PRACTICAL POINTERS

FOR

PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

APRIL 2008

This document is divided into two parts

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

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

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

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

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

Richard T. James Jr. M.D.

Editor/Publisher.

HIGHLIGHTS AND *EDITORIAL COMMENTS*   APRIL 2008

"Under-Recognized And Under-Treated"

4-1 OSTEOPOROSIS IN MEN

- Osteoporosis in men is under-recognized and under-treated. It goes untreated in the majority of men with fractures. One-third of hip fractures world-wide occur in men. Vertebral fractures in men over age 65 are half as common as in women. The majority are painless. They are associated with loss of height, reduced quality of life, respiratory dysfunction, increased risk of death, and subsequent fractures.

- Osteoporosis in men often has secondary causes. The most frequent are corticosteroid use, excessive alcohol, and hypogonadism. Other secondary causes account for about 15% of cases. These include low calcium intake, smoking, and vitamin D deficiency. Since hypogonadism is difficult to detect on the basis of the history and physical exam, measurement of total testosterone level is recommended in all men with osteoporosis. Serum levels of 25-hydroxyvitamin D should be measured. Levels below 30 ng/mL should be treated.

- Bone mineral density (BMD) measured by dual-energy x-ray absorptiometry is a robust predictor of fracture—as in postmenopausal women. The relationship between lower BMDs and fracture is continuous. As in women, the WHO has assigned thresholds based on absorptiometry of the total hip. ("T-scores"):

  Osteoporosis: BMD 2.5 or more standard deviations below the mean for a young adult male.

  Osteopenia: BMD more than 1.0 and less than 2.5 SD

  Normal: BMD within 1.0 SD

  Recent epidemiological data suggest that for any given absolute BMD value at the spine or hip, the risk of fracture is similar among men and women of the same age.

- The WHO has developed a clinical tool to predict risk of fracture. The FRAX risk assessment tool assesses risk, adjusted for country, sex , and age. It includes, in addition to BMD, prior history of fracture, family history of fracture, current smoking, use of systemic corticosteroids, excessive alcohol, and rheumatoid arthritis. (Go to FRAX on Google to access a calculator to determine 10-year individual risk of fracture.)

- Calcium and vitamin D supplements are often recommended. Although there are conflicting data on benefits, a recent systematic review of nearly 64 000 participants in randomized trials showed that 1200 mg or more of calcium and 800 IU or more of vitamin D daily reduced osteoporotic fractures by 12% in both men and women age 50 and over.

- Guidelines

  The International Society for Clinical Densitometry recommends BMD screening in men 70 years of age or older, and recommends earlier screening if there is a fragility fracture or other known factors conferring predisposition to osteoporosis.

  Recent National Osteoporosis Foundation guidelines recommend pharmacological therapy in men age 50 and older with hip or vertebral fractures; in men with a T score below -2.5, and in men with T

score between -1.0 and -2.5 with either a 10-year hip fracture probability of 3% or more, or a probability of a minimal trauma fracture of 20% or more.

Bisphosphonates are recommended as first-line therapy for men age 65 and older whose BMD is in the osteoporotic range.

Diagnosis and treatment of osteoporosis in women has been vigorously pursued. In men, it has been neglected.

I enjoyed this article. Previously, I had not thought much of the possibility of benefits of prevention and treatment in men.

I thought the editorialist was over-enthusiastic, but he raised many good questions.

Should elderly males undergo universal determination of BMD? This would, I believe, burden patients and the system, and not be cost effective.

I believe some clinical indicators may lead to further testing and treatment of older men:

Loss of height. Loss of vigor. History of fracture. FRAX indicator

Increasing kyphosis

Lack of adequate calcium and vitamin D intake (Essentially lack of supplementation). Males as well as females of all ages in the US should receive supplements of vitamin D and calcium routinely

Perhaps screening and treatment of osteoporosis in elderly men will eventually become as popular as among women. There is still a long way to go.

Women Who Were More Adherent To The DASH-Diet Had Lower Risks Of CHD And Stroke.

4-2 ADHERENCE TO DASH-STYLE DIET AND RISK OF CORONARY HEART DISEASE AND STROKE IN WOMEN

The Dietary Approaches to Stop Hypertension (**DASH**) diet is:

High in fruits and vegetables

Moderated in low-fat dairy products

Low in animal protein (red and processed meats)

High in plant protein with substantial amounts whole grains and legumes and nuts.

The diet reduces BP among normotensive as well as hypertensive persons. It also reduces low-density cholesterol .

The DASH-low sodium diet adds restriction of salt, and results in even greater reductions in BP.

This study assessed the associating between adherence to a DASH-style diet (including frequency of intake of sodium and sweetened beverages) and long-term risk of CHD and stroke in women

The analysis included over 85 000 women (ages 34 to 59) who completed a 1980 food frequency questionnaire. At baseline, none of the women had a history of CHD, stroke, or diabetes. The study cohort was followed from 1980 to 2004. Mean follow-up = 11 years

Subjects in the top quintile of adherence to the diet were less likely to report CHD and stroke compared with

those in the bottom quintile. (For CHD, multivariate adjusted relative risk = 0.76 For total stroke, multivariate adjusted RR = 0.82.) Risks of CHD and stroke declined linearly as adherence to the diet rose.

Crude absolute incidence rate of CHD: lowest quintile vs highest quintile of adherence per 100 000 person-years

> Highest adherence   551
>
> Lowest adherence   689
>
> Difference =   138 per 100 000 per year.
>
> (Ie, each year for 11 years, incidence of CHD about 1.3 women per 1000 were spared an episode of CHD.)

Conclusion: Adherence to the DASH diet was associated with a lower risk of CHD and stroke among middle-aged women.

Continuing advice of the importance of adherence to healthy life-styles is a primary responsibility of the "medical home"—primary care.

If You Can't Lose Weight, At Least Get Physically Fit

4-3   THE JOINT EFFECTS OF PHYSICAL ACTIVITY AND BODY MASS INDEX ON CORONARY HEART DISEASE RISK IN WOMEN

This study investigated the combined association of physical activity and body mass index (**BMI**) on CHD. It included over 38 500 women (mean age = 54) at baseline. None had a history of CHD or stroke. Follow-up = 11 years.

Divided BMI into: normal weight (BMI less than 25); overweight (25-29); and obese (30 and over).

Estimated the average hours per week spent during the past year walking, jogging, running, engaging in aerobic exercise, the number of flights of stairs climbed daily, and other physical activities.

Based on the energy cost of each recreational activity, a metabolic equivalent task (MET) score was assigned. (One MET is about 1 kcal/kg of bodyweight per hour.) The energy expenditure in kilocalories per week was estimated by multiplying the MET score by bodyweight and hours per week.

Increased physical activity was categorized as active (over 1000 kcal/week) and inactive (< 1000 kcal/week). [1000 kcal/week approximates the recommendation for 30 min of moderate recreational physical activity 5 days per week.]

Hazard ratios of CHD:

	Normal weight	Overweight	Obese
Active	1.00 (referent)	1.54	1.87
Inactive	1.06	1.88	2.53

In this population of middle-aged and older women, both elevated BMI and reduced physical activity, individually and combined, were associated with an increased risk of CHD.

Physical activity attenuated the risk of CHD from elevated BMI (>25). However, even high levels of physical

activity did not eliminate all of the excess risk of CHD related to overweight and obesity.

Conclusion: Both physical activity and BMI play a role in development of CHD. The risk associated with a high BMI is reduced considerably by physical activity. The risk is not completely eliminated. This reinforces the importance of being physically active as well as lean.

Should Isolated Aggressive Lowering Of Systolic BP And LDL-C Be Applicable To Primary Care?

4-4   EFFECT OF LOWER TARGETS FOR BLOOD PRESSURE AND LDL CHOLESTEROL ON ATHEROSCLEROSIS IN DIABETES

This study compared progression of subclinical atherosclerosis in adults with type-2 diabetes (DM-2) treated to targets of LDL-cholesterol of 70 mg/dL or lower, and systolic BP (SBP) of 115 or lower vs standard targets of LDL-c of 100 mg/dL or lower and SBP of 130 and lower.

Randomized, open-label, trial (2003-2007) followed 499 American Indians (mean age 56; 66% women; 22% smokers) for 3 years. All had DM-2. None had prior cardiovascular events. All had LDL-c 100 mg/dL or greater, and SBP 130 and over.

Randomized to:

1) Aggressive therapy

Goal of reducing LDL-c to 70 and lower; SBP to 115 and lower.

2) Standard treatment.

Goal of reducing LDL-c to 100 mg/dL or lower, and SBP to 130 mm HG and lower.

Step 1 drug for lipid control = statin.. Step 1 drugs for BP control were ACE inhibitors or angiotensin II blockers. Step two hydrochlorothiazide. Step 3 to 5 added calcium blockers, alpha-blocker, and other vasodilators.

Baseline characteristics and outcomes at 36 months:

	Baseline	36 months	
		Aggressive	Standard
Weight (kg)	90	91 *	91
BMI	34	34 *	34
Waist circumference	110 cm	111 *	110
HDL-c	46 mg/dL	48	48
LDL-c	104 mg/dL	72	104
HbA1c	8.0	8.3 *	8.2
SBP	130	117	129
Smokers	22%	-	-

(* Note, there was no attempt to control weight or abdominal obesity. No mention of attempts to discontinue smoking. HbA1c was unchanged.)

.	Mean carotid IMT	-0.012 mm	+0.032 mm
	Left ventricular mass (g)	-14	-7

Compared with baseline, IMT regressed in the aggressive group (-0.012 mm) and progressed in the standard group (+0.038mm). Carotid cross-sectional area also regressed in the aggressive group (-0.02 mm^2) and progressed in the standard group (+1.05 mm^2). Left ventricular mass decreased in both groups, more in the aggressive group.

Adverse events:	Aggressive 39%	Standard 27%
Serious event	N = 4	N = 2
	(hypotension; hypokalemia)	(hypotension)

Adverse events were related to lowering SBP (not to lowering LDL-c), and were more common in the aggressive group.

The study used surrogate endpoints. No difference in clinical endpoints was observed during the 3-year observation period. The reliability of surrogate outcomes remains to be established.

Conclusion: Aggressive treatment of LDL-c and SBP to lower targets resulted in regression of carotid IMT and a greater decrease in LV mass in individuals with DM-2. Clinical events were uncommon, and did not differ between groups. Whether these improvements in IMT and LV mass will result in less risk of CVD events was not determined.

Is this study applicable to primary care? I think not. Primary care practice does not work this way.

Good primary care emphasizes reduction of all risk factors. Risk factors also related to primary care include smoking, BMI, waist circumference, HbA1c, None of these factors was reduced in the study.

In addition, baseline SBP (130) and LDL-c levels (104) were not particularly high. SBP was lowered by only 13 mm Hg; LDL-c by only 32 mg/dL. Aggressive lowering of SBP resulted in more adverse effects.

Surrogate endpoints are not reliable indicators of clinical outcomes.

Angiotensin II blocker and ACE- inhibitor Equally Effective. No Advantage from the Combination

4-5   TELMISARTAN, RAMIPRIL, OR BOTH IN PATIENTS AT HIGH RISK FOR VASCULAR EVENTS

This study compared the angiotensin II receptor blocker (**ATR-b**) telmisartan (*Micardis*; Boehringer Ingleheim) the ACE-inhibitor (**ACE-i**) ramipril (*Altace*; King) and the combination of the two drugs in patients with established vascular disease or high-risk diabetes.

Randomized:

1) Over 8500 patients given ramipril 10 mg daily

2) Over 8500 patients given telmisartan 80 mg daily

3) Over 8500 patients given both combined.

All had a history of coronary, peripheral vascular, or cerebrovascular disease; or diabetes with end-organ damage. (Mean age = 66; 85% had cardiovascular disease; 69% hypertension: and 38% diabetes.)

Follow-up = a median of 56 months.

Primary composite endpoint = death from cardiovascular causes, myocardial infarction, stroke, or

hospitalization for heart failure.

Primary outcome	Ramipril	Telmisartan	Both
	17%	17%	16%

Telmisartan was not inferior to ramipril. Combined drugs were not superior to either alone.

Adverse effects:	Ramipril	Telmisartan	Two combined
Permanent discontinuation	25%	23 %	29 %

Combination therapy increased the risk of hypotension, syncope, renal dysfunction, and hyperkalemia. As a reason for discontinuation, cough (4%) and angioedema (0.3%) were more common in the ACE-i groups.

Conclusion: In patients who had vascular disease or high-risk diabetes, but did not have heart failure, telmisartan was an equally effective alternative to ramipril. There was no additional advantage (and there is some harm) from the combination of telmisartan + ramipril used in full doses in this population as compared with ramipril alone.

This simplifies therapeutic decisions.

It would be reasonable to consider the combination would be more effective than either drug alone because ACE-i do not completely block production of angiotensin II. Adding an ATR-b might offer more complete blockage of action of angiotensin II on the cell. This study did not support this effect.

Combining the two classes of drugs will produce more toxicity.

Note that cough and angioedema were more common in the ACE-i group despite the subjects being considered tolerant to it during a run-in phase. In primary care practice, cough is likely to be much more common than the 4% incidence noted in the study.

Cost: Some pharmacies offer the ACE-i enalapril 20 mg for $4 for a month's supply. Micardis 80 mg costs about $83.00 for a month's supply.

Primary care clinicians might prescribe an ACE-i first as a trial because of its much lower cost. If it is not tolerated, a switch to an ATR-b would be indicated.

If telmisartan is not inferior to ramipril, it is no better. If a drug is 'non-inferior", there is no reason to use it unless it is less expensive or has less toxicity.

A Significant Source Of Discomfort And Distress Well Into The Postmenopausal Years

4-6 PERSISTENT HOT FLUSHES IN OLDER WOMEN

In most women, hot flushes (**HFs**) resolve within a few years. But, some women report HFs for many years after they cease to menstruate.

This natural history study analyzed data from over 3000 women (mean age 65) , 95% of whom were 5 or more years post menopause.

At baseline, 12% of the women reported clinical significant HFs.

Prevalence of HFs was inversely related to time since menopause:

2- 5 years	45%

20 or more years   8%

For a substantial minority of women, HFs are a significant source of discomfort and distress well into the postmenopausal years. Among women 4 to 9 years post-menopause, more than 20% reported clinically significant HFs. Among those 10 or more years post-menopause, nearly 10% reported clinically significant HFs.

Serum follicular stimulating hormone (**FSH**) levels, rather than estradiol levels were associated with greater severity of HFs. Non-estrogen feedback systems may be important in modulating severity of HFs. (FSH levels normally stabilize or decline as time from menopause lengthens.)

The characteristic most strongly associated with HFs was trouble sleeping, even though this symptom did not tend to improve with increasing time since menopause. Trouble sleeping may be a co-morbid symptom of menopause that shares common underlying triggers.

Conclusion: A substantial minority of women who are 5 or more years post-menopausal have clinically significant HFs. More than half of older post-menopausal women who present with HFs can be expected to have persistent HFs after 3 years.

The investigators did not mention therapy for HFs.

These patients are likely to present to primary care clinicians. How should we advise them? I believe it depends on the severity of the symptom. Some patients may be willing to put up with the symptoms without any therapy. Some may ask for helping to sleep. If symptoms are severe enough, I believe some clinicians will prescribe hormonal therapy. Should it be estrogen alone, or estrogen + progestin? Both choices have adverse effects. Regardless of choice, small doses for short periods should be prescribed. Patients should be advised of the adverse effects of prolonged therapy.

Older women who are at higher risk of CVD (smokers, obese, hypertensive, and dyslipidemic) should be advised not to use hormonal therapy.

"Early Disturbances In Kidney Function May Contribute To The Development Of Hypertension"
4-7 DIFFERENCES IN KIDNEY FUNCTION AND INCIDENT HYPERTENSION

Early disturbances in kidney function may contribute to the development of hypertension. Renal ischemia in early stages of kidney disease stimulates the renin-angiotensin-aldosterone and sympathetic nervous systems. This promotes sodium retention and increases peripheral resistance.

This community-based observational cohort study (2000 to 2005) in adults age 45 to 84 (mean age 58) entered over 2700 subjects. None had had hypertension, clinically recognized cardiovascular disease, or kidney disease at baseline. Mean BP at baseline = 113/68.

Measured cystatin C (an indicator of glomerular filtration rate) and urinary albumen-creatinine ratio at baseline.

During the mean follow-up of 3 years, 20% of the cohort developed hypertension.

After adjustment for established hypertension risk factors, each 15 nmol/L increase in cystatin C was associated with a statistically significant 15% greater incidence of hypertension.

Unadjusted hypertension per 100 person-years

Cystatin C quartiles (nmol/L)

1.	31 to 54	4.6
2	54 to 60	6.2
3	60 to 67	6.6
4	68 to 131	8.9

The highest sex-specific quartile of urinary albumen-creatinine ratio was associated with a statically insignificant 16% greater risk of hypertension as compared with the lowest quartile.

.   "We found higher cystatin C levels to be associated with a greater incidence of hypertension, independent of known risk factors, in a multiethnic cohort without clinically apparent kidney or cardiovascular disease."

"These findings suggest that early variations in kidney function in persons without recognized kidney disease might play a role in the pathogenesis of essential hypertension."

Conclusion: Differences in kidney function, indicated by cystatin C were associated with incident hypertension among individuals without clinical kidney or cardiovascular disease.

This article does not directly associate with primary care medicine. I abstracted it mainly to note that the domain of "essential" hypertension (ie, unknown cause) may be shrinking. It has long been considered that the kidney plays an important part in pathogenesis.

I also wanted to know more about cystatin C. It may become the preferred marker of kidney function.

Cystatin C is a proteinase inhibitor, a small molecule that is produced by nucleated cells throughout the body.

It is produced at a constant rate. It is found in blood and other body fluids. When the kidneys are functioning normally, concentrations in the blood are stable. Unlike creatinine, levels are not influenced by muscle mass, gender, age, or race.

It is filtered out of the blood by the glomerulus. It is resorbed by the tubules and then broken down. It does not return to the blood.

When the glomerular fliltration rate is reduced, indicating decreased kidney function, blood levels of cystatin C increase.

It is a better marker of kidney function than creatinine.

[Accessed 4/2/08 from Lab Tests Online (www.labtestsonline.org) a publication of the American Association for Clinical Chemistry.]

ABSTRACTS APRIL 2008

"Under-Recognized And Under-Treated"

4-1 OSTEOPOROSIS IN MEN

The clinical problem:

Osteoporosis in men is under-recognized and under-treated. It goes untreated in the majority of men with fractures. One-third of hip fractures world-wide occur in men. Half of the hip fractures in men occur under age 80. More men than women die in the year after a hip fracture. Up to 40% of hip fractures in men occur in residential care facilities. Twenty percent of men who have a hip fracture have a second hip fracture.

Vertebral fractures in men over age 65 are only half as common as in women. The majority are asymptomatic. They are associated with loss of height, reduced quality of life, respiratory dysfunction, increased risk of death, and subsequent fractures.

The majority of fractures occur in men whose bone mineral density (**BMD**) is not in the osteoporotic range. This underscores the importance of factors other than BMD in determining risk of fracture.

Secondary causes of bone loss in men:

Osteoporosis in men often has secondary causes. The most frequent are corticosteroid use, excessive alcohol, and hypogonadism. In one study of elderly male residents of nursing homes with hip fractures, up to 66% had hypogonadism. In men with spinal fractures, hypogonadism was present in 20%.

Other secondary causes account for about 15% of cases. Vitamin D deficiency (25-hydoxyvitamin D below 25 ng per mL) is associated with increased risk of hip fracture in those over age 65. Other associations include low calcium intake, smoking, and family history of minimal trauma fracture.

Natural history of bone loss in men:

Bone loss accelerates after age 70. Rapid loss is more common in men with deficient testosterone levels. In men, trabecular thinning is due to reduced bone formation, in contrast, women lose bone due to resorption. This may account for the lower life-time risk of fracture in men.

Diagnosis:

BMD, measured by dual-energy x-ray absorptiometry, is a robust predictor of fracture in men, as in postmenopausal women.

The relationship between lower BMDs and fracture is continuous.

As in women, the WHO has assigned thresholds based on absorptiometry of the total hip. ("T-scores")

Osteoporosis: BMD 2.5 or more standard deviations below the mean for young adult male.

Osteopenia: BMD more than 1.0 and less than 2.5 SD

Normal: BMD within 1.0 SD

These thresholds are now applied to other anatomical sites.

Recent epidemiological data suggest that, for any given absolute BMD value at the spine or hip, the risk of fracture is similar among men and women of the same age.

Using male-specific cutoffs for hip BMD, a National Health and Nutrition Examination study of men age 50 and over reported that 6% had osteoporosis and 47% had osteopenia.

BMD measurement is recommended in men 70 years of age and over. Measurements at the femoral neck are preferable to spinal measurements.

Laboratory Tests:

When BMD is 2 SD below the age specific mean for males, further testing is strongly indicated to rule out secondary causes.

Routine tests include: serum calcium, creatinine, liver function tests, thyrotropin, and CBC.

Since hypogonadism is difficult to detect on the basis of the history and physical exam, measurement of total testosterone level is recommended in all men with osteoporosis.

Serum levels of 25-hyroxyvitmain D should also be measured. Levels below 30 ng/mL should be treated.

Vertebral Fracture Assessment

A history of minimal trauma fracture after the age of 50 is the strongest risk factor for vertebral fracture. Minimal trauma vertebral fractures are the most common. They are often clinically silent. Spinal radiographs remain the gold standard.

Management:

Decisions regarding treatment should be based on the absolute risk of fracture. BMD is a key factor in decision making. The WHO has developed a list of clinical factors that can be used to predict risk of fracture. The FRAX risk assessment tool is adjusted for country, sex, age, and includes, in addition to BMD, prior history of fracture, family history of fracture, current smoking, use of systemic corticosteroids, excessive alcohol, and rheumatoid arthritis. (Go to FRAX on Google to access a calculator to determine 10-year individual risk of fracture.)

Biomarkers (low testosterone and low levels of 25-hydroxyvitamin D) are also useful in predicting increased risk.

Non-pharmacological therapy

General preventive and lifestyle measures apply to all men. Observational data suggest a lower risk among older men who maintain a physically active lifestyle.

High intensity progressive resistance training and weight-bearing exercise increase BMD. Balance and strengthening exercises reduce the risk of falls among older adults.

Fall prevention strategies should be implemented.

Calcium and vitamin D supplements are often recommended. Although there are conflicting data on

benefits, a recent systematic review of nearly 64 000 participants in randomized trials showed that 1200 mg or more of calcium and 800 IU or more of vitamin D daily reduced osteoporotic fractures by 12% in both men and women age 50 and over. Reduction was greater in subjects who were compliant in taking the supplements.

The goal is to maintain 25-hyroxyvitamin D levels at 30 ng/mL or higher.

The recommended daily calcium intake for men with osteoporosis is 1200 to 1500 mg.

Pharmacological Treatment

Pharmacological therapy is indicated in men with osteoporosis, and in men with vertebral fracture. Most experts also recommend it for men with osteopenia who have a non-vertebral fracture after minimal trauma.

Bisphosphonates are the favored drug therapy. In men with osteoporosis, treatment with 10 mg alendronate (Generic; *Fosamax*; Merck) daily for 2 years increased BMD and significantly reduced radiologic (but not clinical) vertebral fractures.

Teriparatide (*Forteo*; Lilly; parathyroid hormone 1-34) 20 ug administered daily subcutaneously increases BMD in men with osteoporosis, and reduces risk of vertebral fractures. After teriparatide is stopped, initiation of bisphosphonate therapy is recommended. This results in further gains in BMD. Teriparatide is suitable for men who cannot tolerate or do not have an adequate response to bisphosphonates.

Testosterone replacement therapy given over 3 years to hypogonadal men over age 65 increased BMD of the spine. The effect in eugonadal men is controversial. Adverse effects—polycythemia, sleep apnea, benign prostate enlargement, and possibly prostate cancer—limit use in eugonadal men.

Guidelines

The International Society for Clinical Densitometry recommends BMD screening in men 70 years of age or older, and recommends earlier screening if there is a fragility fracture or other known risk factors conferring predisposition to osteoporosis.

Recent National Osteoporosis Foundation guidelines recommend pharmacological therapy in men age 50 and older with hip or vertebral fractures; in men with a T score below -2.5, and in men with T score between -1.0 and -2.5 with either a 10-year hip fracture probability of 3% or more determined on FRAX, or a probability of a minimal trauma fracture of 20% or more.

Bisphosphonates are recommended as first-line therapy for men age 65 and older whose BMD is in the osteoporotic range.

NEJM April 3, 2008; 358: 1474-82 "Clinical Practice" review article by Peter R Ebeling, Royal Melbourne Hospital, Melbourne, Victoria, Australia.

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4-2 ADHERENCE TO DASH-STYLE DIET AND RISK OF CORONARY HEART DISEASE AND STROKE IN WOMEN

The Dietary Approaches to Stop Hypertension (DASH) diet is:

High in fruits and vegetables

Moderated in low-fat dairy products

Low in animal protein (red and processed meats)

High in plant protein with substantial amounts whole grains and legumes and nuts.

The diet reduces BP among normotensive as well as hypertensive persons. It also reduces low-density cholesterol .

The DASH-low sodium diet adds restriction of salt, and results in even greater reductions in BP.

The diet is now widely promoted by the National Heart, Lung, and Blood Institute for prevention and treatment of hypertension. It is included as an example of a healthy eating pattern in the 2005 Dietary Guidelines for Americans.

Since the diet lowers BP and LDL-cholesterol, it may lower risk of coronary heart disease (**CHD**) and stroke long term.

This study assessed the associating between adherence to a DASH-style diet (including lower intake of sodium and sweetened beverages) and long-term risk of CHD and stroke in women

Conclusion: Adherence to the diet is associated with lower risks.

STUDY

1. The prospective Nurse's Health Study began in 1976 when over 121 000 female nurses responded to a questionnaire regarding health-related information. The questionnaires were updated every 2 years.

2. This analysis included women (age 34-59) who completed a 1980 food frequency questionnaire. At baseline, none of the women had a history of CHD, stroke, or diabetes. The study cohort included over 88 500 women followed from 1980 to 2004.

3. Developed a score that reflects adherence to the DASH-style diet (including low sodium).The DASH score focused on 8 components. Nine possible frequency-of-consumption responses ranged for "never or less than once per month" to "more than 6 times a day" The food frequency questionnaire was designed to assess average food intake over the past year.

4. Ranked individuals by their consumption of foods emphasized in the DASH-style diet.

5. Determined incidence of CHD and stroke during a 24-year follow-up

6. Main outcome = incident cases of myocardial infarction (**MI**), CHD death, and stroke that occurred after 1980 (24 year follow-up) as related to the DASH score.

RESULTS

1. Documented 3105 cases of CHD (2129 non-fatal and 976 fatal). And 2317 cases of stroke (1242 ischemic,

440 hemorrhagic).

2. Women with better DASH scores tended to use multivitamins, exercise more, and consume more fiber and omega-3 fatty acids, and less saturated fats, trans fats, and total energy. They were less likely to be current smokers, and more likely to report a history of hypertension.

3. Subjects in the top quintile of adherence to the diet were less likely to report CHD and stroke compared with those in the bottom quintile. (For CHD, multivariate adjusted relative risk = 0.76 For total stroke, multivariate adjusted RR = 0.82.) Risks of CHD and stroke declined linearly as adherence to the diet rose.

4. Crude absolute incidence rate of CHD: lowest quintile vs highest quintile per 100 000 person-years

Highest adherence   551

Lowest adherence   689

Difference   138 per 100 000 per year.

(Ie, each year for 24 years, incidence of CHD about 1.3 women per 1000 were spared an episode of CHD.)

DISCUSSION

1. Women who were more adherent to the DASH-diet had lower risks of CHD and stroke.

2. Several components of the diet have been linked to lower BP, especially plant foods and fruits. High red-meat and refined grain intake is related to increased BP.

3. The diet may also influence blood lipid levels, lowering LDL-c, but also lowering HDL-c.

4. Inflammation is established as a pathway for development of atherosclerosis and cardiovascular disease. The diet was associated with a lowering of C-reactive protein and interleukin-6.

5. High intakes of red and processed meats have been positively associated with stroke.

CONCLUSION

Adherence to the DASH diet was associated with a lower risk of CHD and stroke among middle-aged women during 24 years of follow-up.

Archives Intern Med April 14, 2008. 168: 713-20 original investigation, first author Teresa T Fung, Simmons College, Boston Mass.

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If You Can't Lose Weight, At Least Get Physically Fit

4-3 THE JOINT EFFECTS OF PHYSICAL ACTIVITY AND BODY MASS INDEX ON CORONARY HEART DISEASE RISK IN WOMEN

Both physical activity and obesity are modifiable risk factors that play significant roles in development of coronary heart disease (**CHD).** They are major public health issues.

The majority of Americans do not meet goals for adequate physical activity.

This study investigated the combined association of physical activity and body mass index (**BMI)** on CHD.

Conclusion: The risk of CHD associated with elevated BMI was considerably reduced by increased physical activity even if there was no weight loss. The risk was not completely eliminated.

STUDY

1. The Women's Health Study (WHS) is a randomized, double-blind clinical trial of low-dose aspirin and vitamin E in primary prevention of cardiovascular disease and cancer.

2. The present study, based on data from the WHS, included over 38 500 women (mean age = 54) at baseline. None had a history of CHD or stroke.

3. Divided BMI into: normal weight (BMI less than 25); overweight (25-29); and obese (30 and over).

4. Estimated the average hours per week spent during the past year walking, jogging, running, engaging in aerobic exercise, the number of flights of stairs climbed daily, and other physical activities. Based on the energy cost of each recreational activity, a metabolic equivalent task (**MET**) score was assigned. (One MET is about 1 kcal/kg of bodyweight per hour.) The energy expenditure in kilocalories per week was estimated by multiplying the MET score by bodyweight and hours per week.

5. Physical activity was categorized as active (over 1000 kcal/week) and inactive (< 1000 kcal/ week). [1000 kcal/week approximates the recommendation for 30 min of moderate physical activity 5 days per week.]

6. Divided subjects into 6 categories: 1) normal weight-active; 2) normal weight-inactive; 3) overweight-active; 4) overweight-inactive; 5) obese-active; 6) obese-inactive.

7. Examined the independent association of both BMI and physical activity adjusted for multiple possible confounders.

RESULTS

1. 948 developed CHD during a mean 11 years of follow-up.

2. At baseline, 34% were considered physically active; 66% inactive;   51% were considered to be of normal weight; 31% overweight; 18% obese.

 3. BMI over 25 was associated with hypertension, elevated cholesterol, and diabetes.

4. BMI was inversely associated with hormone therapy, physical activity, and alcohol use. Inactive women were more likely to be current smokers.

5. Hypertension, high cholesterol, and diabetes moderately attenuated the association between elevated BMI and physical inactivity. These three factors explain a modest portion of the mechanism by which overweight, obesity, and physical-inactivity may contribute to CHD.

6. Hazard ratios of CHD:

	Normal weight	Overweight	Obese
Active	1.00 (referent)	1.54	1.87
Inactive	1.06	1.88	2.53

7. Comparative risk of CHD in absolute terms over 11 years. (*My calculations from table 3 page 889. RTJ)*

	Cases of CHD	%
Normal weight no walking	92/3477	2.7
Normal weight 4 hours/wk or more walking	54/3345	1.6
Obese no walking	101/2142	4.7
Obese 4 or more hours/wk walking	24/678	3.5

DISCUSSION

1. In this population of middle-aged and older women, both elevated BMI and reduced physical activity, individually and combined, were associated with an increased risk of CHD.

2. Physical activity attenuated the risk of CHD from elevated BMI (>25). However, even high levels of physical activity did not eliminate all of the excess risk of CHD related to overweight and obesity.

3. Adipocytes release free fatty acids, interleukins, and cytokines that accelerate atherosclerosis by increasing endothelial dysfunction. coagulability, and inflammation. Physical activity may reduce the risk of thromboembolism by improving endothelial function, reducing vascular resistance, reducing platelet aggregation, and increasing tissue plasminogen activator levels.

CONCLUSION

Both physical activity and BMI played a role in development of CHD.

The risk associated with a high BMI was reduced considerably by physical activity.

The risk was not completely eliminated. This reinforces the importance of being lean as well as physically active.

Archives Intern Med April 28, 2008; 168: 884-90 Original investigation, first author Amy R Weinstein, Beth Israel Deaconess Medical Center, Boston, Mass.

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Should Isolated Aggressive Lowering Of Systolic BP And LDL-C Be Applicable To Primary Care?

4-4 EFFECT OF LOWER TARGETS FOR BLOOD PRESSURE AND LDL CHOLESTEROL ON ATHEROSCLEROSIS IN DIABETES

A number of secondary prevention studies in high-risk patients have suggested that intensive lowering of low density cholesterol (**LDL-c**) may be associated with improved outcomes in individuals with diabetes.

Antihypertension treatment to levels below the recommended goal of systolic BP (SBP) under 130 may delay progression of microalbuminuria to clinical proteinuria in persons with DM-2.

This study compared progression of subclinical atherosclerosis in adults with type-2 diabetes (**DM-2**) treated to targets of LDL-cholesterol of 70 mg/dL or lower, and systolic BP of 115 or lower vs standard targets of LDL-c of 100 mg/dL or lower and SBP of 130 or lower.

The effect was assessed by carotid and cardiac ultrasound.

Conclusion: Reducing LDL-c and SBP to lower targets resulted in regression of carotid intima-media thickness, and a greater decrease in left ventricular mass.

STUDY

1. Randomized, open-label, trial (2003-2007) followed 499 American Indians (mean age 56; 66% women; 22% smokers) for 3 years. All had DM-2. None had prior cardiovascular events. All had LDL-c 100 mg/dL or greater, and SBP 130 and over.

2. Randomized to:

1) Aggressive therapy

Goal of reducing LDL-c to 70 and under; SBP to 115 and under.

2) Standard treatment.

Goal of reducing LDL-c to 100 mg/dL or lower, and SBP to 130 mm HG and lower.

(Note that, at baseline, LDL-c and SBP were already near goals for standard treatment.)

3. Step 1 drug for lipid control = statin. Step 1 drugs for BP control were ACE inhibitors or angiotensin II blockers. Step two hydrochlorothiazide. Step 3 to 5 added calcium blockers, alpha-blocker, and other vasodilators.

4. Primary endpoint = progression of atherosclerosis measured by common carotid ultrasound intima-medial thickness (IMT). Secondary outcomes = other carotid and cardiac ultrasound measures and clinical events.

RESULTS

1. Baseline characteristics and outcomes at 36 months:

| | Baseline | 36 months | |
		Aggressive	Standard
Weight (kg)	90	91 *	91
BMI	34	34 *	34
Waist circumference	110 cm	111 *	110
HDL-c	46 mg/dL	48	48
LDL-c	104 mg/dL	72	104
HbA1c	8.0	8.3	8.2
SBP	130	117	129
Smokers	22%	-	-

(* Note, there was no attempt to control weight or abdominal obesity. No mention of attempts to discontinue smoking. HbA1c was unchanged.)

.	Mean carotid IMT	-0.012 mm	+0.032 mm
	Left ventricular mass (g)	-14	-7

2. Compared with baseline, IMT regressed in the aggressive group (-0.012 mm) and progressed in the standard group (+0.038mm).

3. No of drugs (mean) used

Lipid	1.5	1.2
BP	2.3	1.6

4. Adverse events: Aggressive 39%   Standard 27%

   Serious event   N = 4   N = 2

                     (hypotension; hypokalemia)   (hypotension)

5. Few cardiovascular events occurred during the observation period, with no difference between groups.

6. Plaque scores at 36 months increased slightly in both groups with no difference between groups. The percentage of individuals with one plaque or more increased in both groups with no significant difference between groups.

DISCUSSION

1. The aggressively treated group had improvements in IMT (regression). The standard group had a worsening in IMT (progression).

2. Intensive control of both lipids and BP may be necessary to reverse the atherosclerotic process. (Intimal plaque actually increased.)

3. LV mass declined in both groups, more so in the aggressive group. LV mass predicts, independently of other covariates, lower rates of CVD events, heart failure, sudden death, and atrial fibrillation.

4. Adverse events were related to lowering SBP (not to lowering LDL-c), and were more common in the aggressive group.

5. The study used surrogate endpoints. No difference in clinical endpoints was observed during the 3-year observation period. The reliability of surrogate outcomes remains to be established.

CONCLUSION

Reducing LDL-c and SBP to lower targets resulted in regression of carotid IMT and a greater decrease in LV mass in individuals with DM-2.

Clinical events were uncommon, and did not differ between groups.

Whether these improvements in IMT and LV mass will result in less risk of CVD events was not determined.

4-5   TELMISARTAN, RAMIPRIL, OR BOTH IN PATIENTS AT HIGH RISK FOR VASCULAR EVENTS

In patients who have vascular disease, or high-risk diabetes without heart failure, angiotensin-converting-enzyme inhibitors (**ACE-i**) reduce mortality and morbidity from cardiovascular causes.

The role of angiotensin II-receptor blockers (**ATR-b**) in these patients is not known.

This study compared the ACE-i ramipril (*Altace*; King) the ATR-b telmisartan (*Micardis*; Boehringer Ingleheim) and the combination of the two drugs in patients with established vascular disease or high-risk diabetes.

Conclusion: Telmisartan and ramipril were equivalent. The combination was associated with more adverse effects without any increase in benefits.

STUDY

1. An active run-in phase selected patients for randomization only if they tolerated both medications.

2. Multi-country, multi-center, randomized trial followed:

1) Over 8500 patients given ramipril 10 mg daily

2) Over 8500 patients given telmisartan 80 mg daily

3) Over 8500 patients given both combined.

(These are maximum daily doses recommended by the PDR.)

3. All had a history of coronary, peripheral vascular, or cerebrovascular disease; or diabetes with

end-organ damage. (Mean age = 66; 85% had cardiovascular disease; 69% hypertension: and 38% diabetes.)

4. Many subjects also received antiplatelet therapy, statins, beta-blockers, and diuretics.

5. Follow-up = a median of 56 months.

6. Primary composite endpoint = death from cardiovascular causes, myocardial infarction, stroke, or

hospitalization for heart failure.

RESULTS

1. Outcomes:	Ramipril	Telmisartan	Two combined
Primary outcome	17%	17%	16%

2. Telmisartan was not inferior to ramipril. Combined drugs were not superior to either alone.

3. Adverse effects:	Ramipril	Telmisartan	Two combined
Permanent discontinuation	25 %	23 %	29 %

4. Combination therapy increased the risk of hypotension, syncope, renal dysfunction, and hyperkalemia.

5. As a reason for discontinuation, cough (4%) and angioedema (0.3%) were more common in the

ACE-i groups.

5. Renal impairment was more common in the combined-drug group.

DISCUSSION

1. ACE-i have been convincingly shown to reduce rates of death, myocardial infarction, stroke, heart failure, and revascularization among patients with previous cardiovascular disease and high-risk diabetes. ACE-i reduce degradation of bradykinin. This enhances vasodilation, but increases the risk of angioedema and cough.

2. "Telmisartan was clearly not inferior to ramipril for the prespecified primary outcomes."

3. The number of patients who discontinued therapy was slightly smaller in the telmisartan group than in the ramipril group.

5. The lowering of BP was 2 to 3 mm Hg greater in the combination group compared with the ramipril group. However, despite what might be expected, there was no significant benefit from this reduction.

6. Dual blockade did not produce any additional clinical benefits in this population.

7. In patients with heart failure, angiotensin II levels may increase, and symptoms worsen despite the use of ACE-i. The use of ATR-b, alone, as compared with placebo, reduces the rate of death or hospitalization for heart failure patients with a low ejection fraction.

CONCLUSION

In patients who had vascular disease or high-risk diabetes, telmisartan was equally as effective as ramipril.

There was no additional advantage (and there is some harm) from the combination of telmisartan + ramipril used in full doses in this population as compared with ramipril alone.

NEJM April 10, 2008; 358: 1547-59 Original investigation by the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) investigators, writing committee at McMaster University, Hamilton ON, Canada.

1 Note that these patients had undergone a run-in phase in which they tolerated the ACE-i. Presumably, many were disqualified at that time because of cough. Cough must be more common in patients receiving ACE-i than 4%.

The study was supported by Boehringer Ingleheim. I can detect some spin in favor of telmisartan. RTJ

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A Significant Source Of Discomfort And Distress Well Into The Postmenopausal Years

4-6 PERSISTENT HOT FLUSHES IN OLDER WOMEN

Hot flushes (**HFs**) affect up to 80% of women during the first year of cessation of menses. They negatively affect quality of life, disturb sleep, and interfere with work and leisure activities. They exacerbate anxiety and depression.

In most women, HFs resolve within a few years. But, some women report HFs for many years after they cease to menstruate. Very little attention has been given to the substantial minority of women who continue to have HFs 5 or more years after menopause. It is not clear why hot flashes continue.

These women appear to be at the greatest risk of suffering adverse effects from using estrogens to treat their symptoms.

This study assessed prevalence and natural history of HFs in older post-menopausal women.

STUDY

1. A natural history study analyzed data from over 3000 women who enrolled in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. Ninety five % of these women were 5 or more years post menopause.

2. At baseline, mean age = 65 (all less than 80); a mean of 17 years since menopause. Eleven % had previous oophorectomy.

3. Assessed prevalence, severity, and 3-year change in severity of hot flashes.

4. Severity was assessed by questionnaire at baseline and after 3years:

    "During the past 6 months did any hot flashes bother you or interfere with your life"?

    Response options included: "all of the time" "most of the time" some of the time" little of the time"

         and "none of the time". "Some", "most", and "all" were considered clinically significant.

5. Also assessed symptoms of vaginal dryness and trouble sleeping.

6. Measured serum total estradiol and follicle-stimulating hormone (FSH).

7. Determined clinical and demographic characteristics associated with clinically significant HFs.

RESULTS

1. At baseline, 12% of the women (mean age 65) reported clinically significant HFs.

2. Prevalence of HFs was inversely related to time since menopause:

    2- 5 years   45%

    20 or more years   8%

3. Women were more likely to have HFs if they were less educated, were more recently menopausal, had undergone hysterectomy, or had previously used systemic estrogen.

4. HFs were also associated with higher body mass index, and higher FSH levels, and lower HDL-cholesterol levels.

5. Women with HFs were more likely to report vaginal dryness and trouble sleeping.

6. There were no associations between HFs and smoking, alcohol use, depression, aerobic activity, serum estradiol levels, LDL-cholesterol levels, and thyroid-stimulating hormone levels.

7. After 3 years, of women with clinically significant hot flashes at baseline, 50% reported the hot flashes were worse or unchanged. (Mean age 68.)

8. HFs were more likely to resolve as women moved farther away from menopause.

DISCUSSION

1. For a substantial minority of women, HFs are a significant source of discomfort and distress well into the postmenopausal years.

2. Among women 4 to 9 years post-menopause, more than 20% reported clinically significant HFs. Among those 10 or more years post-menopause, nearly 10% reported clinically significant HFs.

3. Of those who complained of HFs at baseline (age 65), persistent HFs continued for 3 years in 50%.

4. Serum FSH levels, rather than estradiol levels were associated with greater severity of HFs. Non-estrogen feedback systems may be important in modulating severity of HFs. (FSH levels normally stabilizes or declines as time from menopause lengthens.)

5. The characteristic most strongly associated with HFs was trouble sleeping, even though this symptom did not tend to improve with increasing time since menopause. Trouble sleeping may be a co-morbid symptom of menopause that shares common underlying triggers with HFs.

CONCLUSION

A substantial minority of women who are 5 or more years post-menopausal have clinically significant HFs. More than half of older post-menopausal women who present with HFs can be expected to have persistent HFs for 3 years or more.

Archives Intern Med April 28, 2008; 168: 840-46 Original investigation, first author Alison J Huang, University of California, San Francisco.
1 The trial evaluated the effects of 3-years of treatment with the selective estrogen-receptor-mediator raloxifene on osteoporosis in women who were at least 2 years past menopause.

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Early Disturbances In Kidney Function May Contribute To The Development Of Hypertension.

4-7   DIFFERENCES IN KIDNEY FUNCTION AND INCIDENT HYPERTENSION

Does early kidney dysfunction predate hypertension?

Early disturbances in kidney function may contribute to the development of hypertension. Renal ischemia in early stages of kidney disease stimulates the renin-angiotensin-aldosterone and sympathetic nervous systems. This promotes sodium retention and increases peripheral resistance.

The evaluation of early differences in kidney function have been hampered by the imprecision of traditional serologic methods and estimating equations.

Cystatin C is an alternative marker of kidney function. It correlates with formal measurements of glomerular function and is more precise than serum creatinine levels in detecting early kidney dysfunction.

Urinary albumen excretion is a complementary marker for renal function, and partially reflects hemodynamic disturbances within the glomerulus.

This study evaluated serum cystatin C levels and urinary albumen-creatinine ratios as predictors of incident hypertension in subjects without clinically recognized kidney or cardiovascular disease.

Conclusion: Differences in kidney function, indicated by cystatin C levels were associated with incident hypertension among individuals without known clinical kidney or cardiovascular disease.

STUDY

1. A community-based observational cohort study in adults age 45 to 84 (mean age 58) entered
   over 2700 subjects. At baseline, none had hypertension, cardiovascular disease, or recognized kidney disease.
2. Mean BP at baseline = 113/68.
3. Measured cystatin C and urinary albumen-creatinine ratio at baseline.
4. Also explored a second outcome: a clinically meaningful increase in BP of 10/5 mm Hg or more.
5. Primary outcome = incident hypertension. Median follow-up = 3 years.

RESULTS

1. During the mean follow-up of 3 years, 20% of the cohort developed hypertension.
2. After adjustment for established hypertension risk factors, each 15 nmol/L increase in cystatin C was
   associated with a statistically significant 15% greater incidence of hypertension.

Cystatin C quartiles (nmol/L)	Unadjusted hypertension per 100 person-years
1. 31 to 54	4.6
2 54 to 60	6.2
3 60 to 67	6.6
4 68 to 131	8.9

3. Secondary study outcome: A clinically meaningful increase in BP of 10/5 occurred in 48% of participants.
   Associations of cystatin C with this outcome were weaker. After adjustment, each 15 nmol/L increase in
   cystatin C was associated with a 6% greater incidence of a clinically meaningful increase in BP.
3. Higher cystatin C levels were associated with older age and traditional cardiovascular risk factors.
4. The highest sex-specific quartile of urinary albumen-creatinine ratio was associated with a statically
   insignificant 16% greater risk of hypertension as compared with the lowest quartile.

DISCUSSION

1. "We found higher cystatin C levels to be associated with a greater incidence of hypertension, independent of
   known risk factors, in a multiethnic cohort without clinically apparent kidney or cardiovascular disease."
2. Associations between urinary albumen-creatinine ratio and hypertension were attenuated by adjustments for
   baseline BP and other covariates. There was no evidence for a synergistic interaction between cystatin C and
   urinary albumen-creatine ratio.
3. "These findings suggest that early variations in kidney function in persons without recognized kidney disease
   might play a role in the pathogenesis of essential hypertension."
4. Hypertension is present in most individuals with chronic kidney disease. Hypertensive nephropathy
   accounts for about 25% of the population with end-stage renal disease. Chronic elevation of BP promotes
   damage to the intrarenal vasculature, leading to intimal and medial thickening, renal ischemia, and
   glomerulosclerosis.

5. Although hypertension clearly contributes to the progression of established kidney disease, available evidence also suggests that early kidney damage contributes to the development of hypertension. This creates a viscious circle of kidney injury and BP degradation.

6. Taken together, existing data suggest a unifying hypothesis in which early reductions in glomerular filtration rate, whether congenital or acquired because of sympathetic excess, renal arteriosclerosis, or tubulo-intersititial disease, lead to and adverse physiological state in which higher BP is needed to maintain sodium balance.

CONCLUSION

Differences in kidney function, indicated by cystatin C were associated with incident hypertension among individuals without clinical kidney or cardiovascular disease.

This finding complements experimental work implicating early kidney damage in the pathogenesis of essential hypertension.

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