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Estudio PARAGON HF: ¿debemos emplear sacubitril valsartán en la Insuficiencia cardíaca con fracción de eyección preservada?

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PARAGON-HF trial: Should we use sacubitril-valsartan in heart failure with preserved ejection fraction?

Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. **N Engl J Med 2019. DOI: 10.1056/NEJMoa1908655**

In the PARADIGM trial, the use of sacubitril-valsartan (SV) compared with enalapril, showed a significant reduction in the incidence of cardiovascular death and hospitalizations for heart failure (HF), and in the incidence of all-cause mortality in patients with reduced left ventricular ejection fraction (HFrEF). Since then, SV has been added to the therapeutic pool to treat this type of patients. In the case of heart failure with preserved ejection fraction (HFpEF) there is as yet no evidence that any neurohormonal antagonist improves prognosis. The success achieved with SV in HFrEF led the PARAGON-HF trial to test the hypothesis that similar results could be obtained in HFpEF patients.

The PARAGON-HF trial, a multicenter, randomized, active controlled study, included patients ≥50 years of age, with HF in functional class (FC) II-IV, evidence of structural heart disease, EF ≥45% in the last 6 months, and NT-proBNP ≥200 pg/ml if they has been hospitalized in the last 9 months, 300 pg/ml if they had not been hospitalized and a threefold increase level if they presented with atrial fibrillation. There was a single-blind run-in phase in which patients received half the target dose of valsartan and then half the target dose of SV. Those who admitted both phases without intolerance were assigned in a double-blind fashion to SV with a target dose of 200 mg every 12 hours or valsartan with a target dose of 160 mg every 12 hours. The primary endpoint (PEP) was a composite of cardiovascular death and hospitalizations (the first and subsequent ones) for HF. Secondary endpoints were changes in quality of life, renal function impairment (drop in glomerular filtration rate ≥50%, end-stage kidney failure or death of renal origin) and all-cause mortality. It was calculated that 1,847 events would be necessary to demonstrate with 95% power, 22% reduction in the PEP in the SV group, at the expense of 30% decrease in hospitalizations and 10% reduction in cardiovascular death, and with 80% power, 19% reduction in the PEP, at the expense of 25% decrease in hospitalizations and 10% decrease in cardiovascular death.

Among a total of 10,359 patients evaluated between 2014 and 2016, 4,822 overcame both run-in phases and entered the randomized study, and 4,796 patients participated in the final analysis (2,407 in the SV group). Mean age was 72.7 years, and 51.7 % were women. In 77.2% of cases, patients were in FC II and 19.4% in FC III. Median EF was 57% and NT-proBNP was 910 pg/ml. Mean systolic blood pressure was 130 mmHg and glomerular filtration rate was 63 ml/min/1.73 m2. Slightly more than 95% of patients were treated with diuretics, 86% received angiotensin-renin system inhibitors or antagonists, almost 80% betablockers and over 25% aldosterone antagonists.

A total of 1,903 events occurred in a median follow-up of 35 months (more than initially considered necessary), but without statistically significant differences between groups [PEP 12.8% in the SV group and 14.6% in the valsartan group (RR 0.87; 95% CI 0.75-1.01, p=0.059)]. The number of hospitalizations was 690 in the SV group and 797 in the valsartan group (RR 0.85; 95% CI 0.72-1.00, p=0.056). No differences were found in cardiovascular mortality (8.5% vs. 8.9%) or total mortality (14.2% vs. 14.6%). The subgroup analysis evidenced differences according to sex: interaction RR for SV vs. valsartan was 1.03 (95% CI 0.85-1.25) among men and 0.73 (95% CI 0.59-0.90) among women. Similarly, the effect differed for EF: RR 0.78 (95% CI 0.64-0.95) in patients with EF ≤57% vs. RR 1 (95% 0.81-1.23) with EF above this value. Functional class improved more frequently (15% vs. 12.6%) and less frequently worsened (8.7% vs. 9.6%) with SV compared with valsartan (OR for improvement 1.45; 95% CI 1.13-1.86). Also, there was lower incidence of renal function impairment: 1.4% vs. 2.7%. Sacubitril-valsartan produced greater reduction of blood pressure <100 mmHg (15.8% vs. 10.8%, p<0.001) but lower incidence of hyperkalemia. It also generated greater incidence of angioedema (0.6% vs. 0.2%, p=0.02), though in no case involving the airway.

The PARAGON-HF trial allows for a series of comments. From a strictly methodological point of view it did not reach the postulated objective, and can be interpreted as a negative study. However, the p value obtained (0.059) and the fact that the RR 95% CI is slightly over one (95% CI upper limit 1.01) does not rule out a beneficial effect. In any case, it can be interpreted that there was a trend towards improvement that did not reach clear statistical significance in the case of hospitalizations, and evidently not regarding mortality.

The effect in women but not in men is not something that has a clear explanation. Until now, we are unaware that a similar situation has been encountered with other neurohormonal antagonists. Can there be different structural conditions, level of neurohormonal activation, EF (even when all patients have HFpEF) that can unravel this mystery? For the moment, sex does not appear to be a condition that might influence

decision-making. Regarding differences according to EF, the net effect in EF ≤57% and not above this value, is biologically plausible. Ejection fraction in the middle range (41% and 49%) was initially considered as a condition that could be equated with preserved EF (pEF) in terms of treatment. However, the analysis of randomized studies with different neurohormonal antagonists in HFpEF suggests that patients with EF up to 50% could benefit with this treatment, in some cases due to reduction of cardiovascular mortality, and in others due to decreased number of hospitalizations. This has led the authors of the 2019 European Consensus of Heart Failure to postulate that the referred agents "might be considered" in HF patients with mid-range EF. It is possible that sacubitril-valsartan is enrolled in this line of agents, and can have a beneficial effect in patients at the bottom end of the pEF range, which are more similar to patients with lower EF. The lower the EF, the greater the importance of neurohormonal activation, with higher NT-proBNP levels. Regarding the involved pathophysiological mechanisms, patients with HF and EF<55% can be more similar to patients with EF near 40% than to patients with EF of 65% or 70%, in whom other factors different from neurohormonal activation (obesity, dysthyroidism, anemia, kidney impairment and amyloidosis) can be more relevant. Nevertheless, it should be borne in mind that this is an interpretation based on a subgroup analysis, and is by no means enough to postulate an imperative use of sacubitril-valsartan in this context, but only to take it into account as another option if deemed necessary. Perhaps studies directed to specific HFpEF phenotypes might contribute to generate a clearer scenario.

Three studies revalue the role of smoking in cardiovascular disease, and clarify the advantage of smoking cessation

Ding N, Sang Y, Chen J, Ballew SH, Kalbaugh CA, Salameh MJ, et al. Cigarette Smoking, Smoking Cessation, and Long-Term Risk of 3 Major Atherosclerotic Diseases. **J Am Coll Cardiol 2019;74:498-507.**

Duncan MS, Freiberg MS, Greevy RA, Jr., Kundu S, Vasan RS, Tindle HA. Association of Smoking Cessation With Subsequent Risk of Cardiovascular Disease. **JAMA 2019;322:642-650**.

Redondo-Bravo L, Fernandez-Alvira JM, Gorriz J, Mendiguren JM, Sanz J, Fernandez-Friera L, et al. Does Socioeconomic Status Influence the Risk of Subclinical Atherosclerosis?: A Mediation Model. **J Am Coll Cardiol 2019;74:526-535.**

Smoking, one of the most important vascular risk factors, is the focus of three cohort studies that were published simultaneously.

The first one is an analysis of ARIC, a prospective cohort study of 4 communities in the United States, which began enrollment between 1987 and 1989, and carried out follow-up visits every 3 years, then between 2011 and 2013 and the final one between 2016 and 2017. It included 15,792 participants between 45 and 64 years. For this analysis, those with established cardiovascular or peripheral vascular disease or those in whom variables of interest had not been collected were excluded from the study. The status in relation to smoking was defined in 13,355 participants as: never, former or current smokers, date of smoking habit onset, end date in case of former smokers and smokers at the time of inclusion, if they had abandoned their consumption during some period prior to smoking again. In this way, the total smoking time was defined for each individual, and the amount of cigarettes measured in pack-years, estimated by multiplying the number of daily packages (each package, 20 cigarettes) by the number of years of consumption. For each participant, the incidence of peripheral vascular disease (PVD) that required hospitalization, the incidence of coronary heart disease (CHD) leading to acute myocardial infarction or death and stroke were defined.

Twenty-five percent of subjects included in the study were current smokers, 31% former smokers and 44% never smokers. Current smokers compared with never smokers were younger, with a higher prevalence of male gender, lower prevalence of high blood pressure and diabetes, lower body mass index, with standard socioeconomic status and regular physical activity. Former smokers generally presented intermediate values between both extremes. A median follow-up of 26 years revealed a dose-response relationship between time and intensity of smoking and the incidence of atherosclerotic events. After adjusting for age, vascular risk factors, renal function, physical activity and treatment, a progressively increasing pack-year value was associated with progressively greater risk of events. The risks were always greater for the incidence of PVD than for CHD or stroke. Thus, for example, for current smokers with consumption ≥40 pack-years, compared with never smokers, the HR was 3.68 for PVD, 2.14 for CHD and 1.81 for stroke. A separate analysis of consumption duration, and intensity yielded similar results. Current smokers with ≥35 years consumption presented HR of 5.56 for PVD, 2.30 for CHD and 1.91 for stroke, compared with non-smokers. Similarly, current smokers of ≥1 pack/year compared with non-smokers, presented HR of 5.36 for PVD, 2.38 for CHD and 1.88 for stroke. Smoking cessation was associated with reduction in the risk of events. With cessation <5 years and compared with current smokers, the HR for PVD adjusted for the aforementioned variables plus the intensity of consumption was 0.75; 0.78 for CHD and 0.67 for stroke. After 5 years of smoking cessation, the reduction was progressively greater, and always greater for PVD than for the other two endpoints, so that with ≥30 years the HR was 0.22 for PVD, 0.47 for CHD and 0.49 for stroke, values similar to those of never smok-

ers. On average, each year of cessation was associated with a 4% risk reduction for PVD, 2% for CHD and 1% for stroke.

The second analysis is based on the original Framingham cohort, evaluated on its fourth visit (1954-1958) and on the offspring cohort (Framingham offspring) evaluated on the first visit (1971-1975). It considered 3,805 participants of the original cohort and 4,965 of their descendants, free of CHD or stroke at the time of the analysis of baseline characteristics. Among the included participants, 46.9% were current smokers, 13.6% former smokers (7% in the original cohort, 18.6% in the offspring cohort) and 39.5% were never smokers. Median follow-up was 26.4 years. During this period, 38.6% of current smokers abandoned the habit and did not resume it; 84.7% of former smokers remained abstinent during follow-up. Adjusting for age, gender and education, the incidence of CHD did not differ for former smokers of <20 pack-years compared with never smokers, but was higher for former smokers of ≥20 pack-years (HR 1.17, 95% CI 1.04-1.31) Similarly, it was higher for current smokers, both of <20 pack-years (HR 1.25, 95% CI 1.01-1.55), and ≥20 pack-years (HR 1.91, 95% CI 1.70-2.14). The annual incidence of events was significantly higher in the original cohort than in the offspring cohort (10.2 vs. 2.7 ‰ in never smokers and up to 16.75 vs. 7.8 ‰ in current smokers of ≥20 pack-years). Compared with continuing smoking, tobacco cessation was associated with significantly lower risk within 5 years (HR 0.61), with progression of reduction up to ≥25 years of cessation (HR 0.45). Compared with never smoking, being a former smoker involved a similar risk at 16 years; being a former smoker of ≥20 pack-years was associated with greater risk with respect to a non-smoker up to 15 to <25 years after quitting smoking; 10 years in the original cohort, and 25 years in the offspring cohort.

The third study is the PESA CNIC Santander, a cohort study that included 4,149 participants, employees of Banco Santander in Madrid, between 40 and 54 years old, asymptomatic and free of established cardiovascular disease. Income, educational level (university or not), diet, alcohol consumption, physical activity, sleep patterns, laboratory values and presence of subclinical atherosclerosis assessed with carotid, aortic and iliofemoral ultrasound and coronary computed tomography with calcium score was defined in all of them. The presence of subclinical atherosclerosis was established by any plaque or coronary calcium score ≥1. The extent of subclinical atherosclerosis was defined as focal if 1 site was affected, moderate if 2 or 3 sites were compromised, and generalized if 4 to 6 sites were affected. Considering the association between educational level and subclinical atherosclerosis, the variables (lifestyle indicators) linked to both conditions were included in a mediation model, which attempts to explain the mechanism underlying that association. In this model, different pathways were considered: a) the effect of education on lifestyle; b) the effect of lifestyle on atherosclerosis; c) the indirect effect, that is to say the effect exerted by education on atherosclerosis through the included mediators; d) the effect of education on atherosclerosis not mediated by the factors considered; e) the total effect of education on atherosclerosis.

The analysis included 4,025 cohort participants, with mean age of 46 years. Thirty-seven participants were women, 74.5% had university studies and 62.7% had subclinical atherosclerosis which was generalized in 13.5% of cases (6.2% women, 18% men). Adjusting for age, gender and educational level, the income level was not associated with the incidence of generalized atherosclerosis. On the other hand, adjusting for age, gender and income level, the educational level did show a relationship with this incidence, with an adjusted OR of 1.46 (95% CI 1.16-1.85, p = 0.02). After adjusting for age and gender, having no university studies was more frequently associated with being a smoker or former smoker, with the daily number of cigarettes, with somewhat higher blood pressure and blood glucose levels, less sleeping time and a richer diet in saturated fats and processed food. Of these variables, only smoking (status of smoker or former smoker), daily amount of cigarettes and diet appeared associated with generalized subclinical atherosclerosis, and therefore were the variables considered in the mediation model. The factors related to smoking were significant, while the diet lost statistical significance. The effect of education on the incidence of generalized subclinical atherosclerosis was explained in 70.5% of cases by these factors, but with very clear preponderance of smoking: 35% by smoking status, 32% by daily cigarette consumption, and only 3.5% by the diet.

The three studies that we discuss provide interesting data. The ARIC analysis demonstrates something that we do not usually notice: smoking implies a greater increase in the risk for PVD than for CHD or stroke; conversely, smoking cessation decreases the risk of PVD more markedly than that of the other manifestations of atherosclerotic disease. The reasons why smoking increases the risk of atherosclerosis are varied: vasoconstriction, prothrombotic action, endothelial dysfunction and the action of various compounds. The predilection for the peripheral vascular bed has no clear explanation: perhaps hemodynamic and anatomical phenomena (higher blood pressure in lower limbs) can contribute to this phenomenon. And while it is true that the risk of PVD decreases faster, it is no less true that it takes more than 30 years for the risk of a former smoker to be equal to that of a never smoker, abundant reason to recommend a smoker to quit as soon as possible.

The Framingham study emphasizes the relationship of smoking with the risk of CHD. Let us note that the prevalence of current smokers was 47%, notably higher than the 25% current smokers in the ARIC cohort. The explanation surely lies in the fact that ARIC

participants were included between 1987 and 1989, when the adverse consequences of smoking were already known; while those included in the Framingham cohort were from previous decades, when the relationship of smoking with the worst vital prognosis was much less clear or directly ignored. The higher incidence of events in the original cohort with respect to that of the offspring cohort for each category of smoking can be attributed to better control in the latter of accompanying risk factors, basically hypertension. It is interesting to note that the risk of a former smoker is quickly lower than that of someone who continues to smoke, but that it takes decades to match that of someone who never smoked: the residual risk of former smokers persists for a little more than 15 years on average, and it is higher the greater the previous consumption.

The Spanish study is novel due to its data analysis, seeking to unravel the mechanism by which the educational level influences the development of atherosclerotic disease. The first fact that attracts attention is the prevalence of some degree of subclinical atherosclerosis, above 60%, in a population that on average is 46 years old. The study focuses on the generalized form, already present in more than 10% of those studied, and confirms that in young people the fundamental link between worse educational level and atherosclerosis is smoking, responsible for almost 70% of the relationship. A palpable demonstration of how painful it is for young people to be sick from self-inflicted harm.

The three studies are, in short, a new call for attention about the precocity of vascular damage caused by smoking, its extension and persistence. This information should be shared more insistently with patients, beyond simply advising them to quit smoking.

The ISAR REACT 5 study: striking result, complex interpretation

Schupke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wohrle J, et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. **N Engl J Med 2019. DOI: 10.1056/NEJMoa1908973**

Double antiplatelet therapy (DPAT) with a P2Y12 inhibitor and aspirin is a standard of care in the treatment of acute coronary syndromes (ACS). Among P2Y12 inhibitors, ticagrelor (T) and prasugrel (P) have demonstrated superiority over clopidogrel, and its use is a class I indication in ACS with or without ST-segment elevation. So far there has been no head-to-head comparison between both drugs in patients with ACS with planned coronary angiography. Specifically, in NSTE-ACS, the strategy using both agents is different. In the case of T, it is administered prior to treatment before performing the angiography; in the case of P, it is administered once the angiography has been performed. The ISAR REACT 5 study was a phase 4, multicenter, randomized, open-label study that compared both strategies in patients with ACS, either ST-segment elevation acute myocardial infarction (STEMI) or non-ST-segment elevation acute myocardial infarction (NSTEMI) or with unstable angina, in whom a coronary angiography was planned. Patients assigned to T received a loading dose of 180 mg immediately after randomization and then continued with 90 mg every 12 hours. Those assigned to P varied according to the type of ACS: in those with STEMI a loading dose of 60 mg was administered immediately after randomization, while in NSTEMI the load was administered only after knowing the coronary anatomy and before performing a percutaneous coronary intervention (PCI). In all cases, it was then continued with 10 mg daily, but a dose of 5 mg daily was recommended in patients≥75 years and in those weighing ≤60 kg. The primary efficacy endpoint (PEP) was a composite of death, AMI or stroke at one year. Safety was assessed by the incidence of bleeding events according to BARC categories 3, 4 or 5. An annual incidence of 10% for the PEP was estimated in the T group and of 12.9% in the P group, with a RR reduction for T compared with P of 22.5%. The analysis considered that 1,895 patients per group would be sufficient to demonstrate this reduction with a power of 80% and an alpha error of 0.05. Taking into account the patients potentially lost to follow-up, a total sample size of 4,000 patients was deemed necessary.

Between 2013 and 2018, 4.018 patients (2.012 in the T group) from 21 centers in Germany and 2 in Italy were included in the study. Mean age was 64.5 years, and 23.8% were women. The diagnosis at admission was STEMI in 41.1% of cases, NSTEMI in 46.2% and unstable angina in 12.7%. Percutaneous coronary intervention was carried out in 84.1% of cases, revascularization surgery was indicated in 2.1% and medical treatment was chosen in 13.8%. Given the design of the study, in NSTEMI patients, the median time from randomization to administration of the loading dose was 6 minutes in the T group, and 61 minutes in the P group. However, as in the T group the loading dose was administered systematically before angiography, 98.7% of the patients received it, while in the P group, as the loading dose was administered only after the angiography, a smaller proportion of 86.1% of NSTEMI patients received it. At discharge, about 81% of patients in both groups received the drug assigned in randomization and at one year-follow-up, 15.2% in the T group and 12.5% in the P group had discontinued treatment (p=0.03). At the end of this period, the PEP had occurred in 9.1% of the T group and 6.8% of the P group (HR 1.36; 95% CI 1.09-1.70, p=0.006) There was no significant difference in the incidence of death (4.5% vs. 3.7%) or in the incidence of stroke, but the difference was significant in the case of AMI: 4.8% vs. 3%, (HR 1.63, 95% CI 1.18-2.25). There was no difference in the incidence of stent thrombosis (1.3% vs. 1%) or in the incidence of major bleeding (5.4% vs. 4.8%).

The ISAR REACT 5 study is not easy to interpret.

It compares two different strategies with two different drugs, in STE-ACS and NSTE-ACS patients, with different degrees of evidence to justify the conduct adopted. What was known before starting the study?

Regarding treatment with P, in the TRITON study comparing prasugrel with clopidogrel in the context of ACS, 26% of patients presented STEMI and the rest NSTEMI or unstable angina. Per protocol, in NSTEMI patients the administration of P was made once the coronary anatomy was known, during or after PCI. In STEMI patients, pre-treatment with P was allowed. In the ACCOAST study in NSTE-ACS patients, 69% of which underwent PCI, pretreatment with P was compared with placebo. It revealed that pretreatment did not reduce the incidence of ischemic events and, in contrast, it increased the risk of bleeding. In conclusion, in the context of STE-ACS there was no firm evidence to justify pretreatment with P, and the ISAR REACT 5 study followed the conduct of the TRITON study. In NSTE-ACS patients, based on the conduct adopted in the TRITON study and the results of the ACCOAST study, it was decided to administer P once the coronary angiography was performed and the PCI or medical treatment was decided.

In the PLATO study, T was compared with clopidogrel in the context of ACS; both drugs were administered per protocol prior to coronary angiography in both groups to STE-ACS and NSTE-ACS patients. It cannot be argued that there is strong evidence in favor of pretreatment with respect to treatment once the coronary anatomy was known in NSTE-ACS, simply because this conduct was not explored. Concerning STE-ACS, the ATLANTIC study compared pre-hospital vs. hospital administration of T in a population mostly referred to PCI. It only showed a decrease in the incidence of stent thrombosis, without significant difference in the incidence of primary success of the procedure. In conclusion, there is some evidence in favor of earlier administration of T in STE-ACS, and the pretreatment strategy in NSTE-ACS has not been adequately explored.

Given this disperse and difficult to interpret evidence, guidelines finally recommend repeating the conduct adopted in the studies that compared T and P with clopidogrel in terms of their administration, simply because both drugs demonstrated anti-ischemic superiority compared with the latter. However, it is not clear that this form of administration is superior to other strategies.

The ISAR REACT study then established T administration as in the PLATO study, and P as in the TRITON study. The result of the study is striking. Planned as a study that would demonstrate the superiority of T over P, it reports an inverse reality. It is surprising that the incidence of the PEP in the T group has practically coincided with the estimated one (9.1% observed vs. 10% expected), while it has been nearly half in the P group (6.8% observed vs. 12, 9% estimated). Is the difference attributable to drugs? Is it the fact that in NSTE-ACS patients (almost 60% of the total) a strategy that restricts the administration of the P2Y12 inhibitor is finally preferable in those who will effectively undergo PCI? Would the decision to use lower P doses in the elderly or low weight patients have influenced, avoiding a higher incidence of bleeding? Would the greater adherence to P have influenced, favored by the once a day administration only? Is the difference similar in STE-ACS or NSTE-ACS patients? A group of questions that more detailed analyses and further publications will help to answer.

The DAPA HF study: the fast journey of gliflozins from diabetes to heart failure

McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. **N Engl J Med 2019. DOI: 10.1056/NEJMoa1911303**

Randomized studies have shown that sodium-glucose cotransporter-2 (SGLT2) inhibitors or gliflozins reduce the incidence of hospitalization for heart failure (HF) in type 2 diabetic patients with established cardiovascular disease or risk factors for its development. A recent meta-analysis showed a reduction in its incidence of 31% compared with placebo. The effect is independent of the hypoglycemic action, which is, on the other hand, equal to or less than that of other drug classes. Various explanations have been raised for the decrease in the incidence of HF: the natriuretic effect, the preservation of renal function, a favorable metabolic deviation by inducing the consumption of ketone bodies in the myocardial fiber, the decrease in blood pressure, and the sodium-hydrogen exchanger inhibition at the myocyte level, thereby reducing the sodium entry into the cell, and hence calcium entry and overload. The reduction of HF incidence in type 2 diabetic patients and the mechanisms allegedly involved have led to two hypotheses: that these drugs could be useful not only to prevent but to treat HF, and that their action would be favorable not only in diabetic, but also in non-diabetic patients. Different studies with different gliflozins have been initiated in diabetic and non-diabetic HF patients, with preserved or reduced left ventricular ejection fraction (LVEF).

We have just learned the results of the DAPA HF study, the first that has been completed, which compared dapagliflozin with placebo in patients with HF and reduced ejection fraction (HFrEF). It included patients with LVEF ≤40%, in FC II-IV, with NT-proBNP values ≥600 pg/ml (≥400 pg/ml if they had been hospitalized for HF in the last 12 months), and ≥900 pg/ml if they had atrial fibrillation. Patients with type I diabetes, glomerular filtration rate <30 ml/min/1.73m2 body surface area, or systolic blood pressure <95 mmHg were excluded from the study. Participants were randomly assigned to receive dapagliflozin in doses of 10 mg daily or placebo. The primary endpoint

(PEP) was a composite of cardiovascular death or HF worsening, defined as the need for hospitalization or endovascular treatment in the emergency room. An annual incidence of 11% was estimated in the placebo group and a risk reduction of approximately 20% at a mean follow-up of 24 months. A total of 845 events in 4,500 patients was considered to be necessary to demonstrate this difference with a power of 90% and $p<0.05$.

Between 2017 and 2018, 4,744 patients were included in 410 centers in 20 countries, including Argentina. Mean age was 66 years, 23.4% were women, 67.5% of patients were in FC II and 31.6% in FC III. Mean LVEF was 31%, and the etiology was ischemic in slightly over 56% of cases. Forty-two percent of the patients were diabetic, and an additional 3% were diagnosed during hospitalization. The treatment of HF was almost optimal, with 93.5% of patients treated with diuretics, a similar percentage with inhibitors or antagonists of the renin angiotensin system (including 11% treated with sacubitril valsartan), 96% with beta blockers and 71% with anti-aldosterone agents. Twenty-six percent of patients had an implantable defibrillator.

At an average follow-up of 18 months, the incidence of the PEP was 16.3% in the dapagliflozin group and 21.2% in the placebo group (HR 0.74; 95% CI 0.65-0.85, $p <0.001$). This was due to a reduction in hospitalizations for HF (9.7% vs. 13.4%; HR 0.70, 95% CI 0.59-0.83) and cardiovascular mortality (9.6% vs. 11.5%; HR 0.82, 95% CI 0.69-0.98). A reduction in all-cause mortality (11.6% vs. 13.9%; HR 0.83, 95% CI 0.71-0.97) was also demonstrated. The effect was consistent in different subgroups, although more noticeable in FC II than in FC III-IV. There was no difference between diabetics and non-diabetics, or between those treated and not treated with sacubitril valsartan. The incidence of significant volume depletion occurred in 1.2% of those treated with drugs, and 1.7% in the placebo group. The incidence of hypoglycemia was 0.2% in both groups. Severe renal adverse events occurred in 1.6% of cases in the dapagliflozin group and 2.7% in the placebo group ($p=0.009$)

The DAPA HF study represents a real novelty in the treatment of HFrEF for several reasons.

First of all, because a hypoglycemic drug demonstrates a remarkable effect (it not only decreases the number of hospitalizations, but also reduces cardiovascular and total mortality) in patients with pathologies other than diabetes. When we had become accustomed to being content with so many drugs to treat diabetes that were not inferior to their comparator (that is, they did not significantly increase cardiovascular risk), the appearance in the last years of gliflozins and GLP 1 agonists allowed us to be more ambitious: it is possible to improve the vital prognosis of diabetics with cardiovascular disease or risk factors. And when we had practically adapted to this new reality, which generated a revolution in practice guidelines in the last year, the DAPA HF study shows that a gliflozin is able to significantly improve the prognosis of HFrEF, in diabetic and non-diabetic patients. Will it be necessary to remember that when the EMPAREG study (empagliflozin vs. placebo in diabetics with established cardiovascular disease) was published in 2015, HF was not the primary endpoint of the study, and that the decrease in hospitalization with the active drug was a finding that surprised more than one? From the demonstration with various gliflozins, no longer of non-inferiority, but of superiority in very sick diabetic patients, going through the evidence of favorable effects in less ill diabetics, to this reduction in total mortality in patients with HFrEF, only 4 years have passed.

The second point of interest is that until now neurohormonal activation was considered as the fundamental pathophysiological explanation of HFrEF. In fact, as far as treatment is concerned, only neurohormonal antagonists had been shown to reduce mortality in this condition. For the first time a drug that is not a neurohormonal antagonist lowers total mortality. What can the involved mechanisms be? Some of those mentioned at the beginning of this comment? Others we don't know? Not only does the therapeutic battery expand; so does the pathophysiology, pointing to an unknown horizon. The results of ongoing studies with other gliflozins in HFrEF and in HF with preserved EF will undoubtedly consolidate the role reserved for these drugs in the treatment of this disease.

Clear advantage of complete revascularization in the context of ST-segment elevation acute myocardial infarction: the COMPLETE study

Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. **N Engl J Med 2019;381:1411-1421.**

In the context of ST-segment elevation acute myocardial infarction (STEMI), a recurring question has been whether beyond percutaneous coronary intervention (PCI) of the culprit vessel in patients with acute myocardial infarction (AMI), the rest of the arteries presenting with significant lesions should also be intervened. So far we have known some observational studies and four randomized trials: PRAMI, DANAMI 3 PRIMULTI, CULPRIT and COMPARE ACUTE which have suggested a better evolution of patients in whom complete revascularization (CR) has been tested in peri-AMI, but mainly at the expense of a decrease in the need for new long-term revascularization procedures. None of the studies cited have shown a reduction in hard events, such as AMI or death.

The results of the COMPLETE study have just been presented. This is a randomized and multicenter study, in patients who underwent a successful primary PCI after STEMI and who presented significant lesions in other arteries, that compared a CR strategy with PCI in the rest of the arteries vs. a strategy of

not intervening beyond the PCI of the culprit vessel. Patients had to present at least one lesion in a non-culprit artery >70%, or between 50% and 69%, with a fractional flow reserve (FFR) ≤80% and in which it was possible to perform a PCI. Patients with prior revascularization surgery, and those in whom a revascularization procedure by PCI or surgery was already decided, were excluded from the study. Randomization was carried out within 72 hours after the primary PCI, stratified taking into account whether it was the decision of the attending physician to carry out the revascularization of the non-culprit arteries in the context of hospitalization or after discharge (not later than 45 days). In the CR group it should be carried out regardless of the presence of symptoms or ischemia in an evocative test. In the case of chronic total occlusions, PCI should be attempted only if the treating team was experienced in this type of hospitalization and the chance of successful PCI was high. The use of aspirin and ticagrelor 90 mg every 12 hours for 1 year was recommended followed by aspirin and ticagrelor 60 mg every 12 hours if there was no high risk of bleeding. Two co-primary endpoints were considered: the first (PEP1) was cardiovascular death or AMI; the second (PEP2) was the two components of the first plus the need for a new ischemia-guided revascularization procedure. Considering an annual incidence of 5% of the PEP1 in the group of only-culprit vessel PCI, a sample size of 4,000 patients was estimated to demonstrate with a power of 80%, 22% reduction in the CR group.

Between 2013 and 2017, 4,041 patients from 140 centers in 31 countries were included in the study and 2,016 were assigned to the CR group. Mean age was 62 years and 80% were men. In slightly more than 90% of cases, the admission Killip classification was I. Primary PCI of the culprit artery was performed in 92% of cases, 3% was part of a pharmacoinvasive procedure and the rest was rescue PCI. The artery responsible for AMI was the right coronary artery in 48.7% of cases, the anterior descending in 34.2%, the circumflex in 17%, and the left main coronary artery in the remaining cases. In 76% of cases there was a significant lesion in an artery not responsible for AMI, and in 24% in 2 or more arteries. In almost 40% of cases the compromised artery was the anterior descending artery, in 36% the circumflex artery, and in 24% the right coronary artery. Median time to PCI for non-culprit lesions was 1 day in patients in whom it was decided to proceed during hospitalization (63.7%) and 23 days in whom it was decided to intervene after discharge (36.3%). In the first 45 days there was 4.7% crossing from the group with culprit vessel-only PCI to the CR group, and 3.9% in the opposite direction.

During a median follow-up of 35.8 months, PEP1 occurred in 7.8% of the CR branch vs. 10.5% in the group with culprit vessel-only PCI (HR 0.67; 95% CI 0.60-0.91, p=0.004). The difference was in the incidence of AMI (5.4% vs. 7.9%, HR 0.68, 95% CI 0.53-0.86) without significant difference in cardiovascular death (2.9% vs. 3.2%). The incidence of PEP2 was 8.9% in the CR group and 16.7% in the other group (HR 0.51; 95% CI 0.43-0.61, p <0.001). If we add the incidence of unstable angina or heart failure to PEP2, the corresponding figures were 13.5% and 21% (HR 0.62, 95% CI 0.53-0.72). There was no interaction with the moment in which the intervention was carried out, nor was there a difference between subgroups. There was no difference in the incidence of bleeding, stent thrombosis or contrast nephropathy.

As we noted, so far we relied on 4 randomized trials that had evaluated CR in the context of STEMI PCI. The number of patients included in these studies ranged between 296 (CULPRIT) and 885 (COMPARE ACUTE). Non-culprit artery PCI was performed during the index procedure in the PRAMI and COMPARE ACUTE studies, it was deferred but during the same hospitalization in DANAMI-3 – PRIMULTI, or was performed at any time before discharge (immediately or deferred) in the CULPRIT trial. The PCI indication of non-culprit arteries was guided by the angiographic finding of lesions ≥50% in PRAMI and 70% in CULPRIT or by FFR in DANAMI-3 - PRIMULTI and COMPARE ACUTE studies. The primary endpoint (a composite of different events) was significantly reduced with CR in all four studies, but total mortality was not affected in any. Basically, the need for repeated revascularization (a clearly expected finding) was significantly reduced in the CR group in PRAMI, DANAMI-3 - PRIMULTI and COMPARE ACUTE, and non-fatal AMI only in the PRAMI trial. Therefore, CR is recommended by the 2107 European STEMI Guideline as IIa indication.

The COMPLETE study brings together more patients than the sum of the other four, and therefore has greater power to find significant differences in clinical events. It represents a support for the CR strategy by demonstrating a significant reduction of AMI, need for new revascularization and heart failure up to 3 years of follow-up, and answers the question about the right time to carry it out, which until now had not been responded. Under conditions of clinical stability, revascularization of the non-culprit arteries can be performed before or shortly after hospital discharge.

A striking fact is that the decision to perform PCI in these arteries was made based on the estimation of lesion severity. Only in some patients the assessment of FFR was used. Some doubts may arise: what would have happened if such measurement had been routinely used? Probably some patients with lesions >70% would not have undergone PCI. Would that have modified the results? The protocol established that patients randomly assigned to receive only PCI in the culprit artery were not subjected to additional procedures even if there was evidence of ischemia in an evocative test. This may undoubtedly have biased the results in favor of the CR group. And finally, we cannot fail to mention that the CR strategy that was successful in this study

seems to validate the "ocular-stenotic reflex" so often criticized. For now, and until new evidence appears, it is possible that post-AMI CR will acquire greater strength of recommendation in the clinical practice guidelines.

PROVE-HF Study: Looking to explain the PARADIGM-HF trial results

Januzzi JL, Jr., Prescott MF, Butler J, Felker GM, Maisel AS, McCague K et al. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. **JAMA 2019:1-11.**

The PARADIGM trial demonstrated that use of sacubitril-valsartan (SV) was associated with a significant improvement in the prognosis of patients with heart failure and reduced ejection fraction (HFrEF). It has been shown that one of its effects is the decrease in NT pro-BNP levels. However, some observational studies suggest a reverse remodeling effect related with treatment. Ejection fraction (EF) was not assessed at the end of the study in the PARADIGM trial. The PROVE-HF study aimed to analyze the correlation between NT pro BNP changes and reverse remodeling. It included patients with HFrEF initiating treatment with SV (with a target dose of 200 mg every 12 hours), and evaluated baseline, 6- month and 12-month NT pro BNP levels and echocardiographic measurements: EF, left atrial and ventricular dimensions and volumes and diastolic function parameters. The primary endpoint was defined as the correlation (linear association assessed by the r coefficient) relating NT pro BNP changes and remodeling parameters between baseline and 12 months. The secondary endpoint was the same correlation, but at 6 months. Blinded image reading at the moment they were acquired was done to avoid interpretation bias.

A total of 794 patients were included and 654 completed the study. Mean age was 65 years and median EF was 28.2%. Median NT pro BNP was 816 pg/ml and 36.8% of patients had NT pro BNP levels below inclusion values in the PARADIGM trial. The reduction of NT pro BNP levels was 30% at 14 days after SV administration, and reached 37% at 12 months. Ejection fraction increased 5.2% at 6 months and 9.4% at 12 months, reaching a median value of 37.8%. A significant negative correlation was found between NT pro BNP and EF (r -0.38), which implies greater increase in EF as the decrease in NT pro BNP is greater, and positive correlation when the drop in NT pro BNP was accompanied by reduction of atrial and ventricular volumes and the E/e' ratio, with r values ranging between 0.26 and 0.40.

The PROVE-HF study can be interpreted as positive in the sense of having shown correlation between NT pro BNP levels and remodeling parameters: there is greater reduction of ventricular volumes and improved diastolic function, and greater increase of EF the greater the drop of natriuretic peptides. However, it should be pointed out that although significant, the r coefficients have no strong clinical significance: what has importance, more than r, is its square value. In fact, the r2 coefficient explains how much of the change in a variable is described by the variation in the other. Thus, considering, for example, the variation of NT pro BNP explains only 14.4% (0.38^2) of the change in EF, and similar values are attained in the relationship with the other parameters. Other not considered parameters are then much more responsible of reverse remodeling than the decrease of NT pro BNP. Perhaps the most striking result is not the final endpoint, but the demonstration that the decrease in NT pro BNP with SV is almost immediate, and the verification of an increase of almost 10 points in EF at one year of treatment, above that seen with other neurohormonal antagonists. It would have been ideal to have a group treated with enalapril, repeating the PARADIGM comparison, in order to establish the difference in the evolution of EF in both groups, as a means of achieving at least a partial explanation of the prognostic difference between both groups. There are still not clearly explained aspects in the analysis of structural changes and patient evolution.