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Every time a reader of this newsletter enters a drug store, a health food store or a supermarket, the option exists to take a simple preventive action that could have a profound impact on the risk of adverse cardiovascular events and, in particular, those related to coronary heart disease. One does not need a prescription to take definitive action which could be life-saving. What is involved is the intake of long-chain omega-3 fatty acids found in oily fish such as salmon or in capsules of fish oil. The March issue features this subject and the evidence of the importance of achieving and maintaining a long-chain omega-3 fatty acid status which is high enough to offer protection from both sudden cardiac death and the so-called acute cardiac syndrome. The goal is to increase awareness of the huge impact that either eating considerable oily fish or taking enough fish oil has on the risk of these two aspects of coronary heart disease.

The second subject that receives considerable space involves the question of the impact of salt intake on cardiovascular disease. The issue here is a recent paper which is based entirely on the syllogism that salt increases blood pressure, blood pressure is a risk factor for heart disease, and therefore salt increases the risk of heart disease. It will be demonstrated that the story is considerably more complex and that this recent paper, which no doubt will have considerable influence, completely ignores a vast amount of highly relevant literature which profoundly weakens the authors' message.

The important question of what constitutes clinical significance vs. statistical significance in studies is discussed since more and more we are seeing papers which find very small effects, but because they are statistically significant, they are inflated to a position of importance and, in some cases, given heavy media coverage. After all, the only thing that appears to matter is clinical significance. To reduce the risk of some problem by a tiny amount that turns out to be statistically significant should not be of much concern except as a generator of a hypothesis of interest mainly to researchers and certainly not to the general public. This is a problem that in fact appears to be of increasing importance.

Other subjects covered include acetaminophen and asthma, ARB blockers and dementia, statins and cognitive decline and finally, a large meta-analysis concerning the hypothesis that saturated fat is adversely associated with cardiovascular disease.

*This issue concludes with a review of the new book **Fat and Cholesterol Are Good for You!** by Uffe Ravnskø. The story is even better than the title suggests.*

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Wishing you and your family good health and well-being,

William R. Ware, PhD, Editor

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IS THERE AN OPTIMUM OMEGA-6 TO OMEGA-3 DIETARY INTAKE?

This question has been discussed frequently in both the medical-nutritional and in the lay literature. An update by William Harris recently appeared in *Current Opinion in Clinical Nutrition and Metabolic Care*¹ which was focused on cardiovascular issues. The fact that both omega-3 and omega-6 fatty acids (FAs) have important beneficial effects in this context has been discussed on several occasions in this Newsletter, but it appears of interest to examine the recommendations for intake given in this latest publication since the Western diet has a much different omega-3 to omega-6 ratio than the Stone Age or Paleolithic diet.

The current recommendation presented by Harris is that a healthy target for omega-3 long-chain fatty acids such as from fish or fish oil should be about 0.5 g/day whereas for omega-6 FAs, it should be 17 g/day for men and 12 g/day for women. This is described as an important component of a nutritional program for the prevention and treatment of coronary heart disease and the authors point out that these guidelines are consistent with the American Heart Association recommendation to eat two serving per week of oily fish such as salmon. These intakes give ratios of 34:1 and 24:1 for the omega-6 to *long-chain* omega-3.

If one accepts the proposition that our biochemistry is set by genetics essentially fixed more than 50,000 years ago, then perspective can be gained by examining the above recommendation in the light of the estimates of poly-unsaturated fat intake in the late Paleolithic period, i.e. by Stone Age man. There has been considerable research into this question, and the latest results appear to be about 11 g/day of total omega 6 and 14 g/day of omega-3 FAs.² These estimates include both plant and animal sources. Given the uncertainties, the ratio of total

omega-6 to omega-3 is about 1. The frequently quoted number for Western diets is 10:1 or higher.

The principal plant source of omega-3 FAs is alpha-linolenic acid and animal sources represent a small fraction of the total given above for the Paleolithic diet. It is estimated that Stone Age man consumed about 500 mg. of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) from fish and game sources.² Thus the above recommendation is consistent with this while the total omega-6 FA intake suggested is higher, but less than a factor of 2. While the modern omega-6 to omega-3 ratio for the U.S. population of about 10:1 seems very high compared to the 1:1 ratio for Stone Age man, this is simply due to the heavy consumption of vegetable oils rich in linoleic acid and a low consumption of both fish and plant sources of omega-3 FAs. It is important to realize that the conversion of alpha-linolenic acid (ALA) into EPA and DHA, the long chain omega-3 acids, is very inefficient (0.2-6% for ALA to EPA, 0.05% for ALA to DHA). Health benefits of omega-3 FAs focus on EPA and DHA and thus one needs to be careful in reading labels since most do not break down the omega-3 content into ALA and the long chain EPA and DHA and may give a false impression of health benefits.

The paper by Harris suggests that the focus should be on the absolute dietary amounts of omega-3 and omega-6 FAs and also the absolute amounts of EPA and DHA rather than the overall omega-6:omega-3 ratio. Justification for this view is partly derived from studies of the association between the long-chain omega-3 status and the risk of sudden cardiac death or acute coronary syndrome (heart attack or unstable angina or the urgent need for so-called revascularization via bypass, angioplasty or stenting). Some readers may be surprised at recent results in this area. Furthermore, these results allow one to critically examine the recommendation of 0.5 g/d of EPA plus DHA.

The current view regarding assessing an individual's omega-3 status involves measuring either the EPA + DHA content of the red blood cell walls as a percentage of total fatty acid content of the cell walls, or the EPA + DHA content of the blood plasma phospholipid fraction as a percentage of the total FA content of this fraction. The former is called the "Omega-3 Index" and this index can now be calculated from measurements using plasma rather than isolated red blood cell walls.³ The test is available from some clinical diagnostic laboratories or via mail-in sample through an internet contact. When the association between the Omega-3 Index

and the risk of acute coronary syndrome (ACS) is studied, the results seem quite remarkable. A case-controlled study which measured the Index for 768 ACS patients and the same number of age, sex and race matched controls found that when the lowest Index group ($\leq 4\%$) were compared with the highest ($\geq 8\%$), the odds for an ACS were reduced to 0.3, i.e. a 70% risk reduction. The odds ratio per 1 unit increase in the Index was 0.77 (95% CI 0.7-0.85) when BMI, moderate drinking vs. heavy drinking, smoking, no college education, history of a heart attack, diabetes, family CHD or hypertension were included in the analysis.⁴ In a second study, when the lowest vs. the highest quintiles of the plasma EPA + DHA, those in the highest quintile had odds for an ACS of 0.2, i.e. an 80% risk reduction. The highest plasma quintile ($> 2.6\%$) was roughly equivalent to an Index of $> 6\%$. This result was adjusted for a large number of potential confounders.⁵ The same magnitude of risk reductions for sudden cardiac death have been reported over the same range of the Index.⁶ If Big Pharma had a pill that would accomplish this it would be a big deal. Actually, Big Pharma has a very expensive prescription EPA-DHA fish oil pill (Omacor) which appears no different than readily available highly purified fish oil capsules at a fraction of the cost.

The obvious question then is, how much EPA and DHA must one take daily to maintain the Omega-3 Index in the range of 7-8% and is the 0.5g/d recommended by Harris enough? This has been recently studied and it was found that about 1300 mg/d of EPA and 860 mg/day of DHA resulted in values in this ideal range which were reached within 8 weeks of the initiation of supplementation starting with Index levels around 4%.⁷ This was compared with giving 3.5g/d of alpha-linolenic acid from flaxseed oil and 0.9g/d of linoleic acid. This latter supplementation had an insignificant impact on the Omega-3 Index which illustrates the very inefficient conversion mentioned above from alpha-linolenic acid to EPA and DHA. While flaxseeds are considered a good source of omega-3 fatty acids, this is not a good source of what is really needed, the long-chain omega-3 metabolites. A very important aspect of this study was the observation that when supplementation was stopped, the Omega-3 Index rapidly returned to baseline. Thus to achieve the benefits associated with coronary heart disease risk, it is necessary to permanently maintain an adequate intake of EPA and DHA. The authors comment that these observations were consistent with studies reported earlier where in one case, 1.6 g/day of EPA and 0.33 g/day of DHA for a year

raised the Omega-3 Index to a mean value of 9.1% and in another 1.26 g/day of DHA and 0.77g/day of EPA for 20 weeks increased the Omega-3 Index to 11.6%. There appears to be no credible evidence of any significant side effects at intakes of fish oil at this level. At a dose level of 4 capsules per day, prescription Omacor provides 1.86g EPA and 1.5g of DHA.

The above studies concerning the Omega-3 Index and the risk of SCD or ACS ignored the dietary intake of omega-6 fatty acids and focused on manipulating the cell-wall concentration of EPA and DHA. This ignores the high level of total dietary omega-6 FAs compared to omega-3 FAs in Western diets. The argument regarding the danger of this radical departure from the dietary habits of our ancestors views omega-6 FAs to be pro-inflammatory and promoters of aggregation. As Harris discusses,¹ the recent AHA Scientific Advisory indicates that there is little direct evidence that supports a pro-inflammatory or pro-atherogenic effect of linoleic acid, the main dietary source of omega-6 FAs for humans. In addition, higher linoleic acid intakes do not significantly raise cell membrane levels of arachidonic acid, and while this FA is viewed as pro-inflammatory, it is also a precursor for anti-inflammatory compounds. Also, linoleic acid itself is partly converted into other anti-inflammatory compounds. These observations help explain why the theoretical risks associated with high omega-6 intake are not confirmed in observational studies, and why it is common now, as has been discussed in this Newsletter, to see the recommendation to ignore the dietary omega-6 to omega-3 ratio and concentrate on raising the omega-3 intake.

One can also look at the estimated Stone Age total omega-6 to animal derived long-chain omega 3 (mostly EPA and DHA) ratio,² which is about 13:1. Following Harris' recommendation, the omega-6 intake would be about 17 g/day, but the EPA + DHA intake would be at about 0.5 g/day, giving a ratio of 34:1. However, it seems clear that if one wishes to elevate the Omega-3 Index to 7-10%, then an intake of EPA + DHA of 2-3 g/day is necessary, which now reduces the ratio to 9:1 which is in line with estimated Stone Age intake, and the omega-6 intake, mostly from linoleic acid, is only about 50% higher in the modern diet. This provides a different picture from looking at the 10:1 total omega-6 to omega-3 dietary intake ratio in modern Western diets as compared to 1:1 in the Stone Age diet. What is unclear is the efficiency at which Stone Age man converted plant ALA to EPA and DHA. Assuming the estimate of 12.6 g/d of ALA from

plants and animals, at 6% conversion this would add about 0.76 g/d of EPA and DHA which when added to the estimated animal sources of EPA and DHA would yield 1.4 g/d. It is very interesting that this number falls in the range needed give a high Omega-3 Index.

There appear to be only two studies that examined the association between subclinical atherosclerosis and the intake of long-chain omega-3 FAs. In one there was no significant association between intake and the coronary calcium score. However, the highest quartile of intake was only 220 mg/day and thus in this population there may not have been enough with very high intake to show an effect.⁸ In the other, an interventional study, the starting dose was 180 mg of EPA and 120 mg of DHA. While this dose was increased in some cases to achieve triglyceride goals, manipulation of triglycerides with drugs was also being used. Thus the significant slowing or reversal of coronary calcification observed cannot be associated with the omega-3 intervention but some association may still be present.⁹ Nevertheless, a general observation at this point is that the high Omega-3 Index reflects protection against adverse cardiac events rather than coronary atherosclerosis. There is need for a definitive study to clarify this point.

Finally, there is the choice of the source of EPA and DHA, i.e. oily fish such as salmon, herring and mackerel, or using purified fish oil with a known amount of EPA and DHA per capsule. Salmon is a very popular source of omega-3 fats but it is now either farmed or wild. It appears that the EPA and DHA content of farmed salmon is similar to that of the wild salmon,¹⁰ but this may depend on the feed used which may change over the years. A 3.5 oz. serving of salmon contains between 1 and 2 grams of long-chain omega-3 fats which is the basis of the AHA recommendation of two servings a week to achieve about 0.5 g/day. The discussion above suggests that this is not enough. A combination of supplementation and fish consumption appears to offer an attractive compromise. The method of cooking fish may also have an impact on the omega-3 content.¹¹

Mainstream medicine is busy measuring HDL, LDL and triglyceride levels as an essential part of evaluating health status. It can be argued on the basis of the above discussion and the many discussions of Vitamin D and heart disease that have appeared in this Newsletter, that it might be more productive to measure 25-hydroxyvitamin D and the Omega-3 Index and take appropriate action. Finally, as will be discussed in a future issue of the Newsletter, increasing omega-3 long chain FAs intake is implicated in cancer prevention.

CLINICAL VS. SIGNIFICANT STUDY RESULTS

A recent paper titled *Trial and Error* which appeared in the *Journal of the American College of Cardiology*,¹² reopens the long standing debate regarding when statistical significance becomes clinical significance. The position taken is that for relative risk reduction, a threshold needs to be set such that results must exceed this threshold to qualify. If for example it is generally agreed that a reasonable threshold for relative risk reduction is 15%, then to be considered as clinically meaningful, studies must exceed this number. However, the authors then introduce a much more restrictive condition. The 95% confidence interval (limits) must not overlap this value. The 95% confidence interval (CI) represents the range of values considered to occur with 95% probability based on statistical considerations. Thus a result with a RR of 0.75 (25% reduction) with a CI range of 0.55 to 0.9 would not qualify as clinically significant but would be considered statistically significant, but if the limits

were 0.55 to 0.82 it would be considered clinically significant, given an agreed upon 15% threshold.

Application of this standard for clinical relevance would force authors of many if not most studies to admit clinical irrelevance whereas now the results are trumpeted as strongly significant on the basis of a sizeable relative risk reduction independent of the CI as long as it does not include the "no effect value" of 1.00. The number of clinically significant results would dramatically decrease. Also, it should be noted that this "hard nosed" view does not include consideration of absolute benefit vs. relative benefit. A classic example from the MRFIT study was that for those with cholesterol above 266 mg/dL, 1.3% died from a heart attack. For those with the lowest values (below 170 mg/dL), 0.3% died. This result was presented as those having high cholesterol had a 413% greater risk of heart attack than those with cholesterol below 170. But when one looks at the numbers still alive, they were

99.7 and 98.7. The difference in the number of deaths in the two groups was 1%, which is not as dramatic as the commonly stated result of a 413% relative increase (1.3 is 413% of 0.3) In his book *Worried Sick*, Nortin Hadler, M.D. goes so far as to suggest that insurance schemes only pay for procedures where the number needed to treat (NNT) for the prevention of one serious event, which is related to absolute risk reduction, should

be ≤ 50 .¹³ Many interventions trials produce NNT considerably in excess of 50 and some conservative physicians prefer a threshold of 25. In the now famous JUPITER trial which is on track to prompt the recommendation of lifelong statin therapy to huge additional populations, the number needed to treat to prevent one CVD death, heart attack or stroke was about 100.

THE NEW WAR ON SALT

In an article by Bibbins-Domingo *et al* published online in *The New England Journal of Medicine* on January 2010, dire predictions were made regarding the projected effect of dietary salt on future cardiovascular disease.¹⁴ An editorial called for public health action based on the compelling evidence.¹⁵ This of course got the attention of the media. Thus it is of interest to look at the salt-cardiovascular connection both from the point of view presented in the cited paper and in more general terms including the nature and quality of the evidence associating salt intake and CVD, with special attention to just how compelling the evidence really is.

The position presented by Bibbins-Domingo *et al* is based on the following syllogism: (a) It is possible to lower blood pressure by decreasing sodium intake; (b) reducing blood pressure will reduce CVD events; (c) therefore reduced sodium intake prevents CVD events. By using blood pressure vs. salt intake and CVD risk vs. blood pressure they were of course able to construct projections and conclude that modest reduction of dietary salt intake could reduce CVD events. This game has been played by a number of different investigators over the years. The suggested reduction was 3 g/day and population-wide application of the results indicated significant public health benefits in the U.S. population as a whole. It is important to appreciate that this represents an exercise in statistical arithmetics, not a clinical study where large numbers of individuals are randomized to either a normal or a salt-restricted diet and the CVD event rate observed over 5-10 years. In fact, the basis of this study appears to be simply the widely held belief that the relation of systolic blood pressure to risk of death is continuous, graded and strong and that there is no evidence of a threshold. As discussed in the November Newsletter, there is evidence that this model is false. The study by Port *et al*¹⁶ found a clear threshold effect somewhere

around 150-160 mm Hg below which systolic blood pressure presents no risk even when above the 115-120 "healthy" value.

Bibbins-Domingo *et al* state that "There is a considerable body of literature linking higher salt intake with higher blood pressure and increased cardiovascular risk, and randomized trials have shown that a diet that is lower in salt reduces both blood pressure and cardiovascular risk." The literature cited to back up the statement included no studies that had CVD endpoints and were in fact either based on the same syllogism outlined above or simply the calculation of a change in the Framingham risk factor, which represents essentially the same but somewhat cruder approach. If they had cited and discussed the highly relevant literature presented below, a rather different picture would have emerged. Furthermore, how many readers of papers such as that of Bibbins-Domingo *et al* actually dig up the references to see what they really say? This in fact is a serious problem in general and one that peer review has failed to overcome. In the case we are discussing, it is not cherry picking, it is ignoring a whole orchard.

There are a number of prospective studies over the period 1966 to 2008 which examined directly the association between sodium intake and CVD. Bibbins-Domingo *et al* fail to cite or discuss these studies or the results in spite of the obviously direct and important bearing they have on the question under study. One notable study¹⁷ by Cohen *et al* not cited by Bibbins-Domingo *et al* involved salt intake and mortality-based data available from the second National Health and Nutrition Examination Survey (NHANES II). In a community sample of over 7000 individuals considered representative of about 80 million non-institutionalized U.S. adults the association between salt intake and the risk of CVD mortality and all-cause mortality was examined based on multivariable adjusted models and

involving a mean follow-up of almost 14 years. When those with salt intakes of < 5.75 g/day were compared with those with intakes > 5.75 g/day, CVD mortality was 37% *higher* in the lower salt intake group! Alternative thresholds of 2.25 g/day to 6.75 g/day gave similar results, but the results were not observed for those < 55 years old, non-whites, or the obese, *but in any of these subgroups, salt intake < 5.75 g/d was not associated with lower CVD mortality.* For those in the group with intakes > 5.75 g/day the mean intake was 9.25 and for the group below the threshold, the mean intake was 3.95 g/day.

Cohen and Alderman¹⁸ subsequently compared the above results with 10 earlier observational studies of the association of sodium intake with cardiovascular morbidity and mortality in industrial societies and concluded that it was “j-shaped” with risk increasing at high intakes (> 10 g/day), and at lower levels (< 5 g/day) the risk also started to increase, but with no measurable effect for the widely prevalent intakes between these two thresholds. In a recent meta-analysis a small significant relation was found between salt intake and CVD only when one study was arbitrarily omitted while two other studies were included which might have also qualified for omission and probably would have caused the overall result to remain non-significant.¹⁹ In the studies used in the meta-analysis that did not appear to be outliers, 2 showed increased risk, 2 decreased risk and 5 were non-significant. However, when the meta-analysis was stratified for just incident stroke, a 23% increased risk associated with high salt intake was observed which was just barely statistically significant but 9 of the 14 studies used actually found no statistically significant effect at all.

The J-shaped relationship simply means that everyone needs a certain amount of salt, which is not surprising. Going below and above what appears to be a healthy and required range increases adverse events associated with CVD, but the effect is modest. Thus a general recommendation to decrease salt consumption by 3 g/day without regard to an individual's intake appears ill advised and simplistic.

There is another relevant issue which was discussed at length in the November Newsletter. This involved a Cochrane Collaboration study which examined the association between blood pressure treatment targets achieved with anti-hypertensive

drugs and total mortality, CVD mortality, non CVD mortality, heart attacks, and major CVD events.²⁰ When a comparison was made between targets of $\leq 135/85$ compared to $\leq 140-160/90-100$ mg Hg, there was no significant difference in the occurrence of the endpoints. This was consistent with a UK Medical Research Council study the authors cite where 18,000 individuals were randomized to blood pressure lowering or a placebo. The upper limit on baseline diastolic blood pressure was 200 mg Hg. At the end of the study there were 248 deaths in the treated group, 253 in the placebo group.

The high estimate used by Bibbins-Domingo *et al* for the impact of salt reduction of 3 g/day on systolic blood pressure was between 3.5 and 5.6 mm Hg. These two numbers should be compared to the very large range of systolic blood pressures found by the Cochrane Collaboration study to have no impact on a variety of cardiac and cardiovascular endpoints. This suggests a hypothesis that salt is only an issue for those with very high intakes (> 10 g/day) *plus* hypertension characterized by a systolic blood pressure considerably greater than 160 mm Hg. This is presumably not representative of the general population and those making public health recommendations perhaps need to refine their position. In addition, it is well known that with respect to blood pressure response, there are salt-sensitive and salt-resistant individuals. Bibbins-Domingo *et al* assume that the effect of salt reduction on blood pressure is linear over the range of 0 to 3 g/day, but in their population-based calculations this is applied to both salt-sensitive and salt-resistant individuals. Thus they clearly ignore a number of issues along with a number of highly relevant studies which render doubtful their whole approach and conclusions.

Finally, there is the issue of iodine. A number of years ago it became evident that for some, dietary intake of iodine was low enough to constitute a significant health risk and an iodide salt was added to table salt. This had a major impact on the incidence of goitre. If there is now a major move to limit salt which also limits iodine intake, this could have important implications. In addition, the salt problem is rarely discussed in the context of the ratio of dietary sodium to potassium and yet there is important synergism associated with the relative intake of these two alkali metals. It is hard to avoid the conclusion that this whole subject is at a rather primitive stage of development while we are given to believe otherwise.

GOOD NEWS FOR THOSE TAKING ANGIOTENSIN BLOCKERS

Dementia, including Alzheimer's disease is a major concern as one ages and also a major public health issue which could help bankrupt healthcare in the future. A study just published in the *British Medical Journal*²¹ reports on the impact of angiotensin receptor blockers (ARBs), one of a number of hypertension medications in common use. Others include diuretics, beta-blockers, calcium channel blockers and angiotensin converting enzyme inhibitors, the so-called ACE inhibitors. This study looked at the association between blood pressure medications and time to dementia or Alzheimer's disease in a mostly male population (about 800,000 individuals) with a mean age around 74 in a cohort with medical records in the database of the U.S. Veteran Affairs. Three cohorts were followed over a 4 year period: (a) ARB users; (b) ACE inhibitor users; and (c) what they called a cardiovascular comparator which mainly included users of beta-blockers and calcium channel blockers but excluded statins. ARBs included candesartan, irbesartan, losartan and valsartan. Compared to the cardiovascular comparators, ARB use in patients with pre-existing Alzheimer's disease was associated with a 49% decrease in admission to a nursing home and an 18% decrease in mortality. When a combination therapy involving ARBs and ACE inhibitors was compared with ARBs alone, the combination therapy was associated with a 46% decrease in risk of incident dementia, a 55% decrease in the risk of Alzheimer's disease, and a 66% decrease in risk of admission to a nursing home. The authors point out that this is consistent with recent prospective trials. Only minor differences were observed in mean blood pressure measures between the three groups. These results were all statistically significant. A significant dose dependence was seen with all the ARBs except valsartan, and losartan, the most common ARB as of 2006, showed a 18% decrease in risk when the high vs. low dosage was compared. No significant conflicts of interest were declared.

The authors discuss the obvious question of biological mechanisms. Potential mechanisms include:

- The enhanced effectiveness of ARBs over ACE inhibitors in improving the outcomes from stroke, i.e. an impact on vascular function.
- Neuroprotective responses independent of decreases in blood pressure. ARBs appear particularly effective in preventing vascular damage induced by amyloid-beta which is thought to play a role in the pathophysiology of Alzheimer's disease.
- Combination therapy may be particularly effective in reducing neuronal damage associated with stroke or vascular dysfunction.
- ARBs appear to mediate protection against deleterious effects of diabetes and this may have contributed to the positive effects found in the study.

As with most prescription drugs, both ACE inhibitors and ARBs have adverse effects (the internet provides a good source of information) but some may be unaware of the rare side effect termed angioedema which can present as severe swelling of the airway. This can occur after a number of years of use, something that comes as a surprise to those experiencing this medical emergency. Individuals who have had one episode are generally advised to carry an epipen since epinephrine generally provides a satisfactory first-response. Some residents and even some ER physicians may never have seen this side effect and fail to inquire regarding hypertension medication. The same applies to paramedics.

While your editor is not a great fan of prescription drugs and has indirect but personal experience with angioedema induced by an ACE inhibitor, this study appears quite important given the large size of the total cohort, the 4 year follow-up, and the very narrow 95% confidence limits associated with most of the risk reductions (Hazard ratios) which suggests clinical as well as statistical significance (see other report in this newsletter). The results suggest that at the first signs of mental decline, low dose ARBs might actually be justified. Individuals under treatment for hypertension who are taking ARBs should also find these results interesting. Cognitive impairment and Alzheimer's disease are obviously among the most devastating things that accompany aging.

NEWS BRIEFS

ACETAMINOPHEN AND ASTHMA

The prevalence of asthma in the U.S. is estimated at 16 million adults and 7 million children. It is the most common chronic disease in childhood. Asthma plagues the walls of the nurse's stations at summer camps with more each year. A paper just published in the journal *Chest*²² reports on a systematic review and meta-analysis of studies linking acetaminophen (Tylenol or Panadol) with asthma in both children and adults. Nineteen studies involving over 425,000 subjects were examined. Overall, the increased risk among acetaminophen users was 63%. Among children who used the drug during the year prior to diagnosis or in the first year of life, the increased risk was 60% and 47% respectively. The one study that examined the use of high doses of acetaminophen found a 223% increase in the risk of asthma. Both asthma and wheezing were associated with the prenatal use of the drug (28% and 50% increase in risk). These results all easily met the requirements of statistical significance.

The authors present strong arguments against the possibility that their results are confounded, citing the large number of studies used in the analysis and the fact that the results are multinational and involve a variety of prescribing practices and parental driven uses. Possible mechanisms discussed include the impact on glutathione levels, the induction of inflammatory cascade, and the potential adverse influence on the immune system.

The authors comment that the study is very important because acetaminophen is widely used to reduce fever and pain in both adults and children. For high fever, ibuprofen (Advil) appears to be the second most widely used agent. Unlike aspirin, it is not linked to Reye's syndrome and ibuprofen appears to lower the risk of asthma.

STATINS AND COGNITIVE DECLINE

A recent patient survey analysis concerning adverse cognitive effects was published in *Pharmacotherapy* by Evans and Golomb.²³ Dr. Beatrice Golomb from the University of California, San Diego, is actively involved in a research program examining statin adverse effects.²⁴ Golomb and Evans collected data on 171 patients reporting cognitive problems regarded as associated with statin use. Of these, the use of an adverse drug reaction algorithm selected 128 with probable or definite statin related cognitive problems. But in the total group, 143 patients who reported stopping statin therapy reported improvement in cognitive problems, sometimes within days of drug discontinuation. The median time for first-noted recovery was only 2.5 weeks. For some patients, a diagnosis of dementia or Alzheimer's disease was reversed. Nineteen patients whose symptoms improved or resolved after discontinuation of statin therapy reported recurrence of cognitive problems when the therapy was resumed, and for some this rechallenge was repeated several times with the results which were dose dependent. When seven domains of quality of life were assessed, statin therapy adversely impacted each.

These results are consistent with those reported by Dr. Duane Graveline in his recent book *The Statin Damage Crisis* (available from www.spacedoc.com), which incidentally is highly recommended for anyone taking or considering taking statins. Graveline provides a very comprehensive review of problems associated with this class of drug and has personal experience with severe adverse effects. His book *Lipitor, Thief of Memory* may be familiar to some readers and has been mentioned in this Newsletter. His experience with amnesia and memory loss is far from unique with over 1000 cases now having been reported to the FDA just from Lipitor alone, according to his latest book. It is widely believed that only about 1% of adverse reactions ever get reported to the FDA, so the incidence is probably more like 100,000. And it seems that the push is on to get almost everyone on a statin.

LAST WORD ON SATURATED FAT AND CARDIOVASCULAR DISEASE?

The conventional wisdom widely held in medical and nutritional circles is that reducing the intake of saturated fat improves cardiovascular health. This notion permeates guidelines and appears generally accepted as evidence based. An extensive analysis of the pertinent literature published in 1998 by Ravnskov²⁵ which examined a number of studies and found no effect never had any impact on the belief that there was a saturated fat-CVD connection. An in-press article in the *American Journal of Clinical Nutrition*²⁶ reports on a meta-analysis of studies published between 1981 and 2006 which address this issue. A total of 21 studies were included, 13 dealing with CHD and 8 with stroke. All were prospective with a duration ranging from 5 to 23 years and

involving a total of about 350,000 subjects. It was concluded that there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or stroke or total CVD. Subject age, sex or study quality did not change the null result. There were, however, some unresolved issues regarding the influence of nutrients that replaced saturated fat in some studies. But these did not alter the overall conclusions.

A study of this size and scope leaves little incentive for more investigations of the saturated fat-CVD issue. It may indeed be the last word. Even if saturated fat intake raises LDL cholesterol, it does not appear to matter. This is not surprising since a large number of studies that directly studied coronary plaque find that LDL does not drive atherosclerosis.²⁷ One is reminded of Gary Taubes' article with the title *What if It Has All Been a Big Fat Lie?* It is also interesting that this latest analysis fails to cite Ravnskov's large study.

Readers are referred to a Research Review in the June 2009 Newsletter for a detailed discussion of dietary saturated fat and as well to the subsequent Research Review on carbohydrate restriction, an intervention which has been condemned because of the possibility of increased intake of saturated fat.



<http://www.yourhealthbase.com/vitamins.htm>

BOOK REVIEW

***Fat and Cholesterol are Good for You!* by Uffe Ravnskov, M.D., Ph.D.
GB Publishing, Sweden, 2009**

The author is one of the highest profile critics of both the diet-heart disease hypothesis and the cholesterol-heart disease hypothesis. He has published numerous papers in major peer-reviewed journals. This is an update of his earlier book *The Cholesterol Myths*, which now appears to be a collector's item. New hard cover copies of this book published in 2000 now sell from \$125 to over \$200. Chapter by chapter, Ravnskov's new book deals with both the research and lack thereof concerning the connection between heart disease and cholesterol and dietary fats. He carefully documents his arguments and discusses all relevant studies in sufficient detail such that the reader obtains the true picture of what is and is not demonstrated. The book is written so that it is interesting and accessible to both lay and scientifically trained audiences. On the back cover he poses some interesting questions. Here is a sampling.

- Did you know that cholesterol is vital to the cells of all mammals and not a deadly poison?
- Did you know your body produces much more cholesterol than you eat?
- Did you know that your body closely regulates cholesterol production according to dietary intake?
- Did you know that heart patients have not eaten more saturated fat than other individuals?
- Did you know stroke patients have eaten less?
- Did you know that people develop atherosclerosis independent of their cholesterol levels?
- Did you know that high cholesterol is not a coronary risk factor for women?
- Did you know that high cholesterol is not a coronary risk factor for the elderly who are most prone to heart attack?

Thus this book exposes a major set of myths that are the basis of guidelines, treatment practices and in many cases set the direction of research even though there is no evidence or the hypotheses in question have been falsified. Paul Rosch, M.D., Clinical Professor of Medicine and Psychiatry at the New York Medical College,

points out in one of three forewords to the book, "As Ravnskov convincingly demonstrates, no scientific studies support the cardio-protective benefits of lowering cholesterol or saturated fat intake, and those that purportedly demonstrate such rewards are seriously flawed."

At the end of the book there is a chapter dealing with the author's view regarding what he considers a viable mechanism for the cause of heart disease and the book ends with a short chapter titled "What Shall I Do To Avoid a Heart Attack." This of course is the natural question once readers are convinced that what they have been told by the authorities for several decades is flawed or not evidence-based or just pure dogma.

This book is available from Amazon.com.

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The Prostate Monitor

Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

NUMBER 23

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*The feature of this issue of **The Prostate Monitor** involves BPH and its pharmaceutical treatment with alpha blockers or 5-alpha reductase inhibitors or both. Included are recent results of a Cochrane analysis of the benefits of saw palmetto. One of the commonly used 5-alpha reductase inhibitors is finasteride (Proscar) which was found in the Prostate Cancer Prevention Trial to fairly dramatically reduce the risk of prostate cancer. In this issue we discuss the question of whether all men past a certain age should take finasteride for this purpose, or if there is a way of selecting those who would benefit*

most.

No one doubts that high doses of radiation cause cancer and yet high doses are delivered during radiation therapy. Thus there is interest whether or not radiation therapy causes more secondary cancers than would otherwise arise. As discussed, this turns out to be a tricky question.

A recent paper by two radiation oncologists took the position that the best treatment choice for localized prostate cancer is radiation therapy. This position will be discussed but these two physicians are obviously promoting their own speciality.

Other topics in this issue include an attempt by scientists to identify why the traditional Mediterranean diet appears protective for prostate cancer, the current status of intermittent androgen deprivation as compared to continuous treatment, and another look at the perennial subject of false positives in PSA screening.

Wishing you good health,

William R. Ware, PhD, Editor

You can order *The Prostate and Its Problems* at <http://www.yourhealthbase.com/prostate/book.htm>

BENIGN PROSTATIC HYPERPLASIA (BPH)

The lay term for this problem is enlarged prostate. Symptoms include increased frequency of urination, reduced flow rate and difficulties in general associated with urination, and increased frequency during the night. The acute presentation is the inability to urinate at all—so-called acute urinary retention. The problem was already known in the 15th century and in Victorian times men with severe urinary symptoms carried catheters in hollow shafts of their walking sticks or umbrellas in order to deal with a crisis. Even cowboys were said to carry catheters in their hats. In chapter 2 of our book *The Prostate and Its Problems* we discuss BPH in detail including both conventional and alternative therapies and well as prevention of this distressing but highly prevalent problem. Most men will have to confront the problems associated with BPH sometime during their lives.

The first-line treatment for BPH is the so-called alpha-blocker which addresses the problem principally through the autonomic nervous system and functions by reducing vasoconstriction and smooth muscle constriction. The alpha-blocker was historically a popular medication for hypertension. An alternative is the 5-alpha reductase inhibitor (5ARI), the most common being finasteride (Proscar). This drug inhibits the conversion of testosterone to dihydrotestosterone, a steroid thought to be implicated in BPH by influencing prostatic epithelial proliferation. A newer 5ARI is dutasteride (Avodart). When compared to 5ARIs, alpha blockers are either approximately equivalent or slightly better in reducing symptoms. However, the 5ARIs reduce the volume of the prostate and are more effective in preventing the progression to a crisis. One reason the alpha-blocker is the preferred first-line treatment is that the results are apparent in a few days to a week or two, whereas the 5ARIs take much longer to produce symptom reduction. It is not uncommon to prescribe both and then withdraw the alpha-blocker after a few months. Issues associated with the use and side effects of both alpha-blockers and 5ARIs are discussed at length in our book. Since most men will be bothered by BPH in later life, some critically, men need to educate themselves regarding this disorder.

One question which has recently received considerable attention involves the relative merits of monotherapy with either the alpha-blocker or the 5ARI vs. combined therapy. The two issues are relief of symptoms and prevention of progression to acute urinary retention or the need for surgery to relieve obstruction. Two recent reviews have appeared which deal with this subject by examining randomized trials of both short (about 1 year) and long (about 4 years) duration.^{1,2} Some studies have also considered the impact of prostate size on effectiveness. There are only two randomized trials that were of adequate duration to address the acute event question. One used Tamsulosin and dutasteride and went for 54 months, the other tested doxazosin and finasteride over 48 months. Both found that combination therapy was superior to monotherapy as measured in terms of the need for BPH related surgery or the incidence of acute urinary retention. Typical reductions in relative risk were between 70 and 80% and were statistically significant when the comparison was with the alpha-blocker or 5ARI monotherapy. For comparison, one study of 48 months duration that compared a placebo with finasteride found a 55-57% risk reduction for acute events and similar results were found when dutasteride was compared with a placebo. These results were somewhat better to that obtained with the alpha-blocker doxazosin vs. a placebo. Thus it appears that while there are only small differences between alpha-blockers and 5ARIs for the relief of symptoms, for preventing progression to acute events, monotherapy with 5ARIs or combination therapy produce the best results, with the latter considerably superior.

As discussed in this Newsletter, the results from the Prostate Cancer Prevention Trial (PCPT) involving therapy for BPH with 5ARIs found that this drug also reduces the risk of localized prostate cancer. However, there is some question regarding an increased risk of high-grade cancer, although the weight of evidence appears to be swinging toward the belief that the observation that 5ARIs increase the risk of advanced cancer is an artefact due to detection bias. Furthermore, several studies that re-analysed the results of the PCPT trial find weaker or no evidence regarding enhanced high-grade cancers. It has also been suggested that if there is an effect on the incidence of high-grade cancers, it might be due to the selective inhibition of one of the two forms of 5-alpha reductase. Since Dutasteride inhibits both forms,³ it has been suggested that the ongoing trial using this 5ARI may not show enhanced high-grade cancer at all.

5ARIs also reduce PSA levels to about half the pre-treatment level which complicates the use of PSA in screening. It is common to multiply by two to compare with guidelines and the uncertainty introduced does not

appear significant given the limited utility of PSA values in the context of predicting the presence of prostate cancer.

At the time *The Prostate and Its Problems* was published, the evidence suggested that the herbal supplement saw palmetto was equivalent to finasteride in relieving symptoms of BPH. This was based on a 2002 Cochrane meta-analysis. However, recent studies have significantly weakened this conclusion. A new Cochrane review published in 2009 now takes the position that saw palmetto is no better than placebo in improving urinary symptom scores, but they reserve final judgement until better studies become available that are adequately powered with a minimum follow-up of a year and used validated symptom-scale scores.⁴

FINASTERIDE TO PREVENT PROSTATE CANCER

The Prostate Cancer Prevention Trial (PCPT) found that finasteride (Proscar) used to treat BPH also significantly reduced the risk of prostate cancer by close to 25%. However, enthusiasm for this intervention was dampened by the observation of a small increase in advanced cancer. As mentioned above, subsequent studies have found that this result was most probably an artefact related to differential sampling of high grade cancer in small prostate volumes and the current view is that finasteride does not induce high-grade disease. If one accepts this conclusion, then there is the question of the population which would most benefit from this intervention. A recent study attempted to answer this question based on an analysis of the PCPT data.

The PCPT trial randomized men age 55 or more with no previous PC diagnosis, a normal DRE, and a baseline PSA of ≤ 3.0 ng/mL to either a placebo or 5 mg/day of finasteride. Some men developed PC during the 7 year follow-up identified by biopsies “for cause.” The remainder were asked to submit to a biopsy at the end of the study. Biopsies were also recommended for anyone developing a PSA > 4.0 mg/dL (adjusted for the drop due to the drug treatment). An examination of the data led to the conclusion that if a clinician wished to reduce the risk of any biopsy detectable cancer, finasteride should be recommended to all men. If the clinician believed that it was unnecessary to prevent all cancers, but preventing those readily detectable by screening would be desirable, then it would be best to recommend finasteride only to a high-risk subgroup. This group could be reasonably defined by either a threshold of 2 or 1.3 ng/mL and these two cut-offs defined either 20% or 40% of the population respectively. For example, treating only men with a PSA > 2 mg/dL reduced the treatment rate by 83% and resulted in a cancer rate only 1.1% higher than treating all men.⁵

SECONDARY CANCER AFTER RADICAL PROSTATECTOMY VS. RADIATION THERAPY

As was discussed at length in a recent Research Review, low levels of radiation exposure such as are associated with diagnostic procedures may or may not have any impact on the risk of cancer and in fact, contrary to the universally held belief, there is considerable evidence that low levels of exposure may confer protection. However, the doses used in radiation therapy for prostate cancer are in a range where there are grounds for significant concern. A recent study based on Canadian data (Quebec Health Plan, an exclusive insurer in that province) examined this question by looking at the excess rates of secondary cancer in 8455 radical prostatectomy (RP) and 9290 external beam radiation therapy (RT) cases between 1983 and 2003.⁶ The frequency of secondary bladder, lung and rectal cancer was examined. The results were adjusted for age, comorbidity and year of treatment. Since EBRT is not known to cause cancer in the short term, the investigators restricted the analysis to incident cases that occurred after 5 or 10 years. The adjustment for comorbidity took into account the confounding by premature mortality not allowing the development of secondary cancers. Previous studies, mostly based on U.S. populations, had shown increased risk for almost all malignancies associated with RT vs. RP. The rationale for this study was the distinct genetic, dietary, environmental and health economical differences that distinguish men treated for prostate cancer in Quebec as compared to the U.S.

When only cases appearing after 5 years were considered, RT vs. RP carried a 50% increase in risk of bladder cancer, an 80% increase for lung cancer and a 90% increase for rectal cancer. The corresponding numbers when cases were restricted to those diagnosed after 10 years were 100% for bladder cancer, 190% for lung cancer and 60% for rectal cancer. The results after 5 years were all statistically significant, but those related to

the post 10-year period, only lung cancer differences were significant. In absolute terms, the increase in rate of bladder, lung and rectal cancer were 3.9%, 5.2% and 2.4%, yielding numbers needed treat to cause harm of 26, 19 and 42 respectively.

The authors comment on the view of some epidemiologists that it is valid only to consider malignancies that occur 10 or more years after exposure. If one accepts this view, then only lung cancer was significantly enhanced, and at 15 years there was only a 2.2% absolute difference in event-free survival separating RT for RP treated individuals. Thus from this point of view, there is not much reason for concern. This still leaves the 5-year results which should, according to the researchers, be considered in the context of informed consent.

DIET, NUTRACEUTICALS AND PROSTATE CANCER PREVENTION

A recent systematic literature review concerning diet and prostate cancer (PC) has appeared in the journal *Molecular Nutrition and Food Research*.⁷ The review focuses on the Mediterranean diet and its components since compared to many Western countries, Greek men have much lower prostate cancer mortality. Association of PC risk and foods and nutrients common to the Mediterranean diet (MED) were as follows:

- *Lycopene*. Probably reduces risk. Tomatoes and tomato paste are key ingredients in the traditional MED and tomatoes.
- *Selenium*. Probably reduces risk. Marine foods are integral to the MED and octopus, a common appetizer contains about 100 microg/g.
- *Vitamin E*. Possibly reduces risk. The main sources of vitamin E in the MED diet are olive and sunflower oil, nuts and seeds. The form of vitamin E in food is different than tested in randomized trials for PC prevention.
- *Legumes*. Possibly decreases risk. Legume sources in the MED diet include beans, nuts and seeds
- *Omega-3 fatty acids*. Long-chain omega-3 fatty acids may reduce the risk although alpha-linolenic acid may increase the risk. The MED diet contains reasonable amounts of fish and other sea foods but does include some intake of alpha-linolenic acid.
- *Fat*. While traditionally considered a risk factor, recent studies indicate that no risk exists. The MED diet is relatively low in saturated fat but this is not the case for total fat.
- *Olive oil*. Unfortunately, there are no studies dealing with the association of olive oil consumption and the incidence of prostate cancer. However real extra virgin olive oil is rich in antioxidant phytochemicals and is a major component of the MED diet both for salads and as a dip.

It is interesting in this context that Fradet *et al*⁸ found that 0.6 g/d of EPA and DHA reduced the risk of aggressive prostate cancer by 64% based on a case-control study of about 500 men diagnosed with aggressive disease.

The authors of the review comment on the fact that clinical trials focus only on individual foods and nutrients rather than diets as a whole. What is known, as outlined above, suggests that one reason Greek men have low rates of prostate cancer may be due to their overall diet pattern. Since the MED confers a number of benefits unrelated to cancer prevention, it should be seriously considered as an alternative to the Western diet. Nevertheless, the overall evidence in the context of prostate cancer remains rather weak.

IS RADIATION THERAPY FOR PROSTATE CANCER “THE WAY TO GO”???

For localized PC the management options are radical prostatectomy, external beam radiation therapy and radiation therapy using radioactive inserts (brachytherapy). The relative merits of radiation vs. surgery have been debated over the years, but at the same time there have been significant changes in the techniques, and in particular in the use of external beam radiation therapy. Through the use of intensity-modulated radiation therapy (IMRT) it has been possible to better target the prostate and escalate the dose which has resulted in improved outcomes. The combination of IMRT and androgen deprivation therapy (hormone therapy) either before or before and during radiation therapy also appears to have improved outcomes, as has been discussed in the Prostate Monitor.

In a recent short paper in the journal *Oncology*⁹ two radiation oncologists take the position that IMRT is the only way to go. Their argument is that for localized cancer when surgery and IMRT are compared there is no significant difference between outcomes, at least over the first 10 years. They also cite evidence suggesting that the adverse effects as measured by a quality of life score related to urinary symptoms, sexual function, bowel function and vitality of hormone function were higher for IMRT than RP in all categories except bowel function which had only a slightly lower long-term average score. IMRT also ranked higher than RP when the opinion of partners was obtained. They therefore suggest that IMRT should be favored since it avoids surgery with its associated small but finite risk of mortality and its potential morbidities.

There are other pros and cons they do not consider such as the absence of pathological data in most cases for patients undergoing RT since the prostate itself is not available for examination. Also, there is a much longer period before PSA becomes a useful indicator of recurrence and if there is recurrence, salvage radical prostatectomy is now much more difficult. The recommendation also does not consider the small but finite possibility that the treatment will be carried out improperly with overdosing or poor focusing on the organ. In a future Prostate Monitor this problem will be discussed since the potential exists for serious or even fatal consequences and the problem has been popularized by recent media attention concerning selected disasters. On the other side, RT is much easier to integrate into everyday life and has minimal impact in general on the ability to work.

WHERE DO WE STAND ON INTERMITTENT ANDROGEN DEPRIVATION

A systematic review has just appeared in the journal *European Urology* which examines the current status of intermittent androgen deprivation (IAD) compared to continuous androgen deprivation (CAD), i.e. intermittent vs. continuous hormone therapy.¹⁰ The issues discussed are as follows:

- *Survival.* Most studies fail to find significant differences in time to tumor progression or progression free survival or overall survival when IAD is compared with CAD. However, one study found that the risk of 3-year progression was significantly higher in CAD patients than in IAD patients (38.9% vs. 7%, and in patients with a Gleason score > 6, the 3-year progression rates were also significantly higher, but this was not true for those with lower Gleason scores. IAD was better than CAD when judged by the number of deaths from hormone-refractory disease, the number of patients with disease progression and the mean time to tumor progression. In phase III trials, comparisons yield either null results or were in favour of IAD over CAD, in particular with regard to 3-year risk of progression or the progression-free survival.
- *Tolerability and quality of life.* Short-term studies find IAD to have a promising tolerability profile, decreased adverse events and an improvement of quality of life during the off-therapy periods, although not all studies are consistent. IAD appears to be slightly better than CAD in reducing levels of impotence. Also there appear to be smaller numbers of patients withdrawing from treatment due to adverse effects.
- *Who may benefit most from intermittent therapy??* Based on several papers, it appears that men with local or biochemical failures after RT would benefit from IAD because they are treatment-free for longer periods of time and so are less likely to develop hormone-refractory disease. IAD appears to be superior to CAD for patients with poorly differentiated cancer or those without apparent bone involvement. One study identified patients >70 years of age with localized PC, a Gleason score of ≤ 7 and a first off-therapy period of > 1 year as the best candidates for continued IAD. Poor candidates are those characterized with initial bulky tumors with numerous lymph node or bone metastases, PSA doubling times of < 9 months, a high initial PSA or severe pain associated with metastasis. In general, patients with biochemical failure following RT or RP and those who cannot tolerate side effects of CAD and those who wish to remain sexually active would appear to be good candidates.

FALSE POSITIVES IN A FINNISH PROSTATE CANCER SCREENING TRIAL

In this screening trial, men with a PSA ≥ 4 ng/mL were referred automatically for a biopsy. For those with PSA between 3.0 and 3.9 mg/dL, biopsy referral was based on either a positive digital rectal exam (DRE) or a free to

total PSA determination (F/T) using a < 16% cutoff. Men in the screening trial were then re-invited after 4 or 8 years to second and third rounds of screening. A false positive (FP) was defined as a positive screening result based on total PSA and either a DRE or PSA F/T ratio followed by a negative biopsy within a year of the PSA test. Those who had a positive screening result but declined the biopsy were excluded. The overall risk of a FP in the first round was 6.4%, 8.0% in the second and 7.8% in the third round. Of men with a positive screening result in the first round, 67% turned out to be FPs and 27.5% were diagnosed with prostate cancer. In the second round, the numbers were 64.6% and 26.6% whereas in the third round they were 60.7% and 26.7%. Overall, one in 8 men who participated in repeated screening experienced a FP result. The authors comment that FP men constitute a special group that receives unnecessary interventions but may harbor missed cancers. The results of this study underline the urgent need for a better screening protocol.¹¹

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