PRACTICAL POINTERS FOR PRIMARY CARE

INDEX

JANUARY – JUNE 2008

PRACTICAL CLINICAL POINTS

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

LINKS TO THE FULL ABSTRACTS

JAMA, NEJM LANCET, BMJ
ARCHIVES INTERNAL MEDICINE,
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This index is a reference document based on articles abstracted from 6 flagship journals January-June 2008. It provides a means of recalling to memory, in an evening or two, what the editor considered new and important for primary care.

The numbers in the brackets refer to the abstract. For example, [3-6] refers to the sixth article abstracted in March. .

It consists of 4 parts:

1) "Practical Clinical Points": This provides an instant reminder of points of clinical interest and importance which primary care clinicians should advise patients about, consider, and be aware of.
2) "Medical Subject Headings" (MeSH): A list of medical subject headings from aliskiren to vitamin D, arranged alphabetically.
3) "Highlights of Abstracts and *Editorial Comments*" section: linked alphabetically to each MeSH. (There may be several articles listed under a MeSH.) The highlights contain a condensation of each abstract. The *Editorial Comments* are those of the editor alone, based on his years-long experience as a practicing primary care internist and as editor and publisher of *Practical Pointers for Primary Care.*
4) The abstract itself provides more detailed information, and the citation.

Monthly issues for the past 10 years may be found on the website (www.practicalpointers.org).

I hope you find *Practical Pointers for Primary Care* useful and interesting.

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

PRACTICAL CLINICAL POINTS JANUARY – JUNE 2008

ADVISE

Use of the new protocol for emergency cardiac resuscitation—maximizing cardiac compressions, and minimizing positive pressure ventilation. [3-4]

Rate control, rather than rhythm control, as the primary approach for patients with atrial fibrillation and heart failure [6-4]

Overweight patients to become more physically fit. Physical activity will reduce risk of CHD even if the patient does not lose weight. [4-3]

Statin therapy for all patients with diabetes. [1-1]

Multifactorial interventions with drug combinations in patients with type 2 diabetes. They reduce mortality. Interventions include reduction in HbA1c, BP. triglycerides, LDL-cholesterol, and total cholesterol, [2-1]

Careful adjustment of dose, formulation, and delivery of drugs in the frail elderly. [3-8]

Before increasing the dose or adding another drug, ask first if the patient is properly adhering to his present prescription. Medication non-adherence is often the reason for failure of anti-hypertension treatment. [2-2]

Even after age 80, it is not too late to start antihypertension therapy, [5-5]

All patients that they need a "Medical Home" (Ie, primary care). [3-2]

Elderly men, as well as women, to be checked, and treated for, osteoporosis. [4-1]

Empirical antimicrobial therapy for community-acquired pneumonia. [2-3]

Once daily insulin glargine, rather than thrice daily prandial insulin lispro, in select patients with diabetes, is a simple and effective option for achieving overall glycemic control. [3-6]

Empirical treatment of dyspepsia with a proton pump inhibitor is an appropriate first choice for treatment of dyspepsia. Testing for, and treatment of H pylori is no more effective. [3-11]

All patients that vitamin D deficiency is widespread. At least a billion people worldwide are vitamin D deficient. [6-5]

CONSIDER

Ausculting for carotid bruit as a prognostic indicator for cardiovascular death and myocardial infarction. [5-6]

To predict cardiovascular risk over the years, a model based on information easily obtained in one outpatient visit may be no worse, and substantially cheaper and simpler to implement, than the Framingham Risk Prediction Score [3-10]

Whether to prescribe antibiotics to nursing-home patients with advanced dementia. [3-5]

Type 2 diabetes to be a disease primarily of fat metabolism (lipotoxicity). Correction of the abnormalities of fat metabolism leads to correction of the glycemic abnormalities. [3-1]

For patients with type 2 diabetes, very tight glucose control (HbA1c under 6%) may not be safe. It increased risk of death compared with a less intensive strategy (HbA1c 7.0% to 7.9%) [3-7]

Oral prednisone rather than an NSAID for treatment of symptoms of acute gout. [5-4]

For patients over age 50, "Systolic pressure is all that matters." If systolic is controlled, there would hardly ever be a circumstance when diastolic is not controlled. Emphasizing one determination (systolic) will clarify the goal of therapy and remove patients' confusion about "systolic" and diastolic". [6-3]

Reviewing the proper determination of BP in your office. Determination often leaves much to be desired. [6-6]

The non-specific effects of the placebo. Proper use of placebos can produce clinically significant outcomes. [5-1]

Common clinical signs and symptoms cannot identify patients with sinusitis for whom antibiotic treatment is clearly justified. [3-3]

Vitamin D supplementation is related to a decreased risk of falls in elderly women. [1-7]

BE AWARE

Rivaroxaban, a direct inhibitor of activated factor X (Xa) is in stage 3 trials. It is just as effective as enoxaparin as an anticoagulant, and is not related to an increased risk of bleeding. It is given once daily as a standard oral dose, and requires no monitoring. [6-1]

Increased body mass index is associated with increased risk of cancer [2-7]

In patients at high risk for cardiovascular end points, both an angiotensin II receptor blocker and an ACE-inhibitor used alone are equally effective. The combination was not better than either drug alone, and was more toxic. [4-5]

Age is the most important prognostic factor used by the Framingham Risk Prediction Score. However, although age is not modifiable, it is not a constant risk factor. Elderly patients at the same age vary considerably in their risk. [5-2]

A trial of high doses of folic acid and B vitamins did not reduce incidence of cardiovascular disease. The homocysteine-folic acid connection is no longer considered valid. [5-7]

The coronary artery calcium score (determined by CT scan) is reported to predict increased risk of cardiovascular events in patients already considered at high risk. But ask, is it clinically, socially, economically, and ethically acceptable? Does it lead to improved outcomes? [3-12]

Adherence to the DASH diet is associated with lower risk of CHD and stroke in middle-aged women. [4-2]

The ACP has developed a guideline for drug treatment of dementia. Drugs show statistically significant improvement, but not clinically significant improvement. [3-9]

Aggressive control of low density cholesterol (< 70 mg/dL) and systolic BP (< 115) may be related to regression of atherosclerosis of the carotid artery and decrease in left ventricular mass. [4-4]

Aliskiren (a direct inhibitor of renin), combined with an angiotensin II blocker may protect against nephropathy in patients with type 2 diabetes. [6-8]

The new guidelines for prophylaxis for infective endocarditis greatly limit use of prophylactic antibiotics. [1-9]

Fructose and sucrose containing soft drinks increase risk of gout among men. [2-4]

A substantial number of elderly women continue to have hot flushes. Treatment depends on severity and personal informed choice. [4-6]

ACE-inhibitors and angiotensin II blockers have similar benefits in treatment of hypertension. ACE-i have higher rates of cough and lower rates of adherence [1-5]

Early disturbances of kidney function may contribute to the development of hypertension [4-7]

Surgery for spinal stenosis showed significantly more improvement in pain, function and patient satisfaction than non-surgical therapy. [2-6]

Testosterone supplementation given for 6 months to older men with normal levels produce no benefits in functional mobility cognition, and other parameters. [1-8]

Thyroxine monotherapy is adequate to bring T3 levels back to normal in patients after thyroidectomy. [2-10]

MEDICAL SUBJECT HEADINGS (Mesh) JANUARY-JUNE 2008

ALISKIRIN
ANTIBIOTICS
ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS
ANTICOAGULANTS
ATHEROSCLEROSIS
ATRIAL FIBRILLATION

BLOOD PRESSURE MEASUREMENT
BODY MASS INDEX
BREAST CANCER

.

CANCER
CARDIAC ARREST
CARDIOVASCULAR DISEASE
CAROTID BRUITS
CHOLESTEROL
CLOPIDOGREL
COMMUNITY ACQUIRED PNEUMONIA
CORONARY CALCIUM
CORONARY HEART DISEASE
DEMENTIA
DIABETES
DYSPEPSIA

ENDOCARDITIS
ESTROGEN
ETIQUETTE-BASED MEDICINE

FOLIC ACID
FRUCTOSE

GERIATRICS
GLUCOSAMINE
GOUT

HELICOBACTER PYLORI
HIP ARTHROPLASTY
HOT FLUSHES
HYPERTENSION

IRRITABLE BOWEL SYNDROME

KIDNEY FUNCTION

MEDICAL HOME
MEDITERRANEAN DIET
MYOCARDIAL INFARCTION

NEPHROPATHY

OBESITY
OSTEOARTHRITIS
OSTEOPOROSIS

PATIENT IMPORTANT OUTCOMES
PHYSICAL FITNESS
PLACEBO
PNEUMONIA
PRESCRIBING FOR OLDER PEOPLE.
PROGESTERONE
PRIMARY CARE
PROTON PUMP INHIBITOR

RAMIPRIL
RENAL DISEASE

SINUSITIS
SOFT DRINKS
SPINAL STENOSIS
STATIN DRUGS
STROKE

TELMISARTAN
TESTOSTERONE
THYROID DISEASE

VITAMIN D

HIGHLIGHTS AND *EDITORIAL COMMENTS* JANUARY-JUNE 2008

ALISKIRIN

ALISKIRIN: A Direct Inhibitor of Renin (See DIABETES)

6-8 ALISKIREN COMBINED WITH LOSARTAN IN TYPE-2 DIABETES AND NEPHROPATHY

ANTIBIOTICS (See SINUSITIS)

3-3 ANTIBIOTICS FOR ADULTS WITH CLINICALLY DIAGNOSED ACUTE RHINO-SINUSITIS

ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS (See HYPERTENSION; See RENAL DISEASE))

1-5 COMPARATIVE EFFECTIVENESS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS FOR TREATING ESSENTIAL HYPERTENSION

1-6 EFFECT OF MONOTHERAPY AND COMBINATION THERAPY WITH INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM ON PROTEINURIA IN RENAL DISEASE

ANTICOAGULANTS

6-1 ANTICOAGULANT THERAPY

Rivaroxaban Was Significantly More Effective, Just As Safe, And Much More Convenient

The current options for extended thromboprophylaxis are limited. Low molecular weight heparins reduce events, but must be administered subcutaneously. They are cost-effective only if injections are used at home. Vitamin K antagonists (Warfarin) are difficult to manage. They have unpredictable pharmacological effects, numerous food and drug interactions, and require frequent monitoring.

Rivaroxaban (*Xarelto*; Bayer) is a direct inhibitor of activated factor X (Xa). This article describes a phase 3 trial with a suggested dose of 10 mg daily.

The trial randomized over 3100 persons who underwent hip arthroplasty to: 1) 10 mg oral rivaroxaban or 2) 40 mg enoxaparin (*Lovenox*; Sanofi-Aventis) injections daily for a mean of 35 days.

Primary efficacy outcome = composite of deep vein thrombosis (either symptomatic or detected by venography if the patient was asymptomatic), non-fatal pulmonary embolism, or death from any cause at 36 days.

Primary outcomes	Pro-protocol population	Modified intention-to treat
Rivaroxaban	0.8%	1.1%
Enoxaparin	3.4%	3.7%

Major venous thromboembolism occurred in 0.2% of the rivaroxaban group and 2.0% of

the enoxaparin group.

Compared with enoxaparin, rivaroxaban was not associated with any significant increases in major bleeding or any other bleeding events

Conclusion: Once-daily 10 mg rivaroxaban was significantly more effective for extended thromboprophylaxis than once-daily 40 mg enoxaparin. The two drugs had similar safety profiles.

If this or similar drugs continue with the same effectiveness and safety for 2 or 3 years after approval and release to the general populations, I believe they will replace our current anticoagulant therapies.

They will be "blockbusting" drugs.

ATHEROSCLEROSIS (See DIABETES)

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

ATRIAL FIBRILLATION

6-4 RHYTHM CONTROL VERSUS RATE CONTROL FOR ATRIAL FIBRILLATION AND HEART FAILURE

In patients with atrial fibrillation **(AF**), an excessive ventricular rate, a loss of atrial contraction and an irregular ventricular filling rate may have negative clinical consequences.

This multicenter, randomized trial of over 1300 patients (mean age = 67) compared the maintenance of sinus rhythm (rhythm–control) with control of ventricular rate (rate-control) in patients with AF who have HF. All had a left ventricular ejection of 35% or less, symptoms of HF, and a history of AF.

For rhythm-control, electric cardioversion was recommended within 6 weeks after randomization in patients who did not revert to sinus rhythm after antiarrhythmic drugs. Additional cardioversions were recommended for subsequent recurrences of AF. Amiodarone was the drug of choice.

For rate-control, adjusted doses of beta-blockers and digoxin were used to achieve the targeted rate, defined as less than 80 beats per minute during rest, and less than 110 beats per minute during a 6-minute walk.

Prevalence of AF at baseline in the rhythm-control group was 54%; at 3 weeks 33%; at 4 months 17%; at 4 years 27%. During follow-up, 58% of patients had at least one recurrence of AF.

During the study, 21% of the rhythm-control group crossed over to rate-control. 10% of the rate-control group crossed over to rhythm-control, most often due to worsening HF.

During the first 3 years of follow-up, the heart rate goal in the rate-control group was achieved in 88% of patients.

Results; The primary outcome, death from cardiovascular causes occurred in 27% of the rhythm-control group vs 25% in the rate-control. Secondary outcomes: overall survival, risk of stroke, and

worsening HF were similar between groups. No significant differences favoring either strategy were noted in any of 10 prespecified subgroups.

The importance of this trial was that it compared strategies in patients with heart failure. This is consistent with trials that did not show any benefit of rhythm-control in patients without HF.

"The routine use of a rhythm-control strategy did not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy."

Conclusion: "Our results suggest that rate-control should be considered a primary approach for patients with atrial fibrillation and heart failure"

This was not a clean-cut trial. There were many cross-overs. Many subjects did not achieve and maintain the therapeutic goal. Many had to undergo repeated cardioversions.

I believe that, if we could achieve 100% conversion and maintenance of sinus rhythm easily and without toxicity, outcomes in rhythm-control would be more beneficial than in rate-control. As the authors state, AF has adverse effects on cardiac output. And is an independent predictor of death. Normal sinus rhythm is much more efficient. I believe we have not heard the last of attempts at cardioversion.

Meanwhile, rate-control is the preferred and easiest approach to patients with AF, with and without HF.

BLOOD PRESSURE MEASUREMENT (See HYPERTENSION)

6-6 MANY PHYSICIAN PRACTICES FALL SHORT ON ACCURATE BLOOD PRESSURE MEASUREMENT

BODY MASS INDEX (See also PHYSICAL FITNESS; CORONARY HEART DISEASE)

2-7 BODY-MASS INDEX AND INCIDENCE OF CANCER

This systematic review and meta-analysis assessed the strengths of associations between BMI and different cancers.

Literature search identified prospective studies of 20 types of cancer. Analyzed 221 datasets (over 282 000 incident cases of cancer).

Quantified risks of different types of cancer associated with a 5 kg/m^2 (~ 15 kg in men and 13 kg in women) increase in BMI over an average BMI of 23 kg/m^2

In men, a 5 kg/m^2 increase in BMI was strongly associated with: esophageal adenocarcinoma, thyroid , renal, and colon cancers. (Relative risks varied from 1.24 to 1.52.)

In women, a 5 kg/m^2 increase in BMI was strongly associated with: endometrial, gall bladder, Esophageal, and renal cancers. (RR varied from 1.34 to 1.59)

Considering that the majority of men and women in the USA are overweight or obese, and that the prevalence of obesity is expected to increase, excess body weight could contribute to a substantially larger burden of cancer.

Conclusion: Increased BMI is associated with increased risk of common and less common malignancies.

I hesitated to abstract this article. I could not think of a practical application.

It is likely an important clinical point, however, that primary care clinicians should know about.

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

BREAST CANCER

Compromised The Diagnostic Accuracy Of Both Mammograms And Biopsy.

2-5 ESTROGEN PLUS PROGESTIN AND BREAST CANCER DETECTION BY MEANS OF MAMMOGRAPHY AND BREAST BIOPSY

This study examined the effects of combined hormone therapy vs placebo on BC detection by mammography and biopsy.

Randomized over 16 000 postmenopausal women (ages 50 to 79; median = 63) to: 1) Combined 0.625 mg/d (**CEE**) + 2.5 mg/d (**MPA**) *Prempro* Wyeth Ayerst), or 2) Placebo

Followed subjects periodically for over 5 years. Required mammograms and breast examinations every year.

Determined incidence of BC, and recommendations for further breast imaging studies and biopsy.

CEE + MPA group vs the placebo group:

A. Invasive BCs 199 vs 150

B. BC was diagnosed at a more advanced stage

C. More mammograms with abnormalities (35% vs 25%).

D. The cumulative percentage with clinically indicated breast biopsies was higher (10% vs 6%).

Conclusion: Use of combined hormone therapy for 5 years resulted in more than 1 in 10 women having otherwise avoidable mammograms, and 1 in 25 having an otherwise avoidable breast biopsy,
Combined hormone therapy compromised the diagnostic accuracy of both mammograms and biopsy.

A study from the WHI in JAMA April 12, 2006; 295 (See Practical Punters April 2006) reported that CEE alone vs placebo, in over 10 500 women who had undergone a hysterectomy, there was no increase in incidence of BC over 7 years. Indeed, CEE-alone was associated with a small decrease in invasive BC and ductal carcinoma.

Progesterone is the risk factor for BC, not estrogen.

Some investigators have proposed the benefit of progesterone in reducing endometrial cancer when dual hormone is prescribed is offset by the increase in breast cancer.

A similar study from the WHI reported in Archives Intern Med February 13, 2006; 166 (See Practical Pointers February 2006) reported that CEE-alone vs placebo in over 10 000 women over 7 years did not increase the incidence of coronary heart disease. Neither did it protect against CHD.

The USPSTF (Annals Internal Medicine May 17, 2005) recommends against routine use of combined hormone therapy for prevention of chronic conditions in postmenopausal women. There may be an increased risk of coronary heart disease, breast cancer, venous thromboembolism, stroke, and dementia. Harms are likely to outweigh benefits.

Also recommends against routine use of estrogen-alone for prevention of chronic conditions. Harms include: increased risk of venous thromboembolism, stroke, dementia. There is insufficient evidence regarding effects on incidence of breast cancer, and ovarian cancer. Harms are likely to outweigh benefits.

Use of hormonal therapy for menopausal symptoms should be limited to the lowest dose for the shortest period.

CANCER

Associated With Increased Risks Of Some Malignancies.

2-7 BODY-MASS INDEX AND INCIDENCE OF CANCER

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Considering that the majority of men and women in the USA are overweight or obese, and that the prevalence of obesity is expected to increase, excess body weight could contribute to a substantially larger burden of cancer.

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CARDIAC ARREST

A New Protocol Maximizes Chest Compression And Minimizes Positive Pressure Ventilation

3-4 MINIMALLY INTERRUPTED CARDIAC RESUSCITATION BY EMERGENCY MEDICAL SERVICES FOR OUT-OF-HOSPITAL CARDIAC ARREST

Minimally interrupted cardiac resuscitation (**MICR**) is a new approach to out-of-hospital cardiac arrest (**CA**). MICR focuses on maximizing myocardial and cerebral perfusion through a series of coordinated interventions. It is intended to minimize interruption of chest compressions, provide immediate pre-shock chest compressions, delay or eliminate endotracheal intubation, minimize positive pressure ventilation, and decrease the time interval to intravenous epinephrine.

This study investigated whether MICR would improve survival from out-of-hospital CA. Emergency medical service (**EMS**) personnel received training in MICR which included:

1) 200 uninterrupted chest compressions over 2 minutes. (100 per minute)
2) Rhythm analysis with a single shock if indicated
3) Immediately followed by 200 post-shock compressions before any pulse check or rhythm reanalysis
4) Early administration of intravenous epinephrine 1 mg as soon as possible
5) Delayed tracheal intubation until after 3 cycles of chest compression
6) High flow oxygen (without positive pressure)

In 2460 patients with CA who received MICR, survival was 9.1% vs 3.8% in those who did not receive MICR

In 528 patients with witnessed VF who received MICR, 28% survived vs 12% of those who did not receive MICR

Conclusion: Survival to hospital discharge with out-of-hospital cardiac arrest increased after implementation of MICR as an alternate EMS protocol.

How fashions in medicine change! The AHA guidelines in 2000 instructed rescuers to give 15 chest compressions followed by 2 ventilations. It also called for 3 "stacked" shocks without performing chest compression in between defibrillation attempts. This resulted in prolonged time without any chest compression.

I doubt, however, that most bystanders will apply compressions with the force required for adequate perfusion.

Certainly more bystanders will be willing to perform CR if mouth-to-mouth breathing is not recommended.

CARDIOVASCULAR DISEASE

A Model Based on Information Easily Obtained in One Outpatient Visit is No Worse Than, and Substantially Cheaper and Simpler To Implement, Than the Framingham Risk Equation.

3-10 LABORATORY-BASED VERSUS NON-LABORATORY-BASED METHOD FOR ASSESSMENT OF CARDIOVASCULAR RISK *The NHANES I Follow-up study cohort*

The National Health and Nutrition Examination Survey (NHANES) is a prospective cohort

study of over 14 000 participants ages 25-74 at the time they were first examined (between 1971 and 1978).

This follow-up study included participants (n = 6186) who did not report a history of cardiovascular disease (myocardial infarction, heart failure, stroke, angina) or cancer at baseline.

Compared how well non-laboratory-based risk factors could predict first-time fatal and non-fatal cardiovascular disease events as compared with laboratory-based risk factors.

A. Laboratory-based risk factors: age, systolic BP, smoking status, reported diabetes, current treatment for hypertension and total cholesterol.

B. Non-laboratory-based risk factors: substituted BMI for cholesterol.

Follow-up for over 21 years.

The study shows that a non-laboratory-based risk method that uses information easily obtained in one outpatient visit can predict cardiovascular disease outcomes as accurately as one that includes determination of total cholesterol.

At most, the rates of correct classification differed by less than 1%, and none of the differences were significant.

This simpler method is probably no worse, yet substantially cheaper and simpler to implement than the Framingham risk equation.

Conclusion: A method that uses non-laboratory-based risk factors (included BMI, but not total cholesterol determination) predicted cardiovascular events as accurately as one that included total cholesterol. This approach could simplify risk assessment.

Only total cholesterol was considered in the laboratory-based cohort. HDL- c, triglycerides, and HbA1c not measured. The investigators comment that the value of additional laboratory tests seems limited. Nevertheless, primary care clinicians will likely request them.

This is not to say that lipids and HbA1c, and BP should be neglected. They should be treated vigorously—but not to the neglect of weight and diet control, maintenance to a slim waist circumference, and maintenance of fitness.

If a 50-year old man has a systolic BP of 120, does not have diabetes, never smoked, has a BMI of 22, and is physically fit, how much would laboratory results add to determination of his risk? If his LDL-cholesterol is 120, should he be treated with statins? How much would treatment reduce his risk?

We can determine at a glance that a middle-aged man who is obviously obese and has an expanded waist circumference is at high risk. How much would lipid determinations add to assessment of risk and his willingness and ability to reduce risk?

The American public seems obsessed with "cholesterol", and, I believe, often neglects to consider other, likely more important risk factors. This is due in part because taking daily pill for cholesterol is much easier than controlling diet, losing weight, stopping smoking, and maintaining fitness.

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.

"We Should Take Advantage Of Time And Intervene Early"

5-2 AGE AS A MODIFIABLE RISK FACTOR FOR CARDIOVASCULAR DISEASE.

Age is not considered a modifiable risk factor, but it outranks all those that are—lipids, BP, and smoking—as a predictor of cardiovascular events.

An analysis of the Framingham Study showed that age alone produced a receiving operator characteristic curve (ROC curve) of 0.731 for angina, myocardial infarction and coronary disease death. Addition of LDL-cholesterol increased it to only 0.746. Age + systolic BP + smoking produced a value of 0.791, which is marginally different from age alone.

Thus, apart from age and sex, the classical modifiable causative factors for cardiovascular disease seem to affect the individual risk of clinical disease to only a small extent. Yet the evidence of substantial benefit from interventional studies is incontrovertible, To suggest that hypertension and hyperlipidemia are unimportant is unreasonable.

The effect of factors such as dyslipidemia on the development of cardiovascular disease (**CVD**) is established both by the magnitude of the deviation of that factor from normal, and by the duration of exposure. This point is key. Conventional analyses do not distinguish between the biological changes of aging within the arteries—the non-modifiable effects of disintegration of tissues over time—and those produced by exposure over time to risk factors such as atherogenic dyslipidemia. Since arteries are damaged over time, we should take advantage of time and intervene early.

By calculating risk in the short term, and treating age as an independent risk factor, major guidelines discourage drug treatment until clinical events are common.

Early intervention will produce early benefits, but the larger issue is the effect of early intervention on the long-term clinical expression of disease. Cholesterol lowering will produce much greater total benefit if achieved earlier rather than later in life. In the absence of major risk factors by age 50, serious clinical cardiovascular disease by any age is unlikely.

"If age is as important as conventional analyses show, and if its effects are not modifiable, as conventional wisdom declares, the potential for prevention is limited. We believe this distressing conclusion is incorrect. Age can be deconstructed into the time-related effects of disintegration that affect all of us versus the time-related effects of exposure to the modifiable causal factors that affect some of us more than others."

The Framingham Heart Study Prediction Score I have on file (now 10 years old) excludes persons with known heart disease and diabetes. It is designed to predict 10-year risk of CHD.

It includes 1) age; 2) total cholesterol, 3) smoking, 4) HDL-c level, and 5) systolic BP.

It does not include BMI, waist circumference, and physical fitness.

Point scores for a 65 year old man:

Age	*11*
Total cholesterol > 200	*1*
Smoking	*1*
HDL-c < 40	*2*
Systolic BP > 160	*3*

Thus, the total points for age far outweigh the sum of all other risk factors.

A score of 11 for age alone predicts an 8% incidence of CHD over the following 10 years.

Adding all the other risk factors (total = 18) increases risk to over 30%

I believe the authors have a good point. They suggest that the risk score is weighted by age, likely calculated on a basis of average risk for the age.

But not all men age 65 are at the same risk.

We cannot modify age. We can modify the other risk factors. They should be modified at younger ages. I understand the American College of Pediatricians now advises checking of risk factors in some children.

Carotid Bruit Significantly Associated With Increased Likelihood Of Cardiovascular Death

5-6 CAROTID BRUITS AS A PROGNOSTIC INDICATOR OF CARDIOVASCULAR DEATH AND MYOCARDIAL INFARCTION

Clinical trials have shown benefit from carotid endarterectomy for *symptomatic* patients with severe (70-99%) carotid stenosis. However, a carotid bruit is a weak predictor of cerebrovascular events in patients who are otherwise asymptomatic for cerebrovascular conditions.

The uncertainty about prognostic implications has led the USPSTF to recommend against routine auscultation for carotid bruits.

This meta-analysis was based on a literature search which included over 17 000 patients followed up to 4 years. All studies (mostly prospective cohort studies) reported incidence of MI and cardiovascular death in adults. Median range = age 65.

All studies had extractable data for cardiovascular outcomes in individuals with carotid bruits.

Eight studies assessed MI in patients with bruits. The pooled estimate of myocardial infarction was 3.7 per 100 patient –years. In 16 studies assessing cardiovascular death, the pooled estimate of yearly deaths was 2.9 per 100 patient-years. In patients without bruits the rate was 1.1 per 100 patient-years.

“Our study has shown that the presence of a carotid bruit significantly increased the likelihood of cardiovascular death or myocardial infarction .” Cardiovascular death or MI were twice as likely in patients with bruits compared to those without.

The presence of a carotid bruit per se is not an independent risk factor of coronary disease, rather, its presence identifies a subgroup that is at high risk of having similar pathological changes in the coronary arteries. Carotid bruit is only a marker of risk to add to many other risk factors. The incremental value of a bruit is not known.

Conclusion: Auscultation for carotid bruit in patients at risk for heart disease could help select those who might benefit the most from aggressive modification strategy for cardiovascular risk.

I believe many primary care clinicians do listen for carotid bruits in elderly patients and in other patients at high risk.

If the patient has no cerebrovascular symptoms, I would not alarm the patient by mentioning the possibility of TIA and stroke unless other risk factors were present. If symptoms are present, urgent consultation is required.

The presence of a carotid bruit may be associated with increased risk. But, it is not known how much, or whether it is an independent risk factor.

If present in the absence of any other risk factors, I doubt if it indicates increased risk of coronary disease. If other risk factors are present, advice for reduction of all risk factors may be intensified.

Contrary To Past Observational Studies, This Randomized Trial Reported No Benefit

5-7 EFFECT OF FOLIC ACID AND B VITAMINS ON RISK OF CARDIOVASCULAR EVENTS AND TOTAL MORTALITY AMONG WOMEN AT HIGH RISK FOR CARDIOVASCULAR DISEASE.

Elevated homocysteine levels have been directly associated with cardiovascular risk in observational studies. Daily supplements with folic acid, vitamin B6 and vitamin B12, or a combination, reduce homocysteine levels.

In the most recent meta-analysis of observational studies, a 25% lower homocysteine level was associated with a 32% lower risk of CHD in women and a 15% lower risk in men.

This double-blind placebo-controlled trial entered over 5400 professional women (age 42 and older; mean age = 63) All had either a history of CVD, or 3 or more risk factors for CVD.

Randomized to:

1) Combination pill containing folic acid (2.5 mg), vitamin B6 (50 mg), and vitamin B12 (1 mg)

2. Matching placebo.

Main outcome = composite outcome of myocardial infarction, stroke, coronary revascularization, and CVD mortality. Duration of therapy = 7 years.

In the placebo group there was no apparent reduction in homocysteine. In the folate group, levels were significantly reduced

There was no difference at any time in the cumulative incidence of the primary combined end point (combined myocardial infarction, stroke, coronary revascularization, and CVD mortality) between groups. [Active group – 14.9%; placebo – 14.3%.]

The risk of death from any causes was also similar between groups—9.2% vs 9.4%.

"Until further data become available, it is essential to remain firmly grounded on the available evidence, and to admit that, once again, experimental and observational data do not always transfer into therapeutic benefits."

There is no role at present for routine screening for elevated homocysteine levels. And no role for homocysteine lowering by B vitamins.

Conclusion: In this trial, a combination of high doses of folic acid, B6, and B12 over 7 years had no beneficial effect (or adverse effects) on a combined outcome of total major cardiovascular events in population of high-risk of women.

This is another good example of how observational-epidemiological studies may mislead us. Many physicians (including the editor of Practical Pointers) were convinced of the benefits of folic acid in reducing risk.

Fortunately, this intervention caused no harm.

Fashions in medicine, even though seemingly firmly established, do change.

CAROTID BRUITS

Carotid Bruit Significantly Associated With Increased Likelihood Of Cardiovascular Death

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CHOLESTEROL (See DIABETES)

1-1 EFFICACY OF CHOLESTEROL-LOWERING IN 18 686 PEOPLE WITH DIABETES

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

CLOPIDOGREL (See MYOCARDIAL INFARCTION)

2-9 INCIDENCE OF DEATH AND ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH STOPPING CLOPIDOGREL AFTER ACUTE CORONARY SYNDROME.

COMMUNITY ACQUIRED PNEUMONIA (See PNEUMONIA)

CORONARY CALCIUM (See CORONARY HEART DISEASE)

3-12 CORONARY CALCIUM AS A PREDICTOR OF CORONARY EVENTS IN FOUR RACIAL OR ETHNIC GROUPS

CORONARY HEART DISEASE

Is This Screening Program Clinically, Socially, Economically, And Ethically Acceptable?

3-12 CORONARY CALCIUM AS A PREDICTOR OF CORONARY EVENTS IN FOUR RACIAL OR ETHNIC GROUPS

The study presents data that allows determination of the excess risk related to increasing coronary calcium (CC) scores.

This population-based study collected data on risk factors for cardiovascular disease in over 6700 subjects. All received CT scanning to determine CC score. None had cardiovascular disease at baseline.

Over 4 years, there were 162 coronary events (2.5%): 89 myocardial infarction or death from coronary disease (17 died); 73 angina

CC score as a predictor of CHD (any event)

Score	No. /No. at risk	Hazard ratio
0	8/3409	1.00
1-100	25/1728	3.6
101-300	24/752	7.7
> 300	32/833	10

The score contributed to risk independently of other risk factors.

Conclusion: Measurement of CC score added incremental value to the prediction of CHD over that of standard coronary risk factors.

Determining the CC score by CT entails risks from radiation that are not negligible.

The American public is enamored with the latest and most expensive (and "better") drugs and diagnostic interventions.

Note that the subjects who developed a coronary event were at much greater baseline risk as determined by the usual risk factors (including age and sex). We must ask:

1) How would we treat a patient considered to be at high risk as determined by usual risk factors?

2) How would we treat a patient considered to be at high risk as determined by the usual risk factors + a high CC score? (Note that the patients who developed an event over the subsequent 4 years had higher risk factors at baseline and were, on this account already considered at high risk.)

3) Would there be any difference in treatment between 1) and 2)? What additional measures to reduce risk factors would be taken in patients because they had a high CC score?

4) Would knowing that the CC score is high motivate individual patients to be more adherent to risk-factor reductions?

See Practical Pointers April 2006 for a suggested list of key criteria for screening. This includes:

The screening test should be safe, simple, precise, and validated. A suitable cut-off value should be defined and agreed.

Effective treatment should be identified through the screening program, with evidence that early treatment leads to better outcome.

High quality randomized, controlled trials should provide evidence that the screening program effectively reduces morbidity.

The screening program should be clinically, socially, economically, and ethically acceptable.

In addition, individuals who may request the screen, or to whom it is offered by medical personnel, should be

fully informed about pros and cons of screening, including costs.

Does CC screening meet these criteria?

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.

DEMENTIA

Are Strongly Linked

1-2 DIABETES, COGNITIVE IMPAIRMENT, AND DEMENTIA

A recent review reported that, overall, people with type-2 diabetes (**DM-2**) had a 1.2 to 1.7 times greater decline in cognitive performance than those without DM-2, and were 1.6 times more likely to develop dementia.

They were 2 to 3 times more likely to develop vascular dementia, and up to 2 times more likely to develop Alzheimer's disease. Why?

Micro-vascular disease is the hallmark of protracted poor glycemic control. Cerebral micro-vascular may be the cause. The micro-vasculature of the retina offers a window into the status of the small vessels of the brain. Studies have shown an association between retinal micro-vascular abnormalities and cognitive function. Short term changes in blood glucose concentrations may also affect cognitive function. Functional consequences of hyperglycemia, such as altered cerebral blood flow or possible osmotic changes in the brain are likely to impair cognition.

This makes sense to me, especially the link between diabetes and vascular dementia. We must protect our brains as well as our hearts. Prevention lies in 1) preventing development of type-2 diabetes by lifestyle

measures, and using drug therapy to reduce smoking, dyslipidemia and hypertension, as well as HbA1c levels.

"Antimicrobial Exposure Among Nursing Home Residents With Advanced Dementia Is Extensive And Steadily Increases Toward The End Of Life."

3-5 PATTERNS OF ANTIMICROBIAL USE AMONG NURSING HOME RESIDENTS WITH ADVANCED DEMENTIA

This study examined how infections in patients with advanced dementia are currently being managed.

Followed residents (n = 214) with advanced dementia in Boston-area nursing homes from 2003 to 2006. Mean age = 85; mean length of stay was 41 months. 46% died.

These patients had severe impairment of cognition, minimal or no verbal communication, dependence for eating and toileting, incontinence, and loss of ability to walk.

During the observation period, 66% received at least one dose of antimicrobials—a total of 540 courses.

Antibiotic exposure steadily increased toward the end of life—often administered parenterally.

In the 28 to 15 days before death, 18% of decedents received antibiotics.

In the 14 to 0 days before death, 42% of decedents received antibiotics.

Treatment decisions for infections in advanced dementia can be difficult for family members and caregivers.

The 2 purposes for antimicrobial therapy are: 1) prolongation of life, and 2) symptom control. Limited observational studies have failed to demonstrate that therapy achieves either outcome.

Parenteral administration adds to discomfort.

"Our findings further support that antimicrobials may not meaningfully extend the life of patients with advanced dementia." Palliation is the main goal of care. Antimicrobial therapy may relieve terminal symptoms, but it is not clear whether this provides symptomatic relief beyond what may be achieved by high quality palliation.

Antimicrobial use in nursing homes is a major public health issue because of increased antibiotic resistance. When these nursing home residents are admitted to the hospital, they carry resistant organisms with them.

This presents an important ethical dilemma encountered in primary care practice. Families can be seriously conflicted and can have different opinions about terminal care when a parent or spouse becomes demented.

It again emphasizes the need for advanced directives, but more than that, a need for clear and repeated informal instructions to the family before dementia begins. As persons age, I believe all should appoint a chief advocate who will speak for them and express their autonomous decisions about end-of-life care. All members of the family should understand this decision. The primary care clinician should record it along with the more formal advanced directive. This may prevent a great deal of heartache.

I would be willing to wager that no primary care clinicians would opt for antibiotic treatment at the end of life should they be burdened by advanced dementia. They will remember Sir William Osler's observation that pneumonia is "the old man's friend".

Statically Significant Benefit; Questionable Clinical Benefit

3-9 CURRENT PHARMACOLOGICAL TREATMENT OF DEMENTIA: A Clinical Practice Guideline.

The American College of Physicians developed this guideline to present the available evidence on current pharmacological treatment of dementia. This was based on a literature search (59 studies) for evidence of effectiveness of FDA approved drugs for dementia for outcomes in domains of cognition, global function, behavior/mood, and quality of life/activities of daily living.

The drugs discussed in this review have shown statistically significant improvement in scores of various instruments evaluating changes in patients with dementia. Most of these outcomes are not used in routine clinical practice. Interpretation of clinical importance of improvements is challenging.

Many of the improvements demonstrated in the trials, although *statistically* significant, were not *clinically* important.

Adverse effects were tolerable.

No convincing evidence demonstrates that one drug is more effective than another.

Recommendations:

Decisions to initiate therapy should be individualized.

Benefits on average are not clinically significant for cognition, and are modest for global assessments.

Summary estimates showed small effect sizes.

In more advanced dementia, decision makers may not view stabilization or slowing decline in cognition as a desirable goal if quality of life is judged to be poor.

Harms of drugs should be weighed against modest or even no benefit.

Limited evidence suggests, but does not demonstrate conclusively, that a subgroup of patients achieves clinically important improvement.

Currently, we have no way to predict which patients might have a clinically important response.

Evidence does not support prescribing these agents for every patient with dementia.

Evidence is insufficient to determine optimal duration of therapy. A beneficial effect, if any, would generally be observed within 3 months. The effect may be an improvement or stabilization.

No evidence demonstrates when it is appropriate to stop treatment. If slowing decline is no longer a goal, treatment is no longer appropriate.

Faint praise.

I believe these drugs are over-used, and used for too long a time.

The benefit/harm-cost ratio approaches 1. These drugs are expensive.

I believe many patients and families choose treatment hoping for an outlier benefit.

DIABETES

Statin Therapy Should Be Considered For All Diabetic Individuals.

1-1 EFFICACY OF CHOLESTEROL-LOWERING IN 18 686 PEOPLE WITH DIABETES IN 14 RANDOMIZED TRIALS OF STATINS

This study included data from randomized statin drug trials in over 18 000 individuals with diabetes (92% type-2) in the context of over 71 000 persons without diabetes.

Estimated effects on clinical outcomes per 1.0 mmol/L (38 mg/dL) decrease in LDL-c over a mean period of 4 years.

Events per 1 mmol/L (38 mg/dL) reduction in LDL-c at one year in patients with diabetes:

	Statin treatment (%)	Control (%) [No statin]	Absolute difference (%)	NNT
All cause death	11.0	11.9	0.9	100
Major coronary even	8.3	10.5	2.2	50
Stroke	4.4	5.4	1.0	100
Major vascular event	15.6	19.2	3.6	28

Overall there was a 10% proportional reduction in major vascular events in year 1, followed by reduction around 20-30% in successive years. The reductions were similar in subjects without diabetes as well as those with diabetes.

In the subgroups with known vascular disease, the absolute benefit of a statin was larger than in those without known vascular disease.

Statin therapy safely reduces the 5-year incidence of major coronary events, coronary revascularization, and stroke by about a fifth for each mmol/L reduction (38 mg/dL) in LDL-cholesterol, largely irrespective of initial lipid profile or other baseline characteristics.

Standard doses of statins reduce LDL-c by about 40%. This translates into a reduction of at least 1.5 mmol/L (57 mg) for many people. Such a reduction would prevent about one third of patients from having a major vascular event. A generic statin regimen producing a mean reduction of about one mmol/L in LDL-c is cost effective.

The proportional benefit of statin therapy was largely independent of pre-treatment levels of LDL-c, HDL-c, and triglycerides, without any lower threshold below which benefit was absent.

Conclusion: : Statin therapy should be considered for all diabetic individuals.

Are Strongly Linked

1-2 DIABETES, COGNITIVE IMPAIRMENT, AND DEMENTIA

A recent review reported that, overall, people with type-2 diabetes (**DM-2**) had a 1.2 to 1.7 times greater decline in cognitive performance than those without DM-2, and were 1.6 times more likely to develop dementia.

They were 2 to 3 times more likely to develop vascular dementia, and up to 2 times more likely to develop Alzheimer's disease. Why?

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vascular may be the cause. The micro-vasculature of the retina offers a window into the status of the small vessels of the brain. Studies have shown an association between retinal micro-vascular abnormalities and cognitive function. Short term changes in blood glucose concentrations may also affect cognitive function. Functional consequences of hyperglycemia, such as altered cerebral blood flow or possible osmotic changes in the brain are likely to impair cognition.

This makes sense to me, especially the link between diabetes and vascular dementia. We must protect our brains as well as our hearts. Prevention lies in 1) preventing development of type-2 diabetes by lifestyle measures, and using drug therapy to reduce smoking, dyslipidemia and hypertension, as well as HbA1c levels.

Sustained Beneficial Effects On Vascular Complications And Death Over 13 Years

2-1 EFFECT OF A MULTIFACTORIAL INTERVENTION ON MORTALITY IN TYPE 2 DIABETES

A previously reported 8-year prospective randomized trial (Steno-2 study) of intensified multitarget interventions aimed at several risk factors concomitantly vs conventional treatment, reported a reduction in vascular complications of DM-2 by about 50%.

This article reports an observation only follow-up of an additional 5 years to determine death rate, and effects in intensive vs conventional therapy on microvascular and macrovascular diseases over a total of 13 years.

During the first 8 years:

1. Risk factor reductions were much greater in the intervention group: glycated hemoglobin, systolic BP, diastolic BP, triglycerides, LDL-cholesterol and total cholesterol levels remained considerably lower than in the conventional group.
2. Risk of complications: hazard ratios of cardiovascular disease, stroke, myocardial infarction, revascularization procedures, nephropathy, retinopathy, neuropathy and amputations were much lower in the intervention group.

During the last 5 years:

1. Differences in risk factor reductions gradually decreased in the conventional group, so that at the end of 13 years, there were little differences between groups in glycated hemoglobin, BP, triglycerides, LDL-cholesterol, and total cholesterol. This was mainly because the control group received better interventions in the last 5 years.
2. Risk of complications, however remained considerably in favor of the intervention group: hazard ratios of risk of overall death, death from cardiovascular disease, cardiovascular events, and requirement for retinal photocoagulation remained between 0.4 and 0.5.

Conclusion: In patients with DM-2, intensive intervention with multiple drug combinations and behavioral modification had sustained beneficial effects with respect to vascular complications and rates of death from any cause and death from cardiovascular causes.

As compared with conventional care, the benefits of 8 years of intensive risk-factor reduction persisted for5 years after the trial ended. This is not surprising. The earlier and the longer risk-reduction interventions are applied, the greater the benefit in reducing complications.

I believe that if intensive therapy had begun at a much earlier age (eg 30 instead of 55), risk reductions of complications of DM-2 would have been much greater.

The article states that the study did not determine which of the interventions contributed most to the benefits. I believe BP and lipid control would contribute more to reduction in complications than control of HbA1c.

Changing The Emphasis From Sugar To Fat

3-1 REINVENTING TYPE-2 DIABETES: Pathogenesis, Treatment, and Prevention

The lipocentric view depicts the hyperglycemia of DM-2 and the underlying insulin resistance and beta-cell loss as being secondary to the metabolic trauma caused by ectopic lipid deposition (lipotoxicity).

If this is the case, hyperglycemia could be corrected by eliminating the lipid overload.

For several decades, the position has been advanced that abnormal metabolism of lipids, not glucose, is the primary metabolic defect in DM-2. There is now evidence that fatty acids inhibit insulin-mediated glucose uptake in muscle. In the liver, fatty acids inhibit the insulin-mediated suppression of glycogenolysis and gluconeogenesis. (This leads to continuing glucose production and discharge from the liver despite the elevated blood glucose.)

There is broad consensus that ectopic accumulation of unoxidized fatty acids is a major factor in the production of insulin resistance.

Read the full abstract. It is quite convincing.

The consistent weight gain associated with insulin therapy fits nicely into this model.

Favors Insulin Glargine

3-6 ONCE-DAILY BASAL INSULIN GLARGINE VERSUS THRICE-DAILY PRANDIAL INSULIN LISPRO IN PEOPLE WITH TYPE-2 DIABETES ON ORAL HYPOGLYCAEMIC AGENTS

As type-2 diabetes (**DM-2**) progresses, oral hypoglycemic agents often fail to maintain blood glucose control, and insulin is needed.

This study, of inadequately-controlled patients with DM-2, investigated whether once-daily insulin glargine + oral hypoglycemic agents was non-inferior in controlling overall glucose control compared to prandial insulin lispro + oral hypoglycemic agents.

Insulin glargine (*Lantus*, Sanofi-Aventis), a basal insulin given once daily, has a duration of action of about 24 hours, with no discernable peak in insulin concentration. Insulin lispro (*Humalog*, Lilly) short acting is given three times a day at mealtimes.

Outcomes:	Glargine	Lispro
HbA1c		
Baseline	8.7%	8.7%
At 44 weeks	7.0	6.8
Reaching HbA1c less than 7%	57%	69%
Incidence of hypoglycemic events		
(events per patient per year):	5	24
Mean weight gain (kg)	3.0	3.5

Patient-satisfaction was greater in subjects taking glargine

"Our results suggest that treatment with once-daily insulin glargine is non-inferior to three-times daily insulin lispro in achieving overall glycemic control as represented by haemoglobin A1c."

Conclusion: Insulin glargine provides a simple and effective option that is more satisfactory to patients than is insulin lispro. It is associated with less frequent need for blood glucose monitoring, and lower incidence of hypoglycemia,.

Note the mean baseline BMI was 29, and subjects gained about 10 pounds over 44 weeks. This is a consistent effect of insulin therapy. As noted in a preceding article, increasing weight (and lipid deposition) related to overdriving the lowering of blood glucose with insulin may, in some respects, be counterproductive. It increases lipid deposition and lipid toxicity. See the preceding abstract. [3-1]

It Would Be Wise To Avoid Highly Intensive Management That Combines Multiple Insulin Injections With Multiple Oral Agents.

3-7 SAFETY OF VERY TIGHT BLOOD GLUCOSE CONTROL IN TYPE 2 DIABETES.

On February 8, 2008, the glucose arm of a large ongoing randomized, controlled trial of people with type 2 diabetes (**DM-2**) who were at high risk of vascular disease was stopped because of concerns about safety. Intensively controlling blood glucose to a HbA1c under 6% increased the risk of death compared with a less intensive treatment strategy (HbA1c 7.0% to 7.9%).

What should we conclude? It seems that moderately intensive management to targets of HbA1c less than 6.5% or lower—if easily obtained—need not be abandoned. Meanwhile, it would be wise to avoid highly intensive management that combines multiple insulin injections with multiple oral agents.

Cardiovascular disease is the major risk of diabetes. Blood concentrations of other constituents are more important than HbA1c in determining risk—LDL-cholesterol, HDL-cholesterol, triglycerides.

Hypertension, BMI, waist circumference, and a sedentary lifestyle are also major risk factors.

Controlling these factors will likely reduce risk more than reducing HbA1c, and will likely also reduce HbA1c.

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 (hypotension; hypokalemia)	N = 2 (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.

No Benefit In Control Of Hba1c, BMI, Hypoglycemia, Or Use Of Oral Drugs

5-3 EFFICACY OF SELF-MONITORING OF BLOOD GLUCOSE IN PATIENTS WITH NEWLY DIAGNOSED TYPE-2 DIABETES

Self-monitoring of blood glucose is widely advocated for patients with type-2 diabetes (**DM-2**) who do not require insulin. There is conflicting evidence as to its value.

This prospective randomized, controlled trial of self-monitoring of blood glucose vs no monitoring, entered 184 outpatients. All patients were under age 70, and had newly diagnosed DM-2. None were taking insulin. None had previously self-monitored glucose levels. All underwent a structured core education program. The self-monitoring group received additional education on monitoring. Follow-up for one year at intervals of 3 months.

A treatment algorithm was given to all patients for use of oral antidiabetes drugs.

If HbA1c >7.5% add metformin and titrate to a maximum of 2 g daily.

HbA1c still > 7.5%—add gliclazide 80 mg daily (a sulfonylurea not marketed in the US) and titrate to a maximum of 320 mg daily.

HbA1c still > 7.5% consider addition of a thiazolidinedione or transfer to insulin.

Outcome measures at one year:

At baseline HbA1c averaged 8.7%. HbA1c fell in both groups, there was no difference between groups—6.9% vs 6.9%.

Participants in the monitoring group were more depressed—6% higher on the depression subscale. There was also a trend toward increased anxiety in this group.

No differences in treatment satisfaction.

No differences in reported hypoglycemia. No difference in use of oral drugs.

No difference in BMI.

Evidence suggests that some patients consider monitoring uncomfortable, intrusive, and unpleasant.

Conclusion: In these patients with newly diagnosed type-2 diabetes, in comparison with a control group, self-monitoring of blood glucose concentration had no benefit in control of HbA1c, BMI, hypoglycemia, or use of oral drugs.

I believe self monitoring will be more efficacious in patients taking insulin.

Note that the uptake of regular monitoring in the monitoring group was not very high. Of 96 participants, only 63 carried out over 80% of the instructed number of determinations.

In the US, many patients with DM-2 are self-monitoring.. I believe many would not be willing to give it up.

Associated With A Reduced Risk Of Diabetes. Possibly A Protective Effect

6-7 ADHERENCE TO MEDITERRANEAN DIET AND RISK OF DEVELOPING DIABETES

Many studies have shown that the Mediterranean diet (**MD**) has a role in prevention of cardiovascular disease. Some suggest that the diet could protect against type-2 diabetes. (**DM-2**)

This prospective cohort study followed over 13 000 subjects in Spain. None had DM-2 at baseline. Periodic questionnaires assessed food frequency, risk factors, and medical conditions. Determined adherence to the MD using a score index divided into 3 categories (0-2; 3-6; and 7-9—9 being the highest adherence).

Follow-up = median of 4 years.

Identified 33 new-onset cases of DM-2 during follow-up (over 58 000 patient-years).

Patients with the highest MD score (> 6) had a higher level of leisure-time activity, but also had higher baseline prevalence of most risk factors (higher BMI, higher total energy intake, higher BP. a family history of DM-2, and were more likely to be former smokers).

After adjustment for age and sex, there was a significant inverse relationship between adherence to the MD and incidence of DM-2.

	Relative risk of DM-2
Low-score (0-2)	1.00 (reference)
Moderate score (3-6)	0.41
High score (7-9)	0.17

With score as a continuous variable, an increase of 2 points in the MD score was associated with a significant reduction in the risk of DM-2. This was despite the increase in baseline risk factors noted above, “suggesting that the diet might have a substantial potential for prevention”.

Conclusion: Adherence to the Mediterranean diet was associated with a reduced risk of diabetes.

The study would be more convincing if it were continued longer, and if more subjects had developed DM-2.

The most interesting aspect was that those who were more adherent to the diet were less likely to develop DM-2, despite the fact that risk factors for DM-2 in this group were more prevalent. This suggests that the diet has a protective effect on development of DM-2 despite an increased prevalence of factors such as increased BMI and family history of DM-2.

Is the prevalence of DM-2 lower in Mediterranean populations?

Appears To Have A Reno-Protective Effect That Is Independent Of Its BP-Lowering Effect

6-8 ALISKIREN COMBINED WITH LOSARTAN IN TYPE-2 DIABETES AND NEPHROPATHY

Aliskiren directly inhibits production of renin by the kidney, thereby lowering production of angiotensin and aldosterone.

A reduction in proteinuria has been widely used as a surrogate end point for renoprotection.

This study evaluated the renoprotective effects of aliskirin by adding it to treatment with the maximum recommended dose (100 mg/d) of the angiotensin II blocker losartan (*Cozaar*; Merck), and with optimal antihypertension therapy in patients who had hypertension and type-2 diabetes with nephropathy.

Multinational, double-blind trial enrolled 599 patients (mean age 60). All had type-2 diabetes and nephropathy (defined as an early-morning urinary albumin/creatinine ratio of greater than 300 mg per gram). None had an estimated glomerular filtration rate of less than 30 mL per minute per 1.73 m^2 of body-surface area, serum potassium greater that 5.1 mmol/L, or major cardiovascular disease. Mean urinary albumin excretion rate = 500 ug/min. Baseline BP = 135/78

After a 3-month open-label run-in period during which all patients received 100 mg losartan daily, patients were randomized to:

1) Aliskiren 150 mg daily for 3 months followed by 300 mg daily for another 3 months + losartan. (300 mg is the optimum dose for treatment of hypertension..)
2) Placebo + losartan.
3) All patients continued to take other antihypertension drugs aimed at maximal recommended renoprotective dose (target BP < 130/80), except for other drugs blocking the renin-angiotensin-aldosterone system.

By 6 months treatment with aliskiren, the mean albumin/creatinine ratio was reduced by 20% as compared with placebo. A reduction of 50% or more was seen in 25% of aliskiren patients as compared with 13% in the placebo group. The overnight urinary albumin was reduced by a mean of 18% in the aliskiren group compared with placebo.

Adverse events: overall, no difference between groups. The rate of serious adverse events was similar—9%. Hyperkalemia occurred in 5% vs 5.7% of patients.

The benefit of aliskiren appeared to be independent of the small reduction in BP (2/1 mm Hg).

Conclusion: Aliskiren appears to have a reno-protective effect that is independent of its BP-lowering effect in patients with type-2 diabetes who are receiving maximally recommended reno-protective treatment and optimal antihypertension treatment.

Aliskiren (Tektura; Novartis) is approved by the FDA (2007) for treatment of hypertension. Starting dose is 150 mg/d. This is the first time I have abstracted an article abut it.

I believe aliskiren for renal protections is not a practical point for primary care at this time. I would not use the drug for treatment of hypertension until more time passes to evaluate general use.

DIET

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.

6-7 ADHERENCE TO MEDITERRANEAN DIET AND RISK OF DEVELOPING DIABETES (See DIABETES)

DYSPEPSIA

Empirical Acid Suppression Is An Appropriate First Choice.

3-11 HELICOBACTER PYLORI TEST AND TREAT VERSUS PROTON PUMP INHIBITOR IN INITIAL MANAGEMENT OF DYSPEPSIA IN PRIMARY CARE

The aim of this study was to determine the effectiveness of *H pylori* "test and treat" compared with empirical acid suppression in the initial management of dyspepsia in primary care.

Randomized, controlled trial, conducted in 80 general practices, followed 699 patients (age 18-65) who presented with dyspepsia. None had "alarm" symptoms.

Randomized to:

1) *H pylori* carbon-13 urea breath test:

A. Patients with a positive *H pylori* test were offered eradication therapy followed by 3 weeks of 20 mg omeprazole once daily. A follow-up breath test was offered at 12 weeks. (The test is available as a kit and is quite feasible in primary care.)

B.. Patients who tested negative received omeprazole 20 mg once daily for 4 weeks.

2) Proton pump inhibition alone—omeprazole 20 mg daily for 4 weeks.

Test and treat group:	No. tested	No. positive for *H pylori*	Successful eradication
	343	100 (29%)	78%
Proton pump-only (PP-only)	356		

Outcomes at 12 months:

A. Continuing symptoms at 12 months	PP-only	Test and treat
	83%	82%

B. No significant difference in quality-adjusted life-years and costs between groups. The cost of test and treat was higher at the beginning, but costly resource use was higher in the PP-only group. The two cancelled each other.

C. The score for satisfaction was similar between groups

"This study shows that an *H pylori* test and treatment strategy offers no significant advantage over a proton pump inhibitor for the initial management of dyspepsia in primary care."

There was no difference in outcome between patients with heartburn-predominant and epigastric-pain predominant dyspepsia. (One problem has been the shifting role of heartburn in the definition of functional dyspepsia.)

Treatment of dyspepsia is difficult because it is a syndrome, not a disease. Many different symptoms are included, and vary from individual to individual. Severity and duration also vary.

The type and duration of treatment relies heavily on clinical judgment and patient preference.

In this trial, neither treatment was particularly effective at one year.

I believe most primary care clinicians would choose empirical proton pump inhibition. It will be required for longer than one month in many patients.

The antibiotic treatment protocol can be burdensome.

I believe primary care clinicians in the USA would be more likely to recommend endoscopy at an earlier stage in patients with disturbing symptoms.

ENDOCARDITIS

No Longer Recommended

1-9 PROPHYLAXIS FOR INFECTIVE ENDOCARDITIS: *New Guidelines for Dental Procedures*

The new guidelines are based on a growing body of evidence that the risks of taking preventive antibiotics outweigh the benefits in most patients. The new guidelines recommend that patients with conditions for which prophylactic antibiotics were previously recommended no longer receive them, regardless of the dental procedure contemplated:

Mitral valve prolapse
Rheumatic heart disease
Bicuspid valve disease
Calcified aortic stenosis
Congenital heart conditions (Eg, ventricular septal defect, atrial sepal defect, and hypertrophic cardiomyopathy)

Antibiotic prophylaxis is still recommended for patients who would have the greater danger of a bad outcome if they developed IE:

Artificial heart valves
History of IE
Some serious congenital heart conditions
A cardiac transplant that develops a problem with a valve

Primary care clinicians should be aware of these changes.

How fashions in medicine change! A standard question asked patients who developed IE used to be – "Have you had a dental procedure recently?"

In the recent past, it was considered malpractice if antibiotics were not given to patients in the major categories of "risk" listed above. There may have been successful suits brought against dentists by patients who developed IE following a dental procedure who had not received antibiotic prophylaxis.

ESTROGEN (See BREAST CANCER)

2-5 ESTROGEN PLUS PROGESTIN AND BREAST CANCER DETECTION BY MEANS OF MAMMOGRAPHY AND BREAST BIOPSY

ETIQUETTE-BASED MEDICINE

"The Finer Points Of Patient Care Should Be Built On A Basis Of Good Manners."

5-8 ETIQUETTE-BASED MEDICINE

The editorialist comments, that during his recent hospitalization, he found the Old World manners of his European-born surgeon, and his reaction to them, revealing.

"Whatever he might have been feeling, his behavior—dress, manners, body language, eye contact—was impeccable. I wasn't thinking 'what compassion', instead. I found myself thinking 'what a professional—'what a gentleman'. " The impression he made was remarkably calming. "It helped to confirm my suspicion that patients may care less about whether their doctors are reflective and empathetic than they are respectful and attentive."

There have been many attempts to foster empathy and compassion in clinicians, but none to systematically teach good manners. "The very notion of good manners may seem quaint and anachronistic, but it is at the heart of the mission of other service-related professions." Doctors can behave in certain specified ways that will result in the patient's feeling well treated.

How could we implement an etiquette-based approach to patient care? The author proposed that we develop a checklist of physician etiquette for the clinical encounter. This would include:

Ask permission to enter the room. Wait for an answer

Introduce yourself, showing your ID badge

Shake hands (wear gloves if needed)

Sit down. Smile appropriately

Briefly explain your role on the team

Ask the patient how he or she is feeling about being in the hospital

This does not address the way the doctor feels, only how he or she behaves. It complements, rather than replaces, efforts to train physicians to be more humane.

I believe all of us could benefit from these suggestions.

However, reading about them or hearing about them in lectures will not have the impact that observing them from a role model will have.

FOLIC ACID (See CARDIOVASCULAR DISEASE)

5-7 EFFECT OF FOLIC ACID AND B VITAMINS ON RISK OF CARDIOVASCULAR EVENTS AND TOTAL MORTALITY AMONG WOMEN AT HIGH RISK FOR CARDIOVASCULAR DISEASE.

FRUCTOSE (See GOUT)

2-4 SOFT DRINKS, FRUCTOSE CONSUMPTION, AND THE RISK OF GOUT IN MEN

GERIATRICS

Dose, Formulation, And Delivery Need To Be Adjusted According To The Age And Frailty Of The Patient

3-8 PRESCRIBING FOR OLDER PEOPLE

This review highlights some of the difficulties in prescribing for older patients and offers guidance to appropriate prescribing.

Increasing age is associated with changes in pharmacokinetics and pharmacodynamics. Prescribing for elderly patients presents many challenges.

Older patients are often prescribed unnecessary drugs; drugs that are contraindicated in their age group; and are given the wrong dose. They may be given drugs without a specific indication, and lacking an evidence base.

The article includes a discussion of:

Physiological changes occurring with aging

Multiple pathology and polypharmacy in the elderly

Inappropriate prescribing for the elderly

Drugs that pose a particular risk in the elderly

Some guidelines for good prescribing in the elderly:

Regular medication review

Prescribe new drugs that have a clear indication

Try to avoid drugs that pose a particular risk

Use the doses recommended for elderly patients

Use simple drug regimens and appropriate administration systems

Limit authorization for repeat prescriptions

Consider once daily formulations

Limit number of physicians who prescribe for the patient

Avoid treating adverse effects of drugs with other drugs

Enlist pharmacist's help. They have an important role in spotting adverse drug reactions and interactions

Follow the development of electronic prescribing. E-prescribing may reduce errors and improve patient care

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This is an important clinical consideration for primary care.

I noted in a random review of the PDR, that many manufacturers (but far from all) mentioned reduced-dose recommendations for the elderly. I believe many times even these reduced doses may be too high. For

long-term medications prescribed for the elderly (eg, for hypertension) I believe we can start with a lower than recommended doses. This may require a pill cutter.

Then, gradually raise the dose to a modest level. This may be acceptable and provide the desired response.

If the elderly patient then requires a still higher dose, we must choose between raising the dose above the modest level or adding a second drug. I believe adding a second drug would generally be preferable because adverse effects are more likely with higher doses of a single drug than with lower doses of two drugs.

The December 2007 issue of Practical Pointers reported a study of the adverse drug effects seen most commonly in the emergency department. These were not age-limited, but would likely be encountered in the elderly.

Anticoagulants and antiplatelet agents: warfarin, aspirin, and clopidogrel

Antidiabetes agents: insulin, metformin, glyburide, glipizide

Narrow therapeutic index agents: digoxin, phenytoin

"We Should Take Advantage Of Time And Intervene Early"

5-2 AGE AS A MODIFIABLE RISK FACTOR FOR CARDIOVASCULAR DISEASE.

Age is not considered a modifiable risk factor, but it outranks all those that are—lipids, BP, and smoking—as a predictor of cardiovascular events.

An analysis of the Framingham Study showed that age alone produced a receiving operator characteristic curve (ROC curve) of 0.731 for angina, myocardial infarction and coronary disease death. Addition of LDL-cholesterol increased it to only 0.746. Age + systolic BP + smoking produced a value of 0.791, which is marginally different from age alone.

Thus, apart from age and sex, the classical modifiable causative factors for cardiovascular disease seem to affect the individual risk of clinical disease to only a small extent. Yet the evidence of substantial benefit from interventional studies is incontrovertible, To suggest that hypertension and hyperlipidemia are unimportant is unreasonable.

The effect of factors such as dyslipidemia on the development of cardiovascular disease (**CVD**) is established both by the magnitude of the deviation of that factor from normal, and by the duration of exposure. This point is key. Conventional analyses do not distinguish between the biological changes of aging within the arteries—the non-modifiable effects of disintegration of tissues over time—and those produced by exposure over time to risk factors such as atherogenic dyslipidemia. Since arteries are damaged over time, we should take advantage of time and intervene early.

By calculating risk in the short term, and treating age as an independent risk factor, major guidelines discourage drug treatment until clinical events are common.

Early intervention will produce early benefits, but the larger issue is the effect of early intervention on the long-term clinical expression of disease. Cholesterol lowering will produce much greater total benefit if

achieved earlier rather than later in life. In the absence of major risk factors by age 50, serious clinical cardiovascular disease by any age is unlikely.

"If age is as important as conventional analyses show, and if its effects are not modifiable, as conventional wisdom declares, the potential for prevention is limited. We believe this distressing conclusion is incorrect. Age can be deconstructed into the time-related effects of disintegration that affect all of us versus the time-related effects of exposure to the modifiable causal factors that affect some of us more than others."

The Framingham Heart Study Prediction Score I have on file (now 10 years old) excludes persons with known heart disease and diabetes. It is designed to predict 10-year risk of CHD.

It includes 1) age; 2) total cholesterol, 3) smoking, 4) HDL-c level, and 5) systolic BP.

It does not include BMI, waist circumference, and physical fitness.

Point scores for a 65 year old man:

Age	*11*
Total cholesterol > 200	*1*
Smoking	*1*
HDL-c < 40	*2*
Systolic BP > 160	*3*

Thus, the total points for age far outweigh the sum of all other risk factors.

A score of 11 for age alone predicts an 8% incidence of CHD over the following 10 years.

Adding all the other risk factors (total = 18) increases risk to over 30%

I believe the authors have a good point. They suggest that the risk score is weighted by age, likely calculated on a basis of average risk for the age.

But not all men age 65 are at the same risk.

We cannot modify age. We can modify the other risk factors. They should be modified at younger ages. I understand the American College of Pediatricians now advises checking of risk factors in some children.

5-5 TREATMENT OF HYPERTENSION IN PATIENT 80 YEARS OF AGE OR OLDER
(See HYPERTENSION)

GLUCOSAMINE (See OSTEOARTHRITIS)

2-8 EFFECT OF GLUCOSAMINE ON HIP OSTEOARTHRITIS

GOUT

Strongly Associated With Increased Risk Of Gout

2-4 SOFT DRINKS, FRUCTOSE CONSUMPTION, AND THE RISK OF GOUT IN MEN

Fructose is the only carbohydrate known to increase uric acid levels. Fructose accentuates degradation of purine nucleotides, and increases purine synthesis. The urate-raising effect is exaggerated in people with hyperuricemia.

This study examined relation between intake of fructose and sugar-sweetened soft drinks on incident gout in men. Fructose is a mono-saccharide. Half of the disaccharide, sucrose, is fructose. The total fructose intake is therefore equal to the intake of free fructose plus half of the intake of sucrose.

The Health Professionals Follow-up study followed a prospective cohort of over 46 000 men beginning in 1986. No subject had a history of gout. All participants completed a questionnaire on diet, medical history and dugs. All were asked how often during the previous year they had consumed sugar sweetened soft drinks, diet soft drinks, and different types of fruits and fruit juices. The questionnaire was updated every 4 years.

Ascertained the incident cases of gout by biennial questionnaire.

Increasing intake of sugar-sweetened soft drinks was associated with increasing risk of gout. Compared with the reference consumption of less than one serving monthly, the risk of gout for

5-6 servings weekly = 1.3; for one serving daily = 1.5; and for two or more servings daily = 1.9. Relative risk of gout according to fifths of fructose intake were: 1.00; 1.3; 1.4; 1.8; and 2.0

Diet soft drinks were not associated with risk of gout.

Low purine diets are often high in carbohydrates, including fructose. "These data provide prospective evidence that the risk posed by free fructose intake could be at least as large as that by purine rich foods such as meat. "

Conclusion: Consumption of sugar sweetened soft drinks and fructose is strongly associated with increased risk of gout among men .

Both Are Effective. Prednisolone Is Safer.

5-4 USE OF ORAL PREDNISOLONE OR NAPROXIN FOR THE TREATMENT OF GOUTY ARTHRITIS

NSAIDs are now first choice for treatment of acute gouty arthritis despite their gastrointestinal and cardiovascular risks. About 40% of upper g.i. bleeding events are attributable to NSAIDs. Risk is highest during the first week of use. The American Heart Association has recommended restricted use because of cardiovascular risks, which include loss of renal function, fluid retention, and interaction with anticoagulants.

Systemic corticosteroids do not have important drawbacks in the short term.

This randomized, double-blind equivalence trial entered 120 patients (mean age 58) with monoarticular arthritis. All had gout confirmed by identification of monosodium urate crystals in synovial fluid.

A quarter of the eligible patients had to be excluded because of direct safety risks if they had been treated with naproxin.

Randomized to: 1) Prednisolone 35 mg once daily, or 2) naproxin 500 mg twice daily for 5 days.

Primary outcome = pain measured on a 100 mm visual analogue scale. Disability related to the affected joint was also scored on a scale of 0 to 100.

Scores on 100 mm visual analogue scale at baseline and after 90 hours:

	Pain		General disability		Walking disability	
	Prednisolone	Naproxin	Prednisolone	Naproxin	Prednisolone	Naproxin
Baseline	62	59	59	55	71	67
After 90 h	17	13	17	13	17	13
Reduction	45	46	42	42	54	54

Outcomes at 90 hours were within the predefined 10% margin of equivalence. “We conclude that prednisolone was clinically equivalent to naproxin in treatment of gout.”

At 3 weeks, all patients reported complete relief of symptoms.

Adverse effects were similar between groups**.**

Conclusion: Although prednisolone and naproxin were equally effective in the initial treatment of gouty arthritis over 4 days, the present study provides a strong argument to consider prednisolone as first treatment option.

In the USA, prednisone would be used, often at a dose of 40 mg daily.

Treatment should begin as soon as possible.

I believe the choice would depend on which drug is immediately available. Prednisone requires a prescription. It could be kept on hand with the doctor’s permission.

HELICOBACTER PYLORI **(See DYSPEPSIA)**

3-11 HELICOBACTER PYLORI TEST AND TREAT VERSUS PROTON PUMP INHIBITOR IN INITIAL MANAGEMENT OF DYSPEPSIA IN PRIMARY CARE

HIP ARTHROPLASTY **(See ANTICOAGULANT THERAPY)**

6-1 RIVAROXABAN (a new inhibitor of activated factor x) VERSUS ENOXAPARIN FOR THROMBOPROPHYLAXIS AFTER HIP ARTHROPLASTY

HOT FLUSHES

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.

HYPERTENSION

.***Six Factors That Reliably Predict Development of Hypertension***

1-3 A RISK SCORE FOR PREDICTING NEAR-TERM INCIDENCE OF HYPERTENSION

The Framingham Heart Study

In 2003, the Seventh Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of Hypertension created a “pre-hypertension” BP category. Prehypertension is defined as: 1) systolic 120-139 or 2) diastolic 80-89.

The committee strongly advocated lifestyle and behavioral modification for individuals with pre-hypertension. This was based on epidemiological observations which indicated that individuals with BP in the pre-hypertension range are at increased risk for progression to overt hypertension.

The Framingham group developed a simple risk score to predict incidence of hypertension based on factors easily determined in the office. Not all individuals with pre-hypertension are at the same near-term risk of developing hypertension.

Scores were based on individual ranges of risk factors:

1) Systolic BP < 110 to 135-139
2) Diastolic BP <70 to 85-90
3) Age 26 to 79
4) BMI < 25 to > 30
5) Parental hypertension.
6) Smoking

Possible scores ranged from -12 to + 28. Risk of developing hypertension over the next few years rises as the risk factor rises.

Primary care clinicians do not need a detailed risk score to inform patients they are at risk of developing hypertension. If the individual's BP is "high normal", his BMI is high, and if he is older, and a smoker with a family history of hypertension, he almost inevitably will become hypertensive within a few years.

This presents a golden opportunity for preventive intervention.

Not Much Difference In Controlling BP

1-5 COMPARATIVE EFFECTIVENESS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS FOR TREATING ESSENTIAL HYPERTENSION

Inhibitors of the renin-angiotensin-aldosterone system are among the most commonly used and effective anti-hypertension agents. Are ACE inhibitors (ACE-i; the "-pril" drugs) and angiotensin II blockers (ATII-b; the "-sartan" drugs) equally effective in reducing BP ?

This systematic review of 61 clinical studies directly compared benefits and harms of ACE-i vs ATII-b used to treat hypertension. Enalapril (generic) was the most commonly ACE-i studied; losartan (*Cozaar*; Merck) the most studied ATII-b.

ACE-i and ATII-b seem to have similar long-term effects on BP in individuals with essential hypertension. Across studies, the modal differences in systolic and diastolic BP was 0, and generally did not exceed 4 mm Hg.

With use of a single agent, about half of the patients achieved successful BP control with either drug.

They exhibited no consistent differential effects on other potential risk factors

Conclusion: ACE-i and ATII-b have similar effects on BP control. ACE-I have higher rates of cough and lower rates of adherence.

Ask first—"Are you taking your medication properly"

2-2 IMPORTANCE OF THERAPY INTENSIFICATION AND MEDICATION NON-ADHERENCE FOR BLOOD PRESSURE CONTROL IN PATIENT WITH CORONARY DISEASE

This retrospective study over 10 000 patients with CAD in a large integrated managed care organization evaluated the impact of medication non-adherence and therapy intensification on reaching BP goals.

BP control was based on serial BP measurements over time. Median follow-up = 5years. The median number on BP measurements per patient was 20.

Determined adherence to 5 different anti-hypertension drugs based on pharmacy records.

Identified 3 groups based on determinations of systolic BP over time:

1) Normal-normal: mean systolic = 126 mm Hg which remained stable over time. (87%)

2) High-normal: mean systolic started at 146 and decreased to 128. (8%)

3) High-high: mean systolic started with systolic at 154 and ended with systolic of 152. (5%)

Compared with the high-normal group, those in the high-high group had:

1) Non-adherence odds ratio = 1.7

2) Therapy intensification odds ratio = 1.3

Compared with the normal-normal group, those in the high-high group had:

1) Non-adherence odds ratio = 1.5

2) Therapy intensification odds ratio = 2.7

Patients with uncontrolled hypertension (high-high group) were more likely to be non-adherent to treatment and to receive intensification of anti-hypertension therapy.

Medication non-adherence may be an explanation for the continuously elevated BP levels despite upward titration of drug dose and addition of another drug.

Conclusion: Medication non-adherence can help explain why BP levels remain high despite intensification of anti-hypertension medications. Successful BP control is seen with a combination of intensification of therapy and adherence. Interventions to enhance medication adherence must be coupled with therapy intensification

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This is a practical clinical application in primary care practice. It applies, not only to patients with CAD, but to all patients with hypertension.

As a knee-jerk reaction for patients who are not achieving target BP levels, we often increase dose or add a second or third drug.

The correct first response is to ask the patients if they are taking their present medication properly. We may even check with the local pharmacy asking about frequency of prescriptions filled.

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.

"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.]

"It Is Not Too Late To Start Antihypertension Therapy"

5-5 TREATMENT OF HYPERTENSION IN PATIENT 80 YEARS OF AGE OR OLDER

Evidence of benefit in treating hypertensive patients 80 years of age and older is inconclusive. It as been suggested that antihypertension therapy may reduce risk of stroke while increasing the risk of death.

This trial aimed to clarify risk and benefits of treatment in the very elderly.

If the mean systolic BP was between 160 and 199, subjects were randomized to:1) Indapamide (*Lozol*; Servier; a diuretic) sustained release 1.5 mg or 2) placebo.

If needed to reach target BP (less than 150/80), perindopril (*Aceon*; an ACE-inhibitor) 2 mg or 4 mg was added.

Main fatal and non-fatal endpoints in the intention to treat population:

	Rate per 1000 person-years	Absolute difference	
		Active	Placebo
All Stroke	12	18	6
Death from stroke	7	11	4
Death			
From any cause	47	60	13
From cardiovascular causes	24	31	7

From cardiac causes	6	8	2
From heart failure	2	3	1
Fatal or non-fatal			
Any myocardial infarction	2	3	1
Any heart failure	5	15	10
Any cardiovascular event	34	51	17

Adverse events: Only 3 in the placebo group and 2 in the treatment group were classified as possibly having been due to the trial medication.

There have been concerns related to the inverse association of death from any cause and BP in the very old, and about the efficacy and safety of antihypertension therapy in this age group. There was speculation that impaired cardiac and renal function, orthostatic hypotension, cognitive impairment, subjective adverse effects, and polypharmacy would detract from the clinical benefit in the very old.

This study puts the question of usefulness of treating hypertension in the very old to rest, and provides important guidance to physicians.

Conclusion: Antihypertension treatment with indapamide, with or without perindopril in persons 80 years or older, is beneficial.

This is an important clinical observation in primary care.

If an elderly patient is diagnosed as hypertensive for the first time, I believe drug therapy should be begun at lower doses than for younger persons. And very gradually increased.

If antihypertension drugs have already been prescribed, first make sure the patient is actually taking the medicating as prescribed. If so, the dose may be very gradually increased, or a second drug added at low dose.

Other risk factors should not be ignored.

"As Populations Age, The Burden Of CVD Attributable To BP Will Be Almost Entirely Related To Systolic Pressure".

6-3 SYSTOLIC PRESSURE IS ALL THAT MATTERS

Systolic hypertension is much more common then diastolic hypertension. Systolic BP contributes more to the huge burden attributable to hypertension than does diastolic.

There has undoubtedly been confusion about the relative merits of targeting systolic versus diastolic. This has led to poor recognition in the wider medical community of the importance of systolic BP.

Systolic rises; and diastolic falls after age 50, at a time when the risk of cardiovascular disease begins to rise.

The author proposes a simplified view of hypertension for most patients—ie, those over age 50—whereby the thresholds for the diagnosis and treatment of hypertension can be expressed in one dimension, systolic pressure. Distilling the risk imparted by high BP into a single number will greatly assist

in both the communication of an important public health message to patients and policy makers, and in simplification of treatment targets.

As populations age, the burden of CVD attributable to BP will be almost entirely related to systolic pressure.

Trials of lowering BP in patients with isolated systolic hypertension have unequivocally confirmed the safety and impressive cardiovascular benefits of lowering systolic BP. But, systolic BP is more difficult to control than diastolic and invariably requires more drug therapy. If the focus of treatment was on systolic, there would hardly ever be a circumstance when diastolic was not controlled.

This approach focuses on individuals over age 50. Among individuals under age 40, as many as 40% with high BP have isolated diastolic hypertension. In patients under age 50, a continued emphasis of both systolic and diastolic remains appropriate. For these younger people, although diastolic should always be controlled, systolic should be the main target. This approach will produce adequate control of diastolic for all but a few patients.

I enjoyed this article. I believe the author makes a good point. Patients have difficulty understanding (and remembering) "systolic" and "diastolic". One number would be more meaningful, more easily remembered, and much more helpful to the patient in following effects of treatment.

The ASH Now Is Calling For Individuals To Routinely Monitor Their BP At Home.

6-6 MANY PHYSICIAN PRACTICES FALL SHORT ON ACCURATE BLOOD PRESSURE MEASUREMENT

At the meeting of the American Society of Hypertension (**ASH**) in May 2008, experts stated, "Blood pressure reading does not seem to be done correctly in any medical clinic." "And yet, the single most important thing physicians do in their medical life is to take an accurate blood pressure measurement.".

"For patients, a proper assessment of blood pressure is more nuanced and time-consuming than they probably experience during most routine physician visits."

The article repeats the standard method of determining BP: (*See the full abstract. RTJ*)

A recent study reported that 14% of physicians and nurses failed to allow patients adequate time to rest. 24% preferred to take the BP with the patient lying on the table; 13% did not take arm level into account; 26% never, or hardly ever used an obese-cuff when necessary, often due to lack of an appropriate cuff.

Only 28% always or almost always took readings properly.

Home BP devices are gaining favor as a diagnostic tool, and to monitor response to therapy.
The ASH now is calling for individuals to routinely monitor their BP at home.

All of us know the recommended procedure, I abstracted the article to refresh memory.
My experience, when visiting my personal physician, correlates with the lack of proper BP recording. The nurse comes into the examining room, usually after I had tried to relax for 5 or more minutes. She then takes my BP while I am sitting. She takes it only once, and pronounces "Your blood pressure is X/Y"

If patients consistently used home BP readings, many primary care physicians would be less likely to worry about proper (ASH recommended) BP recording in the office. This would be a great time-saver.

IRRITABLE BOWEL SYNDROME

Non-Specific Effects Can Produce Clinically Significant Outcomes.

5-1 COMPONENTS OF PLACEBO EFFECT IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Aside from the provision of a specific therapeutic regimen, a medical encounter might elicit non-specific benefits—what are most often called placebo effects.

Such non-specific effects in a clinical setting can be separated into 3 components: 1) a patient's response to observation and assessment only (Hawthorne effect), 2) patient's response to the administration of a therapeutic ritual (placebo treatment alone), and 3) the patient's response to the patient-practitioner interaction added to the placebo.

This randomized, controlled trial of the effect of placebo therapy entered 262 participants with IBS (ROME II criteria). The placebo was sham acupuncture. Patients were completely unaware of the study's primary aim to examine non-specific effects.

Subjects were randomized to:

1) "Waiting list" controlled for effects of assessment and observation (Hawthorne effect), and the natural course of the disease. Subjects received neither placebo nor interaction with the health care provider.
2) "Limited interaction" provided placebo treatment. At the first visit, participants received limited interaction with the investigator (< 5 minutes). Practitioners explained this was a "scientific study" for which they had been instructed not to converse with the patient. The sham needles were placed, and the patient left alone for 20 minutes after which the practitioner returned to "remove the needles".
3) "Augmented interaction" provided 6 sessions of placebo (sham acupuncture) using the same procedures as with group 2. In addition, each week they received an augmented patient-practitioner relationship that began with the first visit (45 minutes) and continued weekly for 6 weeks. Content included questions concerning symptoms, relationships and lifestyles, non-gastrointestinal symptoms, and how the patient understood the "cause" and "meaning" of the condition. The interviewer incorporated a warm, friendly manner; active listening, empathy, and communication of confidence and a positive expectation.

Outcome assessment at week 3:

	Waiting list (n=87)	Limited (n = 88)	Augmented (n = 87)
Global improvement scale (1-7)	3.8	4.3	5.0
% with adequate relief of symptoms	28	44	62
Improved symptom severity score (0-100)	30	42	82
Improved quality of life score (0-12)	3.6	4.1	9.3

Placebo treatment with only limited interaction with practitioners was slightly superior to staying on a waiting list.. A therapeutic ritual alone (limited placebo treatment) has a modest benefit, in some persons, beyond no treatment.

"These results indicate that such factors as warmth, empathy, duration of time spent with the patient, and the communication of positive expectations might significantly affect clinical outcome."

Conclusion: Factors contributing to the placebo effect can be progressively combined in a manner resembling a graded dose escalation of component parts. Non-specific effects can produce statistically and clinically significant outcomes. The patient-practitioner relationship is the most robust component.

How long did the improvement last?

"Augmented" interaction takes time. This is the problem of its use in primary care.

It would have been interesting if the investigators had added a 4th group—"augmented interaction" without the placebo. Would this be just as effective? Also to compare the alleged "placebo" drug with a substance known to be inactive (eg, lactose).

I do not doubt that many interventional procedures given by practitioners of "alternative medicine" do indeed comfort the patient. (Witch doctors have practiced throughout history.) But, I doubt they have altered the outcome of any underlying physical disease. A response to a placebo does not prove that a serious underlying disease does not exist. Nevertheless, there must be some change in the patient's brain associated with the response. We just do not know what it is.,

Patient compliance is also important in determining outcome. Those who are strictly compliant with the treatment, be it placebo or scientifically established as beneficial, will lead to better outcomes than non-compliant patients.

Many people use placebos with no physician input. They purchase "herbal and alternative" remedies which they have read about or which have been recommended by friends.

If a "placebo" is indeed proved to be effective, it should be entered into the practice of scientific medicine, and no longer termed a "placebo". Every effort should be made to determine the pharmacological basis of its benefit.

Primary care clinicians may not object to their patient using a placebo if it is proven not to be harmful. But they should also add their time in active listening, empathy, communication, and emotional support.

When a scientifically proven therapy is available, physicians should strongly advise against use of placebo treatment .There is, however, a placebo component of all the effective drugs we prescribe. This can be a helpful adjunct to our standard therapy. If a patient is receiving maximum therapy from a standard proven therapy, I would not discourage addition of a placebo if the patient believes it helpful and I am absolutely certain that it is harmless.

KIDNEY FUNCTION (See HYPERTENSION)

4-7 DIFFERENCES IN KIDNEY FUNCTION AND INCIDENT HYPERTENSION

MEDICAL HOME

Everyone Needs A "Medical Home"

3-2 COORDINATING CARE—A PERILOUS JOURNEY THROUGH THE HEALTH CARE SYSTEM

In the USA, 125 million people are living with chronic illness, disability, or functional limitations. These patients receive care from a number of different providers.

Care among multiple providers must be coordinated to avoid polypharmacy, wasteful duplication of diagnostic testing, and confusion about conflicting care plans. Care must be coordinated among primary care physicians, specialists, diagnostic centers, pharmacies, home care agencies, acute care hospitals, skilled nursing facilities, and emergency departments.

Coordination is also required between providers and patients and their families.

Failures in the coordination of care are common.

This report assesses the quality of care coordination, lists barriers to coordinated care, and discusses some solutions to improve care coordination.

Care coordination is virtually impossible without a strong primary care foundation to the health care system. "This foundation may be crumbling." With large patient panels, and a growing number of tasks to be performed, PCPs can no longer provide high-quality short-term, long-term, and preventive care in a 15-minute consultation, let alone perform care-coordinating functions for which they are not reimbursed.

The patient-centered "medical home"[1] has become a prominent concept in health care reform. It envisions a medical practice that is based on: first-contact care, continuity of care over time, comprehensiveness, and responsibility to coordinate care throughout the healthcare system. The medical home is expected to contain health costs by reducing unnecessary hospital admissions and emergency department visits.

The article comments on a "Teamlet" Model to address the inadequacy of the 15-minute visit. It changes the care provider from the lone physician to a two-person (or more) team for patients needing support for self-management of long-term care. It provides care coordination by extending the 15-minute visit into care that is provided apart from the visit. With a two-person team that works together every day, the disadvantages of larger teams which require multiple person-to-person interactions is minimized.

The non-physician team member (a "coach") would ideally be a registered nurse or an advanced-practice clinician. The coach handles care before, after, and between visits, and may accompany the physician during the visit. The coach also assists with paperwork and authorizations, and can help patients obtain necessary tests and appointments. Using reminder systems and check lists, the coach makes sure that consultation reports come back from specialists and that results are transmitted to patients.

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1 *See the full abstract for a statement from the ACP "Principles of the Patient-Centered Medical Home"*

I believe providing a Medical Home to all Americans would be a big step forward in solving our health-care problems. It would enable patients to access health care at an earlier stage of illness and enable greater reductions in risk factors. It would reduce hospitalizations and visits to the Emergency Department. The resultant lower costs would allow more patients to receive health care insurance.

I believe the added time and contact with the patient will allow the" coach" to educate patients and encourage adoption of health lifestyles. Patients must do their part in maintaining healthy life-styles.

They should also be encouraged to inform the physician's team about any out-of-the practice care and mediations they receive.

MEDITERRANEAN DIET

6-7 ADHERENCE TO MEDITERRANEAN DIET AND RISK OF DEVELOPING DIABETES

(See DIABETES)

MENOPAUSE

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.

MYOCARDIAL INFARCTION

A Clustering Of Adverse Events During The 90 Days After Cessation Of Clopidogrel

2-9 INCIDENCE OF DEATH AND ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH STOPPING CLOPIDOGREL AFTER ACUTE CORONARY SYNDROME.

It has been hypothesized that withdrawal of clopidogrel (*Plavix*) may be associated with a "rebound effect"—an increase in adverse events after cessation of the drug. This may be due to a transient hyperthrombotic state.

This study assessed the incidence of death and acute myocardial infarction (**AMI**) after stopping treatment.

Retrospective cohort study of over 3000 patients (mean age 67) with ACS who were treated with post-hospital clopidogrel therapy. About half had received medical therapy; half PCI

Relative risk (RR) of death or AMI within 90 days of discontinuation was higher than risk within 91 to 180 days.

A. Medically treated patients (n= 1568) who stopped clopidogrel during follow-up:

Death or AMI = 17% (n = 263)

Death or AMI during 0 to 90 days after stopping clopidogrel = 61%

Death or AMI during 91 to 180 days = 21%

Death or AMI during 181 to 220 days = 10%

B. PCI treated patients with stents (n = 1569) who stopped clopidogrel during follow-up:

Death or AMI = 8% (n = 119)

Death or AMI during 0 to 90 days after stopping clopidogrel = 59%

Death or AMI during 91 to 180 days = 24%

Death or AMI during 181 to 270 days = 7%

These findings support the hypothesis of a rebound hyper-thrombotic period after stopping the drug.

The magnitude of risk in the initial 90 days was consistent regardless of whether the patients took clopidogrel for 3, 6, 9, or more than 9 months. The association is likely independent of treatment duration.

Even though absolute event rates were low, the relative increase in adverse events in the early period after cessation was nearly 2-fold higher than later periods. Considering the number of patients using clopidogrel, risks are significant when extrapolated to the population of users.

Conclusion: There was s clustering of death and acute myocardial infarctions in the 90 days after withdrawal of clopidogrel therapy.

I wondered if this study would be of interest to primary care.

Some primary care clinicians do follow ACS patients after being discharged by the cardiologist.

Although benefit is not confirmed, it would seem reasonable to taper clopidogrel for a longer period, perhaps up to one year.

Carotid Bruit Significantly Associated With Increased Likelihood Of Cardiovascular Death

5-6 CAROTID BRUITS AS A PROGNOSTIC INDICATOR OF CARDIOVASCULAR DEATH AND MYOCARDIAL INFARCTION

Clinical trials have shown benefit from carotid endarterectomy for *symptomatic* patients with severe (70-99%) carotid stenosis. However, a carotid bruit is a weak predictor of cerebrovascular events in patients who are otherwise asymptomatic for cerebrovascular conditions.

The uncertainty about prognostic implications has led the USPSTF to recommend against routine auscultation for carotid bruits.

This meta-analysis was based on a literature search which included over 17 000 patients followed up to 4 years. All studies (mostly prospective cohort studies) reported incidence of MI and cardiovascular death in adults. Median range = age 65.

All studies had extractable data for cardiovascular outcomes in individuals with carotid bruits.

Eight studies assessed MI in patients with bruits. The pooled estimate of myocardial infarction was 3.7 per 100 patient –years. In 16 studies assessing cardiovascular death, the pooled estimate of yearly deaths was 2.9 per 100 patient-years. In patients without bruits the rate was 1.1 per 100 patient-years.

“Our study has shown that the presence of a carotid bruit significantly increased the likelihood of cardiovascular death or myocardial infarction .” Cardiovascular death or MI were twice as likely in patients with bruits compared to those without.

The presence of a carotid bruit per se is not an independent risk factor of coronary disease, rather, its presence identifies a subgroup that is at high risk of having similar pathological changes in the coronary arteries. Carotid bruit is only a marker of risk to add to many other risk factors. The incremental value of a bruit is not known.

Conclusion: Auscultation for carotid bruit in patients at risk for heart disease could help select those who might benefit the most from aggressive modification strategy for cardiovascular risk.

I believe many primary care clinicians do listen for carotid bruits in elderly patients and in other patients at high risk.

If the patient has no cerebrovascular symptoms, I would not alarm the patient by mentioning the possibility of TIA and stroke unless other risk factors were present. If symptoms are present, urgent consultation is required.

The presence of a carotid bruit may be associated with increased risk. But, it is not known how much, or whether it is an independent risk factor.

If present in the absence of any other risk factors, I doubt if it indicates increased risk of coronary disease. If other risk factors are present, advice for reduction of all risk factors may be intensified.

NEPHROPATHY

Appears To Have A Reno-Protective Effect That Is Independent Of Its BP-Lowering Effect

6-8 ALISKIREN COMBINED WITH LOSARTAN IN TYPE-2 DIABETES AND NEPHROPATHY

Aliskiren directly inhibits production of renin by the kidney, thereby lowering production of angiotensin and aldosterone.

A reduction in proteinuria has been widely used as a surrogate end point for renoprotection.

This study evaluated the renoprotective effects of aliskirin by adding it to treatment with the maximum recommended dose (100 mg/d) of the angiotensin II blocker losartan (*Cozaar*; Merck), and with optimal antihypertension therapy in patients who had hypertension and type-2 diabetes with nephropathy.

Multinational, double-blind trial enrolled 599 patients (mean age 60). All had type-2 diabetes and nephropathy (defined as an early-morning urinary albumin/creatinine ratio of greater than 300 mg per gram). None had an estimated glomerular filtration rate of less than 30 mL per minute per 1.73 m^2 of body-surface area, serum potassium greater that 5.1 mmol/L, or major cardiovascular disease. Mean urinary albumin excretion rate = 500 ug/min. Baseline BP = 135/78

After a 3-month open-label run-in period during which all patients received 100 mg losartan daily, patients were randomized to:

1) Aliskiren 150 mg daily for 3 months followed by 300 mg daily for another 3 months + losartan. (300 mg is the optimum dose for treatment of hypertension..)
2) Placebo + losartan.
3) All patients continued to take other antihypertension drugs aimed at maximal recommended renoprotective dose (target BP < 130/80), except for other drugs blocking the renin-angiotensin-aldosterone system.

By 6 months treatment with aliskiren, the mean albumin/creatinine ratio was reduced by 20% as compared with placebo. A reduction of 50% or more was seen in 25% of aliskiren patients as compared with 13% in the placebo group. The overnight urinary albumin was reduced by a mean of 18% in the aliskiren group compared with placebo.

Adverse events: overall, no difference between groups. The rate of serious adverse events was similar—9%. Hyperkalemia occurred in 5% vs 5.7% of patients.

The benefit of aliskiren appeared to be independent of the small reduction in BP (2/1 mm Hg).

Conclusion: Aliskiren appears to have a reno-protective effect that is independent of its BP-lowering effect in patients with type-2 diabetes who are receiving maximally recommended reno-protective treatment and optimal antihypertension treatment.

Aliskiren (Tektura; Novartis) is approved by the FDA (2007) for treatment of hypertension. Starting dose is 150 mg/d. This is the first time I have abstracted an article abut it.

I believe aliskiren for renal protections is not a practical point for primary care at this time. I would not use the drug for treatment of hypertension until more time passes to evaluate general use.

OBESITY

2-7 BODY-MASS INDEX AND INCIDENCE OF CANCER (See BODY MASS INDEX)

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.

OSTEOARTHRITIS

"No Better Than Placebo"

2-8 EFFECT OF GLUCOSAMINE ON HIP OSTEOARTHRITIS

This 2-year randomized, placebo-controlled trial compared GS with placebo to evaluate effect on symptomatic and radiographic progression of osteoarthritis (**OA**) of the hip.

Entered 222 patients with OA of the hip recruited from general practices in the Netherlands. Patients were representative of those using O-T-C glucosamine. (**GS**)

Randomized to: 1) GS 1500 mg (2-750 mg pills given once daily), or 2) placebo.

Primary outcomes (intention-to-treat):

A. Western Ontario and McMaster Universities (WOMAC) pain and function subscales over 2 years. Scores on these subscales range from 0 to 100. 0 = no symptoms.

B. Joint space narrowing by X-ray after 2 years.

Change from baseline on WOMAC scale (0 to 100) at 2years:

	Placebo	GS	Difference favoring GS
Pain overall	-0.30	-1.90	1.60
Function overall	+0.38	-1.69	2.07
Stiffness	-2.19	-3.43	1.24

(Slightly favoring GS. Neither statistically nor clinically significant.)

Joint space narrowing did not differ between groups at 2 years.

Conclusion: "Glucosamine sulfate was no better than placebo in reducing symptoms and progression of hip osteoarthritis."

Does the fact that glucosamine has remained a popular O-T-C- preparation for years mean that it is effective? I do not think so.

Does the lack of studies reporting definitive outcomes mean that glucosamine is not effective? I do not think so.

I believe we may conclude that benefits of GS, if any, are small. And that there is a large placebo effect.

How should we respond when patients ask about glucosamine? I would not prescribe it. I would not advise patients to avoid it. If the patient experiences relief, fine—even though it may be a placebo effect. I would not deny a patient the benefit of a placebo.

It would have been meaningful if the investigation had included a no-treatment group (GS vs placebo vs no-treatment).

OSTEOPOROSIS

Should Perimenopausal Women Begin To Take Anti-Resorptive Drug Therapy?

1-4 DRUGS FOR PRE-OSTEOPOROSIS; *Prevention or Disease Mongering?*

Now, the size of the osteoporosis drug market seems set to greatly expand, as the push begins to treat women with pre-osteoporosis (osteopenia). Treatment is being encouraged in younger post-menopausal women who are at relatively low risk of fracture.

The author of this commentary believes it is not certain that the risk of fracture warrants drug treatment, given the limited power of osteopenia to predict fracture risk, and the appropriate role of bone mineral density (**BMD**) in guiding prevention. He examined the evidence from previous analyses of trials of osteoporosis drugs and found the evidence of the benefits and harms wanting.

"Against the backdrop of controversy and uncertainty, current attempts to promote drug therapies to people with osteopenia warrant skepticism."

"We need to ask whether the coming wave of marketing targeting those women with pre-osteoporosis will result in the sound, effective prevention of fracture, or the unnecessary and wasteful treatment of millions of more healthy women."

I would reserve judgment on this issue. It seems reasonable to me that earlier and continuing prophylactic treatment of osteoporosis (beginning at the peri-menopause when accelerated bone loss and osteopenia begins) would lower risk of fracture in old age.

Osteoporosis-related fractures are a major cause of disability in the elderly. Should it not be prevented rather than waiting it to develop before treating it? We do not wait for patients to develop type-2 diabetes or hypertension, we begin to treat in the pre-diabetes and pre-hypertension stage.

The benefit/harm-cost ratio of long-term prophylactic treatment may be high. The main unknown factor is harm. Risk of adverse effects of decades-long bisphosphonate therapy are not known. There is some indication that the risk of important adverse effects may be low. A study abstracted by Practical Pointers in December 2006 [12-7] compared: 1) alendronate given for a total of 10 years vs 2) alendronate given for 5 years followed by 5 years of no-drug. Continuing alendronate for a total of 10 years was more effective in maintaining bone mineral density, reducing bone remodeling, and lowering risk of facture. The study reported no difference in toxicity between groups.

Certainly, because of very low toxicity, vitamin D (in larger doses) and calcium supplementation are now welcome as preventive therapy, beginning at an early age. I believe that general agreement that calcium and vitamin D may be given over a long period to prevent osteoporotic fractures depends on the perceived high benefit/harm-cost ratio. Harms are nil. Cost is low.

I believe that in the future, and as they perceive the likelihood of reaching old age will increase, perimenopausal women will opt for earlier preventive therapy.

"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.

PATIENT-IMPORTANT OUTCOMES

Only 18% Of Trials Included Patient-Important Outcomes As Primary Outcomes.

6-2 PATIENT-IMPORTANT OUTCOMES IN REGISTERED DIABETES TRIALS.

Trials measuring biochemical and surrogate markers may help researchers understand how, and to what extent, interventions could affect health. The value of these interventions remains unclear until trials test their effect on outcomes that are important to patients..

This review selected 436 RCTs which enrolled patient with type-2 diabetes.

Determined the outcomes measured, and their type (physiological outcomes, surrogate outcomes thought to reflect an increased risk for patient-important outcomes, and patient-important outcomes).

Patient –important outcomes: death and quality-of-life (stroke, myocardial infarction, amputation, loss of vision, end-stage renal disease). And other morbid events such as hypoglycemia, delayed wound healing, infection, visual disturbances, pain, and functional status.

Surrogate outcomes: intermediate endpoints that may indicate disease progression and increased risk for patient-important outcomes (eg, HbA1c, cholesterol, worsening renal function).

Physiological and laboratory outcomes: response to maneuvers without direct tangible effects on patients (eg, insulin levels).

Primary outcomes of 436 trials:

Patient-important outcomes	18%
Physiological and laboratory outcomes	16%
Surrogate outcomes	61%

Conclusion: Only 18% of RCTs in diabetes measured outcomes important to patients as primary end points.

This is important to primary care, not only for diabetes, but also for many other diseases.

Surrogate outcomes are risk factors. Primary care clinicians depend on them.

Treatment of a surrogate outcome will depend on the primary care clinician's judgment of the benefit/harm-cost ratio of the intervention. And the individual patient's preference, after being fully informed.

Improving some surrogate outcomes will likely be associated with a high probability of reducing risk. Some will seem inconsequential. Clinicians should be able to provide the individual patient with some idea of the degree of possible benefits and harms of interventions. Life-style interventions take priority.

The individual patient's choice depends on many factors:

Cost.

Willingness to accept risk of some degree of harm from the intervention in order to obtain indefinite benefit in the future.

Ability and willingness to continue treatment long-term.

Willingness to accept ongoing monitoring of the effects of treatment.

PHYSICAL FITNESS

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.

PLACEBO

Non-Specific Effects Can Produce Clinically Significant Outcomes.

5-1 COMPONENTS OF PLACEBO EFFECT IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

Aside from the provision of a specific therapeutic regimen, a medical encounter might elicit non-specific benefits—what are most often called placebo effects.

Such non-specific effects in a clinical setting can be separated into 3 components: 1) a patient's response to observation and assessment only (Hawthorne effect), 2) patient's response to the administration of a therapeutic ritual (placebo treatment alone), and 3) the patient's response to the patient-practitioner interaction added to the placebo.

This randomized, controlled trial of the effect of placebo therapy entered 262 participants with IBS (ROME II criteria). The placebo was sham acupuncture. Patients were completely unaware of the study's primary aim to examine non-specific effects.

Subjects were randomized to:

1) "Waiting list" controlled for effects of assessment and observation (Hawthorne effect), and the natural course of the disease. Subjects received neither placebo nor interaction with the health care provider.
2) "Limited interaction" provided placebo treatment. At the first visit, participants received limited interaction with the investigator (< 5 minutes). Practitioners explained this was a "scientific study" for which they had been instructed not to converse with the patient. The sham needles were placed, and the patient left alone for 20 minutes after which the practitioner returned to "remove the needles".
3) "Augmented interaction" provided 6 sessions of placebo (sham acupuncture) using the same

procedures as with group 2. In addition, each week they received an augmented patient-practitioner relationship that began with the first visit (45 minutes) and continued weekly for 6 weeks. Content included questions concerning symptoms, relationships and lifestyles, non-gastrointestinal symptoms, and how the patient understood the "cause" and "meaning" of the condition. The interviewer incorporated a warm, friendly manner; active listening, empathy, and communication of confidence and a positive expectation.

Outcome assessment at week 3:

	Waiting list (n=87)	Limited (n = 88)	Augmented (n = 87)
Global improvement scale (1-7)	3.8	4.3	5.0
% with adequate relief of symptoms	28	44	62
Improved symptom severity score (0-100)	30	42	82
Improved quality of life score (0-12)	3.6	4.1	9.3

Placebo treatment with only limited interaction with practitioners was slightly superior to staying on a waiting list.. A therapeutic ritual alone (limited placebo treatment) has a modest benefit, in some persons, beyond no treatment.

"These results indicate that such factors as warmth, empathy, duration of time spent with the patient, and the communication of positive expectations might significantly affect clinical outcome."

Conclusion: Factors contributing to the placebo effect can be progressively combined in a manner resembling a graded dose escalation of component parts. Non-specific effects can produce statistically and clinically significant outcomes. The patient-practitioner relationship is the most robust component.

How long did the improvement last?

"Augmented" interaction takes time. This is the problem of its use in primary care.

It would have been interesting if the investigators had added a 4th group—"augmented interaction" without the placebo. Would this be just as effective? Also to compare the alleged "placebo" drug with a substance known to be inactive (eg, lactose).

I do not doubt that many interventional procedures given by practitioners of "alternative medicine" do indeed comfort the patient. (Witch doctors have practiced throughout history.) But, I doubt they have altered the outcome of any underlying physical disease. A response to a placebo does not prove that a serious underlying disease does not exist. Nevertheless, there must be some change in the patient's brain associated with the response. We just do not know what it is.,

Patient compliance is also important in determining outcome. Those who are strictly compliant with the treatment, be it placebo or scientifically established as beneficial, will lead to better outcomes than non-compliant patients.

Many people use placebos with no physician input. They purchase "herbal and alternative" remedies which they have read about or which have been recommended by friends.

If a "placebo" is indeed proved to be effective, it should be entered into the practice of scientific medicine, and no longer termed a "placebo". Every effort should be made to determine the pharmacological basis of its benefit.

Primary care clinicians may not object to their patient using a placebo if it is proven not to be harmful. But they should also add their time in active listening, empathy, communication, and emotional support.

When a scientifically proven therapy is available, physicians should strongly advise against use of placebo treatment .There is, however, a placebo component of all the effective drugs we prescribe. This can be a helpful adjunct to our standard therapy. If a patient is receiving maximum therapy from a standard proven therapy, I would not discourage addition of a placebo if the patient believes it helpful and I am absolutely certain that it is harmless.

PNEUMONIA

Empirical Antimicrobial Therapy Is The Cornerstone of C-AP Treatment.

2-3 COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (**C-AP**) is common in elderly patients—annually about 2 per 100 in persons over age 65.

Most are treated as outpatients. In patients suitable for outpatient treatment, mortality is less than 1%. The remaining patients require in-hospital treatment. In those admitted to intensive care units mortality is up to 36%.

Streptococcus pneumoniae is the most common pathogen implicated in C-AP. In hospitalized patients with C-AP, it accounts for about 2/3 of all deaths.

Other bacterial causes include: *Haemophilus influenzae* and *Morxaella catarrhalis* in patients with underlying lung disease; and the so-called atypical pathogens, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella* spp, which are present in about ¼ of C-AP episodes.

Viral pathogens are increasingly recognized as causes of C-AP. Influenza is the leading pathogen.

The editorialist addresses 4 important new additions or changes in management suggested in the most recent guidelines:

1) New diagnostic techniques to make an etiological diagnosis. Tests for antigens of *S pneumoniae* and *Legionella* in urine are easily collected. Results are obtained rapidly and are not affected by prior antibiotic use.
2) A simple predication rule to gauge severity of the C-AP and risk of death
3) Time to antibiotic administration. Suggested to begin in the emergency department.
4) Duration of antibiotic therapy.

I enjoyed this commentary. It packed a lot of information in a few pages. Consult the full abstract for details.

The Johns Hopkins antibiotic guide (www.hopkins-abxguide.org) as of June 2007 suggests 6 antibiotics for empiric outpatient treatment of uncomplicated C-AP. Primary care clinicians must choose. Which one? Amoxicillin is often considered the drug of choice for oral treatment of S pneumoniae, even in the era of escalating penicillin resistance. Since S pneumoniae is the most common cause, would it not be a suitable first choice?

6-9 RECENT CHANGES IN THE MANAGEMENT OF COMMUNITY ACQUIRED PNEUMONIA IN ADULTS

This review article considers:

How is community acquired pneumonia (**CAP**) diagnosed?

What organisms cause CAP?

How has etiology of CAP changed?

Community acquired methicillin resistant staphylococcus aureus. (MRSA)

Which antibiotics should be used for CAP treated in the community?

How quickly should we give antibiotics?

Length of treatment

Severity scores

Please consult the full abstract for useful clinical points.

PRESCRIBING FOR OLDER PEOPLE

Dose, Formulation, And Delivery Need To Be Adjusted According To The Age And Frailty Of The Patient

3-8 PRESCRIBING FOR OLDER PEOPLE

This review highlights some of the difficulties in prescribing for older patients and offers guidance to appropriate prescribing.

Increasing age is associated with changes in pharmacokinetics and pharmacodynamics. Prescribing for elderly patients presents many challenges.

Older patients are often prescribed unnecessary drugs; drugs that are contraindicated in their age group; and are given the wrong dose. They may be given drugs without a specific indication, and lacking an evidence base.

The article includes a discussion of:

Physiological changes occurring with aging

Multiple pathology and polypharmacy in the elderly

Inappropriate prescribing for the elderly

Drugs that pose a particular risk in the elderly

Some guidelines for good prescribing in the elderly:

Regular medication review

Prescribe new drugs that have a clear indication

Try to avoid drugs that pose a particular risk

Use the doses recommended for elderly patients

Use simple drug regimens and appropriate administration systems

Limit authorization for repeat prescriptions

Consider once daily formulations

Limit number of physicians who prescribe for the patient

Avoid treating adverse effects of drugs with other drugs

Enlist pharmacist's help. They have an important role in spotting adverse drug reactions and interactions

Follow the development of electronic prescribing. E-prescribing may reduce errors and improve patient care

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This is an important clinical consideration for primary care.

I noted in a random review of the PDR, that many manufacturers (but far from all) mentioned reduced-dose recommendations for the elderly. I believe many times even these reduced doses may be too high. For long-term medications prescribed for the elderly (eg, for hypertension) I believe we can start with a lower than recommended doses. This may require a pill cutter.

Then, gradually raise the dose to a modest level. This may be acceptable and provide the desired response.

If the elderly patient then requires a still higher dose, we must choose between raising the dose above the modest level or adding a second drug. I believe adding a second drug would generally be preferable because adverse effects are more likely with higher doses of a single drug than with lower doses of two drugs.

The December 2007 issue of Practical Pointers reported a study of the adverse drug effects seen most commonly in the emergency department. These were not age-limited, but would likely be encountered in the elderly.

Anticoagulants and antiplatelet agents: warfarin, aspirin, and clopidogrel

Antidiabetes agents: insulin, metformin, glyburide, glipizide

Narrow therapeutic index agents: digoxin, phenytoin

PROGESTERONE (See BREAST CANCER)

2-5 ESTROGEN PLUS PROGESTIN AND BREAST CANCER DETECTION BY MEANS OF MAMMOGRAPHY AND BREAST BIOPSY

PRIMARY CARE (See MEDICAL HOME)

3-2 COORDINATING CARE—A PERILOUS JOURNEY THROUGH THE HEALTH CARE SYSTEM

PROTON PUMP INHIBITOR (See DYSPEPSIA)

3-11 HELICOBACTER PYLORI TEST AND TREAT VERSUS PROTON PUMP INHIBITOR IN INITIAL MANAGEMENT OF DYSPEPSIA IN PRIMARY CARE

RAMIPRIL (See CARDIOVASCULAR DISEASE)

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

RENAL DISEASE

Achieved Similar Reductions In Proteinuria, Regardless Of The Degree Of Proteinuria.

1-6 EFFECT OF MONOTHERAPY AND COMBINATION THERAPY WITH INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM ON PROTEINURIA IN RENAL DISEASE

This meta-analysis of 49 studies, (6000 subjects) considers the relative effect of angiotensin-converting enzymes(ACE-inhibitors (**ACE-i**) and angiotensin II blockers (**ATII-b**), and their combined administration, on reducing micro-albuminuria and proteinuria in patients with kidney disease.

Studies compared:

ATII-b vs placebo

ATII-b vs calcium blocker

ATII-b vs ACE-i

Combination ACE-i and ATII-b vs ATII-b alone

Combination ACE-i and ATII-b vs ACE-i alone

Both drugs lowered protein excretion by about 1/3, with no difference between them.

Combined ACE-i + ATII-b vs ATII-b alone had an additional impact, reducing proteinuria by another 25% beyond that of ATII-b alone.

The benefit was not dependent on lowering of BP.

Despite the findings, the inferences that patients with proteinuria will benefit from combination therapy with ACE-I and ATII-b is not certain.

Combination therapy carries a great potential for toxicity, especially hyperkalemia.

Conclusion: In patients with micro-albuminuria and proteinuria regardless of the type of renal disease. mono-therapy with ACE-i or ATII-b achieved similar reductions in proteinuria, regardless of the degree of proteinuria. Combination therapy may be more effective.

Admittedly a secondary outcome measure. Long-term use must be assessed to determine clinical benefits such as delay in renal failure.

I believe primary care clinicians must use extreme caution if they use combined therapy. It may be best to defer to a renal specialist with more experience.

RIVAROXABAN (See ANTICOAGULANT THERAPY)

6-1 RIVAROXABAN (a new inhibitor of activated factor x) VERSUS ENOXAPARIN FOR THROMBOPROPHYLAXIS AFTER HIP ARTHROPLASTY

SINUSITIS

Common Clinical Signs And Symptoms Cannot Identify Patients With Sinusitis For Whom Treatment With Antibiotics Is Clearly Justified

3-3 ANTIBIOTICS FOR ADULTS WITH CLINICALLY DIAGNOSED ACUTE RHINO-SINUSITIS

This meta-analysis assessed whether common signs and symptoms could be used to identify a subgroup of patients with sinusitis who would benefit from antibiotics.

The study included 9 trials (over 2500 persons) in which adults with rhino-sinusitis-like complaints were randomly assigned to antibiotic treatment or placebo. Assessed overall effect of antibiotic treatment (mainly amoxicillin) and the prognostic value of common signs and symptoms by the number needed-to-treat with antibiotics to cure one additional person.

Excluded trials in which patients were recruited partly on the basis of results of imaging or laboratory tests or bacterial culture because in the primary care setting such methods are not routinely used or recommended.

The mean number needed-to-treat (NNT) with antibiotics to cure one patient = 15.

The NNT for patients with purulent discharge in the pharynx to cure one = 8.

For other patient-reported symptoms—a previous cold (or two stages of illness), pain on bending, unilateral face pain, and pain in the teeth—estimates were not precise enough to draw any conclusions about their prognostic value other than that these symptoms might not be reliable enough to be of any value.

The implication for primary care is that antibiotics offer little benefit for patients with acute rhino-sinusitis-like complaints.

Conclusion: Common signs and symptoms cannot identify a subgroup for which antibiotic treatment is clearly justified.

This study did not help me to decide when to prescribe antibiotics. Certainly symptomatic therapy will be prescribed.

When is the NNT low enough to justify antibiotics—eight? fifteen?

If X-ray is available and is positive for sinusitis would this tilt toward antibiotic treatment?

I believe primary care clinicians make judgments partially based on how sick and miserable the patient appears.

The "delayed" prescription may be applicable in some cases. Give the patient a prescription and tell him not to have it filled or take it unless within a week he feels much worse or is not getting better.

SOFT DRINKS (See GOUT)

2-4 SOFT DRINKS, FRUCTOSE CONSUMPTION, AND THE RISK OF GOUT IN MEN

SPINAL STENOSIS

Surgery Showed Significantly More Improvement In Pain, Function, and Satisfaction,

2-6 SURGICAL VERSUS NON-SURGICAL THERAPY FOR LUMBAR SPINAL STENOSIS

This study assessed the 2-year outcomes of patients with spinal stenosis (without degenerative spodylolisthesis) between patients undergoing surgery vs those treated non-surgically.

The original design of the study included: 1) a group (n = 289) randomized to surgery (posterior decompression) vs no-surgery, and 2) a group (n = 365) enrolled in an observational cohort. There was a large cross-over to surgery. At 2 years, 43% of those originally assigned to receive no-surgery underwent surgery. Because of this high cross-over to surgery by individuals in the no-surgery groups, the as-treated analysis was the main outcome measure.

Both cohorts combined (as treated):

Roughly, 400 patients in the two cohorts combined received surgery at some point; and 250 received no-surgery.

At 2 years, on the SF-35 0 to 100 scale, the mean improvement in bodily pain and physical function in the surgery cohort vs the no-surgery group was modest (about 10-12 points)

The final SF-36 score for the surgery group was considerably below the present normal scores adjusted for age and sex.

Conclusion: In the as-treated analysis, when the randomized and observational cohorts were combined, patients who underwent surgery showed significantly more improvement in pain, function, satisfaction, and self-rated progress than did patients who were treated non-surgically.

The large cross-over to surgery would indicate that these subjects were very uncomfortable, and would be willing to undergo major surgery to obtain relief. Relief was modest. Certainly no panacea.

STATIN DRUGS

Statin Therapy Should Be Considered For All Diabetic Individuals.

1-1 EFFICACY OF CHOLESTEROL-LOWERING IN 18 686 PEOPLE WITH DIABETES IN 14 RANDOMIZED TRIALS OF STATINS

This study included data from randomized statin drug trials in over 18 000 individuals with diabetes (92% type-2) in the context of over 71 000 persons without diabetes.

Estimated effects on clinical outcomes per 1.0 mmol/L (38 mg/dL) decrease in LDL-c over a mean period of 4 years.

Events per 1 mmol/L (38 mg/dL) reduction in LDL-c at one year in patients with diabetes:

	Statin treatment (%)	Control (%) [No statin]	Absolute difference(%)	NNT

All cause death	11.0	11.9	0.9	100
Major coronary even	8.3	10.5	2.2	50
Stroke	4.4	5.4	1.0	100
Major vascular event	15.6	19.2	3.6	28

Overall there was a 10% proportional reduction in major vascular events in year 1, followed by reduction around 20-30% in successive years. The reductions were similar in subjects without diabetes as well as those with diabetes.

In the subgroups with known vascular disease, the absolute benefit of a statin was larger than in those without known vascular disease.

Statin therapy safely reduces the 5-year incidence of major coronary events, coronary revascularization, and stroke by about a fifth for each mmol/L reduction (38 mg/dL) in LDL-cholesterol, largely irrespective of initial lipid profile or other baseline characteristics.

Standard doses of statins reduce LDL-c by about 40%. This translates into a reduction of at least 1.5 mmol/L (57 mg) for many people. Such a reduction would prevent about one third of patients from having a major vascular event. A generic statin regimen producing a mean reduction of about one mmol/L in LDL-c is cost effective.

The proportional benefit of statin therapy was largely independent of pre-treatment levels of LDL-c, HDL-c, and triglycerides, without any lower threshold below which benefit was absent.

Conclusion: : Statin therapy should be considered for all diabetic individuals.

STROKE

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.

TELMISARTAN

TELMISARTAN; An angiotensin II blocker (See CARDIOVASCULAR DISEASE)

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

TESTOSTERONE

No Benefit Over 6 Months

1-8 EFFECT OF TESTOSTERONE SUPPLEMENTATION OF FUNCTIONAL MOBILITY, COGNITION, AND OTHER PARAMETERS IN OLDER MEN

This randomized trial asked—Does testosterone supplementation benefit older men with low normal testosterone levels?

Double-blind, placebo-controlled randomized trial followed 207 men ages 60 to 80 (mean = 67) to completion of the study. All were generally healthy. All had low testosterone level (under 14 nmol/L; mean = 11). This level was below the 50^{th} percentile of the study population.

Randomized for 6 months to: 1) Testosterone undeceonate 80 mg twice daily by mouth, or 2) Placebo.

There were no differences between groups in functional mobility, muscle strength, cognitive function, bone mineral density. There was no improvement in quality-of-life.

Total body fat decreased in the testosterone group. Total lean body mass increased.

Conclusion: Testosterone supplementation for 6 months to older men with low-normal levels did not affect functional status, or cognition. It increased lean body mass and had mixed metabolic effects.

THYROID DISEASE

T4 Adequately Replaces Serum T3 Levels In Most Patients

2-10 THYROXINE MONOTHERAPY AFTER THYROIDECTOMY

Given the complex regulation of T4 conversion to T3,. it is theoretically possible that replacement therapy with pure T4 may not precisely reduplicate a thyroid hormone milieu that involves two hormones, not one. There had been lingering doubt about whether the serum T3 levels that are attained with T4 therapy are truly normal for the individual patient.

The controversy surrounding thyroid hormone therapy stems, in part, from important aspects of normal thyroid physiology. It is T3, rather than T4 that mediates thyroid hormone action by binding to nuclear thyroid hormone receptors in virtually all tissues. Serum T3 has 2 sources: 1) About 20% comes directly from the thyroid, 2) the other 80% is derived from the mono-deiodination of T4 in peripheral tissues which activates T3. Thus, T4 acts as a pro-hormone for T3. T4 has essentially no intrinsic biological activity of its own.

In a study in the February 20, 2008 issue of JAMA, of patients who underwent total thyroidectomy, replacement T4 given to maintain normal TSH levels, resulted in normal T3 levels in almost all subjects. But, in a few patients, T3 levels, for whatever reason, were lower postoperatively than preoperatively despite normal TSH levels.

The data presented by the study “seems to lay to rest, once and for all, the notion that T4 therapy alone is inadequate to replace serum T3 levels back to normal in the overwhelming majority of patients”.

There may be an occasional patient who does not achieve normal T3 levels when T4 supplementation is adequate. It would be simple to substitute T4 + T3 therapy in these patients as an
n = 1 trial in patients with hypothyroidism who do not attain normal T3 levels despite normalization of TSH, and to those who do not achieve adequate symptoms control.

VITAMIN D

A Clinical Benefit in Reducing Risk Of Falls In A Group Of Elderly Women At High Risk For Falls.

1-7 EFFECTS OF ERGOCALCIFEROL (VITAMIN D2) ADDED TO CALCIUM ON THE RISKS OF FALLS IN ELDERLY HIGH-RISK WOMEN

This double-blind, population-based randomized controlled trial followed over 300 community-dwelling women age 70-90 (mean = 77) living in Perth Australia. All had sustained a fall in the previous year.

All had a serum 25-hyroxy-vitamin D concentration under 24 ng/ml (considered low).

Randomized to: 1) Vitamin D2 1000 IU daily + 1000 mg calcium citrate daily, or 2) Placebo + calcium

Determined rate of falling over the subsequent year.

Overall risk of having a fall:

Treatment group 53%

Control 63%

The benefits of vitamin D supplements in increasing serum 25OHD levels and reducing falls was confined principally to the non-sunny seasons when levels are substantially lower in the control group than in the treated group.

Conclusion: Ergocalciferol (vitamin D2) given in the non-sunny months resulted in maintenance of normal serum levels of 25OHD, and a clinical benefit in reducing risk of falls in a group of elderly women at high risk for falls.

The rapid response in non-sunny months is notable. Apparently vitamin D2 may act very quickly to raise blood levels, and just as quickly reduce risk of falls.

Vitamin D has a high benefit/risk-cost ratio.

Recently many other adverse effects of deficiency of vitamin D are being reported, including increases in mortality, cancer, and cardiovascular events.. Some question if vitamin D should be classified as a vitamin. This is fascinating. Keep tuned.

"At Least A Billion People Worldwide Are Vitamin D Deficient"

6-5 DEFICIENCY OF SUNLIGHT AND VITAMIN D

At least a billion people worldwide are vitamin D deficient due to inadequate sun exposure and lack of vitamin D in the diet.

Up to 25% of adults with vitamin D deficiency have symptoms of osteomalacia. Deficiency causes secondary hyperparathyroidism and increases destruction of the skeleton by precipitating or exacerbating osteopenia and osteoporosis. Unlike osteoporosis, which is painless, osteomalacia in adults can cause non-specific aches and pains in bones and muscles, and severe muscle weakness. It has been misdiagnosed as fibromyalgia, chronic fatigue syndrome and degenerative arthritis.

Vitamin D deficient persons have an increased risk of many cancers. Increasing the intake to 1000 IU per day reduces the risk of colon cancer. Deficiency is also linked to cardiovascular disease[2], autoimmune diseases, infectious diseases, and schizophrenia.

The only way to know a person's vitamin D status is to measure serum 25(OH) vitamin D concentrations. Concentrations of 75-150 nmol/L are recommended. 500 000 IU of D2 once a week for 8 weeks will correct deficiency. 1000 to 2000 IU daily will maintain sufficiency. Toxicity is very rare. Intoxication occurs when concentrations are greater than 375 nmol/L

"Vitamin D" perhaps should no longer be classified as a vitamin.

More reports are appearing about various adverse effects linked to deficiency

At present, I believe the article overstates the relationships. It may take a long time to clarify.

Meanwhile, primary care clinicians should be aware of the possibility that deficiency may be a cause of some symptoms, especially in elderly house-confined patients.