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Should we take into account blood pressure and previous cardiovascular disease when indicating antihypertensive treatment? A meta-analysis of individual data

Blood Pressure Lowering Treatment Trialists C. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021; 397 (10285): 1625-36.

There is universal consensus on the beneficial effect of pharmacological treatment for hypertension (HTN). On the other hand, opinions are not so consistent when it comes to defining whether there is a difference in the benefit achieved in patients with and without underlying cardiovascular disease (CVD), and with respect to the blood pressure levels below which the treatment would stop exercising favorable effect and could even be detrimental. The available information yields disparate results: different meta-analyses have shown, or not, the existence of a J-curve in the relationship between baseline blood pressure and the risk of events, and have concomitantly raised blood pressure threshold values to justify treatment, or they have not been able to do so. We now know a meta-analysis of individual data with the largest number of patients considered in a study of these characteristics. It was carried out by the collaborative group BPLTTC (Blood Pressure Lowering Treatment Trialists' Collaboration), constituted by those responsible of the most important randomized clinical trials of antihypertensive treatment. Studies carried out exclusively in heart failure, or of short intervention in acute conditions, such as acute myocardial infarction (AMI), were excluded. It included randomized studies with at least 1000 patients, comparing antihypertensive treatment with placebo, or a more intensive treatment with a less intense one, that reported the incidence of cardiovascular events during follow-up. Prevalent CVD was defined by history of AMI, ischemic heart disease, or stroke. Patients with baseline heart failure were excluded. The primary endpoint was a composite of AMI, fatal or non-fatal ischemia, fatal or non-fatal stroke, and fatal or requiring hospitalization heart failure. Secondary endpoints were the individual components of the primary composite endpoint, cardiovascular death, and all-cause death.

The meta-analysis included individual data from 344 716 patients from 48 randomized studies (37 of them included patients with and without CVD, 10, only patients with CVD, and one, only patients with-

out CVD). In 54.2% of cases, patients had no history of CVD while the remaining 45.8% did. Mean age was 65 years in both groups. As expected, the prevalence of patients with CVD was higher in men (67.1% vs. 51.3% in women). Mean systolic (SBP) and diastolic (DBP) blood pressure were lower in patients with CVD (146/84 mm Hg. vs. 157/89 mm Hg in those without CVD). The prevalence of ischemic heart disease was 74.9% and that of cerebrovascular disease 35.8% in the group with CVD, and, by definition, 0% in the group without CVD. The prevalence of diabetes was somewhat higher in the group without CVD: 29.6% vs. 27.3%; the same happened with chronic kidney failure: 19.1% vs. 10.7%; and that of atrial fibrillation was around 3% in both groups. Logically, under baseline conditions, patients with CVD had greater use of beta-blockers (44.1% vs. 17.4%), inhibitors or antagonists of the renin angiotensin system (42.1% vs. 38.7%), antiplatelet agents (64.8% vs. 20.2%) and lipid-lowering drugs (54.1% vs. 19.5%).

Median follow-up was 4.15 years (interquartile range 2.97-4.96) and during this period, 12.3% of participants had at least one major cardiovascular event: 4% stroke, 5.6% ischemic event, and 2.4% heart failure. In 8.4% of cases patients died, 40% of them due to cardiovascular causes. The annual incidence of the primary endpoint in patients without CVD, was 3.19% in the control arm and 2.59% in the active treatment arm; in those with CVD, 3.97% and 3.6%, respectively. The relative benefit in the incidence of primary endpoint reduction was around 10%, similar in both groups for every 5 mmHg of SBP reduction with HR 0.89 (95% CI 0.86-0.92) in patients with CVD, and HR 0.91 (95% CI 0.89-0.94) in patients without CVD. There was no significant or statistical difference between patients with and without CVD in stroke reduction (around 13%), coronary events (around 8%), or cardiovascular death (around 5%), in all cases for every 5 mmHg of SBP reduction. There was no significant reduction in all-cause death. There was only interaction regarding risk reduction for the incidence of heart failure (HR 0.89, 95% CI 0.83-0.95 in patients with CVD, vs. HR 0.83, 95% CI 0.77-0.89 in patients without CVD, $p=0.02$).

The other point of interest is that there was no evidence of correlation between the effect of treatment and the incidence of the primary endpoint with baseline SBP. Risk reduction was similar for each endpoint when considering the initial SBP in 10 mmHg categories. (starting with SBP <120 mmHg., and progressing at 10 mm Hg intervals until reaching those with SBP \geq 170 mmHg). In other words, there was no evidence of the existence of a J-curve for the relationship with prognosis.

Traditionally, practice guidelines consider the initiation of antihypertensive treatment from a certain threshold of blood pressure. Some take into account the definition of baseline cardiovascular risk for the decision; others are based exclusively on blood pressure values. Different studies support this approach. Let us recall, for example, the HOPE 3 study, in which treatment with candesartan and hydrochlorothiazide did not improve the prognosis when it was used in patients with SBP <131.6 mmHg. This meta-analysis (which among other merits considers individual data, arising from the largest number of patients known so far in a study of these characteristics, and with the largest number of major events recorded), comes to challenge this concept, by stating that risk reduction of future events for the same decrease in SBP is similar in patients with or without previous CVD, and is independent of baseline SBP. This is certainly true when it comes to relative risk reduction; however, do all patients face the same absolute risk?

The meta-analysis provides some other added data of interest. Let us see: among patients with previous CVD in the control arm, 12.8% of those with a SBP <140 mmHg, and 16.3% of those with a SBP \geq 160 mmHg suffered major events; among those without previous CVD, the corresponding values are 14.8% and 11.5%. Why do patients without established CVD, with SBP <140 mmHg, have more events than their counterpart with previous CVD? It is difficult not to bring up the increased use of statins, antiplatelet agents, beta-blockers, and inhibitors/antagonists of the renin angiotensin system in the latter. When blood pressure figures are higher, on the other hand, and despite the difference in co-treatment, the previous CVD takes its toll.

It is worth remembering that the definition in this analysis of CVD implies a history of ischemic heart disease, AMI, or stroke. Baseline risk may be high, even in the absence of these conditions: a patient with diabetes, tobacco addiction and dyslipidemia presents a high risk of cardiovascular events even when there are still no clinical manifestations of the disease; in fact, we could ask ourselves why a patient with a SBP <130 mm Hg and no previous established CVD was included in some of the studies that feed this meta-analysis, if it was not because he/she had high cardiovascular risk. In this sense, perhaps different blood pressure thresholds should be considered according to baseline risk; or, and this is what the authors of the meta-analysis point to, consider the treatment globally established as a cardiovascular protector, rather than as an antihypertensive therapy (which makes its use independent of blood pressure values). We would have wished, to strengthen this idea, an analysis of adverse events, and, above all, according to the families of therapeutic agents used. Perhaps, the protective effect is not the same for all the drug families that we usually use, and may even be different depending on the major event considered.

Worse prognosis for patients with ST-segment elevation myocardial infarction, without coronary risk factors.

Figtree GA, Vernon ST, Hadziosmanovic N, Sundstrom J, Alfredsson J, Arnott C, et al. Mortality in STEMI patients without standard modifiable risk factors: a gender-disaggregated analysis of SWEDEHEART registry data. **Lancet.** 2021;397(10279):1085-94.

At least one of the traditionally considered modifiable coronary risk factors (MCRF): hypertension (HTN), diabetes (DM), dyslipidemia (DLP) and smoking (SMK) are present in most patients with established coronary heart disease. In the last two decades, an increase in the proportion of patients with absence of all of them has been noted in different registries of acute myocardial infarction (AMI). Will the evolution of these patients be better or worse than that of the rest? Again the SWEDEHEART Registry comes to our aid. As we know, this Registry includes all patients hospitalized in Sweden with a diagnosis of AMI since 1995. In this case, those responsible for the Registry have carried out a retrospective analysis in which they considered all patients included between 2005 and 2018, with hospital diagnosis of ST-segment elevation AMI (STEMI), without previous AMI or a history of any revascularization procedure. They were divided into two groups: those with at least one MCRF present, defined by history, established treatment or hospitalization diagnosis (MCRF+) and those with absence of all of them (MCRF-). Smoking was defined as having smoked at least 1 cigarette a day in the last month; HTN as previous diagnosis or treatment, or upon finding high blood pressure values during hospitalization; DM as previous diagnosis or established treatment; DLP as previous diagnosis or treatment, or a value of LDL cholesterol \geq 135 mg/dL or total cholesterol \geq 212 mg/dL at hospitalization. The primary endpoint of the analysis was all-cause mortality at 30 days after STEMI; secondary endpoints were major adverse cardiovascular events (MACE) at hospitalization and follow-up: AMI, stroke, heart failure, need for revascularization, and cardiovascular death.

The study considered 62 048 patients with STEMI, 9228 (14.9%) of which were MCRF-. In the MCRF+ group, 21.3% had DM, 70.4% HTN, 48.4% DLP and 32.6% were current smokers. Compared with the latter, patients in the MCRF- group were one year older (median 69 vs. 68 years), and with a higher prevalence of male sex (76.5% vs. 65.5%). They had less history of stroke, peripheral vascular disease, or hospitalization for heart failure, cancer or chronic obstructive pulmonary disease. By definition they were not treated with statins or neurohormonal antagonists, and there was a very low proportion of those treated with aspirin (5.2%) compared to somewhat higher values in the MCRF+ group (16.5%). Body mass index, total cholesterol, LDL cholesterol, triglycerides, glycemia and glycosylated hemoglobin values were lower in the

MCRF- group. Time from the onset of symptoms to the start of reperfusion was somewhat shorter in the MCRF- group, and the use of thrombolysis (7.6% vs. 7.8%) or primary angioplasty (71.8% vs. 71.3%) was similar. MCRF- patients had higher troponin concentration and lower left ventricular ejection fraction, (<40% in 27.2% vs. 23.9% in the MCRF+ group). In MCRF- patients the anterior descending artery was somewhat more frequently responsible for AMI but the prevalence of 3-vessel disease was lower (37.9% vs. 43.7%). The incidence of spontaneous coronary dissection was low, but to some extent higher in the MCRF- group: 1.7% vs. 0.8%.

In patients with MCRF-, the incidence of cardiogenic shock (6.3% vs. 4.1%) and all-cause death (9.6% vs. 6.5%) was higher during index hospitalization. At discharge, the indication of statins or neurohormonal antagonists was lower, but similar for antiplatelet agents. At 30 days, the incidence of all-cause death was higher (11.3% vs. 7.9%, HR 1.47, 95% CI 1.37-1.57), attributable to higher cardiovascular mortality. Adjusting for age, LVEF <40%, heart rate, blood pressure, creatinine and prehospital cardiac arrest, the risk of higher mortality for MCRF- patients was maintained, with HR 1.24, 95% CI 1.10-1.39. Although the HR was similar between men and women, women doubled men in 30-day mortality (17.6% vs. 9.3% in MCRF- patients, 11.2% vs. 6.1% in those belonging to FRCM+). The 30-day incidence of AMI or stroke was similar, regardless of the presence or absence of cardiovascular risk factors (CRF), and that of revascularization or heart failure was lower. After adjusting for treatment at discharge, the increased risk of death disappeared (in the case of statins or renin angiotensin system inhibitors/antagonists) or was attenuated (in the case of beta-blockers). At the 12-year follow-up, the MCRF- group compared with MCRF+ presented higher long-term cardiovascular mortality and all-cause mortality, greater in men up to 9 years and in women up to 12 years of follow-up, respectively. But the difference appeared in the first 30 days of follow-up; in fact, when considering only the patients who survived this period, in the rest of the follow-up period, MCRF- patients had a better prognosis than MCRF+ patients.

This observational study focuses on patients with STEMI not widely addressed by the literature: those with absence of traditional CRF. It is true that there are numerous publications on STEMI in young people, who by definition have fewer or no CRF, but what is interesting is that in this publication mean age of MCRF- was 69 years. This means that advanced age, the non-modifiable CRF par excellence, was present. To this we add that another non-modifiable CRF, male gender, was also more prevalent. And bearing in mind the absence of MCRF, is it really so? Yes, if we rely on the definitions considered. Now, with regards to some values: average fasting blood glucose in the MCRF- group was 126 mg/dL and average LDL cholesterol

104 mg/dL. In other words, even outside the definition, the metabolic profile of the patients was not absolutely normal. On the other hand, there were 36% ex-smokers in this group; as current SMK definition considered only tobacco smoking in the previous month, we cannot exclude patients in whom the past habit continued to exert its deleterious effect, because it was close in time. All this pattern of covariates ends up translating into the presence of a 3-vessel disease in almost 38% of patients with MCRF-. And they were clearly less protected patients from the cardiovascular point of view (less aspirin, absence of statins and neurohormonal antagonists). In conclusion, risk is not defined dichotomously, and for each of the aforementioned CRF we must think of a continuum, rather than in presence or absence. So, all these reasons can help us understand why 1 in 7 patients with STEMI were MCRF-.

However, what is higher mortality attributable to? It seemed tempting to think about delayed treatment or less use of thrombolysis or angioplasty, but this was not the case. STEMI size was somewhat larger in the FRCM- group, even though the anterior descending artery was less frequently responsible for AMI, and this translated into a higher incidence of cardiogenic shock and death in hospitalization (is it an expression of less awareness of previous risk, less use of potentially beneficial medication?) But what is interesting is that the worse prognosis compared with patients with MCRF+ was maintained during several years. And even more, when adjusting for discharge treatment, this difference disappeared or was strongly attenuated, which highlights the role that physicians play in patient outcome. Of course, beyond known CRF, factors not taken into account and more prevalent in the group with MCRF- may further contribute to explain the findings. The worst evolution of women with respect to men, regardless of the presence or absence of MCRF, is part of a long list of evidence in this regard. Since in this case there is no specific analysis, we can only speculate, but a higher degree of microvascular disease and structural and metabolic alterations may certainly play a role.

You will earn your bread with the sweat of your brow ... and sometimes at the expense of more cardiovascular disease. Two observational studies

Holtermann A, Schnohr P, Nordestgaard BG, Marott JL. The physical activity paradox in cardiovascular disease and all-cause mortality: the contemporary Copenhagen General Population Study with 104 046 adults. **Eur Heart J.** 2021;42(15):1499-511.
Trudel X, Brisson C, Talbot D, Gilbert-Ouimet M, Milot A. Long Working Hours and Risk of Recurrent Coronary Events. **J Am Coll Cardiol.** 2021;77(13):1616-25.

It is traditionally understood that regular physical activity and greater physical fitness are associated with better cardiovascular and global prognosis. This has

been shown by numerous cohort studies, and is emphasized by clinical practice guidelines. However, recent publications make a distinction about the domain in which this activity takes place: higher degrees of physical activity are associated with a better prognosis when it takes place during moments of leisure, rest or distraction, and on the contrary they seem to worsen the prognosis when it takes place in the workplace. This apparent contradiction (more physical activity associated with a better or worse prognosis depending on the context) is called the paradox of physical activity. A new demonstration of this phenomenon has just been published. It comes from the city of Copenhagen. Between 2003 and 2014, city dwellers were randomly invited to take part in a Population Registry to evaluate the global prognosis and determinants of evolution. A total of 104 046 adults, (43%) agreed to participate. A physical examination was carried out in all of them and data referring to socioeconomic status, education, diet, cardiovascular risk factors, and a vital exhaustion score were collected.

Participants were questioned about the time, intensity and area in which they developed their physical activity. Specifically, regarding occupational physical activity, a standard question was posed: "What has been your physical activity at work during the last year?", with 4 answer options: a) low: predominantly sedentary; b) moderate: sedentary or standing, occasionally walking; c) high: walking, sometimes lifting objects; d) very high: heavy manual work. Regarding physical activity in non-working time, the standard question was: "What has been your physical activity during your leisure time (including transportation to and from work) during the last year?", with 4 answer options: a) low: almost completely sedentary, or light physical activity less than 2 hours a week; b) moderate: light physical activity 2 to 4 hours a week; c) high: light physical activity more than 4 hours a week or vigorous 2 to 4 hours a week; d) very high: vigorous physical activity more than 4 hours a week, heavy exercise or competitive sports several times a week. The association of physical activity at work and during leisure time with the incidence of major adverse cardiovascular events (MACE) was studied after adjusting for baseline variables: cardiovascular death, fatal and non-fatal acute myocardial infarction (AMI), fatal and non-fatal stroke, and all-cause mortality. On the other hand, the relationship between both types of activity was explored.

Data on physical activity in leisure time were known in 103 262 participants. Among them, 6.1% had a low level of activity, 41.8% moderate; 45.2% high and 6.9% very high. Those with less physical activity in leisure time were more frequently women, smokers, obese, with a lower socioeconomic and educational level and less adherence to dietary recommendations. In them, the prevalence of chronic obstructive pulmonary disease and diabetes was somewhat higher. Data on occupational physical activity were known in

74 565 participants: 43.4% had a low level of activity, 33.6% moderate; 19.5% high and 3.5% very high. In the moderate and high levels of activity there was a predominance of women, more than 60% in both cases; on the other hand, among those with very high physical activity, more than 90% were men. Those with the highest level of occupational physical activity were more frequently smokers, obese, with a lower socioeconomic and educational level, lower adherence to dietary recommendations, and greater alcohol consumption.

Median follow-up was 10 years. Regarding physical activity during leisure time, and taking the low level as reference, progressively higher levels were associated with a better cardiovascular and global prognosis. Adjusting for age, gender, health status, and cardiovascular risk factors, MACE risk reductions were 14%, 23%, and 15% for the moderate, high, and very high levels; and for total mortality 26%, 41% and 40% respectively, statistically significant in all cases. When also adjusting for socioeconomic conditions, marital status, vital exhaustion, and heart rate, the strength of the association was reduced in the case of MACE (although maintaining the aforementioned trend) and, on the other hand, it remained significant in terms of total mortality, with reductions of 20%, 33% and 28%.

Conversely, regarding physical activity at work, and taking the low level as reference, progressively higher levels were associated with worse cardiovascular and global prognosis. Adjusting for age, gender, health status, and cardiovascular risk factors, the increased risk for MACE was 4%, 15%, and 55% for the moderate, high, and very high levels; and 6%, 13% and 27% for total mortality, respectively, statistically significant for high or very high activity. After adjusting for socioeconomic conditions, marital status, vital exhaustion, and heart rate, the strength of the association was maintained for MACE in the case of high and very high activity (with an increased risk of 16% and 35%, respectively); however, it disappeared in terms of total mortality.

There was no interaction between physical activity at work and during leisure time with regard to the incidence of events: the risk gradient (favorable or unfavorable) implied by each activity stratum did not vary according to the stratum of the other. To rule out the effect of reverse causality (the sickest work less, but have a higher rate of events, and in this case baseline disease is a confounder of the relationship between physical activity and prognosis), only events that occurred at 1, 3 and 5 years of participant inclusion were analyzed. The findings were in line with what was described.

The other publication of interest refers to the relationship between hours of work and cardiovascular prognosis in patients with history of coronary disease. Different meta-analyses that indicate worse prognosis associated with excess working hours (generally understood as over 48 hours a week), with an increased

risk of coronary events and stroke, have already been published. The publications have focused on the general population.

The authors of this study selected patients <60 years discharged from 30 hospitals of Quebec, Canada, between 1995 and 1997, with an initial diagnosis of acute myocardial infarction (AMI). They should have had a paid job in the previous year, and plan to return to work (at least 10 hours per week) in the following 18 months. A total of 967 patients were included in the study. Based on the number of weekly hours worked after returning to the labor market, 4 categories were established: <35 hours (21.2%), 35-40 hours (49%), 41-54 hours (21.1%) and 55 hours or more (9.7%). The primary endpoint was the incidence of fatal coronary event, non-fatal AMI, or hospitalization for non-fatal unstable angina, with ECG changes or indication for revascularization within 2 weeks. Age, gender, sociodemographic factors, coronary risk factors, variables related to the AMI index, physical activity in the weeks prior to AMI, work factors (psychological demand and decision-making capacity at work, defined by specific questionnaires, support, supervision, and exposure to pollution), and personality factors (hostility, repression of anger, inability to express emotions) were considered as covariates.

Regarding what was expected, given the proportion (9.7%) of patients who worked ≥ 55 hours, there was an underrepresentation of women in this group (1.9% of total of women vs. 10.7% of total of men), and a higher proportion than expected of those under 40 years of age (13.9%), with a good income level (16.4%), untreated hypertension (15.7%), sedentarism (16.9%) and with psychological distress (12, 1%). At a mean follow-up of 5.9 years, and taking as reference the group that worked between 35 and 40 hours a week, the HR (95% CI) adjusted for baseline characteristics for a new coronary event was 1.67 (1.10-2.53), for the category ≥ 55 hours. The HR (95% CI) for those with ≥ 55 hours under work stress in relation to those who worked 35-40 hours and without stress, was 2.55 (1.30-4.98). Taking 40 hours per week as reference, progressive increases of 10 hours were associated with increasing HR: 1.20 for 50, 1.50 for 60, 1.92 for 70, 2.46 for 80, 3.10 for 90 and 3.78 for 100 hours a week.

The two articles presented contain information that we consider complementary. The first compares progressively higher levels of physical activity at work and in leisure time, and their influence on prognosis. It is worth noting that, when referring to physical activity at work, its intensity is graded; and that in physical activity at leisure time, intensity and time spent are considered. The categories are not strictly comparable: moderate physical activity at work is not the same as moderate physical activity at leisure. In the first case, we consider sedentary physical activity or standing, sometimes walking (it is not clear how many hours a day); in the second case we talk about light physical ac-

tivity of 2 to 4 hours a week. Therefore, we should not be tempted to assume that the same physical activity has different consequences depending on the context. What is evident is that a progressive increase in the level of activity has a favorable impact if it has to do with recreation and, on the other hand, worsens the prognosis if it occurs at work. The reasons given are varied: in general, physical activity at work is more static, and its excess is associated with an increase in blood pressure, without improvement in cardiorespiratory fitness. Recreational activity, on the other hand, is linked to an improvement in exercise capacity and a decrease in inflammation markers, diastolic function, and insulin resistance. It is important to emphasize that the relationship with the prognosis for each type of activity was generally maintained despite adjusting for various confounders, from clinical to socioeconomic and living conditions. However, it is very difficult to stop considering that physical activity arises from an obligation, and recreational activity from desire; that companies are not chosen during working hours in general and interpersonal conflicts are more frequent than during leisure; that sometimes the work that is carried out is not the one that satisfies the needs or the aspirations. If we know the relationship between negative emotions and cardiovascular health, if hostility, repression of emotions and anger are prognostic factors, it is not unreasonable, in addition to the traditional mechanistic factors already mentioned, to think of the psychological field as a factor that should be viewed with more consideration.

In this sense, the second analysis partly confirms our assumptions. It is not that their findings are novel in how much excess working hours is associated with worse evolution; different meta-analyses have already shown this. It is novel that it refers specifically to a specific population, that of those who return to work after a coronary event; i.e., those who have already received a warning. In this sense, a multidisciplinary approach (cardiologists, psychologists, occupational therapists, social workers) becomes increasingly important for secondary prevention in the most developed countries in relation to previous and future working conditions. And among the factors most taken into account we find (beyond the patient's conditions from the cardiovascular point of view) precisely the work environment and working hours. But, let us note, the study we are commenting shows that not only time matters, but also the emotional atmosphere: therefore, with respect to the standard category (35 to 40 hours), working 55 hours or more increases the risk 1.67 times; but if we add to this excess of hours the feeling of work tension compared to that of tranquility, the risk increase becomes 2.55. It is true that we are no longer in Paradise, and that we must work to live; but it is clear that the improvement of working conditions, and an adequate balance of work and recreational activity (how? how much? is matter for future analyses) contribute to enriching the present and ensuring a better future.

Fish, fruits and vegetables: new evidence of the relationship between diet and prognosis

Petermann-Rocha F, Parra-Soto S, Gray S, Anderson J, Welsh P, Gill J, et al. Vegetarians, fish, poultry, and meat-eaters: who has higher risk of cardiovascular disease incidence and mortality? A prospective study from UK Biobank. **Eur Heart J.** 2021;42(12):1136-43.

Wang DD, Li Y, Bhupathiraju SN, Rosner BA, Sun Q, Giovannucci EL, et al. Fruit and Vegetable Intake and Mortality: Results From 2 Prospective Cohort Studies of US Men and Women and a Meta-Analysis of 26 Cohort Studies. **Circulation.** 2021;143(17):1642-54.

It is usual to refer to the influence that the dietary factors have on the prognosis. In this sense, it has been pointed out that a high consumption of red meat and processed meat is one of the most adverse factors. At the same time, all the recommendations emphasize favoring fruit and vegetable intake. This has led to considering vegetarian diets as “healthier” diets; and in recent years we have witnessed the explosion of veganism, which rejects the consumption of all food of animal origin, based on reasons ranging from the sanitary to the philosophical. It is often difficult to establish whether the influence of diet on the evolution and genesis of pathologies of a different order (cardiovascular, oncological, diabetes, etc.) lies in what is eaten “too much” or what is eaten “too little”. For example, the Global Burden of Disease study collaborative group reported that in 2017 there were 11 million deaths worldwide due to diet; most of them were attributable to high sodium and low whole grain, fruit and vegetable consumption, and a much smaller proportion was attributed specifically to high consumption of red or processed meats. And to make matters worse, some studies ascribe an adverse influence to vegetarian diets, with increased risk of stroke. Many of the mentioned studies, even though with enough follow-up time, have not had an adequate sample size. For this reason, the analysis we present of the UK Biobank population study, a biomedical and genetic database of more than 500 000 participants between 37 and 73 years of age recruited from the general population of England, Scotland and Wales, becomes relevant. The influence of baseline factors on the vital prognosis and on the development of different conditions in particular is the object of study of this initiative. In this case, the researchers evaluated the effect of different diets on the evolution of cardiovascular disease.

A questionnaire on a touch screen device was administered to the participants, focused on defining the consumption in the previous year of cheese, milk, fish, poultry, and red meat. For each food, the response was dichotomized into consumed or not. Based on the response, 4 types of diet were defined: a) vegetarian: consumers of cheese, milk, and vegetables, but not meat; b) fish consumers: also including vegetables,

cheese and milk, but not poultry or red meat; c) fish and poultry consumers: including all types of foods mentioned except red meat; and d) meat consumers: they consume cheese, milk and all types of meat. Over 45 000 participants who reported changing dietary patterns periodically were excluded. Vegans (n=57) were excluded as their small number made it impossible to analyze them as a separate entity. Overall, 448 396 people were available for the analysis. The vast majority, 94.7%, were meat consumers, while 1.1% were fish and poultry, 2.4% fish and 1.8% vegetarian consumers. Among meat consumers, the proportion of men was higher: 46% vs. 23% who were fish and poultry consumers, 28% fish consumers and 33% vegetarians. Also, among meat consumers, body mass index and the proportion of overweight and obese people was higher (almost 67% vs. 45% to 47% in the other three categories), as well as that of smokers and ex-smokers and multimorbidity. They were also those with the lowest consumption of sugar, fiber, fruits and vegetables. But this does not imply that the other three dietary patterns had an irreproachable diet: for example, vegetarians were those who consumed more packaged potato chips and fish consumers those who drank more sugary beverages, though not excessively different from the other groups.

Without considering the first 2 years after inclusion, median follow-up to assess the incidence of cardiovascular disease and mortality from this origin was 8.5 and 9.3 years, respectively. Twenty four percent of participants presented new cardiovascular disease, and 1.5% cardiovascular death. Taking the meat-consuming group as reference, and adjusting for age, gender, deprivation index, ethnicity, comorbidities, tobacco and alcohol consumption, sedentary lifestyle, and body mass index, the other three groups presented reduced risk of developing cardiovascular disease: 9% vegetarians, 7% fish consumers, significant in both cases, and borderline (6%) poultry and fish consumers. But only fish consumers presented a significant reduction in the risk of developing each of the manifestations of cardiovascular disease, with HR (95% CI) 0.79 (0.70-0.88) for coronary heart disease, 0.70 (0.56-0.88) for acute myocardial infarction, 0.79 (0.63-0.98) for stroke, and 0.78 (0.63-0.97) for heart failure. There was no significant reduction in cardiovascular or total death in any of the other groups considered compared with meat consumers.

And just as the preceding discussion focuses specifically on the intake of different types of meat, the next one emphasizes on that of fruits and vegetables. All the Recommendations of Scientific Societies reinforce the indication of their consumption, which is usually linked to better evolution. Now, what is the appropriate “dose”? How much should we eat daily to ensure better health? National recommendations are not uniform, although they are around 5 daily servings between fruits and vegetables: in the United States 2.5 servings of vegetables and 2 of fruits per day; 5 servings

of fruits and vegetables in England, 6 in Denmark, but 8.5 in Australia. There is even no coincidence in the meta-analyses regarding the beneficial amount: one maintains that there is no increase in prognostic improvement above 5 daily servings, another extends the benefit up to 10. We now know an analysis that uses the data of 2 classic cohort studies, often cited, which have the merit of the large number of observations, long follow-up time and, among other data (risk factors, habits, emergence of diseases), the periodic evaluation of diet and its variations: the Nurses' Study and the Male Health Professionals' Study.

The Nurses' Study (NHS) included 121 700 nurses between 30 and 55 years of age in 1976. In 1984 the first questionnaire on diet was administered, and the data for this year are the baseline data. The Male Health Professionals' Study included 51 529 participants between 40 and 75 years of age in 1986, and the first questionnaire on diet dates from that year. In both studies, the participants were reassessed every 2 years, and follow-up of both cohorts concluded in 2014. Every 2 to 4 years, questionnaires were sent to the participants on the intake frequency of different foods in the previous year. Participants had to report the usual daily consumption (from none to ≥ 6 times a day) of a standard serving of each type of food that was questioned, for example, half a cup of spinach, a banana, half a cup of strawberries. Fruit juices, French fries or mashed potatoes, sauces, tofu, soybeans, garlic, and mushrooms were not included. The consumption of fruits and vegetables, together and separately, was divided into quintiles, and the one with the lowest consumption was taken as reference. For this particular analysis, participants with a history of cardiovascular disease, diabetes or cancer, information on diet not available, and those who reported caloric intake < 800 or > 4200 kcal/day among men, or < 600 or > 3500 kcal/day among women were excluded. In case any of the aforementioned conditions, hypertension or dyslipidemia appeared during follow-up, the analysis was stopped in the immediately previous questionnaire on diet. The endpoint was the incidence of total and specific mortality due to diseases of interest.

Finally, 66 719 women with 30-year follow-up (a total of 1 822 058 persons/year) and 42 016 men with 28-year follow-up (1 033 007 persons/year) were included in this analysis. The reference category (first quintile) was the consumption of a mean of 2 daily servings of fruits and vegetables (0.5 daily servings of fruit, 1.5 of vegetables); the following quintiles corresponded to means of 3.3; 4.2; 5.3 and 7.9 servings. In both men and women, higher consumption of fruits and vegetables was associated with older age, more physical activity and multivitamin consumption, and lower consumption of tobacco and alcohol. In women, it was associated with less dyslipidemia and hypertension and in men with more dyslipidemia and the same prevalence of hypertension.

Taking as reference the lowest quintile of consumption and adjusting for age, gender, race, history of hypertension or hypercholesterolemia, family history of diabetes, cancer or cardiovascular disease, tobacco and alcohol consumption, body mass index, physical activity, multivitamins, aspirin use and a food quality score, multivariate analysis showed total mortality risk reduction, with HR (95% CI): 0.95 (0.92-0.99) for the second quintile, 0.89 (0.86-0.92) for the third, 0.88 (0.85-0.91) for the fourth and 0.89 (0.86-0.93) for the highest. The greatest reduction in total mortality was achieved with a consumption of 5 daily servings of fruits and vegetables: HR 0.87 (95% CI 0.85-0.90). This corresponded to a daily consumption of 2 servings of fruits and 3 of vegetables, with HR (95% CI) with respect to the mentioned references of 0.88 (0.86-0.91) and 0.94 (0.92- 0.97) for fruits and vegetables, respectively. Above that consumption there was no extra reduction in mortality. Similar trends were evidenced for cardiovascular death, cancer and respiratory disease.

To reinforce their findings, the authors carried out a meta-analysis in which, in addition to the 2 studies mentioned, they included another 24 cohort studies, with a total of 1 892 885 participants and follow-up between 4.6 and 30 years. The findings were similar to those referred above, with the highest benefit achieved with 5 daily servings of fruits and vegetables, 2 of fruits and 3 of vegetables, and only a minimal gain above those figures.

We periodically know data from observational studies that focus on diet and the influence of different modalities and constituents on cardiovascular and global prognosis. As we have pointed out, there seems to be a general agreement that a higher consumption of whole grains, fruits, vegetables, and fish is associated with a better prognosis, and the consumption of red and processed meats points in the opposite direction. Some of these studies indicate that the association between a "healthy diet" and risk reduction is stronger than the excess risk attributable to a "not recommended" diet. However, the different dietary patterns are not mutually exclusive: the consumption of some "good" components does not exclude that of other "bad" ones (see the figure for vegetarians and their greater consumption of packaged foods rich in sodium); and the relationships with global risk and that of each of the prevalent pathologies are not univocal. As we are not talking about randomized studies in which all baseline characteristics are balanced between those who consume one diet and another, we cannot rule out that some factors not taken into account or superficially considered (socioeconomic and cultural level, vital attitude, self-care, properly categorized physical activity, prevalence of risk factors, underlying diseases, medication), as well as many times the ingested amounts of each of the foods, can influence the results. To this we must add that the populations studied are not similar in all cases. For example, UK Biobank participants, compared

with the general population of England, Scotland and Wales are older, more frequently female and live in less socio-economically disadvantaged areas than non-participants. They are usually less obese, smokers, or daily alcohol users, and report fewer health problems than the general population. At ages 70-74, all-cause mortality rates and overall cancer incidence were 46.2% and 11.8% lower, respectively, in men and 55.5% and 18.1% lower in women than in the general population of the same age. We can therefore assume a “healthy volunteer” selection bias. This does not imply denying the findings of the study, but it does imply whether in another context the associations would have equal, less or greater strength.

Compared with those who incorporate red meat into their diet, those who do not consume it (whatever their diet) have a better cardiovascular prognosis. This seems to be enough to point out its deleterious effect; but, is any combination of nutrients equally harmful just for the sake of including them? Similarly, in light of the results presented, the idea clearly arises of assigning the benefit of a diet rich in fish to some of its constituents, polyunsaturated fatty acids, in the first place. But the net benefit is seen in the study in participants who eat only fish meat, and not in those who consume fish and chicken. Is the difference then due to the fact that the former must consume a greater quantity of fish because it is their only source of meat, or does poultry meat have some constituent (and how can we not think about how we feed those who will feed us) harmful to our health and that balances the favorable effect of fish? Or, and we think about the next study, is there an unexplored difference in the consumption of fruits and vegetables in those who eat different types of meat? Are the differences that influence the prognosis merely qualitative, or do they also define quantity? The analysis on fruits and vegetables from the analysis of the nurses' and male health professionals' cohorts, clearly points to the latter. But, and reasoning like the dog that chases its tail, does everything happen by quantity? Neither! As the authors well point out, starchy vegetables are not associated with better evolution; and neither are fruit juices. Both are sources of excess carbohydrates, which the modern literature (see the analysis of the PURE study in *Rev Argent Cardiol* 2017; vol 85 no 6) indicates as a cause of worse evolution. Is that why the benefit they provide has a limit, and that we cannot indicate a clear dose-response curve?

In conclusion, the two studies mentioned confirm the benefit of a “healthy” diet; they give some reasons, they owe others. But the “healthy” diet is generally consumed by more “healthy” people. ¿Are we what we eat, or do we eat as we are?

Post-hoc analysis of the SPRINT and MADIT studies: the same for everyone or to each as appropriate?

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At the time of choosing a certain treatment in the context of a disease we can treat all patients equally, resorting to drugs or procedures that have shown efficacy in clinical trials, or decide on the basis of baseline characteristics, risk and potential benefit. We are presenting two analyses of randomized studies that support a rational use of therapeutic agents, beyond global results.

The first is the randomized, open-label, controlled SPRINT study, comparing two strategies in hypertensive patients: reaching a systolic blood pressure (SBP) <140 mmHg [standard treatment (ST)] or SBP <120 mmHg [intensive treatment (IT)]. It included patients with SBP between 130 and 180 mmHg, >50 years of age and at least one additional cardiovascular risk criterion prior clinical or subclinical cardiovascular disease, except stroke; less than 15% 10-year risk of events according to the Framingham score; kidney failure (except that due to renal polycystosis) with glomerular filtration rate between 20 and 59 ml/min/1.73 m²; and age ≥75 years. It excluded patients with diabetes or history of stroke. The primary endpoint was a composite of acute myocardial infarction (AMI), other acute coronary syndromes, stroke, acute decompensated heart failure (HF) and cardiovascular death. An endpoint of kidney dysfunction was also defined: in those with glomerular filtration rate <60ml/min/1.73m², a composite of >50% fall in glomerular filtration rate, dialysis or transplantation, and in those with higher glomerular filtration rate, a drop of 30% to a value <60ml/min/1.73m². The incidence of albuminuria was also explored. The intervening physicians were free to choose the pharmacological treatment in each arm, although they were requested to use evidence-supported drugs. An objective SBP between 135 and 139 mmHg was postulated for the ST arm, and in case of lower values at follow-up the prescribed doses were decreased. A total of 9361 patients were enrolled and in 2015, the Safety Committee recommended early termination of the study, with an average follow-up of 3.26 years. Mean age of participants was 68 years, slightly more than 64% were men and 28% had chronic kidney disease. Mean BP at the beginning of the study was 139.7/78.1 mmHg. Throughout the study, the ST arm reached 134.6 mmHg and the IT arm 121.5 mmHg, with a mean number of antihypertensive drugs of 1.8 and 2.8, respectively. The annual incidence of the primary endpoint was 1.65% with IT and 2.19% with ST (HR 0.75, 95% CI 0.64-0.89), with significant difference after the first years. There was no significant difference in the incidence of AMI or stroke, but acute HF, cardiovascular death (1.03% vs.

1.40%, HR 0.73, 95% CI 0.60-0.90) and all-cause death were significantly different. There was no significant difference in the incidence of serious adverse events (mortal, life-threatening or requiring hospitalization, or justifying additional pharmacological or non-pharmacological measures), but there were significant differences in the incidence of hypotension, syncope and kidney failure, in all cases between 2% and 4% with IT and between 1.5% and 2.5% with ST.

In a recent publication, the authors of the study selected the variables associated with risk of clinical events and adverse events based on previous models and publications and their own experience. They arrived to multivariate models that considered 36 baseline characteristics (age, sex, ethnicity, medical coverage, living alone, smoking state, history of cardiovascular disease, revascularization, left ventricular hypertrophy, dizziness when standing up, depression, systolic and diastolic blood pressure, heart rate, laboratory panel, use of aspirin, statins and non-steroidal anti-inflammatory agents, number and type of antihypertensive drugs, and number of drugs for other diseases) and defined for each patient the baseline risk of the event of interest (primary endpoint, all-cause mortality, treatment-dependent adverse events), and that reached under IT or ST. They considered the absolute benefit (absolute risk reduction of the incidence of the composite primary endpoint, and of all-cause mortality), as well as excess incidence of adverse events of interest (hypotension, syncope, bradycardia, electrolytic abnormalities, acute kidney failure, traumatic falls) of IT compared with ST, as a function of the baseline risk of included patients. Absolute baseline risk at 3.26 years (average follow-up of the study) evidenced a wide distribution, with 10% and 90% percentiles of 2.4% and 14% for the primary endpoint, 0.8% and 8.5% for all-cause death and 2% and 10.2% for treatment-dependent adverse events. Baseline factors more strongly associated with greater risk were older age, kidney dysfunction and history of cardiovascular disease.

The absolute magnitude of benefit (risk reduction with IT compared with ST) increased with baseline patient risk: the greater the baseline risk, the higher the difference between risk with IT and ST. The absolute risk difference between IT and ST was divided into tertiles. For example, for the primary endpoint, the lowest tertile corresponded to an absolute benefit (absolute risk reduction with IT compared with ST) between 0.5% and <1.5%; the middle tertile to a risk reduction between 1.5% and <2.5% and the highest tertile to a risk reduction between 2.5% and 9.6%.

Tertiles were also established for the increase in the risk of adverse events: the lowest tertile corresponded to an absolute risk increase between 0.06% and 2.6%; the middle tertile to an increase between >2.6% and 3.8%, and the highest tertile to an increase between >3.8% and 8.2%. There was a strong correlation between absolute benefit in endpoint reduction and increased risk of adverse events with IT and ST.

This means that the greatest benefit was associated with greater risk of adverse events and the lowest benefit with the lowest risk. Two-thirds of patients with high predicted benefit also had high risk of adverse events, while two-thirds of patients with scarce benefit also had low risk of adverse events. However, it is worth noting that the incidence of serious adverse events was similar in both arms, and that those most frequently encountered in the IT arm were generally mild and transient.

The other analysis is about the indication of implantable cardioverter defibrillator (ICD) for primary prevention in patients with reduced left ventricular ejection fraction (LVEF), which as we know, is class I recommendation for clinical practice guidelines. But we also know that this is, by far, one of the less indications fulfilled in daily practice. In fact, guidelines themselves invite to adequately select patients, although they do not provide practical recommendations for this selection. An interesting analysis was carried out by the authors of the MADIT-II, MADIT-CRT, MADIT-RIT, and MADIT-RISK studies. Let us recall that the MADIT-II study tested ICD plus optimal medical therapy (OMT) vs. OMT in patients with LVEF $\leq 30\%$; the MADIT-CRT study tested ICD vs. ICD combined with resynchronizer (CRT) in patients with LVEF $\leq 30\%$; the MADIT-RIT study tested different electrical cardioversion algorithms in patients with ICD/CRT; and the MADIT-RISK study evaluated a predictive multivariate model of arrhythmic events and adequate and inadequate electrical therapy in patients similar to those of the MADIT-II study.

The authors considered the 4503 patients with ICD included in the 4 studies mentioned above as a derivation cohort, and defined independent predictors of sustained ventricular tachycardia (VT), with heart rate ≥ 200 bpm (registered, monitored or treated with ICD), or ventricular fibrillation (VF). They thus built a predictive score of VT/VF. On the other hand, they defined another score with the independent predictors of non-arrhythmic death (not due to VT/VF). Finally, they generated a cross tabulation of both scores, thus defining a third score, which describes the expected benefit of ICD. The score was validated with the population of the RAID study that tested the benefit of adding ranolazine for primary prevention in patients with ICD/CRT.

Mean age was 64 years and 24% were women. Sixty percent of patients had an ICD and 40% an ICD-CRT. Two-thirds of the patients had coronary etiology and mean LVEF was $25 \pm 6\%$. The 8 independent predictors of VT/VF considered to build the respective score were LVEF $\leq 25\%$, atrial arrhythmia, heart rate > 75 bpm (each adding 1 point), male sex, age < 75 years, SBP < 140 mmHg, previous non-sustained VT and history of AMI (each adding 2 points). The highest attainable score was 13, and patients were dichotomized into low (< 7) or high (≥ 7) score.

The variables used to build the predictive score of

non-arrhythmic death were diabetes, NYHA functional class ≥ 2 (each adding 1 point), age ≥ 75 years, LVEF $\leq 25\%$, atrial arrhythmia, body mass index < 23 kg/m² (each adding 2 points) and use of ICD/CRT (deducted 1 point). The maximum score was 10, and patients were dichotomized into low (< 3) or high (≥ 3) score.

Based on belonging to each category in both scores, a benefit score with the use of ICD was built, which ranged between 0 and 100, and could be calculated with a table or online. The score considered three strata. The first was between 0 and 25 and corresponded to a low expected ICD benefit, which occurred when the VT/VF score was low and that of non-arrhythmic death was high; it implied 11% risk of VT/VF vs. 13% risk of non-arrhythmic death at 3 years. In the second, which was between 25 and 75, the expected benefit was intermediate, that is, both scores were low (the score ranged between 25 and 50) or high (the score ranged between 50 and 75). In this case, the risk of VT/VF was higher than that of non-arrhythmic death (16% and 11%, respectively), the difference between both was about 5% at 3 years. Finally, the expected benefit with the use of ICD was high when the VT/VF score was high and that of non-arrhythmic death was low. According to the model, in this stratum, the 3-year risk of VT/VF was 20%, and that of non-arrhythmic death only 7%. Predictive scores of severe arrhythmia and non-arrhythmic death were submitted to internal and external validation, with C indices (areas under the curve) around 0.70 in all cases.

For a long time, under the logic of Evidence-based Medicine, results from randomized studies were considered as absolute: if the result is favorable, the tested intervention is applicable to all similar study patients; if it is not, it is not applicable to anyone. Subgroup analyses (except those prospectively defined) have been strongly discouraged, due to the danger of false positives (as a result of multiple comparisons) and false negatives (for lack of adequate power to detect significant differences with low number of observations). But this idea that an intervention tested in 100 benefits 100 or 0 does not seem to get along with the aphorism that “there are no diseases, but sick people”, which finally finds its channel in the concept of personalized Medicine or Precision Medicine.

Therefore, in his daily practice, the physician finds himself tugged by what appear to be two contradictory trends: either accept that an indication encompassing all patients is derived from the “global result” of the randomized study, with a similar benefit in all cases (defined by the relative risk reduction with respect to the comparator), or take into account, especially when the decision is more costly in economic terms or risk of adverse events, that there can be differences of magnitude in the relative effect in different subgroups defined by a diverse pattern of covariates, or that with equal relative risk reduction, there is more to gain when the baseline risk is higher because it entails greater absolute risk reduction.

The two studies we commented go along this line. In the SPRINT study analysis, we should not disregard that the more intensive treatment has some advantage with respect to the standard treatment. However, it is clear that the absolute benefit is higher with greater baseline risk; greater risk of adverse events should not be a limitation, as these are generally mild and transient. Benefit and risk values should not be taken “literally” (they originate from models that might have been different, or taking into account other variables), but as a message about the importance patient baseline conditions have at the time of expecting results. Similarly, the analysis of the MADIT studies can help us at the time of deciding an ICD implantation, beyond LVEF, based on the risk of predominantly arrhythmic death, compared with similar risks of arrhythmic death and death for progressive heart failure. In no case is ICD implantation discouraged, but it is true that, with medical coverage and resource limitations, it is important to be able to discriminate those cases in which the ICD is more strongly indicated. Do we find any limitation in the analysis? Yes, that the studies considered date from an era before the incorporation of sacubitril/valsartan and gliflozins to the gold standard treatment of heart failure with reduced LVEF. Further observational analyses (in the absence of randomized studies) seem necessary to finish defining the benefit of ICD in this context.

Conflicts of interest

JT is deputy director of the Argentine Journal of Cardiology