHF during an 8-year follow-up.

RESULTS

1. During follow-up 156 subjects developed CHF.
2. Development of CHF according to quartiles of plasma homocysteine;

Quartile	1	2	3	4
Women developing CHF	10/386 (2.6%)	16/389 (4.1%)	20/385 (5.2%)	42/387 (10.9%)

[Absolute difference between quartile 1 and 4 = 8.3%. NNT(8 years to benefit one) = 12]

3. Results for men – NNT = 17
4. After controlling for established risk factors for CHF, including the occurrence of MI, plasma homocysteine levels higher than the median values (over 11 umol/L in women and over 12 umol/L in men) were associated with an adjusted hazard ratio for CHF of 1.9 for women, and 1.8 for men.
5. The relation between plasma homocysteine in those without coronary heart disease at baseline and risk of future CHF was maintained in both men and women.

DISCUSSION

1. In older adults without prior myocardial infarction, elevated plasma homocysteine was related positively and strongly with risk of CHF.
2. In women, the risk of CHF doubled at the second quartile. A 4-fold risk was observed for those with values in the top quartile vs those in the lowest quartile.
3. In men, the risk of CHF became evident only at values exceeding the median.
4. In a small subgroup of individuals who underwent echocardographic evaluation within 30 days of their first CHF hospitalization, homocysteine levels above the median were associated with both systolic and diastolic CHF.
5. What might the mechanisms be for the association?

   The myocardium might be uniquely susceptible to homocysteine-induced injury.

   Homocysteine is a risk factor for coronary atherosclerosis and MI.

   Homocysteine may lead to myocardial ischemia by promoting endothelial dysfunction of coronary resistance vessels.

   Homocysteine levels in patients with coronary syndromes are associated with greater myocardial injury as evidenced by higher troponin levels.

   Homocysteine may have a critical role as a source of oxidative stress, a factor known to promote myocardial dysfunction.

6. "Our study design would support the importance of non-ischemic mechanisms in addition to the well-recognized ischemic mechanisms."
7. "Our findings are consistent with the hypothesis that elevated plasma homocysteine levels are important risk factor for CHF."
8. Folic acid, alone or in combination with vitamins B6 and B12, lowers homocysteine levels, and may reduce risk of CHF.

CONCLUSION

An increased plasma homocysteine level independently predicted risk of development of CHF in adults without prior myocardial infarction.

JAMA March 12, 2003; 289: 1251-57 Original investigation, first author Ramachandran S Vasan, National Heart, Lung, and Blood Institute's Framingham Heart Study. www.jama.com

Comment:

I abstracted this article for its general interest, and because many persons might consider supplementation with folic acid a reasonable preventive measure, given its high putative benefit/harm-cost ratio. RTJ

3-15 OUTCOME OF ELDERLY PATIENTS WITH CHRONIC SYMPTOMATIC CORONARY ARTERY DISEASE WITH AN INVASIVE VS OPTIMIZED MEDICAL TREATMENT STRATEGY.

What is the benefit of revascularization in older patients with symptomatic coronary artery disease? What is the risk? Outcomes may differ from those of younger patients.

This trial assessed the long-term value of invasive [coronary by-pass graft surgery (**CABG**) and percutaneous coronary intervention (**PCI**)] vs "optimum" medical management in older patients in terms of quality of life and prevention of major cardiac events.

Conclusion: One-year outcomes in older patients with angina were similar with regard to symptoms, quality of life, non-fatal myocardial infarction (**MI**), and death. The invasive approach carried an early intervention risk. Medical management posed about a 50% chance of later hospitalization and revascularization.

STUDY

1. Prospective, randomized trial entered 282 patients (mean age = 80). All had class 2 or higher chronic angina despite treatment with 2 or more anti-anginal drugs. Comorbidity and risk factors were universal in these patients.
2. Randomized to: 1) coronary angiography followed by revascularization (if feasible), or 2) optimized medical therapy.
3. Optimized medical therapy was not described fully. The number of anti-anginal drugs was increased and the dosages were increased.
4. Main outcomes = quality of life assessed by standardized questionnaire, and major adverse cardiac events (death, non-fatal MI, or hospitalization for acute coronary syndrome).
5. Follow-up = one year.

RESULTS

1. Intervention group (n = 155 assigned):

PCI	79
CABG	39

(Not all patients in the intervention group actually received an intervention.)

2. At one year:	Invasive (n = 140)	Medical (n = 142)
Later revascularization	10%	46%
Mortality	11%	8%
Death or non-fatal MI	17%	20%
Overall major adverse cardiovascular events		
At 6 months	19%	49%
At one year	25%	64%

(Note that half of the patients assigned to medical therapy underwent revascularization within the year.)

3. There was a persistent and marked relief of symptoms and improvement in quality of life in both

groups. The improvements were greater in the intervention group in the first 6 months, but the difference disappeared at one year.

DISCUSSION

1. Previous short-term trials in elderly patients reported greater benefits from invasive therapy, but at a risk of excess early mortality.
2. In this trial, the early unfavorable mortality observed in the intervention group disappeared during late follow-up.
3. The advantage of invasive therapy regarding symptom relief and improvement in quality-of-life noted after 6 months also disappeared during late follow-up.
4. Significantly more optimized medical patients needed to be hospitalized for uncontrolled symptoms, and significantly more received late revascularization for that reason.
5. In this study, rates of death, and death or non-fatal MI, were similar after one year and there was no longer a significant difference in angina relief or improvement in quality-of-life between treatment groups. Thus, would it not be reasonable to wait until revascularization becomes urgently necessary? If symptoms are acceptably controlled by optimized medical therapy, they may not have to undergo the risks of revascularization.
6. However, if medically treated individual patients cannot accept the 50% chance of hospitalization with later revascularization, they can choose early revascularization. .

CONCLUSION

After one year, there was no difference in quality-of-life between optimized medical therapy vs early invasive therapy. However, about half of the medical group needed hospitalization and later revascularization during the year. Death and non-fatal MI occurred at similar rates.

This implies that elderly patients with severe angina have a difficult choice.

JAMA March 5, 2003; 289: 1117-23 Original investigation, first author Matthias Pfisterer, University Hospital, Basel, Switzerland. www.jama.com

Comment:

This is a good example of dilemmas patients face when fully informed of the risks and benefits of two alternative therapies. Patient-preferences will guide the decision.

Primary care clinicians should be aware of the expertise and track record of their interventional cardiologist colleagues in order to advise patients of the risks involved.

Several considerations would tilt me toward intervention in select patients:

1) “Optimal” medical therapy is difficult to achieve in primary care practice, and brings adverse side-effects. The investigators were expert.
2) An 80 year old patient may welcome the early relief of symptoms and be willing to accept the chance of intervention-related death in order to achieve some degree of comfort, albeit temporary.
3) That an individual patient faces a 50% chance of intervention within a year (and its risk)

might tilt him or her toward earlier intervention.

5) I believe it more likely now, with the advent of sirolimus-coated stents, that outcomes from PTCA will be more favorable than outcomes in the study. RTJ

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Weight Loss Independently Predicts A Poor Prognosis

3-16 PROGNOSTIC IMPORTANCE OF WEIGHT LOSS IN CHRONIC HEART FAILURE AND THE EFFECT OF TREATMENT WITH ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS

Cachexia is a serious complication of several chronic diseases, including chronic heart failure (HF). Weight loss in chronic HF is linked to impaired survival.

Angiotensin-converting-enzyme inhibitors (ACE) ameliorate symptoms of HF, reduce morbidity, and improve survival in patients with chronic HF. The benefits cannot be explained solely by its hemodynamic mode of action. ACE may modify the neuro-hormonal axis and endothelial function. ACE are most successful in preventing death when catecholamine levels are raised. Elevated levels of catecholamines are closely related to cardiac cachexia.

This study assessed the frequency of weight loss in patients with chromic HF, whether the degree of weight loss predicts mortality, and whether weight loss can be prevented by ACE.

Conclusion: Weight loss occurs frequently in chronic HF. It predicts early mortality. Weight loss may be retarded by ACE.

STUDY

1. Investigated weight changes in over 1900 patients (mean age 61) with chronic HF randomized to 1) enalapril vs 2) placebo. **1**
2. At baseline, all patients had an ejection fraction less than 35%, were clinically stable, and were included only if they were free of edema. .
3. Determined prognostic effect of weight loss at cut points of 5%, 7.5%, 10%, and 15%.
4. Mean follow-up = 35 months. During follow-up 39% died.

RESULTS

1. Effects of weight loss:
   A. Over follow-up, 42% of patients had weight loss from baseline of 5% or more.
   B. Weight loss was independently related to reduced survival. All cutpoints for weight loss were significantly associated with impaired survival after adjustment for age, sex, NYHA class, and left ventricular ejection fraction.
   C. 29% of all deaths occurred on the background of newly developed weight loss of 7.5%or more; 38% of the people who died had a weight loss of 6% or more. These deaths were in a population of patients judged clinically stable and non-cachectic at baseline.
   D. Weight loss of 6% or more at any time during follow-up occurred in 36%. This was the

strongest predictor of death (adjusted hazard ratio compared with no weight loss = 2.1)

E. Over 4 months, patients who lost more than 15% of their original weight had 3.3 times the risk of death as persons who maintained their original weight.

2. Effect of enalapril:

Patients taking enalapril had a lower hazard of weight loss . Over 36 months, the hazard ratio of those taking enalapril vs those taking placebo gradually widened. The delay in weight loss associated with enalapril was such that a 30% cumulative proportion of patients with weight loss of 6% or more was reached after 24 months in the placebo group vs 32 months in the enalapril group.

(By my calculation from their figure 2 page 1080, at 36 months enalapril(as compared with placebo) was related to a reduction in risk of weight loss-- from over 40% in placebo group to 30% in enalapril group. RTJ)

However, enalapril was not protective of survival in those with severe cachexia (weight loss over 15%)

DISCUSSION

1. Substantial weight loss is a common event in persons with chronic HF. It is a gradual and graded process. Spontaneous reversal is a rare event. In chronic HF, the wasting process affects muscle, fat, bone, and heart. Contributing factors include: anorexia, malabsorption, mental depression, and upregulation of catecholamine levels. ACE have a favorable blunting effect on catecholamine levels.
2. Weight loss was *independently* linked to impaired survival.
3. "We suggest that weight loss of 6% or more should be the cutpoint to define the presence of cachexia in chronic heart failure." At 9 months, patients with weight loss 6% or more had up to a 100% higher subsequent death rate.
4. Enalapril delayed the development of cardiac cachexia by about 8 months, and delayed death by 6 months.

CONCLUSION

Cardiac cachexia is common in chronic HF. It independently predicts a poor outcome.

Lancet March 29, 2003; 361 1077-83 Original investigation, first author Stefan D Anker, Virchow-Klinikum, Berlin, Germany. www.thelancet.com

1 Patients from the SOLVID trial "Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fraction and Congestive Heart Failure" NEJM 1991; 325: 293-302

Comment:

I did not abstract this article to stress the benefits of ACE in patients with HF. This is well established. My main purpose was to point out that weight loss in HF is a sign of poor prognosis. This may help clinicians and Hospice to determine if Hospice care is appropriate for patients with chronic HF. The determination of remaining length of life (eg, 6 months) may be more predictable in patients with cancer, but a patient with cardiac cachexia may also be considered at risk of death within a relatively short period.

Hospice at Charlotte NC requires that 2 criteria in patients with HF must be met:

1) Optimum medical treatment with diuretics and vasodilators (usually ACE inhibitors). OR, angina pectoris at rest, resistant to standard nitrate therapy. AND

2) Significant symptoms of recurrent congestive heart failure at rest (NYHA Class IV)

Documentation of other factors supporting eligibility include:

Resistant arrhythmias, history of cardiac arrest; brain embolism of cardiac origin; ejection fraction less than 20%.

Other factors that may support terminal status include:

Persistent edema; orthopnea; cachexia; progressive weight loss of > 10% in past 6 months.

I believe many patients with heart failure would benefit from Hospice care if these entrance criteria were interpreted liberally. RTJ

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A Better Risk Marker?

3- 17 APOLIPOPROTEINS VERSUS LIPIDS AS INDICES OF CORONARY RISK AND AS TARGETS FOR STATIN TREATMENT.

Presently, LDL-cholesterol is the fundamental index of risk of atherosclerotic disease. It is a measure of the mass of cholesterol in the LDL fraction.

In contrast , apo-lipo-protein B **(APO-B)** is a measure of the total number of atherogenic particles. APO-B is a *risk* factor, as is LDL-cholesterol. The *higher* the ABO-B, the *higher* the risk. In contrast, **APO-A1** is a *protective* factor, as is HDL-c. The higher the APO-A1, the *lower* the risk. Many studies show that APO-B is a better marker of risk of vascular disease and a better guide to the adequacy of statin treatment than any cholesterol index. The ratio of apolipoprotein B to apolipoprotein A-1 **(APO-B/APO-A1)** is superior to either APO-B alone or APO-A1 alone in predicting risk. The ratio APO-B/APO-A1 is a better predictor of risk than the ratio of total cholesterol/HDL cholesterol. .

(*Note that apo-lipo-proteins are proteins; not fats; not cholesterol. They are an intrinsic part of atherogenic lipids including LDL, HDL, VLDL, .IDL, and lipoprotein (a). "Apo" denotes "derived from". RTJ)*

Why should APO-B be a better indicator of risk than LDL-cholesterol? APO-B is contained in *all* atherogenic particles, not only in LDL, but also in very low density lipoproteins, intermediate density lipoproteins, and apolipoprotein (a).

APO-A-1 is contained in anti-atherogenic particles such as HDL types, and thus is inversely related to risk.

Many persons have normal or low LDL-c levels, but remain at risk. Many persons with myocardial infarctions have almost normal concentrations of lipids. APO-B may be a better indicator of risk in these patients in part because their LDL contains a higher proportion of small, dense LDL particles, which are more atherogenic than the larger, less dense particles. APO-B levels are higher in these individuals than in persons with a lower proportion of small dense LDL particles and a greater proportion of larger, less dense particles. The numbers of atherogenic particles and their ratio might be a more important risk factor than the amount of lipids carried per particle. (Suppose individual A has a LDL-c of 100; individual B also has a LDL-c of 100. But A has a higher

proportion of small, dense LDL particles and a lower proportion of large, less dense particles. The APO-B will be higher in person A than in B, and his risk will be higher. Conversely, if A has more large, less dense LDL particles, and B has more small dense particles, A's risk will be lower.

The authors cite large prospective studies which reported that APO-B was highly predictive of fatal acute myocardial infarction (MI) and coronary events.

The largest study (AMORIS[1]) compared concentrations of LDL-cholesterol vs apolipoproteins as predictors of fatal acute MI. The study followed over 175 000 adults for up to 5.5 years. APO-B (a direct risk factor) and APO-A1 (inversely related to risk) were more significant predictors of risk when compared with any concentration of total cholesterol and triglyceride in both sexes and at all ages. The strongest predictor was the APO-B/APO-A-1 ratio. The ratio was better than any cholesterol ratio as a predictor of cardiovascular risk.

The AFCAPS/TexCAPS, a *primary* prevention trial, assigned over 3300 patients to a placebo arm. Baseline values for LDL-cholesterol and APO-B were significant predictors of cardiovascular events. The strongest predictor was the APO-B/APO-A-1 ratio, with a risk ratio of about 2.0

The LIPID Trial included over 4500 patients with coronary disease (a secondary prevention trial) in the placebo arm followed for 6 years. The hazard ratio for risk of a cardiovascular event was 1.14 for LDL-c and 2.06 for APO-B/APO-A-1 ratio, indicating a stronger risk predicted by the ratio as compared with LDL-c.

What about effect of statin drug therapy on apolipoproteins? The authors suggest that determination of lowering of apolipoproteins related to statin therapy is a better measure of effectiveness in preventing cardiovascular events than is determination of lowering of cholesterol. The authors suggest that lowering LDL-c may seem adequate, but the lowering of APO-B may not be adequate. This would indicate that a higher dose of statin is indicated. Thus APO-B guided therapy should be substantially more effective in prevention than treatment guided by LDL-c.

Statin therapy guided by APO-B has practical advantages. APO-B can be accurately and inexpensively measured by autoanalyzers. It does not require the fasting state.

The authors conclude that measurement of apolipoproteins should now be introduced broadly into clinical practice.

Lancet March 1, 2003; 363: 777-80 "Viewpoint". Commentary , first author A D Sniderman, McGill University, Montreal, Quebec, Canada. www.thelancet.com

Comment:

I abstracted some points from "High Apolipoprotein B, Low Apolipoprotein A-1 And Improvement In The Prediction Of Fatal Myocardial Infarction" (AMORIS study) Lancet December 15,, 2001, 358: 2026-33, first author Goran Waldius, Karolinska Institute, Stockholm, Sweden.

We are still pursuing the search for the best, most accurate, most reproducible, least costly risk factor for cardiovascular disease. LDL-cholesterol remains the choice at present. Other candidates are forthcoming, including C-reactive protein and APO-B. It will be interesting to follow the search. RTJ