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William R. Ware, PhD - Editor

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This issue begins with an editorial comment on what modern medicine has to offer those with chronic disease. The motivation involved reflection on the remarkable successes that have been achieved by alternative medicine for the treatment of Alzheimer's and Parkinson's disease, heart failure, cancer and type 2 diabetes, all of which have been reported recently in issues of this newsletter. In a future issue, the success of alternative medicine in treating and even curing autism will be featured. Yet alternative medicine is aggressively opposed and discouraged by mainstream practitioners and opposition is also strong among academic experts. This is an unfortunate and complex situation involving money, egos, dogma and the necessity of preserving confidence in the only system readily available to the general public.

Also discussed in this issue is the standard practice of Big Pharma of achieving a patent medicine by a minor modification of a naturally occurring molecule. In this case it is docosahexaenoic acid (DHA) which we evolved to obtain mostly from eating fish. A modified form has recently been approved as a prescription drug even though its bioavailability is probably less than the natural product and the cost certain to be vastly higher. Evidence is presented that there appears also to be no therapeutic advantage. Other subjects addressed include alcohol and rheumatoid arthritis, cataracts and statins, job-related stress and cardiovascular disease, statins and vascular calcification in diabetics, and finally the importance of certain micronutrients in preventing pancreatic cancer. For this cancer, prevention is the only answer since it is generally fatal within 6 months of diagnosis, no matter what heroic measures are taken by oncologists.

If you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

CHRONIC DISEASES AND MAINSTREAM MEDICINE. AN EDITORIAL COMMENT

The major chronic diseases of adult and especially older individuals are type 2 diabetes, cardiovascular disease and heart failure, Alzheimer's and Parkinson's disease, cognitive impairment, kidney disease, and arthritis including rheumatoid arthritis. These are all characterized by progression although the rates vary considerably. Even though

diagnosis and staging have reached impressive levels and are constantly improving, some of these diseases have long silent periods where presence and progression cannot be detected.

In primary prevention, assessment of risk factors for chronic diseases is standard practice, and advice regarding diet and exercise is frequently provided, the former thought by some to be uninformed. Identified risk factors are also addressed by pharmacotherapy, an approach with generally better compliance. A patient may be told that taking this pill every day forever will reduce the risk of some chronic disease by, say 40%. But the patient may not be told that for every 100 patients taking this pill, only one patient benefits over, for example, 10 years. Same pill, same data justifying the intervention. Many drug treatments for secondary prevention suffer from the same large number of patients needed to treat to obtain one favourable result. This calls into question the common belief among the general public and the profession that the pharmaceutical approach to prevention is actually effective. At issue here is a realistic standard for effectiveness.

Mainstream medicine appears able to do the following in the context of therapy for the above chronic diseases.

- Relieve or more frequently moderate symptoms.
- Slow, and on rare occasions arrest progression and on very rare occasions produce regression in measures of a chronic disease. Regression is all too often minor and perhaps even trivial but measurable, and as well may not be durable.
- Alter biomarkers, surrogate or otherwise, in a theoretically favourable direction. However, there is a lack in many cases of convincing data as to the long-term impact on mortality or morbidity, especially when the changes in biomarkers are small or the relationship between the biomarker and acute events is weak.

Absent from this list is the word *cure*. Chronic diseases are considered in general to be incurable. Conventional treatments do not cause dramatic reversal in coronary plaque such that it disappears, nor do they reverse the cardiac functional decline associated with heart failure with the return to normal function. The pathological manifestations in the brain of Alzheimer' and Parkinson's disease, as seen at autopsy or in scans, do not disappear nor do the symptoms and disabilities. Cures for type 2 diabetes generally come from alternative medicine where difficult to follow diets are maintained for long periods with return of insulin sensitivity and normal HbA1c, but mainstream medicine uses medication and apparently ineffective diets and does not generally achieve cures. For kidney disease, when drug therapy becomes ineffective it is treated with dialysis, removal of a diseased kidney(s) and the last resort, a kidney transplant.

The kidney example might give the impression of achieving a "cure" but it involves replacing damaged parts with used but better parts. Similar approaches involve bypassing damaged areas with replacement parts. These approaches are similar to car or appliance repair. To call curing the damage caused by arthritis by joint replacement is a special use of the term. The same is true of cardiac revascularization, which also only provides a permanent "cure" in a fraction of patients undergoing these procedures. Stents and grafts plug up again. Other examples of the part replacement approach to a cure include organ transplants of hearts, kidneys, lungs and livers. In many cases the new but used parts function normally and procedure is a success, although the accompanying lifelong immune suppression has serious side effects. Thus, the surgeon with access to high quality spare parts plays a significant role in mainstream medicine being able to cure a very limited number of disorders. When this approach fails, it is frequently a death sentence. The repair and replacement field will probably be vastly different a decade from now due to the active research approaches, such as the use of stem cells.

There is also a distinct difference between the part replacement cure and the cure commonly obtained by treating infections with antibiotics or fungal infections with antifungal agents. If successful, the problem is gone. But drug resistant bacteria present a serious and growing problem, and damage to the gut with

antibiotic use, especially frequent use, may cause a new problem frequently difficult to diagnose.

Furthermore, what mainstream medicine appears unable to accomplish except on rare occasions, is therapy without side effects. Patent medicines are notorious for side effects and recalled when the magnitude of the problem becomes unacceptable, which does indeed occur regularly. By definition, almost all patent medicines involve the introduction of an agent into the human system it never seen before, and in addition, in many cases cause an abnormal alteration in biochemical pathways with a multiplicity of unintended consequences. Side effects prompt more medication until some individuals end up still sick and taking a staggering number of drugs (nursing home average, 10-20).

Evidence of benefit from a treatment of a chronic disease is frequently inflated, especially in the case of patent drugs. Universal use is made of relative measures which can be very large but conceal minute or nil real benefit as measured by the number needed to treat to obtain one beneficial result. Millions take statins in the belief that this will significantly reduce their risk of developing heart disease, but the evidence is compelling that statins do not impede the progression of coronary artery plaque. Screening for chronic diseases results in over-diagnosis and over-treatment, again with unintended consequences. The treatments mainstream medicine has to offer for chronic diseases are frequently described as evidence based, but as discussed in the last IHN, the evidence can be flawed by dishonest, biased, or downright fraudulent studies and still pass inspection by regulators. According to a just-published study appearing in the *New England Journal of Medicine*, we have reached the point where industry sponsorship of clinical trials influences physician's (internist's) perception of methodological quality and reduces their willingness to believe and act on industry supported trial findings, independent of the trial's quality.[1] The industry willingly pays fines for criminal fraud and offers settlements measured in billions of dollars, as a cost of doing business but money will not combat the new perception of the industry based on a steady stream of negative if not shocking revelations such as ghost writing and suppression of undesirable results. And money will probably not restore faith in what is really at issue, integrity, honesty and a corporate philosophy that puts patient benefit and safety first. Unfortunately, companies with high ethical standards can suffer unfairly from guilt by association.

When one reads books and articles by medical doctors who have integrated alternative medicine in their practices, a common thread that runs through their narratives is that when they began to practice after completing their medical training, it soon became apparent that in many cases what they had been taught was not working. The patients either did not improve or got worse. The endocrinologist Dr. Diana Schwarzbein, in her book *The Schwarzbein Principle,* tells the same story in the context of treating diabetics soon after starting to practice. This experience can be a powerful incentive for some to examine and try alternatives, the use of which is contrary to their training, indoctrination and official guidelines. However, awareness of success spreads by word of mouth and in some cases their clinics become well known locally and then in some cases nationally or internationally. Some started to write newsletters to increase awareness that there were alternatives that work, as measured by their standards and experience as medical doctors. Examples include Drs. Stephen Sinatra, David Brownstein, Robert J. Rowen, Julian Whittaker, and Jonathan V .Wright. But those who step outside the conventional box run great risk of harassment from peers and the local medical societies which "govern" them. Some have the courage, but most appear unwilling to risk their careers. This is the way the system works, and it is one reason why alternative medicine has a steep hill to climb.

There is also a stigma attached to alternative medicine due to a long history of quack medicine, treatments with no biological plausibility, and treatments that when studied proved worthless. Thus, the negative or sceptical attitude of mainstream medicine is easily understood, but is nevertheless not a justification for *a priori* rejection of all alternative approaches unless rigorous clinical trials indicate efficacy, an unrealistic requirement since potential profits do not justify the expense of trials. There is also the

problem of trials of alternative therapies or supplements intentionally or inadvertently designed to fail. There is obviously a real risk of rejecting a therapy which really works, in fact so well that the randomized controlled clinical trials may not be necessary. No one has ever suggested that randomized controlled trials are required for snake anti-venom therapy.

In recent issues of IHN, several alternative approaches for chronic disease having strong biological plausibility are reviewed in some detail. These included medium chain triglyceride oil and coconut oil to treat Alzheimer's or Parkinson's disease, Coenzyme Q-10 for heart failure, salvestrols for the treatment and prevention of cancer and carbohydrate restriction for type 2 diabetes. These approaches appear vastly more effective than conventional therapy, but being alternative and non-pharmaceutical (translate—not patentable), they are ignored and patients wishing to try them may be aggressively discouraged.

Prevention of chronic disease today focuses mainly on targets (risk factors) such as lipids, blood glucose and blood pressure. Millions have been spent on research but aggressive lowering has been found to have little or no impact on mortality or morbidity. This approach appears to be ineffective in significantly preventing cardiac events, diabetes and mortality and may cause harm.[2] Underlying causes are ignored. Mark Hyman likens this to mopping up the floor around an overflowing sink rather than turning off the faucet, which is why patients end up taking medications targeting risk factors for life.[2] The practitioner is not to blame for this state of affairs since there is a lack of effective officially sanctioned tools to deal in a truly effective manner with many of the daily challenges faced. The culture in which he or she works aggressively discourages thinking outside the box or trying unapproved, non-pharmaceutical approaches, although the pharmaceutical industry has been sensationally successful in promoting approved drugs for non-approved (off-label) interventions.

Hyman directs attention instead to a comprehensive approach of treating the whole system and not the symptoms with a whole-food plant-based diet rich in omega-3 fats, phytonutrients, antioxidants, taking supplements, engaging in exercise, limiting toxic substance intake, and what is probably the most important intervention, psychological stress management. Readers are encouraged to study the book *Ultra- Prevention* by Mark Hyman and Mark Liponis (Scribner, 2005), for an introduction to the "systems' approach to medicine. Other books by these two MDs who clearly think outside the box are also highly recommended (see Amazon.com).

FDA APPROVES NEW EPA PRESCRIPTION "DRUG"

The issue here is prescription omega-3 formulations intended in general for the same indications that prompt the recommendation for taking over-the-counter preparations. The prescription versions are of course generally considerably more expensive. The classical example in this context is the preparation Omacor® (now called Lovaza®) a mixture of the ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The ethyl ester occurs when ethyl alcohol reacts with the acid group on the fatty acid (COOH) to replace the "H" with an ethyl group (CH_2CH_3). The ethyl esters of these two fatty acids do no apparently occur naturally. To understand the difference between the esters and the free acids, one must understand that when we obtain these long-chain omega-3 fatty acids from fish, they are ingested as triglycerides with the two acids and a third molecule attached to a glycerol backbone. Digestion in the small intestine produces the two free fatty acids EPA and DHA. These metabolic products are then absorbed by the intestinal enterocytes and then reassembled as triglycerides and transported into the circulation. When instead one ingests the free esters of EPA and DHA, the ester group is more slowly broken off by enzyme action and the reassembly is less efficient because of the missing third molecule present when the natural triglyceride is broken up. This suggests that transportation to the blood is more efficient with the natural triglyceride and this is

confirmed by numerous studies of comparative bioavailability which on average find a 25% decrease.[3,4] One reason for the preparation of the esters involves making the distillation process of concentration and separation of EPA and DHA more efficient. In fact, omega-3 preparations where the label describes the preparation as concentrated or refined will probably be a mixture of the ethyl esters of EPA and DHA, not the natural triglyceride containing these two acids we evolved to metabolize after eating fish.

In the pharmaceutical industry play-book, one of the basic approaches to drug development is to find a natural product that works, make a minor modification in the molecular structure, patent it and then attempt to get regulatory approval, after which the new drug can be sold at significant if not astronomical mark-up compared to the natural product available at the local health food store. The FDA in the US has just approved the drug with the temporary name AMR101 for the oral treatment of highly elevated triglycerides. The modification made to achieve drug status in this case was to convert the acid moiety on EPA to an ester with the non-proprietary name *icosapent* ethyl also known as ethyl eicosapentaenoic acid or EPA ethyl ester. The drug is almost pure EPA ethyl ester with no DHA or DHA ethyl ester. According to a news release in *heartwire* , the FDA approval was primarily based on the 12-week phase III MARINE clinical trial.[5] This trial involved about 230 patients with very high triglyceride levels (TG ≥500 and ≤ 2000 mg/dL). The company is also seeking approval for use of this new drug on patients on statins with high TG levels based on the data from the ANCHOR clinical trial.[6] In this trial the participants had much lower but still elevated TG levels ≥ 200 and ≤ 500 mg/dL. These triglyceride levels can be put in context by considering the data from a national survey in the US.[7] The population percentages for ≥ 200 mg/dL was 18%, ≥ 500 mg/dL, 1.7%, and > 1000, 0.4%. Thus about 82% had levels below 200 and the Marine study results were relevant to less than 2% of the total population and the ANCHOR study about 16%.

The MARINE study found that 2 g/day of the drug lowered TGs by 19% for those with TG levels up to 700 mg/dL and 33% for those above 750 mg/dL. For 4 g/day, the figures were 33% and 45%.[5] For individuals with TGs between 200 and 500 mg/dL, the ANCHOR study found for 2g/day and 4g/day that the TG lowering was 10% and 22%, respectively.[6]

It is interesting to compare these results to studies that mostly used fish oil or an omega-3 oil derived from algae. A recent analysis of 18 studies found 2 g/day of EPA and/or DHA lowered TGs by 15% and 4 g/day by 25%. Baseline TG levels ranged from 80 to 230 mg/dL.[8] There do not appear to be studies that focus on the natural treatment of the very small population having TG levels ≥ 500 mg/dL. However, the ANCHOR results appear to be similar to what would be expected from using a product from the health food store.

Triglyceride levels are being used in these studies as surrogate markers for cardiovascular risk. However, as the ANCHOR authors point out and document, recent clinical trials have failed to show a decrease in cardiovascular events with triglyceride lowering. In addition, a weakness in both MARINE and ANCHOR is that there was no comparison with over-the-counter preparations, either omega-3 or other compounds. Nevertheless, the new drug is anticipated to have a huge market since it will go head to head with Lovaza which has a market of about one million US$ per year. AMR 101 has the perceived advantage of not elevating LDL cholesterol, although there do not appear to be studies regarding the increase in cardiovascular risk when LDL is elevated by a small amount with a drug, and inverse extrapolation from statin trials is not justified because studies find a very small impact of lipid lowering when considered as absolute risk reduction, especially in individuals who do not have heart disease.

MICRONUTRIENTS AND RISK OF PANCREATIC CANCER

Most readers probably were acquainted with or know of someone who died of pancreatic cancer. A high profile recent fatal case was that of Sally Ride, the space pioneer. The mortality rate is almost 100% and death occurs rapidly. It is almost always diagnosed when in a late stage since unless advanced, pancreatic cancer does not produce symptoms.

A study has just appeared in the journal *Gut* which examined the role of dietary micronutrients and the risk of developing pancreatic cancer.[9] The study involved over 23,000 men and women recruited in 1993 to 1997 and followed for 17 years with the statistical analysis carried out at the end of 10 years as well since this was the primary endpoint. Dietary intakes of vitamin C, E, selenium and zinc were estimated by a 7 day food diary and serum vitamin C levels were obtained at recruitment.

Between 1 and 10 years, 49 participants (55% women) developed pancreatic cancer on follow-up, which increased to 86 after 17 years (56% women). The mean time between recruitment and diagnosis for those diagnosed within the first 10 years was 5.8 years and for 17 years it was 8.6 years. Median post-diagnosis survival for the two study periods was 5.0 months and 6.0 months.

Those whose diet provided the highest 3 quartiles of vitamins C and E and selenium reduced their risk by two-thirds after 10 years follow-up compared to the lowest quartile and the risk was statistically significant. However, while protection was also seen after 17 years, the results were only close to statistical significance. When those in the highest vs. the lowest quartiles of baseline serum vitamin C were compared, the risk reduction at 10 years was 80% and 57% at 17 years, both statistically significant.

The highest quartiles for the daily intake of vitamin C, vitamin E, selenium and zinc had ranges of 111 to 655 mg/day, 12 to 75 mg/day, 72 to 276 microg/day and 10 to 25 mg/day whereas in the lowest quartile the numbers were < 51, < 7, < 44, and < 7 in the same units. It is noteworthy that the intake in the highest quartiles is not particularly high. Life Extension One-A-Day comes near the upper end the ranges given, but for some popular brands, 2-3 tablets/day would be required if supplements were the sole source.

The protection from selenium intake exhibited a threshold, and when exceeded there was a risk reduction of about 50%. This result is consistent with another recent study where selenium intake was estimated by toenail analysis. For those with high selenium levels, the risk reduction was 75% to 90% for the risk of pancreatic cancer.[10]

These studies exhibit very large effect sizes, and while the number of cases was low and the intake and serum vitamin C measured only once, they are not dismissed easily and suggest a strong dependence of the pathophysiology of pancreatic cancer on micronutrients or what can also be described as cofactors for important enzyme reactions.

ALCOHOL AND RHEUMATOID ARTHRITIS

This question has be examined in a follow-up study reporting in July, 2012 in the *British Medical Journal*.[11] Data was collected in 1987 and 1997 and follow-up was from 2003 to the end of 2009. Two tables present the relative risks stratified by either consumption or type of drink. Alcohol consumption in this cohort was modest by most standards, with the heaviest drinkers in the > 4 drinks per week. The table stratified by consumption provided 12 results, 11 statistically non-significant, with > 4 drinks per week reaching statistical significance after adjustment for age and smoking. Stratification by drink type produced 18 non-significant relative risk results. The one result out of 30 was enough for Journal Watch (New England Journal of Medicine Newsletter) to comment, “This prospective study affirms that moderate alcohol consumption is associated with lower risk for rheumatoid arthritis in women.” No mention of the uncertainty introduced by 29/30 results that were all non-significant. Also, if

one compares never drinkers (21/4290 cases) with > 4 drinks/week (37/7497 cases), the absolute risk one can calculate in each group is exactly the same with a rate of 0.49%. or 5/1000, i.e. *no absolute risk reduction*. Are we to believe that one starts seeing a benefit at less than one drink per day (about ½ drink, actually). Furthermore, how much faith can one put in alcohol consumption measured in 1987 and 1997 and then looking at cases up to the end of 2009, a maximum of 22 years. Also, > 3 drinks per week produced the only other significant risk reduction but 2-4 drinks per week did not. Bit odd.

The real picture seems to be that this study had too few cases, had too long a period between consumption assessment and the end of the trial, and the amount of alcohol consumed might even be considered almost negligible. But the take-home message in the abstract was a 37% decrease in RH risk for > 4 glasses/week.

Drinking alcohol in moderation is protective in an amazing number of disorders including autoimmune diseases. It was suggested in an earlier issue of IHN in a review of the methanol-formaldehyde hypothesis that part of the protection derives from blocking the metabolism of dietary and inhaled methanol to give formaldehyde which is highly toxic. Thus it is plausible that if the alcohol intake had been considerably higher in this study, a much more convincing positive result would have been obtained.

ASSOCIATION OF CATARACT WITH TYPE 2 DIABETES AND STATIN USE

Diabetes is a known risk factor for cataracts. Statins are commonly prescribed for diabetics. Little is known about the association between statin use and cataract, partly because only short term studies included this side effect. However, animal studies have clearly shown a correlation between the risk of cataract development and chronic statin treatment. Contradicting earlier studies, a recent study of a large UK population found an increased risk suggesting additional studies were indicated.[12,13]

A study has just reported that involved 6397patients with data that allowed the examination of the question of independent effects from diabetes and statins.[14]. The results expressed as odds ratios from multivariable analysis found 1.60 for type 2 diabetes and 1.57 for statin use, i.e. 60% and 57% risk increase. When stratified by type of cataract, only cortical was not found to be significantly associated with statin use. For the other two types, the odds ratios were both 1.48.

It is informative to look at the actual incidence percentages stratified by type 2 diabetes and statin use. The results are given in the following table and suggest large absolute risk increases.

Percent Incidence of cataracts comparing statin use with and without diabetes

Age range, years	40-49	50-59	60-69
Type 2 diabetes			
% Statin use	29.4	65.3	93.5
% No statin use	12.0	56.0	80.4
No diabetes			
% Statin use	16.7	56.3	87.2
% No statin use	11.0	34.6	81.3

For the 30-39 age group the number of cases was very small. For > 70 in all four stratifications in the table the percentage with cataracts was above 98%. The results are not informative.

Critical comments from specialists published in *heartwire* focus on the view that cataracts are a minor problem compared to the problems statins are viewed as preventing. However, for both non-diabetics and diabetics who do not have established heart disease, the number needed to treat to prevent one acute cardiac event by lipid lowering with statins is between one and three per hundred treated, (see the April 2009 IHN Research Review and the following references.[15,16]) These numbers needed to treat also look even less impressive when one considers the side effects of statins, mostly under-reported.

JOB-RELATED STRESS AND CARDIOVASCULAR DISEASE RISK IN WOMEN

Chronic psychological stress is a well-established risk factor for cardiovascular disease (CVD) and much more important than cholesterol. One important source of stress is job strain and job insecurity. A study just published has examined this question in a 10 year follow-up study of over 22,000 women with a mean age of 57 years.[17] Questionnaires were used to establish the nature and intensity of job-related stress. Stress was stratified into four types: (a) *low strain* with low demands and high control; (b) *passive strain* with low demands and low control; (c) *active strain* with high demands and high control; and *high strain* with high demands and low control. When low strain was used as the reference, analysis yielded statistically significant increased risk mostly for the high strain group. In this comparison, depending on adjustment for confounders, for total CVD the increase risk ranged from 38 to 63%, for heart attack, 67 to 88%, and need for coronary revascularization 41 to 59%. For CVD mortality, the results were not significant and for ischemic stroke (clot induced) statistical significance was model dependent but was a significant 83% in the least adjusted model.

If one looks at absolute risk increases only for those endpoints which yielded model independent statistically significant relative risks results, for total CVD, with low strain as the reference, 87 women had to be exposed to high strain for one event to occur, whereas for heart attack, exposure of 234 was necessary for one event. From this point of view, most women stood up very well to high strain. This again illustrates the difference in interpretation that is associated with the relative vs. the absolutes view of the same data. On the basis of the relative risk increases with their highly respected statistical significance, some women would start thinking about changing jobs, but once they realized that although they were in the high strain group, there was rather high probability compared to the low strain group that they would nevertheless not experience an acute event, the concern would probably be greatly diminished. The media only trumpets the relative risk since the big perceived risks are the stuff of news.

STATINS AND VASCULAR CALCIFICATION AMONG TYPE 2 DIABETICS

Diabetes dramatically increases the risk of cardiovascular disease. Many diabetics are routinely put on statins as dictated by the standard of practice. A study has just appeared in the journal *Diabetes Care* which suggests that there may be some unintended consequences.[18] This study examined the association between statin use and the progression of coronary and aortic calcification (CAC and AAC) in a group of type 2 diabetics. After adjustment for baseline coronary artery calcium and other confounders, at the end of the study progression of CAC was almost double in frequent statin users compared to infrequent users. AAC was not impacted. In a subgroup not initially receiving statins, progression of both CAC and AAC was significantly increased in frequent statin users. The average follow-up was about 4 years and statin use was checked every 3 months.

Frequent users reported statin use at more than 50% of these follow-up visits.

The authors comment that these results are consistent with an earlier study. Results of this earlier study were believed to be due to higher baseline CAC and insufficient lowering of LDL at follow-up in statin users. However, in this new study, there were no significant differences in baseline CAC or AAC and at the end of the study, more frequent statin users has significantly lower and nearly optimal LDL levels.

It is well established that the extent and progression of CAC is strongly positively correlated with the risk of acute cardiovascular events. It is also well established with randomized controlled trials that statins do not reduce the progression of CAC and several studies found a suggestion of increased progression. This increase in progression now appears to be confirmed by two studies. Thus statins are significantly increasing one of the strongest risk factors for a problem for which we are told they provide vital protection, even with TV ads on the evening news.

The Cholesterol Treatment Trialists' Collaborators meta-analysis [19] found for diabetics with no vascular disease that about 40 needed to be treated with statins to prevent one acute cardiovascular event (NNT), but this number strongly depends on the cohort risk which is some primary prevention studies of diabetics has been very high. Other primary prevention studies found NNT numbers of 166 and 142.[16] Thus even though statins appear to increase the progression of CAC in diabetics, the result is not correlated with a significant increase in acute events.

Thus some compensatory mechanism appears to be involved where the increase in CAC is neutralized by some non-lipid-lowering effect such that the overall result is no or little effect. One non lipid-lowering action of statins which is frequently invoked is an anti-inflammatory action which is regarded as weak. This subject was featured at the 2012 Congress of the European Society of Cardiology (*heartwire*, August 26). Paul Ridker of CRP fame from Brigham and Woman's Hospital, Harvard University, in a talk at that meeting pointed out that there has not been an anti-inflammatory trial of the scope of the dozens of lipid- lowering trials with event endpoints. Recently, Ridker announced a study that will test a strong prescription anti-inflammatory (methotrexate) in connection with reducing acute CVD events with the hope of a large effect. The study will involve subjects who have had a heart attack and have type 2 diabetes or metabolic syndrome and are already on a statin, i.e. a very high risk cohort.

The online *heartwire* also mentioned that Novartis is also involved in a trial of canakinumab, a monoclonal anti-human interleukin agent currently used for the treatment of inflammatory diseases. This will be a primary event prevention trial.

These studies will please those who have for some time been calling for the issue of inflammation to be directly addressed, given that based on NNT, for most patients taking statins there is little or no benefit and it is clearly time for a new approach. There do not appear to be any large randomized controlled long-tern clinical trials using natural anti-inflammatory products for either primary or secondary prevention of acute events. However, a just published study examined the effects of curcuminoids (curcumin found in turmeric) on the frequency of heart attack after coronary artery bypass surgery. The incidence of in hospital MI was reduced from an astounding 30% in the placebo group to 13 % in the intervention group.[20] Curcumin with enhanced bioavailability is readily available from supplement vendors. Its use for centuries as a spice suggests it is quite safe. And curcumin is certain to be cheaper than any prescription drug that might finally be approved for cardiovascular prevention which acts via an anti-inflammatory mechanism.

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