DRAFT
HYPERTENSION: THE EVIDENCE

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High blood pressure (HBP), or hypertension, is a common medical condition among adults. It is estimated that about one in three young adults are hypertensive, while this percentage increases to about 60% for those over 60 and affects more than three out of four people older than 70[1]. A new study in Lancet[2] asserts that in 2010 HBP was the leading risk factors (even worse than smoking) for global disease burden. Furthermore, the US government's Centers for Disease Control and Prevention (CDC)[3] list the yearly age-adjusted deaths attributed to hypertension and hypertensive heart disease at 17.3 per 100,000 (about the same as diabetes mellitus). In medical journals there are great numbers of published studies about hypertension with a widespread agreement among them that *"the treatment of hypertension has been one of medicine's major successes of the past half-century. The remarkable advances in therapy have provided the newfound capability for lowering blood pressure in almost every person with hypertension*[4]. The medical studies agree that there is room for saving additional lives as a significant proportion of hypertensives are not aware of their condition. This is because often there are no symptoms caused by high blood pressure to warn of its existence. Indeed hypertension is often referred to as the *"silent killer"* in the medical literature[5].

The reason for writing this paper is to review the research evidence concerning hypertension and determine if indeed the treatment of hypertension is one of medicine's major successes and not part of the well-known and convincingly demonstrated problems[6-8] of medical research. Although the majority of hypertension studies claim great advantages by lowering HBP this review finds severe conflicts in the findings among the various hypertension studies as well as serious epistemological, methodological and statistical problems that cast doubts to such claim.

1. The conflicting findings in studies between hypertensives and normotensives

There are a great number of medical studies comparing the life expectancy and CV and related disease between normotensives and hypertensives. This section reviews some of these studies and highlights their conflicting conclusions instead of their agreement as done in the meta-analyses studies that generally conclude[9]: *"throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg*."

More than five year loss in life expectancy: A major, often-cited study[10] published by Franco and co-authors, based on the famous Framingham data, concluded *"Compared with hypertensives, total life expectancy was 5.1 and 4.9 years longer for normotensive men and women respectively."*

Another study[11] based on examining 18,863 men employed in the Civil Service in London, England, known as the Whitehall Study concluded that he difference in life expectancy between men with the lowest systolic blood pressure and those with the highest was 5.2 years (see Table 3, p. 6 of this study), in other words a result very similar to that reported by Franco et al. using the Framingham data.

Five years loss of life expectancy due to hypertension seems extremely large if the total gain for *all* preventive and curative measures is five years according to the seminal paper by Bunker, Frazier and Mostellar[12] and between less than one month to slightly more than one year to people at average risk according to Wright and Weinstein[12.5]. Moreover, the five year loss is an average for all hypertensives. What would then be the loss for a 75 years old, heavy smoker, with cholesterol, doing no exercise and obese whose SBP is 190? In addition, if the loss in life expectancy in USA, with 23.5% hypertensives, is five years what will be in Japan where the average prevalence is 50.1%[13]? (Interestingly the life expectancy in Japan, the highest in the world, is 4.8 years more than that of the USA).

Minor losses in life expectancy: One of the latest studies by Ford[14], based on the US National Health and Nutrition Examination Survey (NHANES) I and NHANES III data and that included close to 23,000 participants, arrived at the conclusion that, among all hypertensive participants, the age-adjusted mortality rate was 18.8 per 1,000 person-years for NHANES I and 14.3 for NHANES III, while the corresponding rates for non-hypertensive people were 13.3 and 9.1 per 1,000 person-years respectively.

Thus, there were 5.5 more deaths (18.8 - 13.3) per 1,000 person-years for NHANES I and 5.2 (14.3 - 9.1) per 1,000 person-years for NHANES III, or 0.55% and 0.52% (two extremely consistent rates) more deaths respectively between hypertensive and non-hypertensive participants. These percentages indicate that for every 182 deaths of non-hypertensive people there will be 183 deaths in hypertensives in NHANES I and 192 and 191 respectively in NHANES III. These results, as well as those referring to cardiovascular diseases (CVD), are considerably lower than in the Franco et al. and Whitehall studies. In addition, Ford, concludes when discussing the clinical perspective of his study:

> *"The current study's results show that the age-adjusted mortality rate from all causes decreased by 4.6 per 1000 person-years in 2 national cohorts of hypertensive adults who were recruited from 1971 to 1975 and from 1988 to 1994. However, this decrease was comparable to the decrease of 4.2 per 1000 person-years among nonhypertensive adults".*

In other words, there was a *decrease* in mortality rates between 1971 to 1975 and 1988 to 1994 among hypertensives that was *bigger* than among normotensives. Although the difference in the rates of decrease was small only 0.4 per 1000 person-year it is statistically significant because of the large number of participants included in the studies.

Port and his co-authors[15], disagrees about the effects of HBP on direct or cardiovascular deaths. Their conclusion was:

> *"Contrary to widely cited interpretations, reanalysis of the Framingham 18-year data showed that the relation between systolic blood pressure and all-cause and cardiovascular mortality is not strictly increasing. The linear logistic model used to generate that relation was rejected by the Framingham data. Instead, risk is unrelated to systolic pressure to at least the 70th percentile for each age and sex, and sharply increases with blood pressure higher than the 80th percentile".*

Exhibit 1 below, taken from Port and co-authors, shows that overall deaths related to HBP hardly increase until a systolic blood pressure of around 175 is reached. But even if blood pressure increases to about 185 the number of deaths rises from around 15 to 28, an increase of 13 per thousand or 1.3%. Only when blood pressure exceeds the 185 mark does the number of deaths start to increase steeply. In this case, the difference between normal blood pressure and that over 190 is 27 (42 - 15) extra deaths per thousand, or 2.7%.

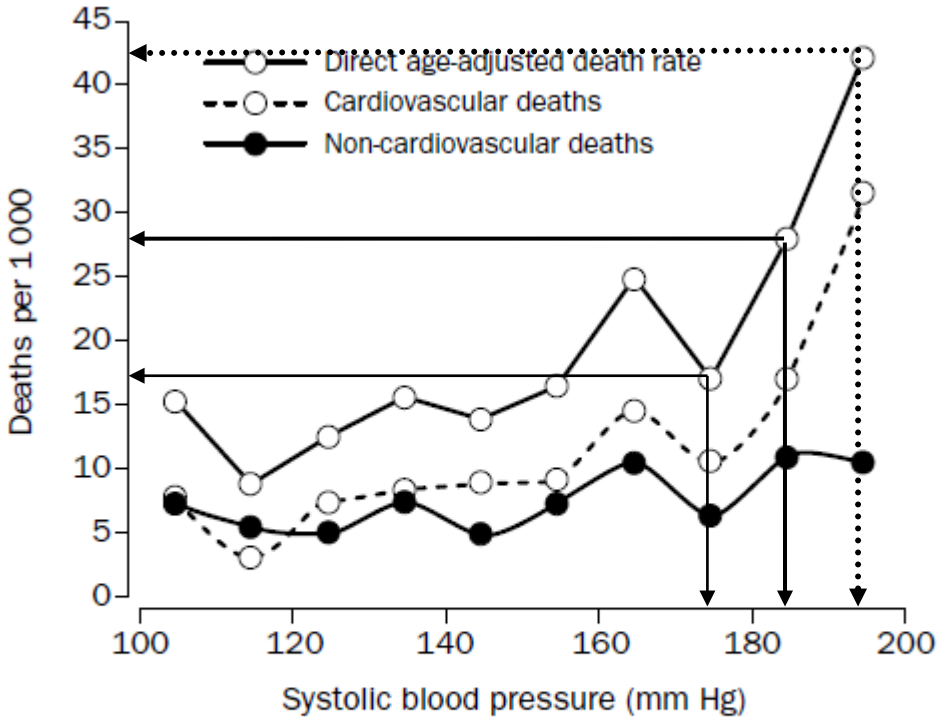

Exhibit 1: Actual age-adjusted rates for men aged 45-74 years related to systolic blood pressure (based on age-specific rates in Framingham study). The direct age-adjusted rate is the sum of the lower two curves (Exhibit 1 is taken from[15], while the horizontal and vertical straight lines have been added by the author).

Other studies, although most agreeing that HBP increases the chances of cardiovascular and related diseases and reduces life expectancy arrived at estimates that are in between those already mentioned. As the purpose of this paper is not to survey the thousands of studies on hypertension but rather to highlight their conflicting findings it will proceed considering epistemological, methodological and statistical problems with hypertension studies that may explain the reasons for their conflicting findings.

2. Major epistemological concern: Hypertension studies do not prove causality

The great majority of hypertension studies compare the differences in death rates and CV and related disease between hypertensives and normotensives by demonstrating statistically significant differences or by proving important correlations between the two groups. But such differences and correlations *cannot* prove causality. BP may be caused by stress, in which case heart attacks could be the result of such stress rather than HBP. Many studies have shown significant differences in HBP among people in various regions (in rural India for instance the age-adjusted hypertension rate is 5.5% while in urban areas is 30.7%[16]), countries[2], races and of course ages. This means that many factors can be responsible for blood pressure levels. Proving causality (i.e. that HBP *causes* extra deaths) is, therefore, practically impossible as a number of confounding factors can be responsible for these deaths. In addition to stress, cultural traits, life style factors, marital status, personality characteristics, dietary habits, generic factors or some other reason may raise blood pressure. Alternatively, it may be that with age some organ or body part mal-functions and that increased blood pressure is required to minimize the negative consequences of such mal-function the same way that fever helps fight disease. Finally, concluding that

high blood pressure increases death rates is not of much practical value. What hypertensives need to know is if they will benefit if they treat their HBP and if such benefits would outweigh the cost (monetary and negative side effects) involved.

3. Comparing treated and non treated hypertensives

The correct epistemological question is: How much life expectancy increases and CV and related disease decrease if hypertension is treated? The number of studies attempting to answer this question are considerably fewer than those comparing normotensives and hypertensives, most of them refer to older people[17-20] and they compare the effectiveness of various types of drugs to treat hypertension[20-23]. Overall, the findings of these studies are even more conflicting than the studies comparing normotensives to hypertensives. Their conclusions range from considerable increases in mortality rates and CV and related disease to significant benefits if hypertension is not treated.

A meta-analysis[24] on the effects of treatment concluded that *"treatment with any commonly-used regimen reduces the risk of total major cardiovascular events, and larger reductions in blood pressure produce larger reductions in risk."* A study by Gu[25] and co-authors, based on 5,086 hypertensive participants with a higher than 140/90 blood pressure, concluded that *"uncontrolled and untreated hypertension was associated with increased risk of total and cardiovascular mortality among the general hypertensive population"*. Another study by Barengo et al.[26] found that in men, all-cause and CVD mortality was significantly higher in the hypertensive subgroups compared with the normotensive group but in treated and controlled hypertensive women at baseline did not have any increase in CVD or all-cause mortality. One more study by Dahlöf and co-authors[27], on people between 70 and 84 years old, found highly significant and clinically relevant reductions in cardiovascular morbidity and mortality among patients who treated their HBP.

A study by Gudmundsson and colleagues[28] based on 19,390 participants (9,328 men and 10,062 women) aged 33 to 37 years at the time of attendance from 1967 to 1996 concluded that there was no significant benefits by treating hypertension with drugs. Another study[20] investigating the association between cardiovascular outcomes and antihypertensive drug treatment for around 30,000 older women found that those receiving no medications compared to those receiving diuretics as monotherapy had a smaller but not statistically significant chance, for coronary disease, stroke, and CVD death. However, the crude cardiovascular death rate of hypertensives taking *no* medication was the lowest (0.011%) compared to those receiving one or two drugs therapy with the highest death rate (0.035%) occurring among those taking diuretic and calcium channel blocker. These results occurred even though the baseline systolic BP of the no medications group was higher (149mm Hg) than for those receiving drug treatment.

A newer study by Almgren et al.[29] that compared treated hypertensives and normotensives concluded:

> *"In spite of a substantial reduction of their blood pressure, treated hypertensive middle-aged men had a highly increased risk of stroke, MI and mortality from coronary heart disease compared with nonhypertensive men of similar age. The increased risk of cardiovascular complications escalated during the latter course of the study."*

A meta-analysis by the Cochrane foundation identified (going all the way back to 1953) eleven published randomized control trials comparing the effects of treatment[30] of mildly hypertensives (those with BP between 140 to 160 and 90 to 100). From these eleven studies four passed the criteria and were included in the meta-analysis. Consequently, after the treatment of 7,080 participants for four to five years with antihypertensive drugs as compared to placebo, it was concluded that treatment did not

reduce coronary heart disease, stroke, or total cardiovascular events. In addition, it found that withdrawals due to adverse effects by drug therapy reached 9%. Finally, a study investigating the long-term effects of a randomized, placebo-controlled, clinical trial (SHEP)[17.5] of patients aged 60 years or older with isolated systolic hypertension of more than 160 mm Hg found moderate gains of 105 days for all-cause mortality and 158 days for cardiovascular death. In addition, the active treatment group had higher survival free from cardiovascular death vs the placebo group but similar survival for all-cause mortality.

4. Treated, uncontrolled hypertensives: Methodological issues

There is a big paradox[4] associated with the treatment of hypertension. Although, the number of people treated for hypertension increases over time so does its prevalence and, worse, the number of treated hypertensives with "uncontrolled blood pressure" (defined as treated hypertensives whose BP is greater than the 140/90 therapeutic goal). For instance, in the Gu and co-authors[25] study mentioned above 62% of treated hypertensives did not achieve the therapeutic goal of lowering their blood pressure below 140/90. The percentages of treated, "uncontrolled" hypertensives reported in the paper by Chobanian[4] ranged from 10% to 35% while that cited by Jeffrey and co-authors[31] was between 26% and 35%. However, a study by Lindholm[32] concludes that "Population surveys indicate that the proportion of patients achieving even conservative blood pressure targets may be only 20% or lower". Other studies[33-35] talks about *treatment-resistant* hypertension (when BP cannot be lowered to below the 140/90 level even after the patients have taken more than three hypertensive lowering drugs) that could affect 20% to 30%[34] of hypertensives, masked[35.5] and even malignant[33] hypertension. The high percentages of uncontrolled hypertension are disturbing and are probably the major cause of drop-out rates from treatment that approach 10% as the combination of drugs to lower BP increases negative side effects and discourages people to continue their treatment as their BP level cannot be lower to the therapeutic goals.

There are three major methodological issues when categorizing people with HBP: First, can uncontrolled hypertensives receiving treatment be classified in the category of "hypertensives"? Definitional speaking they are hypertensives since their BP is greater than the 140/90 limit. Methodologically, however, there is a major flaw for doing so as the reason for the inability to lower hypertension with medical drugs may be caused by pathologies that increase the chances of death or CV related diseases[33]. Second, can treated, uncontrolled hypertensives be classified in the category of normotensives, even though they are technically hypertensives? Methodologically this cannot also be correct. Until now some studies like that of Franco et al.[10] included as hypertensives all those with a BP greater than 140/90 with no regards to whether they were treated or not. Other studies as that by Ford[14] included as "non-hypertensives" all treated persons whether or not their BP was lower than the 140/90 mark. This definitional difference of who is included as hypertensive/non-hypertensive may explain part or all of the huge difference in the conclusions of these two studies as the number of treated, uncontrolled hypertensives was particularly high at the time the Framingham data was collected. The last methodological issue relates to those that drop out of treatment after receiving BP lowering medication for a period of time. These people must be excluded from hypertension studies for two reasons. First, they may suffer from treatment-resistant hypertension that could not be cured by medication encouraging quitting their treatment, and secondly their body may have lost all, or part of its ability to control BP on its own after getting used to BP lowering medication.

It is simpler to design and implement studies classifying people as "normotensives" and "hypertensives" but as mentioned above this is not methodologically correct. The classification must have at least *four* categories ("normotensives", "hypertensives non-treated", "hypertensives treated and controlled" and

"hypertensives treated but uncontrolled") to establish the benefits of treatment as well as the consequences of treated/uncontrolled hypertension. Until such studies are designed and successfully implemented the findings of available ones that only distinguish between "normotensives" and "hypertensives" must be utilized with extreme care, given their conflicting findings.

A paper[36] surveyed hypertension treatment and control in five European countries (Germany, Sweden, England, Spain, and Italy) and two North America ones (USA and Canada) and another paper[37] reported about treatment and control in Japan. Hypertension treatment in the European countries and Japan is about half that of the USA while the controlled of hypertension is between 5% and 10% in these countries versus around 30% in the USA, yet all of these countries have a higher life expectancy than the USA. Such numbers do not make sense, at least at the macro level, if indeed the treatment and control of hypertension reduces mortality rates.

4. Statistical concerns

In addition to epistemological and methodological issues there are also statistical concerns with medical studies in general and hypertension in specific. As in all statistical studies there are measurement errors that influence the results. Such errors can be due to differences in measuring BP by direct or indirect instruments[38,39], or between successive times[39.5]. Furthermore, there are problem with "white coat"[40] and "masked hypertension"[41], as well as the maximum BP[42] that seems to be even more important than the average. These errors can and do seriously affect the findings of hypertension studies in particular when BP is measured only once using non-standardized procedures.

A bigger problem than measurement errors is the way that statistical models are developed. In theory one or more prior hypotheses must exist and then tested with the collected data to accept or reject it/them. In practice a "fishing expedition" is used in the great majority of cases where the researchers attempt to identify significant statistical results and/or relationships that are consistent with "conventional wisdom". In the process if some results or relationships are contrary to such wisdom they are ignored and not reported. But in "fishing expeditions" when many hypotheses are considered, some will be found to be significant by chance while others may exist because of spurious correlations. An example is a paper by Yates et al.[43]looking at the factors that distinguish male participants that reached 90 years of age (called the survivors) and those that did not. Two statistically significant factors of survivors were "**shorte**r" height and "**arthritis"**, clearly spurious that contributed to reaching the age of 90. At the same time information about the participants who had their hypertension treated and those who did not, although known, was ignored and its effects not reported even though it would have been much more important than most of the other information presented.

In an article published in *Reuters*, Begley[44], its author, describes a situation where other scientists went through a paper line by line, figure by figure trying to replicate an experiment in a published paper and never got the result reported in this paper. When the lead author was asked he said they had done the experiment six times and got this result once, but put it in the paper because it made the best story. Unfortunately, publication biases encourage researchers to produce "new", "interesting" results agreeing with the conventional wisdom. Whether or not these results are correct or can be replicated is another story of little concern to the authors as long as their paper is published.

A lot of hypertension studies use regression as the primary statistical tool to explain life expectancy, or deaths, and the statistically significant factors involved. However, it is customary among statisticians and econometricians to report R^2 when presenting regression results[45]. R^2 is a goodness of fit statistic. If, for

example, the objective of regression is to measure losses in life expectancy associated with, say, the variables smoking, BMI, and cholesterol, it indicates the percentage of such losses explained by these three variables. It may well be that the influence of all variables is statistically significant, as the results are based on large data sets collected through big surveys, but this is not enough if R^2 is small. If R^2, for instance, is 0.15 it means that the three variables used (smoking, BMI, cholesterol) explain only 15% of the variation in losses in life expectancy, while the remaining 85% is unaccountable. In addition, it is *imperative* that the residuals of the regression model must be tested to make sure that they are random. Moreover, small R^2 coupled with non-random residuals can further diminish the explanatory power of regression and even render its results useless. Unfortunately, none of the medical studies on hypertension I have read report the value of R^2, or states that the residuals are random. Some medical studies outside the hypertension area[46] have reported R^2 values which are extremely small, as little as 0.01, or rarely exceeding 0.3. With such small values the explanatory power of regression is minimal and its results cannot be trusted (in my experience any R^2 value less than 0.5 or 0.6 is associated with a huge uncertainty, making any kind of predictions is unreliable. This is particularly true when wanting to predict future cases that will inevitably be different than those when a model was fitted to past data.

Conclusions

In his widely cited paper Ioannidis[6] states: *"There is increasing concern that in modern (medical) research, false findings may be the majority or even the vast majority of published research claims".* This is an extraordinary statement that renders practically useless empirical based medicine, as it is impossible to separate the false from the true findings, and renders meta-analyses of little or no value. Worse the medical profession is well-aware of the serious problems associated with medical research, yet it has done nothing to deal with them or initiate possible, effective solutions.[7] This paper has shown that the area of hypertension suffers from the same falsification problems as the rest of medicine and has deliberated the epistemological, methodological and statistical reasons involved. Popper's theory advocates "falsifiability" as the criterion distinguishing science from non-science. According to Popper even one single study whose results are contrary to the accepted theory is enough to falsify it. Given the huge extent of falsification, medicine cannot be, therefore, considered a "science" and its findings, unless replicated and verified by independent sources, would need to be applied with extreme care.

Medicine can be extremely useful when treating heart attacks, strokes, traumas from car accidents or bullet shots. The same is true with the use of antibiotics to cure infectious disease and reduce suffering and probably with vaccination that has eradicated terrible diseases such as smallpox, diphtheria, polio and measles among others. But in many other cases the harm from treatment can exceed the benefits producing iatrogenics as with Galen's "medicine", bloodletting and tonsillectomy and all the way to the widespread utilization of preventive breast and prostate cancer tests. According to Taleb[47] Iatrogenics, concerned with costs and benefits, is linked to small and visible benefits coupled with large, delayed and hidden non-linear costs and this may well be the case with the treatment of hypertension. Are the benefits from such treatment greater than the monetary costs and especially the negative side effects, including a life- long dependence of medical drugs? This is a critical question that must be answered by objective, scientific evidence. This, unfortunately, has not been done until now bringing the treatment of hypertension to follow the course of other preventive procedures like those of breast and prostate cancer that are continued despite the strong scientific evidence that such tests produce more harm than good[48]. In a recent letter of Dr Susan Bewley[49] to England's cancer head she wrote: ""I declined screening when it was offered, as the NHS breast screening programme was not telling the whole truth. … Large groups of well educated, well intentioned, and kind people can be wrong" and she continues by saying "It's uncomfortable to change set beliefs in the face of changing evidence but unforgivable not

to." It is time to consider that significant changes must also apply to hypertension practices and, to use Dr Bewley words, it is unforgivable not to do so.

There is a lot that can be done to deal with medicine's problems and avoid iatrogenics: some right away some in the longer term. First, patients must be provided with the whole truth in an objective and balanced way. In judgmental psychology the importance of framing[50] is well known. If the results are presented in a negative fashion decisions can be totally different than if presented in a positive way. It is obvious that if hypertensives are told that their life expectancy will be reduced by five years, they will be more likely to take drugs to lower it than if they are told that it will only be a few months or that various studies have come up with highly conflicting estimates and that the actual loss is highly uncertain. It would also help them to make the right decision if they know that in a study[43] of male doctors it was found that among those who reach the age of 90, 41.6% were hypertensives and among those who reached the age of 87.6, 49.1% were hypertensives. It would be also useful if they are told that although about 67% of people over 70 are hypertensives about 0.04% between 65 and 74, 0.1% between 75 and 84 and 0.39% over 85 die each year due to their HBP (including hypertensive heart disease) according to the USA CDC. This means that the great majority of older people die from something else even though they have high blood pressure. In addition, the negative side effects (ranging from sexual dysfunctions to depression and increased suicide rates) of hypertension must be made clear. Potential patients should be also told that the great majority of people treated to reduce their BP would not achieved the therapeutic level of 140/90 even if they take three or more drugs to do so and that the drop-out rates from treatment approaches 10%.

In the medium term meta-analyses must be solely entrusted to independent organizations, like the Cochrane Collaboration, to ensure their objectivity and, consequently professional medical organizations must be obliged to base their guidelines on these meta-analyses in order to avoid conflicts of interests. In addition, the implementation of the guidelines must be enforced as there is strong evidence that this is not done by primary care providers[50.5]. In the long run it would be imperative to make sure that all published studies based on data must be replicable. To do so a small percentage of the budget of publically funded medical research institutes should be devoted to build data bases for storing the data and all supporting information so that all data based studies could be replicated (there should be a clear warning that no data base study will be published unless it can be replicated, or alternative that no findings will be used unless they can be fully replicated). The possibility of replication would discourage researchers to publish false or questionable results and would put medical research to the road of science by reducing the degree of falsifiability in their findings.

HBP is a symptom, possibly like fever, and apart from a few cases it is not known what is causing it. Could it be that there are beneficial reasons for HBP? For instance, a study of patients with acute heart failure found that those with lower SBP at admission had higher in-hospital and postdischarge mortality rates while higher SBP at admission was associated with lower in-hospital mortality rates[51]. Does this mean that high SBP helps patients recover from acute heart failures? Are additional benefits of HBP we do not know as a study found that if you are a man your best alternative is not to be aware of your hypertension while the worse is to treat it but not manage to control it? This study[26] separated men and women into five categories (i. normotensives, ii. hypertensives treated whose BP has been controlled iii. hypertensives treated whose BP has not been controlled iv. hypertensives aware of their HBP but not treated and v. hypertensives not-aware of the HBP) and showed that if you are a hypertensive man you would minimize your chances of overall as well CV related mortality if you do not find out about it. If you find out your chances of dying increases but according to this study you should still do not treat your hypertension. If you are a hypertensive women and if drug(s) manage to control your hypertension then

the benefits will be somehow better than if you were not aware of it, but you will be much worse off if your hypertension could not be controlled (around 60% of cases). This evidence is consistent with the vast literature of Self-Rated Health (SRH)[52-54] which advocates that the way we feel today is the best predictor of how long we will live. Is Mother Nature wiser that we think, in particular if HBP serves some useful therapeutic function?

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