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Three studies with gliflozins in different contexts, and a meta-analysis

Three significant studies exploring the use of sodium-glucose cotransporter 2 inhibitors or gliflozins and a meta-analysis involving one of these studies have been recently published and another one disclosed a year ago. Each of them has relevant information that promises to influence decision-making in patients affected by prevalent diseases and with a strong prognostic impact.

VERTIS-CV study

Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. **N Engl J Med. 2020;383(15):1425-35.**

The recent ADA congress reported the results of the VERTIS-CV study with ertugliflozin. This study included patients with type 2 diabetes, HbA1c between 7% and 10.5% and established atherosclerotic disease. A rare situation arose with this study. There was an original protocol of approximately 4,000 patients whose inclusion ended in 2013 It was, as was common then, a non-inferiority study. Following the results of the EMPAREG Outcomes study, which demonstrated the superiority of empagliflozin over placebo in patients with type 2 diabetes, with a reduction in the incidence of major adverse cardiovascular events (MACE), cardiovascular mortality and all-cause mortality, an amendment was proposed for the VERTIS-CV study. The number of patients was doubled and a superiority hypothesis was raised for cardiovascular and renal events. The study excluded patients with FC IV heart failure, or with glomerular filtration <30 mL/min/1.73 m2. This was a multicenter, double-blind, placebo-controlled, event-driven study. Patients were randomly assigned to placebo, or ertugliflozin in daily doses of 5 mg or 15 mg, in a 1: 1: 1 ratio. The primary endpoint was the incidence of MACE: a composite of cardiovascular death, non-fatal acute myocardial infarction (AMI), and non-fatal stroke. Secondary endpoints were a composite of cardiovascular death or hospitalization for heart failure, cardiovascular death, and a composite of renal death, transplantation, dialysis, or doubling of serum creatinine. A non-inferiority MACE analysis was performed with a 30% margin, taking into account all the patients who had taken at least one dose. A superiority and by intention-to-treat analysis was considered for the secondary endpoint. Among 14,607 patients initially considered, 8,246 were finally randomized and analyzed. Mean follow-up was 3.5 years and 88% of the patients completed the study. In the placebo group 27.9% of participants discontinued the treatment compared with 23.5% of patients in the ertugliflozin group.

Mean age was 64 years and 70% were men. Mean duration of diabetes was 13 years, mean HbA1c 8.2%, mean glomerular filtration rate 76 mL/min/1.73 m2 and 22% of patients had glomerular filtration rate <60 mL/min/1.73m2. Seventy-six percent of patients had a history of coronary heart disease, 58% of coronary bypass graft surgery and 25% of heart failure. As in the other studies, almost 80% were on metformin medication and almost half of the patients on insulin. After 18 weeks, HbA1c was reduced by 0.5% and after 1 year there was an average weight reduction between the two doses of 2.6 kg and of 3 mmHg in systolic blood pressure. The incidence of the primary endpoint was 11.9% in both groups (HR 0.97; 95% CI 0.85-1.11, p <0.0001 for non-inferiority); the HR was 0.91, 95% CI 0.77-1.07 for the 5 mg dose and 1.04, 95% CI 0.89-1.21 for the 15 mg. dose. There was no significant difference for any of the primary endpoint components, with HR 0.92, 95% CI 0.85-1.11 for cardiovascular death, and neither were there significant differences in subgroup analyses. There was also no significant difference for the endpoint of cardiovascular death or hospitalization for heart failure with an incidence of 8.1% for ertugliflozin and 9.1% for placebo, and a HR of 0.88, 95% CI 0.75-1.03, p=0.11. In subgroup analyses, those treated with diuretics derived more benefit than those who did not receive this medication. There was a significant difference in hospitalization for heart failure: 2.5% vs. 3.6% (HR 0.70, 95% CI 0.54-0.90, p=0.006). There was a tendency to reduce the incidence of the renal endpoint: HR 0.81, 95% CI 0.63-1.04. The incidence of adverse events was similar with drug and placebo, with excess urinary tract infections (12% vs. 10%), fungal genital infections both in men and women, but with no difference in the incidence of hypoglycemia, amputation or fracture.

EMPEROR-Reduced Study

Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. **N Engl J Med. 2020;383(15):1413-24.**

The next study to be analyzed is the EMPEROR-Reduced study. It included patients with heart failure, left ventricular ejection fraction (LVEF) ≤40%, in functional class II-IV, under optimal medical treatment and with glomerular filtration rate ≥20 mL/min/1.73 m2. To ensure the inclusion of patients with sufficiently severe heart failure, NT-proBNP ≥600 pg/mL was required in those with LVEF ≤30%, ≥1000 pg/mL if LVEF was between 31% and 35%, and ≥2500 pg/mL if LVEF was between 35% and 40%. It was also possible to include patients with LVEF >30% who, not having the required value of NT-proBNP, had been hospitalized for heart failure in the previous year. In case of presenting atrial

fibrillation, twice as much NT-proBNP was required for each LVEF category than in sinus rhythm. After a screening period of 4 to 28 days, patients meeting the inclusion criteria were assigned in a double-blind manner to empagliflozin 10 mg. daily or placebo.

The primary endpoint of the study was a composite of cardiovascular death or hospitalization for heart failure. Secondary endpoints were the number of hospitalizations for heart failure and the drop of glomerular filtration rate. To estimate the number of patients to be included, an annual incidence of 15% in the primary endpoint was assumed in the placebo group, a power of 90%, a two-tailed p value of 0.05 and a reduction in the primary end point of about 20%. In principle, it was established that 2,850 patients would be sufficient, but that if the incidence of events was slower than expected, the number could be increased to 4,000. Finally, 3,730 patients were included in the study. Mean age was 67 years, 76% were men, and 49.8% of patients had diabetes which was of ischemic etiology in 51.8% of cases. Seventy-five percent of patients were in FC II and 24.4% in FC III. About 31% had been hospitalized for heart failure in the year prior to inclusion. Mean LVEF was 27.5% and median NT-proBNP was approximately 1,900 pg/mL. Mean baseline glomerular filtration rate was 62 mL/min/1.73 m2. They were remarkably well-treated patients: 94.7% with beta-blockers, 69.7% with renin angiotensin system inhibitors or antagonists, an additional 19.5% with sacubitril/valsartan, and 71.3% with antialdosterone agents. In 31.4% of cases, a cardioverter defibrillator and in 11.8% a cardiac resynchronizer had been implanted.

Mean follow-up was 16 months with an annual incidence of the primary endpoint of 15.8% in the empagliflozin group and 21% in the placebo group (HR 0.75; 95% CI 0.65-0.86, p <0.001). There was a large reduction in hospitalizations for heart failure (10.7 vs. 15.5% per year; HR 0.70, 95% CI 0.58-0.85). There was a significant difference in the annual drop of glomerular filtration rate, greater in placebo than in the active treatment group: 1.73 mL/min/1.73 m2, 95% CI 1.10-2.37 mL/min/1.73 m2. There was a reduction in the composite renal endpoint (sustained drop in glomerular filtration rate of 40% or more, or a sustained filtration rate <15 mL/min/1.73 m2 in those with initial values ≥30 mL/min/1, 73 m2, or <10 mL/min/1.73 m2 in those with initial filtration rate <30 mL/min/1.73 m2, or need for chronic dialysis or kidney transplantation) from 3.1% in the placebo group to 1.6% in the empagliflozin group, HR 0.5, 95% CI 0.32-0.77.

This study did not show a significant reduction in cardiovascular mortality (7.6% vs. 8.1% per year; HR 0.92, 95% CI 0.75-1.12) or in all-cause mortality (10.1% vs. 10.7% per year; HR 0.92, 95% CI 0.77-1.10). During the study, an annual reduction of 0.16% in Hb A1c, 0.82 kg in weight, and 0.7 mmHg in systolic blood pressure was verified with treatment compared with placebo. Conversely, a 2.36 increase was observed in the hematocrit.

The DAPA-HF and EMPEROR-Reduced meta-analysis

Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. **Lancet. 2020;396(10254):819-29.**

It should be recalled that in patients with LVEF ≤40%, the DAPA-HF study with dapagliflozin had shown a reduction in cardiovascular mortality (6.5% vs. 7.9% per year; HR 0.82, 95% CI 0.69-0.98) and all-cause mortality (7.9% vs. 9.5% per year; HR 0.83, 95% CI 0.71-0.97). This difference with the EMPEROR-Reduced study triggered a series of speculations. The day after the results of EMPEROR-Reduced were known, a meta-analysis was published considering both studies with gliflozins in the context of heart failure with reduced LVEF: the EMPEROR-Reduced, we just commented, and the DAPA-HF trial.

The patients in both studies had similar age, gender distribution, heart rate, and baseline blood pressure. There was also no clinically significant difference in the prevalence of atrial fibrillation, ischemic etiology, or diabetes. EMPEROR-Reduced patients had lower LVEF and higher NT-proBNP values (almost 4 points less LVEF, and 450 pg/mL more NT-proBNP, reflecting the study inclusion criteria). Glomerular filtration rate was slightly worse (mean of 62 mL/min vs. 66 mL/min in the DAPA-HF). In contrast, there was a higher prevalence of patients in FC III in the DAPA-HF study (31% vs. 24%), which reveals the lack of perfect correspondence between symptoms and imaging or biochemical assessments. Both studies agreed on the excellent treatment of heart failure, with high use of antialdosterone agents and beta-blockers. There was greater use of sacubitril/valsartan and electrical therapy (cardiodefibrillator and resynchronizer) in the EMPEROR-Reduced patients.

In the EMPEROR-Reduced study, the annual incidence in the placebo group of the cardiovascular death or heart failure hospitalization endpoint was higher than in the DAPA-HF study: 21% vs. 15.3%. The difference was fundamentally in the higher incidence of hospitalizations: 15.5% vs. 9.8% per year, while the annual cardiovascular mortality in both studies was practically identical: 8.1% vs. 7.9% and all-cause mortality slightly higher: 10.7% vs. 9.5%.

The meta-analysis ruled out heterogeneity between both HR for all-cause mortality, with a resulting combined HR of 0.87 (95% CI 0.77-0.98). In other words, we can estimate a global reduction in total mortality of about 13% (95% CI 2%-23%). A similar situation occurred for cardiovascular mortality, with a combined HR of 0.86 (95% CI 0.76-0.98). The effects on hospitalization for heart failure were similar in both studies, and therefore the estimated global effect was expected: a reduction of 31% (95% CI 22% -38%). Finally, it should be kept in mind that the DAPA-HF study had not demonstrated a reduction in a renal endpoint slightly different from that of the EMPEROR-Reduced study (in this case, a

drop in glomerular filtration rate of 50% or more, or a sustained filtration value <15 mL/min/1.73 m2 or need for chronic dialysis or kidney transplantation): HR 0.71; 95% CI 0.44-1.16. The meta-analysis again raises a lack of heterogeneity between the results of both studies, with an overall HR of 0.62 (95% CI 0.43-0.90).

DAPA-CKD Study

Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. **N Engl J Med. 2020; 383 (15): 1436-46.**

Finally, we present the DAPA-CKD study. It included patients aged at least 18 years, with or without diabetes, with an estimated glomerular filtration rate between 25 and 75 mL/min/1.73 m2, and an albumin creatinine index between 200 mg/g and 5000 mg/g. They had to be medicated with a renin-angiotensin system inhibitor or antagonist at maximum tolerated dose. Patients with type I diabetes, polycystic kidney, heart failure in FC IV, and those with vascular events or revascularization in the last 2 months were excluded. It was established that patients with an estimated glomerular filtration rate between 60 and 75 mL/min/1.73 m2 should not constitute more than 10% of those included.

Patients were randomly assigned in a double-blind manner to dapagliflozin 10 mg/day or placebo. The primary endpoint of the study was a composite of: a) drop in estimated glomerular filtration rate ≥50%; b) end-stage renal failure defined as a filtration rate <15 mL/min/1.73 m2, sustained for at least 28 days, need for dialysis for at least 20 days or kidney transplantation; and c) death of cardiovascular or renal origin. The secondary endpoints were a renal endpoint, formed by those already mentioned, except for cardiovascular death, a composite of cardiovascular death or hospitalization for heart failure, and all-cause mortality. The sample size was defined by an expected 7.5% annual incidence of the primary endpoint, so 681 events in at least 4,000 patients would be enough to demonstrate, with a power of 90% and a 2-tail p value <0.05, a reduction of 22% in the group treated with dapagliflozin. An interim analysis was established when 75% of the events had occurred, and the possibility of early study end if superiority of the drug over placebo was demonstrated with a one-tail p-value <0.001.

In February 2017, the first patient was included, and in March 2020, when 4,304 patients had been randomly assigned and 408 endpoints had occurred (60% of those planned), the study was suspended due to the notable superiority of the dapagliflozin group. Mean age was 62 years, 67% were men. 67.5% suffered from diabetes, 10.9% from heart failure and mean systolic blood pressure was 137 mmHg. Ninety-seven percent of patients were treated with renin angiotensin system inhibitors or antagonists. The average estimated glomerular filtration rate was 43 mL/min/1.73 m2, and the median albumin/creatinine index was 950 mg/g.

The incidence of the primary endpoint was 9.2% in the dapagliflozin group and 14.5% in the placebo group (HR 0.61; 95% CI 0.51-0.72, p=0.000000028). There was a very significant reduction in the drop of the estimated glomerular filtration rate ≥50% (HR 0.53; 95% CI 0.42-0.67) and in the incidence of end-stage kidney failure (HR 0.64; 95% CI 0.50-0.82), both due to a drop in the incidence of filtration rate <15 mL/min/1.73 m2, sustained for at least 28 days (HR 0.67; 95% CI 0.51-0.88) as well as for the need of dialysis for at least 20 days (HR 0.66; 95% CI 0.48-0.90). The mean annual fall in glomerular filtration rate was 2.86 mL/min/1.73m2 in the dapagliflozin group and 3.79 mL/min/1.73 m2 in the placebo group with an annual difference of 0.93 mL/min/1.73 m2 (95% CI 0.61-1.25 mL/min/1.73 m2).

There was a significant reduction in the renal endpoint (6.6% vs. 11.3%, HR 0.56; 95% CI 0.45-0.68, p=0.000000018), the composite of cardiovascular death and heart failure (4.6% vs. 6.4%, HR 0.71; 95% CI 0.55-0.92, p=0.0089) and in all-cause mortality (4.7% vs. 6.8%, HR 0.69; 95% CI 0.53-0.88, p=0.0035).

In subgroup analyses, there were no differences according to age, sex, diabetes, glomerular filtration rate, or albumin/creatinine index. The effect seemed to be greater in those with systolic blood pressure <130 mm Hg than in those with higher values. The incidence of serious adverse events was lower in the dapagliflozin group than in the placebo group (29.5% vs. 33.9%, p .0016). The incidence of hypoglycemia was also significantly different (0.7% vs. 1.3%, p=0.03).

These three studies refer to the use of gliflozins in diseases strongly linked by physiopathology and natural history: diabetes, heart failure and kidney failure. In this sense, they can be seen as approaches to different edges of a common problem. Each of them deserves some particular comments.

The VERTIS-CV study enrolls in the tradition of type 2 diabetes studies with gliflozins that we learned about in the last five years: EMPAREG Outcomes with empagliflozin, CANVAS and CREDENCE with canagliflozin, and DECLARE with dapagliflozin. As in these studies, a non-inferiority goal is initially postulated with respect to placebo, and similarly to these studies, complies with it. But unlike previous studies, it does not manage to demonstrate a significant reduction in overall mortality and that of cardiovascular origin (as EMPAREG Outcomes), in the incidence of MACE (as EMPAREG Outcomes, CANVAS and CREDENCE), in the incidence of a composite endpoint of cardiovascular death and hospitalization for heart failure (as DECLARE and CREDENCE) or in the progression of kidney damage (as in the four studies cited). Despite this, a meta-analysis of the 5 studies does not indicate evident heterogeneity in the results: ertugliflozin may aspire to share the seat with its peers, although at first glance it appears not as effective. And it is interesting to note that the profile of the population included in the VERTIS-CV study is remarkably close to that of EMPAREG Outcomes: mean age (63 years in EMPAREG Outcomes vs. 64 years in VERTIS-CV), proportion of men (72% vs. 70%), mean HbA1c (8.06% vs. 8.2%), glomerular filtration rate (74 mL/min/1.73 m2 vs. 76 mL/min/1.73 m2), prevalence of atherosclerotic dis-

ease (100% in both cases), prevalence of coronary heart disease (75% vs. 76%), peripheral vascular disease (24% vs. 18%) and history of stroke (23% vs. 20%) are similar. The only marked difference that appears between EMPAREG Outcomes and VERTIS-CV is the prevalence of heart failure: 10% and 24%, respectively. Treatment for diabetes does not differ either, with similar percentages of metformin, sulfonylureas, and insulin use. Even the annual incidence of MACE in the placebo groups of both studies is similar: 4.39% in EMPAREG Outcomes, 4.03% in VERTIS-CV. Why do we emphasize these similarities? Because in recent years, when explaining why the effect on MACE and cardiovascular and overall mortality was greater and significant in EMPAREG Outcomes than in CANVAS or DECLARE, it was said that, since the profile of EMPAREG Outcomes patients was of greater severity and involvement than in the other studies, it was easier to demonstrate a reduction of harder endpoints. The results of VERTIS-CV come to disarm this explanation. In populations with similar baseline characteristics and evolution, empagliflozin in EMPAREG Outcomes demonstrates evident superiority, while ertugliflozin in VERTIS-CV must be satisfied with non-inferiority. It is clear that there are reasons that escape us, beyond the suspicion of different effectiveness of both drugs, for reasons that pharmacologists could perhaps explain better. There is indeed an endpoint where ertugliflozin achieves similar effects to the other gliflozins: it is the reduction in hospitalization for heart failure. Faced with the heterogeneity of these agents at other endpoints, the effect on heart failure is clear and homogeneous, as if it were, undoubtedly, the true "class effect". And this leads us to consider the results of the EMPEROR-Reduced study.

The EMPEROR-Reduced study confirms the beneficial effect of gliflozins in the context of heart failure with reduced LVEF. It confirms the ability of these agents to reduce the endpoint of cardiovascular death and hospitalization for heart failure, already demonstrated in the DAPA-HF study. It goes further than the DAPA-HF study in significantly demonstrating the ability of these agents to slow the progression of renal function decline; it apparently remains in debt for not showing a significant reduction in mortality. As we pointed out, this led to various explanations, which point to differences in drugs, populations, follow-up time, etc.

To begin with, it is worth noting that the inclusion criteria of the EMPEROR-Reduced study allowed assuming a priori a sicker population than that of DAPA-HF, simply due to the fact that higher values of NT-proBNP were required as LVEF approached 40 %, unlike DAPA-HF that admitted the same NT-proBNP value throughout the LVEF range. And, indeed, the goal was met: lower LVEF, higher NT-proBNP than in the dapagliflozin study. And yet… there were fewer patients in FC III, and the same annual cardiovascular mortality in the placebo group in both studies. We cannot, therefore, fail to consider the best baseline treatment of EMPEROR-Reduced patients: almost twice the amount of sacubitril/valsartan and greater use of electrical therapy may contribute to explain a similar prognosis despite its greater severity. In the field of speculation it may also be assumed that in the course of hospitalizations for heart failure (almost 15% per year in the placebo group, compared to 10% in DAPA-HF) the treatment may have improved even more, with crossover of renin angiotensin system inhibitors or antagonists to sacubitril/valsartan and the adoption of other measures that could have contributed to improve the short-term prognosis.

Can the results of DAPA-HF and EMPEROR-Reduced be read as descriptors of different realities? Can it be understood that one of the drugs reduces mortality and the other does not in the context of HF with reduced LVEF? Clearly not. Let us remember the HR and its 95% CI for total mortality in both studies: 0.83 (95% CI 0.71-0.97) in DAPA-HF, 0.92 (0.77-1.10) in EMPEROR-Reduced. The 95% CI of both studies overlap, to the point that the HR of each study is included in the 95% CI of the other. This alone is enough to understand the absence of difference. The meta-analysis confirms the lack of heterogeneity and postulates a common effect measure. We do not adhere to the idea that the shorter follow-up was responsible for the difference between the two studies: the gap was only 2 months (16 vs. 18), which does not seem to be enough time to significantly change the direction of the evidence. Instead, we prefer to think that it is quite possible that, in a better-treated population, the effect of a new treatment requires more time and more patients to manifest. In conclusion, the DAPA-HF and EMPEROR-Reduced studies can be seen as two manifestations of a new reality, in which gliflozins are drugs that are added to the arsenal of drugs capable of significantly improving the lot of patients with heart failure and reduced LVEF. So is understood by the recently published SAC-FAC joint recommendations.

We come to the DAPA-CKD study, which we understand as the true novelty among the studies we have analyzed. VERTIS-CV and EMPEROR-Reduced confirm things we already knew in the field of diabetes and heart failure. The DAPA-CKD study is as novel as the DAPA-HF study was at its time: the latter expanded the field of action of gliflozins to heart failure with reduced LVEF; the former does the same for kidney failure. It is true that patients with diabetes predominate in the study, but a third of the participants are not affected by this disease. The evidence in DAPA-CKD completes the path started in previous studies: gliflozins are nephroprotective beyond diabetes and heart failure, and they are also nephroprotective in patients who already have kidney damage, free of both diseases. They slow the progression of renal decline, but also improve the vital prognosis. What are the mechanisms presumably involved in cardiovascular and renal protection? Many and very varied: the promotion of an intracellular "fasting" state that activates the autophagy mechanism allowing to restore functioning organelles and eliminate damaged ones; a metabolic deviation favorable to the oxidation of fatty acids and an increase in the production of ketone bodies, a more convenient energy source for the myocardium; a reduction of epicardial fat, which improves diastolic function; an anti-inflammatory effect with improvement of endothelial

function and reduction of fibrosis; a reduction of sodium reabsorption in the proximal convoluted tube by blocking the sodium hydrogen exchanger 3 (NH3), with natriuresis, reduction of stiffness and blood pressure, with a preferential decrease in interstitial rather than intravascular volume; blockade of the NH1 exchanger in the myocardium, thereby reducing the entry of sodium into the fiber, with a decrease in the entry of calcium and the activation of intracellular cascades that promote necrosis and apoptosis; retitution of the glomerular tubule feedback, with reduction of glomerular hyperfiltration due to restoration of the afferent arteriole tone and delay in the progression of nephropathy. Other mechanisms involved in the delay of kidney damage are hemodynamic improvement, an anti-inflammatory effect, blood pressure and uric acid reduction, and enhanced erythropoietin production, with an increase in the hematocrit.

And why do we say "allegedly"? Because until now, mechanistic studies have not been able to unravel which of all those mentioned mechanisms is responsible for the phenomenon. We prefer to think that, if death is multivariate, the mechanisms that contribute to delaying it must also be manifold. To conclude, the spectacle we witness is overwhelming: in 5 years drugs that were tested under the assumption of non-inferiority in the field of diabetes (we were satisfied that they did not generate significant cardiovascular damage and that they complied with their hypoglycemic role) become agents of first choice in diseases that, obviously, are much more closely related than we believed.

Having Takotsubo syndrome does not exclude coronary heart disease. Data from an international registry

Napp LC, Cammann VL, Jaguszewski M, Szawan KA, Wischnewsky M, Gili S, et al. Coexistence and outcome of coronary artery disease in Takotsubo syndrome. **Eur Heart J. 2020;41(34):3255-68**.

Takotsubo syndrome is often clinically indistinguishable from an acute coronary syndrome. Most patients present with chest pain and troponin elevation, and almost half present with ST-segment elevation on the ECG. The traditional diagnostic criteria require the absence of obstructive coronary artery disease, and for this reason the diagnosis of certainty requires the performance of a coronary angiography. When the motility disorder on echocardiography or angiographic ventriculogram coincides with the distribution territory of a coronary artery, the diagnosis of Takotsubo syndrome is excluded. The routine performance of coronary angiography to certify the diagnosis has evidenced that a not inconsiderable proportion of patients with the syndrome present with accompanying coronary artery disease. A recent analysis of the international Takotsubo registry (which includes 40 centers from 12 countries) adds numbers to this coexistence. This registry incorporates prospective and retrospective patients, based on clinical, ECG, laboratory, and imaging data.

A total of 1,016 patients who underwent angiography and ventriculography able to be analyzed were considered in this analysis. Mean age was 68 years and almost 91% were women. At the time of diagnosis, 78% had chest pain and 42.6% had ST-segment elevation. In 58.6% of cases, the motility disorder was apical and in the rest in another location (mid-ventricular, basal or focal). Mean left ventricular ejection fraction (LVEF) was 41.4%. In 35.7% of cases, patients did not have coronary artery disease; 41.3% evidenced non-obstructive coronary artery disease, and the remaining 23% (n=234), obstructive coronary artery disease, defined as lesions ≥50%. Compared with the rest, patients with obstructive coronary artery disease were older, more frequently men, and with a higher prevalence of coronary risk factors. There were no differences among the 3 groups in the frequency of chest pain or hemodynamic parameters. Although small in magnitude, a difference in mean LVEF was demonstrated according to the severity of coronary artery disease: 42.6% in patients with normal coronary arteries; 41.5% in patients with non-obstructive coronary artery disease, and 39.4% in those with lesions ≥50%. Among the latter, lesions ranged from 50% to 69% in one third of cases, and in the remaining two thirds they were ≥70%, including 4.7% with total occlusion. One third of patients with significant coronary artery disease presented with single vessel disease and the rest with 2 or more vessel disease. The anterior descending, circumflex, and right coronary artery were affected in 62%, 32%, and 43% of patients, respectively; in 4.7% of cases, there was a lesion of the left main coronary artery and in 3.4%, chronic total occlusions. In three patients, an acute occlusion was diagnosed.

The 234 patients with significant coronary artery disease were matched for age and sex with 234 patients from a Swiss registry of acute coronary syndrome (52.1% with ST-segment myocardial infarction, 40.6% with non-ST-segment myocardial infarction, and the rest with unstable angina) to analyze differences in baseline variables, form of presentation and outcome. Compared with patients with acute coronary syndrome, patients with Takotsubo syndrome and coronary artery disease presented less frequently chest pain (75% vs. 86%) and more frequently dyspnea (52% vs. 34%) but with a similar prevalence of coronary risk factors (except for a greater presence of diabetes among patients with Takotsubo syndrome, 35% vs. 26%) and ST-segment elevation (slightly more than half of the cases). There was also no difference in the number of cases with T-wave inversion, but the incidence of ST-segment depression was significantly lower: 7% vs. 31%. In patients with Takotsubo syndrome and obstructive coronary artery disease, LVEF was lower and natriuretic peptide values higher than in their counterpart with acute coronary syndrome. There was no significant difference in troponin values, and CPK values were slightly higher in the latter. The incidence of ventilatory assistance, cardiogenic shock, and death increased with the extent and severity of coronary artery disease in Takotsubo patients. The need for ventilatory assistance was greater in patients with Takotsubo syndrome and obstructive coronary artery

disease than in their counterpart with acute coronary syndrome. In contrast, there was no difference between these two cohorts in the incidence of cardiogenic shock (slightly more than 10%) and hospital mortality (close to 5%). Among Takotsubo patients and considering the entire spectrum, only the presence of obstructive coronary artery disease and a physical condition trigger were predictors of 30-day mortality in a multivariate analysis.

The data from this registry confirm that in a not inconsiderable proportion of patients with Takotsubo syndrome there is accompanying coronary artery disease, a fact that should not be surprising, considering in this subgroup the higher prevalence of men with vascular risk factors. As expected, a greater extent of coronary artery disease implies a worse prognosis. If years ago, the presence of coronary artery disease led to disregard the diagnosis of Takotsubo syndrome, now the situation seems to be the reverse: the registry reveals that many patients with this syndrome and accompanying coronary heart disease are discharged without statins, as if the presence of the heart disease would detract from the underlying coronary artery disease. What role does coronary heart disease play in Takotsubo syndrome? It is not clear that it is a determinant of its manifestation. In fact, we can argue that most patients do not have it; and, on the other hand, it is almost always a stable condition. There are, indeed, reported cases of acute coronary syndrome that, like other clinical conditions (stroke, sepsis or surgical stress), can generate a Takotsubo syndrome; but they are the minority. Comparison of patients with Takotsubo syndrome and coronary artery disease with patients with primary diagnosis of acute coronary syndrome yields some data of interest: the magnitude of troponin elevation is not a criterion to differentiate them; the vital prognosis is the same, but the need for respiratory assistance is greater. We still do not fully understand the pathophysiology of Takotsubo syndrome; the coexistence with coronary heart disease multiplies the risk and the questions.

Hypertension in young people: Its importance should not be underestimated

Luo D, Cheng Y, Zhang H, Ba M, Chen P, Li H, et al. Association between high blood pressure and long term cardiovascular events in young adults: systematic review and meta-analysis. **BMJ. 2020; 370: m3222**.

The association of high blood pressure with an increased risk of adverse cardiovascular events is out of the question. For a logical question of greater prevalence, the bulk of the information in this regard comes from older adults and the elderly. In randomized studies of antihypertensive drugs, the age of the patients included is also generally over 50 years. The volume of studies published on the prognosis imposed by hypertension to younger people is much smaller. For this reason, the recent publication here presented of a systematic review and meta-analysis focused on this relationship is welcome.

The analysis only included prospective, observational cohort studies of people between 18 and 45 years of age, for whom data on blood pressure and the incidence of cardiovascular events were available during follow-up. Studies in which the participants were afflicted by other pathologies that obscured the prognosis and inpatient studies were excluded. Blood pressure allowed categorizing those included into 5 categories: optimal (<120 / <80 mm Hg), normal (120-129 / 80-84 mm Hg), high normal (130-139 / 85-89 mm Hg), grade 1 hypertension (140-159 / 90-99 mm Hg) and grade 2 hypertension (≥160 / ≥100 mmHg) blood pressure. After an exhaustive review, 17 studies were selected, with 4,533,292 young adults, and an average follow-up of 14.7 years. The annual incidence of cardiovascular events for participants with optimal blood pressure was 1.97 ‰. Compared with them, the increase in blood pressure was associated with a progressive increase in the RR of events: 1.19 (95% CI 1.08-1.31) for those with normal blood pressure; 1.35 (95% CI 1.22-1.49) for those with high normal blood pressure; 1.92 (95% CI 1.68-2.19) for those with grade 1 hypertension and 3.15 (95% CI 2.31-4.29) for those with grade 2 hypertension. The annual risk of event difference with respect to optimal blood pressure varied from 0.37 ‰ (95% CI 0.16-0.61 ‰) for normal blood pressure, to 4.24 ‰ (95% CI 2.58-6.48 ‰) for grade 2 hypertension.

Specifically, the annual incidence of coronary events was 1.07 ‰ for participants with optimal blood pressure. The RR for these events was 1.09 for normal blood pressure; 1.25 for high normal blood pressure; 1.65 for grade 1 hypertension and 2.27 for grade 2 hypertension. The annual incidence of stroke was 0.94 ‰ for participants with optimal blood pressure, with a RR of 1.14, 1, 27, 1.89 and 2.87 for the subsequent categories. The annual incidence of all-cause mortality was 3.12 ‰ for optimal blood pressure, and greater risk was evident for people with grade 1 hypertension (RR 1.42) and grade 2 hypertension (RR 2.01) Considering blood pressure as a continuous variable, greater risk of coronary events and stroke was evident from a systolic blood pressure of 120 mmHg and a diastolic blood pressure of 80 mmHg, and greater risk of all-cause mortality, starting at 150-160 mmHg and 80-90 mmHg, respectively. The attributable population fraction at risk of cardiovascular events was calculated as 23.8%, adding 2.1% for normal pressure, 8.6% for high normal pressure, and 13% for hypertension.

We attend daily middle age patients who remember having had high blood pressure records many years before, which were not deemed important. Many times, it is the same patient who abandons follow-up; others, it is the doctor who does not pay attention to the finding. White coat hypertension, hyperadrenergic state, emotional hyperresponsiveness are explanations that are quickly resorted to. An undoubted merit of this systematic review on the impact of hypertension in young adults is the number of people observed and the length of follow-up. This enables to establish a graded relationship of risk with increasing categories of blood pressure. The attributable population fraction at risk is higher than for older adults, perhaps because over the years other pathologies add to hypertension and decrease its relative importance as a factor responsible for major events. Among the limitations of the

analysis, the heterogeneity between the different studies considered should be noted. A more precise analysis of factors not considered (dyslipidemia, hyperglycemia, comorbidities) could have reduced it. The demonstration of an increase in the relative risk of events should be assessed taking into account the baseline risk, which is low. Therefore, the number needed to treat to prevent a cardiovascular event is 552 for grade 1 hypertension, 1,236 for grade 2 hypertension, and close to 1,500 for high normal blood pressure. Large-scale interventional studies will be necessary to define the indication for antihypertensive treatment in young adults; meanwhile, the search for etiology in the cases with higher values, and the dietary and physical activity advice from an early age seem strategies of sure return.

Body mass index is not enough to assess the prognostic impact of obesity

Jayedi A, Soltani S, Zargar MS, Khan TA, Shab-Bidar S. Central fatness and risk of all cause mortality: systematic review and dose-response meta-analysis of 72 prospective cohort studies. **BMJ. 2020; 370: m3324.**

Traditionally, the definition of overweight and obesity rests on the calculation of body mass index (BMI). We know that the association of both conditions has a worse cardiovascular prognosis and higher mortality, as evidenced in numerous meta-analyses. However, the consideration of BMI as a measure of excess adipose tissue has received numerous criticisms, since in reality this measure does not allow to differentiate weight gain due to increased fatty tissue from that due to increased muscle mass. On the other hand, it also does not allow to discriminate the increase in abdominal and perivisceral fatty tissue (associated with increased inflammatory activity, oxidative stress, endothelial dysfunction, increased risk of diabetes, hypertension, coronary events and heart failure, neurological events and kidney dysfunction) from the femoral-gluteal fat deposit, associated with better prognosis. For this reason, it is suggested that other specific assessments of central obesity could be preferable to BMI when defining prognosis. In this sense, a systematic review and meta-analysis of observational studies providing data of interest on the subject is relevant.

It considered 72 prospective cohort studies, with a total of 2,528,297 participants, 30 studies from Europe, 22 from the United States of America, 16 from Asia, 2 from Canada, one from Brazil, and one from Trinidad and Tobago.

Fifty of them defined the association of waist circumference with all-cause mortality during follow-up. Each 10 cm increase in waist circumference was associated with a significant increase of 11% in total mortality (HR 1.11, 95% CI 1.08-1.13), 8% in men and 12% in women. The strength of association increased when adjusting for BMI, the HR reaching 1.17, 95% CI 1.13-1.22. In both men and women, the association assumed the shape of a J-curve, with the lowest HR in men for a waist circumference of 90 cm, and in women between 60 and 80 cm. The association was not significant over 60 years of age.

Hip circumference showed an inverse relationship with mortality: each increase of 10 cm was associated with a HR of 0.90 (95% CI 0.81-0.99). The inverse association was stronger when adjusting for BMI and waist circumference (HR 0.78); On the other hand, not considering these factors changed the strength of the association (HR 1.04, 95% CI 1.02-1.06).

Thirty studies analyzed the relationship of the waist-hip index with mortality. Considering that an increase in waist circumference and a drop in hip circumference are adverse parameters, finding a worse prognosis when increasing the waist-to-hip ratio is logical, with a 20% higher risk of mortality for each 0.1 increase in the index. The association was stronger in women, and weaker over 60 years of age.

The relationship between the waist-height index and mortality was also positive and direct, with a HR of 1.24 (95% CI 1.12-1.36) for each 0.1 increase in the relationship. Adjusting for BMI, the HR reached 1.42. In contrast, thigh circumference showed an inverse relationship with mortality, with a HR of 0.82 (95% CI 0.75-0.89) for each 5 cm increase. Hence (as in the case of the waist-to-hip ratio) each increase in the waist-to-thigh ratio of 0.1 was associated with a significant increase in mortality of 21%.

All the cited associations were stronger when adjusted for BMI.

This meta-analysis, valuable for including prospective cohort studies from different geographic locations and more than two and a half million participants, highlights the importance of a more accurate assessment of overweight and obesity conditions, and reveals the weaknesses of BMI, which is not a specific measure of central obesity, the one truly associated with a worse prognosis. Let us remember, on the other hand, that many times the BMI is determined by questioning the patient, and we all tend to declare more height and less weight than the real one. In this sense, the waist circumference seems more specific, and in fact its prognostic capacity is independent of the BMI. Despite this, there is a strong correlation between both measures. That is why the waist-hip index provides some additional information: it refers not only to abdominal fat but also to the femoral-gluteal adipose tissue. And since measuring the hip circumference is sometimes considered a somewhat complicated procedure, the waist-to-height ratio may be an alternative. Again: it is clear that these must be actual measurements, not estimates.

The marked heterogeneity of the studies should be mentioned as a limitation of the analysis. For each of the mentioned associations, the I2 value was above 70%, except for the relationship of the thigh circumference with prognosis, which in any case presented an I2 value of 47%. Do its limitations exclude BMI as a measure of interest and utility? Clearly not. We can make an analogy with the ejection fraction: we know that it is not perfect, but it is a measurement accessible to all. Other types of assessments (strain, for example) have a better prognostic capacity, but are more difficult to measure. In conclu-

sion: measurement of BMI seems to be a necessary but not sufficient condition to assess obesity and its relationship with future evolution.

Usefulness of catheter ablation in patients with atrial fibrillation and heart failure: a meta-analysis

Chen S, Purerfellner H, Meyer C, Acou WJ, Schratter A, Ling Z, et al. Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. **Eur Heart J. 2020; 41 (30): 2863-73.**

Atrial fibrillation and heart failure are frequently coexisting conditions. Both increase their incidence and prevalence with age, and have common precursors: hypertension, obesity, and valve disease. Each of them creates conditions that favor the occurrence of the other. The loss of atrial kick, a rapid and irregular ventricular response, dyssynchrony, ultrastructural alterations, the development of mitral regurgitation, and the sympathetic activation present in atrial fibrillation favor the development of heart failure. Structural changes, with left chamber hypertrophy and dilation, hemodynamic phenomena, electrical remodeling, and the neurohormonal and inflammatory activation typical of heart failure create the adequate substrate for the development of atrial fibrillation. In the context of heart failure, the prevalence of atrial fibrillation is higher as the functional class progresses. In numerous observational and randomized heart failure studies, patients with atrial fibrillation have a worse prognosis.

A series of randomized studies compared a rhythm control with a rate control strategy in patients with both conditions. Studies carried out before 2010 were: RACE-HF, AFFIRM-HF, AF-CHF, CAFÉ II. As we know, no significant differences could be demonstrated in mortality or incidence of embolic events between both strategies, and in fact there was a higher rate of hospitalization in the rhythm control branch. The explanation lies in the use of antiarrhythmic drugs in the rhythm control branch, with the inherent difficulty in achieving persistent maintenance of sinus rhythm, in addition to the adverse effects due to the use of medication, which increase in patients with impaired ventricular function.

In the last decade, catheter ablation therapy for atrial fibrillation, especially the isolation of the pulmonary veins, has grown dramatically. Studies have been published suggesting improvement in ventricular function, and the CASTLE-AF study even indicated a prognostic improvement in patients with heart failure and reduced left ventricular ejection fraction (LVEF). However, the fact that it was a highly selected population (only one patient out of 10 evaluated was included) reduced the impact of their conclusions. More recently, we learned about the results of the CABANA study, in which the intention-to-treat analysis did not show a clear advantage for ablation therapy, while a per-protocol analysis held the opposite. In the CABANA study, 15% of the patients had heart failure, and in the subgroup analysis the effect of the intervention was not significantly different.

We now know of a meta-analysis that considers all the studies carried out in the last decade in patients with atrial fibrillation and heart failure in which catheter ablation for atrial fibrillation was compared with medical therapy. It considers 6 studies (including the CASTLE-AF study) and the subgroup of patients with heart failure of the CABANA study. It includes a total of 1,112 patients, with mean age of 64 years, 78% men, mean duration of atrial fibrillation of 14 months, mean left atrial diameter of 48 mm and an average follow-up of 2.7 years. Except in the CABANA study, the control group was frequency control with medication; in the CABANA study it was pharmacological control of frequency or rhythm. We do not have the LVEF data of the CABANA study; in the other 6 studies it was less than 35%.

Compared with medical treatment, ablation was associated with lower all-cause mortality (10.7% vs. 18.9%, OR 0.51, 95% CI 0.36-0.74, p = 0.0003), lower rehospitalization rate (30.6% vs. 47.5%, OR 0.44, 95% CI: 0.26-0.76, p = 0.003), and similar stroke rate (2.8% vs. 4.7%, NS). The average improvement in LVEF after the procedure was almost 7%.

Atrial fibrillation, in the context of heart failure, can be a risk factor or marker. Patients with atrial fibrillation are older, symptomatic patients, with a higher prevalence of comorbidities. Thus seen, arrhythmia is a marker of higher risk. But, on the other hand, we know that atrial fibrillation aggravates heart failure, increases the risk of ventricular arrhythmia, leads to the use of drugs with a proarrhythmic effect, and increases the risk of an embolic event. For all these reasons it can also be considered a risk factor. If so, removing it would help improve the prognosis. Until now, drug-based pacing has not been shown to be better than rate control. The use of invasive therapy raises another scenario: higher success rate, and prevention of the adverse effects of medication. Several observational studies have already highlighted the benefits of catheter ablation. But logically these "real world" studies are subject to the presence of confounders that may be the ones truly responsible for the best evolution. In this sense, the meta-analysis that we present has the advantage of including only randomized studies. The doubt can be raised about external validity: these are studies carried out in reference centers, by trained operators, with very low rate of complications. Beyond reducing mortality and hospitalization rate by half, the improvement in LVEF deserves to be highlighted. Many times, we consider that the severe LVEF impairment is responsible for the presence of atrial fibrillation, and that this is an irreversible condition. The meta-analysis indicates that the situation may be the reverse: arrhythmia conditions functional impairment; its removal improves it. Of course, this strategy, which improves the prognosis in patients with heart failure and severe ventricular dysfunction, is applicable in well-selected cases. Patients in whom the operators did not trust a priori in a reasonable possibility of success have not been included. Properly defining predictors of successful therapy seems to be the next challenge.