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This document is divided into two parts

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

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

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

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

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

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* JANUARY 2008

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?

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.

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.

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.

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.

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.

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.

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 50th 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.

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.

ABSTRACTS JANUARY 2008

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

Diabetes, and its associated dyslipidemia, substantially increases the risk of atherosclerotic vascular disease. Identification of treatments to prevent vascular events is a major public health priority.

Previous observational studies have shown a log-linear relationship between LDL-cholesterol levels and risk of coronary heart disease (**CHD**). The MRFIT study reported that for every 1 mmol/L (38 mg) reduction in total cholesterol, risk of death from CHD was reduced by about 50%.

There is still uncertainty about whether outcomes in patients with diabetes depend on the type of diabetes, the lipid profile, and other factors.

This study aimed at clarification.

Conclusion: In patients with diabetes, as well as in those without, statins were related to a highly clinically significant reduction in risk of vascular events.

STUDY

1. 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.
2. The trials were unconfounded (ie, no modification of other risk factors was intended).
3. Estimated effects on clinical outcomes per 1.0 mmol/L decrease in LDL-c (38 mg/dL) over a mean period of 4 years.

RESULTS

1. 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

(All statistically significant..)

2. 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.
3. In the subgroups with known vascular disease, the absolute benefit of a statin was larger than in those without known vascular disease.

DISCUSSION

1. 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.
2. Larger reductions in LDL-c were associated with greater proportional reductions.
3. The absolute benefit was proportional to the baseline risk of a participant, and the absolute reduction in LDL-c.
4. Benefits were similar regardless of whether subjects had diabetes, or did not have diabetes.
5. Standard doses of a statin reduce LDL-c by about 40%. This translates into a reduction of at least 1.5 mmol/L (57 mg/dL) for many people. Such a reduction would prevent about one third of patients from having a major vascular event.
6. 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.
7. A generic statin regimen producing a mean reduction of about one mmol/L in LDL-c is cost effective.

CONCLUSION

Statin therapy should be considered for all diabetic individuals.

Lancet January 12, 2008; 371: 117-25 Original investigation by the Cholesterol Treatment Trialists' (CTT) Collaborators. The Clinical Trials Service Unit (UK) and the National Health and Medical Research Council Clinical Trials Centre (Australia) coordinated this collaboration jointly

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Are Strongly Linked

1-2 DIABETES, COGNITIVE IMPAIRMENT, AND DEMENTIA

Several studies over the past 15 years have indicated that diabetes, (especially type-2 diabetes; **DM-2**) is associated with an increased risk of cognitive impairment and dementia. A recent review reported that, overall, people with 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? The DCCT epidemiological trial found no relation to frequency of severe hypoglycemia, and no decline in cognitive function over 18 years in people with type-1 DM. It did find an associating between higher mean HbA1c levels and moderated decline in motor speed and psychomotor efficiency.

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.

Genetic predisposition, hypertension, dyslipidemia, macro-vascular disease, depression, and drug therapy could all contribute to cognitive impairment. BMJ January 5 2008; 336;6 Editorial. First author Mark J Strachan, Western General Hospital, Edinburgh, UK

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Six Factors That Reliably Predict Development of Hypertension

1-3 A RISK SCORE FOE 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. Cardiovascular disease risk increases in a graded fashion as BP increases, beginning at a BP level of 115/75.

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.

This created a challenge to primary care clinicians.

There is evidence that the risk of development of hypertension in persons with pre-hypertension can be lowered with treatment with drugs and lifestyle changes.

The risk for progression to hypertension depends on clinical factors such as baseline BP, body mass index, and age. An individualized approach to risk stratification and targeted treatment may be desirable.

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.

This longitudinal Framingham cohort study followed over 1700 non-hypertensive individuals (mean age 42; range 20-69; mean BP at baseline = 116/54). None had diabetes. Scores for predicting the 1-, 2-, and 4-year risk of developing new-onset hypertension were based on baseline characteristics of individuals.

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 - > 30
5) Parental hypertension.

6) Smoking

Possible scores ranged from -12 to + 28. Risk of developing hypertension rises as the risk factor rises. Those with higher scores will likely gain more from lifestyle and drug interventions.

Individuals with the lowest score had a 4-year risk of developing hypertension of 1 in 500.
Individuals with the highest score had a 4-year risk of developing hypertension of 85 in 100.

Annals Int Med January 15, 2008; 148: 102-110 Original investigation, first author Nisha I Parikh, Framingham Heart Study, Framingham, Mass.

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

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

In 1994, a small study group associated with the WHO (partially funded by the drug industry) defined normal bone mineral density (**BMD**) as that of young adult women. This instantly categorized many older women as having abnormal bones. The group proposed osteoporosis should be diagnosed when BMD was 2.5 standard deviations below the mean of healthy young women. And osteopenia be diagnosed when BMD was 1.0 to 2.5 standard deviations below the mean. These criteria are still used.

The group admitted that these cut-off values were arbitrary. Others have observed that these criteria were intended for epidemiological studies and not as clinical treatment thresholds.

There is currently widespread agreement that most drugs now approved for treatment of women with post-menopausal osteoporosis reduce the risk of fractures. For osteoporosis, these drugs are cost-effective, although not necessarily for osteopenia.

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 predictive power of osteopenia to predict fracture risk, and the appropriate role of 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."

BMJ January 19, 2008; 336: 126-29 "Analysis", commentary, first author Pablo Alonso-Coello, Universidad Autonoma de Barcelona, Spain

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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 ?

ACE-i do not completely block the production of ATII. ATII-b do not completely block action of ATII in the cell. **1**

This review summarizes the evidence in long-term treatment of essential hypertension

Conclusion: Not much difference in controlling BP. ACE-i is related to cough.

STUDY

1. 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.
2. All studies lasted at least 12 weeks.

RESULTS

1. 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.
2. With use of a single agent, about half of the patients achieved successful BP control with either drug.
3. They exhibited no consistent differential effects on other potential risk factors: lipid levels, progress to type-2 diabetes or diabetes control, markers of carbohydrate metabolism, left ventricular mass and function, and progression to renal disease and effect on urinary protein excretion. No difference in quality-of-life.
4. The tendency to favor ATII-b for monotherapy seemed driven primarily by differences in tolerability and adherence. Cough was 7% more commonly reported in the ACE-I groups. Angioedema with ACE-i was uncommon.

DISCUSSION

1. With the exception of cough, evidence does not strongly support the hypothesis that ACE-i and ATII-b have clinically meaningful differences in benefits or harms in patients with essential hypertension.

2. Compliance may be greater with ATII-b
3. Evidence of long-term effects (and basic clinical outcomes) was restricted by lack of long-term studies.
4. “This review indicates that, for the relatively low-risk individual with essential hypertension, any differences between ACE-i and ATII-b in major events, or changes in risk factors are likely to be small.”

CONCLUSION

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

Annals Intern Med January 1, 2008; 148; 16-29 Original investigation, first author David B Matchar, Duke University, Durham, NC

Funded by the Agency for Healthcare Research and Quality, US Department of Health and Human Services.

1 This study did not consider dual therapy. See the following abstract for discussion on this point.

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ACE-I And ATII-B Are Equally Effective In Reducing Proteinuria. Combination Therapy Is More Effective.

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

Reduction in proteinuria is associated with delayed progression to chronic kidney disease. Experimental data suggests that urinary protein excretion not only reflects the severity of the underlying renal disorder, but also contributes to progression of renal disease.

This meta-analysis 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.

Conclusion: ACE-I and ATII-b reduce proteinuria, independent of the underlying disease. Their effect is similar. Combined ACE-I and ATII-b is more effective.

STUDY

1. This meta-analysis considered 49 studies (over 6000 patients).
2. Patients had proteinuria related to diabetic renal disease and other causes.
3. 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

3. Determined degree of proteinuria at baseline. Measured changes in protein excretion over a few months to one year.
4. Micro-albuminuria defined as excretion of 30 to 300 mg of albumin per day; proteinuria as over 300 mg/d.
5. To assess the BP-independent effect in studies, compared ATII-b with calcium blockers (which are without intrinsic anti-proteinuric action) in which baseline BP was similar.
6. Main outcome = treatment effects on degree of proteinuria. .

RESULTS

1. Anti-proteinuric effects:

   ATII-b vs placebo: Protein excretion was reduced by about 1\3 in the treated group

   ATII-b vs calcium blocker also reduced by about 1/3

   ACE-I vs ATII-b: similar effectiveness.

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

2. Effect of BP reduction on anti-proteinuria:

   Although ATII-b and calcium blockers reduced BP to a similar effect, ATII-b showed a greater anti-proteinuric effect, reducing excretion by about 1/3

3. Adverse effects:

   Many studies reported a variety of adverse effects. ATII-b resulted in fewer discontinuations than placebo, and a tendency for fewer discontinuations than calcium blockers and ACE-I. (ACE-I discontinued mainly die to cough.)

DISCUSSION

1. ATII-b and ACE-i seem to have similar effects in reducing urinary protein excretion.
2. Concomitant therapy with both ACE-i and ATII-b leads to greater reduction in proteinuria.
3. ATII-b reduce proteinuria by about 1/3 compared with placebo and calcium blockers.
4. Despite the findings, the inferences that patients with proteinuria will benefit from combination therapy with ACE-I and ATII-b is not certain..
5. Most drugs that reduce BP also reduce urinary protein excretion. In this study, although calcium blockers and ATII-b resulted in similar BP-lowering, ATII-b resulted in more lowering of urinary protein. This probably reflects the specific effect of ATII-b on the renin-angiotensin system. Inhibition of the system reduces proteinuria by decreasing the systemic BP and the intraglomerular filtration pressure.
6. ACE-i blocks formation of angiotensin II, the main effector peptide of the renin-angiotensin system. But they do so incompletely. At clinically recommended doses, ATII-b does not block all receptors. Combining both may achieve a more complete blockage
7. The anti-proteinuric effect of these drugs is fully reversible within 4 weeks.

8. Combination therapy carries a great potential for toxicity, especially hyperkalemia.
9. “Because proteinuria fulfills many criteria of a reliable surrogate marker, the additional reduction in proteinuria by combining an angiotensin receptor blocker with an angiotensin converting enzyme inhibitor may be of direct relevance to the patient’s renal prognosis.”

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.

Adverse effects of combination therapy are a concern, especially hyperkalemia.

Annals Int Med January 1, 2008; 148: 30-48 Original investigation, first author Regina Kunz, University Hospital, Basel Switzerland.

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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

About one out of three older than age 65 falls each year. Six % of them sustain a fracture as a result.

A recent systematic review concluded that vitamin D supplementation reduces risk of falling, especially in institutionalized individuals.

This study evaluated the effect of vitamin D2 + calcium supplementation vs calcium alone on risk of falling in older women at high risk of falling.

Conclusion: Patients with a history of falls reduced the risk of subsequent falls when receiving vitamin D2 supplementation.

STUDY

1. 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.
2. All had a serum 25-hyroxy-vitamin D concentration under 24 ng/ml (considered low).
3. Randomized to: 1) Vitamin D2 1000 IU daily + 1000 mg calcium citrate daily, or 2) Placebo + calcium
4. Determined rate of falling over the subsequent year.

RESULTS

1. Overall risk of having a fall:

Treatment group	53%
Control	63%

Absolute difference = 10%; NNT to prevent one fall over one year = 10.

2. When those who had at least one subsequent fall were grouped by the season of the year, vitamin D2 supplementation was related to lower risk during the non-sunny months, but not in the sunny months:

3. Percentage of subjects who had at least one fall according to season:

	Non-sunny months	Sunny months
Vitamin D	25%	28%
Control	36%	27%

(Statistically significant difference depending on season)

3. Compared with controls, supplements considerably improved 25OHD serum concentrations in the non-sunny months. Because of the effect of sunshine on controls, there was no difference between groups in the sunny months.

DISCUSSION

1. 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.
2. The effectiveness of the intervention could be considered to be the result of the maintenance of higher 25OHD levels which are attained by ultraviolet exposure during the sunny months in the southern hemisphere.
3. These data are consistent with the hypothesis that a 25OHD level lower than 24 ng/mL is a reasonable predictor of individuals who may benefit from supplementation.
4. Ergocalciferol (D2) is less potent per unit than cholecalciferol (D3). Benefits of D3 may be greater.
5. The authors propose that a serum level of 25OHD of 24 ng/mL or higher should be considered adequate to prevent risk of falling in elderly women living in the community.

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.

Arch Intern Med January 14, 2008; 168: 103-08 Original investigation, first author Richard L Prince, University of Western Australia, Perth.

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No Benefit Over 6 Months

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

Male aging is associated with a gradual, progressive decline in testosterone. Decline is also associated with other signs of aging such as decreased muscle mass and strength, decrease in bone mass, and increase in abdominal fat mass.

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

Conclusion: No benefit over 6 months in functional or cognitive status.

STUDY

1. Double-blind, placebo-controlled randomized trial followed 207 men ages 60 to 80 (mean = 67) to completion of the study.
2. 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.
3. Randomized for 6 months to: 1) Testosterone undeceonate[1] 80 mg twice daily by mouth, or 2) Placebo.
4. Main outcomes measures = functional mobility, muscle strength, cognitive function, bone mineral density, and body composition.

RESULTS

1. There were no differences between groups in functional mobility, muscle strength, cognitive function, bone mineral density. There was no improvement in quality-of-life.
2. HDL-cholesterol levels *decreased* in the testosterone group. Hemoglobin levels increased.
3. Total body fat decreased in the testosterone group. Total lean body mass increased.
4. Prostate volume, PSA, and lower urinary symptoms were not significantly changed. Two prostate cancers developed in the placebo group
5. Many reported adverse drug events—no difference between groups.

DISCUSSION

1. Age-related decline in testosterone levels has been suggested to adversely affect quality-of-life. However, most studies have not shown any benefit.
2. The most important concern of androgen supplementation in old age is development and progression of prostate cancer and benign prostate hyperplasia. No such effect occurred in this short 6 month period.

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.

JAMA January 2, 2008; 299: 39-52 Original investigation, first author Marielle H Emmelot-Vonk, University Medical Center, Utrecht, Netherlands.

1 Not available in the USA. There are a number of other preparations available. Most are given by injection or by patch.

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No Longer Recommended

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

For decades, the American Heart Association (**AHA**) has recommended that patients with certain heart conditions take antibiotics shortly before dental treatment. This was done with the belief that antibiotics would prevent infectious endocarditis (**IE**).

In the journal *Circulation* in October 2007, the AHA published new guidelines for prophylaxis. Most patients for whom prophylactic antibiotics were previously recommended no longer need them.

Bacteria from the mouth can enter the bloodstream during basic daily activities such as brushing or flossing. Indeed, IE is more likely to occur as a result of these everyday activities than from a dental procedure.

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 no longer recommended for common procedures of the gastrointestinal tract, and urinary tract.

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

From the American Heart Association and the American Dental Society websites.

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