“AREDs was designed to assess simultaneously the clinical course of AMD and cataract, and the potential safety and efficacy of pharmacologic doses of antioxidant vitamins and zinc in reducing the incidence or slowing the progression of AMD and/or cataract”

AREDs Investigators Distort Findings

In my opinion, the Age-Related Eye Disease Study (AREDS) investigators promoted a nonsignificant results into a conclusive recommendation. Here is how they did it.

The primary study outcomes for AREDS are explicitly stated in the “Participants and Methods” section of the article: (1) progression to advanced age-related macular degeneration (AMD) and (2) a 15-letter decrease in visual acuity. These outcomes were to be evaluated in all patients by independent tests of significance of the 2 primary treatments. This carefully specified primary analysis led to 4 tests, none of which was statistically significant. One, testing the effect of zinc on progression to advanced AMD, achieved a level of significance defined by the investigators as suggestive.

Despite these negative results, the investigators recommend combined treatment with antioxidants and zinc based on their secondary analysis. Two analytic approaches provided them with significant results. First, the authors restricted the analysis to a subgroup. The mainstream practice of clinical trials warns that unless the main overall comparison is significant, investigators should be conservative in their interpretation of significant subgroup results. Second, they featured the combined treatment group, which in secondary analysis broke the boundary of statistical significance, thereby disregarding the primary analysis in which neither treatment was significant.

In its discussion of relevant literature, the “Comment” section is as selective as the analysis. At a planning meeting, the AREDS chairman recounted his efforts to review retinal photographs from the first published study of zinc and AMD and his disappointment at learning they had been lost shortly after publication. By this criterion alone the relevance of that small clinical trial is depleted. Nevertheless, the AREDS investigators report its finding to support their recommendation. Some major epidemiological studies that are not supportive, glancingly mentioned in the introduction, have no voice in the “Comment” section.

Adverse effects reported by the investigators include an increase in hospitalizations for urinary tract problems among participants treated with zinc and yellowing of the skin among participants taking antioxidants. They modified the protocol for current and former smokers during the course of the study because of published reports of increased mortality among smokers supplementing with beta carotene. Furthermore, they caution that the health effects of long-term use of their proposed treatment are unknown.

Analyses in clinical trials are complex endeavors. Austin Bradford Hill observed that the inferences we draw turn on our personalities. In an article in the New York Times, Gina Kolata spoke to public frustration at reports of clinical research that convert suggestive results to conclusive ones. A public that is concerned with AMD, physicians who need to advise and treat, and industry representatives who wish to provide us with products that are effective all depend on us to get it right in clinical research. In my opinion, the message that should have emerged from AREDS is that these treatments failed to demonstrate efficacy in preventing AMD and are not recommended for that use.

Daniel Seigel, ScD
Cushing, ME

To the Editor: The review of age-related macular degeneration by Jager et al. (June 12 issue) does not refer to an editorial accompanying the report of the Age-Related Eye Disease Study (AREDS) in the Archives of Ophthalmology in 2001 and two subsequent letters, all of which criticized the study analysis for setting aside a negative result in which dietary supplementation with high doses of vitamins and minerals was ineffective and instead reporting on a subgroup in which the result was positive. The investigators argued that the excluded patients had too few end points to be eligible for treatment. However, the group of patients who received the supplement had greater disease progression and provided valuable data regarding early intervention.

Discarding prespecified negative analyses and reporting on positive subgroup analyses has been repeatedly discouraged. The omission of the above information perpetuates the myth that the supplement used in the AREDS was effective, at the price of a treatment that has no benefit and carries undetermined risks.

Daniel Seigel, ScD.

References
ICMJE Form for Disclosure of Potential Conflicts of Interest

- The time frame for this reporting is that of the work itself, from the initial conception and planning to the present.
- The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work.
- Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf...
  ...include all monies from sources with relevance to the submitted work...
- If there is any question, it is usually better to disclose a relationship than not to do so.
- For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome.
- Authors should err on the side of caution.

* This means money that your institution received for your efforts on this study. (ex. Royalties)

AUTHOR RESPONSIBILITIES

Public trust in the scientific process and the credibility of articles depend in part on how transparently conflicts of interest are handled during the planning, implementation, writing, peer review, editing, and publication of scientific work.

In AREDS, the pharmaceutical company holds the IND with FDA and has safety reporting responsibilities...

The NIH holds a royalty-bearing license issued to Bausch & Lomb for the Age-Related Eye Disease Study Supplement.
The boldest failure to disclose conflict of interest occurred on the opening page of AREDS Report 

"The AREDS Patent"

Despite AREDS2 research data supporting a lower zinc dose, 25mg, the National Eye Institute, with AREDS patent assignee and sponsor, Bausch & Lomb, refused to modify their respective recommendations and formulations as such would presumably nullify patent protections.

Truths:
- B & L execs, in cahoots with the AREDS Study Chairman, wrote the patent.
- U.S. government holds a paid, royalty-bearing license on the AREDS formulas.
- North America is the only market, worldwide, for zinc overdoses in eye vitamins.
- The entire AREDS era of publications from 1999-2014 misrepresent conflict of interest.

NEI researchers shirk their fiduciary duty to patients and practitioners.

The physician-patient relationship is a member of a special class of legal relationships called fiduciary relationships. Through the creation of fiduciary duties, the law recognizes that there are relationships in which the parties inherently have unequal power. In the words of one court:

The physician-patient relationship has... its foundation on the theory that the former (physician) is learned, skilled and experienced in those subjects about which the latter [the patient] ordinarily knows little or nothing, but which are of the most vital importance and interest to him, since upon them may depend the health, or even life, of himself or family. Therefore, the patient must necessarily place great reliance, faith and confidence in the professional word, advice and acts of the physician. The essence of the fiduciary relationship is that the patient's interests must be paramount. This is in contrast to the usual legal rule of caveat emptor ("let the buyer beware"). In most businesses, the law assumes that there is an arms-length transaction: the buyer and the seller have, in theory, the same access to information and the same bargaining power. For example, a merchant in a retail store encourages customers to buy the items that have the greatest profitability for the store. The merchant may not be more knowledgeable or have a more favorable information and to make reasonable overstatements of the product's virtues. In contrast, the physician is expected to recommend treatments based only on the patient's medical and psychological needs.

Physicians should be familiar with fiduciary duties from the literature on informed consent medical treatment. The fiduciary duty extends to all aspects of the physician-patient relationship. Breaching the financial aspects of the fiduciary duty to a patient can subject the physician to liability under commercial laws. Understanding the factors that make the physician-patient relationship a fiduciary one will help physicians recognize potential violations.

http://biotech.law.lsu.edu/Books/lbb/x236.htm
Q. What were the results of this study? (AREDS)
The results of the study were negative. The drug had no beneficial effect on vision, and it did not stop the progression of AMD, in any of these three groups of patients.

Q: Were there any financial conflicts of interest in this study?
The Principal Investigator and Study Chairman of the AREDS Study, Dr. Frederick Ferris, has the patent to this drug. The AREDS study was financed partly by Storz, which is now part of Bausch and Lomb, the company that manufactures these pills.

Q: So why does anybody think these drugs work?
After the study was completed, the researchers went back and changed their research design. They arbitrarily threw out all patients with mild AMD from the study. This is a strange decision. Patients with mild disease are the ones who should benefit the most from this drug. Then, they changed their definition of “success”, from: “preventing vision loss and progression”, to: “preventing AMD events”.

After these manipulations, the data seemed to show that the drug prevented what they called “AMD events”, but it did so for only in one group of patients, the one who had intermediate AMD in one eye, and advanced AMD in the other. The study did NOT show that these patients had any vision benefit from taking this drug.

Q. Is it standard scientific practice to change criteria after a study is over?
No. This manipulation has caused a storm of criticism in scientific meetings, and in the scientific literature. Scientists are not supposed to throw out a negative result, and then report on a small subgroup that seems to have a positive result. It does not conform to standard scientific practice. In short, the value of PreserVision has not been proven by accepted scientific methods.

This practice is termed HARKing (Hypothesizing After Results are Known)

What to do with HARKed Results?

Erick Turner, M.D. October 2, 2012 at 5:36 pm
What about “spun” papers? In a 2008 NEJM paper on antidepressants, our group presented data on 11 clinical trials that were negative according to the FDA but positive in the corresponding journal article. This was because primary outcomes, as specified a priori in the protocol, either disappeared or were downplayed, and secondary outcomes or post hoc findings were presented as the main results. This phenomenon has been called HARKing (“hypothesizing after the results are known”). Should such spun papers, which remain part of the public record, be retracted, or should corrected versions be published?

rory robertson (former fattie) October 2, 2012 at 5:58 pm
Dr Turner, I reckon any such unreasonable efforts should be ridiculed in public commentary by competent people in the space who can see clearly the deception being attempted. The drivers of deliberate deception – including the authors and the offending journals – should be hounded/disrespected by serious people at every opportunity. And the papers corrected or retracted depending on the hard facts.

Critical trials, epidemiology, and public confidence.
 Critics in the media have become wary of exaggerated research claims from clinical trials and epidemiological studies. Closer to home, reviews of published studies find a high frequency of poor quality in research methods, including those used for statistical analysis. The statistical literature has long recognized that questionable research findings can occur when investigators fail to set aside their own outcome preferences as they analyze and interpret data. These preferences can be related to financial interests, a concern for patients, peer recognition, and commitment to a hypothesis. Several analyses of published papers provide evidence of an association between financial conflicts of interest and reported results. If we are to regain professional and lay confidence in research findings some changes are required. Clinical journals need to develop more competence in the review of analytic methods and provide space for thorough discussion of published papers whose results are challenged. Graduate schools need to prepare
The scandal of poor medical research

We need less research, better research, and research done for the right reasons

What should we think about a doctor who uses the wrong treatment, either wilfully or through ignorance, or who uses the right treatment wrongly (such as by giving the wrong dose of a drug)? Most people would agree that such behaviour was unprofessional, arguably unethical, and certainly unacceptable.

What, then, should we think about researchers who use the wrong techniques (either wilfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common. 1,2 This is surely a scandal.

When I tell friends outside medicine that many papers published in medical journals are misleading because of methodological weaknesses they are rightly shocked. Huge sums of money are spent annually on research that is seriously flawed through the use of inappropriate designs, unrepresentative samples, small samples, incorrect methods of analysis, and faulty interpretation. Errors are so varied that a whole book on the topic, 3 valuable as it is, is not, comprehensively, in any case, many of those who make the errors are unlikely to read it.

Why are errors so common? Put simply, much poor research arises because researchers feel compelled for career reasons to carry out research that they are ill equipped to perform, and nobody stops them. Regardless of whether a doctor intends to pursue a career in research, he or she is usually expected to carry out some research with the aim of publishing several papers. The length of a list of publications is a dubious indicator of ability to do good research; its relevance to the ability to be a good doctor is even more obscure. A common argument in favour of every doctor doing some research is that it provides useful experience and may help doctors to interpret the published research of others. Carrying out a sensible study, even on a small scale, is indeed useful, but carrying out an ill designed study in ignorance of scientific principles and getting it published surely teaches several undesirable lessons.

In many countries a research ethics committee has approved all research involving patients. Although the Royal College of Physicians has recommended that scientific criteria are an important part of the evaluation of research proposals, 4 few ethics committees in Britain include a statistician. Indeed, many ethics committees explicitly take a view of ethics that excludes scientific issues. Consequently, poor or useless studies pass such review even though they can reasonably be considered to be unethical. 5

The effects of the pressure to publish may be seen most clearly in the increase in scientific fraud, 6 much of which is relatively minor and is likely to escape detection. There is nothing new about the "massaging" of data or of "data torture", as it has recently been called 7 - Charles Babbage described its different forms as long ago as 1830. 8 The temptation to behave dishonestly is surely far greater now, when, all too often the main reason for a piece of research seems to be to lengthen a researcher's curriculum vitae. Ballir suggested that "there may be greater danger to the public welfare from statistical dishonesty than from almost any other form of dishonesty." 9

Evaluation of the scientific quality of research papers often falls to statisticians. Responsible medical journals invest considerable effort in getting papers refereed by statisticians; however, few papers are rejected solely on statistical grounds. 10 Unfortunately, many journals use little or no statistical refereeing: bad papers are easy to publish.

Statistical refereeing is a form of fire fighting. The time spent refereeing medical papers (often for little or no reward) would be much better spent in education and in direct participation in research as a member of the research team. There is, though, a serious shortage of statisticians to teach and, especially, to participate in research. 11 Many people think that all you need to "do" statistics is a computer and appropriate software. This view is wrong even for analysis, but it certainly ignores the essential consideration of study design, the foundations on which research is built. Doctors need not be experts in statistics, but they should understand the principles of sound methods of research. If they can also analyse their own data, so much the better. Amazingly, it is widely considered acceptable for medical researchers to be ignorant of statistics. Many are not ashamed (and some seem proud) to admit that they "don't know anything about statistics."

The poor quality of much medical research is widely acknowledged, yet disturbingly the leaders of the medical profession seem only minimally concerned about the problem and make no apparent efforts to find a solution. Manufacturing industry has come to recognise, albeit gradually, that quality control needs to be built in from the start rather than the failures being discarded, and the same principles should inform medical research. The issue here is not one of statistics as such. Rather it is a more general failure to appreciate the basic principles underlying scientific research, coupled with the "publish or perish" climate.

As the system encourages poor research it is the system that should be changed. We need less research, better research, and research done for the right reasons. Abandoning using the number of publications as a measure of ability would be a start.

DOUGLAS G ALTMAN
Head
Medical Statistics Laboratory, Imperial Cancer Research Fund, London WC2A 3PX

AREDS Misses on Safety - Bruce I. Gaynes, OD, PharmD Chicago, Ill

I have read with interest the article pertaining to the Age-Related Eye Disease Study (AREDS) in the October 2001 issue of the ARCHIVES. However, I believe that while the results are of clinical interest, the findings of the AREDS pertaining to age-related macular degeneration (AMD) should be interpreted with caution. Although inorganictrace elements and vitamins are essential nutrients required for health maintenance, it is erroneous to address the use of such entities as therapeutics without a clear understanding and appreciation of their relevant pharmacokinetic and pharmacodynamic properties. Furthermore, consideration of factors such as biological variability and dose-response, which express therapeutic action in terms of efficacy as well, are in large part provided within the AREDS study design. Characterization of the pharmacologic response to various high-dose vitamin and nutrition administration requires stringent assessment of population-, disease-, and formulation-specific variables that may influence the occurrence of adverse effects in ways not described in the AREDS. For example, changes in drug disposition with age are characterized by alterations in lean body mass, which influences the volume of distribution and partition coefficients pertinent to fat-soluble vitamins, particularly alpha-tocopherol. Furthermore, individuals who use vitamin A as a source of beta-carotene should be advised that absorption of vitamin A (retinol) varies considerably depending on the formulation of the preparation as well as the amount of dietary fat an individual typically ingests. In addition, febrile infections and stress may markedly decrease serum retinol, whereas chronic renal disease may result in significantly elevated serum retinol, requiring the need for an alteration in intake. Moreover, the AREDS neglects to address consideration of causality, as well as the temporal relationship and outcome of reported adverse events, particularly those noted as "circulatory." Furthermore, the obvious observation of the various prescription and nonprescription products is lacking. The AREDS also does not address the need for continuing surveillance of the safety of vitamin and nutrition therapy for AMD in terms of elucidation of unexpected idiosyncratic reactions, an important yet complex task because of the ease of accessibility of such agents. Additionally, and perhaps of greater significance, it is unknown how the results of ongoing prospective trials of vitamin and nutrition therapy for disorders other than AMD will affect those currently following AREDS recommendations. Vitamins and nutrients are not only ubiquitous in nature and easily obtained from nourishing diets, they are also aggressively marketed by pharmaceutical companies eager to promote perceived as well as validated claims of health benefit. In addition, the clever marketing strategies of pharmaceutical companies, such as those promoting doses that "exceed AREDS recommendations," demonstrate the need for clinicians to closely monitor vitamin and nutrient intake. I believe that the AREDS would recommend the use of clear and concise safety guidelines for entities that are largely unregulated and widely promoted with an array of ingredients, formulations, and equivalency provided for public interpretation.

From AREDS Report#8

In the original study design, participants in Categories 2, 3, and 4 were pooled for data analysis and that remains the primary analysis. However, by years there were only 15 AMD events in Category 2 distributed across all 9 treatment groups (3 in the placebo group). The low event rate makes it impossible to assess treatment effects in this category for the AMD outcome and less likely that any of the treatments would be recommended for clinical practice. Of course, this is an important finding for those participants most likely to benefit from an effective treatment (Categories 3 and 4).

Note the authors concede the study design changed after results were known. Further, using the single AMD endpoint of progression to advanced disease leaves a gaping hole in our knowledge about actual disease progression from one stage to the next-i.e. Category 1 or 2, moving to Category 2 or 3, respectively. This is, arguably, of greater importance to the vast majority (80%) of those with AMD, hoping not to develop high risk for progression. A critical analysis of this unpublished data has been missing, particularly considering statements by the former NEI associate director, privy to unpublished data, indicating early AMD subjects suffered harm from AREDS interventions.

Dr. Ambati is Professor and Vice Chair of Ophthalmology and Visual Sciences, Professor of Physiology and the Dr. E. Vernon & Eloise C. Smith Endowed Chair, University of Kentucky, Lexington. The CNIB presented him the 2014 prestigious Chanchlani Global Vision Research Award for excellence in AMD research.

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Dr. Gaynes is an assistant professor of Ophthalmology at Loyola University Chicago Stritch School of Medicine, holding advanced degrees in Doctor of Optometry, Masters in Drug and Doctor of Pharmacy.

**TABLE 5. Multivariate Five-State Markov Model for AMD Progression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 → 2 (Early AMD)</th>
<th>2 → 5</th>
<th>3 → 4 (Intermediate AMD)</th>
<th>3 → 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>P*</td>
<td>0.20</td>
<td>0.28</td>
<td>0.56</td>
<td>0.51</td>
</tr>
</tbody>
</table>

**Note**: a stronger trend toward harm in the early stage than even the purported benefit for those in the intermediate stage consuming AREDS formulas. Reminding the reader this study population includes only 2560 subjects for which genetic material was available from the original 4757 AREDS participants-limiting its power to detect important relationships-it nevertheless supports published statements from past NEI Associate Director, Dr. Daniel Seigel, the AREDS formulas increase early AMD progression.1


**FIGURE 1. AMD progression through a five-state Markov model among subjects without advanced AMD at baseline. *Included 696 stage 2 subjects at baseline and 494 subjects who progressed from stage 1 to stage 2 during the study. †Includes 1151 stage 3 subjects at baseline and 376 subjects who progressed from stage 2 to stage 3 during the study.**

**INTERACTIONS**

May 7, 2002

 Benefits Are Not Plain to See

"For a Proven Product, Blurry Claims" [April 23] suggested that Bausch & Lomb, which manufactures a dietary supplement called Ocuvite, is prohibited from telling consumers about the product's proven ability to treat macular degeneration, a disease causing loss of vision in the elderly. In fact, there is nothing in the law that prevents Bausch & Lomb from making proven claims.

Under the Federal Food, Drug and Cosmetic Act, each manufacturer makes a choice about how much evidence it wants to submit to the Food and Drug Administration and the types of claims it wants to make about its product. A manufacturer who chooses to market a product as a dietary supplement is not required to submit proof of its claims, forgoes government review of the product's safety and effectiveness, and generally avoids requirements about product warnings and quality control. In exchange for this lenient treatment, the manufacturer can make only limited claims related to preserving health ("maintains healthy eyes").

Alternatively, the same manufacturer can choose to market the product as a drug and submit evidence of the product's safety and effectiveness, provide adequate directions for the product's use and adhere to quality control standards. In exchange, the manufacturer is entitled to make significant disease-treatment claims ("for the treatment of age-related macular degeneration"). In this case, Bausch & Lomb chose to avoid submission of data and other regulatory requirements and is now marketing its product with vague and misleading claims.

It makes sense that Ocuvite should not be marketed for treatment of a serious disease when the risks of the product are not described on the label, who exactly can benefit from the product is misleadingly stated and the manufacturer is not held to the same quality control standards as for drugs.

Rep. Henry A. Waxman (D-Calif.)

Washington

The story presented only the perspective of Bausch & Lomb and the chairman of the AREDS study.

By contrast, in Lee Jampol's editorial accompanying the [published] study results, he asked whether there are "weaknesses in this trial that could cast doubt on its conclusion that the supplements were effective." He then described such weaknesses in detail and admitted to finding them troubling.

I wrote a letter published in the March issue of the Archives of Ophthalmology arguing that the investigators had distorted the study results. The treatments had in fact failed to demonstrate effectiveness. The analysis had violated several fundamental principles found in every textbook of clinical trials.

Rather than wring our hands over the policies of the FDA, we should be thankful that that regulatory agency has a professional understanding of clinical trial methodology and would not, I am confident, approve the marketing of these supplements for the prevention of vision loss. The claims for efficacy of this product start with the investigators, where they are not blurry, just unfounded.

Daniel Seigel, ScD
Cushing, Maine
Review of AREDS Report 38 publication and supporting information

Rafal Kustra, PhD
Associate Professor, and
Director, Informonics Lab for Statistical Genomics
Dalhousie School of Public Health, Division of Biostatistics
University of Toronto, CANADA
August 24, 2015

Executive summary. The data presented in AREDS 38 does not show a beneficial effect for any dietary supplement in the prevention or delay of AMD making the identification of subgroup effects difficult. Data from the AREDS Report 8 which is the only publication to show this “main effect” is presented as a departure point for a subgroup analysis, which is inappropriate. Reports 8 and 38 use very different statistical techniques to analyze progression events making them not directly comparable. AREDS Report 38 also has many internal data consistencies making it impossible to know what data was actually analyzed by the authors. The primary data can be used to test the hypothesis that there is an interaction between genetics and treatment. When the primary data is lifted from the manuscript and basic modeling statistics are performed, a strong interaction between CfH, ARMS2 and response to zinc use is observed.


The 2001 Age Related Eye Diseases Study (AREDS) reported on the effect of 3 treatments (zinc, antioxidant and zinc-antioxidant) on the risk of progression from dry AMD to advanced AMD. The study concluded that the combination of zinc and antioxidants (the “AREDS Formulation”) was most efficacious in delaying or preventing the onset of advanced disease in the subset of patients with extensive drusen in at least one eye (AREDS category 3 or 4). These conclusions were based on the unplanned analysis of a subset of 2556 from the total study population of 4732 individuals. Within this subset, 775 progression events were reported. The report does not provide numbers of participants in each arm for Category 3 and 4 only, though data in Table 3 provides data for this group combined with Category 2 participants, allowing the following estimate:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>626</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>674</td>
</tr>
<tr>
<td>Zinc</td>
<td>628</td>
</tr>
<tr>
<td>ARDS</td>
<td>633</td>
</tr>
<tr>
<td>Total (cat 3+4)</td>
<td>2563</td>
</tr>
</tbody>
</table>

This represents discrepancy from 2556 category 3/4 participants reported in Table 4 (difference of 0.2%) but it is close to 2562 reported participants in these same 3 categories. Table 4 supplements a letter publication in June of these authors (supplementary table S6). The data presented in Table 4 of the 2001 AREDS report for patients with category 3 and 4 disease at the time of enrollment will be considered further here1, the authors conclude that zinc alone and the AREDS Formulation were both superior to placebo in lowering the risk of progression to advanced AMD (p = 0.01) with reduction of risk of 30% and 34%, respectively. Antioxidants were not superior to placebo after correcting the statistical significance threshold for multiple hypothesis testing (p=0.03), though the absolute reduction in progression rate was 24%. These results were analyzed using repeated measures logistic regression. Repeated timed assessments of patients identified 8% who spontaneously “recovered” from advanced disease, allowing them to be returned to the “at risk” pool of patients. For this reason survival modeling techniques, such as CoxPH regression were considered unsuitable. It is unclear from the reported data what the effect of dietary supplements would be if “reversion” from advanced disease was considered to be variation in retinal image interpretation rather than deviation from the established understanding of the pathophysiology of this disease.

2. AREDS Report 38.

The AREDS Report 38 study analyzed a subset of the entire AREDS study set described above. Out of 2562 AREDS participants with Category 3/4 AMD (supplementary Table S9), SNP analysis was performed on 1237 of these selected for DNA availability. The authors don't explain how and why these 1237 samples were selected among those with their secondary markers measured (CFH SNPs rs128253 and rs3766405, and ARMS2 deletion) to reach the reported sample size of 1413 for this analysis. Here we concern ourselves only with the results on primary CFH/ARMS genetic markers.

The main results of the AREDS 38 report are shown in Figure 1B, with results for secondary markers shown in Fig. 1C. The analysis was performed using Cox PH regression model. Figure 1B shows the hazard ratios from repeated-measures analysis lifted from AREDS report 38. HRs are measures of relative risks and are similar, but not the same as ORs. In AREDS Report 38, data is presented for 3 treatment groups (zinc alone, antioxidants alone and the AREDS Formulation) stratified by 9 genetic risk groups (27 analyses). Only one combination of genetic risk group and treatment was superior to placebo with p-value = 0.001 (one risk allele for each of CFH and ARMS2 treated with the AREDS Formulation). The paper reports an overall test of interaction between genetic factors and treatment effects with p-value = 0.06. It is worth noting that this omnibus test does not need to be corrected for multiple testing. Hence, if one takes a standard 0.05 confidence threshold, the test, while formally failing to detect a significant interaction between the whole set of 9 tested genotypes and 3 treatment arms does suggest the modification of supplement therapeutic effect by genetics.

There are 2 major problems with the AREDS 38 study as reported. A main effects analysis is not reported. Figure 1A reports main effects from the AREDS 8 study not from the data in the AREDS 38 study. This is highly misleading, since that study used a much larger sample size (over twice as large) and a different modeling approach (repeated-measures logistic regression vs Cox PH regression used in AREDS Report 38). Without the demonstration of main effects an interaction would be interesting to see the comments of the peer reviewers on this point.

The analysis presented in AREDS 38 should not have been attempted before examining the cell sizes. A simple examination of Fig 1B (or SupTable 6b) shows that many subgroups used in the analysis has extremely low cell sizes. For example, for 3 genotype groups 0/0/0.0/2 (nomenclature refers to the number of AMD risk alleles at the CFH and ARMS2 loci, respectively), no count of events is larger than 5. Insufficient cell counts are observed for most other genotype groups except those with CFH=2 is customary in cases such as this in some biologically or clinically relevant way before any formal analysis and hypothesis testing is conducted (as has been described for a similar analysis). Doing so will prevent interpretation of invalid confidence intervals and p-values but also limit the number of hypothesis testing and results multiple testing correction. If done in a sensible way it may lead to greater power for the analysis as a whole.

3. Repeat analysis of the AREDS 38 data from published data

Due to the unavailability of primary survival data for the patients in AREDS 38, we employed a series of sample 2x2 table analysis and logistic regressions to revise this study’s methodology. When follow-up periods have little variability this technique will approximate the results from Cox regression models. Figure 3 and from AREDS Report 8 shows over 80% of participants were followed for at least 6 years and relatively small number of events occurred in year 7. Simple event count based analysis should closely approximate results from time-to-event (e.g., Cox regression) analysis.

3.1 Data problems for event counts

AREDS Report 38, Fig 1B and SupTable 6b purport to show the number of events and totals in each combination of treatment and combined genotype group (27 total subgroups). While the numbers showing group sizes (third column in SupTable 6b and Total column in Fig 1b) generally agree, the counts of events (and, hence, non-events) show large discrepancies between these two, amounting to deviations in event rates. For example in Figure 1B group “00” subjects (no risk alleles at either CFH or ARMS2) who were treated with antioxidants 3 events for the corresponding placebo group is reported while SupTable 6b reports 2 events for this group. For genetic group “01” (no CFH risk alleles and 1 ARMS2 risk allele) Figure 1B reports 7 events for placebo but 5 events are reported in SupTable 6b. In this genetic group 9 vs 5 events for antioxidant treated patients are reported. Some discrepancies are quite large. For group “21” (2 CFH risk alleles and 1 ARMS2 risk allele), Zinc, and AREDS Formulation treatment groups Figure 1B reports 36, and 30 progression events respectively, while SupTable 6b reports 26, and 20 events. There are internal inconsistencies in Figure 1B as well. For the “21” genetic group the number of events in placebo treated patients is quite different. Figure 1B reports 20 and SupTable 6b reports 20 for the comparison to AREDS Formulation treated patients (these should obviously all be the same). Figure 1B and SupTable 6b show totally discrepant data for genetic group “22” (2 risk alleles for both CFH and ARMS2) outcomes:

- for patients treated with antioxidants, Zinc and the AREDS Formulation, Fig 1B shows counts: 19, 18 and 14, while SupTable 6b reports 15, 16, 12 events. Placebo counts are also different: 14 in figure 1b and 10 in SupTable 6b.

Given the discrepancy between the primary data tables/figures presented in the paper one source was selected (figure 1b) by us to perform a repeat analysis of interaction between genetic makeup and treatment groups.
2. Marginal treatment analysis

Using combined counts from SuppTable 5 (no DNA and DNA) representing all 2562 participants with AREDs category 3 and 4 disease one can attempt to replicate the results of Report 8, Table 6. Using Odds Ratio estimates and ChiSquare tests for a series of 2x2 tables, the following results are obtained:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Odds Ratio</th>
<th>99% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidants</td>
<td>0.279</td>
<td>(0.582-1.090)</td>
<td>0.055</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.357</td>
<td>(0.620-1.135)</td>
<td>0.118</td>
</tr>
<tr>
<td>ARDS f</td>
<td>0.797</td>
<td>(0.579-1.095)</td>
<td>0.062</td>
</tr>
</tbody>
</table>

These should be compared with the results reported in (right-hand side of Table 4 in the AERDS book). ARDS Report 8 used repeated measures logistic regression appropriate using a simple 2x2 table analysis of the AERDS Report 38 data. This is reasonable because of low transient event counts (8%, as reported in AERDS 8) and follow-up periods with low variability. We find significant discrepancies while the OR for progression observed in antioxidant treated patients is approximately the same in the AERDS Report 8 and AERDS Report 38 (0.797 vs 0.76 using unadjusted estimates), the other treatments show markedly different ORs. This is a cause for serious concern about data integrity. None of the treatments in AERDS Report 38 show significance at the 0.01 level (threshold used in AERDS Report 8). This is in contrast to AERDS Report 8 which reported progression data from Zinc and antioxidant-Zinc treated patients in comparison to placebo-treated individuals to be different at p-values below 0.01 and that for antioxidant-treated individuals to be different from placebo-treated patients at p-values below 0.05 (SuppTable 10). For some comparisons the OR for progression in placebo treated patients, we see large discrepancies between the marginal (i.e. blinded to genetic data) results inferred from the numbers in AERDS Report 38 and those reported in AERDS Report 8.

A similar reanalysis was performed using data from participants with available DNA samples (ie, group used for most of the results in AERDS Report 38). It also shows largely insignificant treatment effects.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Odds Ratio</th>
<th>99% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidants</td>
<td>0.911</td>
<td>(0.574-1.446)</td>
<td>0.603</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.482</td>
<td>(0.253-0.948)</td>
<td>0.033</td>
</tr>
<tr>
<td>ARDS Formulation</td>
<td>0.722</td>
<td>(0.449-1.128)</td>
<td>0.075</td>
</tr>
</tbody>
</table>

This shows that this subset of the AERDS data is markedly different than the full AERDS sample used in AERDS Report 4. Combined with our failure to replicate the main results of AERDS Report 8 using counts from (non-DNA and DNA) datasets demonstrates a flaw in overall data integrity.

2.3 Treatment by geno-type analysis

Given that the data used in AERDS Report 38 shows no overall treatment analysis as an interaction of genetic factors with treatment must be understood as a purely exploratory analysis. We cannot conclude that genetic make-up does not modify the treatment effect, since we do not observe a significant treatment effect. In this case, one would only expect to observe significant treatment differences among genetic subgroups if genetic modification was very large.

Data reanalysis: We have generated genetic subgroups in a sensible way to obtain larger cell sizes more suitable for analysis. First we attempt to replicate the AERDS Report 38 results shown in Fig 1B using 2x2 table analysis or using an equivalently logistic regression since timed survival data is not available for genetic group *no risk alleles* within CH1 or ARMS2J genes) using data from Fig 1B for determining risk for progression to advanced AMD we obtain OR: 0.74, 1.22, 0.93 for antioxidant, zinc and AERDS formulation-treatment individual compared to placebo-treated patients, respectively. This compares respectively to (hazard ratios) HRs=0.69, 1.34, 0.39, reported in the AERDS report which used a Cox regression analysis. This shows that the low ORs are extremely low ORs are accurate approximations of HRs. There also appears to be satisfactory agreement for larger genotype groups with more events, like *202* (2 CH1 risk alleles and no ARMS2 risk alleles). We derive the OR (progression) within this genotype group to be 1.16, 2.41, 1.22 for antioxidant, zinc and AERDS formulation respectively compared to placebo-treated patients. This compares to the AERDS Report 38 published HR within this genotype group of 1.08, 1.56, 1.78 respectively. In this genotype group with larger event counts the OR and HR diverge slightly, though we do get the same order of effect among the treatment groups. We conclude that the Odds Ratios we derive adequately approximate HRs reported in AERDS Report 38 for groups with small and larger numbers of progression events.

We studied interaction between genetic and treatment groups on progression events using logistic regression and data from Fig 1B (35 degrees of freedom in total). The overall effect for interaction between genetic and treatment is significant with a p-value < 0.0002, even if the general p-value for treatment group is not significant (0.300). This should be compared with the interaction p-value=0.06 reported from the Cox regression model in AERDS Report 38. This provides strong support for genetic modification of treatment response. This analysis did not involve grouping of genetic risk groups.

Dichotomizing treatment arms into those containing Zinc, Zinc, and AREDs and those without (Placebo and antioxidant alone) we examined the interaction between Zinc treatment and genetics. Using either allelic dosage (number of risk alleles 0, 1, or 2), or dominant/recessive coding for ARMS and CH1, respectively, we detect significant modification of Zinc treatment effect by genetics. We report results from allelic dosage model, noting that results from dominant/recessive model were even stronger. Across all genetic subgroups, Zinc reduces the odds of progression across advanced AMD (p-values 0.34 and 0.19 in allelic dosage and dominant/recessive models, respectively). Both CH1 and ARMS2J were independently associated with AMD progression risk with OR of 1.33 (p=0.021) and 2.77 (p=0.00001) respectively. Highly significant interactions between CH1 and zinc or with ARMS2J and zinc treatment were observed in this model but with opposite effects. Zinc treatment reduces the odds of progression for CH1 carriers and produces an OR of 0.54 (p=0.007) meaning that zinc attenuates the risk associated with ARMS2J risk alleles. In contrast, the coincidence of a risk allele at CH1 with zinc has an OR of 1.56 (p=0.015), meaning that the risk associated with CH1 risk alleles is augmented by zinc treatment.

Similar models for antioxidant vs no antioxidant treatment dichotomy did not show significant interaction (or main treatment effects).

Given that CH1 and ARMS2J interact with zinc treatment individually and oppositely, one logical combination of genetic subgroups is worth highlighting. A subgroup analysis of genetic risk group *202* (2 high CH1 risk and no ARMS2 risk alleles) was used to determine the significance of zinc on progression. The results show that zinc decreases the odds of progression in this group producing an OR of 0.54 (p=0.007) meaning that zinc attenuates the risk associated with ARMS2J risk alleles. In contrast, the coincidence of a risk allele at CH1 with zinc has an OR of 1.56 (p=0.015), meaning that the risk associated with CH1 risk alleles is augmented by zinc treatment.

In general the summation of these analysis point to the deleterious effect of CH1 with zinc-containing treatments and enhanced beneficial effect of Zinc for people with at least one ARMS2J risk allele. All these results broadly support the conclusions of Awh et al. though the significance levels are lower.

4. Discussion

The AERDS Report 38 by Chew et al was written as a direct response to Awh et al. Carefully constructing genetic subgroups based on this approach would have reduced number of hypothesis and avoided very small counts. A fragmented interaction analysis, that was performed in AERDS Report 38 effectively subdivides the data into cells many of which contain event counts well below numbers suitable for analysis. The AERDS Report 38 contains a number of serious analytic and manuscript preparation errors reported by Awh et al. There is no description of the main effect of treatment on progression risk from THEIR DATA SET. The treatment effect reported in the AERDS 8 report was not replicated. Their use of results reproduced from the AERDS 8 Report in Fig 1A is quite misleading. It is also reproduced with error, since the confidence interval significance is 99%, not 95% as stated, which leads to interpretation of statistical significance of treatment (Fig 1A). The AERDS Report 38 data is based on different, much larger dataset than that used in AERDS Report 38. Secondly, the data was derived using a different modeling approach (repeated measures logistic vs Cox regression used by Chew et al). Even using AERDS Report 38 data on all Category 3 and 4 patients at baseline (regardless of DNA availability) which is the full AERDS sample, we fail to observe a significant treatment effect. Without demonstrating a significant treatment effect in the data set under study, very little can be concluded by failing to detect significant genetic effect modifiers via interaction study. Even leaving apart a dogma of statistical inference - that one never accepts the null hypothesis, one can only fail to reject it - without demonstrating significant treatment effect in the first place, one cannot conclude anything by failing to detect significant effect modifier signal (here, putative genetic factor interaction with treatment).

Notwithstanding this, a simple logistic regression using the counts obtained from Fig 1B suggests that such effect modification may in fact be present (with a threshold p-value for interaction (24 d.f) equal 0.0025). With lack of significance there is no evidence of interaction. This suggests a very strong interaction between treatment and genetic factors.

A worrisome aspect of Chew et al report is the number of inconsistencies in data presentation. The numbers of patients and events reported in their main results figure (Fig 1B) differ significantly from the supposed data reported in Supplementary Table 6b. This is especially so for the division of participant outcomes between Events and Non-Events. There are also discrepancies between SuppTables 6a and 6b tables. SuppTable 6a is represented as a collapsed (marginalized) version of SuppTable 6b, without the ARMS2 subgrouping. An example of discrepancy is found for the CH1-Zinc row in SuppTable 6a. There are 4 too many events (and 4 too few events) compared to that reported in SuppTable 6b. With these data issues and without access to the full data, any reanalysis is very tentative. However using the reported data we find that the genetic modifier effect on AERDS treatment is significant and largely similar to that reported by Awh et al.4
I have reviewed the AREDS38 report and the Kustra review of this report.

**AREDS 8**

The AREDS 8 report used generalized estimating equations as the primary method of analysis. With this analysis, each positive disease event is regarded as a random occurrence, which can come and go similar to an asthma attack. But, it is clear that AMD does not come and go, it comes and stays. The effect of this analysis is to count a positive outcome multiple times, which does not make sense for a disease such as AMD. The generalized estimating equations method attempts to control for the multiplicity by estimating the correlation between repeated outcomes for the same subject which will tend to make standard errors smaller and p-values smaller than they should be if they were just counted once. It is clear that the appropriate method of analysis for AMD is survival analysis preferably using the eye as the unit of analysis. It appears that the AREDS 38 report used survival analyses so I think the AREDS investigators have conceded this point. They haven't reanalyzed their primary data using this method, which I feel is urgently needed.

**AREDS 38**

The goal of this analysis was to study possible interaction effects between genes (specifically CFH and ARMS2) and treatment. In general, I feel that there are major inconsistencies in the presentation of data. For instance, Table 1B, which is found in the main text, and Supplementary Table 6B should yield the same data counts, but they are quite different. Conversely, the counts in Supplementary Tables 6A and 6B, which also should have the same data, are for the most part consistent with each other with 1 or 2 exceptions. The exceptions are that the CFH = 1, Zinc group should have 11 events, not 15. The ARMS2 = 0, Zinc group should have 19 events, not 25. Finally, in both Suppl. Tables 6A and 6B, the total number of events is 303, not 385 and the total number of people who did not have an event is 934 not 852.

There are many issues with Table 1B beyond just the placebo counts. Thus, I have used Supplementary Table 6B as the template for my analysis and made the edits to Supplementary Table 6A so that they agree with Suppl. Table 6B (the latter is more detailed). My slightly edited version of Suppl. Table 6A that I used for my analysis is reproduced below. In the published analysis, the number of genetic subgroups is very large relative to the number of endpoints. Many strata have less than 5 events. I agree with Dr. Kustra that a more sensible approach would be to combine groups together, especially since interaction tests generally don’t have that much power. So, I have attempted to do this separately for CFH and ARMS2 based on data abstracted from the paper.

In CFH, I combined the 0+1 risk allele groups because of the small sample size in the 0 risk allele group. The OR=0.448 in the 0+1 risk allele group and 1.033 in the 2 risk allele group which is statistically different (p=0.036). In ARMS2, I combined the 1+2 risk allele groups because of the small sample size in the 2 risk allele group. The OR=1.42 in the 0 risk allele group and 5.12 in the 1+2 risk allele group which is also statistically different (p=0.015).

In addition, I have looked at heterogeneity of Zinc+ vs. Zinc- treatment by CFH and ARMS2, respectively, using similar methods. There was significant heterogeneity for both CFH (p = 0.038) and ARMS2 (p = 0.013). Furthermore, I looked at heterogeneity of Antioxidant+ vs. Antioxidant- treatment by CFH and ARMS2, yielding p-values of 0.335 and 0.902, respectively, suggesting that the major determinant of heterogeneity of the effect of combination treatment is driven by zinc rather than antioxidants.

Thus, overall, my analyses of heterogeneity of the effect of Combination (i.e., Antioxidants plus Zinc) treatment by CFH and ARMS2 indicate significant heterogeneity by both CFH (p = 0.036) and ARMS2 (p = 0.015), consistent with amplification of disease progression risk in those with CFH risk alleles who receive zinc treatment compared to placebo-treated and amelioration of disease progression risk conferred by ARMS2 risk alleles in those who receive zinc compared to placebo. The effect of zinc on AMD progression risk interacts with CFH and ARMS2 genotypes in opposite ways.

**Summary**

So, in summary, I agree with the report by Dr. Rafal Kustra, although I have summarized the data in a different manner. There definitely is an interaction between the number of risk alleles for the CFH gene and for the ARMS2 gene and the efficacy of the combination treatment currently recommended (antioxidants and zinc), though the effect is opposite. Regarding the overall treatment effect, it is best to use the overall study sample rather than just the individual genotypes sample. Ideally this overall sample should be analyzed with survival analyses, but the primary data set is not available in this publication. I also think that separate analyses should be performed for geographic atrophy and neovascular AMD.

---

B. Rosner, 11/2/15

AREDS Treatment Analysis by CFH and ARMS2 genotypes - Reanalysis of AREDS 38 data

<table>
<thead>
<tr>
<th>CFH Risk Alleles</th>
<th>AREDS Treated</th>
<th>AREDS Non-Treated</th>
<th>Placebo Group</th>
<th>Placebo Non-Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Total</td>
<td>Progress</td>
<td>Non-Progress</td>
<td>Progress</td>
</tr>
<tr>
<td>0</td>
<td>59</td>
<td>8</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>1</td>
<td>235</td>
<td>24</td>
<td>58</td>
<td>37</td>
</tr>
<tr>
<td>0 plus 1</td>
<td>156</td>
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<td>135</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ARMS2 Risk Alleles</td>
<td>AREDS Treated</td>
<td>AREDS Non-Treated</td>
<td>Placebo Group</td>
<td>Placebo Non-Placebo</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
<td>Progress</td>
<td>Non-Progress</td>
<td>Progress</td>
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<td>2</td>
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<tr>
<td>1 plus 2</td>
<td>158</td>
<td>45</td>
<td>113</td>
<td>58</td>
</tr>
</tbody>
</table>

Sincerely,

Bernard Rosner, Ph.D.
Professor of Medicine (Biostatistics)
Research Abstract

My primary research interests are in the areas of (1) statistical modeling of longitudinal data with emphasis on cardiovascular and pulmonary outcome variables (2) analysis of clustered data problems with emphasis on ophthalmologic applications (3) measurement error problems with emphasis on cancer and nutritional epidemiology. More recently (in the past five years), I have written several papers on developing models for breast cancer incidence. These can be used generally to model the incidence of any cancer.

http://www.dfhcc.harvard.edu/insider/member-detail/member/bernard-a-rosner-phd/

Research

Dr. Rosner’s research activities are focused on several areas currently including (a) longitudinal data analysis, (b) analysis of clustered continuous, binary and ordinal data, and (c) methods for the adjustment of regression models for measurement error.

Dr. Rosner’s work on longitudinal data analysis has involved comparative analyses of several longitudinal data models on the same datasets involving serial measurements of blood pressure and pulmonary function over a 20-30 year period. These analyses are important since they enable one to predict future blood pressure levels based on current levels, which is important for screening purposes.

Dr. Rosner’s work on the analysis of clustered binary data has involved analyses of ophthalmologic and otolaryngologic data where clustered data are the rule rather than the exception. Clustered data also appear frequently in coronary regression studies where multiple diseased arteries are sampled from the same subject at different points in time.

His work on measurement error methods has been applied mainly in nutritional epidemiology where dietary exposures are measured with error and one wants to assess the relationship between cancer and cardiovascular disease outcomes and nutrient intake, while adjusting for measurement error.

http://www.hsph.harvard.edu/bernard-rosner/

Publications

AREDS is not the standard of care for early AMD patients
- NEI researchers have always discouraged this due to identified hazards

Here’s why:
“...patients who received the supplement had greater disease progression and provided valuable data regarding early intervention.”
-Daniel Seigel, ScD NEJM, 2008

For those participants who initially had early AMD (Category Two), the antioxidants and zinc used by the AREDS researchers did not slow the progression to intermediate AMD. Consequently, there is no apparent need for those diagnosed with early AMD to take the combination...

Early AMD patients should never take a zinc formula. Neuroscience studies indicate:

“Zinc-induced precipitation may contribute to the initial development of sub-retinal pigment epithelial deposits in the retina as well as reducing the progression to advanced age-related macular degeneration in higher risk patients.”

Vitamin E and the Risk of Prostate Cancer: Updated Results of The Selenium and Vitamin E Cancer Prevention Trial (SELECT)
n= 35,533
Conclusions - Dietary supplementation with Vitamin E significantly increases the risk of prostate cancer among healthy men. (HR, 1.17; 99% CI 1.004-1.36, p=.008)

Zinc Supplement Use and Risk of Prostate Cancer
n= 46,974 ...men who consumed more than 100 mg/day of supplemental zinc had a relative risk of advanced prostate cancer of 2.29 (95% confidence interval = 1.06 to 4.95; P < .003), and men who took supplemental zinc for 10 or more years had a relative risk of 2.37 (95% confidence interval = 1.42 to 3.95; P trend <.001).

Vitamins E and C in the Prevention of Cardiovascular Disease in Men: The Physicians’ Health Study II Randomized Trial
n= 14,641
Conclusions - vitamin E was associated with an increased risk of hemorrhagic stroke (HR, 1.74; 95% CI, 1.04–2.91; P=0.036)

The Women’s Angiographic Vitamin and Estrogen (WAVE) Trial
n= 423 In postmenopausal women with coronary disease... a potential for harm was suggested with each treatment. (HR, 1.5; 95% CI, 0.80–2.9)

Effects of long-term vitamin E supplementation on cardiovascular events and cancer (HOPE-TOO): a randomized controlled trial.
n= 9,541 In patients with vascular disease or diabetes mellitus, long-term vitamin E supplementation does not prevent cancer or major cardiovascular events and may increase the risk for heart failure. (RR, 1.13; 95% CI, 1.01–1.26; P = .03) & (RR, 1.21; 95% CI, 1.00–1.47; P = .045)