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The dose of aspirin should be different according to body weight, concludes a meta-analysis of individual data

Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JF, Roncaglioni MC, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. **Lancet 2018;392-:387-99. http://doi.org/cstg**

Aspirin reduces almost completely platelet thromboxane synthesis by the irreversible inhibition of cyclooxygenase 1. However, the reduction of vascular events is not of the expected magnitude according to this inhibition. We know that in the presence of a high body mass index (BMI) there is an increase in platelet synthesis and turnover. Aspirin is deacetylated in the intestinal wall, the red blood cells, and the liver whose masses increase in relation to the increase in BMI. In addition, the higher the BMI, the greater the mass of albumin, hemoglobin and fibrinogen, which are proteins acetylated by aspirin. In conclusion, the bioavailability of aspirin may decrease in the presence of weight gain, and this may translate into a decrease in therapeutic efficacy. A meta-analysis of individual data from 9 primary cardiovascular event prevention and 5 secondary stroke prevention studies sheds more light on the dose relationship of aspirin, body weight and events.

Among the primary prevention clinical trials, 7 explored the use of low dose (75-100 mg daily) and 2 the use of high dose (≥300 mg daily) aspirin vs. control. In the meta-analysis, the OR for the incidence of cardiovascular events was 0.77 (95% CI 0.68-0.87) in patients weighing <70 kg, and 0.94 (95% CI 0.86-1.04) in those weighing ≥70 kg. The ability of low doses to reduce the incidence of events decreased with the increase in body weight, with an OR of 0.75 (95% CI 0.65-0.85) for those weighing 50-69 kg. In those weighing <50 kg there was no significant effect, and there even seemed to be an excess mortality risk that disappeared when dosage was discontinued from patients with BMI <18.5 kg/m2. Low doses showed a reduction in the incidence of stroke only in women, but the difference disappeared when adjusting for body weight. Body weight and smoking were strong predictors of the effect of low doses of aspirin on the incidence of cardiovascular events: the effect was significant in non-smokers weighing <70 kg, significant but of lower magnitude in those who had only one of both conditions, and not significant in those who had both. A similar trend occurred in men and women, diabetics and non-diabetics, and age above or below 70 years. There was no beneficial effect of low dose aspirin with weight >70 kg, and on the contrary, excess cardiovascular events were observed (OR 1.33, 95% CI 1.08-1.64). The excess risk of bleeding that occurs with the use of aspirin was lost in patients weighing >90 kg. A similar result was found for secondary stroke prevention studies: aspirin at doses of only 50 mg daily was associated with risk reduction solely in patients weighing <70 kg.

In contrast, the evaluation of high doses of aspirin showed beneficial effects (reduction of events and even mortality) only in cases with high body weight. Doses of 325 mg showed a significant 17% reduction of events in patients weighing ≥70 kg, and doses of at least 500 mg, a significant reduction of 55% in patients weighing at least 90 kg.

As a consequence of the available information, the authors developed an administration scheme that adapts the dose based on body weight to achieve the greatest effectiveness: 75-100 mg daily in patients weighing between 50 and 69 kg, 300-325 mg daily for those weighing 70-89 kg and ≥500 mg for those weighing ≥90 kg. The risk of sudden death doubled in patients who received a higher dose of aspirin than that suggested in this scheme according to their weight.

The use of aspirin in primary prevention is still being discussed. A 2009 meta-analysis with 95,000 patients established a relative reduction of approximately 12% for a combined endpoint of cardiovascular death, acute myocardial infarction and stroke, at the expense of 30% increased risk of bleeding. Another meta-analysis of 2012, with more than 100,000 patients confirmed the reduction of events, especially of AMI, but again with a significant increase in bleeding. Therefore, the indication of aspirin in this context differs among practice guidelines, and it is generally assumed that it depends on the balance between ischemic and hemorrhagic risk.

This analysis challenges a universally accepted prescription: that of a single dose of aspirin for all patients, regardless of their condition. It is interesting how with some medications we naturally incorporate the idea of a weight-adjusted dose: for example, antibiotics and beta-blockers when we refer to oral medications, inotropes when we use intravenous medications. This has not happened with other pharmacological treatments. The finding of this meta-analysis regarding the lack of effect of low dose aspirin in primary prevention in almost 80% of men and 50% of women weighing >70 kg places at the center of debate the conclusions reached so far about the role of aspirin in this scenario. Would the study results be similar if the dose were adjusted to weight, or would a more remarkable reduction of cardiovascular events with lower incidence of bleeding be achieved?

It seems clear that using the same dose in all patients is not the approach that will lead us to the best

result. But it is also true that this meta-analysis includes many studies dating from times when patients' profile and co-treatment were different, and that the dosage scheme based on weight should be evaluated prospectively.

Trajectory of left ventricular ejection fraction, its determinants and meaning

Lupon J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, Lopez-Ayerbe J et al. Dynamic Trajectories of Left Ventricular Ejection Fraction in Heart Failure. **J Am Coll Cardiol 2018;72:591-601. http://doi.org/csth**

Left ventricular ejection fraction (LVEF) is one of the strongest prognostic determinants in the context of heart failure (HF). Most pharmacological and non-pharmacological therapeutic measures are taken according to the value of LVEF. In general, in cohort studies of patients with HF, LVEF is assessed at the beginning of follow-up. In order to define its influence on the diagnosis, the value considered is the initial one. We know, however, that LVEF can vary over time, as a consequence of the natural history of the disease, by the exacerbation or attenuation of factors that determine it, and as a response to treatment. In fact, the most recent classification of chronic HF, that of the European Society of Cardiology and the Argentine Society of Cardiology, considers Heart Failure with Reduced Ejection Fraction (HFREF), when LVEF is <40%; Heart Failure with Preserved Ejection Fraction (HFPEF), when LVEF is >50%; Heart Failure with Mid-Range Ejection Fraction (HFmrEF), when LVEF is between 40% and 50%, and Heart Failure with Recovered Ejection Fraction (HFrecEF), when LVEF is >40% but was previously lower than that value. Heart failure with mid-range EF is an entity whose meaning is a matter of debate, and which seems to have some characteristics similar to HFREF and others to HFPEF. In the absence of specific clinical trials, some postulate that its treatment should be similar to that of HFREF and others to that of HFPEF. And with respect to HFrecEF, the length of the treatment period previously instituted for HFREF is also not clear.

We now know the data of a Spanish Clinic registry of HF whose distinctive feature is that many of the patients had several determinations of EF during follow-up. Between 2001 and 2015, 1,921 patients were referred to the Clinic due to a history of hospitalization or reduced EF. Among these patients 1,656 had EF <50% and 1,160 at least 2 echocardiograms, one on admission and the other at follow-up. This last group forms the chore of the publication. Their average age was 65 years, 76% were men with ischemic etiology in 57% of cases, 70% were in FC II and 23% in FC III. Mean LVEF was 30.4±8.4%. Each patient had an average of 3.6 echocardiograms during follow-up (ranging from 2 in 398 patients to 9 in 16 patients). Treatment was optimized throughout follow-up, with elevated use of angiotensin-renin antagonists and beta-blockers (more than 90%), antialdosterone agents (67%), digoxin (41%), and ivabradine (20%). Use of devices was similar to that of other cohorts (almost 15% of cardiodefibrillators and 6% of resynchronizers). Mean EF was 30% on admission to the cohort, 38% at one year, and between 41% and 43% in the following measurements made every 2 years up to 15 years of follow-up. In summary, it was possible to define a marked increase in the first year, a plateau for a decade and a slow and smooth decline thereafter. Different etiologies showed specific trajectories. The initial increase in EF was greater in non-ischemic etiologies, mainly in hypertensive patients; improvement lasted less in the secondary forms due to cardiotoxicity or valve diseases, whereas there was full recovery in the alcoholic etiology. In the ischemic etiology, the initial improvement was lower. Regarding the type of HF, in HFREF, the EF improvement was remarkable in the first year (9±12%) and it tended to continue improving later. At the end of follow-up, 56% of patients persisted with HFREF, 21% had shifted to HFmrEF and 23% had passed to HFPEF. On the other hand, in patients with HFmrEF the initial increase was much lower (3±9%), and at the end of follow-up, 39% persisted in that category, 25% passed to the lower category and 36% to the higher.

Women had greater EF than men at the beginning and up to 9 years; then EF declined and at 15 years their values were similar to those of men. Patients who presented events during follow-up (hospitalization or death) had lower baseline value and less improvement with a more pronounced fall in EF than those who had a favorable outcome.

The first thing to be clarified is that EF is a changing determination, with a biological variation that may reach 30% in a day. It depends on loading conditions, ischemia, neurohormonal and inflammatory activation, etc. In addition, there is interobserver and intraobserver variability in its measurement. In fact, the changes described had a. strong variation: let us note the standard deviations of the measurements which are greater than their corresponding mean value (9±12% in HFREF, 3±9% in HFmrEF.)

Heart failure with mid-range EF seems an unstable entity, with 60% of patients changing category. But also 44% of patients with HFREF also experience significant changes, and it is regrettable that patients with HFPEF have not been included. How many will remain in this category after 15 years? Are the modifications evaluated valid or do they represent a mixture of real change and measurement error? The overall change of EF in the course of the first year undoubtedly expresses the improvement effect of pharmacological treatment, but also possibly the natural history in the context of an initial measurement made in the presence of a hypertensive crisis, myocarditis, peripartum heart disease, or exaggerated alcohol consumption, all conditions in which an improvement can be expected once the acute phase has passed. Note that in patients with ischemic etiology the improvement was less, and how in women whose prevalence of non-ischemic etiology

is higher than in men, had a more pronounced initial improvement. All these data make us reject strata classification according to EF as watertight categories, and lead us to reassess the value of long-term longitudinal studies that assign patients to a subgroup according to an initial assessment.

Generally, in the long term, and in spite of therapeutic efforts, EF tends to descend. Heart failure is not curable, and the mechanisms that condition its existence and progression eventually prevail. Achieving a pronounced and sustained improvement over time is undoubtedly an essential part of therapeutic success.

The variation of BMI from childhood to adulthood has a strong influence on the evolution of cardiovascular risk

Buscot MJ, Thomson RJ, Juonala M, Sabin MA, Burgner DP, Lehtimaki T, et al. Distinct child-to-adult body mass index trajectories are associated with different levels of adult cardiometabolic risk. **Eur Heart J 2018;39:2263-70. http://doi.org/gdpfd7**

It is well known that body mass index (BMI) impacts on the incidence of cardiovascular events. Over the last few years we have published reports on its prognostic value in childhood and adolescence, and, of course, in adulthood. We now have access to a prospective cohort study, of the nature we have been accustomed to by Scandinavian researchers, which links in a longitudinal follow-up BMI determinations in individuals in all these stages of life and demonstrates how they overlap to define the presence of risk factors.

The Cardiovascular Risk Study in Young Finnish individuals included children and adolescents between 6 and 18 years old in 1980 and assessed the influence of a series of clinical and paraclinical conditions on their evolution up to middle age. Follow-up was extended until 2011, when the participants were between 37 and 49 years old. The analysis we present refers to a subgroup of 2,631 participants (54% women) in whom there were at least 3 BMI determinations: one at the time of inclusion, one in the last visit in 2001, 2007 or 2011, and one between both. The endpoint was the development of type 2 diabetes, hypertension, dyslipidemia and intima-media thickness measured in 2001 and 2007. Overweight was defined as BMI between 25 and 29.9 kg/m2 and obesity as BMI ≥30 kg/m2.

On average, participants had 5.4 BMI measurements from the first to the last visit. Based on the study results, it was possible to define 6 courses of evolution or trajectories statistically different from each other. Group 1 (55.2%) corresponded to those who always had normal BMI; Group 3 (33.4%) to those who progressively increased their BMI to become overweight in adulthood; Group 4 (4.2%) to those who increased their BMI rapidly in early adulthood and became obese in middle age; Group 5 (4.3%) to those who were already overweight in childhood and adolescence and around 20 years of age became stably obese; Group 6 (1.2%) to those who were already obese in childhood and became even more obese (BMI ≥ 40 kg / m2) in adulthood. We left for the end group 2 (1.6%) because it corresponded to those who starting from a condition of overweight or obesity in childhood, reached or consolidated their obesity at age 25 but then reversed it reaching a normal BMI in adulthood.

Considering a global prevalence of 54% of women and 46% of men, there was overrepresentation of women in group 1 (63%) and of men in group 3 (60%). During follow-up and with reference to group 1, groups 3 to 6 had significantly higher risk (adjusted for family history, socioeconomic status in adulthood and physical activity) of presenting, diabetes, hypertension, dyslipidemia and a high intima-media thickness in adulthood. There was no significant increase in risk for group 2, except for the increase in intima-media thickness. The probability of presenting in the evolution at least one of these endpoints grew progressively from 20% in group 1 to 70% in group 6. A more accurate analysis of the findings showed that the risk of developing diabetes was higher when obesity is exacerbated in adulthood (groups 4 and 6) than when reached in adolescence and then remaining stable (group 5). The risk of hypertension was linked to the number of years in which overweight or obesity occurred. The risk of dyslipidemia, on the other hand, was similar in all the categories that presented with excess weight (groups 3 to 6).

This highly detailed longitudinal analysis illustrates the temporal relationship between overweight and obesity and the development of related entities. It confirms the enormous influence that excess weight exerts since childhood and adolescence. This is the only way to explain the more than 3 times greater risk of presenting high intima-media thickness in group 2, the one that normalizes BMI in adulthood. But it also shows that a behavior aimed at returning to normal conditions serves to significantly reduce the risk of presenting major cardiovascular risk factors, until it is almost indistinguishable from the one presented by individuals who live their entire lives with normal weight. A similar study with a larger number of participants, that placed emphasis on the distribution of body fat and on more accurate indicators of alteration in carbohydrate metabolism, could undoubtedly improve the conclusions of the present study and further understand the relationship between obesity, risk factors and cardiovascular disease. But beyond the specific subject matter, we can draw a general teaching of what is presented: the enormous value of a prospectively designed long-term registry, with clear objectives and the decision to carry it out.

Functional capacity and risk of complications in the postoperative period of non-cardiac surgery

Wijeysundera DN, Pearse RM, Shulman MA, Abbott TEF, Torres E, Ambosta A et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. **Lancet 2018;391:2631-40. http://doi.org/gdtsd5**

Surgical risk assessment depends strongly on the functional capacity of the patient. There are different ways to define it. The most usual one is a subjective assessment carried out before the procedure by a cardiologist, clinician or anesthesiologist according to the responses to an unstructured interrogation. As an alternative, the use of a defined and validated questionnaire can be proposed, or directly the performance of a stress test with an objective determination of functional capacity. It is not clear which is the best approach.

The multicenter METS study was conducted between 2013 and 2016 in 25 hospitals (5 in Canada, 7 in the United Kingdom, 10 in Australia and 3 in New Zealand). It included patients of 40 years of age or older, submitted to elective non-cardiac surgery with a requirement of at least one night of hospitalization and who had at least one risk factor for a cardiac complication or a risk factor for coronary heart disease. The patients were interviewed by an anesthetist who subjectively defined their functional capacity according to the interrogation, classifying it as poor (when capacity was estimated as <4 METS, moderate (when capacity was estimated between 4 and 10 METS), or good (when it was >10 METS).

Also, the patients answered the DASI questionnaire which includes a series of questions about their ability to perform activities of varying intensity, from elementary self-care (bathing, eating, etc.) to the most demanding ones (such as carrying out heavy activities around the house, participating in strenuous sports, running short distances, etc.). The answer to each of these questions is yes or no, and each affirmative answer corresponds to a score that increases as the activity becomes more demanding. The maximum score is 58.2. Additionally, a cardiopulmonary test (CPT) was carried out with determination of oxygen consumption in a cycle ergometer, as a way to objectively test exercise stress capacity and the value of plasma NT-pro-BNP was measured in all patients. After surgery, a daily ECG was performed on the patients and troponin and creatinine were measured until the third day or discharge.

The primary endpoint of the study was the incidence of death or acute myocardial infarction (AMI) in the first 30 days after surgery. The secondary endpoint was death at 1 year. The incidence of myocardial injury at 30 days was also determined based on troponin elevation above the 99th percentile, and the occurrence of severe or fatal postoperative complications.

The analysis included 1,401 patients in whom the CPT was performed, with a median of 9 days before surgery. Mean age was 65 years and 61% were men. Fifty-six percent of patients had history of hypertension, 19% of diabetes and 12% of coronary heart disease. In 38% of cases they were medicated with renin angiotensin system inhibitors-antagonists, 24% with aspirin and 17%.with beta-blockers.

Prior to surgery, the functional capacity was considered to be poor (<4 METS) in 8% of cases. Mean oxygen consumption was 19.2±6.5 ml/kg/min, and 16% had maximum consumption <14 ml/kg/min, corresponding to <4 METS. The subjective assessment had a sensitivity of only 19.2% and a specificity of 94.7% to predict an oxygen consumption <14 ml/kg/min. Although there was a statistically significant association between the different evaluations, the correlation coefficients among them were poor. Thus, between oxygen consumption and the DASI score, Spearman's coefficient was only 0.43. The negative correlation of oxygen consumption and the DASI score with NT pro-BNP was even poorer (correlation coefficients of -0.21 and -0.25, respectively). The subjective evaluation tended to show worse values for the questionnaire and the CPT when the assumed capacity was worse, but there was much variation in each stratum.

Surgery was intra or retro peritoneal in 33% of cases, urological or gynecological in 30%, orthopedic in 24% and in other locations in the rest. General anesthesia was used in 54% of cases, local anesthesia in 31% and combined anesthesia in the remaining 15%. The primary endpoint occurred in 2%, and the secondary endpoint in 3% of cases. In 13% there was death or myocardial injury in the first 30 days. Regarding the predictive capacity of each of the assessments, in a model adjusted for age, sex and high-risk surgery: a) subjective assessment did not predict any of the events of interest; b) low oxygen consumption only predicted moderate or severe complications, but not the primary or secondary endpoints; c) the DASI score showed a statistical association with the primary endpoint and with the incidence of death or myocardial injury at 30 days; d) NT pro-BNP showed association with the incidence of death or myocardial injury at 30 days and with death at one year.

This study clearly demonstrates that the subjective assessment of functional capacity has no reliable association with its objective determinations, and even with more structured assessments such as the DASI questionnaire. Regarding the prognostic capacity of hard events (death or AMI) neither the subjective assessment nor the oxygen consumption yield adequate assessments. Decreased oxygen consumption indicates a higher risk of pulmonary, infectious and reoperation complications, but not of cardiovascular complications. Perhaps this is related to the fact that the treatment of cardiovascular disease has greatly improved since the studies that evaluated its predictive capacity for major events. On the other hand, the structured questionnaire appears as a reliable tool. It still remains unclear why the questionnaire is a reliable tool whereas, the objective determination is not.

Some limitations must be mentioned. Only 27% of potentially eligible patients agreed to participate in the study, raising doubts about the external validity of the findings. None of the predictive models reached a ROC area >0.74, indicating that at least 1 out of 4 times the discrimination of who will present an event is wrong. It should be considered that the association between the different ways of assessing exercise capacity was statistically significant, but clinically poor.

This study shows that the subjective assessment of functional capacity is not reliable to define surgical risk, but functional capacity is not the only factor that influences the prognosis of a surgery. Baseline conditions, concomitant diseases, cardiovascular history, and type of procedure are strong conditioning factors of surgical outcome. The multicenter study VISION, with 15,133 patients of >45 years of age undergoing non-cardiac surgery, found 11 independent predictors of death at 30 days: age, recent high-risk coronary disease, peripheral vascular disease, heart failure, active cancer, chronic obstructive pulmonary disease , urgent or emergency surgery, general or major vascular surgery, and major neurosurgery. We invite you to read SAC's Argentine Consensus Statement of Cardiovascular Risk Evaluation in Noncardiac Surgery (Rev Argent Cardiol 2016; 84: suppl 1) that presents a complete and methodologically impeccable review and suggestions of responsible behavior on the topic.

Healthy habits ensure a much longer life. Evidence from two cohort studies with more than 120,000 participants

Li Y, Pan A, Wang DD, Liu X, Dhana K, Franco OH, et al. Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. **Circulation 2018; 138:345-55. http://doi.org/gddh65**

Large cohort studies have repeatedly indicated that a healthy lifestyle is associated with longer life expectancy. A meta-analysis of 15 studies in 17 countries, with 531,804 participants and a mean follow-up of 13.2 years, revealed that 60% of premature deaths can be attributed to smoking, excessive alcohol consumption, physical inactivity, an unhealthy diet and obesity. Studies carried out in European countries, Canada and Japan suggest a potential gain in life expectancy of up to 18 years with lifestyle changes. A recent publication confirms the value of a healthy lifestyle and quantifies the expected effect of its adoption on life expectancy in the United States.

The analysis took into account data from two prospective cohort studies: a) the NHS, initiated in 1976 included 121,700 nurses between 30 and 55 years of age, who at the beginning of the study answered a questionnaire referring to medical information, lifestyle and related variables. In 1980, 92,468 nurses also answered a questionnaire on eating habits. New questionnaires were made every 2 to 4 years, referring to smoking, physical activity, diet, consumption of aspirin, vitamins, hormone replacement therapy, etc. b) the HPFS, starting in 1986 included 51,529 40 to 75 year-old men working in different health branches (dentists, optometrists, podiatrists, veterinarians, pharmacists) who answered questionnaires similar to those of the previous study. Both studies were followed up until 2014.

On the other hand, data from the NHANES survey were used to define the distribution in the adult American population of variables related to health status: diet, body mass index (BMI), alcohol consumption, smoking and physical activity. These 5 variables were used to construct a low risk score of all-cause, cardiovascular or cancer fatal events. Each of the variables was dichotomized in low and non-low risk. Based on a previously validated score of healthy diet, low risk diet was defined as the one within the 40% higher values of the healthy diet score. Low risk was define as follows: for smoking not to smoke; for physical activity at least moderate activity >30 minutes a day; for alcohol consumption 5 to 15 g/d in women and 5 to 30 g/d in men; and low risk BMI between 18.5 and 24.9 k/m2. In each case, 1 point was assigned to low risk and 0 to high risk, so that score values between 0 and 5 were assumed for each individual. The higher the score, the healthier the lifestyle and the lower the estimated risk of events. We excluded individuals who reported very low (<500 cal/d in women, and <800 cal/d in men), or very high (>3,500 cal/d and >4,200 cal/d, respectively) caloric intake, or who had a BMI <18.5 kg/m2. Altogether, 78,865 women and 44,354 men were included. The NHANES survey data were used to estimate the distribution of the low risk score in the adult population and vital statistics from the CDC to define the age-specific mortality rate. Life expectancy associated with different categories of each of the variables, and with each value of the score emerged from the combination of all these data.

Median follow-up was 34 years for women and 27 years for men. In the NHS study, 6.6% of the participants had score 0, 24.3% score 1, 34% score 2, 24.8% score 3, 9.1% score 4 and only 1.2% score 5. In the HPFS study, the corresponding values were 9.9%, 27.4%, 31.9%, 21.1%, 8.3% and 1.5%. Note the low proportion of participants with high scores in both studies. Each component of the present score (value 1) was associated with lower risk of total, cardiovascular and cancer mortality. Those with a score of 5, compared to the rest of the participants, presented a HR of 0.39 (95% CI 0.33-0.46) for total mortality, 0.48 (95% CI 0.37-0.63) for cancer mortality, and 0.28 (95% CI 0.19-0.42) for cardiovascular mortality and the comparison of those with score 5 with respect to score 0 yielded a HR of 0.26 (95% CI 0.22-0.31) for total mortality, 0.35 (95% CI 0.27-0.45) for cancer mortality and 0.18 (95% CI 0.12-0.26) for cardiovascular mortality. The population attributable risk (what proportion of the population's mortality can be attributed to a factor) of not adhering to the 5 markers of healthy lifestyle was 60.7% for total mortality, 51.7% for cancer mortality and 71.7% for cardiovascular mortality. At 50 years of age life expectancy for a woman with a score of 0 was calculated in 29 years, and for a woman with a score of 5 in 43 years, implying a gain of 14 years. In the case of a man of 50 years, the corresponding values were 25.5 and 37.6 years respectively, (gain of 12.1 years). In women and men, 30.8% and 34.1% of this gain was attributable to a decrease in cardiovascular death, and between 21% and 23% to a decrease in death from cancer, respectively.

This analysis is impressive due to the methodology chosen, the number of participants and the extension of follow-up. It points out how cardiovascular disease and cancer share some factors that favor their development. It clearly illustrates the importance of diet, physical activity and the prevention of harmful habits in the determination of life expectancy. The estimated gain far exceeds that expected with any pharmacological treatment. Nevertheless, it is evident that most of the population leads an unhealthy lifestyle. Although the initial data of the studies considered go back more than 30 years, much more recent ones in the United States (2001-2006), confirm an adherence to a healthy lifestyle of less than 10% of the population. Although smoking has declined, dieting has only experienced minimal changes, obesity has increased and regular physical activity has decreased. Should emphasis be placed solely on individual behavior? Probably not. The environment, the socioeconomic and working conditions, the availability of protected time for physical activity, economic access to healthier foods, all play a clear role in a healthy lifestyle. We are talking about a social illness, which can be modified with large-scale preventive policies.

Is obesity a determining factor of worse prognosis? The importance of how to define it

Iliodromiti S, Celis-Morales CA, Lyall DM, Anderson J, Gray SR, Mackay DF, et al. The impact of confounding on the associations of different adiposity measures with the incidence of cardiovascular disease: a cohort study of 296 535 adults of white European descent. **Eur Heart J 2018;39:1514-20. http://doi.org/gdjk65**

Although it is usual to highlight the adverse prognostic effect of overweight and obesity, an important body of information suggests that in many circumstances the opposite phenomenon occurs. The presence of an "obesity paradox" (better prognosis in the obese than in those who are overweight, and better prognosis in these than in those who have normal weight) has been documented in acute and chronic heart failure, acute coronary syndromes, hypertension, atrial fibrillation, etc. And that is only in the context of cardiovascular conditions. There is similar information in patients with renal failure, chronic obstructive pulmonary disease, neoplasms, etc. Moreover, there are also data that suggest the same phenomenon even in presumably healthy people. All this leads to discuss the role of excess weight and its true meaning. In the vast majority of cases the definition of obesity depends on the assessment of body mass index (BMI): a value between 25 and 29.9 kg/m2 indicates overweight, one ≥30 kg/m2 implies obesity. But there are other ways to determine an excess of adipose tissue: the waist circumference (WC), the waist/hip ratio (WHR), the waist/height ratio (WHtR), and the total body fat percentage (BFP). A British cohort study helps to clarify the phenomenon described.

The UK Biobank study recruited 502,664 participants between 40 and 69 years of age, from 2006 to 2010. Clinical history, physical examination and laboratory data, as well as the determination of body composition by bioimpedance was available from all the participants. Follow-up was extended until mid-2015. This study excluded participants with already diagnosed cardiovascular disease, and non-white people, delimiting a cohort of 296,535 participants (58% women) with a median follow-up of 5 years. The primary endpoint was the incidence of fatal and non-fatal cardiovascular events in men (5.7%) and women (3.3%).

In a detailed analysis of the influence of overweight and obesity on prognosis, a BMI of 22 kg/m2 was considered as reference value. The WC, WHR, WHtR and BFP values were defined as reference values that by regression corresponded to the aforementioned BMI. The corresponding values in women and men at a BMI of 22 kg/m2 were 74 and 83 cm for WC, 0.78 and 0.88 for WHR, 0.38 and 0.42 for WHtR and 30% and 18% for the BFT, respectively. The prognostic value of each marker was adjusted according to the presence of smoking and comorbidities.

In the case of BMI, the relationship with cardiovascular events was expressed by a J curve: there was high risk for values <18.5 kg/m2; the lowest risk corresponded to values between 22 and 23 kg/m2 and then the risk increased progressively up to 35 kg/m2 in men and 45 kg/m2 in women. In non-smoking men without comorbidities the risk associated with low BMI disappeared. The rest of the markers on the other hand showed a progressively increasing relationship with the risk of fatal and nonfatal events from the lowest values of each determination, none of them showing a J curve. The adjustment for smoking and comorbidities did not change in any of these cases the associations described with events. The linear association of BMI with the other markers was variable, with correlation coefficient of 0.43 for WHR to 0.83 for WHtR.

The association of low BMI values with events finds an explanation here: there are confounding factors that justify it. Smokers are thinner than non-smokers; those with various non-cardiovascular pathologies (rheumatologic or inflammatory diseases) tend to lose muscle mass more than fat, and also have a higher risk of cardiovascular disease. This explains why the BMI (which expresses fat mass and lean mass) can be associated with a high rate of cardiovascular events when it is low: this occurs if this is due to habits or pathologies linked to low BMI, but also with cardiovascular disease. If adjusted for these factors, low BMI is no longer a predictor of cardiovascular disease. On the other hand, the adiposity evaluated by other markers not subject to these confounding factors, does not present this phenomenon, and it turns out that the lower the better. This is a good reason to promote a healthy diet and regular physical activity and not rest when evaluating our patients exclusively by BMI.

We must abandon the use of adrenaline in the management of patients with cardiogenic shock

Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, et al. Epinephrine Versus Norepinephrine for Cardiogenic Shock After Acute Myocardial Infarction. **J Am Coll Cardiol 2018;72:173-82. 10.1016/j.jacc.2018.04.051**

Use of vasoactive drugs plays a central role in the treatment of cardiogenic shock (CS). Vasopressors (mainly dopamine, noradrenaline and adrenaline, and to a lesser extent phenylephrine and vasopressin) are used in up to 90% of cases to increase blood pressure, and, thus, the flow of blood and nutrients to the peripheral tissues. The indication of these agents is mainly based on empirical criteria and the opinion of experts, since there are many randomized studies that have compared their effects in this context. Only in a randomized study comparing dopamine with noradrenaline, in a subgroup of patients with CS, excess arrhythmia and a trend towards greater mortality was found in the dopamine branch, leading to a decreased use of this drug. Adrenaline and noradrenaline remain as reference drugs, each with its advantages and disadvantages. Adrenaline generates greater increase of the cardiac index, but is more thermogenic and therefore induces higher increase in myocardial oxygen consumption. A multicenter study carried out in 9 intensive care units in France has just been published, shedding some light on the differences between the two drugs.

The study was carried out between 2011 and 2016 and included patients with the ususal definition of CS, including systolic blood pressure (SBP) <90 mm Hg or mean blood pressure (MBP) <65 mm Hg, with clinical manifestations of hypoperfusion, cardiac index <2.2 l/min/m2 and wedge pressure >15 mm Hg. Cardiogenic shock should be secondary to acute myocardial infarction, with early angioplasty revascularization. All the patients had to have a Swan Ganz catheter. They were initially treated with an open-label vasopressor and randomly assigned to a double blind treatment with adrenaline or noradrenaline. As MBP increased, the vasopressor infusion administered openly was decreased until completely closed, keeping the infusion of the drug under study. Both drugs were increased at doses of 0.02 μg/kg/min until achieving a MBP of 65 to 70 mm Hg. At 0, 2, 4, 6, 12, 24, 48 and 72 hours after randomization, clinical, hemodynamic, echocardiographic and laboratory variables were associated with the reference diagram. The primary efficacy endpoint was the increase in cardiac index.

Once 57 patients had been included, with an average left ventricular ejection fraction of 34%, and 56 patients in mechanical ventilation, the study was discontinued when a marked excess of refractory CS in the adrenaline branch (n=27) was verified. This final endpoint had not been considered in the initial protocol, but the examination of the patients' evolution led to define it as CS with progressive worsening of the clinical condition, increased lactate levels and acute functional impairment of other organs (liver, kidneys) despite the use of adrenaline or noradrenaline at doses >1 μg/kg/min, or dobutamine (used in both arms in 67% of cases) at doses >10 μg/kg/min, and/or need for counterpulsation balloon implantation and sustained hypotension despite adequate filling pressures. The incidence of refractory CS was 37% in the adrenaline arm vs. 7% in the norepinephrine arm (p=0.008). Concomitantly, there was a trend towards excess mortality at 7 days (30% vs. 10%) and 28 days (48% vs. 27%), although at two months the difference became less evident (52% vs 37%, p=0.25). As a correlate, adrenaline produced a higher increase in heart rate, the double product (heart rate × SBP), lactic acid production and the incidence of metabolic acidosis, all with p <0.05. There was no difference in the mean and maximum doses of both drugs, changes in blood pressure or other hemodynamic measurements. Regarding the primary endpoint, except for some partial superiority at 2 and 4 hours in favor of adrenaline, there was no significant difference between the two drugs.

The most notable difference between adrenaline and noradrenaline is that the former stimulates β2 receptors (both drugs are α1, α2 and β1 receptor agonists). Up to 30% of myocardial β receptors are β2; the stimulation of atrial β receptors generates an increase in heart rate. Hence, the specific stimulation of the β2 atrial receptor by adrenaline leads to a greater increase in heart rate, and therefore myocardial oxygen consumption. This explains, in a state of decreased oxygen supply, such as shock, due to the presence of coronary heart disease (most patients with CS have multiple vessel disease) and drop of coronary perfusion pressure, an exacerbation of ischemia and, consequently, anaerobic metabolism with enhanced production of lactic acidosis, resulting in decline of contractile efficiency. In fact, the cardiac index was the same but at the expense of higher heart rate in the adrenaline branch. A postulated deleterious effect on the microcirculation in different organs and systems, among them the renal bed, may be added to the detrimental effect at the cardiac level. A recently published meta-analysis of individual data (Intensive Care Med 2018; 44: 847-856) points in the same direction and goes even further considering 16 observational studies with 2,583 patients. It indicates that in the treatment of CS, the use of adrenaline compared with other inotropic and vasodilator regimens, is associated with 3 to 4 times increased risk of mortality.

Importance of the coronary calcium score to predict 10-year atherosclerotic events. An analysis of the MESA study.

Budoff MJ, Young R, Burke G, Jeffrey Carr J, Detrano RC, Folsom AR, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovas-

cular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). **Eur Heart J 2018; 39: 2401-8. http://doi.org/cszt**

Coronary artery calcium identification and quantification by means of the coronary calcium score (CCS) has shown prognostic value of events in studies carried out in a predominantly white population during variable follow-up periods. A recent publication of the multicenter study MESA expands in different ways the predictive value of the score.

The MESA cohort study included 6,814 people of diverse ethnicities (38% white, 28% black, 22% Hispanic, 12% Chinese), free of cardiovascular disease, from 45 to 84 years of age, recruited in 6 locations in the United States of America. The initial visit took place between 2000 and 2002, and clinical, anthropometric and laboratory data were collected. A coronary computed tomography scan was also carried out to determine the presence of coronary calcium and assign the CCS of each participant measured in Agatston units (from 0 if coronary calcium (CC) was absent to higher values the greater the CC presence). The average participant age was 62 years, and the presence of CC was shown in a variable percentage according to ethnicity, from 43.5% in the black population to 57% in the white population. The primary endpoint of the analysis was the incidence of the first event that is characteristic of atherosclerotic disease: definite or probable acute myocardial infarction (AMI), resuscitated cardiac arrest, fatal coronary heart disease, fatal or non-fatal stroke, and other cause of death attributed to atherosclerosis or cardiovascular disease. Four CCS categories were considered: 0, 1 to 100, 101 to 300 and >300. Median follow-up was 11.1 years, and the relationship of the CCS with the incidence of events was evaluated.

Progressively increasing values of CCS were associated to a growing incidence of atherosclerotic events in general, and only considering the most serious cases. For those with score 0, the risk of events at 10 years ranged between 1.3% and 5.6% and for those with a score >300, the events ranged between 13.1% and 25.6%. The association of CCS with the incidence of events was consistently adjusted by age, sex, race or ethnicity, educational level and use or not of lipid-lowering medication. At 10 years, those with a score >100 had a risk of events >7.5%.

This study expands and consolidates the knowledge we have about the usefulness of the CCS. It confirms the very low risk associated with the absence of coronary calcification, as indicated by other cohort studies. It shows that already at values greater than 100 a risk is expected for which the administration of statins is recommended, when previous publications considered a value of 300. It extends the predictive capacity to atherosclerotic events in general, beyond coronary or cardiovascular events, because CC expresses systemic, not local, disease. And it shows its usefulness in different races or ethnicities. The determination of CCS has been recommended with greater emphasis in patients at intermediate risk. This is indicated by international practice guidelines and the updated 2016 SAC cardiovascular prevention consensus. It would have been interesting to find in the publication we have commented a baseline risk analysis, or one quantifying the gain in predictive capacity by adding the value of CCS to traditional risk factors. Finally, a question that we had already formulated when referring to a substudy of the PESA study, which showed the presence of subclinical atherosclerosis in almost 40% of individuals with an optimal profile of risk factors: will imaging studies replace clinical assessment when defining risk?