JORGE THIERER

Bariatric surgery and prognosis: a meta-analys

Syn NL, Cummings DE, Wang LZ, Lin DJ, Zhao JJ, Loh M, et al. Association of metabolic-bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants. **Lancet. 2021;397(10287):1830-41.**

The incidence and prevalence of obesity have grown steadily around the world in recent decades. An essential part of the metabolic syndrome, obesity is associated with various pathologies, including high blood pressure, diabetes, obstructive sleep apnea, coronary artery disease and cancer. In 2019, 5 million deaths in the world were attributed to obesity. Various diets, behavioral therapy, pharmacological agents and, in the most extreme cases, bariatric surgery, are among the therapeutic weapons available to treat it. The latter has demonstrated improvement and even remission of associated pathologies, such as type 2 diabetes, sleep apnea and dyslipidemia. But the effect of bariatric surgery on long-term outcomes and specifically on harder endpoints, including long-term mortality, is not so clearly defined. This is attributed, among other factors, to the fact that most of the patients included in randomized studies are middle aged (and therefore a low event rate is to be expected), and to a follow-up that is often insufficient to demonstrate differences with conventional treatment.

We now know of a meta-analysis that included randomized and observational cohort studies in which bariatric surgery was compared with other treatment alternatives in obese patients. Studies of high methodological quality were selected and those that had specifically included obese patients with a particular pathology, except type 2 diabetes, were excluded. Information was also obtained from the so-called "gray literature". After an extensive review, 17 articles were selected, 16 of which corresponded to observational studies with cohorts of patients undergoing or not bariatric surgery and paired by different procedures, and one to a randomized study. Complex statistical procedures and specific algorithms were used; the event-free survival curves of the different studies were digitally processed to define their incidence in the successive follow-up stages; the population exposed in each stage and group was considered and the information could be reconstructed at the level of individual data. This information was finally meta-analyzed, adjusting for baseline characteristics, to obtain summary effect measures.

Among a total of 174 772 obese patients, 65 785 (37.6%) were treated surgically and the rest received traditional care. Median follow-up was 69.4 months. During this period, the annual incidence of all-cause mortality was 3.6 % in the surgical group and 8.9 % in the conventional care group (adjusted HR 0.50; 95% CI 0.48-0.53; p<0.0001). The number needed to treat (NNT) to prevent one death was 24.4 over a 10-year time frame, and 10.8 over 20 years. The meta-analysis estimated a median life expectancy gain of 6.1 years with surgery. A significant difference was verified between patients with and without diabetes. In the former, the adjusted HR was 0.41 (95% CI 0.37-0.45) and the NNT was 8.4 over a 10-year period and 5.3 over 20 years, with a median 9.3-year longer life expectancy in patients with surgery. In those without diabetes, the adjusted HR was 0.70 (95% CI 0.59-0.84), with a NNT of 29.8 over a 10-year time frame and 19 over 20 years, and a median 5.1-year longer life expectancy in surgically treated patients. There were no differences in adjusted mortality between the different surgical modalities (Roux-in-Y gastric bypass, gastric banding or sleeve gastrectomy). Considering a world population of 184 million severely obese patients, 30% of which have diabetes, and only 1% undergoes bariatric surgery, it was estimated that increasing this value to 2.5% among diabetic and 1.5% among non-diabetic patients would translate into more than 19 million life-years gained.

The link between the presence of obese and a poor cardiovascular and global prognosis has been consistently demonstrated in a large number of observational cohort studies. Between 39% and 49% of the world population is overweight (body mass index (BMI) ≥25 and <30 kg/m²) or obese (BMI ≥30 kg/m²). It is specifically estimated that there are more than 600 million obese adults in the world. Slightly more than 40% of deaths due to high BMI in obese people are attributable to cardiovascular disease. This is explained by the strong association of obesity with hypertension, diabetes and earlier development of atherosclerotic disease, a phenomenon in which dyslipidemia and inflammatory activation (adipose tissue is a source of pro-inflammatory cytokines) are strongly involved. Beyond these connections, there remains a substantial residual risk attributable to obesity in multivariate analyses, which forces us to think about other mechanisms not yet unraveled. The diagnosis of obesity generally lies on the measurement of BMI, but it is not an adequate predictor of the presence of excess visceral or intra-abdominal adiposity, which has proven to have pro-inflammatory and atherogenic activity, compared with subcutaneous adiposity. Therefore, additional measures such as waist circumference and waist-hip ratio assessments allow refining the classification and event prediction. Nevertheless, the criterion to participate in interventional and many observational studies is still fundamentally BMI due to its simple calculation.

Weight loss undoubtedly generates metabolic im-

provement, with attenuation of insulin resistance and inflammation. Weight reduction with diet, exercise or the usual pharmacological treatment has not consistently proved to generate a significant reduction in coronary events and even less mortality in obese patients. But the advent of GLP-1 agonists seems to mark a new stage in this regard. These agents have revealed to significantly reduce weight and visceral adiposity and improve biochemical parameters in patients with diabetes and obesity. We already know the favorable effect on cardiovascular and all-cause mortality of GLP-1 agonists in obese and non-obese patients with diabetes. We do not yet have results of randomized studies in obese patients without diabetes that demonstrate prognostic improvement with GLP-1 agonists. Regarding bariatric surgery, it is usually indicated in patients with BMI ≥40 kg/m², or between 35 and <40 kg/m² with severe medical problems linked to obesity. It has even been considered with a BMI between 30 and <35 kg/m² and difficult diabetes management. So far, we knew about the observational evidence on the reduction of major events in the Swedish SOS study, with non-randomized treatment assignment. In this study (around 4000 patients between surgery and usual treatment groups), surgical treatment was associated with a 3-year longer life expectancy. The undoubted merits of the present meta-analysis are the demanding quality criteria for incorporating studies, the large number of patients included, a mean follow-up of almost 6 years, the fact of presenting all-cause mortality as the endpoint, and the methodology used to reach the level of individual data, a cumbersome task but one that increases the reliability of the estimations. The effect of bariatric surgery appears powerful, especially in the context of diabetic patients, but also in those without this pathology. Even the gain in life expectancy doubles that of the SOS study, for various reasons, including an unequal distribution of baseline conditions that may have biased the evolution in favor of the control group in that study, decreasing the advantage that offers surgery. The weaknesses of the present analysis are that the control treatment is not standardized (which is logical because they are observational studies of the last 14 years); that the proportion of the different pharmacological agents that are part of the control group is not clear; and, of course, that the vast majority are studies in which the groups were generated by matching methods after the intervention, and only in the SOS study the treatment groups were defined prospectively, though none of them were randomly allocated. Therefore, it is not possible to exclude residual confusion and indication bias; thus, characteristics not taken into account may have influenced the results. In conclusion, with the evidence so far available, bariatric surgery seems to offer advantages over conventional treatment in patients with the usual criteria considered to deem this procedure as an option, especially in the presence of diabetes. There is still lack of evidence from randomized studies and from studies with new pharmacological treatments that can also improve the prognosis.

Excess pericardial fat predicts increased risk of heart failure

Kenchaiah S, Ding J, Carr JJ, Allison MA, Budoff MJ, Tracy RP, et al. Pericardial Fat and the Risk of Heart Failure. **J Am Coll Cardiol. 2021;77(21):2638-52.**

Based on the association of obesity with poor cardiovascular prognosis, several observational studies have been carried out focused on the relationship of the different body locations of fatty tissue with the occurrence of different endpoints: diabetes, coronary heart disease and heart failure. On the one hand, epicardial fat, located between the myocardium and the visceral pericardium, has cardioprotective properties but on the other hand, it is a source of pro-inflammatory and fibrosis-inducing cytokines, and has been associated with the development of coronary atherosclerosis. Less is known about the biological effect of paracardiac fat, located outside the parietal pericardium, and also a focus of metabolic activity. MESA investigators present now a study that analyzes the association of pericardial fat (a combination of epicardial and paracardiac fat) with the incidence of heart failure. As recalled, MESA was a prospective cohort observational study, which included between 2000 and 2002 a population of 6814 participants free of patent cardiovascular disease at the time of inclusion, with 45 to 84 years of age, 53% women and of diverse ethnic origin (38% Caucasian, 28% African American, 22% Hispanic and 12% Chinese American) who lived in 6 communities of the United States of America. In this publication, they analyzed the data of 6785 participants who underwent a cardiac computed tomography scan that allowed defining pericardial fat volume (PFV) located around the proximal portion of the major coronary arteries. The association of PFV with the incidence of heart failure was defined, adjusting for age, gender, race or ethnicity, cigarette and alcohol consumption and physical activity in a partial model, and also for diabetes, hypertension and dyslipidemia in a complete model.

Mean and median PFV were 80±42 cm^3 and 71 cm^3, respectively. Women had lower PFV than men, with means of 69 vs. 92 cm^3. During a median follow-up of 15.7 years, 5.7% of participants developed heart failure. The optimal cutoff points to dichotomize PFV as normal or high were 70 cm^3 in women and 120 cm^3 in men. Participants with high PFV had higher body mass index, waist circumference, hip circumference, waist-hip ratio, prevalence of hypertension, dyslipidemia and diabetes, and higher values of inflammatory biomarkers. There was a linear association of PFV with the incidence of heart failure. Each PFV increase of one standard deviation (42 cm^3) implied 34% increase in the risk of heart failure, greater in women (68%) than in men (25%) when adjusting only for age. In the model with full adjustment, the overall increase in risk was 22%, 44% in women and 13% in men, statistically significant in all cases. When considering high vs. normal PFV in the full adjustment model, the overall HR (95% CI) for the development of heart failure was 1.77 (1.42-2.20); 2.06 (1.48-2.87) in women and 1.53 (1.13-2.07) in men.

The independent prognostic value was maintained when adjusting for the different anthropometric indices associated with obesity. In a subgroup of people in whom an abdominal computed tomography was performed, a poor correlation of PFV with subcutaneous abdominal fat (r=0.18) but moderate with visceral fat (r=0.65) was verified. The association of PFV with the incidence of heart failure was maintained when abdominal fat was considered in the model; and in the same way it was sustained when including values of NT pro-BNP, interleukin 6 and C-reactive protein. Regarding the type of incident heart failure, elevated PFV was a good predictor in multivariate analysis of heart failure with preserved (HR 2.32; 95% CI 1.66-3.23) and mid-range (HR 2.05; 95% CI 1.02-4.11) ejection fraction, but not with reduced ejection fraction (HR 1.20; 95% CI 0.84-1.73).

Under normal conditions, epicardial adipose tissue acts as brown fat: it nourishes adjacent tissues, generates fatty acid combustion, and promotes the synthesis of adiponectin, which in turn has an anti-inflammatory and anti-hypertrophic effect. Under conditions of increased systemic inflammatory activity (obesity, diabetes), there is an increase in pericardial fat (PF), which shifts its metabolic profile towards lipolysis and the production of pro-inflammatory cytokines and leptin, with inflammation, interstitial fibrosis and microvascular rarefaction in the underlying myocardium. In several observational studies, this increase in PF is linked with an increased incidence of coronary events, after adjusting for age, gender and BMI. There is an association of PF with different vascular risk factors and visceral obesity. Its relationship with all-cause mortality has even been pointed out when considering age, gender, lifestyle, lipids, blood glucose, and circulating cytokines in a predictive model. Beyond these associations, it is significant that some anatomopathological studies in humans or laboratory animals have evidenced in the anterior descending artery the development of atherosclerosis in the epicardial segments, but not in the intramyocardial segments, which suggests a paracrine effect of cytokines generated by PF (in contact with the epicardial, but not the intramyocardial segments). It is then understood that PF (fundamentally its epicardial component) acts as a local transducer of systemic inflammatory phenomena, promoting lipogenesis in the epicardium and the subsequent production of cytokines, and installing a vicious circle where more systemic inflammation is followed by more local adipogenesis, and vice versa.

The aforementioned mechanisms then explain why the relationship of high PFV with double heart failure risk indicated in the mentioned article is not unexpected, and even less that the risk is concentrated in the development of heart failure with preserved or borderline ejection fraction, forms in whose genesis inflammation, insulin resistance and endothelial dysfunction play a primary role. Nor is it unexpected that weight loss in obese patients, or drugs that reduce the progression to, or hospitalization for heart failure in patients with diabetes (SGLT2 inhibitors or metformin), or in heart failure with preserved ejection fraction (statins or mineralocorticoid receptor antagonists), reduce PFV, while insulin or gliptins, which increase it, show a neutral effect or increase of hospitalization for this cause.

Is there a place for valve replacement in moderate aortic stenosis and heart failure with reduced ejection fraction?

Jean G, Van Mieghem NM, Gegenava T, van Gils L, Bernard J, Geleijnse ML, et al. Moderate Aortic Stenosis in Patients With Heart Failure and Reduced Ejection Fraction. **J Am Coll Cardiol. 2021;77(22):2796-803**.

In approximately 10% of aortic stenosis (AS) cases, there is simultaneous presence of heart failure with reduced ejection fraction (HFrEF). When AS is severe, valve replacement is usually decided; on the other hand, contradictions arise in the case of moderate AS. Some reports indicate a worse long-term prognosis for HFrEF in the presence of moderate AS, whereas others do not attribute to valve disease a decisive influence on the outcome. The discrepancy, logically, extends to the proposed treatment, from close follow-up with delayed valve replacement until AS becomes severe, to earlier intervention. There is new information available from an observational study of 3 centers, in Canada and the Netherlands.

In this study 262 HF patients with left ventricular EF (LVEF) <50%, and moderate AS were retrospectively selected, defined by an aortic valve area >1 and <1.5 cm^2 and peak transvalvular velocity >2 and <4 m/sec. The same number of patients with HF, without AS was included, matched with the previous ones by gender, age, functional class, LVEF, and glomerular filtration rate. The primary endpoint of the study was all-cause mortality after diagnosis. The secondary endpoint was a composite of death and hospitalization for HF. A follow-up of at least 1 year was defined. Mean age was 74 years, 77% were men, 71% hypertensive and 37% diabetic. In patients with AS, mean valve area was 1.24 cm^2 and mean transvalvular gradient 2.55 m/sec. Despite matching, LVEF was somewhat higher in the AS group (means of 38.5% vs 36.6%, p=0.01).

In a mean follow-up of 2.9±2.2 years and after adjusting for age, gender, body mass index, coronary risk factors, previous myocardial infarction, functional class and LVEF, the presence of moderate AS was the strongest predictor of mortality (HR 2.98; 95% CI 2.08-4.31; p <0.0001). Similarly, it was the strongest predictor of the composite endpoint (2.34; 95% CI 1.72-3.21; p <0.0001). In an analysis restricted to the 44 patients with AS who underwent valve replacement, and the corresponding matched patients, AS continued to be an independent predictor of death (HR 2.91; 95% CI 2.05-4.16; p = 0.01). When considering the 262 patients with AS, valve replacement appeared associated with better survival (HR 0.59; 95% CI 0.35-0.98). This was specifically associated with percutaneous implantation (TAVI), (HR 0.43; 95% CI 0.18-1; p = 0.05), but not with surgical replacement.

Among patients with HFrEF, AS can present differ-

ent profiles. In the case of severe AS (mean transvalvular gradient ≥40 mmHg), practice guidelines indicate valve replacement, without a limit of reduced LVEF to contraindicate treatment. In patients with mean gradient <40 mmHg (low flow-low gradient), dobutamine stimulation can offer different results. If mean gradient increases above 40 mmHg, and a valve area ≤1 cm² persists, the indication for replacement is maintained. If the mean gradient does not increase above 40 mmHg, but the valve area is still ≤1 cm², another imaging method is suggested, for example, a computed tomography with calcium score evaluation, to define if it is a severe AS (in which case replacement is suggested) or a pseudo AS. When the gradient does not increase, but the valve area exceeds one cm², it is understood as a pseudo-severe AS, actually a moderate AS. In this case, so far, the indication to continue with medical treatment for HFrEF predominates.

The problem is that many times the presence of even moderate AS implies hemodynamic overload for a damaged ventricle, with increased wall stress and myocardial O2 consumption, increased filling pressures and decreased coronary perfusion gradient, especially in patients with concomitant coronary artery disease, and diastolic and systolic dysfunction. However, if in severe AS ventricular dysfunction can be attributed to a significant increase in afterload, and we clearly understand that valve disease worsens the prognosis per se, in the case of moderate AS this is more difficult. How much of ventricular dysfunction is due to valve disease as a cause, and how much to other underlying phenomena, as for example coronary artery disease in the first place? And this is not an idle question, because, given the increased risk of a valve replacement in the presence of HFrEF we should be sure that the clinical condition will improve and the downward spiral of ventricular function will at least be interrupted if the intervention is carried out.

In the study here presented, moderate AS was an independent factor of poor prognosis, even when patients with valve disease had a 2-point higher LVEF. In previous observational studies, the information in this regard was discordant, and moderate AS sometimes weighed on the evolution and sometimes not. We must remember that in the presence of ventricular dysfunction the progression of AS to more severe forms becomes faster, so that different follow-up times as well as different patterns of covariates may have influenced the results. If the pathophysiological considerations and part of the observational studies support this criterion, valve replacement should be indicated. This is where we stumble with the lack of firm evidence, as there are no published results of clinical trials to date that have prospectively raised the comparison between valve replacement and full medical treatment. The results of the analysis in question suggest that TAVI in this group of patients would have advantage over medical treatment. This benefit would not be seen with surgery. Despite the comparison was carried out in patients matched by baseline conditions, the non-randomized nature of the intervention should not be ignored. In this sense, the TAVR UNLOAD study, currently under development, may bring a less methodological reprehensible response. It includes 600 patients, with moderate AS, LVEF between 20% and 50%, in FC ≥2, and with NT-proBNP >1500 pg/mL. They will be assigned, under optimal medical treatment in all cases, to receive TAVI or not. The endpoint is a composite of all-cause mortality, stroke, hospitalization for heart failure or valve disease, and changes in quality of life, hierarchically analyzed. We do not know if it will imply a definitive answer (it will be necessary to see the effect of the intervention and the pattern of medical treatment instituted, in times in which what is understood by optimal treatment of HFrEF has varied so much), but it will undoubtedly represent a progress on this topic in which therapy is still controversial.

Triglycerides, glycosylated hemoglobin and their association with atherosclerosis: revealing data from a Spanish study

Raposeiras-Roubin S, Rossello X, Oliva B, Fernandez-Friera L, Mendiguren JM, Andres V, et al. Triglycerides and Residual Atherosclerotic Risk. **J Am Coll Cardiol. 2021;77(24):3031-41.**

Rossello X, Raposeiras-Roubin S, Oliva B, Sanchez-Cabo F, Garcia-Ruiz JM, Caimari F, et al. Glycated Hemoglobin and Subclinical Atherosclerosis in People Without Diabetes. **J Am Coll Cardiol. 2021;77(22):2777-91.**

As reported, the Spanish PESA study, with a prospective observational cohort design in 4184 individuals between 40 and 54 years of age, free from manifest cardiovascular disease, evaluated through imaging studies the presence, progression, and clinical repercussion of atherosclerotic disease in different arterial territories. Patients with morbid obesity, renal dysfunction (glomerular filtration <60 mL/min/1.73m²), active cancer or any other condition that reduced life expectancy were excluded. The risk of major cardiovascular events was defined with the SCORE study values, and people with low (<1%) or moderate (1-<5%) risk at 10 years were included. Clinical, anthropometric and laboratory variables were evaluated on admission. A vascular ultrasound study was performed in all participants in 7 territories: bilateral carotid, iliac and femoral arteries, and infrarenal aorta. The presence of atherosclerosis was defined by the occurrence of plaques (focal protrusions >5mm thick, or >50% of the surrounding intima media, or diffuse intima-media thickness >1.5 mm). The coronary calcium score was determined in all participants, and a ^{18}F-fluorodeoxyglucose positron emission computed tomography was performed in a subgroup of patients to assess the presence of vascular disease, considering the 7 aforementioned territories, plus the ascending and descending aorta and the aortic arch. The study investigators have just published two analyses associating metabolic factors to subclinical atherosclerosis.

The most important lipid factor related to the development of atherosclerotic disease is undoubtedly LDL cholesterol. The role of other lipids has been pointed out, especially in patients with non-elevated LDL cholesterol, including triglycerides (TG). Treat-

ment guidelines recommend the use of statins in patients with TG >200 mg/dL when cardiovascular risk is high. New evidence on the relationship of TG with atherosclerosis in patients without an indication for statins according to guideline recommendations comes from the PESA study.

In this substudy, the analysis focused on TG, divided into three categories: high (≥150 mg/dL), high normal (100-149 mg/dL) or low normal (<100 mg/dL) values. LDL cholesterol was categorized according to European guidelines as normal or high, considering the baseline cardiovascular risk, with cutoff values of 116 mg/dL in low-risk people, and 100 mg/dL in those with moderate risk.

A total of 3754 participants was included in the analysis, with mean age of 45.5 years, 61.2% men, and 84.9% with low risk of major events at 10 years. Mean LDL cholesterol was 133±29 mg/dL, and slightly over 27% of participants had normal values. Mean TG was 92±52 mg/dL; 10.5% had high, 20.8% high normal and the remaining 68.7% low normal values. Compared with those with low normal values, participants with high values were older, with a poorer risk factor profile, and higher risk of events.

Subclinical atherosclerosis was detected in 52.5% of participants with low normal TG values, in 68.8% with high normal values and in 73% with high values. After adjusting for age, gender, traditional vascular risk factors, glycosylated hemoglobin (HbA1c), LDL and HDL cholesterol values, body mass index, family history, alcohol consumption, physical activity, and diet, high TG values compared with low normal ones were independently associated with the presence of subclinical non-coronary atherosclerosis (OR 1.38; 95% CI 1.05-1.68; p=0.008). The number of involved territories increased with the TG level: 13.9% of participants with low normal, 23.2% with high normal and 31.8% with high TG levels had at least 3 compromised territories. The association of elevated TG with respect to low normal values and the presence of atherosclerosis was independent of the LDL cholesterol category: OR 1.42; 95% CI 1.11-1.80 with high, and 1.85; 95% CI 1.08-3.18 with normal LDL cholesterol values. When considering TG as a continuous variable, and in the multivariate analysis, a significant 3% increase in the probability of atherosclerosis was verified for each TG increase of 10 mg/dL: 4% among those with normal LDL cholesterol (p=0.041) and 2% in participants with elevated LDL cholesterol (p=0.052).

There was no association of TG values with the calcium score, but there was a weak correlation with ultrasensitive C-reactive protein (r=0.29). ^{18}F-FDG uptake was higher the higher the TG value: the adjusted OR for high values compared with low normal values was 2.09; 95% CI 1.09-3.40.

Another important analysis is the one that establishes the association of alterations in carbohydrate metabolism with atherosclerosis. Traditionally, risk scores point out the presence of diabetes. However, although it is known that prediabetes carries an increased risk of events, this condition is not considered in the equations used, and HbA1c, a precise estimate of carbohydrate metabolism alterations, is not taken into account in the assessment of risk in people who do not have diabetes (HbA1c ≤6.4%). By using the same methodology mentioned for the TG analysis, those responsible for the PESA study highlighted the association of HbA1c values with subclinical atherosclerosis.

In this analysis, they considered 3973 participants without diabetes, with a mean age of 45.7 years and 62.3% men. Eight HbA1c categories were considered: ≤4.8% (reference); 4.9-5%; 5.1-5.2%; 5.3-5.4%; 5.5-5.6%; 5.7-5.8%; 5.9-6%; and 6.1-6.4%. Mean HbA1c was 5.4±0.3%. In an analysis with greater clinical sense, 3 categories were taken into account: values ≤5.2%, 5.3-5.6%, and 5.7-6.4% (prediabetes). Patients with prediabetes (22.6% of the total) had higher prevalence of the other risk factors, body mass index and risk of cardiovascular events according to the SCORE study.

When considering the 8 HbA1c categories mentioned, a progressively increasing prevalence of subclinical atherosclerosis became evident, from 46.1% in the reference category to 82% in those with HbA1c 6.1-6.4%. This was confirmed in each vascular territory considered separately. In a multivariate analysis taking into account age, gender, risk factors, body mass index and family history, a progressively increasing association of HbA1c categories with the number of plaques, compromised territories and calcium score was evidenced, reaching OR between 2 and 2.5 for the 6.1-6.4% category with respect to the reference category. However, not only a significant association was shown in the prediabetes range, but even the values 5.5-5.6% (21.2% of the total) had a significant association with subclinical atherosclerosis in a multivariate analysis, with OR 1.36; 95% CI 1.03-1.80. When considering SCORE values, it was evidenced that participants with moderate risk of events had a greater extent of atherosclerotic disease than those with low risk. The addition of HbA1c to the SCORE values allowed increasing the ROC area in predicting the extent of atherosclerosis, from 0.73 to 0.75 (p <0.001). But the association between increasing HbA1c values and subclinical atherosclerosis occurred in participants at low risk (84%, p <0.001) and not in those at moderate risk (p=0.33). Therefore, the additive value of HbA1c was found in the low-risk stratum. For 4 SCORE components (age, gender, smoking and blood pressure), a greater risk of atherosclerosis was evidenced with progressively increasing HbA1c values. In the case of cholesterol, the same occurred in those with values ≥200 mg/dL; on the other hand, with lower values, risk only increased in the range of prediabetes.

Although LDL cholesterol is the most important lipid factor involved in the development of atherosclerotic disease, the fact that despite adequate control of its values a significant residual risk still persists leads us to focus on other lipids involved. In this sense, TG have been targeted by numerous studies. It has been pointed out that they are not atherogenic agents per se, but act

as biomarkers of lipoproteins rich in these agents, and these lipoproteins are the ones which effectively exert the detrimental effect. Lipoproteins bind to apolipoprotein B and contain cholesterol, which they deliver to macrophages in atheromas. They are also pro-inflammatory agents, and this contributes to promote the development of atherosclerosis. The action of lipoprotein lipase is essential to hydrolyze these particles and reduce vascular risk.

An excess of cardiovascular and all-cause mortality, between 12% and 13%;, has been demonstrated for every 88 mg/dL increase of plasma TG levels, and this coincides with a reduction of the same order in a meta-analysis that globally considers various agents (niacin, fibrates, omega 3 acids), mainly in the presence of low HDL cholesterol. The lack of a clear evidence of event reduction with each of these specific agents, and the demonstration of the favorable effect of lifestyle changes and statins in reducing TG levels, resulted in the specific treatment not appearing to be a primary endpoint, but rather an adjunct to primary statin therapy. Practice guidelines only suggest reducing its values when there is risk of pancreatitis, or in patients with not so high values but with a high risk of events. In this case the agent of choice seems to be icosapent ethyl, based on the results of the REDUCE IT study, where the use of this drug was associated with a significant reduction of cardiovascular death and major cardiovascular events in patients with values >135 mg/dL, with established cardiovascular disease or diabetes and other risk factors, and with LDL cholesterol <100 mg/dL. In fact, in the STRENGTH study, a combination of omega 3 acids did not achieve the same effect. Therefore, a more precise analysis of the mechanisms of action and of the population profile involved in both studies is needed, and again calls into question the effect of the specific treatment of hypertriglyceridemia, pointing out that it goes beyond the reduction of the values per se.

The PESA group analysis raises the bar. Participants, in their middle age, do not have established cardiovascular disease; 85% have a low 10-year event risk, TG are >150 mg/dL only in 10% of cases, and in the vast majority they are out of any indication for treatment. However, if we pay careful attention to the baseline characteristics, the cardiovascular risk profile increases with each category of TG value; hence, the prevalence and the values of the other risk factors progressively increase. What is interesting is that, after adjusting for all of them, TG appear independently associated with the extent of atherosclerotic disease, and correlates, albeit weakly, with the presence of inflammation. Beyond the creation of categories, TG are linked to atherosclerosis by being considered as a continuous variable. Elevated TG then become an indication of the presence of atherosclerosis even when the symptoms do not suggest it. It is still disturbing, however, that even in people with low TG, the prevalence of atherosclerosis exceeds 50% of cases.

The HbA1c substudy seems more novel. Clearly, diabetes is a vascular risk factor, due to mechanisms that have been tirelessly repeated: the association with other risk factors, but also the role of hyperglycemia as a potent inducer of inflammation, and the increased insulin resistance, with neurohormonal activation, altered lipid metabolism, endothelial dysfunction, and a prothrombotic condition are all causes that explain this increased risk. Diabetes is considered in all prognostic scores for cardiovascular events, and its presence is an indication for specific treatment, but also for statins. In this sense, it is striking that prediabetes, which has consistently proved to be an independent predictor of risk, is not taken into account in the scores, and that there are not such precise indications for treatment. And, again, the analysis of the PESA group unveils the relationship between the alteration of carbohydrate metabolism and atherosclerosis. It focuses on patients without diabetes, and same as with TG, the presence of a "dose response gradient" is evidenced, which, beyond prediabetes (where it was expected) indicates excess risk with HbA1c values that we would understand as normal. And in this case, it is striking that the same relationship with blood glucose is not present, which opens the door to suspect that HbA1c is perhaps indicating the presence of another agent (advanced glycation end products?) as responsible.

Thus, in people without established cardiovascular disease, and with low risk of events when the traditional predictors are considered, there is a high proportion of atherosclerotic disease related to two factors that are not generally considered when defining risk, and with values outside the current indication for treatment. The relationship is continuous, not categorical. As these are cross-sectional studies (the presumed exposure and the event are defined simultaneously), causality cannot be strictly established. Are TG and HbA1c responsible factors, or do they point to an underlying mechanism, for example inflammation? The increase in each of them has been indicated as a result of inflammatory activation, but at the same time as its inducer. The answer is not simple. Another question. In the presence of subclinical atherosclerotic disease, should pharmacological treatment be indicated to reduce TG and HbA1c considering lower thresholds than the current ones? This is on the same line, although with even less evidence, than proposing lower cutoff values for LDL cholesterol or blood pressure. So far, a behavior of this type is proposed when global cardiovascular risk is high. But in the HbA1c substudy, 56.5% of people with low score according SCORE had subclinical atherosclerosis, and it was in these low-scorers that HbA1c added more to prognostic discrimination. And one last remark: with imaging studies we go from a definition of disease "risk" based on clinical criteria or laboratory values, to an accurate demonstration of the "presence" of disease. How could we speak of low risk if the imaging study gives us back the presence of atherosclerotic plaques in more than one territory? Will our way of approaching disease, and the criteria for establishing treatment in the so-called "primary prevention" change? And what shall we call "primary prevention"?

Association of sodium intake with mortality: an ecological study in 181 countries

Messerli FH, Hofstetter L, Syrogiannouli L, Rexhaj E, Siontis GCM, Seiler C, et al. Sodium intake, life expectancy, and all-cause mortality. **Eur Heart J. 2021;42(21):2103-12.**

The relationship between high sodium intake and the development or worsening of hypertension is an uncontested concept, attested by a large number of observational studies and meta-analyses. The recommendation to limit sodium intake is common to all clinical practice guidelines, with different cutoff values depending on the guideline and whether it refers to healthy or hypertensive people, or with other pathologies such as heart failure in which a consumption of up to 2 g of sodium (equivalent to 5 g of table salt) is usually recommended. Therefore, as a corollary, the assumption arises that a higher sodium intake should be associated with a worse cardiovascular evolution and higher mortality could even be suspected. A correlation or ecological study challenges this assumption.

The relationship between sodium intake, life expectancy, and all-cause and specific mortality was considered in 181 countries. Population, socioeconomic, gross domestic product, and life expectancy data for each country were obtained from sources of the United Nations and the World Health Organization. The national per capita sodium consumption standardized by age was obtained from a publication of 2010, estimated from the analysis of urinary sodium in 24-hour samples. For each country, the healthy life expectancy at birth and at 60 years of age, and the age-standardized mortality rate were considered. The concept of healthy life expectancy refers to the years of life that a person is supposed to live in complete health, taking into account the years lost due to disability, and adjusting for age, gender and comorbidities. The data for each predictor variable were those corresponding to the year 2010, to coincide with the year of sodium consumption assessment. Since the relationship found between sodium intake and life expectancy or mortality was non-linear, a quantile regression model was established, in which this relationship was separately explored for the 25th, 50th and 75th percentiles of each outcome.

Sodium consumption ranged from 1.48 g/day per capita in Kenya to 5.98 g in Kazakhstan. Healthy life expectancy at birth ranged from 42.7 years in the Central African Republic to 74.8 years in Singapore, and at 60 years between 9.8 years in Sierra Leone and 20.3 years in Japan. In an unadjusted analysis, the model that best described the association of sodium consumption with healthy life expectancy was a non-linear one, which showed an increase both at birth and at 60 years of age, until reaching a consumption of 4-5 g of sodium (equivalent to 10-12.5 g of salt). With higher consumption values, the relationship remained stable, and only decreased slightly with the highest values. There was no relationship between sodium consumption and mortality from non-communicable diseases, but there was a negative correlation with all-cause mortality (lower mortality with higher intakes). The cited associations were maintained when adjusting for body mass index and gross domestic product. The association was significant for the 25th, 50th, and 75th percentiles in the case of healthy life expectancy and all-cause mortality; on the other hand, in the case of healthy life expectancy at 60 years of age, it was only significant in countries in the 25th percentile of this expectancy.

A similarly adjusted analysis, focused on the 46 countries with the highest per capita domestic product, again revealed a positive association of sodium consumption with healthy life expectancy at birth (R2=0.53) and negative with all-cause mortality (R2=0.50); on the other hand, there was no relationship with healthy life expectancy at 60 years of age.

As has been consistently demonstrated, since higher sodium intake is systematically linearly associated with higher blood pressure levels, then, one could also assume a linear relationship with cardiovascular and global mortality. The available information in this regard is not conclusive. Some meta-analyses suggest that a high sodium intake in the diet is associated with an increased risk of stroke. In a randomized study of patients with high normal pressure, sodium consumption showed a linear relationship with mortality, with the greatest reduction achieved in those with consumption <2.3 g per day. On the other hand, the observational PURE study reported, in more than 100 000 participants from 17 countries, a J curve when relating urinary sodium excretion (as an expression of its consumption) with evolution, with an excess risk of mortality for values ≥7 g or <3g daily. And a careful analysis of all the available information questions the indication of such a low consumption, by pointing out that the majority of the world population consumes between 2.3 and 4.6 g of sodium per day, and this does not imply that their cardiovascular risk is high. On the contrary, figures higher and lower than this reference values seem to be associated with a higher risk of cardiovascular events and mortality. Age (the impact of a high consumption is greater in the elderly), hypertension (in its presence, high consumption implies a greater risk) and the concomitant intake of potassium (greater risk in the presence of diets low in this mineral) act as effect modifiers.

The study we are discussing is novel in terms of its design to evaluate the relationship between sodium intake and mortality. This is a correlation or ecological study. In this type of study, the observation units are not healthy or sick people, as in the observational or randomized studies analyzed so far, but rather conglomerates (countries, provinces, cities). For each one, the association between 2 continuous variables is proposed, one that is understood as a predictor and the other as a result, and then the existence of a linear relationship, globally considering the association between both in all the observations, is verified. In this particular case, the association between sodium intake (inferred from urinary excretion) and several evolution estimators: mortality and healthy life at birth and at 60 years of age was ex-

plored. Significant aspects are data from practically all the countries and the consideration of a healthy life expectancy (a way of adjusting for the risk of stroke, which could increase with sodium consumption). And clearly this parameter increases, and mortality from all causes decreases until reaching a consumption of 4-5 g and, by analyzing the curves, a milder positive effect even above these figures can be pointed out.

It is true that a problem with this type of study is falling into the so-called ecological fallacy: assuming that what happens at a global level is reproduced at the individual level in each observation unit. For example, ecological studies confirm that countries with a higher gross domestic product have a higher average BMI. It could then be thought that this relationship is reproduced in each country. But the opposite is true: people with higher incomes have a lower average BMI. In the case of the study at hand, the fear of falling into this fallacy is removed: the data from this ecological study seem to be in line with, or at least not contradict, the evidence from studies focused on individuals. It has been repeatedly pointed out that a low sodium intake generates activation of the renin angiotensin system; alterations in lipid levels and kidney function have also been postulated, although not always corroborated. It is important to note that, in the case of cohort studies, it has been said that part of the association between low sodium intake and poor prognosis could be due to reverse causality: sicker people consume less sodium and therefore their prognosis is worse. In the case of this study, the relationship between sodium consumption and mortality occurred in all countries, from those with the lowest average life expectancy to those with the highest longevity. We would have liked to know the adjustment for potassium consumption figures, or for the prevalence of hypertension and cardiovascular disease in each country. And it is also clear that the relationship is not univocal: the country with the highest sodium consumption is not the one with the highest healthy life expectancy, and, in fact, the model that best describes the relationship is a non-linear one. But, clearly, the data from this study contributes to question widespread beliefs and guideline indications, and to wait for the generation of more evidence from interventional studies, surely pragmatic and based on large registries.

Anticoagulation in COVID-19 patients: ACTION study.

Lopes RD, de Barros ESPGM, Furtado RHM, Macedo AVS, Bronhara B, Damiani LP, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. **Lancet. 2021; 397 (10291):2253-63.**

In the year and a half that has elapsed since the start of the COVID-19 pandemic, different pathophysiological hypotheses have been formulated to explain the speed and severity of its progression and lethality. Among the mechanisms involved, macro and microvascular thrombosis has played a fundamental role. And, in fact, one of the consistently altered biomarkers in the course of the disease is D-dimer, whose elevation indicates more severe patients with a worse prognosis. This has led to the idea of anticoagulant treatment as one of the lines that should be systematically implemented. However, the modality or duration of anticoagulation to ensure the best results is not clearly defined. To answer this question, the ACTION study was carried out in 31 centers in Brazil. It was a randomized, controlled, pragmatic and open-label study, with blind adjudication of treatment.

Patients hospitalized for COVID-19 (confirmed by C-reactive protein, antigen or IgM assessment dating up to 14 days before randomization, whether or not the patient was hospitalized at the time of the examination), with D-dimer values above the normal maximum value in each center, were included in the study. Patients were randomly assigned in a 1: 1 ratio to receive therapeutic anticoagulation (TA) or prophylactic anticoagulation (PA). Therapeutic anticoagulation was carried out for 30 days in stable patients with rivaroxaban (20 mg per day, or 15 mg per day in patients with creatinine clearance between 30 and 49 mL/min or treated with azithromycin), and in unstable patients with subcutaneous enoxaparin (1 mg/kg twice a day) or intravenous unfractionated heparin (with the aim of achieving an activated partial thromboplastin time between 1.5 and 2.5 times the normal value). Unstable patients were switched to rivaroxaban once stabilized. Prophylactic anticoagulation was carried out with enoxaparin or unfractionated heparin, with the standard doses for prevention of venous thromboembolism. If a precise indication appeared, the patient was switched from PA to TA. Treatment crossover was only considered when going from PA to TA or vice versa, not when changing the therapeutic agent within the same modality. The primary efficacy endpoint was a composite of time to death, length of stay, and oxygen therapy duration in the first 30 days. A composite of venous thromboembolism, systemic embolism, acute myocardial infarction, ischemic or hemorrhagic stroke, and major adverse events in the extremities, with or without the addition of all-cause death, was considered as a secondary endpoint. The primary safety endpoint was the incidence of major or clinically relevant bleeding. Due to the open nature of the study, an independent committee, blind to the given treatment, adjudicated the events.

The intention to treat analysis was used for the results employing the win ratio method, which consists in pairing each member of a branch with each member of the other branch. Thus, pairs of patients are established in a number that is equal to the product of the number of patients in one branch by the number of patients in the other. For example, if there were 10 patients in each branch, 100 pairs of patients would be formed. In this case, the analysis was performed with stratification according to the clinical condition, stable or unstable. The results were evaluated at 30 days. Hierarchically, mortality was first analyzed in each pair. If one of the patients died and the other survived, the latter was con-

sidered the "winner." If both died, the "winner" was the one who had lived the longest time until death (at least 1 more day). If this first comparison was tied (because both had died with no difference in survival time, or both had survived until day 30), hospital length of stay was considered, and the one who had had shorter hospitalization was declared the winner (at least 2 days less). Had there been a tie again, the duration of oxygen therapy was considered, and the one who had had a shorter therapy (at least 2 days less) was declared the winner. If again no difference could be found, the comparison was finally declared tied. The win ratio is the quotient between the number of "wins" and the number of "losses" for each modality. A statistically significant value >1 (more wins than losses) in one branch implies that this modality is better than the other with respect to the endpoint considered. This analysis was repeated in each clinical stratum for each composite endpoint separately, and for the secondary endpoint. A mortality rate of 7%, an absolute reduction in mortality of 2% and reduction of 1.5 days in hospital stay and oxygen therapy duration were assumed.

Between June 2020 and February 2021, among a total of 3331 patients screened, 615 were included in the study, 311 in the TA group and 304 in the PA group. Mean age was 56.6 years; 60% were men and 25% were diabetic, and the average BMI was 30 kg/m2. In 75% of cases, patients received oxygen therapy (high-flow cannula 8%, orotracheal intubation 7% and non-invasive ventilation 1%), but only 6% were clinically unstable at the beginning of the period considered. Median time from symptoms onset until hospitalization was 8 days, and from hospitalization to randomization 2 days. In the TA group, the anticoagulant was rivaroxaban in 90% of the cases and in the PA group, 84% started with subcutaneous enoxaparin. More than 99% of patients fulfilled the protocol in each branch. The percentage of "wins" was 34.8% for TA, 41.3 for PA and 23.9% of comparisons were ties. The win ratio for TA was 0.86 (95% CI 0.59-1.22; p=0.40). There was no difference in any of the components of the primary efficacy endpoint, or in all-cause mortality (11% in the TA group, 8% in the PA group). There was no difference in the subgroup analysis that considered age, oxygen therapy, use of corticosteroids, risk factors, and cardiovascular history. There was a difference in the incidence of major or clinically relevant bleeding (8% in the TA group, 2% in the PA group) with RR 3.6 (95% CI 1.6-8.3; p=0.001%).

Especially in severe forms of SARS-CoV-2 infection, the activation of thrombotic phenomena is frequent, with conditions of disseminated intravascular coagulation, thrombotic microangiopathy, and venous and arterial thromboembolism. Endothelial dysfunction, hypoxia, and cytokine storm with a notable increase in inflammatory and procoagulant activation are among the responsible mechanisms mentioned. Some of the clinical manifestations of this prothrombotic state are arterial ischemia of the lower limbs, the presence of renal dysfunction or stroke, and, of course, lung thromboembolism, which has been attributed a substantial part of the deaths, often sudden, caused by the virus. Also, in patients with respiratory distress syndrome, the presence of microthrombi has been demonstrated at arteriolar and capillary levels in the pulmonary circuit. Not surprisingly, the elevation of D-dimer is a universal predictor of death in this context. A third of patients with COVID-19 have an elevation of this marker, but this occurs in just under 25% of survivors, and in just over 80% of deceased patients. Hence, there is only one step to assuming that anticoagulant treatment should be established in patients with COVID-19 when activation of coagulation is suspected. Unlike conventional sepsis, in which anticoagulation has not been shown to improve the prognosis, in COVID-induced pneumonia there is evidence from observational studies on the better evolution of anticoagulated patients. It is true that we do not have randomized trials of anticoagulation vs. standard treatment; the observational evidence has been judged so strong that in severe forms of the disease the decision to anticoagulate the patient is universally accepted. It is not clear what the anticoagulant dose or the best agent should be. And even D-dimer has not always been used as a criterion to decide indication, agent or scheme. The ACTION study is then understood as the attempt to answer these doubts. However, it is clear that patients with a clear indication for TA were not included in the study due to the presence of an already established thromboembolic phenomenon, disseminated intravascular coagulation, etc. The conclusion about the lack of difference for TA vs. PA applies to patients in whom PA would be routinely indicated.

A separate paragraph for the design and method of analysis of the study. In the face of explanatory clinical trials, (restrictive in the inclusion criteria for physicians and patients and very demanding and strict in procedures, comparisons and follow-up), which undoubtedly gives them great internal validity but makes them little representative of reality, the pragmatic studies such as ACTION, more lax in each of the aforementioned aspects, and therefore with greater external validity, gain an increasing place in clinical research, especially when, as in this case, a new agent is not tested, but strategies with known treatments are compared. The win ratio method, in turn, is gradually reaching greater diffusion, since it allows generating a huge number of comparisons with few participants, and significantly increases the power to detect significant differences. Its ability to define advantage or lack of it with clinical sense therefore stands out. It is not enough that there is a significant difference in the response variable, but the difference must be clinically significant: when is a better result effectively a "victory", and when, even if it is better, can it be labeled as a "tie"? For example, in the case of length of hospital stay, and even when it was shorter in one member of the comparison than in the other, it was only possible to speak of victory if it was two days shorter. Designs more representative of everyday reality, novel methods of analysis; clinical research is slowly changing its standards. We believe that for the better…