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This issue features a discussion of the new "Guideline for the Treatment of Cholesterol to Reduce Atherosclerotic Cardiovascular Events". The release of this guideline was accompanied by a report on the development of a new calculation protocol for estimating the 10-year risk of these events. The release in late November occurred with great fanfare, media coverage, and remarks in the medical news services suggesting a great event. The negative reaction was impressive. The new guidelines maintain the emphasis on relative risk reduction in judgements of efficacy which lead directly to the prescription pad. In the discussion in this issue of IHN, absolute risk reduction will be emphasized, which rather changes the picture. This is just another way of looking at exactly the same data. The continued emphasis on using relative risk reduction and ignoring absolute risk reduction appears deliberate on the part of both mainstream medicine and the pharmaceutical industry. Critics of the mainstream approach to cardiovascular disease always turn to the absolute view, believing that what is important is the percentage of those treated who fail to experience benefit and it is well known that one can have a very large and impressive relative risk reduction in a trial, but 99% or more of the subjects fail to have any benefit. It has even been found that when physicians are interrogated about this, it is not uncommon to be told that if patients were properly informed about numbers like the above 99%, they would not agree to take the recommended medications. What this really means is that something better does not exist when the issue is drug therapy. Furthermore, diet and lifestyle changes are in fact frequently viewed as relatively ineffective due to poor compliance, resistance to diet changes which are also either insignificant or difficult to sustain. Thus taking medication has become the default treatment. The ignored message from hundreds of clinical trials is find something else that works a lot better. New drugs have, at least historically, included many me-too drugs which share similar, small absolute risk reductions with other members of their class. Those who judge better by a somewhat larger relative risk reduction are guilty of self-deception. In the area of prevention and treatment of chronic diseases with drugs, it appears that the answer to this challenge is still in the distant future.

This issue also provides an addition to the earlier discussions of ferritin reference ranges and the hazard of iron behaving badly. Evidence based on DNA damage is presented which suggests that oxidative stress from iron in fact has no threshold. In addition, benefits obtainable from ferritin reduction by blood donation or blood-letting in the context of non-alcoholic fatty liver disease are discussed. Other subjects include the sensational results from a subgroup analysis of the recent trial on EDTA chelation, the use of melatonin in the treatment of neurodegenerative diseases, and a new look at exercise in the elderly.

At the end of the newsletter, there is a short research review which concludes our excursion into the issue of the drug treatment of elevated blood sugar in type 2 diabetics.

Wishing you and your family a Happy Holiday Season and good health in the coming year,

William R. Ware, PhD, Editor

Highlights

NEW GUIDELINES ON ASSESSMENT AND TREATMENT OF CARDIOVASCULAR RISK

In November the American Heart Association and the American College of Cardiology (AHA/ACC) released a new and quite different set of guidelines, replacing those that evolved from the Adult Treatment Panel III (ATP III) introduced in 2001.[1,2] There was much fanfare with, for example, NBC making it one of the top stories on the evening news, including interviewing a doctor. The spin was highly favourable. The story was also picked up and presented as a big deal by organizations that provide breaking news information to professionals such as the *New England Journal of Medicine* online *Journal Watch*, Medpage Today, and Heartline (heart.org). This was a big event which would change how statins were prescribed.

The following are the key points of the new guidelines: Treating to LDL targets was no longer recommended. Instead clinicians should determine where a patient fits in one of four mutually exclusive groups and should initiate statin therapy as follows.

- Patients with clinical evident atherosclerotic cardiovascular disease (ASCVD) should receive high intensity statin therapy if younger than 75 and moderate intensity therapy if older (secondary prevention).

- Patients with LDL cholesterol levels ≥ 190 mg/dL (4.9 mmol/L) would receive high intensity statin therapy (primary prevention in a population judged high risk).

- Diabetic patients aged 40-75 with LDL levels of 70-189 mg/dL (11.8 to 4.9 mmol/L) and without clinical ASCVD should receive at least moderate intensity statin therapy and possibly high-intensity therapy when the estimated 10-year ASCVD risk is ≥ 7.5% (primary prevention in a population judged high risk due to diabetes).

- Patients without clinical ASCVD or diabetes but with cholesterol levels of 70-189 mg/dL and an estimated 10-year risk of ASCVD of ≥ 7.5% should receive moderate- or high-intensity statin therapy (pure primary prevention).

ASCVD includes coronary heart disease, stroke and peripheral arterial disease, all of presumed atherosclerotic origin. The 10-year risk of ASCVD is to be determined by a new calculation protocol (algorithm) made available on the internet.

The big changes relative to ATP III involve expanding the disease definition to include stroke and peripheral artery disease, eliminating LDL targets, a pillar in the ATP III approach, and eliminating the 10-year low, intermediate and high risk categorises (less than 10%, 10% to less than 20%, and greater than or equal to 20%). The new guidelines included a revised algorithm for calculating 10-year risk in the absence of ASCVD which appears to have somewhat different weighting factors. This latter aspect is important given the central role of the threshold of 7.5% for treatment, which is clear in the above summary.

Within a week of the release of the guidelines, a critical comment was actually published online by the *Lancet*.[3] In it, Paul Ridker and Nancy Cook from the Center for Cardiovascular Disease Prevention, Brigham and Woman's Hospital, Boston, an affiliate of Harvard Medical School, presented the results of testing the new risk calculator against data from three large US studies, the Woman's Health Study, the Physicians Health Study, and The Woman's Health Initiative Study. They concluded that the new algorithm "systematically overestimated observed risk by 75-150%, roughly doubling the actual observed risk." This is how overtreatment can be stimulated. Paul Ridker is a famous cardiologist and was principal investigator of the JUPITER statin study.

Age and systolic blood pressure (SBP) play a significant role in the new risk algorithm and thus the thresholds for recommending statins. The following table illustrates this for a male, non-smoker, free of diabetes with total cholesterol 170mg/dL, and HDL cholesterol 50 mg/dL, the levels given as optimal on the calculator page. A SBP of 110 mm Hg and no blood pressure treatment were considered optimal.

		ASCVD RISK (%) BP TREATMENT	
AGE	SBP	NO	YES
50	120	2.5	2.9
60		6.7	7.8
65		10.2	11.9
70		17.1	19.8
50	130	2.8	3.3
60		7.6	8.9
65		11.7	13.6
70		17.1	19.9
50	140	3.2	3.8
60		8.6	10.1
65		13.2	15.3
70		19.3	22.3

Thus if a patient is being judged for pure primary prevention, a treated BP of 120 mm Hg which is at the threshold of pre-hypertension, statins are indicated between age 60 and 65. If untreated, they are recommended by age 65. If the patient is in the middle of the pre-hypertensive range at 130, statin therapy is indicated if the patient is 60 or over. At the threshold of hypertension, an SBP of 140, one crosses the statin treatment point somewhere between 50 and 60 years of age, independent of BP treatment. This is for an individual with what is described on this website as optimum total and HDL cholesterol, no smoking and no diabetes. Thus the AHA/ACC guidelines recommend patients optimum in all respects other than BP be given statins when the age-and BP treatment status yields an ASCVD risk ≥ 7.5%, which would be a very common result in older populations. Furthermore, receiving treatment for elevated BP increases the estimated ASCVD risk significantly even when the treatment results in normal or pre-hypertensive levels.

In terms of absolute risk reduction, antihypertensive therapy has only a small effect on the risk of stroke and CHD events. In a pooled placebo controlled trial analysis, ACE inhibitors were found to have numbers of patients needed to treat to achieve one benefit (NNT) of 50 and 55, respectively (around 98% of patients experienced no benefit), and calcium channel

blockers were even less effective with NNT of 83 and 111 for the same endpoints (around 99% had no benefit.[4] It will be noted that there is an increase in ASCVD risk with antihypertensive therapy compared to no therapy at the same resultant SBP, as is seen in the above table. The same phenomenon can be observed using the Framingham Cardiovascular risk calculator but not the Framingham calculator which assesses heart attack risk. It would appear that elevated BP carries risks that are not completely reduced by BP lowering. In fact, already in 2001, the persistence of a risk gradient despite intensive BP lowering was recognized and studied.[5]

The new Guidelines make a point of the need to balance risk reduction and side effect risks, but of necessity they must ignore the evidence that side effects are under-reported and thus this analysis is hopeless. This is at present highly controversial. Some reviews of the literature find the prevalence of adverse side effects at 18-20%,[6] and note the significant percentage of those prescribed statins stop staking them because they do not like the side effects. Those who claim that they are very low rely on industry sponsored studies which in this context are considered by critics to be notoriously biased.

Abramson *et al* also discuss adverse side effects. While the data are limited, they cite numbers needed to harm (NNH), i.e. the number of treated patients where one adverse side effect will be observed over some period. For muscle pain it is 19, musculoskeletal disorders, 47, muscle injury 37. For diabetes the data is variable, but new diagnoses in the industry supported JUPITER study were at a rate of 11/1000 women taking the statin. A 2010 study found for cataracts, the NNH were 52 and 33 for men and women, respectively.[7] Other side effects include liver dysfunction, acute kidney failure, cognitive symptoms, neuropathy, sexual dysfunction, decreased energy, exertion fatigue, psychiatric symptoms including memory loss, confusion, and aggressive reactions. It will probably be many years, if ever, before there is informative, numerical clinical study data on these side effects not generated by the industry.

The group of medical scientists writing the treatment guidelines included a substantial percentage (47% of the 15 authors and 42% of 12 expert reviewers) who declared ties with the pharmaceutical industry. One co-chair of the writing group was involved with a total of six pharmaceutical companies. But the percentage may be higher since, contrary to the conflicts of interest guidelines used in many countries and journals, one could claim “none” if on the day they joined the AHA/ACC project they terminated industry relationships and agreed to abstain for two years after the end of the projects. It turns out that the chairman of writing group was deeply involved with companies that make statins up to the time he joined the project.[8]

The changes in the guidelines, which were welcomed with great enthusiasm judging by statements in the online “medical press,” are estimated to have the potential of increasing the number of patients on statins in the US by 70 million. Thus the perennial (or impertinent) question, how well do they work? The positive answer is part of the standard dogma. However, those who have concerns have recently become very vocal, even before the guidelines appeared.[9,10] When they were published the critics even achieved coverage in *The New York Times*.[11] One of the authors (RFR) of the newspaper piece is the editor of JAMA—Internal Medicine.

Clinical trials are at the heart of the matter and in particular a meta-analysis by the Cholesterol Treatment Trialists (CTT).[12] In an analysis published in the *British Medical Journal* (BMJ) just before the guideline release, Abramson *et al* analyzed the data.[6] The CTT study examined the benefits of statin treatment in primary prevention stratified by 10-year risk. He points out that when composite endpoints were used, there was bias introduced by the presence of the soft endpoint revascularization (bypass surgery or balloon angiography) which involves physician attitudes and hospital pressure for performance figures. In CTT for the group at < 10% 10-year risk, 35 % of the events were revascularization. Abramson *et al*

chose to correct for this potential source of bias by eliminating this endpoint. This reduced the absolute risk reduction of events now restricted to cardiovascular death, heart attack and stroke rather than the composite from 1.1% to 0.75%. This meant that 140 low 10-year risk (< 10%) individuals required treatment with statins for 5 years to prevent one major coronary event or stroke. This is the NNT. The odds ratio of 5% relative risk reduction associated with this analysis was non-significant. Non-significant odds ratios or hazard rations in meta-analysis studies are bad news for proponents of the tested treatment.

Instead of focusing on the 10% threshold, even though it is above that of the new guidelines, consider the total cohorts in the primary prevention trials used in the CCT meta-analysis. The picture does not change substantially. Now we are including high-risk patients (the up to the 20% 10-year risk by the older standards). Wright performed a meta-analysis on 11 studies which provided mortality data, and on 12 that had major CHD events.[13] These studies involved pure primary prevention (no clinically evident heart disease) where high-risk subjects were included. For mortality, the relative risk reduction was 7% and not statistically significant, and for major CHD events, the relative risk reduction was 26%, and significant. However, the absolute risk reductions for mortality and major CHD events were 0.3% and 1% yielding numbers needed to treat for 4-5 years to prevent one event of 333 and 100. The corresponding percentages who did not benefit were 99.7% and 99.0%.

In the guidelines publication, one can find mention of absolute risk reduction and NNT, but it is merely acknowledged that they exist. No numbers are given. Relative risk reductions are used to justify therapy. However, the guideline writers state that the evidence includes “clear net absolute benefit.” Thus the writers appear to be making sure that it is recognized (for those who read the fine print) that the writers are aware of the absolute vs. relative problem and are choosing to ignore it. The whole process of risk assessment by algorithm and treatment decisions reminds one of handicapping horses, where the data on the horses in a race are fed into an algorithm and arranged in the order of their chances for winning.

Conclusion? There appear to be several problems with the new guidelines and the risk calculator. While the guidelines are based on evidence, the relative risks are statistically significant, and there is evidence of net absolute benefit, the issue is the percentage of those treated who have no benefit. This number is so close to 100% that it becomes something that, if told to patients, would convince them to run the other way. Some might even ask, is there nothing better? Most professionals and certainly the industry know this very well, but due to several motivating factors, it is ignored or suppressed. Another problem is the observation that the risk calculator may overestimate by a huge percentage the risk and lead to overtreatment. Added to this is the use of one threshold for statin treatment, which has apparently been lowered. Finally, while the writing group makes a big point of risk vs. benefit, they appear unwilling or unable to admit that the risk of adverse side effects is not well defined and that the statin treatment trials that also generated side effect data were industry sponsored and subject to bias and serious underestimation. Independent studies seem to back up this suspicion and it appears impossible to conduct meaningful risk/benefit analysis. Finally, the admission that the old LDL targets were not evidence based raises serious questions concerning the ease with which mythology can be introduced into clinical practice and viewed as sacred truth.

SENSATIONAL RESULTS FROM EDTA CHELATION TRIAL

As reported in IHN, in the randomized, placebo controlled Trial to Assess Chelation Therapy (TACT) first reported, it was found that forty 3-hr infusions of EDTA mixed with some vitamins and minerals resulted in a significant drop in the primary endpoint (all-cause mortality, new heart attack, stroke, revascularization or hospitalization for angina) and it was noted that the benefit appears stronger in patients with self-reported diabetes.

A subgroup analysis has just appeared which compares the chelation results for diabetics vs. non-diabetics with a placebo control.[14] TACT enrolled patients age ≥ 50 who had had a heart attack (MI) > 6 weeks before enrolment. Individuals were excluded for a number of reasons including evidence of kidney liver disease, and diseases of copper, iron or calcium metabolism. Diabetes before enrolment defined a pre-specified subgroup. The results are surprising. The primary endpoint was death, new MI, stroke, coronary revascularization (bypass or angioplasty) or hospitalization for angina. The secondary endpoint was new MI, cardiovascular related death or stroke. TACT had good statistical power with 200 cardiovascular events ascertained in the diabetic subgroup. The MI patients with diabetes had a median LDL level of 83 mg/dL, 76% were on statins, 61% on oral anti-hyperglycemia drugs and 26% on insulin, with similar numbers for the placebo group.

The results are given below. Only absolute results are provided. These numbers were obtained from the event rate vs. time graphs. ARR is the absolute risk reduction, NNT the number needed to treat over 5 years to prevent one event listed in the endpoints. These results apply to the diabetic subgroup vs. the placebo group. The follow-up to the end of the study included a significant period after EDTA infusions has stopped.

END POINT	ARR (%)	NNT
Primary	16	6.5
Secondary	5	20
MI	5	20
Death	9	11

For the four endpoints in the above table, relative risk reductions ranged from 40% to 52% and were statistically significant. There was no benefit for non-diabetic patients.

By clinical trial standards even for secondary prevention, these numbers are remarkable. In an interview with *Medscape,* Dr. Lamas, the principal investigator, commented that when these results are shown to endocrinologists, they "go bananas*."* The reason is simple. Their tool box contains no drugs that significantly impact these endpoints, as has been discussed several times in IHN and a final discussion provided in a mini research review in this issue. As discussed recently in IHN, the frequently cited small benefit regarding MI found in the UKDPS study disappears in meta-analysis and the study had been described as seriously flawed.

EDTA chelates metals including iron and thus it could be postulated that the above dramatic effects are due to iron reduction. Iron, as has been discussed recently in IHN, is involved in the risk of developing diabetes and reducing iron levels to near iron depletion has been found to result in improved glucose metabolism. However, using what little information is available on the actual iron loss the standard EDTA infusion produces, it appears that the iron reduction, even over 40 infusions, removes only about 2% of what is accomplished by three donations of 450 mL of blood. Blood donation or phlebotomy removes iron mostly contained in the hemoglobin and then iron homeostasis is restored rapidly with no permanent anemia unless iron stores were already dangerously low. Furthermore, it was reported that there were no effects of the EDTA therapy on glycemia which should have been observed if iron stores were reduced significantly. Iron may still be involved, but what is going on is complex since both non-diabetics and diabetics had arterial plaques, some of which ruptured to produce heart attacks and strokes, but vastly less frequently in the diabetics compared to the non-diabetics due to something EDTA did that was different in these two groups.

The authors of the study suggest possible mechanisms may involve oxidative stress and the formation of advanced glycation products, many of which require metal-catalyzed oxygen chemistry for their formation. However, the mechanisms responsible for the large effect of EDTA chelation in their study and also the durability after infusions stopped remains unclear at this time.

MORE ON RISK OF TOO MUCH IRON

In the October 2013, INH the question of body iron stores and chronic diseases was discussed with the conclusion that considerable data exist demonstrating that the current reference ranges used to evaluate the blood test for ferritin are misleading and do a disservice to patients. In fact normal levels of iron body stores appear to present significant health risks. While preparing a manuscript on his topic for submission to a journal, your editor found some additional evidence which considerably strengthens the conclusions of the October report. There are two issues. One involves iron and oxidative DNA damage while the other concerns iron and non-alcoholic fatty liver disease, a very prevalent disorder which is often a comorbidity to type 2 diabetes.

Urinary 9-hydroxydeoxyguanosine (8-OHdG) is a reliable and frequently used biomarker of systemic oxidative DNA damage.[15,16] Given such a marker, the obvious question concerns correlation with body iron stores. Two studies have addressed this important question. Hori *et al* [17] studied over 500 healthy Japanese aged 21-67. As expected, men had much higher ferritin levels than women and levels in women over 50 years were much higher than younger women. The correlations between 8-OHdG and ferritin measured by Spearmen rank correlation coefficients were 0.47, 0.76 and 0.73 for men overall, women aged less than 50 and women 50 years or older i.e. strong correlations since 1.0 corresponds to perfect. These correlations were essentially unchanged after adjustment for potential confounders. From the plots in the report, for men most of the ferritin levels were below 300ng/mL and for women 100 ng/mL. The range of 8-OHdG for the three groups clustered in a range of about a factor of 4.

An earlier study by Nakano *et al*[16] found similar results. In a study of over 2500 healthy individuals aged between 22 and 89 that there was a smooth, almost linear 2.5 fold increase in 8-OHdG for men as ferritin ranged from 10 to about 300 ng/mL. For women, 8-OHdG was increased by a factor of 3 for ferritin levels ranging from about 9 to 160 ng/mL.

These results suggesting no threshold are consistent with a study of vascular function where when two groups, both with low ferritin levels (52 vs. 17 ng/mL), were compared, flow mediated vascular dilation was significantly greater in the very low ferritin group.[18] It is also consistent with the study described above where ferritin levels correlated with oxidative stress and insulin resistance had no apparent threshold.[19]

These are very important results since they not only indicate a strong dependence of DNA oxidative stress on ferritin levels as a marker for active iron, but the range of levels falls close to the reference range for normal and these were healthy individuals. Thus throughout the normal reference ranges for both genders, iron as measured by body stores is a continuously increasing risk factor for DNA damage, and thus mutations and the associated downstream problems. Iron inflicted DNA damage appears just above the level of near iron depletion level, i.e. there is evidentially no threshold, Furthermore, the reduction in risk of cancer during a follow-up of 12 years in a controlled trial is also consistent with the above results.[19]

Lowering ferritin with phlebotomy has been found to reduce 8-OHdG in patients with chronic hepatitis C. The mean ferritin level was 259 ng/mL at baseline and after phlebotomy it dropped to around 10 ng/mL at 4 months and was 7.1 ng/mL at 6 years, the study end. At 4 months, 8-OHdG as measured by two methods dropped to half the baseline value and at the

end of the study corresponded to that of normal controls. At and after about 1.5 years, ALT levels were normalized.[20]

A second study from this research group examined the impact of reducing iron stores to a near depletion on the development of hepatocellular carcinoma (HCC--liver cancer) from chronic hepatitis C.[21] At baseline the mean ferritin level was 371 ng/mL (range 77-1180). Phlebotomy reduced iron levels rapidly to < 11 ng/mL and it was held in near this value for 12 years. The incidence of HCC in the phlebotomy group was 11.4% whereas in a control group it was 32.5%. This yields a number needed to treat to prevent one progression to HCC of 5 over 12 years, an extraordinary number by clinical trial standards.

Regarding the second issue, non-alcoholic fatty liver disease (NAFLD) starts with simple hepatic steatosis (fatty liver) and can progress to non-alcoholic steatohepatitis (NASH). One hypothesis for the pathogenesis of this disorder is the so-called two-hit model where the first hit involves insulin resistance, visceral obesity and increased hepatic steatosis. The second hit involves one of a number of insults, which lead to increased liver inflammation and oxidative stress. The increased deposition of iron as the disorder progresses, suggests it is involved in the second hit, given its role in producing reactive oxygen species as well as other pathogenic effects including altered insulin singling and lipid metabolism. Iron may also be involved in the initial development of steatosis.[22] High ferritin levels (threshold 1.5 X upper limit of normal or 450 ng/mL for men, 300 for women ng/mL) has been found independently associated with advanced hepatic fibrosis, an indication of end-stage liver diease.[23] The following iron depletion studies are thus of interest.

- The effect of phlebotomy on insulin resistance in a group of patients with NAFLD and strongly elevated ferritin levels found a significant reduction (HOMA-IR decreased from 4.81 to 3.12) when ferritin levels were reduced from 438 to 52 ng/mL. Aniline transaminase (ALT), a liver enzyme, decreased from a mean of 58.1 to near normal 34.3 IU/L.[24]
- A study involving 42 type 2 diabetic or carbohydrate intolerant subjects included 18 also diagnosed with NAFLD based on elevated ALT (>30 IU/L) and ultrasound evidence of steatosis. DNA testing excluded patients with hemochromatosis. Both the NAFLD and non-NAFLD groups had mean baseline ferritin levels below the reference range upper limits (299 and 220 ng/mL respectively). Phlebotomy produced near iron deficiency with ferritin at 31-15 ng/mL and ALT fell from 61 to normal levels of 32 IU/L in the NAFLD group whereas there were insignificant ALT changes observed in the NALFD-free group. Metabolic changes associated with ferritin declines were seen in fasting insulin, and the oral glucose tolerance test even though there were no changes in medication. Stronger effects were observed in the NAFLD group.[25]
- In a study where ferritin levels were manipulated with diet, 12 patients with NASH were placed on a calorie, fat and iron restricted diet. Baseline mean ferritin levels were 280 ng/mL initially and 128 ng/mL at 6 months of intervention. ALT levels decreased from 104 to 42 IU/L over the same period. Large changes were also seen in aspartate aminotransferase (AST) levels. Both males and females had similar baseline ferritin levels which means that women had on average ferritin levels above the gender specific upper limits of normal, but not by very much.[26]

Conclusion? Individuals with NAFLD need to be concerned about their ferritin levels and consider blood donation. The absence of a threshold in the DNA damage studies suggests that achieving a target for ferritin of 30-40 for women and 50-70 ng/mL for men might produce benefits. Programs for achieving optimum health should probably include three blood donations per year which potentially could achieve these levels. The blood donation services check for anemia.

MELATONIN TO TREAT MILD COGNITIVE IMPAIRMENT, ALZHEIMER'S AND PARKINSON'S DISEASE

If one looks at the March 2013 Mayo Clinic patient guide for Alzheimer's disease (AD) on the internet, it is stated that treatments currently work by temporarily improving symptoms of memory loss and problems with thinking and reasoning but that these treatments do not stop the underlying decline and death of brain cells and as more cells die, AD progresses. In the August 2012 patient guide from the Mayo Clinic on Mild Cognitive Impairment (MCI) which generally precedes AD, it is stated that no MCI drugs or other treatments are specifically approved by the FDA for this disorder. For MCI, they also state that "…no supplement has shown any benefit in a clinical trial." This does not appear to be true. Consider melatonin.

Melatonin has attracted considerable interest in the context of aging, partly because there is evidence of a declining nocturnal surge of this hormone. The decline for many individuals starts in the 40s and the response to the darkness trigger has almost disappeared for some by age 70. There is however a considerable inter-individual variation.[27] Melatonin is a powerful antioxidant and it is hypothesized that this decline with age contributes to the aging process. For example, administration of melatonin to patients with AD significantly delayed progression of the disease and the rate of brain atrophy as measured by MRI. It has been suggested that this is the result of melatonin protecting neurons from degeneration leading to cell death induced by free radical attack.[28] In addition, the sleep disturbances seen in MCI and AD have been attributed to the dysfunction of the circadian variation of melatonin.[29]

The majority of studies concerning aging and melatonin have involved animals since addressing the issue of longevity in humans would require unrealistically long studies. So far, significant life extension in animals has only been achieved with calorie restriction. However, calorie restriction in animals substantially increases melatonin.[27]

Mild cognitive impairment (MCI) generally occurs prior to dementia and may offer a more attractive opportunity for intervention than when dementia is fully established. Thus there has been considerable clinical research on the role of melatonin in treating sleep disorders and improving cognitive function.

A recent study has added to the evidence of efficacy of this approach.[30] In a retrospective study, 96 outpatients complaining of subsequently confirmed MCI symptoms were involved. Of these, 61 received 3-24 mg of fast release melatonin daily before bedtime. The remainder served as the control. Patients receiving melatonin showed significantly better performance in every neuropsychological test used. This coincided with a decrease in mood-related symptoms and with improvement in disorders of the sleep/wake cycle.

The authors cite an earlier review concerning the treatment of MCI with melatonin.[29] Five double-blind, randomized placebo-controlled trials and one open label retrospective trial with a total of 651 MCI patients all agreed in indicating that daily before-bed treatment with melatonin improved sleep quality as well as cognitive performance. Doses varied from 1 to 9 mg per day and from short term to 1-3.5 years. When compared with similar studies on AD patients, the impact on MCI was greater and more consistent, partly attributable to the uneven response and variable stages of the AD. These results suggest that early intervention with this therapy may be critical to efficacy. These are among the MCI clinical trials the Mayo Clinic chooses to ignore, claiming they do not exist.

A 2013 review examined clinical trials of melatonin for AD and Parkinson's disease (PD).[31]. Thirteen studies are examined which had sleep problems as the main concern. Eleven had positive findings, two negative. Six of the trials were randomised and controlled, five open label and 2 case reports. One open label study also noted lack of progression of cognitive

and behavioral signs during the 22-35 month intervention with 9 mg of melatonin. A double blind placebo controlled trial found cognitive function improved over 4 weeks with a 3 mg dose. This review also discusses two short-term PD studies. In both, sleep disorders were helped by melatonin but the studies lasted only two and four weeks.

According to comments in research papers and reviews, melatonin appears safe, even at elevated doses. It is taken by large numbers of healthy individuals to address sleep problems and correct jet lag. Obviously this is an interesting, inexpensive intervention. In studies, melatonin is generally taken 1-2 hours before bedtime.

NEWS BRIEFS

IMPACT OF NON-EXERCISE PHYSICAL ACTIVITY ON LONGEVITY IN ELDERS

This study just published in the *British Journal of Sports Medicine* is somewhat unique because it addresses the issue of being active without actually engaging in intentional exercise, presumably a very common situation among older populations without significant disabilities but not willing to walk 30 minutes three or four times a week, the sort of numbers one frequently sees in guidelines. The setting was in Sweden.[32] Non-exercise physical activity (NEPA) included performing home repairs, cutting the lawn, hedge etc., car maintenance, taking bicycle rides, hunting, fishing, and gathering wild fruit. Independent of regular physical exercise, NEPA was found to provide cardiovascular and metabolic benefits and increased longevity in older adults. A cumulative survival graph (Kaplan-Meier) was included which allowed the comparison of moderate to high NEPA with low NEPA, both with or without intentional exercise. For the comparison between the extreme behaviors, M/H NEPA + exercise with low NEPA and no exercise, there was a 6% absolute risk reduction in all-cause mortality over 13 years. This is equivalent to 16 individuals having to adopt this optimum lifestyle to prevent an adverse event over this period. For M/H NEPA but no intentional exercise, the corresponding NNT was 33 (97% got no benefit). The message is simple. Resist the temptation to sit more and do less in retirement and also engage in intentional exercise frequently.

SWEDEN FIRST WESTERN NATION TO REJECT LOW-FAT DIET DOGMA

Sweden has abandoned the long-standing almost universally accepted dogma concerning the benefits of low fat diets and now officially favors low-carbohydrate, high-fat nutritional advice. The move, according to a story in the UK *Mail Online* (October 22, 2013), was in response to a two-year study from an independent *Swedish Council on Health and Technology Assessment* involving the review of 1600 publications through May 2013. Readers of IHN have frequently been exposed to the overwhelming scientific evidence in favour of this view and the absence of evidence supporting the low-fat dogma, evidence that already was convincing over a decade ago, and the health disaster this false notion appears to have precipitated.

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RESEARCH REVIEW

MICROVASCULAR COMPLICATIONS OF TYPE 2 DIABETES

The complications of diabetes are generally divided into two groups, macrovascular and microvascular. The former include heart disease as manifest mostly by heart attacks and strokes. The latter involve problems with vision, kidneys, and peripheral circulation. Advanced microvascular disease results in blue feet, gangrene, amputations, blindness and kidney failure.

The conventional wisdom is that by controlling blood sugar, type 2 diabetics can significantly decrease the risk of microvascular complications. In fact because there is growing awareness that even intensive glucose control does not reduce macrovascular risk,[1] the emphasis is shifting to microvascular. That is all there is left. Expert opinion generally considers the evidence convincing. In the past five years, several studies have reported results that seem at variance with the view of microvascular benefits accruing from intensive blood sugar control. A damage control paper appeared reviewing the major negative studies that attempted to neutralize the impact of these results on both clinicians who have little else to offer and the pharmaceutical industry which has a strong interest in maintaining the status quo.[2] Many of the authors had strong ties with the pharmaceutical industry. It is thus of interest to examine of what the microvascular trial evidence actually consists and to what extent can it be regarded as clinically significant.

One of the most frequently cited trials is the United Kingdom Prospective Diabetes Study (UKPDS).[3,4] This study actually started in 1983 and reported 10 year results finally in 1998. Over this period, the primary and other endpoints were changed a number of times and the announced termination date repeatedly extended. Furthermore, the study was not blinded for the investigators and the results of interim analysis were available. This study protocol is obviously open to bias. To quote one critic, “It seems that the authors continued the study until they obtained a result that was significant without adjusting for repeatedly looking at the data.”[5] An investigator involved in the trial commented in 2008 that “UKPDS broke almost all the rules of trial design. We are taught to believe that a study protocol should be predetermined and set in stone, but this study went to the other extreme, elevating the ad hoc into an art form.”[6] Thus the key study appears flawed. At the end of the study period,

participants were followed for a number of years but as regards glucose control, apparently did whatever they pleased. Thus, one can argue that the only results meriting attention are those for the actual study, and as pointed out above, the validity of the actual trial has been questioned.

UKPDS actually included several concurrent studies. UKPDS-34 compared intensive treatment with what was termed conventional treatment, evidentially starting with diet followed by drugs.[3] The conventional treatment involved maintaining blood sugar below 15 mmol/L (270 mg/dL). When marked hyperglycemia occurred drug treatment was initiated which included a sulphonylurea or insulin. The intensive treatment group had as its target fasting blood glucose of < 6 mmol/L. Metformin or one or more sulphonylurea were used as well as insulin. Changes in the drug protocols occurred during the trial, leading to confusion which makes it difficult to interpret the published results. Upon comparison of the intensive vs. conventional groups at presumably the end of the study, strongly insignificant microvascular results were obtained for death from peripheral vascular disease, amputation, death from kidney disease, kidney failure, blindness in one eye, need for photocoagulation, cataract extraction and ocular haemorrhage. The same picture emerged when sulphonylurea plus metformin were compared with sulphonylurea alone. Except for an initial drop in fasting glucose and HbA1c, both the intensive and conventional groups experience steady progression of these two markers over the course of the trial and they were always diagnostic of diabetes. UKPDS-34 had 21 individual endpoints, both microvascular and microvascular. With that number of endpoints, the random chance of obtaining a false positive is 66%.[7]

In UKPDS-33,[4] which reported at the same time as UKPDS-34, intensive drug therapy with sulphonylureas or insulin was compared with convention treatment defined above, and seven of eight microvascular endpoints yielded results showing no significant impact. Only the need for retinal photocoagulation resulted in a significant microvascular relative risk reduction and this was close to being insignificant and did not agree with the results in UKPDS-34, which were negative. Photocoagulation is also considered by some to be a soft endpoint since the judgement of the attending physician is involved.

The investigators also provided graphs of fasting blood glucose and HbA1c vs. time for conventional and metformin use and for conventional and in intensive therapy. Drug therapy caused a sharp drop in both at about year 1 and then values increased in parallel with almost the same rate after 6 years. In other words, the treatments used did not have much influence on the relentless progression of the disease except allowing it to progress with somewhat lower fasting glucose and HbA1c levels. This is part of what mainstream medicine calls strong evidence of benefit in the context of preventing microvascular complications.

The large ACCORD study reporting in 2008 found no macrovascular benefits associated with intensive treatment of hyperglycemia in type 2 diabetics compared with standard treatment.[8] ACCORD was stopped after a mean treatment time of about 3.5 years of follow-up because of increased mortality in the intensive compared to the standard therapy groups. The target for intensive therapy was HbA1c <6% whereas the standards therapy aimed at 7.0-7.9%. All subjects started with HbA1c levels of ≥ 7.5%.At baseline, both groups were on anti-hyperglycemic drugs. Only macrovascular events were reported in the 2008 paper and no benefits were found for intensive vs. non-intensive treatment. After the decision was made to stop the trial, the intensive treatment group was switched to standard therapy. In a report covering the posts termination follow-up out to 5 years, it was concluded that the strategy of intensive therapy could not be recommended for the high-risk, advanced type 2 diabetics involved in the trial.

There was a microvascular ACCORD eye study which started at the same time as the main trial and involved 4 years of follow-up.[9] The report in 2010 was corrected in 2011. The revised results for the impact of intensive vs. standard glucose control on diabetic disorders of the retina were not statistically significant, nor was the original published result.

A more detailed account of the parallel microvascular studies in the ACCORD trial was published in 2010.[10] The investigators report results up to the trial termination and for an additional post-trial follow-up. Since having a study interrupted and the treated and controls subsequently given the same therapy with continued follow-up confuses the issue, only the actual trial results will be discussed. No eye related endpoints were found to have significant benefit in the comparison of the standard and intensive groups. Only the incidence of micro- and macro albuminuria (kidney function marker) had significant relative risk reductions for the intensive vs. the standard therapy. The NNT provided in the paper were 39 and 73 respectively (97.4 and 98.6% failed to benefit). However, the clinical significance of these results is somewhat diluted by the observation that both before and after the trial termination, there was a steady increase in blood creatinine levels, another kidney function marker. Since there were no differences in the behavior of this marker between the intensive and standard groups, it appears that the intensive therapy had no beneficial influence on the actual progression of kidney disease in these patients. The authors actually point out that given the 15 endpoints studied, there was a 54% chance of randomly obtaining a false positive result.

Next we come to the ADVANCE study, which was one of two reporting in 2008 that shook up the world of diabetology.[11] ACCORD was the other. ADVANCE was a randomized trial lasting 5 years which aimed in the treated group to achieve a target HbA1c of 6.5% with intensive glucose control using Gliclazide. Controls followed conventional guidelines for treatment. The control group maintained an HbA1c of close to baseline (7.4%) whereas the intensive group dropped to 7.0% within 6 months and 6.5% within 36 months which was then maintained. Contrary to the UKPDS, no effect on visual complications was found and the only benefit for microvascular complications involved kidney disease. Among the primary endpoints, the benefit regarding new or worsening kidney disease had a number needed to treat (NNT) of 90 indicating that 98.9% of the subjects derived no benefit. For the secondary endpoints, the benefit associated with new-onset microalbuminuria had an NNT of 50 (98% no benefit). There were 14 secondary endpoints designated, and thus there was a 51% chance of randomly obtaining a false positive. The results were non-significant for peripheral vascular events, and new or worsening neuropathy.

A study which also looked at microvascular benefits examined the efficacy of metformin vs. a control group of patients who had withdrawn from the drug and were treated by a non-drug approach.[12] The urinary albumin/creatinine ratio (kidney function) and the progression of eye problems associated with the retina were included in the outcomes and no benefit was found in the comparison of treated vs. untreated patients for any endpoint. The trial was randomized and lasted 4 years, and in terms of the control group, was similar to a placebo controlled trial.

A smaller randomized trial, the Veterans Affairs Diabetes Trial (VADT) which reported in 2009 involved a comparison between intensive and standard glucose control in type 2 diabetics with suboptimal response to therapy. In this study 1791 men, mean age 60, were randomized to two groups with a median follow-up of 5.6 years. Median HbA1c dropped from 8.4% in the standard therapy group to 6.9% in the intensive group. The only microvascular complication to show an indication of benefit from intensive glucose control was the progression to kidney disease. But statistically significant increased incidence of nephropathy was only seen in an analysis when micro- and macroalbuminuria were combined.[13]

Prompted by the ADVANCE and VADT results and earlier studies related to kidney complications, a study involving meta-analysis was reported in 2012. It investigated intensive vs. standard glucose control to determine if this decreased significant renal clinical outcomes such as doubling of serum creatinine levels, end-stage renal disease or death from kidney disease during the years of follow-up. No evidence of benefit was found when 7 trials with follow-up from 2 to 15 years were included.[14]

Rightly or wrongly, mainstream medicine regards the meta-analysis as the path to truth and enlightenment. What do other meta-analyses say about the treatment of the microvascular complications of type 2 diabetes? Hemmingsen et al included both composite microvascular outcomes and disorders of the retina and kidney.[15] This meta-analysis found no benefit for lowering the risk of kidney disease. For composite microvascular outcomes, 98.5% failed to benefit, whereas for disorders of the retina, the results was 97.7%. Boussageon et al published a meta-analysis in 2012 which included only studies where metformin could be compared with either a placebo, diet or other drug interventions. The analysis examined peripheral vascular complications, amputation, and a microvascular composite and found no significant benefit.[16]

Thus, it appears that the evidence needed to back up the view that blood glucose control for reducing the risk of microvascular complications in diabetics is almost entirely absent. Some studies find suggestions of a modest benefit with large NNT. Furthermore, one does not know how much weight to give the photocoagulation result in UPDPS because of the flaws described above. The current position of mainstream medicine, rather than resting on a convincing base of evidence, appears to be influenced by there being nothing else to offer patients with type 2 diabetes. The patients see improvements in their glucose control are naturally convinced that there is benefit. They believe they are preventing complications. This is why, form their point of view, they are taking the drugs. Unfortunately, the treatment does not appear to provide significant benefit.

The reader is referred to the November IHN where a diet-based approach to type 2 diabetes is discussed which accomplishes near or total reversal that appears to be durable (drugs or insulin no longer needed). Most patients on the diet were successful. The data presented above indicate that most treated with drugs do not benefit. They are on drugs for life and mostly just get worse. No drug treatment can accomplish what the diabetes reversal diet protocol does and the benefit occurs in 8 weeks. The contrast to the relentless progression of this disorder in patients treated with anti-hyperglycemic drugs, even to low, near normal targets of fasting glucose and HbA1c, is striking.

We are not talking about some rare disease but a worldwide epidemic that, along with the horror of the complications, threatens to financially bring down so-called health care systems and is encompassing younger individuals each year. Recall that type 2 diabetes is no longer called “adult onset.”

This review completes the discussions in IHN on the absence of efficacy associated with drug treatment of type 2 diabetes in the context of diabetic complications.

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