INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 264 **FEBRUARY 2016** **25th YEAR**

In 2006, the Royal Society of Medicine in the UK published a scholarly book by Richard Smith, a former editor of the *British Medical Journal,* titled *The Trouble of Medical Journals.* Little has changed since this very critical book was published. Finally an editorial has appeared in the *Annals of Internal Medicine* (published online January 20, 2016) announcing a proposal by the International Committee of Medical Journal Editors which if implemented would solve one of the major problems associated with the dissemination of the results of clinical trials, an area that many critics view as in need of reform. The sixteen-member committee is made up mostly of editors of major medical journals such as the *Annals of internal Medicine, the Journal of the American Medical Association (JAMA), The New England Journal of Medicine, Canadian Medical Association Journal, Lancet, PLOS Medicine, and the German,* New Zealand, Ethiopian and Danish, Chinese and British Medical Journals. The proposal would require as a condition of publication of clinical studies that the researchers make available the patient data used in the publications (but not all the patient data) within six months of publication. Those wishing access would have to have an adequate reason. The data would be required to meet standards of availability and content and the patient identification would be protected. This enables independent verification of study conclusions. Concern in this area is prompted by several factors. First it is not uncommon for there to be a large difference between the magnitude of positive results found when one compares studies from industry with truly independent studies. A classic example is the anti-viral drug Tamiflu, which was viewed as effective until several UK researchers, after heroic effort, managed to get the patient data form the company involved. It was found on reanalysis that the benefits were negligible except for severe hospitalized cases. The new results were published in the *British Medical Journal,* but the reanalysis appears to have been largely ignored. The drug is currently being advertised on US prime time TV. This is a drug that many governments spent huge sums stockpiling to be prepared for a flu pandemic. See the June 2014 IHN for an account of the *Tamiflu Saga*.

While some regard the proposal as not going far enough, the new proposal is a courageous move by the major journals, some of which are very high impact publications that those doing clinical research aspire to use to publish their results. However, journals that publish clinical studies sell reprints in large quantities for industry drug reps to pass out to physicians and at

meetings to promote their products. Drug companies have also traditionally resisted the release of patient data claiming proprietary rights, and is appears that even the FDA appears to resist the release of studies and data submitted for regulatory approval, citing the same reason. Critics claim that this encourages the biased treatment of clinical data and the approval of drugs on the basis of inflated benefits and downplayed adverse effects. The increase in transparency that will result in this new initiative would be most welcome, given the current atmosphere of suspicion and distrust. In fact, it is increasingly common to hear of someone who first looks at who supported a study and what were the author affiliations with the industry. The involvement of the industry encourages distrust in the results if not the reaction to not even read the paper. The new initiative will also eventually have an impact on guidelines which depend mostly on industry-supported studies and studies where many of the investigators had strong financial ties to industry. Thus future guidelines may eventually reflect consideration of true benefits rather than benefits that are clouded by suspicion of bias or worse.

Read Dr. Ben Goldacre's book *Bad Pharma* for insight as to how this proposal will impact an industry which has over the years enjoyed considerable freedom from independent examination of clinical trial data and analysis. This book is mostly written for the lay audience but is actually occasionally cited in peer reviewed medical journal articles.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

ARE CURRENT AND PROPOSED CARDIOVASCULAR ASSESSMENT PROTOCOLS FATALLY FLAWED?

The risk of heart disease that arises from atherosclerosis can be assessed either from traditional risk factors such as age, gender, cholesterol, blood pressure and hereditary factors (family history) or from a disease-based view that incorporates the existence and severity of the underlying disease itself, i.e. coronary artery atherosclerosis. For over two decades, the former approach has been the unanimous choice of clinicians and is reflected in the guidelines that have evolved over the years with the associated risk calculation schemes that yield 5-year or 10-year event risks. The disease-based approach involves the coronary artery atherosclerosis as measured by the calcified artery plaque burden or coronary artery calcium score (CACS). The score is obtained by a special non-invasive CT scan which involves both radiation and patient inconvenience. Nevertheless, there are considerable data, especially from the Multi-Ethnic Study of Atherosclerosis (MESA), which allow one to examine the value of this added information to the patient's risk assessment. A recent study has reinforced the view that the approach using the traditional risk factors is fatally flawed and the problem can be remedied by using the extent of actual coronary atherosclerosis.[1]

In 2013 new guidelines from the American Heart Association and the American College of Cardiology (AHA/ACC) concerning the assessment of risk and prevention of events was published which still uses the traditional risk factors. These guidelines were immediately controversial because of the way they grouped patients into four general categories and for introducing a rather low treatment threshold for 10-year risk of ≥ 7.5% for atherosclerosis/cardiovascular disease events with a threshold of 5% to ≤7.5% for "consider" rather than recommend this drug treatment. This threshold applied only to those free of diabetes or a history of cardiovascular disease or a LDL level ≤ 190 mg/dL. The guidelines were not criticized for ignoring the extent of atherosclerosis.

This recently published study cited above examines the impact of knowing the coronary artery calcium score on the recommendations for statin use according to the new AHA/ACC guidelines which ignore CACS. The study used a risk calculation based on the MESA cohort database which incorporates the traditional risk along with optional input of the CACS.[2] The issue of CAC is well illustrated by considering the question of the impact zero atherosclerosis as indicated by CACS = 0 on the recommendations for statin treatment according to the new guidelines. After all, with no plaques to rupture, there will be no heart attacks or strokes.

The MESA study population consisted of 4758 participants age 59 ±9 years with 47% males. The follow-up was about 10 years and the MESA calculator was used to establish the 10-year risk and determine a recommendation for statin treatment using the AHA/ACC guidelines. When the CACS was ignored, the norm for current risk assessment, this resulted in 50% of the MESA cohort qualifying for either moderate or high intensity statin treatment, driven mostly by exceeding the ≥ 7.5% 10-year risk threshold. Other factors favoring treatment were a history of cardiovascular disease, LDL ≥ 190 mg/dL and diabetes. However, in this group eligible by the guidelines for

moderate or intensive statin treatment, 41% had zero coronary calcium (CACS = 0). For those with the recommendation to consider statin treatment because the 10-year risk was between 5% and 7.5%, 57% had CACS = 0. With no LDL targets, it would be expected that the statin use would be long-term. However, those with CAC = 0 in fact had very low risk of cardiovascular or coronary heart disease acute events, risks that would never justify any drug intervention at all. Thus when CACS = 0 was considered, treating those indicated by the guidelines would have resulted in about half of the treatment-eligible group being seriously over-treated and thus exposed to the side effects of the treatment with virtually zero potential benefit. Note that the CAC values as well as the MESA 10-year risks were based on start of study values and were being used to predict events over the next 10 years. However, this use of these baseline values is exactly what current guidelines employ.

These results make it clear that risk assessment that does not include an evaluation of the coronary plaque burden by CT scan results in gross misclassification and potentially serious overtreatment and makes one question the merit of any risk assessment that does not take into account the measured extent of existing disease. The current accepted assessment and associated guidelines appear to be dangerously if not appallingly flawed.

Another way to look at the above study is to consider the group of almost 5000 participants. At issue is the question of the need to take preventive action for atherosclerosis related acute events. That is what AHA/ACC and earlier guidelines are all about. If CAC was measured first, then in retrospect, 44%, i.e. those that turned out to be eligible for a recommendation or consideration of statins could be immediately dismissed as at a risk so low that the recommended treatment was definitely not indicated. The remaining 56% could then be evaluated accordingly with an approach considered sensible or “approved” to provide a plan for prevention. Aside from MESA and its calculator, there is no way to proceed realistically. Studies that are used to establish guidelines based on risk of events are also flawed because they include unidentified individuals who should never have been in the study due to near zero risk. If CAC was used in risk assessment, it seems clear that a much smaller number of individuals would qualify for therapy, something that would not sit well with the pharmaceutical industry and would result in considerable “loss of face” for professionals who have spent their careers promoting the “ignore CAC” approach and supporting statin therapy projecting the view that these are miracle drugs which reduce the risk of heart disease by approximately 25 %, which incidentally ignores the fact that such relative risk reductions are almost meaningless at best and deceptive at worst.

A study in the journal *Atherosclerosis* that just appeared online strongly reinforces the MESA results.[3] The study group consisted of individuals in the US judged at elevated risk for CVD. A consecutive series of 9715 individuals eligible for the study, mean age 53, range 43-74, 41% female, underwent coronary artery calcium scoring (CAC score) and were followed for a mean of 14.6 years. Here we are concerned only with the baseline CAC score. Over the entire age group, approximately 30% to 60% had one or more major risk factors such as hypertension, an unfavorable blood lipid profile termed

dyslipidemia (high total or LDL cholesterol, low HDL cholesterol, high triglycerides or current use of lipid-lowering drugs such as statins), were smokers and had a family history of coronary artery disease. Overall, 50.1% had a zero calcium score and while the percentage dropped slightly with age, it was still 48% at age ≥ 70. Thus we see that even for individuals classified as high risk by traditional risk factors, about 50% had a CAC score indicating very low risk of CVD events and CVD-related mortality. When the researchers looked at the independent associations of risk factors with all cause death using a multivariable model, over all age groups dyslipidemia was not a significant factor.

Note that we are dealing with the issue in primary prevention and an additional consideration is that even if statin therapy is indicated, the absolute benefit would almost certainly be less than 3% and thus 98% would achieve no benefit even in a high-risk cohort over 10 years of treatment. That is, most statin studies for true primary prevention that found little benefit for hard non-fatal events and none for mortality used mostly high-risk cohorts.

This subject is discussed in much greater detail in the perspective and commentary on the subject of cardiovascular risk assessment included in this issue of IHN.

BOTTOM LINE

What seems clear is that a CT scan for coronary calcium would find approximately half of all those screened had CACS = 0 and based on the studies discussed above the traditional risk factors thus become irrelevant and can be ignored unless repeat scanning after a few years finds a non-zero and significant calcium score. But CT screenings are not at all common and lipid-lowering therapy for primary prevention is widespread. Thus the current risk assessment approach is fatally flawed. Researchers continue to fine-tune their assessment protocols while ignoring the biggest risk factor of all.

If one is to follow the recommendation to take statins long-term, and the guidelines without LDL targets imply just that, then in addition to the apparent poor risk/benefit which arises from both low absolute benefit and significant side effect risks, there is the cost issue. Cost is strongly related to both the statin and whether or not it is generic. In 2013 for example, the lowest generic cost was about $300 per year. For non-generic, Lipitor was $500 and Crestor $900. However, cheaper cut-rate drugs are also available although one wonders regarding the origin, purity, and actual amount of drug present relative to the indicated amount. Drug cost, probably long term must be compared to the cost of the coronary artery calcium scan, which over the years had dramatically declined. The current range appears to be $150 to $400. The cost can depend on whether or not it includes a consultation regarding the results. At Cedars Sinai hospital in Los Angeles, their website indicates $285 gets you the whole package while for $185, just a scan, a lipid panel blood test and a report to the referring physician. Thus even in comparison to the lowest cost non-generic statin, the price of knowing ones calcium score is cheap and if the results turn out to be a zero or very low score, then over the years a huge saving is achieved. This can be viewed in the context that approximately

the probability of a zero calcium score as documented above is about 50-50, and changes only by a small amount for the older individuals. If the score is high, this should provide strong incentive for considering the alternative to statins, i.e. a traditional Mediterranean diet including fish augmented with nuts, no smoking, exercise, and aggressive psychological stress elimination. While statins can reduce the progression of certain minor subtypes of plaque, the impact on the progression of calcified plaque and thus the CAC score is nonsignificant[4] and it is this score that has been extensively studied and found to be a powerful predictor of adverse cardiovascular events. This is important since individuals may be told that they must take statins because of an elevated CAC score in order to reverse and or control their coronary atherosclerosis.

It is interesting that guidelines do not favor screening for CAC. This is still a controversial area. While radiation is an issue, it becomes smaller each year as better equipment is designed. Furthermore, the very small risk associated with radiation seems trumped by the ever-growing risks of statin treatment. Critics would probably say that the resistance by mainstream medicine to widespread screening is related to the fear that this would lower the use of their miracle drugs, a notion based on the fantasy generated by focus on large relative risk reductions. For a full discussion of the issues raised here, see the perspective and commentary included with this issue.

WHAT ARE THE MAJOR RISK FACTORS FOR PANCREATIC CANCER AND WHICH ARE MODIFIABLE?

Pancreatic cancer (PC) is one of the four or five most common causes of cancer-related mortality. Frequently diagnosed at a late stage, it has a very poor prognosis. A recent paper which appeared in the *International Journal of Epidemiology* addresses this issue and provides estimates for a number of factors as to how much they contribute to the overall risk.[5] The authors of this study examined 117 meta-analytical or pooled data reports dealing with exposure to 37 potential risk factors and obtained what they term “robust information about the suspected causes of PC.” These results are important since many of the major risk factors are potentially modifiable.

In this study the authors quantify the contribution of risk factors to the incidence of this disease by using what is called the *Population Attributable Fraction* (PAF). The PAF is the proportional reduction in population disease expressed as a percentage that would occur if exposure to a risk factor were reduced to a level where it was no longer important. For example, for smoking this would mean no tobacco use.
The PAF results (given as a range) along with the percentage of the populations exposed were as follows for the most significant factors.

RISK FACTOR	POPULATION EXPOSURE, %	ATTRIBUTABLE FRACTION, %
Smoking	24-40	11-32
H. pylori infection	25-30	4-25
Non O-blood group	50-60	13-19
Diabetes	4-17	1-16
Obesity	20-40	3-16
Red or processed meat	1.1-1.5	2-9
Heavy alcohol consumption	1.1-1.5	< 9
Family history	1.7-1.8	3-7
Chronic pancreatitis	0-1	< 3

Of these 9 factors, six are modifiable and the authors estimate that they constitute about two-thirds of the risk.

The authors make the following comments:

- Insulin resistance is related to the risk factors for diabetes and obesity such as central adiposity, high blood glucose, the metabolic syndrome, fructose intake and reduced physical activity. Thus these are also risk factors.
- Other factors such as tobacco, alcohol, pancreatitis and *H. pylori* infection are known triggers for inflammation, an established pathway to PC carcinogenesis.
- Other studies in general confirm the finding of this study concerning the importance of tobacco, alcohol, blood group, obesity, family history, infection, and pancreatitis.
- The discovery that *H. pylori* is associated with PC is quite recent and yet appears responsible for a significant percentage of cases of PC. It is a common and treatable gastric infection.
- Job and occupation exposure to toxins is an additional risk factor, but the strength of the evidence was poor. However, exposure to chlorinated hydrocarbon solvents (carbon tetrachloride for example) constitutes a major occupational risk factor. Exposure to nickel and formaldehyde are also important.

The indicated preventive actions are thus clear and involve dealing with obesity and diabetes, avoiding heavy consumption of at least processed meat and alcohol, avoiding smoking and being sure no chronic *H. pylori* infection is present. The issue of non-processed meat was discussed in the last newsletter and may be much less important than processed meat in the context of cancer.

While conventional treatments for PC offer dismal prognosis, it is possible that an alternative therapy using Salvestrols is effective (See IHN September 2013, May 2014). Salvestrols are a mixture of fruit extracts found in cancer cell culture screening to have high potency for inducing cell toxicity and cell death in cancer cells but normal cell are

not targeted. This unique feature of the enzyme present only in cancer cells allows targeted therapy and has been known and carefully studied for over a decade.[6] Salvestrols work because this enzyme metabolizes, among other chemicals, polyphenols in fruit to yield a cytotoxin. Some believe that this is our natural defense against cancer if we eat a variety of fruits. Since this is a combination of natural products, there are no clinical trials, only case histories (See May 2014 IHN). Nevertheless, Salvestrols are currently being used worldwide for alternative cancer therapy.

In his collection of medically documented case histories,[7] Dr. Brian Schaefer describes a 62 year old man who had bladder cancer which was successfully removed surgically. It was subsequently found that he had a kidney tumor and one at the tip of his pancreas. An oncologist regarded the pancreatic tumor as an adenocarcinoma and warned the patient of a very limited survival time. At this point the patient started Salvestrols and made a modest move towards more organically grown foods. Eight weeks after starting Salvestrols, an ultrasound indicated shrinkage of the pancreatic tumor which was confirmed by MRI and in addition revealed a concurrent shrinkage of the kidney tumor. Six months after starting Salvestrol supplementation a new ultrasound found no evidence of pancreatic or kidney cancer. This was confirmed by an MRI. Schaefer relates that the oncologist was astonished and told the patient that he was cancer-free and that the kidney had healed very well. A one-year checkup for the bladder cancer found no evidence of cancer. Either surgery got it all or Salvestrols finished the job and cleaned up cancer cells circulating around or establishing new homes, i.e. metastasis. When the case history was being prepared, the patient had been 16 months in remission and was in good health. He continued to take Salvestrols at a reduced dose for prevention of recurrence, a decision supported by a number of case histories where the greatest success in maintaining remission involved continuing taking the supplement. This makes sense since tumors contain billions of cancer cells and it is highly likely that evidence of remission and the disappearance of a tumor does not imply total absence of tumor cells, either at the site or already circulating,. Dr. Schaefer also knows of other individuals who have been able to go into remission with pancreatic cancer, but he has been unsuccessful in getting them to cooperate in assembling medically-documented case studies.[8]

Evidence-based medicine views case histories as about as low as one can go in evidence quality, but with alternative treatments lacking the financial support of the pharmaceutical industry, clinical trials are rare. However, in the case of Salvestrols, there are no side effects. These are simply extracts of selected fruit commonly consumed (which incidentally must be organically grown to get maximum cytotoxicity). They have now been and are continuing to be used on hundreds of patients worldwide. Those electing to try them no doubt feel they have nothing to lose. What we lack is systematic reporting of results. The case histories documented by Dr. Schaefer and discussed in the May IHN are an important start.

BOTTOM LINE
Pancreatic cancer is really bad news, conventional treatments are generally ineffective and prognosis poor. Thus anything one can do to reduce the risk of incidence is well worth the effort. The study discussed suggests serious consideration of the modifiable factors in the above table. All offer no insurmountable difficulties for implementation and it is important to recognize that all would have health benefits that extent well beyond reducing the risk of this terrible disease. It is suggested that one consult with their physician regarding *H. pylori* and the elimination of diabetes using the Newcastle diet. See the October 2014 issue of IHN in order to have a basis for a discussion concerning curing diabetes.

MORE EVIDENCE CONCERNING DANGERS OF FRUCTOSE CONSUMPTION

Over the past decade, there has been growing concern about increasing fructose consumption that has gone hand in-hand with table sugar consumption, the latter reaching mind-boggling amounts in recent years. In fact, average sugar consumption in the US is 150-170 pounds per year (68-77 kg). Sucrose, aka table sugar is a molecule made up of one molecule of glucose and one molecule of fructose. High fructose corn syrup on the other hand is merely a blend of fructose and glucose in nearly the same proportions. High fructose corn syrup is a very common sweetener used in many prepared foods and beverages. Concern regarding fructose stems from its unique metabolic and neuroendocrine properties. It is metabolized mostly in the liver, serves as the basis for fat synthesis, increases liver triglyceride levels, generates reactive oxygen species and chemically reacts with molecules by adding a molecule of fructose. It does not suppress the hunger hormone ghrelin and thus rewards continued ingestion.

Consumption of 160 pounds of sugar per year is roughly equivalent to 800 calories a day or 30% of the caloric intake for a 2500 calorie per day diet. And these numbers are averages meaning that many consume higher amounts. This is partly made possible because some of the sugar intake is hidden in added sugar.

A recent study using prepared meals investigated the impact of replacing fructose in the diet with the same number of calories of starchy food including what is considered junk food to examine the effect on markers of the metabolic syndrome in children.[9] The study was led by Dr. Robert Lustig who is in the department of pediatrics, University of California-- San Francisco medical school. Calories as a percentage of total calories were reduced from 28% to 10% from sugar and from 12% to 4% from fructose. Calorie intake was adjusted to maintain weight and the controlled diet study ran over 9 days. At the end of the study researchers found improvements in diastolic blood pressure, LDL cholesterol, triglycerides, fasting blood glucose and insulin and liver function. What was remarkable was that these significant changes occurred over only 9 days and in fact represented a reversal of the metabolic syndrome, even though the replacement calories came from less than ideal food. Thus the notion that “a calorie is a calorie” is an oversimplification since how the food representing the calories is metabolized is critical.

These studies involved eliminating excessive sugar consumption at constant calorie intake. The results make it clear that the detrimental health effects of sugar are independent of its caloric value or effects on weight. Additional studies will be needed to clarify the observed effects in adults and as well, their durability.

This study also adds strength to the new American dietary guidelines which set a limit on calories from sugar to 10% of total calories. A gram of sugar is equivalent to about 4 calories and a teaspoon full 16 calories.

It has been estimated that sugary soft drink consumption alone kills about 200,000 individuals per year,[10] and it is well known that that a countries' sugar consumption is closely related to the incidence of type 2 diabetes.

BOTTOM LINE

The developed world is awash in fructose. We evolved on diets that were very low in fructose since sugar was mostly absent from the diet aside from that obtained from raiding the homes of honey bees (the sugar in honey is also mostly fructose and glucose) and that obtained from fruit. Obviously there was no high fructose corn syrup, an industrial product. If one looks at the fructose content of fruits and vegetables, very few are in the range of 20-30 g per 100g of food, and most are much lower, indicating that the current intake is vastly greater than possible from natural foods. While adaptation can occur, it is hard to believe that it could ever encompass the huge and almost unbelievable daily sugar intake and thus fructose consumption we see in the developed world. Furthermore, one can anticipate future studies that will find more and more reasons why this huge sugar binge currently occurring has long-term adverse consequences of a serious nature. The above study only provides a glimpse of the total danger of sugar. Two books by Dr. Lustig are recommended for more insight: *Fat Chance. Beating the odds against sugar, processed food, obesity and disease,* and *Pure, White and Deadly. How sugar is killing us and what we can do to stop it.* The latter is a classic by Professor John Yudkin brought up to date by Dr. Lustig.

ADOLESCENT BARIATRIC SURGERY REVERSES TYPE 2 DIABETES

In a multicenter study just reported in the *New England Journal of Medicine* and also presented at the Obesity Society annual meeting in Los Angeles, the health status three years after bariatric surgery was examined in a group of 242 adolescents.[11] Most underwent the Roux-en-Y gastric bypass which reroutes what is eaten to mostly bypass the stomach but 28% were treated with the sleeve gastrectomy, which restrict flow into the stomach. The average age was 17 years and the mean weight was 327 pounds i.e. morbid obesity.

Three years after the surgery, the mean weight had decreased by 27% with the bypass and sleeve approaches yielding almost the same weight reductions. Remission occurred in 89% of those who at baseline had abnormal kidney function, remission of

elevated blood pressure occurred in 74% and remission of dyslipidemia (low HDL, high triglycerides) was observed in 66%. These favorable changes occurred without a return to anything close to a normal weight for an adolescent.

But that is not all. The results for diabetes were nothing short of sensational. Before surgery, 29 (13%) had type 2 diabetes. At 3 years, 19 of 20 (95%) participants who had data available for evaluation were cured of their diabetes with HbA1c at 5.3% and fasting blood glucose at 88 mg/dL and presumably no diabetes medications. Prediabetes was found at baseline in 19 participants for whom end of study data was available, and 76% no longer had prediabetes. However, surgical intervention is not without its post-surgical complications. In this study, 8% had major complications within 30 days and 13% underwent additional abdominal surgery within the subsequent 3 years.

The authors conclude that the study supports the benefits of this type of surgery and indicates significant durability of multiple benefits, at least over 3 years, for severely obese adolescents. For these subjects, there does not appear to be an alternative therapeutic approach with these results which subjects are likely to undertake with significant adherence to the protocol.

BOTTOM LINE
While major drastic surgery may seem like overkill for obesity, several decades of experience with obesity clearly indicate that it presents an almost intractable problem using only the conventional approach of diet and exercise and weight loss drugs have a significant downside. Individuals eligible for bariatric surgery high may want to first consider the 8-week Newcastle diet which will also yield significant weight loss and unless the diabetes is of long duration, also cure it. There are no adverse side effects whereas for bariatric surgery this is not only the case, but the bypass surgery is presumably difficult to reverse.

TREATING EXCESS STOMACH ACID AND RISK OF CHRONIC KIDNEY DISEASE

A study just published has examined the question of an association between kidney disease and the use of the anti-acid class of drug called proton pump inhibitors (PPIs). The study was prompted by the high prevalence of chronic kidney disease in the US (approximately 14% of adults) and the fact that the increasing prevalence cannot be explained by trends in known risk factors.[12] Over 10,000 subjects were followed for about 20 years. The authors provided estimated absolute risks of chronic kidney disease over 10 years. For those taking PPIs, the risk was 11.8% whereas for those who did not use them, 8.5%, giving a 3.3% absolute risk increase. The comparison was only between users and non-users and thus there was no duration of use or dose results provided. Ten years does not mean ten years of use.

Chronic kidney disease is a serious matter and can lead to dialysis which has its own set of serious side effects, and eventually to the need for kidney transplant. Anyone on dialysis will tell you that it has a significant impact on quality of life, especially if the hospital is remote.

Indications for the use of PPIs include so-called heartburn and stomach acid related disorders such as gastroesophageal reflux disease (GERD) which can involve serious damage to the esophagus which in turn is a risk factor for Barrett's esophagus which is a risk factor for cancer. Damage includes narrowing of the esophagus or inducing an ulcer in the esophagus. In addition PPIs are indicated for stomach ulcer prevention and treatment. Most treatments are short term, but the availability of this class of drug without prescription has resulted in widespread use which at least in some cases involves taking the drug over the long term for problems outside the above indications. In the paper describing the research cited above, the authors comment that in 2013 more than 15 million Americans used prescription PPIs and cite a study suggesting that up to 70% of these prescriptions are without a justifying indication, and that 30% of PPI users could discontinue use without developing symptoms. They call for a reduction of unnecessary use.

On the risk side of the balance sheet, not only do we have an increased risk of chronic kidney disease, but according to US FDA drug safety communications:

- Risk of *Clostridium difficile* associated diarrhea.
- Risk of low magnesium levels, a serious problem frequently overlooked and not checked with blood tests.
- Possible increased risk of fractures of the hip, wrist, and spine.

In addition, there is a fundamental issue. Humans evolved to have high stomach acidity (low pH) which has been the case for eons. The acid is hydrochloric acid excreted into the stomach. The high acidity is required for the converting of protein into its constituent amino acids which are then metabolized, and is also required for the absorption of some nutrients. The high-acid environment is also a shield against undesirable bacteria which are prevented from colonizing in the stomach or bowel. This suggests that the reasons must be compelling for changing this fundamental aspect of our gastrointestinal system. To make such a profound change as reducing the acidity to near neutral over a long period of time would be expected to have deleterious consequences, and yet this is done by millions of individuals, in many cases simply because they find occasional indigestion with acid reflux unpleasant. In fact, in some cases, this type of indigestion is resolved by *increasing stomach acid, not decreasing it.*

The pharmaceutical industry tends to minimize the importance of PPI side effects and there are not enough industry independent studies to have a clear picture of the problem. Thus one frequently sees the argument that there is insufficient data to justify concern for some proposed side effect. However, absence of evidence of risk does not imply that there is no risk. Furthermore, side effects experienced by long-term users

who are obtaining the PPIs over-the-counter is a vast unknown, and yet these may represent a majority of long-term users.

BOTTOM LINE

This is a perfect example of a drug intervention that alters a basic aspect of human physiology. Another involves the statins which inhibit a pathway which then has repercussions for a large number of vital functions downstream. As regards stomach acid, it appears that one should significantly reduce it only for very compelling reasons. It should be a general principle of medicine that one does not mess around with major physiology that has evolved over eons without considering carefully what is really being done.

REFERENCES

(1) Nasir K, Bittencourt MS, Blaha MJ et al. Implications of Coronary Artery Calcium Testing Among Statin Candidates According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2015 October 13;66(15):1657-68.

(2) McClelland RL, Jorgensen NW, Budoff M et al. 10-Year Coronary Heart Disease Risk Prediction Using Coronary Artery Calcium and Traditional Risk Factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) With Validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). *J Am Coll Cardiol* 2015 October 13;66(15):1643-53.

(3) Hartaigh B, Valenti v, Cho I, Schulman-Marcus J, Gransar H. 15-Year Prognostic Utility of Coronary Calcium Scoring for all Cause Mortality in the Elderly. *Atherosclerosis* 2016;In Press.

(4) Zeb I, Li D, Nasir K et al. Effect of statin treatment on coronary plaque progression - a serial coronary CT angiography study. *Atherosclerosis* 2013 December;231(2):198-204.

(5) Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int J Epidemiol* 2015 February;44(1):186-98.

(6) Schaefer B. Development of Blood Tests for Early Cancer Detection. *The International Journal of Phytotherapy* 2013;1(2):6-12.

(7) Schaefer BA. *Salvestrols. Journey to Wellness*. Clinical Intelligence Corp. Book available at Amazon.com; 2013.

(8) Schaefer B. Personal communication. 2012.

(9) Lustig RH, Mulligan K, Noworolski SM et al. Isocaloric fructose restriction and metabolic improvement in children with obesity and metabolic syndrome. *Obesity (Silver Spring)* 2015 October 26.

(10) Singh GM, Micha R, Khatibzadeh S, Lim S, Ezzati M, Mozaffarian D. Estimated Global, Regional, and National Disease Burdens Related to Sugar-Sweetened Beverage Consumption in 2010. *Circulation* 2015 August 25;132(8):639-66.

(11) Inge TH, Courcoulas AP, Jenkins TM et al. Weight Loss and Health Status 3 Years after Bariatric Surgery in Adolescents. *N Engl J Med* 2015 November 6.

(12) Lazarus B, Chen Y, Wilson FP et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA Intern Med* 2016 January 11;238-46.

International Health News **has an arrangement with iHerb to facilitate subscribers ordering supplements from a reliable source as well as assisting the newsletter in meeting its expenses. Dr. Ware, the editor, is not involved with this aspect of *IHN*, receives no financial benefit from these sales, and is only concerned with the scientific content of the newsletter.**

Please use the link below to access the Vitamin Store.

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

FREE subscription

http://www.yourhealthbase.com/subscribe.htm

Editor: William R. Ware, PhD

INTERNATIONAL HEALTH NEWS is published 10 times a year by
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com

ISSN 1203-1933

INTERNATIONAL HEALTH NEWS does not provide medical advice. Do not attempt self-diagnosis or self-medication based on our reports. Please consult your healthcare provider if you are interested in following up on the information presented.

PERSPECTIVE AND COMMENTARY

CARDIOVASCULAR RISK ASSESSMENT AND OVER-DIAGNOSIS

William R. Ware, Ph.D.

INTRODUCTION

Why is it important to understand the various aspects of cardiovascular disease (CVD) risk assessment? The answer is that most readers will sooner or later receive the suggestion that it should be done, if this has not already happened. It will come up in any routine, insurance or job-related physical exam and is also quite likely during a visit to the doctor for practically any reason. The philosophy is simple. Heart disease or cardiovascular disease, a more comprehensive term since it includes stroke, is fairly prevalent and mainstream medicine regards these diseases as treatable with very impressive relative risk reductions and thus the physician feels a responsibility of assessing risk and advising preventive action.

Unfortunately, there are conflicting interests in CVD assessment since the results strongly influence drug prescriptions and thus impact the industry sales and profits. Since the drugs in question generate huge sales and the more assessments done that result in pharmaceutical intervention the better. Cholesterol is a big factor in this assessment. In 1950 almost no one had heard of cholesterol but in 2015, practically everyone in the developed world and many others know if they have high cholesterol. We have gone through decades of fear related to dietary cholesterol and elevated blood cholesterol and this has had a significant impact on dietary choices for many individuals as well as the willingness to accept treatment.

Not everyone knows that this entire subject from assessment to treatment is controversial. Some may be aware that not everyone agrees with the conventional wisdom which seems to some like a religion based on dogma but clarity seems impossible to achieve due to the need to evaluate evidence which involves considering the impact of industry bias and influence. There is now a significant literature written by skeptics, both books for the general public and for the medical journal literature. There is also an international organization of cholesterol skeptics called THINCS that includes a number of prominent medical scientists and physicians and has a useful and informative website. The point is that the debate deserves recognition.

This perspective and commentary will examine a number of issues including the challenge of risk assessment, and the risks and benefits of drug therapy for elevated cholesterol.

ASSESSING RISK AND ESTABLISHING GUIDELINES

Note: To convert mg/dL to mmol/L, for total or HDL or LDL cholesterol, divide by 38.7. For triglycerides, divide by 88.5. We will use mg/dL

Assessing CVD risk has received an amazing amount of research attention since the 1960s with at least several thousand studies reported in the literature. The most powerful approach involves large population studies which collect vast amounts of data on a large group of subjects and then by sometimes quite sophisticated statistical analysis recover the most important factors determining the risk of acute coronary events five or ten years later. Once these factors have been identified and quantified, paper and pencil or free online calculators are available which enable the input of parameters and yield the 5- or 10-year risk of acute first events. There are over 6 such calculators online with fill-in pages and physicians even use these on their iPads or other hand-held devices right in the examining room as they review the patient's information and provide interpretation and a recommendation. The most famous is based on the US Framingham Study. The results provided by these calculators of course depend on the populations that were studied and when the data was collected. There are some factors that are important but unmeasured and in particular the presence and extent of coronary atherosclerosis. The applicability of the calculator to the individual patient will depend on the match with the population and thus calculators for Europe may not perform well in North America. The most common parameters involved are age, gender, total cholesterol (TC), high-density cholesterol (HDL), systolic blood pressure and occasionally diastolic pressure, and yes or no answers to questions such as family history of cardiovascular disease, presence of diabetes, smoking, and whether or not cholesterol-lowering and blood pressure drugs are used. The reason for blood pressure lowering drugs being a risk factor is the implication of an early history of untreated high blood pressure turns out to have a permanent effect on the risk of CVD disease even if currently treated. The events at issue are generally "hard" which means that there is little leeway in diagnosis or ordering a procedure, which is not the case with balloon angioplasty, coronary artery bypass or acute angina. Hard endpoints generally include just fatal and non-fatal heart attack or stroke and cardiovascular-related mortality.

Readers may have picked up something odd in the above parameters. LDL, the so-called bad cholesterol, is not an input in most calculators. Furthermore, LDL is not measured in clinical practice but rather calculated by what is called the Friedewald equation which includes triglycerides (TG) and is based on the following equation, which incidentally fails at high TGs where another equation is used. The Friedewald equation is LDL = TC – HDL – 0.2 x TG (mg/dL). The factor 0.2 changes if mmol/L units are used. The message is that your doctor knowns your LDL because the TC, HDL and TG were measured. However the TGs and the LDL are not used in most risk calculators since TG levels are not an input and LDL cannot be calculated. Thus correlations from population studies being used to get the 10-year risk are ignoring these two lipids even though the data is available. Either can be high or low. Yet the current guidelines all focus on LDL, the older one (ATP III) using its level as a target, the newer one

(AHA/ACC) using it as a threshold in deciding statin therapy in some patient presentations. Strange, even though the TC/HDL ratio is considered a strong risk predictor. The designers probably say that including LDL does not improve the risk estimate.

The older assessment protocol involved establishing the existence of five major risk factors, smoking, hypertension (BP ≥ 140/90, low HDL (< 40 mg/dL), family history of coronary heart disease and age. This was combined with the 10-year risk to set LDL goals and actual LDL levels used to decide therapy recommendations including so-called therapeutic lifestyle changes. This is the approach used for many readers and has been around since 2001 with a few subsequent modifications.[1]

In 2013 a new kid arrived on the block called *The AHA/ACC Assessment and Guidelines for the Treatment of Cholesterol and the Reduction of Cardiovascular Risk in Adults*.[2] These new guidelines and risk assessment method were the joint effort of the American Heart Association (AHA) and the American College of Cardiology (ACC), which incidentally are not government organizations. The following guidelines were advanced to determine the recommendation of statin therapy for any adult age ≥ 21. Note that most relevant studies rarely enroll subjects younger than 40. The AHA/ACC guidelines identify four distinct groups of individuals where statins are indicated.

- Known presence of cardiovascular disease due to atherosclerosis. Everyone, no qualifying considerations except for deciding between intensive and moderate statin dose.
- LDL >190 mg/dL. Again, no qualifying considerations and no specific treatment target levels.
- Diabetics between 40 and 75 years of age with LDL levels between 70 and 189 mg/dL. This LDL range encompasses from the 15th to the 97th percentile of Americans, i.e. almost all.[3] The 10-year risk will vary significantly between age 40 and 75 and also for a given LDL level even in diabetics, but this is disregarded. More about this later.
- If the 10-year risk of cardiac event or stroke exceeds 7.5% based on the new AHA/ACC calculator, statin treatment is recommended. Everybody, no restrictions or qualifications. For those between 5% and 7.5% 10-year risk *considering* statins is recommended. This applies to those who did not qualify for the above three groups.

Note the absence of gender except for the last recommendation where gender is a strong factor in the 10-year risk calculation. For the other groups, gender apparently does not matter even though the AHA/ACC risk calculator and all other calculators make it clear that it is a major determinant of the 10-year risk. Also, mainstream medicine appears unwilling to admit that lipid lowering for women has no benefit in primary prevention.[4, 5] A paper published in Lancet in April 2015 will be taken by some as finally showing that statins benefit women, but if one looks at the meta-analyses in

the supplementary data, it is clear that the analysis used for the argument presented in the main text just achieved statistical significance because of an expanded set of end points, and when the analysis was done with only major hard cardiovascular endpoints, the earlier conclusion reached by a number of investigators persisted, i.e. no benefit, even for women with 5-year risk up to 30%[6] (see Web figure 5 in the supplementary material of this paper.) These hard endpoints are of the greatest significance and a used in almost all of the calculators described above. In fact, data from the CDC indicates that in 2011-2012, statin use by men was at 30% of the population with women at 26%, numbers that do not reflect the huge differences in risk and benefit and suggest that clinical decisions are being made without concern for gender. The use of calculators at least reflects the gender difference in risk but of course does not deal with the effectiveness of the treatment being considered. In addition, studies have not looked at individuals over 75 and yet the highest percentage usage of statins is in this age group. The pharmaceutical industry benefits by having these issues ignored. Young men and especially women have low risk of hard cardiovascular events and any analysis of treatment benefits vs. risk of adverse drug reactions will generally fail for this age group, especially if the magnitude of the real risk of adverse side effects is recognized.

Critics would argue that the new guidelines represent a one-size fits all approach based on generation of fear of cardiovascular disease and a pill that solves the problem with a large relative risk reduction. All of this can be cynically described either as misguided or possibly part of an agenda to extend the use of statins to a much wider population by putting a deceptive spin on the presentation of the data.[7]

OTHER PROBLEMS AND ISSUES WITH THE NEW GUIDELINE

This is important because it appears that the new guidelines are rapidly gaining acceptance and will probably be used to evaluate readers of IHN in the near future. An obvious question is the evidence justifying the 7.5% threshold. Turning to the 50-page major publication concerning the new guidelines,[8] one finds at the place where this aspect of the guideline is introduced along with seventeen references and the highest evidence quality grade of A. The recommendation is for primary prevention in individuals without prior history of cardiovascular disease or diabetes and applies to anyone not fitting into the first three groups described above. In the set of seventeen references offered as the source of evidence, there are two dealing with daily living aspects, one with angina, a clinical study of an elderly cohort, one paper on the risk of triglycerides, two irrelevant secondary prevention trials, and three dealing with diabetics, even though diabetes does not enter into the 7.5% issue. Of the remainder, most were even less relevant and those that might have been were examined and found to in no way deal with the question of the 10-year threshold risk in the context of the guidelines in question. In other words, no relevant evidence appears to have been cited when the authors were justifying this item in the guidelines, even though it is probably the most radical of the recommendations and is awarded of the highest grade for strength of evidence. Also, how could such a precise number as 7.5% arise? Why not 7 or 8 or even the historical 10% instead?

It appears the basis of the 7.5% comes from the 2012 meta-analysis by the Cholesterol Treatment Trialists' Collaboration which found that a 39 mg/dL reduction in LDL resulted in benefit in the ≥ 5% to < 10% 5-year risk range which used the soft endpoint of coronary revascularization along with the standard hard endpoints.[9] This expanded endpoint always inflates the risk. In that study, for individuals without vascular disease, the estimated **absolute** risk reductions for this risk range predicted to result from substantial LDL lowering was 0.5%, i.e. 99.9% did not benefit.

In addition, there is a problem that critics were quick to pick up. AHA/ACC provided a new event risk calculator online at the time of the online release of the peer reviewed paper presenting the new guidelines. The new assessment calculator came under almost instant and severe criticism as overestimating risk by a significant amount with the prediction of associated overtreatment and unjustified adverse side effects.[10, 11] This is an important issue since it is malpractice in many situations not to measure cholesterol levels and blood pressure and using this and other data is integral to the risk assessment and decisions concerning drug treatment and how aggressive it should be. Risk assessment requires the use of an algorithm or for convenience an online calculator that is consistent with the intended population. Critics said the AHA/ACC calculator was not suitable for North America today. The potential for the new guidelines to result in overtreatment was recently reinforced by a study that looked at the increase in individuals eligible for statin treatment as compared to the old guidelines (ATP III).[12] The investigators used a sample US population as of 2005-2010. In comparison with the old guidelines, it was found that AHA/ACC would increase the number of adults either taking or being eligible for statins from 43 million to 56 million, and most of this increase would be in adults without cardiovascular disease who are not receiving statin therapy. Among those without cardiovascular disease who are not receiving statins and between the age of 60 and 75 years, the new guidelines would increase those eligible from 30%-45% to 67% for men and from 21% to 54% for women. These increases were mostly from those identified by using the 7.5% threshold for risk estimation. The bottom line is that new AHA/ACC guidelines would increase the number eligible for statins by 12.8 million. Since this would also apply to other countries, although not necessarily to the same extent, it is clear that this is a big deal for Big Pharma.

Furthermore, critics were quick to point out that these new guidelines bearing the imprimatur of two highly respected medical associations, the American Heart Association and the American College of Cardiology may be biased by pharmaceutical influence as suggested by the declared conflicts of interest present among some the experts involved. There however is an additional problem. It is universally agreed that the intelligent use of drug therapy must involve the consideration of risk reduction (benefit) and the magnitude of the risk of adverse drug reactions. The guidelines above are predicated on the belief that statins provide highly significant **relative** risk reductions ranging from 25% to 40%, and side effects, generally expressed in absolute terms, are very minor. Those who look only at relative risk reductions live in an fantasy land because few patients benefit and the risk of side effects is unknown because of study design and suppression of data.[13] As will be discussed below, it now appears that the risk of adverse side effects is quite large, and is in fact much larger than the absolute benefits.

A paper has just appeared which provides a comprehensive examination of overestimation associated with five commonly used cardiovascular risk calculators including the new one from AHA/ACC.[14] The comparator database taken as a reference standard was from the Multi-Ethnic Study of Atherosclerosis (MESA) which represented a large, modern, US community-based, sex-balanced multiethnic population. The MESA database has already been used in studies that have resulted in almost 1000 publications. From this database, the expected event rates were calculated and compared to those predicted by five calculators. Four including AHA/ACC were found to seriously overestimate event rates and thus 10-year risk by anywhere from 37% to 154%. The overestimation was attributed to outdated and inappropriate databases in the context of the US population. It would appear clear that the new AHA/ACC calculator enhances greatly the already present potential for over-diagnosis and over-treatment associated with the AHA/ACC guidelines. The acceptance of the new guidelines and calculator appears to usher in a new era, the merits of which appear highly debatable and should prompt great concern.

WHAT WE CAN LEARN FROM THE MESA CARDIOVASCULAR RISK CALCULATOR

It is interesting to see if the new guidelines make any sense using the MESA-based online 10-year risk calculator. Let's look at the second group in the guidelines. If LDL is ≥ 190 mg/dL, statin therapy is indicated with no concern for anything else except age ≥ 21. Take a male and female subject and assign various ages such as 45, 55 and 65. Assume HDL at 55 mg/dL, a near optimum level, and an ideal systolic blood pressure according to the latest research at 120mm Hg. In Table 1 we will examine the 10-year risk of hard cardiovascular events assuming a high-risk situation with TC at 290 mg/dL, a TG level at the top of the normal range, i.e. 150 mg/dL and this via the Friedewald equation yields a very high LDL level of 205 mg/dL. We will assume a non-Hispanic white person, no diabetes, no smoking and no family history of cardiovascular disease. Thus aside from the oldest age, neither individual has any so-called major risk factors used in the older guidelines, but of course the older guidelines recognize the high LDL as a red flag. The MESA calculator offers the option of including or ignoring the coronary artery calcium score (CACS), also called coronary plaque burden. Table 1 shows both results for CACS = 0 along with the calcium score required to obtain the same risk as that calculated by ignoring this factor which is what most calculators do. For perspective, it is generally agreed that a CAC score of zero is associated with a very small risk of cardiovascular events and that as plaque develops and progress, the risk increases. Nevertheless, a zero calcium score is common in the general population. The greater the age, the greater the risk of having a CACS > 0 and CAC scores can exceed 1000. More will be said later about its potential role in improving risk assessment with the CAC score. Incidentally, CAC is measured by a special scan involving x-radiation and is not routinely part of the heart disease risk assessment.

Table 1. 10-year risk of hard cardiovascular events according to two calculators for a male and female with high total cholesterol (TC) of 290 mg/dL and high LDL of 205 mg/dL. See text above for other parameters used.

AGE	GENDER	% 10-Y RISK CACS=0 MESA	% 10-Y RISK CACS IGNORED MESA	CAC SCORE	% 10-Y RISK AHA/ACC
45	Male	2.2	3.6	5	3.0
55		2.6	5.6	16	7.0
65		3.1	8.7	47	14
45	Female	1.5	1.7	1	1.2
55		1.8	2.7	5	2.6
65		2.1	4.2	12	6.0

Even though TC and LDL were high, the MESA calculator finds no high risk if we use ≥ 20% or even 10%, the traditional threshold of going from low to intermediate risk. A risk of > 7.5% is only found for the male age 65. Likewise the AHA/ACC calculator finds a risk above 7.5% only for this individual. As expected, women have much lower risks and having a zero calcium score results in negligible risks for men and women even with a very high LDL level and older age. In addition, only small CAC levels are needed to reconcile the difference between the CACS = 0 and results when CAC is ignored. These results are based on data obtained from real events in individuals matching the input parameters but the two calculators use different populations. However, most clinicians, independent of whether they use the older guidelines or the new one, would probably tell anyone with an LDL of 205 mg/dL that they must take a cholesterol-lowering drug or they are going to have a heart attack or stroke and may well die from the event. Note that the calculators did not ask for LDL but our individuals had this high value by virtue of a high TC but optimal HDL (which were part of the input) and an assumed high normal triglyceride level. It can be concluded that according to the MESA calculator even the high TC and LDL indicate what was traditionally considered low risk (<10%) was never reached and for women, very low risk was found.

We can also investigate the importance of total TC and LDL in diabetics in the 10-year risk by examining the range of LDL from 190 to 95 mg/dL which is close to the range used in the new guidelines. Diabetics in the age and LDL ranges in the table below all are eligible for a recommendation of statin therapy. The same set of calculations was done for the equivalent non-diabetic.

Table 2. 10-year risk of hard CVD events for a non-diabetic male according to two risk calculators.

AGE	TC mg/dL	LDL mg/dL	% 10-Y RISK CACS=0 MESA	% 10-Y RISK CACS IGNORED MESA	CAC SCORE	% 10-Y RISK AHA/ACC
45	275	190	2.1	3.6	7	2.8
	235	145	1.8	2.4	2	2.1
	180	95	1.4	2.2	5	1.3
55	275	190	2.5	5.6	20	6.6
	235	145	2.1	4.5	17	5.5
	180	95	1.6	3.4	14	4.1
65	275	190	2.9	8.7	60	13.5
	235	145	2.5	7.5	50	12.1
	180	95	1.9	5.3	40	10.1

Table 3. 10-year risk of hard CVD events for a diabetic male according to two risk calculators.

AGE	TC mg/dL	LDL mg/dL	% 10-Y RISK CACS=0 MESA	% 10-Y RISK CACS IGNORED MESA	CAC SCORE	% 10-Y RISK AHA/ACC
45	275	190	3.0	5.9	11	5.3
	235	145	2.6	4.8	10	4.0
	180	95	2.0	3.6	8	2.6
55	275	190	3.6	9.2	35	12.4
	235	145	3.0	7.5	30	10.4
	180	95	2.4	5.6	20	7.7
65	275	190	4.3	14.1	95	24.4
	235	145	3.6	11.6	85	22.1
	180	95	2.9	8.8	70	18.5

Considerably lower numbers would have been obtained for women. The old guidelines assigned an automatic > 20% 10-year risk to anyone with diabetes which had the result that all diabetics were advised to take statins. Yet for the MESA population, not only is 20% never reached, exceeding 10%, the traditional intermediate risk threshold does not occur until age 65. The AHA/ACC risks are much higher, consistent with the finding that this calculator appears to overestimate risk, as mentioned above. We also see a profound effect of the presence of coronary calcium on risk prediction with small if not

insignificant risk throughout the age, TC and LDL ranges for both diabetics and diabetics with CACS = 0. No plaque, no events trump the CVD risk of diabetes. These tables also illustrate the large variation in risk encompassed by the AHA/ACC guidelines when a wide range of age and LDL levels is used, even though it is not an input parameter in their calculator nor can it be calculated due to the absence of TG input. If one is lucky enough to have a CAC score of or very near to zero, high cholesterol is not an issue for the risk of acute events, as illustrated by the CACS = 0 column even at age 65. ***Even the diabetic with CACS = 0 has a very low risk.***

CHOLESTEROL AND CORONARY CALCIUM (ATHEROSCLEROSIS) PREVALENCE AND PROGRESSION

It is common to read in the medical literature that cholesterol causes atherosclerosis and its progression. This has the status of dogma and appears widely believed. However, it does not appear to be true. It was already pointed out in 2000 by Uffe Ravnskov that autopsy evidence did not support the hypothesis that blood cholesterol was a factor in the progression of atherosclerosis.[15] Furthermore, this was not due to the delay in some cases in the blood collection. In 2009, the author of this perspective reinforced this view with a paper citing numerous studies where coronary plaque was measured along with total cholesterol and also frequently LDL cholesterol. Studies included the modern determination of atherosclerosis as measured by coronary calcification by electron beam computed tomography and autopsy studies. In a set of eighteen studies no correlation was ever found between prevalence or progression of calcified plaque and this included diabetics.[16, 17] Autopsy studies find the same result. Recent studies have confirmed this view. As part of the Multiethnic Study of Atherosclerosis (MESA) the question of the association between total cholesterol, LDL and HDL cholesterol and the progression of coronary calcium were examined.[18] In the MESA cohort, no association was found with either LDL or total cholesterol. The strongest associations were with age, gender, hypertension, current smoking, and diabetes, with the latter being strongest. Another MESA study found no association with progression and total cholesterol in individuals with low Framingham 10-year risk score.[19]. In a rural US population, no association between hypercholesterolemia (high blood cholesterol) and the prevalence of CAC was found.[20] Finally, in a MESA study; LDL was found to have an insignificant influence on newly detected CAC.[21] Thus the evidence that falsifies the hypothesis that cholesterol drives atherosclerosis continues to grow, but medical mythology is well known to have a long half-life.

In addition, a number of studies failed to find that statin treatment had any influence on the progression of atherosclerosis as quantified by CAC.[22-24] However, we are told that statins cause a regression of atherosclerosis as measured by ultrasound methods of examining coronary arteries or carotid arteries (in the neck), but the clinical significance of the small changes in plaque volume seems highly debatable and the data limited to a few small studies.[25]

CORONARY ARTERY CALCIUM SCORE—THE IGNORED KEY TO CARDIOVASCULAR RISK ASSESSMENT

In 2001 Dr. William Davis, MD, wrote a book titled *Track Your Plaque* which made a strong case for the value of the CAC score in determining risk of CVD and no doubt encouraged many to get the CT scan even at what was then considerable cost. His views have been subsequently strongly reinforced by many studies. The above tables certainly illustrate the impact of the CAC score on the 10-year risk of hard CVD events found in the MESA population. A CACS = 0 reduces risks to a few percent or less ***independent of other risk factors and even for diabetics***. Thus it is of interest to examine what fraction of the US adult population has zero calcium. Is it so small that it can be ignored? Alternatively, is it too large to ignore? In the MESA cohort which involved individuals between 45 and 84 with a mean age of 58 and composed of 37% men, 40% of the men and 62% of the women had CACS = 0.[26] Another MESA study which looked at 10-year trends of coronary calcification also had baseline data on CACS = 0. In subject examinations in 2012, 32 % of the entire cohort (47% male) had CACS = 0.[27] Again the age range was 45 to 84. In the Dallas Heart Study, a score of < 10 was used to define significantly low coronary calcium. For Caucasian men 59% qualified, whereas for women, 76%. For the combined genders, the number was 62%. The mean age was 54.[28]

A Korean study also provided CACS = 0 by age. For men the percentage with CACS = 0 went from 93% for < 40 years to 57% at 50-59 and 38% at 60-69. The corresponding numbers for women were 99% to 84% to 67%.[29] Thus population studies providing a single percentage for CACS = 0 must be examined with caution since gender and the presence of young adults can influence the results. However, the studies discussed above, this was not an issue.

Thus the answer to the question posed above. The prevalence of CACS = 0 is way too large to ignore. The guidelines discussed above encompass a broad swath of the population and the very significant percentage of prevalence of CACS = 0 simply means that many individuals at negligible risk are being treated with statins simply because they meet the conditions set forth by the old or new guidelines, guidelines that ignore this major risk factor for CVD. The treatment frequently is lifelong, accompanied for some with serious side effects and not insignificant financial cost, either to the individual, the insurance provider or the government. Almost everybody knows if they have high cholesterol, but almost no one knows their calcium score. They do not realize that there is a very significant probability that they do not have significant coronary atherosclerosis and thus a near zero risk for heart disease. While non-calcified plaque can be present, the existing evidence suggests that once the CAC score is zero, the remaining plaque does not present much of a risk since the risk is already very low.

These results can be viewed as indicating that the population probability of a zero calcium is roughly 50-50 for men and even higher for women, and this is independent of traditional risk factors including diabetes. If the score is high, this should provide a strong incentive for considering the alternative to statins, i.e. a traditional

Mediterranean diet including fish augmented with nuts, no smoking, exercise, and aggressive psychological stress elimination. While statins can reduce the progression of certain subtypes of plaque, the impact on the progression of calcified plaque and thus the CAC score is nonsignificant, [30] and it is this score that has been extensively studied and found to be a powerful predictor of adverse cardiovascular events. It is interesting that guidelines do not in general favor screening for CAC. While radiation is an issue, it becomes smaller each year as better equipment is designed. Furthermore, the small and not well-studied risk associated with a single dose of radiation seems trumped by the ever-growing evidence for risks of statin treatment. Critics would probably say that the resistance by mainstream medicine to widespread screening is related to the fear that this would lower the use of their miracle drugs, a notion based on the fantasy generated by focus on large relative risk reduction.

Having a CT scan for coronary calcium is equivalent to screening. Opposition to screening generally arises from a cost benefit analysis and consideration of the risks associated with screening such as false positives and over-diagnosis. In the case of the calcium scan, there are essentially no false positives or false negatives. There is a risk of radiation exposure but then innumerable CT scans are done each day worldwide. Let's do a cost/benefit analysis.

The cost of the coronary artery calcium CT scan has over the years had dramatically declined. The current range appears to be $100 to $400. The cost can depend on whether or not it includes a consultation regarding the results. At Cedars Sinai hospital in Los Angeles, their website indicates $285 gets you the whole package while for $185, just a scan, a lipid panel blood test and a report to the referring physician. A result of CACS = 0 or even a very low number means that there is no coronary heart disease which eliminates a very big risk factor and a source of worry. In addition, the risk of hard coronary acute events is now near zero. No plaque, no plaque ruptures. This means very low risk independent of traditional risk factors and even diabetes. There is now no point in a risk assessment since the results, unless CAC = 0 is an input parameter, are meaningless. It would be malpractice to prescribe statins to anyone with a zero calcium score for the purpose of preventing CHD. Thus even in comparison to the lowest cost generic statin, the price of knowing ones calcium score is cheap and if the results turn out to be a zero or very low score, then over the years a huge saving is achieved. Drug cost is strongly related to both the statin and whether or not it is generic. In 2013 for example, the lowest generic cost was about $300 per year. For non-generic, Lipitor was $500 and Crestor $900. However, cheaper cut-rate drugs are also available in the US from discount super stores although one wonders regarding the origin, purity, and actual amount of drug present relative to the indicated amount.

In the absence of a calcium scan very roughly there is a 50-50 chance of zero calcium. However, there is also a quite significant chance of being prescribed a statin in keeping with the guidelines. Consider the figures cited above reflecting the large percentage of the population on statins, and this number is bound to go up with the new assessment and treatment guidelines. Knowledge that CACS = 0 allows one to ignore the recommendation and avoid the costs of the drug, perhaps for the remaining lifetime

which could be 40-50 years, and in addition avoid the adverse side effects of this class of drug. By avoiding taking the statin long term, it is obvious that the CT scan is highly cost effective. At most, the scan involves a one-time expenditure of $400 and an hour or two of time.

CONCLUSIONS

We appear to have reached the point where an assessment risk calculator, which appears to seriously overestimate risk of CVD hard events, is gaining acceptance. Critical comments do not appear to have had any impact on the adoption of new guidelines which use this calculator and which, in addition, will almost certainly significantly increase the number of individuals recommended for statin treatment.

Studies over several decades have revealed a highly significant fault in cardiovascular disease risk assessment which results from not measuring coronary artery calcium. How serious this omission is can be seen by the fact that a highly significant fraction of individuals in the US population, especially those between 45 and 75 years of age, have zero plaque and heart disease caused by atherosclerosis is not an issue at all for them. Yet many are treated for life with serious unintended consequences which include increasing the risk of diabetes. Indeed, the extent of this increased risk appears much greater than initially thought and appears to even exceed the small benefits of statin therapy by a factor of 10. Yet widespread CT scanning to screen for coronary calcium would probably be impossible simply because of lack of equipment and personnel and professional reluctance. The great prevalence of statin therapy is in part due to the simplicity of the surrogate markers, blood lipids. But individuals can request a calcium scan and will probably get it but the cost will probably not be covered by insurance.

The issues raised in this perspective and commentary are very serious. Evidence of the risk of adverse effects associated with statins seems to increase steadily as more research is done and this contradicts the industry and mainstream medicine view that the risks are smaller than the benefits. A study just published found a 12% **absolute** risk increase in the incidence of diabetes in a follow-up study of 7 years involving a cohort of healthy US adults.[31] This and other recent studies of statins causing diabetes alone appear to falsify the view that benefits outweigh risks.[31-34] The risks of incident type 2 diabetes is high enough to generate serious concern since it must be compared to 1-3% absolute benefits, and given the tendency for statins, if tolerated, to be generally taken for life in the mistaken belief regarding the meaning of the reduction of risk is 25% to 40%. This is a relative risk, mostly meaningless and certainly deceptive. This was discussed in a recent paper in *Expert Reviews of Clinical Pharmacology* titled "*How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease".*[7] What is at stake is both serious event risk category misclassification, over-estimation of risk, over-diagnosis and overtreatment in the face of ever-growing evidence that the danger of statin treatment significantly outweighs the benefit. Even for secondary prevention after an acute atherosclerosis-associated event, the statin benefit is rarely more than a few percent. When there is negligible downside to a treatment, then low effectiveness can be

tolerated. The magnitude of drug adverse effects frequently becomes known only when examined by unbiased researchers with no support from industry. This is rare and adverse drug effects is not a popular research area.[13] However, this is now happening. The number of new studies dealing with the association of statin treatment and newly diagnosed type 2 diabetes is an encouraging sign.

If statins help only a small percentage of those subjected to them, then what does one do when this therapy is suggested but rejected as inadequately effective when the risk of adverse effects are considered? The answer is too long for this perspective and commentary. However, the advice most commonly seen from integrative practitioners and even some mainstream sources is not to smoke, eat a traditional Mediterranean diet and include fish and nuts, exercise daily, drink alcohol, preferably red wine, in moderation with the main meal unless addiction is an issue, and avoid or attempt to deal with psychological stress. This last action is much underappreciated and of course difficult.[35] To this might be added that diabetics should consider attempting to cure their disease with the Newcastle diet,[36] but should not be surprised if their doctor has never heard of it and does not believe it could possibly work. The Mediterranean diet will not cure diabetes. Knowledge of a high 10-year risk of an acute cardiovascular event should help provide incentive for lifestyle changes, but the above discussion suggests that unless it includes a CT scan for coronary plaque, a key risk factor is being ignored with the potential for totally unwarranted concern and worry. If one has had an acute event associated with atherosclerosis, the problem of risk assessment and treatment is more complex than what has been discussed here which deals mostly with primary prevention.

Finally, it is important to understand that many of the arguments and views presented above are based on data that concerns large populations rather than a given individual and depend simply on probabilities of acute events based on limited input parameters. Thus a low 10-year risk should not lull one into ignoring the onset of symptoms associated with stroke or a heart attack. This is especially true for women who frequently present differently than men during the onset of such cardiovascular events. When in doubt call 911 or whatever the appropriate number is. Paramedics generally can very quickly come up with sound advice regarding need to be seen in the ER and it is not wise to disregard this recommendation. Frequently within minutes of arriving they will already have the results of an ECG plus a good initial picture of the presentation. At least that is the case in Southwestern Ontario where I live and presumably in larger cities in North America. There is also a window in time where stroke type evaluation plays a critical role on the indicated medication and long-term outcome. Emergency stroke centers attempts to take advantage of this window in cooperation with the EMS (paramedics).

DISCLAIMER

The above perspective and commentary is not intended to provide medical advice in any way whatsoever but merely to provide information for the consideration by the reader. Readers should depend on their physician for medical advice.

REFERENCES

(1) ATP III guidelines At-A-Glance. *http://www nhlbi nih gov/files/docs/guidelines/atglance pdf* 2015. AccessedApril 11, 2015.

(2) Lopez-Jimenez F, Simha V, Thomas RJ et al. A summary and critical assessment of the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: filling the gaps. *Mayo Clin Proc* 2014 September;89(9):1257-78.

(3) Elshazly MB, Quispe R, Michos ED et al. Patient-Level Discordance in Population Percentiles of the Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio in Comparison With Low-Density Lipoprotein Cholesterol and Non-High-Density Lipoprotein Cholesterol: The Very Large Database of Lipids Study (VLDL-2B). *Circulation* 2015 August 25;132(8):667-76.

(4) Eisenberg T, Wells M. Statins and Adverse Cardiovascular Events in Moderate-risk Females: A Statistical and Legal Analysis with Implication for FDA Preemption Claims. *J Emperical Legal Studies* 2008;5(3):507-50.

(5) Petretta M, Costanzo P, Perrone-Filardi P, Chiariello M. Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis. *Int J Cardiol* 2010 January 7;138(1):25-31.

(6) Fulcher J, O'Connell R, Voysey M et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015 April 11;385(9976):1397-405.

(7) Diamond DM, Ravnskov U. How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease. *Expert Rev Clin Pharmacol* 2015 March;8(2):201-10.

(8) Stone NJ, Robinson JG, Lichtenstein AH et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014 June 24;129(25 suppl 2):S1-S45.

(9) Mihaylova B, Emberson J, Blackwell L et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012 August 11;380(9841):581-90.

(10) Ridker PM, Cook NR. Comparing Cardiovascular Risk Prediction Scores. *Ann Intern Med* 2015 February 17;162(4):313-4.

(11) Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. *Lancet* 2013 November 20.

(12) Pencina MJ, Navar-Boggan AM, D'Agostino RB, Sr. et al. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med* 2014 April 10;370(15):1422-31.

(13) Goldacre B. *Bad Pharma*. Toronto: McClland & Stewart; 2012.

(14) Defilippis AP, Young R, Carrubba CJ et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015 February 17;162(4):266-75.

(15) Ravnskov U. *The Cholesterol Myths*. Washington: NewTrends Publishing, Inc; 2000.

(16) Ware WR. The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression. *Medical Hypotheses* 2009;In press.

(17) Ware W. Does cholesterol drive atherosclerosis? in Atherosclerosis: risk factors, preventgion and treatment, edited by Murakami,E; Sakamoto,H. Nova Publishers; 2012.

(18) Gassett AJ, Sheppard L, McClelland RL et al. Risk Factors for Long-Term Coronary Artery Calcium Progression in the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc* 2015 August;4(8):e001726.

(19) Okwuosa TM, Greenland P, Burke GL et al. Prediction of coronary artery calcium progression in individuals with low Framingham Risk Score: the Multi-Ethnic Study of Atherosclerosis. *JACC Cardiovasc Imaging* 2012 February;5(2):144-53.
(20) Mamudu HM, Paul T, Veeranki SP, Wang L, Panchal HB, Budoff M. Subclinical Atherosclerosis and Relationship With Risk Factors of Coronary Artery Disease in a Rural Population. *Am J Med Sci* 2015 October;350(4):257-62.
(21) Alluri K, McEvoy JW, Dardari ZA et al. Distribution and burden of newly detected coronary artery calcium: Results from the Multi-Ethnic Study of Atherosclerosis. *J Cardiovasc Comput Tomogr* 2015 July;9(4):337-44.
(22) Houslay ES, Cowell SJ, Prescott RJ et al. Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial. *Heart* 2006 September;92(9):1207-12.
(23) Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. *J Am Coll Cardiol* 2005 July 5;46(1):166-72.
(24) Henein MY, Owen A. Statins moderate coronary stenoses but not coronary calcification: Results from meta-analyses. *Int J Cardiol* 2010 September 13;Published ahead of print, September 4, 2010.
(25) Nicholls SJ, Tuzcu EM, Sipahi I et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007 February 7;297(5):499-508.
(26) McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2006 January 3;113(1):30-7.
(27) Bild DE, McClelland R, Kaufman JD et al. Ten-year trends in coronary calcification in individuals without clinical cardiovascular disease in the multi-ethnic study of atherosclerosis. *PLoS One* 2014;9(4):e94916.
(28) Jain T, Peshock R, McGuire DK et al. African Americans and Caucasians have a similar prevalence of coronary calcium in the Dallas Heart Study. *J Am Coll Cardiol* 2004 September 1;44(5):1011-7.
(29) Park HE, Kim MK, Choi SY et al. The prevalence and distribution of coronary artery calcium in asymptomatic Korean population. *Int J Cardiovasc Imaging* 2012 June;28(5):1227-35.
(30) Zeb I, Li D, Nasir K et al. Effect of statin treatment on coronary plaque progression - a serial coronary CT angiography study. *Atherosclerosis* 2013 December;231(2):198-204.
(31) Mansi I, Frei CR, Wang CP, Mortensen EM. Statins and New-Onset Diabetes Mellitus and Diabetic Complications: A Retrospective Cohort Study of US Healthy Adults. *J Gen Intern Med* 2015 April 28.
(32) Cederberg H, Stancakova A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia* 2015 March 10.
(33) Culver AL, Ockene IS, Balasubramanian R et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med* 2012 January 23;172(2):144-52.
(34) Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *BMJ* 2013;346:f2610.
(35) Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004 September 11;364(9438):937-52.

(36) Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med* 2013 March;30(3):267-75.

Editor: William R. Ware, PhD

INTERNATIONAL HEALTH NEWS is published 10 times a year by
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com

ISSN 1203-1933