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William R. Ware, PhD - Editor

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For some time now we have been hearing that a significant percentage of fish is not what it is labeled, obviously substituting a cheaper species. It has been estimated that of the estimated 28% of the fish in the US mislabeled, more than half of the substitutes are actually high mercury species. Deception in fact appears rampant. In the Canadian financial press of September 24 it was reported that many large companies are allowed by regulators to adjust their accounting using methods that go beyond accepted accounting practices in order to present the best picture possible to investors regarding financial health and growth. This has developed over a decade and today is widespread. The same picture emerges in the US. One can react by thinking "what else is new?" Fiddling or massaging data and using "spin" have been around a long time and it is surprising that is has only recently infected the accounting practices on a large scale in North America.

Let's consider medical studies, both experimental and clinical. We have reached the point where one can never really tell if what is being presented is correct, biased, or even completely fake. Conflicts of interest are easy to conceal. Studies suggest a significant number of research results reported in the literature are outright wrong or cannot be reproduced. Many wrong studies have a long half-life since only limited Brownie points go to the researchers that report failure to duplicate reported results. When fraudulent studies are detected they may be retracted and researchers, if academic, may be fired. Cooking or making up data may be the result of individuals with an agenda that does not include either finding or defending truth, but rather catering to industrial and/or career interests. In areas such as pertain to unsafe consumer products, environmental threats or medication dangers, the pressure or temptation can run very high. Sometimes it does not seem even worthwhile to examine the literature in certain areas since one knows that *a priori* great bias is potentially present and that it is a meaningless undertaking.

Investigators who critically examine the validity of clinical trials, especially those with high impact on practice guidelines and industry profits, know only too well the difficulties they face in obtaining the actual primary patient data from companies without which the task may be impossible. This exercise can take years and the use of the freedom of information laws and when this fails, public shaming in national and international press sometimes works. Even

regulators in possession of secret data generally bow to the pressures of industry, claiming respect for confidentiality which apparently trumps public interest. Successes in acquiring suppressed or hidden data and recalculating trial results sometimes expose shocking deceptions. Furthermore, the pharmaceutical industry and many academic investigators know that those who read their reports frequently lack much knowledge of biostatistics and can be easily fooled by how results are presented. Critics would probably agree that the use of relative risk reductions rather than absolute risk reductions is Exhibit A in the game of deception. It is very encouraging to see absolute risk benefits or reductions now appearing more frequently in the medical literature without requiring the reader to do calculations or even discover that the authors have made it impossible to get the desired numbers.

Finally, a recent large review (24 pages in length) attempted to settle once and for all the proposition that the benefits of statins outweighed the risks. Reminds one of reports to congress or a parliament with hundreds or thousands of pages which no one reads. The lead author pressured the editor of a major journal containing two papers already in the literature that he regarded as a threat to the message of this review. He wanted them retracted. The editorial board took this pressure seriously enough to convene an independent review board to consider the proposed retractions. This sort of activity is unusual and the attempt failed. The papers are still out there for everyone who wants to read them.

Wishing you and your family continuing good health,

William R. Ware, PhD, Editor

Highlights

A BLOOD PRESSURE PARADOX

Consider an individual who has learned that coronary heart disease or cardiovascular disease risk can be estimated by using an online calculator. Fill in your lab numbers and some other data and get an absolute 10-year risk. This person tries the AHA/ACC calculator and gets a number, but also notices having answered the question regarding blood pressure medication use which in this case was yes. Out of curiosity the calculation is repeated with the answer no and it is found that the risk drops dramatically. This was viewed as somewhat odd. Being on blood pressure medication

increases the risk of events at the same blood pressure level. Really! Playing around with other calculators like the one from the Multiethnic Study of Atherosclerosis (MESA) produced similar but variable results but always increases in risk. These observations seem strange given that the idea in taking the medication was to reduce the risk of these events, but now perhaps after some years of adherence and maintenance of very well controlled hypertension, the net result does indeed appear to be that the medication increases the risk significantly compared to an individual with the same characteristics and the same BP, but untreated. The effect can even be about 40% or more. What is going on? Achieving normal or target BP may have occurred but did not eliminate the risk. This is in fact called the *Residual Cardiovascular Risk in Individuals on Blood Pressure Lowering Medication* and there is a significant recent literature.

The picture that emerges from a number of studies is that there is a period during which individuals develop hypertension but it is untreated. During this period what is termed subclinical disease develops silently and includes one or more of the following: heart damage involving thickening of the left ventricular walls of the heart, left ventricular pumping dysfunction, increased coronary and carotid atherosclerosis, peripheral artery disease as indicated by abnormal differences in arm and ankle blood pressure, and kidney dysfunction indicated by albumin in the urine (microalbinuria). These subclinical diseases progress in the presence of elevated BP and increase the risk of adverse cardiovascular events. At some point in time commencing BP lowering with medication may occur which can reduce the BP even to within the normal range. The problem is that this does not result in sufficient reversal of the subclinical disease and there remains a residual risk. Thus when comparing two more or less identical patients, one with normal untreated BP and one who has been under treatment for some time but with the same BP, there is found to be on average a considerably higher risk of CVD related events in the treated patient which appears counter intuitive until it is recognized that the individuals are not really identical because of the probable presence of subclinical disease. The increased risk turns up in almost all studies and is reflected in the results produced by the online calculators which have this effect included in their algorithms based on data from clinical or follow-up studies.

This view of the residual risk is based on the following study observations.[1-3] High levels of BP were associated with higher burden of subclinical disease and greater hazard for incident CVD in follow-up. At similar BP levels, treated hypertensives had a more substantial burden of subclinical CVD. The increase of CVC risk was also related to the duration of hypertension, hypertension treatment and the BP range. The higher the BP at initiation of treatment the higher the burden of some or all subclinical diseases and thus the lower probable success of the patient returning to a lower risk level when BP was brought down to normal or near normal. The MESA data[2] revealed that participants aged ≥ 50 years at baseline, those with well controlled hypertension (120-140/89-90) but on antihypertension drugs still had twice the risk of incident CVD in the next 9.5 years compared with participants with ideal BP levels without treatment.

In a recent publication describing meta-analyses of randomized trials compared the absolute risk reductions for CVD events associated with treatment and the absolute

residual risk, defined as the risk seen in the treated group.[3] In other words, one could have a 2% absolute risk reduction and still the treated could have 6% residual risk even after the medication produced a risk reduction, The study stratified by absolute event risk in the control group and found that the residual risk for most events (stroke, CHD, heart failure, CVD mortality or all-cause mortality) depended strongly on the risk in the control group and the prevalence of a residual risk was universally found in all the studies included in the analysis. These results made it clear that while the absolute risk reductions were greater when the initial risk was higher, there remained a much higher on-treatment risk. That is, blood pressure lowering can significantly reduce the risk of CVD-related events, but the treatment does not return the patient to the risk implied by the on-treatment BP. Instead, it is still elevated to an extent determined by the absolute untreated risk. The way to potentially avoid this problem is to recognize prehypertension very early in its appearance and take either pharmaceutical or natural steps to return the BP to normal. In other words minimize the duration of elevated BP.

BP prior to initial diagnosis, called antecedent BP and its role in CVD risk has also been studied in two large adult cohorts and the results showed that the use of a long-term average BP improved the prognostic utility of CVD risk predictions and that antecedent BP showed a significantly stronger risk on CVD than current BP.[4, 5] Needless to say, this type of data is not usually collected or even available. A recent study based in part on the CARDIA Study results also clearly indicates that these problems frequently start in young adulthood (≥ 18) and subclinical disease is strongly dependent on the *cumulative* exposure to elevated BP.[2, 6]

The seriousness of this problem is shown in a recent paper titled *Patients with Undiagnosed Hypertension Hiding in Plain sight.*[7] An examination of electronic medical records revealed that approximately 13 million people in the US were neither aware that they met the clinical criteria for hypertension nor were they taking anti-hypertensive medications.

The above observations have considerable significance in the context of the debate concerning safe or optimum untreated BP levels and the thresholds for intervention with medication or other means of lowering BP. Furthermore, the subclinical disease induced by elevated BP can occur at young ages and suggests the importance of frequent blood pressure measurements even early in adulthood. In fact, as obesity or diabetes increases in the under 18 population, one can argue for screening in this group, incidentally with appropriate size cuffs which may not always be available. It is not clear that much attention is paid to BP or even frequently measured until individuals reach 40-50 years of age. This appears to be a serious mistake.

How prevalent is hypertension in young adults? Data from the National Health and Nutrition Examination Survey (NHANES) (2007-2010) found in the age group 20-34, 9.1% for males, 6.7% for females. In the age range 35-44 the numbers were 24.4% and 17.6%.[8] Obviously there are grounds for concern since it is quite likely that many of these cases go unnoticed. Subclinical disease is developing and is silent. The longer this goes on, the greater the residual risk after normalization of BP.

The above discussion exposes some serious issues. The NHANES results for young adults does not indicate the most important factor, how long had the hypertension been present which determines the extent of subclinical disease. Data involving patients on antihypertensive medication when used to calculate CVD risk does not take this into account either. Furthermore, accurate and meaningful blood pressure determinations are not as simple as it might seem since some patients may not have rested long enough, the measurement may be hurried with way too rapid rate of fall of the cuff pressure, and there may be a white coat effect or some other reason why the office or clinic measurement is not valid.

If one is concerned with preventive medicine and public health issues, then in the ideal world everyone would have a valid blood pressure determination every two years and prehypertension would be considered a matter of as much concern as true hypertension. This would prevent young adults from going for years with undiagnosed prehypertension or hypertension and the strong possibility of associated progressing silent subclinical cardiovascular disease. Treating newly discovered hypertension without knowledge of prior BP history leads to the risk that the patient finds false security in the hypertension medicine and the achieved BP levels without realizing that there exists a substantial CVD event risk even when the BP is optimally controlled. It would also appear that there has been very little research concerning reversing the components of subclinical disease, numbering at least 5, and if this would reduce the event risk.

Pharmaceutical reversing of atherosclerosis is a fantasy with researchers rejoicing over very small changes in either coronary or carotid burden when large decreases are needed in order to be significant. Contrary to what we are told by the industry, statins are trivially effective in reducing atherosclerosis and thus the decrease in risk is negligible if viewed realistically. Treating left ventricular hypertrophy mostly involves blood pressure reduction, but this heart disorder is partly responsible for the residual risk that remains when BP is normalized. It is not clear if conventional treatments of microalbuminuria would impact the CVD risk or mostly address biomarker levels. It does not appear that focusing on subclinical disease responsible for the enhanced CVD risk is standard practice aside from statins, anti-hypertensives, and aspirin, all of which appear only very modestly effective if at all. This underscores the importance of identifying undiagnosed prehypertension early and dealing with it, hopefully to prevent progression of to both hypertension and significant subclinical disease. In fact, there would be opposition to dealing with prehypertension by those who regard a systolic blood pressure of greater than 120 as still below the threshold of concern in spite of considerable literature in the context of residual CVD risk to the contrary (see Fig 2[1])

How does one control BP without drugs? Online the Mayo Clinic offers this current advice with documentation.

- Weight loss and attention to waist measurement (men < 40”, women < 35”).
- Regular physical activity—at least 30 minutes daily.

- Diet rich in whole grains, fruits, vegetables and low-fat dairy and skimp on saturated fat (the so-called DASH diet designed for this purpose).
- Boost potassium intake which can be done through consumption of fruits and vegetables or with supplements or both.
- Limit sodium intake to 2300 mg/day (the merits of this limit are debatable).
- Consume small amounts of alcohol (1 drink a day for women, 2 for men)
- Don't smoke.
- Consider chronic psychological stress as a contributing factor and attempt to reduce it. This is the tough one since many sources or triggers domestic or workplace related, are difficult to change. But this type of stress is well documented to increase the risk of both atherosclerosis and CVD.

However, there does not appear to be any evidence that these actions, while generally regarded as beneficial to health, will reverse the subclinical disease we are discussing. Purchasing a good automatic home monitor appears to be an excellent idea.

THE BOTTOM LINE

Periodic screening, for pre-hypertension or hypertension, perhaps every 2 years, would seem to be indicated for anyone because after a young age many no longer has a yearly physical exam. These results also highlight the problem of early adulthood where there appears to be inadequate concern for the silent development of chronic diseases which are incorrectly viewed as problems only of much older individuals. Ignored are the growing prevalence of obesity, diabetes and inactivity among young adults, and the consumption of both junk and toxic foods and beverages including tap and some bottled water.

FLU VACCINE EFFECTIVENESS

It is that time of year when the flu vaccination campaign will soon be on full strength with sidewalk boards in front of drug stores and pressure from the media as well as its direct to consumer advertising, and during visits to doctors' offices. In some jurisdictions, flu vaccination will be mandatory, particularly among health care workers.

As readers of IHN know, relative risk reductions can be deceiving. Get your shot and you will reduce your risk by about 60%, a number promoted by the US Centers for Disease Control in their internet contributions to the campaign.

In early 2014 the Cochrane Acute Respiratory Infections Group published a lengthy report where they examined efficacy in both preventing influenza -like illness (ILI) and laboratory verified confirmed actual influenza.[9] The vaccine is effective only against viral influenza. They looked at only randomized trials involving either placebo control or no immunization. Hundreds of thousands of individuals were included. They expressed the summary results as the number needed to vaccinate (NNV) to prevent one case. The age range was 16 to 65.

For the standard inactivated vaccine, the authors give an NNV of 40 for ILI and 71 for confirmed influenza (97.5% and 98.5% failed to benefit). For laboratory confirmed viral influenza, 2.4% of the unvaccinated and 1.1% of the vaccinated contracted influenza. The reason this 1.3% absolute reduction does not give 71 but 77 is due to rounding. Live attenuated aerosol vaccines used mostly for children had a NNV of 46 (97.8% no benefit) for viral influenza. Contrary to what we are told, vaccination was found to show no appreciable effect on working days lost or hospitalization. For pregnant women, only observational studies were available giving for ILI a NNV of 92 (98.9% no benefit).

These results can be compared with two meta-analyses published in 2012 and 2013 which also looked at placebo-controlled randomized trials and were limited to the laboratory confirmed influenza. These results were discussed in the November 2014 IHN. Osterholm *et al*[10] examined the efficacy of influenza vaccination that met these conditions. He also looked at on study restricted to children. It was required that vaccine efficacy be reported for all circulating influenza strains. Meta-analyses of qualifying trials were conducted separately for adults and children or just adults.

Tricco *et al*[11] compared the efficacy of influenza vaccines depending on whether or not they were matched to at least one of the strains circulating that year. Both matched and unmatched randomized controlled trials involving either the standard trivalent inactivated vaccine (TIV) or nasal spray containing live attenuated influenza vaccine (LAIV). All the meta-analyses examined by Trico *et al* had a mixture of studies involving children and adults in varying proportions, but more than half of the studies using LAIV involved mostly or entirely children. The results of these two studies are given in the table below. Both papers provided enough information to calculate absolute results, actually by two methods which gave very close to identical results. The published papers ignored absolute results. For the convenience of readers, the summary table is reproduced below. NNT is equivalent to NNV. RRR is the relative risk reduction.

VACCINE EFFICACY META-ANALYSES						
Study	No. Studies	Age	NNT	RRR	No Benefit	Vaccine
Osterholm[10]	8	18-64	64	60%	98.4%	TIV
Osterholm[10]	7	0.5-7	8	84%	87.3%	LAIV
Tricco[11]	12	A&C	93	62%	98.9%	TIV-Matched
Tricco[11]	11	A&C	204	51%	99.5%	TIV-Mismatched
Tricco[11]	15	A&C	18	77%	94.4%	LAIV-Matched
Tricco[11]	15	A&C	48	60%	97.9%	LAIV-Mismatched

TIV—Trivalent influenza vaccine LAIV—Live attenuated influenza vaccine
A&C – Adults and children

The lower NNT in the table for LAIV vaccines reflects the preponderance of children treated since this type of vaccine is much more effective for children. This is clear from the Osterholm study on children 0.5 to 5 years of age. Note that for the results which can be compared with the Cochrane results the NNT are comparable to the equivalent

NNV. Readers unclear regarding these calculations can see the details in the Appendix, November 2014 IHN. The Cochrane analysis did not include children. Side effects of the flu vaccination are a taboo subject. Vaccines are safe we are told.

THE BOTTOM LINE

The most significant numbers are the percentages that do not benefit from the flu shot. If the concern for health care workers is that they will come down with the real influenza and present a risk to patients, then the absolute risk reduction of slightly over 1% seems rather trivial. Since the question of adverse effects is controversial and political, it is not possible to do a risk/benefit analysis, but it seems clear that telling patient that they should get their flu shot because it will reduce their risk of getting the flu by 60% leaves quite a bit unsaid.

OVERESTIMATION OF CARDIOVASCULAR EVENT RATES

The paper by Rana *et al*[12] that has been discussed in the last two issues of IHN merits some final comments. The investigators divided the cohort of over 300,000 non diabetics into four groups with 10-year AHA/ACC risk of hard cardiovascular events including low and high at < 5% to ≥ 10%. It is of interest to look at the difference between the baseline characteristics of these two groups to see what was important in being either low or high risk. The relevant numbers are presented in the table below. All enter into the numerical risk calculation.

	AHA/ACC 10-YEAR EVENT RATE	
CHARACTERISTIC	**LOW < 5%**	**HIGH ≥ 10%**
MEAN AHA/ACC RISK	2.1%	17.4%
NORMAL WEIGHT	40%	27%
AVERAGE AGE, YEARS	49	65
MALE	20%	65%
CURRENT SMOKER	6%	15%
SYSTOLIC BLOOD PRESSURE	120	133
HYPERTENSION MEDICATION	19%	61%
TOTAL CHOLESTEROL, mg/dL	195	201
HDL CHOLESTEROL, mg/dL	58	52
LDL CHOLESTEROL, mg/dL	115	122

This table reveals that the major factors were age, gender, being overweight, smoking, slightly elevated blood pressure and taking blood pressure medications. The differences in cholesterol were small and for HDL, in the direction of decreased risk for the high 10-year risk. The lack of dependence on average cholesterol levels for being in the high or low risk category further reinforces the view that cholesterol is not very important. The increase in risk when taking BP meds comes up on most risk algorithms, always increases it, as was discussed above.

In the supplementary material, the authors present for the non-diabetic cohort the observed 5-year cardiovascular event rates for the subgroup taking statins stratified by the AHA/ACC 10-year risk group. The event rates for the non-statin cohort are given in the main text of the paper and thus one can calculate the absolute risk reduction (ARR) due to statin treatment. While this was not one of the endpoints of the study, the data is there to make an *estimate* of the effectiveness of statins in the Kaiser Permanente Health Group. ARR is the absolute risk reduction, i.e. the difference in the percent events between the treated and untreated groups. The event rates are for 5 years as given in the paper which is similar to the follow-up time in many statin studies. NNT (one over the treated event rate minus the untreated event rate expressed in probabilities, not percentage, i.e. divide percentages by 100) is the number needed to treat with statins to prevent one event over 5 years. RRR (treated rate minus untreated rate divided by untreated rate) is the relative risk reduction. The deceptive nature of the large percentages is evident. One in 400 can benefit and yet believe their risk has gone down 28%. This is from the same data, only different spin.

RISK GROUP AHA/ACC	NO STATINS EVENTS %	STATINS EVENTS %	ARR %	% NO BENEFIT	NNT	RRR %	FEMALE %
< 5%	0.2	0.2	0	100	∞	-	77
5% - ≤ 7%	0.65	0.55	0.1	99.90	1000	15	51
7% - ≤ 10%	0.9	0.65	0.25	99.75	400	28	45
≥ 10%	1.85	1.35	0.50	99.50	200	27	35

The major weakness of this approach is that individuals were not randomly assigned to statins or the control group but the analysis still can give some indication. Instead it is like a follow-up trial with the treated group compared with a control group. It appears that the strongest factor influencing the increase in events for the untreated risk group, i.e. the group with no statins, and the associated increase in ARR is the large change in the gender distribution as we go from the low to the high-risk group. The average age changes by about 15 years which is an important factor, but not for women, and statin lowering trials generally yield no benefit for women of any age. Therefore the decrease in the percentage of women is expected to have a large effect and would explain part of the trend in the table. The group most characteristic of many statin trials is the high-risk group and the ARR are smaller than seen in industry-supported trials which on average produce an ARR of about 1.0% to 1.5% for primary prevention including high-risk individuals. The Kaiser population is probably at lower risk than the AHA/ACC numbers indicate and ARRs of 0.6% to 0.7% have been reported for low risk cohorts in a critical reanalysis of a major meta-analysis effort (The Cholesterol Trialists Collaboration).[13] The approximately 2% events over 5 years in the untreated ≥ 10% risk group indicates the Kaiser high-risk cohort on average had individuals with lower event rates than commonly found in some industry trials that included very high risk subjects and had much higher untreated event rates.

MONITORING RATHER THAN SURGERY OR RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER

This has been an area of active discussion and study for a number of years. The term watchful waiting is also used as well as monitoring or active monitoring to describe this alternative. The appeal of this approach naturally depends on the stage and estimated seriousness of the cancer and the earlier the stage and the more insignificant the cancer appears, the more attractive this option becomes. There is also the issue of comorbidities and life expectancy and the desire among some patients to avoid the adverse effects of treatment if they have a life expectancy of the order of or shorter than that associated with withholding treatment. Watchful waiting is also promoted as a means to avoid over-treatment in early prostate cancer, a problem that has arisen with PSA screening and the frequent discovery of very early stage cancer.

Early stage or localized cancer is most frequently found by a needle biopsy prompted by prostate specific antigen (PSA) being higher than the guideline threshold for concern at the time although it can be discovered from pathological examination of tissue removed in the treatment of benign prostatic hyperplasia or bladder cancer. At the time the study described below was initiated, early stage prostate cancer could not be identified with imaging nor could it be felt with the digital rectal exam in the stage involved. It is termed T1 stage with T1c referring to identification by a biopsy generally indicated as desirable by an elevated PSA.

A 10-year prostate treatment options study has just been published in the New England Journal of Medicine which addresses the issue of active monitoring.[14] Patients with early-stage prostate cancer were randomized to surgery (radical prostatectomy), some type of radiation therapy accompanied by pre- and concurrent androgen (hormone) deprivation therapy, or active monitoring, a variation of watchful waiting. In the latter group, the option of electing treatment during the study was allowed and was common, a decision based on various considerations including progression and patient attitude. The median age was 62, 76% had stage T1c, the median PSA was 4.6 ng/mL, and 77% had pathology based on the biopsy tissue samples described by a so-called Gleason score of 6, the lowest on a scale of 6-10.

It was found that independent of the group into which the men were randomized, the survival after 10 years was 99%, although surgery and radiation therapy were associated with a lower incidence of metastases and disease progression. In addition, about half the men in the monitoring group elected either surgery or radiation therapy by the end of the follow-up. About 84% of those in the active monitoring group were free from disease progression at the end of 10 years whereas in the treated groups, the recurrence-free survival was about 90%. In other words, there was some treatment failure and this prompted additional treatment.

The authors estimated that 27 men would need to be treated with surgery and 33 with radiotherapy rather than active monitoring to prevent one patient from having metastatic

disease. To avoid clinical progression, 9 men would have needed to be treated with surgery or radiation to prevent one case.

In a second paper published by the same group at the same time in this journal, the adverse effects of treatment were followed in 1643 men from the above study.[15] These patient-reported outcomes were obtained at 6 and 12 months and annually thereafter for 6 years. The following negative side effects were found:

- Of the three treatment options, prostatectomy had the greatest negative effect on sexual function and urinary continence, and while there was some recovery, these negative effects remained worse in the prostatectomy group throughout the trial.
- For radiation therapy, the negative effect on sexual function was greatest at 6 months, but function then recovered somewhat and became stable. Radiation therapy had little treatment impact on urinary continence.
- For the active monitoring group sexual and urinary function declined slowly, but it is not clear how much this was due to individuals in that group abandoning monitoring and having treatment.
- Bowel function was worse in radiation group than in the other two at 6 months,
- No significant differences were found among the three gropes in anxiety, depression, or general health-related or cancer-related aspects of quality of life.

The authors estimate that treating 4 men with surgery or 8 men with radiotherapy rather than active monitoring would cause one additional case of erectile dysfunction at 2 years. With regard to urinary incontinence the numbers for surgery and radiotherapy were 5 and 143 men for one additional case.

THE BOTTOM LINE

Informed patient decisions regarding treatment options in early prostate cancer are not simple and many men cannot adhere to the initial decision to watch and wait, as active monitoring can also be called. This is not surprising if they see their clinical picture deteriorating. Nevertheless, there is negligible impact on life expectancy during 10 years following the decision, no matter what it was.

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