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**NEW GUIDELINES FOR PREVENTION OF CARDIOVASCULAR DISEASE FROM THE
AHA AND ACC [11-1]**

DIETARY PATTERNS IN MIDLIFE AFFECT HEALTH IN OLDER AGE [11-2]

FALL PREVENTION EXERCISES PREVENT FRACTURES IN OLD AGE [11-3]

**HPV SCREENING OFFERS GREATER PROTECTION AGAINST INVASIVE CERVICAL
CANCER THAN CYTOLOGY [11-4]**

ADDING NUTS (AND PEANUTS) TO DIET REDUCES MORTALITY [11-5]

TESTOSTERONE THERAPY—IS IT SAFE? [11-6]

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I hope you will find *Practical Pointers* interesting and helpful.

Richard T. James Jr. M.D.

Editor/Publisher.

A Step Forward, But Questions Remain

11-1 NEW AMERICAN GUIDELINES FOR PREVENTION OF CARDIOVASCULAR DISEASE: Review and Critique

Guidelines released by the American Heart Association and the American College of Cardiology (AHA/ACC) on November 13, 2013 for the management of cholesterol is a major step in the right direction. The guidelines emphasize prevention of stroke as well as heart disease and focus appropriately on statin therapy rather than alternative unproven therapeutic agents.

The new guidelines recognize that more intensive treatment is superior to less intensive treatment for many patients, and show that, for individuals in whom statin therapy is clearly indicated, the benefits on heart attacks, stroke, and cardiovascular death significantly outweigh the risk of developing diabetes or myopathy.

The guidelines recommend moderate- or high-intensity statins for 4 groups:

- 1) Patients who have established cardiovascular disease.
- 2) Patients with an LDL-c of 190 and above
- 3) Patients with diabetes who are between ages 40-75 and LDL-c levels of 70 and over.
- 4) Primary prevention: Patients age 40-75 with an estimated 10-year risk of CVD of 7.5% or higher. (A calculator is available to download)

These changes are substantial and will improve patient care.

By eliminating emphasis on LDL-c treatment targets during follow-up, the new guidelines greatly simplify care.

It is in the realm of primary prevention that the guidelines are likely to be controversial. They use a newly developed risk prediction algorithm to recommend institution of statins for primary prevention in patients with a predicted 10-year risk greater or equal to 7.5%.

In patients with diabetes, the threshold of greater than 7.5% is used to select between high-intensity and moderate-intensity statin regimens, defined as regimens that reduce LDL-c by more than 50%, or between 30% and 50%.

The guidelines could result in more than 45 million middle-aged Americans who do not have cardiovascular disease being recommended for consideration of statin therapy.

It is reasonable to ask if any global risk prevention score is needed in 2013 to allocate statins in primary prevention. Between 1995 and 2008, 6 major primary care prevention trials, which included more than 55 000 men and women, showed statins to be effective in primary prevention of MI and stroke among those with raised LDL-c, reduced HDL-c, raised C-reactive protein, diabetes, or

hypertension. Thus, guidelines that rely on randomized trials rather than estimates from epidemiological models could be used instead of this guideline

No trial of statins has ever used a global risk predictions score as an enrollment criterion, so prescription on such a metric might be difficult to defend in an evidence-based climate.

Statins cannot be recommended simply on the basis of high risk without regard for underlying clinical conditions. Two trials enrolled individuals with very high risk in the settings of heart failure or renal failure, and found no evidence of event reduction with statins despite large reductionism in LDL-c.

Other than age, the major drivers of high global risk are smoking and hypertension, which should be treated rather than writing a prescription for a statin drug. The new guidelines also address lifestyle factors:

Consider a 55 year old male smoker with hypertension (systolic BP 145) with a LDL-c of 75 and HDL-c of 75. According to the new algorithm, this patient has a 10-year risk of 9.6%. Thus, a statin is recommended despite the already low LDL-c.

A 60-year old non-smoking woman with a systolic of 120, and a HDL-c of 50, and an LDL-c of 180. Her 10-year risk is 3.8% and thus should not be considered for a statin.

As with all guidelines, context will continue to have a role in physicians' decisions.

Another concern is whether the new prediction algorithm correctly assesses the level of vascular risk. To be useful, prediction models must calibrate well so that the prediction risk estimates match as closely as possible the observed risk in external populations. The authors of this commentary calculated the predicted 10-year risk of the same atherosclerotic events using the new prediction algorithm and compared these estimates with observed event rates in large primary prevention cohorts. (The Woman's Health Study, the Physician's Health Study, and the Women's Health Initiative Observational Study). In all 3 of these cohorts, the new AHA/ACC risk prediction algorithm systematically overestimates observed risks by 75%-150%, roughly doubling the actual observed risk.

Similar overestimation of risk was observed in 2 external validation cohorts used by the guideline developers themselves, an issue readily acknowledged in the report. Thus it is possible that as many as 40-50% of the 33 million middle-aged Americans targeted by the new guidelines for statin therapy do not actually have a risk that exceed the 7.5% thresholds suggested for treatment.

These miscalculations should be addressed before the new models are widely implemented.

The new AHA/ACC cholesterol guidelines take several steps forward that will simplify and improve care for higher risk patients, including those with diabetes. At the same time reliance on the

new risk predication algorithm could put many primary prevention patients on statin therapy when there is little trial evidence of benefit while potentially denying statins to other patients despite trial evidence of efficacy.

In primary prevention, instead of predicting risk and presuming benefit, an alternative based on trial evidence would reduce this problem and result in evidence-based public health recommendations for statin therapy in patient groups for whom we have data showing efficacy.

STATINS: NEW AMERICAN GUIDELINES FOR PREVENTION OF CARDIOVASCULAR DISEASE

Lancet, November 30, 2013;382:1762-65 “Comment” first author Paul M Ridker, Brigham and Women’s Hospital, Boston Mass.

STATINS: NEW US GUIDELINES SPARKS CONTROVERSY

Lancet November 23, 2013; 382:1680 Editorial by the Lancet Staff.

WIDER USE OF CHOLESTEROL DRUGS URGED

Charlotte Observer November 2013 by Marilyn Marchione Associated Press

ACC/AHA PUBLISHES NEW GUIDELINES FOR MANAGEMENT OF BLOOD CHOLESTEROL

November 12, 2013 by AHA

<http://newsroom.heart.org/news/acc-aha-publish-new-guideline-for-management-of-blood-cholesterol>

An important and provocative proposal. However, I do not believe it is ready for application to primary care medicine. The new risk calculator has not been prospectively tested. It may overestimate risks.

The focus is on statins. Other preventive applications are maintained (diet, BP, smoking, weight control, exercise). No mention of aspirin for prevention.

What the new guidelines stress:

- 1. No treatment to LDL-c target. Thus, no need for repeated LDL-c determinations.*
- 2. For primary prevention: Cut point for statin use is lowered from 20% over 10-years to 7.5%.*
- 3. Prescription for high-dose statins for established atherosclerotic disease, diabetes with risk*

over 7.5%. Also high-dose for LDL-c > 190.

4. Avoid use of other lipid-lowering drugs.

5. Begin therapy at an early age.

6. Stresses prevention of stroke as well as ASHD.

7. If risk is not clear, may add family history, C-reactive protein, coronary artery calcium score, and ankle-brachial index.

8. More conservative use of statins in patients older than age 75 who have no evidence of ASCVD.

We will hear more about these new guidelines.

11-2 THE ASSOCIATIONS BETWEEN DIETARY PATTERNS AT MIDLIFE AND HEALTH IN AGING: Observational study

Over the past decades, premature deaths have been substantially reduced. But this increase in life expectancy has increased the number of years lost to disability.

Maintaining health and well-being in aging populations is a major challenge.

Midlife factors may underlie development of chronic health problems, which evolve over years or decades before emergence of clinical disease.

The present study investigated the associations between dietary patterns at midlife and the prevalence of healthy aging an average of 15 years later.

STUDY

1. The Nurses Health Study (NHS) began in 1976 when 121 700 female nurses age 30 to 55 completed a health questionnaire. Follow-up questionnaires were sent periodically. Subsequently, participants completed food frequency questionnaire (FFQ), surveys of health outcomes, and a cognitive study.
2. The present study, based on this data, included 10 679 participants with dietary data and no major chronic diseases between 1984 and 1986 (median age 59).
3. Determined health status 15 years later related to diet patterns in midlife.
4. Assessment of Dietary Patterns:

To assess dietary quality in midlife, the 1984 and 1985 FFQ were averaged. Outcomes were determined based on two different diets: the Alternative Healthy Eating Index-2010 (AHEI-2010) and the Alternate Mediterranean Diet (A-MD)

1) The AHEI-2010 includes:

Greater intake of healthful foods: vegetables (excluding potatoes), fruits (excluding juice), whole grains, nuts, legumes, long-chain omega-3 polyunsaturated fatty acids, and other long-chain polyunsaturated fatty acids, and moderate intake of alcohol (0.5 to 1.5 drinks per day)

Lower intake of harmful foods: sugar sweetened beverages and fruit juices, red and processed meats, trans fats, and sodium.

Each component was scored from 0 (worst) to 10 (best) according to intake.

Total scores ranged from 0 (non-adherence) to 110 (perfect adherence).

2) The A-MD score was developed to address adherence to the traditional Mediterranean diet.

It includes: vegetables (excluding potatoes), fruits, nuts, whole grains, legumes, fish, moderate alcohol, and high mono-unsaturated fatty acid/saturated fatty acid ratio.

(Beneficial)

Red meat and processed meat and high intake of alcohol. (Harmful)

For items hypothesized to be beneficial, 1 point was given if intakes were above the median; for those harmful, 1 point was given if intake was below the median.

Total scores ranged from 0 to 9.

3. Multiple possible confounding covariates were considered.

4. Assessment of healthy aging.

Considered persons free of 11 chronic diseases with no impairments of cognition, no physical disabilities and intact mental health.

5. Populating for analysis:

After exclusions, 10 670 participants were available for analysis.

RESULTS

1. Of 10 670 participants (at 15 years)

Considered healthy agers --only 11%

Usual agers (89%) had 1 or more chronic diseases, or limited cognitive, physical, or mental health concerns,

2. Baseline (1985) age standardized characteristics of healthy and usual aging

Healthy agers	Usual agers
(n = 1174)	(n = 9499)

Mean age	58	59
AHEI-2010 score	53.2	50.6
At midlife		
A-MD score	4.5	4.3
At midlife		

Healthy agers ate more fruit, vegetables, whole grains, and moderate alcohol, and less unsaturated fat, red meat, and sodium.

3. Compared with usual agers, healthy agers had lower prevalence of obesity and smoking, and exercised more at midlife. They also had low prevalence of hypertension, and hypercholesterolemia.

4. Odds ration of healthy aging according to quintiles of scores:

	Q1	Q5
AHEI-2010 score (median)	38	64
Healthy agers (number)	181	298
Multiple adjusted OR	1.00	1.34
A-MD score	2.0	6.5
Healthy agers	176	289
Multivariate adjusted OR	1.00	1.46

5. Greater adherence at midlife to both diets was strongly associated with greater odds of healthy aging. Compared with women in the worst quintile of diet scores, women in the highest quintile had 34% and 46% greater odds of healthy aging.

6. Most components of both diets were associated with healthy aging, although associations were generally weaker than the overall dietary pattern. There were statistically significant associations with healthy aging (upper vs lower quintiles) for intake of fruits, and alcohol, and lower intake of sugar-sweetened beverages and processed meats. .

DISCUSSION

1. Greater adherence in midlife to healthy dietary patterns was associated with approximately 40% greater odds of healthy aging for both diets. Both diets capture common healthful dimensions. Both focus on greater intake of plant foods, whole grains, fish, long-chain omega-3 fatty acids, moderate intake of alcohols, and lower intake of red and processed meats.

2. In a pooled analysis of past studies including more than 2 million participants, each 2-point increase

in the Mediterranean Diet score was related to a 10% reduction in cardiovascular disease, 6% reduction in cancer, and 13% reduction in risk for neurodegenerative diseases.

3. Other studies of healthy eating have reported a lower incidence of insulin resistance and the metabolic syndrome, slower progression of atherosclerosis, less depression, improved cognitive function, and improved physical functioning.
4. The study concerned mostly white professional women, and might not be generalizable to other populations.

CONCLUSION

Higher quality diet in midlife was associated with increased odds of good health and well-being among individuals surviving to older age.

Annals of Internal Medicine November 5, 2013;159:584-91 Original investigation , first author Cecilia Samieri, Harvard Medical School, Boston, Mass.

Funded by the National Cancer Institute

A complex and detailed and important study.

Primary care clinicians should be role models in adhering to a healthy diet and reminding almost all patients to do likewise.

A healthy diet can be as tasty and appealing as an unhealthy diet.

We do not have to attain a perfect diet score to gain benefits.

Balance Training A Key Factor

11-3 THE EFFECT OF FALL PREVENTION EXERCISE PROGRAMMES ON FALL-INDUCED INJURIES IN COMMUNITY DWELLING OLDER ADULTS:

Systematic Review And Meta-Analysis Of Randomized Trials

The study asks: Are fall prevention exercises for older people living in the community effective in preventing different types of fall-related injuries?

This study of randomized controlled trials examined the effect of fall prevention exercise interventions designed for community-dwelling older adults on 4 different categories of falls, based on severity of medical care.

A systematic search identified relevant studies reported in the literature up to July 2013. All studies were randomized, controlled trials of fall prevention exercises targeting persons over age 60 living in the community.

Four different categories of injurious falls were distinguished: 1) All injurious falls, 2) falls resulting in medical care, 3) severe injurious falls, and 4) falls resulting in fracture.

Included studies where exercise was compared with no intervention (usual activity or usual care).

Results:

Identified 17 trials involving 4305 participants eligible for analysis.

Exercise (vs no exercise) had a significant effect on all categories of injurious falls, with pooled estimates of the rate ratios of 0.63 from injurious falls, 0.70 for falls resultant in medical care. 0.57 for severe injurious falls, and 0.39 for falls resulting in fractures.

All interventions included a balance training component, which has been found to be a key factor in determining the effectiveness of exercise on falls.

BMJ November 20, 2013; 347:11 A short abstract of original investigation, first author Fabienne El-Khoury, University Paris Sud

BMJ2013;347:f6234

DOI: 10.1136/bmj.f6234 for full abstract

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Residents of Retirement Complexes, as I am, are fully aware of the frequency of falls and the injuries they cause.

We already know this. Now how to act on it?

11-4 HPV SCREENING OFFERS GREATER PROTECTION AGAINST INVASIVE CERVICAL CANCER THAN CYTOLOGY: Commentary

An analysis of 4 large trials has found that screening for the human papilloma virus is more effective at protecting against invasive cervical cancer than the traditional cytology-based screening.

With a longer time between tests, the cost of screening is likely to fall.

Presently, in England, women who have a borderline or abnormal result on cytology are currently tested for HPV, but HPV is now the primary screening test.

When results of the 4 trials were combined (176 000 women), followed for an average of 6.5 years, 107 invasive cancers were found. Detection of cancer was significantly higher in women who had undergone HPV testing.

The increased detection was especially evident in women aged 30-35.

HPV screening every 5 years was more protective against invasive cervical cancers than cytology every 3 years.

The cumulative incidence of invasive cancer after 3.5 years after a negative smear test = 15.4 per 100 000 women. After a negative HPV test = 4.5 per 100 000.

The researchers calculated that HPV screening provided 60% - 70% greater protection against invasive cervical cancer than did cytology.

BMJ November 9, 2013;347:2-3 BMJ 2013;347:f6624

“News” by Zosia Kmietowicz BMJ staff.

11-5 ASSOCIATION OF NUT CONSUMPTION WITH TOTAL AND CAUSE-SPECIFIC MORTALITY: Observational study

Nuts are nutrient-dense, rich in unsaturated fatty acids, fiber, vitamins, minerals, and phytosterols .

The FDA (2003) concluded, that for most nuts, consumption of 1.5 ounces per day is part of a low-fat diet, and “ may reduce risk of heart disease”.

A more recent primary prevention trial showed reduction in major cardiovascular events among participants assigned to a Mediterranean diet supplemented with walnuts, hazelnuts, and almonds.

Studies of nut consumption have shown reductions in oxidative stress, inflammation, visceral adiposity, hyperglycemia, insulin resistance, and endothelial dysfunction. In other studies, increased nut consumption has been associated with lower risk of type-2 diabetes, colon cancer, hypertension, gallstones, diverticulitis, and death from inflammatory diseases.

This study examined the association of nut consumption with total and cause-specific mortality in two large, independent cohort studies on nurses and other health professionals, with 30 years of follow-up, and more than 27 000 deaths.

STUDY

1. The Nurses’ Health Study (NHS) is a large prospective study of female nurses enrolled in 1976. The

Health Professionals Follow-up Study (HPFS) is a large prospective study of male health professionals enrolled in 1986.

2. For this analysis, the baseline was defined as the first validated food-frequency questionnaire (FFQ; 1980 and 1986). At baseline, 92 468 women and 49 934 men completed the questionnaire. After exclusions for cancer, heart disease and stroke, 76 464 women and 42 492 men were included in the final analysis.
3. A validated FFQ administered every 2 to 4 years asked how often participants consumed a 1 ounce serving of nuts during the preceding year in 6 steps from “never ” to “seven or more times per week”.
4. The question regarding nuts was split into peanuts and other nuts.
5. Primary endpoint was death from any cause.

RESULTS

1. During follow-up, nut consumption remained relatively constant.
2. Participants who consumed nuts more frequently were leaner, smoked less, were more likely to exercise, use vitamins, and consume more fruit and vegetables, and drink more alcohol.
3. Nut consumption and total mortality:

During 30 years of follow-up (2 135 482 person-years) among women there were 16 200 deaths. During 24 years of follow-up (903 377 person-years) among men, 11 229 deaths.

Age-and multivariate adjusted analysis showed a significant inverse association between frequency of nut consumption and total mortality among both men and women.

4. Total mortality according to nut consumption (multivariate analysis):

	Frequency of nut consumption	
	Never	7 or more times per week
A. Women		
Person-years	390 915	29 822
No. of deaths	3343	202
Multivariate Adjusted HR	1.00	0.79
B. Men		
Person-years	130 848	40 127

No. of deaths	1860	536
Multivariate adjusted Hazard Ratio	1.00	0.80

C. Pooled

Multivariate adjusted Hazard Ratio	1.00	0.80
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(HRs decreased gradually as number of servings increased from 0 to 7 or more.)

4. Nut consumption and cause-specific mortality:

In multivariate analysis, nut consumption was inversely associated with risk of most major causes of death for both men and women.

In the pooled analysis, significant inverse associations were observed for death due to cancer, heart disease, and respiratory disease.

5. The associations with total and case-specific mortality for peanuts were similar to that for tree nuts.

When consumption of nuts two or more times a week was compared with no nut consumption, the hazard ratios for death was very similar for peanuts (0.83) and for tree nuts (0.88).

6. The inverse association between nut consumption and mortality was stronger for obese persons than for normal weight persons.

DISCUSSION

1. After adjusting for potential confounders, there was an inverse association between nut consumption and total mortality including death from heart disease, cancer, and respiratory diseases.
2. As compared with participants who did not eat nuts, those who consumed nuts 7 or more times a week had a 20% lower death rate. Results were similar for tree nuts and peanuts.
3. There may be concern that frequent nut consumption can result in weight gain. However, in this and other studies, increased nut consumption was associated with less weight gain.
4. Strengths of this study include the large sample, and 30 years of excellent follow-up. The results are consistent with a wealth of existing observational and clinical-trial data.
5. Nutrients in nuts, such as unsaturated fatty acids, high-quality protein, fiber, vitamins, minerals, and phytochemicals, may confer protection.
6. Recent trials have shown a protective effect of a Mediterranean diet against cardiovascular disease.

One component of the diet was the availability of an average of 30 grams of nuts per day.

CONCLUSION

There was a significant inverse relationship of nut consumption with total and cause-specific mortality.

Nevertheless, epidemiological observations establish associations, not causality, and not all findings of observational studies have been confirmed by randomized clinical trials.

NEJM November 21, 2013; 369: 2001-11

DOI:10.1056/NEJMoa1306352

Original investigation, first author Ying Bao, Harvard Medical School, Boston .Mass

Funded by the National Institutes of Health

We have learned much about healthy living in the past 10-20 years, based on sound scientific principles. Primary care clinicians carry the opportunity and privilege of teaching patients about it. I believe many patients would benefit from a short list of healthy living applications given periodically to patients regardless of the reason for consultation.

Concerns About Safety

11-6 ASSOCIATION OF TESTOSTERONE THERAPY WITH MORTALITY, MYOCARDIAL INFARCTION, AND STROKE IN MEN WITH LOW TESTOSTERONE LEVELS: Retroactive Cohort Study

Rates of testosterone (T) prescription have increased markedly in the past decade, reaching a market of \$1.6 billion in 2011.

Professional society guidelines recommend T for patients with symptomatic T deficiency. In addition to improving sexual function and bone mineral density, T increases fat-free mass and strength, and has been shown to improve lipid profiles, lower insulin resistance, and increase time to ST depression during stress testing.

The effect of T therapy on cardiovascular outcomes and mortality is not known.

This study evaluated the associations between T therapy and all-cause mortality, myocardial infarction, and stroke among male veterans.

STUDY

1. The VA Clinical Assessment Reporting and Tracking (CART) Program collects patient and procedural data at the point-of-care for all procedures performed in 76 VA cardiac catholization laboratories. CART was implemented in 2005.
2. This is a retroactive cohort study of all male veterans who underwent coronary angiography between 2005 and 2011 who had a total T level checked at the time of angiography.
3. The final cohort was limited to patients who had a total T level less than 300 ng /dL, the generally agreed threshold for biochemical hypogonadism.
4. The primary endpoint was a combined all-cause mortality or hospitalization for MI or ischemic stroke.
5. The investigators wanted to determine whether the association of T therapy with adverse outcomes was modified by the presence of coronary artery disease (CAD), given the uncertainty regarding the safety of T therapy in older men with comorbid CAD.

RESULTS

1. The primary cohort was 23 173 men who underwent coronary angiography between 2006 and 2011 and who had a total T checked.
2. After exclusions for prior use of T, missing coronary anatomy information, having T prescribed after MI, hematocrit levels > 50%, and T levels over 300 ng/dL, a cohort of 8709 (38%) remained. All had a T level < 300
3. Of the 8709 patients, 1223 received T therapy.
4. At baseline:

	T therapy n = 1223	No T n = 7486
Age (mean)	61	64
Total T (ng/Dl (mean)	176	206
Hypertension	90%	92%
Hyperlipidemia	85%%	88%
Diabetes	53%%	56%%
Congestive heart failure	18%	24%
Cerebrovascular disease	11%	16%
Prior MI	20%	29

Coronary artery disease (CAD) 55%% 60%
(A high risk group)

6. Between groups, there was no difference in BP, LDL-cholesterol or use of beta-blockers.
- 7.. Among T patients, the baseline T level was 173; increasing to 332 with treatment.
8. Average follow-up was 27.5 months.
9. Absolute rate of events after several statistical manipulations (%):

	T therapy	No T	Absolute difference
At 1 year	11.3	10.1	1.3
At 2 years	18.5	15.4	3.1
A t 3 years	25.7	19.9	5.8

10. T therapy was associated with increased risk of all-cause mortality, MI, and stroke (Hazard Ratio = 1.29 at 3 years).
11. There was no significant difference in the effect size between those with and those without CAD.

DISCUSSION

1. The association was constant among patients with and without CAD.
2. The increased risk of adverse events associated with T therapy was not related to differences in risk factor control or rates of secondary prevention medications.
3. These findings raise concerns about the potential safety of T therapy.
4. Potential mechanisms by which T may increase CAD risk: Increase in platelet thromboxane receptors and platelet aggregation; monocyte activation in the endothelium promoting atherosclerosis; and a worsening of sleep apnea, a risk factor for atherosclerosis.
5. Although physicians should continue to discuss symptomatic benefits of T therapy with patients, it is important to inform them that long-term risks are not known and T might be harmful.
6. This was an observational study. Unmeasured confounders and hidden bias might exist.

CONCLUSION

Use of T therapy in this cohort of veterans with significant medical co-morbidities was associated with increased risk of mortality, MI, or ischemic stroke.

These findings were not modified by the presence of CAD.

JAMA November 6, 2013;310:1829-36 Original investigation, first author Rebecca Vigen, University of Texas at Southwestern Medical Center, Dallas.

In this issue of JAMA (pp 1805-06) an editorial by Anne R Cappola, Perelman School of Medicine University of Pennsylvania, comments on this study:

Because T therapy is prescribed for 2.9% of US men age 40 and older, observational data from existing cohorts can contribute meaningfully to assessment of risk.

Any pharmaco-epidemiology study is susceptible to confounding and bias, which the authors attempted to alleviate.

Perhaps the most important question is the generalization of results of the study to broader population of men taking T. Men taking T for “low T syndrome”, for anti-aging, and for physical enhancement may be relatively young. Does the 29% increase in MI, ischemic stroke or mortality apply to these groups? Is the benefit worth the increased risk?

In the light of the high volume of prescriptions and persuasive marketing, prescribers and patients should be wary.

This is a provocative study, but not a very strong study. We obviously need further observation.

T therapy has been widely advertised, and increasingly requested without knowledge of adverse effects, which I believe are considerable. I would not prescribe T, telling a patient who requests it that the adverse effects may be serious and are not known.

I am surprised that men without established coronary disease and without high levels of risk factors were just as likely to experience adverse effects as men with established CAD and high rates of risk factors. This seems counterintuitive.

Widely advertised without adequate knowledge of adverse effect, I believe T therapy may have been approved prematurely. .

And what about prostate cancer?

