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Diet, physical activity and outcome. Three publications of the PURE study confirming and challenging our knowledge.

Miller V, Mente A, Dehghan M, Rangarajan S, Zhang X, Swaminathan S, et al. Fruit, Vegetable, and Legume Intake, and Cardiovascular Disease and Deaths in 18 Countries (PURE): a Prospective Cohort Study. **Lancet 2017;390:2037-49. http://doi.org/gcppdr**

Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of Fats and Carbohydrate Intake with Cardiovascular Disease and Mortality in 18 Countries (PURE): a Prospective Cohort Study. **Lancet 2017;390:2050-62. http://doi.org/gcjj9f**

Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, et al. The Effect of Physical Activity on Mortality and Cardiovascular Disease in 130 000 People from 17 High-Income, Middle-Income, and Low-Income Countries: the PURE Study. **Lancet 2017;390:2643-54. http://doi.org/cdfc**

Patients are universally advised to practice at least low physical activity on a regular basis and to privilege intake of fruits and vegetables in their diet, reducing fat intake. Many of these recommendations are based on epidemiological studies and in some randomized trials with insufficient number of observations or inadequate follow-up on some occasions. In addition, many regions of the world have not been represented and the methods used to collect the information about diet and physical activity have not always been too rigorous. There have also been differences in the estimation of the effect achieved by following certain dietary guidelines regarding the outcomes prevented and the magnitude of the result. We have already commented on the PURE epidemiological study. On this occasion, three reports have been published with information that confirms and challenges our "common sense".

The PURE study was a prospective cohort study in individuals aged 35–70 years without cardiovascular disease from 613 communities in seven urban and rural geographical regions: North America, South America, Europe, South Asia, Southeast Asia, China and Africa. The study included 18 countries with different gross national income per capita: three high-income countries (Canada, Sweden and United Arab Emirates), seven upper-middle income countries (Argentina, Brazil, Chile, Malaysia, Poland, South Africa, and Turkey), four lower-middle income countries (China, Colombia, Iran, and the occupied Palestinian territory) and four low-income countries (Bangladesh, India, Pakistan, and Zimbabwe),

Among the different baseline characteristics (demographic, clinical and socio-economic characteristics, physical examination, medication, etc.) the participants completed food frequency questionnaires. Preexisting food frequency questionnaires were used in some countries, while these questionnaires were specifically developed for other countries. A subgroup of participants completed 24-hour dietary recalls for each season and a food list was compiled. There was a good correlation between the food frequency questionnaires and the food lists. Country-specific nutrient databases were constructed to convert food into nutrients.

The first of these studies focuses on the effect of vegetable, fruit and legume intake. Potatoes and other tubers were not included as vegetables. Legumes were analyzed separately from vegetables. Fruit and vegetable juices were excluded from the analysis. The association between the intake of these foods and the outcome was evaluated. The main clinical outcomes were a primary composite endpoint of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and heart failure, each of these outcomes evaluated separately, and the incidence of total mortality and non-cardiovascular mortality. One serving was defined as 125 g of fruits or vegetables and 150 g of cooked legumes.

The information of 135,335 healthy individuals with adequate follow-up was collected between 2003 and 2013. The participants were divided by number of fruit, vegetable, and legume servings per day, from less than one to greater than eight. Median servings per day ranged from three to four. People who consumed more fruits, vegetables, and legumes had higher education, higher level of physical activity, lower rates of smoking, and higher energy, red meat and white meat intake, and were more likely to live in urban areas. During a median follow-up of 7.4 years, higher fruit, vegetable and legume intake was inversely associated with the composite endpoint, each of its components, non-cardiovascular mortality and total mortality in unadjusted models and after adjusting for age, sex, and center. But after adjusting for smoking habits, diabetes, rural or urban location, physical activity, caloric intake, educational level, meat and cereal intake, only the association between fruit, legume and vegetable intake and non-cardiovascular mortality and total mortality remained significant, with a

non-significant trend for cardiovascular mortality (p = 0.056). Three to four servings per day presented a HR for total mortality of 0.78 (95% CI, 0.69-0.78) compared with less than one serving per day, with no further decrease in mortality with higher consumption. When each component was considered separately, legume and fruit intake was associated with lower total mortality (particularly in South Asia, China, Palestine, and South America). The association of higher vegetable intake with lower mortality was more irregular: it was not observed globally, but only in South Asia, North America and Europe. Of importance, the isolated analysis of fruit intake was adjusted for vegetable intake and similarly, the analysis of vegetable intake was adjusted for fruit intake.

The second study analyzes fat and carbohydrate intake in the population already described. Based on the questionnaires completed by participants, they were categorized into quintiles according to the percentage of calories provided by each particular nutrient. For carbohydrate intake, the lowest quintile corresponded to those who obtained a median percentage of energy of 46.4%, and the highest quintile to those who obtained a median percentage of energy of 77.2%. For fat intake, the lowest quintile and the highest quintile corresponded to those who obtained a median percentage of energy of 10.65 and 35.6%, respectively. Carbohydrate intake was higher in South Asia (where 65% of the population obtains at least 60% of energy from them) and Africa, while North America and Europe had the highest fat intake and South America the highest protein intake. After a median follow-up of 7.4 years, multivariate analysis did not show a significant association between carbohydrate intake and major cardiovascular events, but a significant association with higher risk of total mortality (HR for quintile 5 vs. quintile 1 was 1.28, 95% CI 1.12–1.46) and non-cardiovascular mortality (HR 1.36, 95% CI 1.16-1.60). There was no association between fat intake and cardiovascular events. Total fat intake was associated with lower risk of total mortality (HR for quintile 5 vs. quintile 1 was 0.77; 95% CI, 0.67–0.87) and non-cardiovascular mortality (HR 0.70: 95% CI 0.60 0.82) and with a strong trend toward stroke reduction (HR 0.82, 95% CI, 0.68–1). The association with lower risk of total and non-cardiovascular mortality was observed with saturated, monounsaturated and polyunsaturated fatty acids. A model based on the mentioned information observed that isocaloric (5% of energy) replacement of carbohydrate with polyunsaturated acids was associated with 11% lower risk of mortality. Finally, higher protein intake was also associated with better outcome, with 12% reduction in total mortality and 15% reduction in non-cardiovascular mortality.

The third analysis investigates the effect of physical activity on the outcome. In this case, a questionnaire was used to assess 1-week total physical activity, including recreation, occupation, housework and transportation, reported in METS (metabolic equivalents of O2 consumption)-minutes per week. Total physical activity was categorized as low (<600 MET-minutes per week), moderate (600–3000 MET-minutes per week), and high (>3000 MET-minutes per week), corresponding to less than 150 minutes per week, 150–750 minutes per week, and more than 750 minutes per week of moderate intensity physical activity. The analysis was performed in 130,843 participants. Eighteen percent of the participants were in the low physical activity group, 37% in the moderate physical activity group and 45% in the high physical activity group. The prevalence of hypertension and diabetes decreased as physical activity increased. There was a trend toward higher physical activity in high-income countries, with medians between 3,227 MET-minutes per week compared with 2,520 MET-minutes per week in low-income countries (p <0.0001). The difference was mainly due to recreational physical activity (518 MET-minutes per week in high income countries vs. 0 en low-income countries) without significant differences in non-recreational physical activity. During the mean follow-up of 6.9 years, a multivariate analysis adjusted for age, sex, education, smoking status, country income level, urban or rural residency and family history of cardiovascular disease evidenced that higher level of physical activity was associated with better cardiovascular and global prognosis. For all-cause mortality, moderate compared with low physical activity implied a HR of 0.80 (95% CI, 0.74–0.87) and high physical activity compared with moderate physical activity resulted in a HR of 0.81 (95% CI, 0.75 - 0.87). There were similar reductions for major cardiovascular events, which was less evident in the case of heart failure. Overall, the association of physical activity with better outcome was non-linear: above 3,000 MET-minute per week for total activity, and above 5,000 MET-minute per week for non-recreational activity (equivalent to 750 minutes and 1,250 minutes of moderate activity per week, respectively) the additional benefit was not significant. In high- and upper-middle-income countries, the decline in the risk of death and major events when moving from moderate to high activity was steeper than in lower-income countries.

These three publications of the PURE study support and challenge assumptions strongly held by the medical community. The first study confirms the beneficial effect of at least moderate quantities of vegetable, fruit and legume intake. The best prognosis is achieved between 375 and 500 grams per day, as higher quantities do not seem to ensure better outcome. The potential beneficial effects of vegetables on our health have been highlighted on many occasions. Antioxidants, vitamins, polyphenols and fiber are associated with a reduction in blood pressure, improvement of endothelial function, prevention of atherosclerotic phenomena and decrease in insulin resistance. Of importance, although the better prognosis could then be expected to be associated with a reduction in major cardiovas-

cular events and cardiovascular mortality, this does not happen. Mortality decreases, but basically due to a reduction in non-cardiovascular mortality. We can speculate with a reduction in mortality from cancer or degenerative diseases, but the publications do not provide sufficient data to support a determined theory. The beneficial effect also seems to be more associated with fruit and legume intake rather than with vegetables. This study has some limitations. Firstly, the information was based on food questionnaires validated in some countries but specially created in others for the occasion. The categorization used (fruits, vegetables, legumes) does not allow a finer analysis of the information. Do all the vegetables have the same impact on prognosis? And does the same apply to all fruits or all legumes?

The second study had probably more counterintuitive conclusions. Not in terms of carbohydrate intake (considering that the detrimental effect seems to occur among those who consume more than 65% of energy from carbohydrates) but because of the better prognosis associated with higher fat intake. In fact, the lowest quintile, taken as a reference, corresponds to a very low figure (only 10.6% of the energy intake from fat, which makes us think of high carbohydrate intake) but an increase to less than twice (18.6% in the second quintile) is sufficient to lower the risk of total mortality by 10%. Although the argument of vascular damage associated with a high fat intake is permanently put forward, higher values are associated not with an increase, but with a decrease or lack of effect in the incidence of major cardiovascular events, and this applies to saturated or unsaturated fatty acids. Some criticisms made for the previous study also apply to this one: the use of forms that were not always validated and rough categorization that in the case of carbohydrates is a serious deficiency (refined sugars are not differentiated from whole grains, as if everything were the same!). As in the previous study we noted that the effect of increased intake of carbohydrates and fats is reflected in non-cardiovascular mortality and, thus, in total mortality. How shocking for us cardiologists, so convinced of the crucial importance of diet in the outcome of cardiovascular health, to find that the reduction of total mortality in this large cohort study follows another pathway, and that diet prevents other conditions to which we pay less attention! Probably, it should be mentioned that this cohort is made up of 50 year-old individuals on average, without cardiovascular disease, with a mortality rate of about 0.5% per year and in which more than half of all deaths are due to non-cardiovascular causes.

The last study is less challenging for the established knowledge. Moderate physical activity is good, and intense physical activity is somehow better. The effect of physical activity on cardiovascular events and cardiovascular mortality is clear. The effects of exercise on endothelial function, insulin resistance, metabolic profile and diastolic function are well-known and, un-doubtedly play a role in the outcome. Of importance, the study included all types of physical activity, even occupational activity.

Once these particular comments have been made, we shall continue with a global view and many questions. These publications include the same individuals but they are analyzed from different viewpoints. How can we integrate vegetables, fruit and legume intake in a pattern of carbohydrate and fat intake and, even more, with physical activity? Beyond the formal adjustment, aren't there any factors not considered and expressed by these dietary and physical activity patterns? Is a person who eats a lot of fruit and vegetables, few carbohydrates and a moderate amount of fat just that? Cannot we suspect the presence of an attitude of self-care for health, psychological disposition, free time or the availability of particular resources, that is different from the less compliant persons? And can these characteristics be associated with a better search for medical care, for example, with earlier consultation? And, in consequence, could this have influence in the health status? Raw data from studies focused on diet show that it is strongly associated with cardiovascular mortality. This association is lost after adjusting for baseline conditions and household location, among others. What other factors not considered could have moved the magnitude or direction of the association with total mortality even further? As an example: why does increasing the level of non-recreational activity (daily life, work) improve the outcome in the richest countries more than in the poorest ones? What does this increase consist of and under what different conditions? Should dietary counseling be the same for everyone, regardless of baseline conditions? Do carbohydrates for diabetics and proteins for patients with renal failure have the same influence than in healthy people? We should not forget that the three publications are observational studies, without random allocation of diets or plans of physical activity. The presence of residual confounding factors can never be ruled out.

Despite all the limitations mentioned above, we are in fact in the presence of a broadly representative cohort study, including many participants from regions that are not usually represented, with a rigorous design and a long follow-up. The study provides information that encourages a thorough analysis, looking for associations and patterns that have not yet been established. In the meantime, would it be very wrong to assume that we can advise and recommend ourselves eating a variety of foods and being more active?

Heart valve replacement: which prosthesis to choose? A cohort study contributes to find an answer

Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, et al. Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. N Engl J Med 2017;377:1847-57.

The indication of aortic valve replacement (AVR) or mitral valve replacement (MVR) implies deciding the implantation of either a mechanical or biologic prosthesis, each of them associated with advantages and disadvantages.

Biologic prosthetic valves do not usually need anticoagulation but are associated with a higher risk of reoperation in young patients because of structural valve deterioration. Mechanical valves require anticoagulation due to the clear risk of thromboembolism, which in turn, increases the risk of bleeding. Therefore, mechanical valves are recommended in persons <50 years, biologic valves in persons >70 years and either type in persons ranging from 50 to 70 years of age. The evidence to justify these decisions comes from small-scale randomized trials and a few registries, but we lack information from robust studies with many observations to define these criteria.

A retrospective cohort study was conducted to fill this gap, comparing the outcome of patients undergoing AVR or MVR with both types of prostheses. The study, conducted in California, USA, examined data from patients treated at 142 nonfederal hospitals between 1996 and 2013 and included patients with isolated AVR and no concomitant procedure and patients with isolated MVR or with concomitant tricuspid valve repair, atrial fibrillation ablation, or coronary-artery bypass surgery.

Exclusion criteria included previous cardiac surgery, multiple valve replacement, aortic or mitral valve repair, and thoracic aortic surgery. Since patients with mechanical or biologic prostheses have differences beyond age that may justify different outcome (in fact, patients treated with biologic prostheses had a higher prevalence of comorbidities), those with similar baseline characteristics were selected among all the patients available using a propensity score. In this way, the study compared patients with similar profile independently of the type of prosthesis implanted. Patients were stratified according to age; for AVR the categories were 45 to 54 years and 55 to 64 years of age and for MVR, the categories were 40 to 49 years, 50 to 69 years, and 70 to 79 years. The primary endpoint was overall mortality and the following results were obtained according to the type of valve implanted:

a) **AVR:** Among the 45,639 patients undergoing AVR, 9,942 were selected; 6,097 (61%) received mechanical prostheses and the rest of the patients received biologic prostheses. Mean age was 57 years in both groups. The use of biologic prostheses increased over the study period, from 21.6% between 1996 and 2001 to 52.8% between 2008 and 2013. Therefore, median follow-up was 5 years for biologic prostheses and 8.4 years for mechanical prostheses. 30-day mortality was similar for both types of prostheses. Implantation of a biologic prosthesis was associated with significantly higher 15-year mortality than receipt of a mechanical prosthesis in patients between 45 to 54 years

of age: 30.6% vs. 26.4% with mechanical prosthesis, adjusted HR 1.25, 95% CI 1.03-1.52. In this age group, the use of biologic prosthesis was associated with lower risk of bleeding and stroke. In the group of patients between 55 and 64 years, there were no significant differences in mortality at 15 years (36.1% with biologic prosthesis vs. 32.1% with mechanical prosthesis, p=0.6) but recipients of biologic prosthesis had lower risk of bleeding. When age was examined as a continuous variable, the mortality benefit that was associated with mechanical valves was extended to 53 years. In both age groups, the use of biologic valves was associated with higher risk of reoperation, and this effect was more pronounced among younger patients.

b) **MVR:** Among the 38,431 patients undergoing AVR, 15,503 were selected; 9,982 (64%) received mechanical prostheses and the rest of the patients received biologic prostheses. Recipients of biologic prosthesis were significantly older (median age 68.2 vs. 62.8 years). The use of biologic prostheses increased over the study period, from 22.9% between 1996 and 2001 to 49.3% between 2008 and 2013. Median follow-up was 4.6 years for biologic prostheses and 7.6 years for mechanical prostheses. 30-day mortality did not differ significantly according to valve type among patients >50 years. However, implantation of a biologic prosthetic valve was associated with higher perioperative mortality among patients between 40 to 49 years of age (5.6% vs. 2.2%; OR, 2.62; 95% CI, 1.28 to 5.38). Implantation of a biologic prosthesis was associated with significantly higher 15-year mortality than receipt of a mechanical prosthesis among patients between 40 to 49 years (44.1% vs. 27.1%; adjusted HR, 1.88, 95% CI 1.35-2.63) and between 50 to 69 years of age (50% vs. 45.3%; adjusted HR, 1.16, 95% CI 1.04-1.30), but no differences were observed in patients >70 years: 78.3% vs. 77.3%. The use of biologic prosthesis was associated with lower risk of bleeding in patients >50 years and of stroke in those between 50 and 69 years. When age was examined as a continuous variable, the mortality benefit that was associated with mechanical valves persisted until 68 years. Again, the use of biologic valves was associated with higher risk of reoperation.

The choice of prosthesis for valve replacement is determined by the baseline characteristics of the patients, the etiology of heart valve disease and the anatomic involvement, the feasibility of adequate monitoring of anticoagulation therapy and the presence of baseline conditions favoring or contraindicating such treatment. Age is a key factor at the moment of decision-making; in fact, age increases the prevalence of comorbidities (discouraging the use of anticoagulation) and reduces the possibility of prosthesis degeneration with subsequent need for reoperation. Both phenomena support the indication of biologic prostheses in elderly patients. The 2017 European Society of Cardiology guidelines for the management of heart valve disease recommend a mechanical prosthesis in patients <60 years for pros-

theses in aortic position and in patients <65 years for prostheses in mitral position, and strongly recommend bioprostheses in patients >65 years for AVR and in those >70 years for MVR.

The 2017 American Heart Association (AHA)/ American College of Cardiology (ACC) guidelines do not make differences regarding to the valve affected and recommend mechanical prosthesis in patients <50 years and biologic valves in those >70. In 2015, the consensus statement of the SAC recommended mechanical prosthesis in patients <60 years and biologic prosthesis in those >70 years.

Due to the lack of randomized trials, this study is a non-negligible source of the best "evidence" available and adds data about mortality to the risks already known about each type of prosthesis. In the case of AVR, these data open the possibility to choose a biologic prosthesis in patients >55 years (similar mortality with lower risk of bleeding) but only in patients >70 years in case of MVR (because until that age mortality seems lower with mechanical prosthesis). In younger patients, the higher mortality with biologic prosthesis is associated with higher risk of reoperation. We have presented a non-randomized, observational study affected by the presence of residual factors associated with the selection of one type of valve or the other which can be really responsible for the outcome of patients. This phenomenon is called a confounding factor due to the indication, suggesting that the indication of a certain treatment is associated with adverse outcome, not because of the treatment itself but because of the conditions that led to adopting such treatment. Nevertheless, matching patients by many baseline conditions contributes to reduce such bias but does not completely eliminate it. How long shall we have to wait for a randomized study? The question of which prosthesis to choose when the conditions do not impose a particular type deserves an unequivocal answer.

In cardiogenic shock, focus on the culprit vessel and postpone the others. Lessons from the CULPRIT SHOCK study

Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, et al. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. **N Engl J Med 2017;377:2419-32.**

In the context of acute myocardial infarction (AMI) with multivessel disease, the different guidelines recommend immediate percutaneous coronary intervention (PCI) to the culprit coronary artery with the option of staged revascularization of significant nonculprit lesions. In patients with cardiogenic shock (CS) secondary to acute AMI, immediate complete revascularization is recommended as nonculprit stenoses may generate ischemia due to significant reduction of perfusion pressure and higher filling pressure

which reduces transmural perfusion gradient. In fact, patients with CS were excluded from randomized trials comparing immediate revascularization of the culprit vessel vs. complete revascularization. Observational studies suggest that immediate complete revascularization could paradoxically be associated with worse outcome due to the use of an increased dose of contrast material, volume overload and renal impairment and higher risk of complications expected when performing more procedures. The appropriate strategy remains unclear.

The CULPRIT SHOCK trial was designed to clarify this question. The trial was conducted in 83 centers in Europe and included patients with acute AMI with CS (defined as systolic blood pressure <90 mm Hg for ≥30 min or the use of inotropic agents to maintain a systolic pressure of at least 90 mm Hg, clinical signs of pulmonary congestion and of impaired organ perfusion, manifested by oliguria, altered mental status, cold and clammy skin and limbs or lactate level > 2.0 mmol per liter) and stenosis of at least two major vessels eligible for immediate PCI. Exclusion criteria were age >90 years, life expectancy <6 months for reasons other than CS, the onset of shock >12 hours before randomization, resuscitation for >30 minutes, an assumed severe deficit in brain function with fixed dilated pupils, an indication for primary urgent coronary-artery bypass grafting, or glomerular filtration rate <30 ml/min. Patients were randomly assigned, in a 1:1 ratio, to either PCI of the culprit lesion only (with the indication of staged revascularization of nonculprit lesions generating ischemia by means of noninvasive testing or with the use of fractional flow reserve), or immediate multivessel PCI of all major coronary arteries with more than 70% stenosis. The primary endpoint was a composite of all cause death or severe renal failure leading to renal-replacement therapy (dialysis, hemofiltration, or hemodiafiltration) within 30 days after randomization.

A total of 686 patients were included. Median age was 70 years, 76% of patients were men and 60% presented ST-segment elevation. Median blood pressure was 100/60 mmHg and median heart rate was 90 bpm. Sixty-three percent of the patients had three-vessel coronary artery disease and the infarct-related artery was the LAD coronary artery in 42% of cases, the right coronary artery in 28%, the left circumflex coronary artery in 21% and the left main coronary artery in the rest of the cases. The femoral access was used in 82% of the patients and drug-eluting stents were implanted in almost all the patients. Aspiration thrombectomy of the culprit lesion was more common in the culprit-lesion-only PCI group (17.5% vs. 11.4%). In this group, the total dose of contrast material was lower (190 vs. 250 ml) and total duration of fluoroscopy was shorter (median 13 vs. 19 min). All these differences were significant. Crossover from the culprit-lesion-only PCI group to the multivessel PCI group was reported in 12.5% of the patients and from the multivessel PCI

group to the culprit-lesion-only PCI group in 9.4%. Staged revascularization was performed in 17% in the culprit-lesion-only PCI group. At 30 days, the rate of the composite primary endpoint occurred in 45.9% of the patients in this group vs. 55.4% in the multivessel PCI group (RR, 0.83; 95% CI, 0.71 to 0.96; p=0.01). A significant difference was found for all-cause mortality (43.3% vs. 51.6%; p=0.03) with a strong trend for greater rate of renal-replacement therapy (11.6% vs.16.4%, p=0.07). The rates of recurrent myocardial infarction, rehospitalization for congestive heart failure, bleeding, and stroke did not differ significantly between the two groups.

The use of higher dose of contrast material and longer duration of the procedure seem to be the initial causes of the adverse outcome of patients in the multivessel PCI group. These findings can also be explained by some aspects associated with the study design. The protocol did not exclude arteries with total chronic occlusion from the multivessel PCI group. Management of these lesions demands greater dose of contrast material and is not associated with better outcome. Probably, treating chronic occlusions of nonculprit arteries in patients with CS could have contributed to obscure the results of the multivessel PCI group. The protocol requested patients in the culprit-lesion-only PCI group to undergo a second procedure to treat the other significant stenoses and did not consider those procedures as an adverse event, as opposed to other protocols. In any case, and beyond these subtle comments, the difference in mortality is significant and is not a matter of interpretation.

Undoubtedly, there will be a subgroup of patients in whom immediate multivessel PCI will still be indicated (patients with better kidney function who can tolerate higher dose of contrast material or patients with hemodynamic instability in the cardiac catheterization laboratory despite PCI of the infarct-related coronary artery?). Yet, we understand that this randomized study (with evidence of quality) will surely be taken into account in future practice guidelines, emphasizing the old concept that perfect is sometimes the enemy of good.

Self-reported physical fitness is enough to predict outcome. A cohort study with over 400.000 observations

Yates T, Zaccardi F, Dhalwani NN, Davies MJ, Bakrania K, Celis-Morales CA, et al. Association of walking pace and handgrip strength with all-cause, cardiovascular, and cancer mortality: a UK Biobank observational study. **Eur Heart J 2017;38:3232-40**.

Physical fitness is an important predictor of cardiovascular and all-cause mortality and can be evaluated by different ways, as walking pace and handgrip strength. Is it possible that self-reported walking pace, without the need for any objective measurement, can

provide predictive information? And, which is the association of this subjective estimation with handgrip strength measurements? The answer is provided by a British cohort study.

Between 2006 and 2010, 420,727 individuals who at baseline were free from cancer and cardiovascular disease were incorporated to the UK BioBanK study. The following information was recorded: anthropometric and demographic data, diet, lifestyle and medication. Walking pace was subjectively assessed by asking the patients to describe it as slow, average or brisk. Handgrip strength was assessed through an objective measurement using a dynamometer. Mean age was 56.4 years and 54.8% were women. The population was divided by sex according to handgrip strength.

Among women, the bottom tertile corresponded to a mean handgrip strength of 17.2 kg and the top tertile to 30.4 kg. Handgrip strength was lower in older patients, while self-reported walking pace increased with greater handgrip strength: 31% of women in the bottom handgrip strength tertile reported brisk walking pace vs. 49% in the top tertile. Among men, the bottom tertile corresponded to a mean handgrip strength of 30.6 kg (greater than the top tertile among women) and the top tertile to 49.3 kg. Handgrip strength was also lower in older male patients, while self-reported walking pace increased with greater handgrip strength: 34% of men in the bottom handgrip strength tertile reported brisk walking pace vs. 48% in the top tertile.

During a median follow-up of 6.3 years, total mortality was 2%: 1.2% due to cancer, 0.4% due to cardiovascular disease and the rest due to other conditions. Walking pace was inversely associated with cardiovascular and total mortality in men and women but not with cancer deaths.

Handgrip strength was associated with cardiovascular mortality in men and with total mortality in men and women. The strength of the inverse associations between walking pace and mortality was greater when body mass index (BMI) was lower. For men, the HR for all-cause mortality in slow walkers compared with fast walkers ranged from 2.16 to 1.31 for participants in the bottom and top BMI tertiles, respectively. For women, the corresponding HR were 2.01 and 1.41, respectively.

The association between physical fitness with prognosis is well-known. In fact, a meta-analysis of 33 studies and 102,980 participants performed in 2009 demonstrated that 1-MET increase of maximal exercise capacity was associated with 13% risk reduction of all-cause mortality, and an adjusted 70% higher risk for those with low compared with high function capacity. This study provides the novel finding that even a self-reported and subjective assessment of exercise capacity evaluated through the walking pace can predict outcomes and invites us to be inquisitive when questioning our patients.

The question then is whether such fitness is a

marker or a risk factor. What does reduced physical fitness mean? Inflammation, decreased daily physical activity, unrecognized diseases, inflammatory activation, low muscle mass for the same BMI? If physical fitness is a marker, one should act on its conditioning factors to improve the prognosis. If it is a factor, improving it specifically with training or daily physical activity will lead to a better evolution.

Coronary circulation: a new way of understanding the association between pathophysiology and outcome.

Gupta A, Taqueti VR, van de Hoef TP, Bajaj NS, Bravo PE, Murthy VL, et al. Integrated Noninvasive Physiological Assessment of Coronary Circulatory Function and Impact on Cardiovascular Mortality in Patients With Stable Coronary Artery Disease. **Circulation 2017;136:2325-36.**

Coronary flow reserve (CFR) can be estimated as the ratio of maximal myocardial blood flow (MBF) during pharmacologically-induced coronary vasodilation to resting MBF. Coronary flow reserve is an integrated measure of flow through both the large epicardial coronary arteries and the microcirculation, and its impairment is a strong predictor of adverse prognosis. A decrease in maximal MBF or an increase in resting MBF reduces CFR: Therefore, it has been proposed that the integration of CFR with maximal MBF could be a better assessment of the conditions of coronary circulation and allow for comprehensive evaluation of patients with known or suspected stable coronary artery disease.

All the patients referred for a rest/stress cardiac positron emission tomographic (PET) scan at Brigham & Women's Hospital between 2006 and 2013 were included in this study. Flow was determined with labelled rubidium or ammonia and dipyridamole, adenosine, regadenoson, or dobutamine were used as the stress agents. The presence of necrosis and ischemia was documented. Rest and maximal MBF (in ml/g/min) were considered and CFR was calculated. Multivariate analysis was used to evaluate their impact on follow-up mortality after adjusting for age, sex, coronary risk factors, body mass index, known coronary artery disease, left ventricular ejection fraction (LVEF), revascularization procedures, and type of radiotracer or stress agent used for PET imaging. A cutoff value of 1.8 ml/g/min was considered for maximal MBF and of 2 for CFR. Values below these cutoff points were considered abnormal. Four groups were defined based on whether there was concordant or discordant impairment of these coronary flow indices.

A total of 4,029 patients were included; mean age was 66 years and 50% were women. The indication for the test was chest pain in 45% of the cases, dyspnea in 29% and preoperative risk evaluation in 14%. Known coronary artery disease was present in 40%

of the patients (28% had previous myocardial infarction) and 10% underwent revascularization within 3 months after the PET scan. Median LVEF was 57%. Median maximal MBF was 1.75 ml/g/min and median CFR was 1.72.

After a median follow-up of 5.6 years, 24.9% of the patients died, 9.7% due to cardiovascular causes (particularly among elderly patients, with greater prevalence of men and coronary risk factors, left ventricular dysfunction and impaired CFR and maximal MBF). In multivariate analysis, a HR for mortality of 1.83 (95% CI, 1.47-2.27) was associated to per unit decrease in CFR and a HR of 1.35 (95% CI, 1.13-1.61) per unit decrease in maximal MBF. Coronary flow reserve was a stronger predictor than maximal MBF. In fact, adjusted annual mortality was 1.5% in patients with both CFR and maximal MBF below cut-off values; it was also 1.5% in impaired CFR with preserved maximal MBF, 0.8% in preserved CFR with impaired maximal MBF and 0.5% when both CFR and maximal MBF were preserved above the cut-off value. At the end of 8.4 years follow-up, adjusted HR for mortality was 2.95 (95% CI, 1.89-4.59) when both CFR and maximal MBF were impaired; 2.93 (95% CI, 1.91-4.50) in patients with impaired CFR and preserved maximal MBF and 1.52 (95% CI, 0.81-2.86) in preserved CFR with impaired maximal MBF.

This study is very interesting from the physiopathological viewpoint. The concept of CFR integrates the response of the entire coronary circulation, and is a stronger predictor than maximal MBF, probably because it reduces errors in the measurement of the latter.

The group of patients with impaired CFR and maximal MBF had the highest burden of myocardial necrosis and ischemia: 47% of patients in this group had left ventricular involvement >10%, suggesting significant prevalence of obstructive coronary artery disease. In contrast, in the group with normal CFR and maximal MBF, mortality was so low that the presence of obstructive coronary artery disease was very unlikely. The findings of the intermediate groups are more striking. In the group of patients with impaired CFR and preserved maximal MBF, 70% were women and only 15% presented necrosis or ischemia involving >10% of the left ventricular mass.

Women have higher resting MBF than men, and this can contribute to explain the lower CFR. In addition, angina with normal epicardial vessels is more common in women. But it remains unclear if this group's risk is due to flow-related conditions or to other factors associated with female sex. On the contrary, patients with preserved CFR but impaired maximal MBF had better outcome despite 30% of the patients had necrosis or ischemia involving >10% of the left ventricular myocardium (which would suggest higher prevalence of obstructive coronary artery disease).

This study demonstrates a strong association between the characteristics of coronary artery flow and outcome. Possibly, factors not considered may contrib-

ute to explain at least this association in some way. Obviously, a systematic study using PET scan is by no means easy, due to costs and availability; and we can only regret that coronary angiography was not performed, as it would have strongly contributed to explain these findings.

Is the absence of risk factors good enough? Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in low-risk patients

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The LDL-cholesterol (LDL-C) hypothesis considers LDL-C as a strong determinant for the development of atherosclerosis and a causal factor in cardiovascular events. Evidence supporting this hypothesis stems from observational and interventional studies, mainly with statins but also with their association with ezetimibe and, recently, with PCSK9 inhibitors.

In general, these studies have included patients with normal or slightly elevated LDL-C values, but with a certain cardiovascular disease risk profile determined by the use of different population-based scores and equations. A sub-analysis of the PESA trial, led by Dr. Valentin Fuster, demonstrates that even when all risk factors seem to be controlled, we cannot remain calm.

The PESA study enrolled 4,184 cardiovascular disease-free persons between 40 and 54 years. Subjects with cancer or any disease expected to decrease life expectancy were excluded from the study. This sub-study included nonsmokers with untreated blood pressure <140/90 mm Hg, untreated plasma glucose <126 mg/dl and total cholesterol <240 mg/dl, LDL-C <160 mg/dl, and HDL-C ≥40 mg/dl. This subpopulation represents 42.5% of the total PESA study population. A subgroup of individuals with "optimal" risk factors was also considered, with untreated blood pressure <120/80 mm Hg, untreated plasma glucose <100 mg/dl, glycosylated hemoglobin (HbA1c) <5.7% and total cholesterol <200 mg/dl.

The 10-year risk of atherosclerotic cardiovascular disease was calculated using the equation recommended by the AHA/ACC and the Framingham risk score was used to estimate the 30-year risk. Baseline clinical and paraclinical variables were defined, including different biomarkers. All the patients underwent cardiac computed tomography and coronary artery calcification score was calculated and expressed in Agatson units. Vascular ultrasound was performed to determine the presence of plaques or intima-media thickness >1.5 mm. Subclinical atherosclerosis (SA) was defined as the presence of atherosclerotic plaques by vascular ultrasound or coronary artery calcification score ≥1. Participants were classified as disease free (0 vascular sites affected) or having focal (1 site), intermediate (2 to 3 sites), or generalized atherosclerosis (>3 sites).

The population consisted of 1,379 individuals; mean age was 45 years (51% in the 40 to 44 years of age subgroup) and 50% of patients were women. The majority of individuals (94.6%) had low 10-year cardiovascular risk (<5%) and the 30-year risk according to the Framingham risk score was low (<10%) in 54.6% of the patients and moderate (10-20%) in 35.6%. However, SA was present in 49.7% of participants: 46.7% had peripheral atherosclerotic plaques, 30.1% in the iliofemoral arteries and 22.7% in the carotid arteries. Coronary artery calcification was detected in 11.1% of participants, the majority of them with scores between 1 and 100. Among participants with optimal risk factors, 37.8% had SA. In multivariate analysis, male sex, age, LDL-C, and HbA1c were the only variables independently associated with the presence of SA. The same variables, and additionally VCAM-1 (vascular cell adhesion molecule) and cystatin C, were also associated with multiterritorial extent of the disease. Similar results were obtained in an analysis restricted to individuals with LDL-C <130 mg/dl. It was not possible to make the same analysis with LDL-C <100 mg/dl because of the low number of observations. As LDL-C levels rise, there is a linear and significant increase in the prevalence of SA in men and women, ranging from 11% in the 60 to 70 mg/dl category to 64% in the 150 to 160 mg/dl subgroup.

This study challenges our view of cardiovascular risk factors, showing that half of the participants with recommended values and almost 40% of those with "optimal" values have SA. The role of LDL-C is reinforced in the analysis, since only its values and those of glycosylated haemoglobin appear as a modifiable target independently linked to the incidence of SA. Should we then lower the cut-off values considered in primary prevention? Will it be necessary to detect SA in persons with apparently optimal conditions? Undoubtedly, further publications will be needed for a better characterization of the risk of atherosclerosis, the diagnostic yield and the benefit of recategorization offered by different studies, the cost-effectiveness of its implementation and the population to be screened. Perhaps, we may be witnessing a paradigm shift in which biochemical values may not be sufficient for decision-making.