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Three relevant studies regarding antihypertensive treatment

Blood Pressure Lowering Treatment Trialists Collaboration. Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis. **Lancet 2021;398:1053-64. doi: 10.1016/S0140-6736(21)01921-8**.

Chow CK, Atkins ER, Hillis GS, Nelson MR, Reid CM, Schlaich MP et al. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines vs. standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. **Lancet 2021;398:1043-52. doi: 10.1016/S0140-6736(21)01922-X**.

Blumenthal JA, Hinderliter AL, Smith PJ, Mabe S, Watkins LL, Craighead L et al. Effects of Lifestyle Modification on Patients With Resistant Hypertension: Results of the TRIUMPH Randomized Clinical Trial. **Circulation 2021;144:1212-26. doi: 10.1161/CIRCULATIONAHA.121.055329.**.

We recently read three publications on antihypertensive treatment, a large meta-analysis and two randomized trials, which we comment on in the next lines.

Although it is clear that hypertension (HTN) implies an increased risk of major cardiovascular events throughout the whole age range, some discrepancies and doubts persist regarding the behavior in elderly patients. It is true that previous meta-analyses have indicated benefits derived from treatment in older patients, but in general a cut-off value of 65 years has been considered, and we do not have precise data on groups with narrower age limits. Elderly patients have been underrepresented in large randomized studies, and only the HYVET study specifically included patients aged 80 years or older, but with systolic blood pressure (SBP) ≥160 mm Hg. The discussion about a J-curve for SBP in relation to the incidence of events, and the evidence about a decrease in blood pressure (BP) values in the last years of life, when this incidence is higher, have often raised doubts about the SBP limits that should be considered to establish antihypertensive treatment, and it is common (as stated in several practice guidelines) to recommend that no attempt should be made to reduce SBP below 150 mm Hg.

The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) has been carried out by the principal investigators of all major randomized clinical trials of pharmacological HTN treatment. On this occasion, it presents a meta-analysis of individual data from 51 randomized studies with 358 707 participants. The aim of this study was to evaluate the response to treatment according to age and baseline blood pressure values. The primary endpoint was the incidence of a composite of fatal or non-fatal stroke, fatal or non-fatal acute myocardial infarction (AMI) and heart failure leading to hospitalization or death. "Intervention" was considered as active treatment in studies that compared drugs with placebo, more intense treatment when comparing treatment strategies of different magnitude, and treatment that achieved the greatest blood pressure drop when comparing different drugs. Regarding age, patients <55 years were considered, and then increasing intervals of 10 years (55-64 and successive) until reaching ≥85 years. For SBP, the following categories were considered: <120 mm Hg, and then increasing intervals of 10 mm Hg (120-129, and successive) until reaching ≥ 170 mm Hg; and for diastolic BP (DBP), the baseline interval was <70 mm Hg, with increasing intervals of 10 mm Hg (70-79, and successive) until reaching ≥110 mm Hg.

Twelve per cent of patients were <55 years old, 35.8% were between 55 and 64 years, 35.8% between 65 and 74 years, 15.1% between 75 and 84 years and 1.3% were older. As age increased, the prevalence of female gender, atrial fibrillation, peripheral vascular and cerebrovascular disease increased. Also, SBP was higher and DBP lower. The use of diuretics and anticoagulants was greater; and that of beta-blockers, anti-platelet agents and lipid-lowering drugs was lower. Median follow-up duration decreased with age, from 4.5 years in those younger than 55 years to 2.8 years in those ≥85 years. For each 5 mm Hg drop in SBP, the reduction in the incidence of the primary endpoint was greater in the youngest group, with a HR of 0.82 in those <55 years, 0.91 in each of the following 3 intervals and 0.99 in those ≥85 years (p value for interaction 0.05). However, as the incidence of major events increased as age progressed, the absolute reduction in events was greater in older ages (from 1.5% in those <55 years to 2.6% in those ≥85 years, p value for interaction 0.024). The same trend was evidenced for each of the components of the primary endpoint, and also when a decrease in DBP of 3 mm Hg was considered. As the older age groups were less numerous, their estimation of relative and absolute risk reduction was less precise. In a next step, the effect of lowering SBP by 5 mm Hg or DBP by 3 mm Hg was evaluated within each age range, according to baseline values of SBP (from <120 to ≥170 mm Hg) or DBP (from <70 to ≥110 mm Hg), and no heterogeneity was found in the effects; the benefit was similar in each age interval, for each of the SBP or DBP categories considered.

In a previous publication (Rev Argent Cardiol 2021; 89: 166-175) we commented on another meta-analysis of individual data performed by the same collaborative group we present today, which indicated that the relative reduction of major cardiovascular events was independent of baseline SBP, even with initial values <120 mm Hg. The conclusion was that perhaps we should consider routine antihypertensive treatment beyond the purely hemodynamic effects on blood pressure, and contemplate a global cardiac and vascular protective action. The first analysis revealed that antihypertensive treatment should be taken into account even in supposedly normotensive patients, especially if justified by the overall cardiovascular risk. With the publication that we bring up today, the authors take another step in the same direction. Now, age is the barrier to pull down as a criterion for establishing BP cutoff values to start treatment, or the goal to be achieved. Most practice guidelines recommend treating patients older than 80 years only if SBP values are above 150-160 mm Hg. But this vast meta-analysis of individual data, with almost 59 000 patients aged at least 75 years, and almost 4800 aged at least 85 years, comes to question this indication. It is true that the relative risk reduction is low between 75 and 84 years (HR 0.91), ¡but it is the same as between 55 and 64, or between 65 and 74 years!, added to the fact that because the absolute risk is greater in older patients, the reduction of events is more marked. In patients ≥85 years of age, in whom relative risk reduction is almost non-existent (HR 0.99), the absolute risk reduction is also the highest, with a confidence interval ranging from a reduction of 5.2% to an increase of 0.1%. And coming back to the previous meta-analysis, it is shown that there is no difference in the effect according to baseline BP in any of the age ranges considered. Do age considerations disappear and should we indicate treatment in a nonagenarian with BP 130/80 mm Hg? It is clear that frail elderly patients, institutionalized patients, and those with a high burden of concomitant diseases have not been included or incorporated in very small numbers in randomized trials. In them, the prevalence of orthostatic hypotension, diabetes and renal failure is much higher; and these are the most exposed patients to present adverse events with the treatment. Probably some of them closely followed-up and with not very ambitious pressure objectives, could paradoxically obtain the greatest benefit. In conclusion, and taking both meta-analyses into account, age alone should not be a criterion for tolerating high blood pressure levels; the general condition (history, cardiovascular disease, comorbidities, frailty) is what should guide the blood pressure goals and the choice of drugs in each patient.

The second publication refers to a randomized study that explored the strategy of a polypill in the context of hypertension. There was non-definite prior evidence from open-label or small studies about the advantage of combining quarters or halves of the usual doses of antihypertensive drugs in a pill compared to monotherapy with any of these drugs. The QUARTET study tested the strategy of using a single capsule with quarter doses of four different antihypertensive drugs vs. monotherapy. The four drugs that made up the so-called quadpill were irbesartan 37.5 mg; amlodipine 1.25 mg; indapamide 0.625 mg and bisoprolol 2.5 mg. The monotherapy was irbesartan at a dose of 150 mg, in a capsule indistinguishable from the previous one which also contained placebos so that the number of components was the same as in the quadruple pill. The study included: a) patients without prior treatment, with office-based measurements of SBP between 140 and 179 mm Hg, and/or DBT between 90 and 109 mm Hg, or with values in 24-hour outpatient monitoring of SBP ≥135mm Hg and/or DBP ≥85 mm Hg, measured in the last 12 weeks; or b) patients already on monotherapy with in-office-based measurements of SBP between 130 and 179 mm Hg, and/or DBP between 85 and 109 mm Hg, or with values in 24-hour ambulatory monitoring of SBP ≥125mm Hg and/or DBP ≥80 mm Hg measured during the last 12 weeks. Blood pressure determinations were made at the start, at 6 and 12 weeks, with an automated BP device in the office (1 in the presence and then 3 in the absence of the investigator) and with 24-hour ambulatory monitoring. If at 6 weeks office-based BP was >140/90 mm Hg, amlodipine 5 mg could be added; the addition of more medication was left to the discretion of the treating physician. At 12 weeks, the participants were invited to a one year extended follow-up, with blind maintenance. The primary endpoint was the change in the mean value of 3 office-based SBP measurements, with the automated device and the investigator out of the room. Secondary points were the changes in mean SBP at one year, in mean DBP at 12 weeks and one year, and the proportion of patients who in both groups reached BP values <140/90 mmHg and 120/80 mm Hg, as well as variations in ambulatory monitoring. A total of 650 patients was considered sufficient to demonstrate a 4 mm Hg reduction in the mean SBP automatically measured at the office in the absence of the investigator with the quadpill. Finally, 591 participants were included, 300 in the intervention group and 291 in the control group, with a mean age of 59 years, 54% previously untreated and 46% on monotherapy before inclusion. Mean office-based BP was 141/85 mm Hg with the investigator absent and 153/89 mm Hg with him present.

At 12 weeks, mean BP was 120/71 mm Hg in the intervention group and 127/79 mm Hg in the monotherapy group, with mean differences of 6.9 mm Hg for SBP and 5.8 mm Hg for DBP, both statistically significant. This occurred even when in the intervention group 15% of the patients received additional medication (9% amlodipine) compared with 40% in the control group (33% amlodipine). The percentage of patients who reached values <140/90 mm Hg was 76% with quadruple therapy vs. 58% with monotherapy (RR 1.3; 95% CI 1.2-1.5) and the percentage of patients that reached values <120/80 mm Hg was 46% vs. 26% (RR 1.75; 95% CI 1.38-2.22). Mean SBP in the 12-week ambulatory monitoring was 7.5 mm Hg lower in the quadpill group. In 71% of cases, patients had a 12-month extended follow-up. The different studies replicated the 12-week findings. The incidence of severe adverse events at 12 weeks was 3% in the quadruple therapy group vs. 1% in the monotherapy group. There was no significant difference in the rate of medication discontinuation (4% vs. 2.4%), but the incidence of SBP <100 mm Hg and heart rate <50 bpm was higher (6% vs 2.5% and 12.4% vs 0.4%, respectively, in both cases with p <0.01). There were, however, no reports of syncope, falls, or acute kidney injury.

One of the critical problems that arises with HTN is the low proportion of diagnosed patients, and among them, that of adequately treated patients. Lack of awareness about the risks posed by HTN, therapeutic inertia and lack of adherence to treatment play a fundamental role. In this sense, the combination of two or three medications in a single pill has shown to improve adherence (by reducing the number of pills to be taken) and BP control. By using low doses, the incidence of adverse events associated with the usual doses is also prevented. However (another demonstration of inertia) monotherapy remains the approach of choice for most clinicians. The QUARTET study is novel in that it is the first to compare four drugs with just one. Here the problem of adherence linked to the complexity of the administration is not at stake (it is a pill in each group), and in fact it is not the endpoint of the study, but efficacy and safety. And clearly very low doses of 4 different drugs are much more effective than a standard dose of just one of them. Although the end point of the study is the decrease in BP, it is to be expected that with adequate follow-up the difference achieved in SBP and DBP will translate into a reduction in clinical events. The results achieved with such small doses are striking, revealing that attacking HTN by acting on different pathophysiological pathways with doses not considered in individual studies is much more effective than using a single agent, with only one mechanism of action. A demonstration of the complex pathophysiology of HTN (and let's think if the same does not happen in pulmonary hypertension or heart failure, where combined therapies are also recommended compared to the traditional approach with a single drug). Unlike other studies, and perhaps precisely because of the use of so many agents, the incidence of adverse events is not lower with quadruple therapy, and the appearance of significant bradycardia in more than 10% of cases reveals the beta-blocker, even when the dose is only a quarter of the usual. And, beyond the very auspicious results, and if we refer to adherence, it is clear that at the moment we do not have a "quadpill" in the real world, and that, if we want to replicate the results of the study, we will have to instruct our patients to divide the pills and combine them "by hand", thus going back to the beginning of the comment. We also have to wonder if the differences would have been of the same magnitude when comparing the quadruple combination of quarter doses with one of two medications by half (and which ones?).

Resistant hypertension (RH) is defined as the sustained presence of SBP values ≥ 130 mm Hg or DBP ≥ 80 mm Hg despite treatment with at least 3 antihypertensive drugs, one of which is a diuretic. This condition is estimated to affect 5% of the general population and 20-30% of hypertensive patients (an even higher proportion if they have diabetes or chronic kidney failure). Different therapeutic alternatives have been proposed, from the addition of anti-aldosterone agents to renal denervation. Something that is striking is the lack so far of studies of adequate dimensions and follow-up evaluating the effect of lifestyle modifications on RH.

The TRIUMPH study compared two strategies in patients with RH: the usual diet and exercise prescription, vs. a strategy where compliance with both was supervised in the context of a rehabilitation program. Patients with RH with SBP ≥130 mm Hg or DBP ≥80 mm Hg despite treatment with at least 3 antihypertensive drugs (one of them a diuretic) or with lower values of SBP and DBP, but with the requirement of at least 4 drugs were included in the study. They should have a body mass index (BMI) ≥25 kg/m2, a glomerular filtration rate ≥40 mL/min/1.73m2, and lack of regular physical activity. Patients were randomly assigned in a 2: 1 ratio to an intensive strategy or usual medical management. The first consisted of receiving instructions from a nutritionist on the DASH diet, with caloric and sodium restriction (<2.3 g daily), plus a weekly 45-minute group counseling with a clinical psychologist to receive advice and motivation on modifications in diet and lifestyle, and supervised physical activity 3 times a week for 30 to 45 minutes, at 70% to 85% of maximum heart rate according to weight and age. The usual treatment consisted of a single one-hour session with a health trainer and the delivery of written material with the same diet and exercise indications that were established in the intensive group. The primary endpoint was the change in SBP evaluated in the office, for which 4 BP measurements were taken after 5 minutes of sitting, discarding the first measurement and recording the average of the other 3, with the procedure repeated in three sessions throughout the first 3-4 weeks of the study. In this way, a baseline value was obtained and compared with that measured at 4-month treatment. Changes in office-based DBP, SBP and DBP measured in 24-hour ambulatory monitoring, and changes in baroreflex sensitivity, heart rate variability, pulse wave velocity, and flow-mediated vasodilation were secondary endpoints.

Among 266 patients submitted to initial screening, 140 were finally included: 90 assigned to intensive strategy and 40 to usual treatment. Mean age was 63 years, and average BMI 36 kg/m2. A third of patients had diabetes, and a quarter had chronic kidney failure. Mean BP was 139/79 mm Hg in the office and 133/71 mm Hg in ambulatory monitoring; the average number of antihypertensive drugs they received was 3.5. In the intensive group, the attendance to classes and exercise sessions was fulfilled by approximately 90% of patients. Adherence to drug treatment exceeded 90% in both groups. In the intensive group, the increase in exercise capacity and weight loss was significantly greater (6.9 kg vs 3.9 kg). At the end of the study, there was a decrease in SBP in both groups, greater in the intensive lifestyle change group: 12.5 mm Hg, compared with 7.1 mmHg in the usual approach group, with a difference between the two of 5.4 mm Hg (95% CI 1.2-9.7). There was also a difference in the reduction of DBP (2.2 mm Hg, 95% CI 0-4.4). At the same time, ambulatory BP monitoring showed a decrease in daytime and nocturnal SBP and in daytime DBP, with a trend for nocturnal DBP in the intensive strategy group, but no changes in the usual approach group. Baroreflex sensitivity, heart rate variability, and flow-mediated vasodilation showed more favorable changes in the intensive treatment group.

A first observation that quickly arises has to do with the failure noted by the authors of randomized studies to explore an intensive lifestyle change in the context of RH, to the point that this is the first publication in this regard. And this, certainly, must have to do with the fact that when it is established that a patient has RH, and is included in a clinical trial to test an intervention or a drug, there are things that are taken for granted. ¿How will RH be considered, if the patient is overweight, sedentary and eats with salt? It is unthinkable! In the long journey of treating hypertension, it is assumed that the initial steps have been taken, and that when we arrive at RH it is because what should be done initially has failed. Well, this study suggests that it is not so; that there is an opportunity for improvement and that which is believed is sometimes not supported by reality. The message aims to demonstrate that simple, foundational measures are effective even in patients treated with more than 3 drugs. Should we think then that these patients have true RH, or are they "pseudo-resistant"? This finding should be noted on the credit of the study. For the debit: the initial values of BP meet the definition of RH, but it is also true that they do not seem excessively high, which favors that almost 60% of the intensive strategy group, and almost 40% of the usual treatment group reach values <130/80 mm Hg. Only 5 patients had baseline SBP values >160 mm Hg.

And a reflection, at the risk of not complying with what "should be said." ¿How not think about dyslipidemic and diabetic people who do not respect their diet, patients with heart failure who eat with salt, patients with chronic obstructive pulmonary disease or coronary heart disease who continue to smoke? At the very origin of all these pathologies, as in hypertension, there are environmental and genetic factors, and the much-cited "lifestyle". And it is true that, as we can see, lifestyle can make us sick or healthier. But it is not a minor fact that certain behaviors are often sustained because, beyond the risk that appears in the future, they generate immediate satisfaction or gratification. Perhaps our linear thinking ("this is going to hurt you, you must abandon it; this is going to help you, you must carry it out") does not take into account other variables, desire, pleasure, and finally addiction. It is clear that not everybody fails to comply out of ignorance; many times they knowingly transgress the recommended limits or do not have "healthy" behaviors. Different studies have shown that lifestyle changes are initially beneficial; the issue is how long they are sustained, and how many of those who started persist in them. In the TRIUMPH study, meetings with psychologists, nutritionists and supervised physical activity were necessary; this is an investment of time and resources that must be sustained over time, added to the fact that they worked with a population willing to embark on the adventure. Rather than being negative these lines want to invite us to consider the value of social determinants (what we may eat, how much time we have for rest and recreational physical activity, which is not the same as that developed in the work, see again Rev Argent Cardiol 2021; 89: 166-175) and initial education, to generate lasting habits without needing to force changes when damage is present and harmful wishes and behaviors are already ingrained.

Problems that keep us awake

Ai S, Zhang J, Zhao G, Wang N, Li G, So HC et al. Causal associations of short and long sleep durations with 12 cardiovascular diseases: linear and nonlinear Mendelian randomization analyses in UK Biobank. **Eur Heart J 2021;42:3349-57.doi: 10.1093/eurheartj/ehab170.**

Mahmood A, Ray M, Dobalian A, Ward KD, Ahn S. Insomnia symptoms and incident heart failure: a population-based cohort study. **Eur Heart J 2021;42:4169-76. doi: 10.1093/eurheartj/ehab500.**

Beyond the traditional cardiovascular risk factors, a series of less considered conditions also imply a greater probability of an adverse cardiovascular evolution. Among them are sleep disturbances. Two new publications are added to the available evidence.

The association of sleep duration with cardiovascular disease is known. Excessively short or prolonged sleep duration associated with a higher risk of events is described in J or U curves. However, different confounders can be pointed out (employment, depression, comorbidities) that may be largely responsible for this association. On the other hand, reverse causality cannot be excluded: sicker people can sleep less than normal, the unemployed more; so that it is not the duration of sleep that defines the presence of disease but vice versa. Mendelian randomization studies are a tool to exclude confusion and reverse causality. They are an example of an instrumental variable, a topic that we referred to in Rev Argent Cardiol 2021; 89: 372-381. They start from the idea that each of us receives his/her genetic endowment randomly. This endowment is present in us from conception, and therefore does not depend on the environment, socioeconomic conditions, etc. If there are certain genes linked to a defined exposure, but not to the event itself, the fact that those genes are part of our genome implies that we have been randomly assigned to that exposure. And if it is clearly demonstrated that those with these genes more frequently present a certain event or outcome, that implies that the exposure is linked to the event beyond any confounder.

The study we are commenting on comes from the British Biobank registry, which we have already referred to on other occasions. It recruited more than 500 000 participants between 40 and 69 years of age. In this case, the information of 404 044 individuals, including the data of self-reported hours of sleep per day (rounded to the nearest integer, and including naps), and the genetic report on 78 single nucleotide polymorphisms (SNP) known to be linked to sleep duration, was used. Patients were categorized according to the duration of sleep reported as short (≤6 hours), normal (7-8 hours) or prolonged (≥ 9 hours). Those with duration <4 hours or >11 hours were excluded from the analysis. With the genetic information, a score was built for each patient, adding the number of alleles linked to an increase in sleep duration. The association of the genetic score with the prevalence of different cardiovascular conditions was evaluated. Linear and nonlinear Mendelian randomization analyses were performed to identify the association of sleep duration as a continuous variable (defining the change in risk associated with a 1-hour increase in duration), and specifically the relationship of short and long sleep with cardiovascular health. All relationships were adjusted for age, gender, and hereditary components. Due to the fact that 12 different cardiovascular events were considered as the response variable, and to avoid the risk of false positives by multiple comparisons, each relationship with $p < 0.0042$ between the genetic score and a cardiovascular event was defined as significant.

Patients with normal sleep duration were younger, of better socioeconomic and educational level, lower body mass and deprivation indexes, and lower prevalence of established cardiovascular disease than those with short or long sleep. The genetic score showed a strong association with sleep duration as a continuous variable. The genetic score was divided into quartiles. The lowest quartile was taken as reference, and in relation to this category, in the linear analysis, those with the highest quartile (determining the longest sleep) had 14% and 4% lower chance of presenting pulmonary embolism, and hypertension (HTN), respectively, and 7% less chance of presenting atrial fibrillation or chronic coronary heart disease. The OR for each extra hour of sleep duration ranged from 0.51 for pulmonary embolism to 0.81 for HTN. But, in addition, a non-linear analysis found a significant L relationship between genetically determined sleep duration and the presence of HTN, cardiomyopathy, acute myocardial infarction (AMI) and chronic coronary heart disease. The specific genetic prediction of short sleep was significantly associated with HTN, coronary heart disease, chronic ischemic disease and pulmonary embolism, and showed a tendency to be associated with atrial fibrillation (AF). In contrast, no predictive association was seen of prolonged sleep with cardiovascular disease.

The second study refers to the association of insomnia with the incidence of heart failure. Insomnia symptoms are varied. They include difficulty in falling asleep, difficulty staying asleep, waking up early, and the feeling that sleep has been unrefreshing. Up to 50% of middle age people and 75% of elderly individuals report having some of these symptoms. Different observational studies have indicated the association of insomnia with a higher incidence of AMI, stroke, AF, and mortality. A publication that demonstrates its association with the incidence of heart failure has been now added.

Data from a national survey that is carried out in the United States of America every 2 years, in which people aged 50 years or older are questioned about health, employment, income and family structure were considered. The analysis was based on surveys conducted from 2002 (the first survey that asked participants about insomnia symptoms) to 2018. Only responses from those free of baseline heart failure were considered. The emergence of heart failure was defined during follow-up, by self-report or by reports of treating doctors or relatives in the event of the condition being fatal. They were specifically questioned about each of the cited symptoms. The options "most of the time", "sometimes" and "rarely or never" were raised. When the answer was "most of the time" for the questions about difficulty falling asleep, waking up during the night, and waking up too early with inability to go back to sleep, and "rarely or never" when it was asked if the sleep was usually restful, it was interpreted that the symptom was present. The surveys from 2002 to 2016 were used to collect data on insomnia and those from 2004 to 2018 to define the incidence of heart failure.

Finally, 12 761 participants, with mean age of 66.7 years and 57.7% women, were included in the study. Among them, 38.4% acknowledged having at least one insomnia symptom: 23.4% one symptom, 8.8% two, 4.4% three, and 1.8% all four. The most frequent symptom was waking up during the night (25%), and the others ranged from 11.5% to 13.2%. At the mean follow-up of 16 years, 12.7% of participants developed heart failure. In the analysis of the relationship between insomnia and this incidence, statistical models were used that considered the presence of variables (age, gender, race, vascular risk factors, other pathologies, educational level, income, marital status, depression, level of cognition) that can be simply confounders, or in some cases given their temporal variation, also act as intermediary factors. The presence of insomnia symptoms showed a strong association with the outcome: the hazard ratio (HR) for the presence of one to four symptoms was 1.22, 1.45, 1.66 and 1.80, respectively. The lowest HR was the one corresponding to waking up during the night (1.14) and the highest the one related to a non-restorative sleep (1.25).

The first study should be celebrated by the amount of information collected, the power of the data and the complexity of the analysis. In principle, it demonstrates the association of genetically predicted sleep duration with the incidence of cardiovascular disease, beyond any confounding factor. There is a determining relationship between the two. But it is interesting to note that it is the few hours of sleep that are associated with a large part of the spectrum of the disease, from HTN to pulmonary embolism. There were already previous studies of Mendelian randomization that indicated the association of short sleep with cardiovascular disease, but only with some entities or in a global way. This analysis is accurate for each of the disease manifestations. And, on the other hand, the idea of the association with prolonged sleep falls, both in linear and non-linear analysis. The confounding factors, certainly depression among them, must be strongly linked to the unfavorable evolution. The second study, by other means, reaches a similar conclusion, with respect to a specific condition, heart failure. It adequately dissects the relationship between insomnia and pump failure, establishing a dose-response gradient between the number of manifestations and the outcome, and points out that whatever the isolated symptom, the risk is similar: the difference between the specific HR for each symptom is low. And it is remarkable how both studies complement each other: in the one of Mendelian randomization, it is regrettable that heart failure was not one of the studied manifestations of cardiovascular disease; on the other, how not ask ourselves about the data of sleep duration. Beyond defining insomnia (although we can clearly think it short), we do not know if there is recovery of some of the hours lost during the night with a nap, albeit brief, during the day.

Aside from speculation, we confirm the extraordinary influence that rest and restful sleep have on cardiovascular health. Neurohormonal activation, exacerbation of inflammatory phenomena and oxidative stress, increased heart rate and decreased variability, increased insulin and growth hormone resistance, and the burst of cortisol release, are all links between short sleep, insomnia, and cardiovascular disease. Regarding both articles, the reference to sleep apnea is missed, since, undoubtedly, it could explain a substantial part of what has been demonstrated, due to its strong relationship with the aforementioned mechanisms. And finally, the idea that, in the face of evidence, delving into the questioning about the quality of sleep of our patients, and certainly, resorting more frequently to the polysomnographic study and consultation with specialists could be beneficial for many of them. Meanwhile, advice on good sleep, concerning sleep hygiene, its conciliation and maintenance, can help combat what is acquired and inherited.

Frailty Predicts Cardiovascular Events

Damluji AA, Chung SE, Xue QL, Hasan RK, Moscucci M, Forman DE et al. Frailty and cardiovascular outcomes in the National Health and Aging Trends Study. **Eur Heart J 2021;42:3856-65. doi: 10.1093/eurheartj/ehab468**

Frailty is theoretically defined as a clinically recognizable condition of greater vulnerability as a result of decreased functional reserve associated with aging in multiple systems, thereby reducing the ability to cope with everyday or acute stressful factors. In the absence of a gold standard, frailty was operationally defined by Fried et al. in 2001 when three of the five phenotypic criteria that indicate compromised energies are met: exhaustion, poor grasp or grip strength, low walking speed (some consider low speed to get up), poor physical activity, and involuntary weight loss (4.5 kg in the last year). Different observational studies have shown that frailty is associated with a higher risk of cardiovascular complications and mortality. But in general, the frailest people have a higher prevalence of cardiovascular disease. The prognostic role of frailty regarding cardiovascular events in people without established pathology of this origin is still unknown.

In the study we are commenting on, 3259 participants, part of a prospective cohort study of people with Medicare, aged 65 years or older, were included in the study. At the time of inclusion, they had no history of known coronary artery disease or stroke. Baseline data (physical and cognitive capacity, daily life activities and variables referring to social, physical and environmental aspects) were collected in 2011. Self-care capacity and independence in household tasks and mobility, from just getting up from bed to being able to move outside the home were specifically evaluated. Memory, orientation, and executive ability were explored. A person was considered frail when he/she met at least 3 of the 5 domains described by Fried, pre-frail when they met one or two, and non-frail if none were present. The follow-up endpoint was a composite of all-cause death, AMI, coronary heart disease, stroke, and peripheral vascular disease, with follow-up censored when the first of these outcomes occurred. To avoid the problem of competitive risks, an endpoint that excluded mortality was also considered.

Among patients, 16% of the participants were considered frail, 37% pre-frail, and 47% non-frail. Compared with non-frail participants, the frail group was older (82 vs. 75 years), with a higher prevalence of women (68% vs. 55%), and with a higher prevalence of chronic diseases (2 or more in almost 90% vs. just under 48%). The prevalence of hypertension, diabetes, anxiety, depression was higher, as well as probable dementia (40% vs. 3.5%). In all cases, the pre-frail group presented intermediate values. In a mean 6-year follow-up, the age-adjusted incidence of the endpoint including mortality was 87.5% in frail, 68.6% in pre-frail, and 49.6% in non-frail patients. Age-adjusted all-cause mortality was 58.6% in the frail and 14.3% in the non-frail group. Each of the endpoint components had a greater incidence in frail than in pre-frail patients, and in the latter than in non-frail ones. In a multivariate model that considered age, gender, ethnicity, residence, income, body mass index, smoking, diabetes, hypertension, dependency and number of chronic diseases, frailty and pre-frailty were independent predictors of each outcome considered Thus, for the composite endpoint that included all-cause death, the HR (95% CI) was 1.77 (1.53-2.06) in frail patients, and 1.34 (1.21-1.49) in pre-frail patients. For the endpoint without considering mortality, the respective HRs were 1.59 and 1.29; and for all-cause death 2.70 and 1.64; statistically significant in all cases. The same occurred for each separate component: AMI, stroke, coronary or peripheral vascular disease.

The link between frailty and cardiovascular disease has been known for years. Different observational studies highlight two aspects of this connection: cardiovascular disease increases the risk of presenting frailty, and frailty is an independent predictor of poor outcome in patients with cardiovascular disease. And, precisely, it has been pointed out that many of the predictors or determinants of cardiovascular disease are also seen in frailty. Poor physical activity, poor nutrition, diabetes, hypertension, and smoking can increase the risk of both cardiovascular disease and frailty. Low-grade persistent inflammatory activation appears as an essential condition associated with (responsible for, consequence of) each of these factors. Now, this new study gives a twist and establishes that the relationship is bidirectional: not only does cardiovascular disease precede frailty, but (and after adjusting for the presence of these common factors that we mentioned) frailty predicts the onset of cardiovascular disease.

However, we can formulate some objections, not to refute these findings, but, perhaps, to think about a closer relationship. First, people with a history of diagnosed coronary artery disease or stroke were excluded from the study, but not those with peripheral vascular disease. This allows us to assume that patients with this pathology were part of the cohort, and therefore more predisposed to have other manifestations of vascular disease during follow-up. And, on the other hand, it is known that in people with frailty the prevalence of subclinical atherosclerosis is higher, which may have gone unnoticed; it is possible that precisely by virtue of older age, which increases the prevalence of silent symptoms, and inactivity that reduces the appearance of symptoms, many of these "fragile" patients already had presence of the disease. However, all this does not exclude the presumption of causality, although perhaps with association measures of lesser magnitude. It is clear that frailty, as an expression, cause or consequence of vascular disease is an adverse prognostic marker. To confirm its causal role in cardiovascular damage (which is a true prognostic factor), it should be shown that measures that combat it (physical activity, nutritional support, and cognitive stimulation) reduce it. But we think that even if this were not the case, facing the problem and seeking to mitigate it (the passage of years is irreversible) is imperative in an increasingly elderly population, and therefore, increasingly exposed to limitations in the end stage of life. And, on the other hand, if this were the case, should the treatment of risk factors be more aggressive in frail patients? Because there is the paradox that being the patients who could obtain the greatest benefit from intensive antihypertensive and lipid-lowering treatment, for example, they are the most exposed to presenting intolerance and complications.

Polypill with or without aspirin and its effect on primary prevention of cardiovascular disease: an individual data meta-analysis

Joseph P, Roshandel G, Gao P, Pais P, Lonn E, Xavier D et al. Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease: an individual participant data meta-analysis. **Lancet 2021;398:1133-46. doi: 10.1016/S0140-6736(21)01827-4.**

Different clinical trials have demonstrated that a combination of fixed doses of two or more antihypertensive drugs and a statin, with or without aspirin, (which in a single presentation is called polypill) are effective to reduce the risk of major cardiovascular events in primary prevention. However, some points (magnitude of the benefit, usefulness of aspirin, effect on some specific events or on certain subgroups) are not completely clear. An individual data meta-analysis of the 3 large trials testing this strategy vs. placebo: PolyIran, TIPS-3 and HOPE-3 was performed to answer these questions. The PolyIran trial (which as its name indicates was carried out in Iran) included 6838 patients with or without cardiovascular disease, who were assigned, in a pragmatic and cluster design to a polypill with hydrochlorothiazide 12.5 mg, enalapril 5 mg (or valsartan 40 mg), atorvastatin 20 mg and aspirin 81 mg, or basic treatment with blood pressure (BP) measurement and counseling on the management of risk factors. The TIPS-3 trial included 5712 patients without evidence of cardiovascular disease, but with an intermediate risk of events according to the Framingham score, who were randomly allocated in a double-blind fashion to a polypill with atenolol 100 mg, hydrochlorothiazide 25 mg, ramipril 10 mg and simvastatin 40 mg, with the addition of aspirin 75 mg and a monthly injection of vitamin D vs. placebo of each of these interventions in a 2×2×2 factorial design. Finally, the HOPE-3 trial compared in a 2×2 factorial design candesartan 16 mg and hydrochlorothiazide 12.5 mg vs. their placebos, and alternatively rosuvastatin 10 mg vs. placebo, in 12 705 patients without established cardiovascular disease but also at intermediate risk.

The meta-analysis here presented considered two strata according to the administration or not of aspirin. The aspirin stratum included the TIPS-3 patients allocated to the polypill and aspirin or the placebo of both, and all the patients of the PolyIran trial. The stratum without aspirin considered patients of the HOPE trial allocated to both active strategies (candesartan-hydrochlorothiazide and rosuvastatin) vs. both placebos to respect the polypill concept, and all the TIPS-3 patients. A total of 18 162 participants were included, half of them women, with mean age of 63 years. In 49.8% of cases, patients were hypertensive, 23.4% smokers or ex-smokers and 19.4% had diabetes. Mean systolic blood pressure (SBP) was 137.7 mmHg, mean LDL-cholesterol 121.7 mg/dL, and mean risk of events at 10 years according to the Framingham score was 17.7%.

The primary outcome of the study was a composite of cardiovascular death, acute myocardial infarction (AMI), stroke or any arterial revascularization procedure. An expanded outcome also included unstable angina and heart failure, and all-cause death was another endpoint. At a mean of 2.1 years, mean LDL-cholesterol was 22 mg/dL lower in the fixed-dose combination group and at 5 years mean SBP was 4.7 mmHg lower in the same group. At a median follow-up of 5 years, the primary outcome occurred in 3% of the intervention group and 4.9% of the control group (HR 0.62, 95% CI 0.53-0.73, p <0.001). The number needed to treat (NNT) to prevent an event was 52 during 5 years. The greatest magnitude effects occurred in relation to AMI, stroke and revascularization, in all cases with HR between 0.52 and 0.59, and 0.65, 95% CI 0.52-0.81 for cardiovascular death. There were no differences in all-cause death. In the aspirin stratum (8951) participants) the incidence of the primary outcome was 2.6% in the intervention group and 4.8% in the control group; the HR was 0.53 (95% CI 0.41-0.67) and the NNT at 5 years was 37. The main differences were found with respect to AMI, stroke and cardiovascular death, without differences in all-cause death. In the aspirin stratum (12 061 patients), the incidence of the primary outcome was 3.3% in the intervention group and 4.9% in the control group, with a HR of 0.68 (95% CI 0.57-0.81) and a NNT at 5 years of 66. The main differences occurred regarding AMI, stroke and revascularization, without difference in all-cause death.

The polypill effect was verified in the different subgroups analyzed. The absolute event reduction was greater at older age. Muscle pain was reported in 8% of cases, dizziness in slightly over 10% and dyspepsia in a third of cases. The incidence of hemorrhagic stroke, kidney dysfunction or fatal bleeding was ≤0.5%. There was slightly more digestive bleeding in the intervention group, but the difference (0.4% vs. 0.2%) did not reach statistical significance. In the control group, use of antihypertensive and lipid-lowering drugs at the onset of the study increased from 19.1% and 1.8%, respectively, at study onset, to 31.6% and 8.7%, respectively, in the last visit. In the intervention group, 72.1% of patients were receiving the combination strategy on the last visit.

This meta-analysis of individual data confirms the efficacy of an antihypertensive and a statin combination therapy, with or without aspirin, in primary prevention patients at intermediate cardiovascular risk. The results in terms of BP and LDL-cholesterol reduction were lower than expected, despite evidencing a significant reduction of clinical events. When the polypill concept was developed almost 20 years ago, the estimated reductions of risk factors and events were greater than finally verified. The rate of treatment abandonment (almost 30% in this meta-analysis) and the start of antihypertensive drugs in many patients of the control group may contribute to explain this phenomenon. Moreover, we should consider that the real risk of events was lower than expected by the risk scores used: in fact, a rate of 5% major events occurred in the control group at 5 years, compared with an estimated risk of 18% at 10 years by the Framingham score.

Another point that deserves to be highlighted is the analysis of strata with and without aspirin. The meta-analysis by Zheng et al published in JAMA in 2019 included a total of 13 trials that randomly assigned 164 255 participants in primary prevention to aspirin vs. control or placebo. Use of aspirin was associated with a significant reduction of 11% in a composite cardiovascular outcome and a NNT of 265 (absolute risk reduction of 0.38%) compared with 43% greater risk of severe hemorrhagic episodes, an increase of 0.47% absolute risk and a number needed to harm (NNH) of 210. Therefore, clinical practice guidelines do not consider the routine use of aspirin in primary prevention, but its benefit in patients at high ischemic risk and low hemorrhagic risk cannot be excluded. In the meta-analysis we comment here, for a similar incidence of the primary outcome in the control group with aspirin or without aspirin strata (4.8% and 4.9%, respectively), the incidence of events was lower in the polypill group with aspirin (2.6%) than in the polypill group without aspirin (3.3%), and the NNH for digestive bleeding was 554. An additional data to think that the idea of its universal administration should be abandoned, but also that of its absolute proscription.