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Semaglutide in the treatment of patients with heart failure with preserved ejection fraction and obesity. STEP-HFpEF study

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One of the many adverse consequences of obesity is heart failure (HF). In the Framingham study it was seen that each unit increase in body mass index (BMI) translated into an excess risk of 5% in men and 7% in women for the development of HF. And this was confirmed in several prospective cohort studies, including the Physicians' Health Study, in which, compared to thin people, those who were overweight had an excess risk of HF of 49%, and those who were obese had an excess risk of HF of 180%. This increased risk is independent of the presence of confounding factors such as hypertension, diabetes, dyslipidemia, or coronary heart disease. However, once HF is installed, different observational studies agree on the existence of the so-called obesity paradox: the prognosis of patients with HF, who are overweight or obese, is better than that of their counterpart with normal or low weight. Among other factors, this phenomenon is attributed to tolerance to higher doses of beta-blockers or inhibitors/antagonists of the renin-angiotensin system due to higher blood pressure, to the greater metabolic reserve in a catabolic state such as HF, to the anti-inflammatory action of adipokines. produced by adipose tissue, to having lower levels of adiponectin, which increases energy expenditure, etc. A striking fact is the lower values of natriuretic peptides (NP) in obese patients compared to non-obese patients, attributed among other factors to the decrease in wall stress (a fundamental determinant of the generation of NP) due to pericardial restriction, and the increase in its clearance in adipose tissue due to its excess.

In recent years, strong emphasis has been placed on the relationship between obesity and HF with preserved ejection fraction (HFpEF). In the Northern Hemisphere, fundamentally a very high proportion of patients with HFpEF are overweight/obese. In fact, obesity is recognized as one of the predominant phenotypes presented by patients with HFpEF, linked to greater volume overload and elevation of left ventricular filling pressures at rest and exertion, more biventricular concentric remodeling and dilation of the right cavities, greater elevation of pulmonary pressures with a lower capacity for pulmonary vasodilation. Added to this, the pericardial restriction linked to the increase in ventricular volume coinciding with excess epicardial fat. So, obese HFpEF patients have lower effort capacity and poorer quality of life.

In the HF treatment, the effect of weight loss in obese patients has been evaluated very little, in low-n studies, often observational. In recent years, GLP-1 receptor agonists have gained a predominant place in the pharmacological treatment of obesity. Among them, semaglutide has been and continues to be extensively evaluated in the STEP program. Depending on the presence or absence of diabetes, an average weight loss between 10% and 15% is recognized. It is in this context that we now know the results of the STEP-HFpEF study.

This trial included patients with HF, left ventricular EF (LVEF) ≥ 45%, FC II to IV, with a BMI ≥ 30 kg/m^2, and a distance walked in the 6-minute walk test (6MWT) of at least 100 meters. They also had to have a Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) < 90. The KCCQ is a standardized 23-item self-administered instrument that quantifies heart failure in different domains: related symptoms (frequency, severity, and recent changes), physical function, quality of life and social function. Scores are expressed on a scale from 0 to 100; higher scores express better status. The KCCQ-CSS specifically expresses the symptoms and physical function domains. And, at least, one of the following had to be added: invasive demonstration of elevation of LV filling pressures, elevation of NP according to BMI coincident with echocardiographic alterations, or history of hospitalization for HF in the last year, with current diuretic treatment or echocardiographic abnormalities. Those who had changed their weight by more than 5 kg in the last 3 months or had an HbA1c value ≥ 6.5% or a known history of diabetes were excluded.

Patients were randomly assigned, stratified by BMI (< 35 vs. ≥ 35 kg/m^2) and in a 1:1 ratio, to receive semaglutide or placebo. Semaglutide was administered as a weekly subcutaneous injection, starting with 0.25 mg for the first 4 weeks and increasing the dose until reaching the goal of 2.4 mg weekly at week 16. There were 2 primary end points: the change in the KCCQ-CSS and percent change in body weight assessed at week 52. There were also confirmatory secondary endpoints. One of them was the change in 6MWT distance from baseline to week 52. Another, a hierarchical composite end point that included death from any cause, number and timing of HF events (hospitalization or ur-

gent emergency room visit with intravenous therapy) in both cases from baseline to week 57; differences of at least 15, at least 10, and at least 5 points in change on the KCCQ-CSS through week 52; and a difference of at least 30 m in the change in 6MWT at week 52. This hierarchical end point was evaluated with the win ratio method, in which for each component the number of wins and losses was compared between the semaglutide and placebo groups. Finally, the change in C-reactive protein (CRP) was evaluated. It was estimated that with 516 participants there would be a 90% power to detect a difference between groups of 4.1 points in the change in the KCCQ-CSS, and 99% to detect a difference of 9.9% in weight loss. with p values of 0.04 and 0.01 respectively. To assess the difference in the end points, an intention-to-treat analysis and a per-protocol analysis were used, considering all randomized patients who had received at least one dose of the instituted treatment.

Between March 2021 and March 2022, 529 patients were randomly assigned, 263 to semaglutide; 16% of patients in both groups discontinued treatment prematurely. Of those who did not do so, at week 52, 83.7% were receiving the planned dose of semaglutide, and 97.8% were receiving the placebo. More than 70% of patients were included based on elevated NT-proBNP values, almost 15% due to demonstration of elevated filling pressures, and the remainder due to a history of hospitalization for HF. Fifty-six percent were women; the median age was 69 years. The median body weight and BMI were 105.1 kg and 37 kg/m^2 respectively; 66% had a BMI ≥ 35. The median KCCQ-CSS was 58.9 points and the median of the 6MWT was 320 m. The median LVEF was 57% and the median NT-proBNP was 450.8 pg./mL. Near 82% were hypertensive; 52% had a history of atrial fibrillation (AF) and 15.3% had been hospitalized for HF in the previous year. Two thirds of the patients were in FC II, the rest in CF III-IV. Eighty percent received diuretics, the same number renin-angiotensin system inhibitors/antagonists or sacubitril valsartan, and 79% betablockers; 35% mineralocorticoid receptor antagonists and less than 4% gliflozins.

In the intention-to-treat analysis, at week 52 the mean change in the KCCQ-CSS score was 16.6 points with semaglutide and 8.7 points with placebo, with an estimated difference of 7.8 points, 95% CI 4.8-10.9; p<0.001. In the per-protocol analysis, the corresponding changes were 19.1 and 10.3 points (estimated difference, 8.8 points; 95% CI, 5.9 to 11.7). The weight change in the intention-to-treat analysis was -13.3% for semaglutide and −2.6% for placebo, with an estimated difference of −10.7%, 95% CI −11.9 to −9 ,4 %; p<0.001. In the per-protocol analysis, the corresponding changes were −15.1% and −2.4% (estimated difference, −12.7%, 95% CI, −13.9 to −11.5%). The change in 6MWT at week 53 was 21.5 m in the semaglutide group and 1.2 m in the placebo group (estimated difference, 20.3 m; 95% CI, 8.6 to 32.1; p<0.001); the results were similar in the per protocol analysis. There was a greater decrease in CRP with semaglutide: 43.5% vs 7.3% decrease in the geometric means, and a greater decrease in NT-proBNP: approximately 20% vs 5%.

In the hierarchical end point analysis, semaglutide treatment resulted in more wins than placebo, with a win ratio of 1.72 (95% CI, 1.37 to 2.15; p < 0.001) in the intention-to-treat analysis and 2.1 (95% CI 1.67 to 2.63) in the pe- protocol analysis. Although there were more victories for semaglutide in all hierarchical point components, the bulk of the effect was a change of ≥ 15 points on the KCCQ-CSS. There was no difference in the incidence of death (1.1% vs 1.5%) but there were fewer cardiac events with semaglutide (arrhythmias, hospitalization for HF, etc.: 2.7% vs 11.3%). The incidence of serious adverse events was half with semaglutide: 13.3% vs 26.7%.

STEP-HFpEF is the first randomized study that evaluates the action of an agent that generates weight loss in hundreds of obese patients with HF. Due to the strong association with preserved LVEF, a population with HFpEF was chosen. Now, being a study in HF, we would have preferred that the study objectives and therefore the primary end points were clearly related to the pathology. It seems obvious that a drug that results in a drop in body weight will generate a greater decrease in body weight than a placebo. And likewise, it is not unexpected that if patients with marked obesity (average BMI of 37 kg/m^2) lose weight as expected (approximately 10%), their quality of life will improve. That is why we insist: these are not results that surprise us. We believe the study offers more, paradoxically, with secondary and confirmatory endpoints effectively linked to HF. As we already saw, at the same amount of IC, the most obese patients have lower NT-proBNP values. And it is often said that as these patients lose weight, their peptide levels increase, as the adipose tissue (where their clearance occurs) decreases. In this study, however, weight loss was associated with a decrease in natriuretic peptides. This implies that HF clearly improved, and that the NT-proBNP corroborated this. Similarly, the improvement in walking (not exciting, it must be recognized), coinciding with a decrease in NP, can be thought of as an expression of less HF. Finally, although not sized to demonstrate a significant reduction in cardiac events, the difference in favor of semaglutide in their incidence suggests a beneficial effect that will have to be corroborated in future studies. This prognostic improvement coinciding with weight loss seems to argue against the obesity paradox. Perhaps, voluntarily losing weight when there is marked obesity (in this study there were 66% of patients with at least grade II obesity and more than 25% with grade III obesity) is beneficial, and on the other hand, unintentional loss due to malabsorption, inflammation and activation of catabolic phenomena is what is truly associated with worse outcomes. It remains to corroborate the effect of GLP-1 agonists in overweight, and even normal weight, HF patients. Given the postulated effects of vascular protection, nephroprotection and anti-inflammatory, we can ask ourselves this question.

Switching to resynchronization therapy in patients with a pacemaker or defibrillator and ventricular dysfunction. BUDAPEST- CRT Study

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As we know, dyssynchrony induced by left bundle branch block (LBBB) generates ventricular dilation, drop in left ventricular ejection fraction (LVEF), mitral regurgitation, and onset and progression of heart failure (HF); finally, mortality increases. In patients with HF, sinus rhythm, LVEF < 35%, LBBB and QRS width > 150 msec, resynchronization therapy (CRT) with biventricular pacing is a class I A indication. In patients with pacemaker stimulation of the right ventricle generates a conduction pattern similar to a LBBB. In 30% of cases, this is associated with left ventricular dysfunction. The BLOCK-HF study, in patients with LVEF ≤ 50% and indication for definitive pacing in whom a predominant pacing rhythm was assumed, biventricular pacing was associated with a better outcome than exclusive pacing of the right ventricle. Until now, there was no demonstration that in patients with low LVEF, who have a pacemaker or cardiodefibrillator (ICD), upgrading to CRT would improve the prognosis. The BUDAPEST-CRT study set out this objective.

Patients with a pacemaker or ICD placed more than the last 6 months, with HF in CF II-IV, LVEF ≤ 35%, paced QRS width ≥ 150 msec and stimulation of the pacemaker or ICD in at least 20% of beats were included. Patients with intrinsic LBBB, marked dilation of the right ventricle, and those with pathologies that, such as renal failure, shortened life expectancy to less than 1 year, were excluded. Patients were randomly assigned in a 3:2 ratio to receive upgrade to CRT-D (resynchronization with ICD), or ICD alone. If the patient already had an ICD, and was assigned to ICD at randomization, there were 2 options: do nothing, or upgrade to CRT-D, keeping the resynchronization function inactive. The primary end point was a composite of all-cause death, hospitalization for HF, or a <15% reduction in LV end-systolic volume at one-year follow-up. It was considered that 360 patients would be sufficient to demonstrate a significant difference in the primary end point, with 80% power and 2-tailed p value < 0.05, with an incidence of 80% in the ICD arm and 68% in the CRT-D arm, and a monthly loss of 1%.

Between November 2014 and August 2021, 360 patients were included, 215 of them in the CRT-D arm and 145 in the ICD arm, in 17 sites in 7 countries, most of them in Hungary. The mean age was 72.8 years, 89% were men; 47% were in FC II, the average LVEF was 25%; 58% had ischemic etiology, 35% had diabetes, 56% had atrial fibrillation (AF), 49% had been hospitalized for HF in the last year. Ninety-two percent of the patients were treated with renin-angiotensin system inhibitors/antagonists and an additional 6% with sacubitril valsartan; 91% with beta blockers and 62% with mineralocorticoid receptor antagonists. Sixty-eight percent had a pacemaker placed, and 32% had an ICD. The average pacing amount was 85% in the CRT-D arm and 88% in the ICD arm. Median follow-up was 12.4 months. During it, 32.4% in the CRT-D arm and 78.9% in the ICD arm reached the primary endpoint (OR adjusted for age, sex, FC, etiology, diabetes, AF and indication for ICD for secondary prevention secondary 0.11; 95% CI 0.06-0.19, p < 0.001). The composite of death from all causes and hospitalization for HF occurred in 12.3% vs 36%, HR 0.27, 95% CI 0.16-0.47. The difference resided specifically in the lower incidence of hospitalization, with no significant difference in mortality. CRT-D compared to isolated ICD generated a difference in the drop in LV end-diastole volume of 39 ml, and in an increase in LVEF of almost 10% in absolute terms. The incidence of ventricular arrhythmia was lower, 0.5% vs 14.5%; and the incidence of complications linked to the procedure 12.3% vs 7.8%.

This randomized study demonstrates the value of upgrading to CRT in patients with pacemakers or ICD and ventricular dysfunction. Although it may be argued that in the presence of ventricular pacing, ventricular dysfunction is not always due to it (consider, for example, the presence of valvular or coronary disease, or high-response AF), the fact that it was stipulated that the QRS should have a width > 150 msec, and that in the study the proportion of paced beats was at least 85% allows us to assume causality, or at least contribution, in the relationship between pacemaker therapy and ventricular dysfunction. The upgrade to CRT generated a notable reverse remodeling effect, but the most important thing is that there was a net clinical benefit, with a significant reduction in hospitalization for HF. There was no decrease in mortality, but the follow-up was short (about 1 year) to be able to demonstrate it. The reduction in ventricular volumes and the increase in LVEF, the decrease in ventricular arrhythmia and the aforementioned reduction in the hospitalization rate, allow us to assume that in a longer period we would have seen a reduction in mortality. The benefit achieved becomes more important if we consider that more than half of the patients had AF, a condition that restricts the favorable effect of CRT. As limitations we can mention that they were the long inclusion time necessary to reach the expected number of patients, which implies around 3 patients per site per year, and casts some doubt on the external validity. We can also ask ourselves if the notable effects that were verified would occur if the pacing rate were lower. Although not significant, there was a difference in the incidence of complications with a greater number of them in the upgrade arm. Would taking the risk be justified in patients with a much lower stimulation rate?

Ideal timing of complete revascularization in ST-segment elevation AMI and multivessel disease. MULTSTARS AMI Study

Stahli BE, Varbella F, Linke A, Schwarz B, Felix SB, Seiffert M et al. Timing of Complete Revascularization with Multivessel PCI for Myocardial Infarction. **N Engl J Med 2023. https://doi.org/10.1056/NEJMoa2307823**

An old dilemma that arose when considering the best course of action for acute ST-segment elevation myocardial infarction (STEMI) was whether to proceed with exclusive revascularization of the culprit vessel versus also intervening in the rest of the vessels with significant lesions. Until 2019, there were 5 randomized trials (n=2487) that compared both strategies, with percutaneous coronary intervention (PCI) of non-culprit vessels carried out during the index procedure, or deferred, but during the same hospitalization. The need for repeated revascularization and, in some of them, the incidence of non-fatal AMI decreased. In none of these studies was a reduction in cardiovascular or all-cause mortality demonstrated. The COMPLETE study, published at the end of 2019, compared both strategies in similar patients. Randomization was carried out within 72 hours of primary angioplasty, and was done in a stratified manner, considering the decision to perform revascularization of non-culprit arteries during hospitalization or after discharge (no later than 45 days), regardless of the presence of symptoms or ischemia in an evocative test. PCI was decided if the lesion was >70%, and according to the result of fractional flow reserve (FFR) measurement if it was 50%-69%. The complete revascularization strategy demonstrated a greater than 30% reduction in a composite of cardiovascular death and AMI, basically due to a reduction in AMI, with no effect on mortality. There was also a significant reduction in the need for repeat revascularization and heart failure up to 3 years of follow-up, with no difference between performing revascularization of non-culprit arteries before or shortly after hospital discharge. No reduction in cardiovascular or all-cause mortality was demonstrated in COMPLETE. A meta-analysis involving the 6 aforementioned studies (n=6528, mean age 63 years) with a median follow-up of 2 years demonstrated that complete revascularization reduced cardiovascular mortality by almost 40% (HR 0.62, 95% CI). 0.39-0.97). There was also a significant reduction in the incidence of reinfarction (HR 0.65, 95% CI 0.53-0.80) and repeat revascularization (HR 0.29, 95% CI 0.22-0.38). The number needed to treat was 45 to prevent a reinfarction and only 8 to prevent a new episode of revascularization. No reduction in all-cause mortality could be demonstrated.

One point not completely resolved was the moment at which PCI of the non-culprit arteries should be performed. At the initial moment, in the same act in which the artery responsible for the AMI was treated, or in a delayed manner? The MULTISTARS AMI study, multicenter, randomized, and open, aimed to answer this question, based on the hypothesis of non-inferiority of the strategy of intervening on non-culprit arteries at the time of primary PCI versus deferred PCI of these arteries, between 19 and 45 days from the index procedure. Patients with STEMI within 24 hours of symptom onset, who had multivessel disease (defined as the presence of ≥70% stenosis in at least one non-culprit artery, with a diameter between 2.25 and 5.75 mm), and who had successfully undergone PCI of the infarct related artery, were included. Patients had to be hemodynamically stable and were randomly assigned 1:1 to undergo immediate PCI of non-culprit lesions vs. staged PCI (between 19 and 45 days later). Everolimus-eluting stents were used. Whether PCI was guided by FFR or intravascular imaging (including the use of intravascular ultrasonography or optical coherence tomography) was left to the discretion of the operator. The primary end point was a composite of death from any cause, nonfatal MI, stroke, unplanned revascularization driven by the presence of ischemia, or hospitalization for heart failure at 1 year. Unplanned revascularization was defined as revascularization carried out in the presence of angina, ECG changes, or evidence of ischemia in an evocative test.

To calculate the sample size, a primary end point composed of death from any cause, non-fatal MI, or unplanned revascularization was initially considered. To demonstrate non-inferiority, 1200 patients would be necessary. In July 2019, after the inclusion of 217 patients and due to slow enrollment, the primary end point was modified, and stroke and hospitalization for heart failure were added. Based on an estimated annual incidence of 18% for this expanded primary end point, a noninferiority margin of 1.46 and a one-sided significance level of 0.05 were assumed. A sample size of 800 patients was thus defined, necessary to reject the null hypothesis. Considering a dropout rate of 5%, it was decided to recruit 840 patients. An intention-to-treat analysis was performed, and the results were corroborated in a per-protocol analysis. It was established that, if the non-inferiority of immediate PCI compared to delayed PCI was demonstrated, an analysis would then be carried out to demonstrate the superiority of this strategy.

Between October 2016 and June 2022, 2907 patients in 37 centers in Europe were considered for inclusion; 840 patients were included, 418 randomly assigned to immediate PCI and 422 to deferred PCI of non-culprit arteries. The patients had a mean age of 65 years, 79% were men. 52% had hypertension, 15% diabetes and 27% dyslipidemia. Almost 6% had previous AMI. The location of the AMI was anterior in just over 40%, lateral in 42%, inferior in 12% and posterior in 21% (the sum exceeds 100% due to AMI with more than one strict ECG location). The culprit lesion was located in the in the left anterior descending artery in 40%, in the circumflex artery in 17%, and in the right coronary artery in 43%. In 82% of cases, only one artery had a lesion considered not culprit, and in 18% its presence was defined in 2 arteries. The location of the non-culprit le-

sions was in the left anterior descending artery in just over 50%, in the circumflex in 45% and in the right coronary artery in 34%. The median time from the initial to the deferred procedure in the corresponding arm was 37 days. There was a 2.9% crossover from the immediate to the deferred branch. The use of FFR or image guidance for the procedure decision in non-culprit arteries was low, but more frequent when the PCI was performed on a delayed basis, 13.2% vs. 6.3% in immediate PCI; in both cases FFR was mainly used. In the immediate revascularization branch, a total of 3 stents were used in total; in the delayed revascularization arm, a median of 1 stent in the initial procedure, and a total of 3 when also considering the distant procedure. The median volume of contrast medium was 250 ml in the immediate CTA arm, compared to 170 ml in the initial procedure and 333 ml in total in the delayed CTA arm. The duration of the index procedure was logically longer in the immediate arm, with medians of 73 versus 52 min, but when considering the distant procedure, the final duration was longer in the delayed arm, 105 min. The median total length of hospital stay was 4 days in the immediate arm and 5 in the deferred arm.

At 1 year, the incidence of the 5-component primary endpoint was significantly lower in the immediate non-culprit arteries revascularization arm: 8.55 vs 16.3%, with RR 0.52; 95% CI 0.38-0.72; $p < 0.001$ for non-inferiority and $p < 0.001$ for superiority. The difference was mainly due to the lower incidence of non-fatal AMI (2% vs 5.3%) and unplanned revascularization (4.1% vs 9.3%), both with a significant difference. In contrast, there was no difference in the incidence of all-cause mortality (2.9% vs 2.6%), stroke (1.2% vs 1.7%), or hospitalization for heart failure. The large difference between both groups occurred in the first 45 days after randomization, with incidence of the primary end point of 3.6% in the immediate arm vs. 10.7% in the staged PCI arm, with HR 0.33; 95% CI 0.18-0.59. There was no significant difference between 45 days and one year.

In the context of STEMI, complete revascularization is a class I indication. Practice guidelines, the most recent the European Society of Cardiology (ESC) 2023 guideline for acute coronary syndromes, establish that the revascularization procedure of non-culprit arteries in a STEMI can be performed up to day 45. The MULTISTARS AMI study confirms the usefulness of proceeding with initial complete revascularization in the treatment of STEMI. It is regrettable, once its results are known, that the study was not designed as one of superiority. If so, and in view of the significant advantage that initial complete revascularization gained over staged revascularization (reduction by half of the primary composite end point, with a significant reduction in non-fatal AMI, although without a difference in total mortality), perhaps a definitive answer could be proposed to the issue of the ideal moment to carry out this revascularization. Evidence based on strict methodological criteria allows us to speak only of non-inferiority. A point to note is that the advantage of initial complete revascularization was established within the first 45 days. It is the early events that are prevented. Seeing the facts in this way, it is legitimate to ask if the comparison we are witnessing is the only valid one: immediacy vs. a procedure carried out at a median of 37 days. It has been argued that, since initial complete revascularization is only non-inferior to delayed revascularization, postponing revascularization of non-culprit lesions allows it to be carried out in conditions far from the index infarction, with the patient being more stable, better medicated, etc. But if MULTISTARS AMI demonstrates a notable initial gain (risk reduced by one third), can it not be considered for practical purposes that, in descending order, we could initially prefer initial complete revascularization, and then, finally, deferred complete revascularization? Beyond that, of course, individual criteria must always prevail in the decision: hemodynamic stability, renal function, frailty, comorbidities, time of day and physical condition of the treating team, among others.

Complete revascularization in elderly patients with AMI. FIRE Study

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Although complete revascularization appears clearly indicated in patients with AMI and multivessel disease, doubt persists about its indication in elderly patients. We know that in them the coronary artery disease is more extensive, the presence of comorbidities is greater, and this includes kidney dysfunction and anemia; that the propensity to bleed is greater, and that, in short, these are more fragile patients and are therefore exposed not only to a worse evolution of their AMI, but also to more complications linked to the different therapeutic procedures. In this sense, is a complete revascularization strategy justified in them or should only the infarct related artery be treated at the moment, and treatment of the rest of the lesions deferred? The FIRE study was dedicated to answering this question.

FIRE was a multicenter randomized study that, in patients at least 75 years old, with STEMI or NSTEMI and multivessel disease, compared a strategy of revascularization of only the artery responsible for the AMI with another of revascularization of all arteries with significant lesions. Patients had to have undergone a successful PCI of the infarct related artery, and also have at least one lesion in an additional artery, with a minimum diameter of 2.5 mm and a stenosis of between 50 and 99%. Patients in whom it was not possible to clearly define a culprit lesion, those with a non-culprit lesion in the left main coronary artery, those with previous or planned surgical revascularization, and those with a life expectancy of less than one year were excluded. After PCI of the culprit lesion, patients were randomly assigned either immediately or within 48 hours to undergo

this PCI alone (in which case no further study was performed), or to, based on physiology (invasive, hyperemic or non-hyperemic demonstration, or by angiographic images, of decreased fractional flow reserve with cut-off values of 0.80, 0.89 and 0.80 respectively) to define the presence of non-culprit lesions with indication of PCI in other arteries. In case of values equal to or less than those mentioned, PCI of those lesions was performed. The primary end point was a composite of death, AMI, stroke, or revascularization directed by demonstration of ischemia within 1 year of randomization. The secondary endpoint was a composite of cardiovascular death or AMI. The primary safety end point was a composite of contrast-induced acute kidney injury, stroke, and BARC 3, 4, or 5 bleeding. It was assumed that with an annual incidence of the primary end point of 15% in the culprit artery-only revascularization arm, a 30% reduction with complete revascularization, 80% power, a 2-tailed p value <0.05, and a loss of 2%, 1385 patients would be required. The analysis was done by intention to treat.

Between 2019 and 2021, 1445 patients were included, 725 in the single revascularization arm of the culprit artery. The median age was 80 years, 36% were women, 32% had diabetes, 46% had estimated glomerular filtration rate <60/ml/min; 35% of the cases corresponded to STEMI. The average left ventricular ejection fraction (LVEF) was 49%. The assigned strategy was fulfilled by between 96% and 97% of patients in both arms. The artery responsible for the AMI was the left anterior descending, the right coronary, and the circumflex artery in just over 45%, 28% and 18% respectively. Just over 5% corresponded to the left main coronary artery. The number of non-culprit vessels per patient was 1 in 70% of cases and ≥ 2 in the remaining 30%. The determination of fractional flow reserve in the complete revascularization branch was invasive in 65% and non-invasive in 35% of cases. At least 1 functionally significant lesion in a non-culprit vessel was found in almost 50% of cases, and PCI was performed in a similar proportion. The median hospital stay was slightly longer in the complete revascularization arm: 6 vs. 5 days. The use of dual antiplatelet therapy was the rule, and there was more than 95% indication of statins and more than 75% indication of neurohormonal antagonists at discharge.

At one-year follow-up, the incidence of the primary end point was 15.7% in the complete revascularization arm versus 21% in the exclusive infarct related artery revascularization arm (HR 0.73, 95% CI 0 .57-0.93, p= 0.01). The incidence of the secondary end point was lower: 8.9% vs 13.5% (HR 0.64, 95% CI 0.47-0.88), and also the incidence of all-cause mortality: 9.2% vs 12.8% (HR 0.70, 95% CI 0.51-0.96). There was no difference in the primary safety end point. There were no differences according to age, diabetes, or type of AMI (STEMI vs NSTEMI)

The FIRE study extends the benefit of early complete revascularization in two directions: towards older patients, and towards NSTEMI. Regarding age, patients aged 75 years or older are traditionally underrepresented in randomized studies, unless the study design emphasizes their inclusion. And in daily practice, complete revascularization is usually left aside for the reasons we mentioned at the beginning: more extensive coronary artery disease, more calcified lesions, more comorbidities, fear of complications, assumption of therapeutic futility. In this sense, the FIRE results are a resounding denial of these preconceptions. This does not imply, however, that the results can be extrapolated to any elderly patient in these circumstances. More than half, for example, had preserved kidney function; the incidence of stroke in the control arm in the complete revascularization arm (1.7%) was lower than in previous studies. All of this speaks of a population that is not so fragile, less prone to complications from the procedure. Individual choice is still the rule, but we now know that a complete procedure is possible.

Regarding the evidence in NSTEMI, let us remember that complete revascularization appears in the recent European guideline on acute coronary syndromes as an indication 2a, but with level of evidence C. The BIOVASC study had already demonstrated the non-inferiority of an initial complete revascularization compared to of the delayed one in patients with STEMI and NSTEMI. We have 936 patients with NSTEMI in this study, and the evidence of superiority of complete revascularization is resounding. It remains for discussion whether determining the lesion severity guided by physiology is imperative. In the FAME study, 20% of angiographic lesions 71-90% were non-significant with FFR. And in FIRE, half of the patients with presumably significant lesions did not require PCI after functional determination (values above the cut-off value). This certainly may have avoided unnecessary procedures. For the aforementioned guideline, physiology-guided determination in the context of NSTEMI is II b with level of evidence B. Will the indication change in the future following the FIRE results?

The value of atrial fibrillation ablation in patients with end-stage heart failure. CASTLE-HTx study

Sohns C, Fox H, Marrouche NF, Crijns H, Costard-Jaeckle A, Bergau L et al. Catheter Ablation in End-Stage Heart Failure with Atrial Fibrillation. **N Engl J Med 2023. https://doi.org/10.1056/NEJMoa2306037**

Atrial fibrillation (AF) and heart failure (HF) are conditions that frequently coexist. Both increase their incidence and prevalence with age, and have common precursors: high blood pressure, obesity, and valvular disease. Each of them creates conditions that favor the appearance of the other. The loss of the atrial kick, a rapid and irregular ventricular response, dyssynchrony, ultrastructural alterations, the development of mitral regurgitation and the sympathetic activation present in AF favor the appearance of HF. Structural changes, with hypertrophy and dilation of the left cavities, hemodynamic

phenomena, electrical remodeling, neurohormonal and inflammatory activation typical of HF create the appropriate substrate for the appearance of AF. In the context of heart failure, the prevalence of AF is greater as the functional class progresses. In numerous observational and randomized studies in HF, patients with AF have a worse prognosis. A series of randomized studies conducted before 2010 compared a rhythm control strategy with a rate control strategy in patients with both conditions. No significant differences could be demonstrated in mortality or incidence of embolic events between both strategies, and in fact there was a higher hospitalization rate in the rhythm control arm. The explanation lies in the use of antiarrhythmic drugs in the rhythm control arm, with the inherent difficulty in achieving persistent maintenance of sinus rhythm, in addition to the adverse effects from the use of the medication, which increase in patients with impaired ventricular function. In the last decade, catheter ablation therapy for AF, especially pulmonary vein isolation, has grown markedly. Studies have been published that suggest improvement in ventricular function. The CASTLE AF study reported improved prognosis in patients with HF and depressed left ventricular ejection fraction (LVEF). However, the fact that it was a highly selected population (only one patient out of every 10 evaluated was included) diminished the impact of its conclusions. Different meta-analyses confirm the favorable effect of AF ablation in the context of HF, especially in improving LVEF and functional capacity. There is, however, consensus that patients with more advanced HF, worse ventricular function and functional class, greater atrial dilation, and fibrosis, have a lower chance of successful ablation.

We now know about the CASTLE-HTx study, which included patients with end-stage HF and symptomatic AF, referred for evaluation for ventricular assistance or heart transplantation. To be included, they had to have LVEF ≤ 35%, deterioration in functional capacity and be clinically stable. All of them had an implantable device with the ability to detect arrhythmia. Patients were randomly assigned 1:1 to catheter ablation of their AF and optimal medical therapy (OMT) or to receive OMT alone. The ablation procedure was isolation of the pulmonary veins. Electrical cardioversion was attempted after transseptal puncture and before ablation. If cardioversion was unsuccessful, ablation was performed and attempted again later. Antiarrhythmic medication was suspended after ablation and was only resumed in case of AF recurrence. The primary endpoint was a composite of death from any cause, left ventricular assist device implantation, or emergency heart transplantation. Secondary endpoints were each of the primary components, cardiovascular death, change in LVEF, and AF burden, defined as the percentage of time in AF in the 3 months prior to the 6- and 12-month visit. Under the assumption of an year event rate of 20% in the OMT arm, and a decrease by half in the ablation arm, it was understood that 194 patients would be necessary to demonstrate this effect with 80% power and two-tailed alpha error of 0.05

Between November 2020 and May 2022, 194 patients were included, 97 in each arm. In May 2023, the study was suspended when a notable reduction in events was demonstrated in the ablation arm, with a p value <0.001. The average age of the patients was just over 63 years, 80% were men, 31% were in FC II, 55% in FC III and the rest in FC IV. The mean LVEF was 27%; AF was paroxysmal in 31% and persistent in the rest, including almost 14% with persistent AF for more than a year. AF had an average duration of between 3 and 4 years. In 61% the etiology of HF was non-ischemic. The implantable device was ICD in 56.5% and CRT-D in 37.5%; in the rest, a pacemaker, or a device to monitor the rhythm. Only 25% of patients could perform a walking test. Ninety-five percent were treated with beta blockers, 46% with amiodarone, 37% with renin angiotensin system inhibitors/antagonists, 63% with sacubitril valsartan and 50% with mineralocorticoid receptor antagonists; 25% received gliflozins.

Of the 97 patients assigned to the ablation arm, the procedure was performed in 81 (84%), only pulmonary vein isolation in 51, and some additional procedure in 30. Of the 97 assigned to OMT alone, 16 underwent an ablation procedure. The median follow-up was 18 months. During it, the primary end point occurred in 8% of the ablation arm and 30% of the OMT arm (HR 0.24, 95% CI 0.11-0.52, p < 0.001). There was a significant reduction in death from any cause (6 vs 20%) and urgent implantation of a left ventricular assist device (1 vs 10%). There was a tendency to reduce the indication for urgent heart transplantation (1 vs 6%). At 6 and 12 months there was an increase in LVEF of just over 1% in the OMT arm, and more notable in the ablation arm, with an average difference between both arms of 5.5% at 6 months and 6.4% at 12 months. The AF burden was reduced by 31% at 6 and 12 months in the ablation arm, compared to 8% in the BMT arm.

The CASTLE-HTx study confirms the beneficial effect of AF ablation in patients with HF and impaired ventricular function. Some objections may be raised about the terminal IC character; almost a third of the patients were in CF II, and 18-month mortality was 20% in the OMT arm; Both data allow us to assume a not so serious condition in all participants. But, on the other hand, we should consider the high rate of use of neurohormonal antagonists, with more than 90% having an ICD or CRT-D; and, finally, that the most serious patients were deliberately excluded: those who were on the urgent transplant list, those who were on circulatory assistance and those who had a life expectancy <12 months. The reduction in AF burden appears to be the phenomenon responsible for the prognostic improvement. The limitations are that it is a single-center study, the short follow-up, and the small number of patients, although that was anticipated in the initial sample size calculation. It seems increasingly difficult to do more similar randomized studies; perhaps observational studies will clarify the remaining doubts.