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A meta-analysis helps to clarify the usefulness of gliflozins in the treatment of type II diabetic patients with atherosclerotic disease or risk factors

Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. **Lancet 2019;393:31-9. http://doi.org/gfhx6s**

Sodium-glucose cotransporter 2 inhibitors (SGLT2I) or gliflozins are drugs that generate glucosuria and natriuresis. Different randomized studies (EMPA-REG Outcomes with empagliflozin, CANVAS with canagliflozin and more recently DECLARE with dapagliflozin) have demonstrated their ability to improve prognosis in type II diabetic patients with established atherosclerotic disease (cardiovascular, cerebrovascular or peripheral vascular) or risk factors for their development However, the results have not been completely conclusive and there are some discrepancies according to the study considered. We have just known a meta-analysis that takes into account the three studies mentioned and sheds some light on the subject.

A total of 34,322 patients; 7,020 corresponding to the EMPA-REG study, 10,142 to the CANVAS study and the greater part, 17,160, to the DECLARE study were included in the analysis. As recalled, in the EMPA-REG study all patients had established atherosclerotic disease, in the CANVAS study 65.6% had established disease, and 34.4% had only risk factors (RF) and in the DECLARE study patients with vascular RF were more prevalent (59.4%), whereas the remaining 40.6% had already diagnosed disease. Therefore, in this meta-analysis a differentiation was made between patients with one or the other condition: overall, 60.2% had established vascular disease and 39.8% only RF.

Globally, gliflozins were associated with a reduction in the incidence of major adverse cardiovascular events (MACE), a composite of cardiovascular death, non-fatal acute myocardial infarction (AMI) and non-fatal stroke (HR 0.89, 95% CI 0.83-0.96). However, the reduction occurred specifically among patients with established atherosclerotic disease (HR 0.86), and not in those with only RF (HR 1). The separate analysis of each composite endpoint component showed a significant reduction in cardiovascular mortality of about 16% and non-fatal AMI of approximately 11%, with no effect on the incidence of non-fatal stroke. There was a reduction in total mortality, but with great heterogeneity between studies (significant reduction in the EMPA-REG study and not in the other two studies).

However, there was greater coincidence between both sources of patients in the reduced incidence of cardiovascular mortality or hospitalization for heart failure (HHF), mainly at the expense of the latter. Gliflozins were associated with a HR of 0.76 (95% CI 0.69-0.84) among patients with vascular disease, and 0.84 (95% CI 0.69-1.01) in those with only RF. The reduction in the incidence of a composite endpoint of renal events, defined in a non-uniform manner, but consistent with a marked increase of creatinine, onset of dialysis or death of renal origin was also comparable between both types of patients. In patients with vascular disease, the HR was 0.56 (95% CI 0.47-0.67), and in those with RF it was of 0.54 (95% CI 0.42-0.71).

Due to the use of different inclusion criteria, baseline renal function was not similar in the three studies. The proportion of patients with glomerular filtration rate <60 ml/min/1.73 m2 was 25.9% in the EMPA-REG study, 20.1% in the CANVAS study and only 7.6% in the DECLARE study. The meta-analysis globally considered three strata of glomerular filtration rate: patients with >90, those between 60 and 90, and those with <60 ml/min/1.73 m2. The worse the renal function, the greater the reduction of HHF: (HR 0.88 in those with glomerular filtration rate >90 ml/min/1.73 m2, and 0.60 among those with glomerular filtration rate <60 ml/min/1.73 m2). In contrast, the situation was reversed for the reduction of renal function worsening (HR of 0.44 and of 0.67, respectively, for the groups of better and worse glomerular filtration rate).

After the publication of the three large gliflozin studies, in dissimilar populations and with results that are not always conclusive, this meta-analysis has the virtue of consolidating knowledge and highlighting points that seem irrefutable. This family of drugs has, in diabetic patients with RF for atherosclerotic disease or already established vascular disease, two consistent effects: it reduces the incidence of heart failure and delays and reduces significant renal function worsening. We can expect a more remarkable outcome on the incidence of heart failure in patients with already renal function impairment, and, logically, a more obvious nephro- protective effect if the renal function is still preserved, but the truth is that in all the functional renal strata either effect is present. If, however, we focus on preventing harder events, the effect is evident in patients who already have established disease and not in those who only have RF. It could be argued that the latter will be the ones that in time will end up getting sick, and that the reduction of heart failure risk and renal dysfunction are already present at this stage; but, specifically concerning major cardiovascular events, many more years of follow-up would

be necessary to demonstrate an effect.

It seems clear then that the indication of gliflozins is becoming more and more necessary (sharing this condition with some GLP 1 agonists as liraglutide) in type II diabetic patients who already have established atherosclerotic disease or heart failure, because in them it is possible to improve cardiovascular and renal prognosis, and even decrease mortality (despite the reservations about it being a class effect, due to the heterogeneity observed). In patients with only RF (who have a lower baseline risk of events), their indication can be considered in order to reduce the incidence of heart and kidney failure.

According to the recent consensus between ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes) in type II diabetic patients, if after the indication of metformin the glycosylated hemoglobin remains above the proposed goal and atherosclerotic disease or renal dysfunction are present, gliflozins and some GLP 1 agonists are first choice drugs. If the patient specifically has heart failure there is preference for gliflozins. If there is no atherosclerotic disease or renal dysfunction, these agents can be considered, but also gliptins and thiazolidinediones. And, if there are cost problems, even sulfonylureas could be contemplated. As can be seen, the therapeutic range is broad; but for the diabetic patients treated by cardiologists, in general with already installed atherosclerotic disease, the indication of drugs that improve the cardiovascular prognosis is more and more urgent. A vision of the treatment no longer focused on lowering the levels of glycosylated hemoglobin but on decreasing the rate of cardiovascular events is the one that should predominate. Glifozins are a fundamental part of this approach.

A new criterion to indicate valve replacement in aortic stenosis? The predictive role of myocardial fibrosis

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In general, surgical decision in severe aortic stenosis relies on the presence of symptoms. Among asymptomatic patients, the emergence of ventricular dysfunction, an abnormal stress test, presence of echocardiographic signs of extreme valve involvement (peak velocity >5.5 m/s), the development of pulmonary hypertension or at least a threefold elevation of natriuretic peptide levels are factors associated with worse outcome and are thus postulated as criteria to decide surgery. Myocardial fibrosis is a new factor recently reported in the study we comment.

Between 2003 and 2015, a prospective observational study of patients with severe aortic stenosis undergoing surgical valve replacement (AVR) or transcatheter aortic valve implantation (TAVI) was carried out in 6 British centers. Severe aortic stenosis was defined by the presence of at least one of the following criteria: valve area <1 cm2, peak gradient >64 mmHg or mean gradient >40 mmHg, or peak velocity >4 m/s. Baseline clinical variables and complementary studies were recorded and their long-term prognostic value was defined. The primary endpoint was all-cause mortality and the secondary endpoint was cardiovascular mortality. Doppler echocardiogram and cardiac magnetic resonance imaging were performed, and three patterns were defined based on the presence of late gadolinium enhancement: absence of fibrosis or scar, scar with infarct pattern or scar without infarct pattern.

Six hundred and seventy-four patients were included in the study; 399 underwent AVR and the rest TAVI. Mean age was 75±14 years, and mean valve area was 0.38±0.14 cm2/m2. Patients undergoing TAVI were older, with greater prevalence of women, atrial fibrillation and coronary heart disease, and lower prevalence of hypertension or bicuspid valves. In these patients valve area was lower, ventricular volumes were larger and ventricular function was worse. The presence of fibrosis was detected in 51% of patients (33% with non-infarct pattern and 18% with infarct pattern), without difference in the prevalence according to the treatment adopted, although the infarct pattern was more frequent in patients subjected to AVR and the non-infarct pattern in TAVI cases. Patients with scar were older, with higher ventricular mass and volumes and poorer ventricular function.

Median follow-up was 3.6 years and annual mortality was 6.2% (3% with AVR and 10% with TAVI). Among 52 baseline variables, 28 were predictors of all-cause mortality in univariate analysis. Multivariate analysis showed that three of these variables were independent predictors: age, with HR 1.5 (95% CI 1.11-2.04) per each 10-year increase; Society of Thoracic surgeons (STS) score (HR 1.12, 95% 1.03-1.22) and the presence of fibrosis in magnetic resonance imaging (HR 2.39, 95% CI 1.40-4.05). Independent predictors of cardiovascular mortality were age, female sex, ventricular function and again the presence of scar with HR 3.14 (95% CI 1.65-5.99).

The prognostic value of fibrosis was the same with any of the two patterns (infarct or non-infarct). The presence of coronary heart disease was not an independent predictor of events.

Over time, an increasing number of publications have reported on the prognostic value of myocardial fibrosis in different pathologies. This is expected, because fibrosis implies loss of contractile mass, it is substrate for arrhythmias, generates greater diastolic dysfunction and hence heart failure, and is the expression or result of hypertension, ischemia, endothelial dysfunction and inflammatory activity. The study presented here highlights its importance in the context of aortic stenosis and, as already pointed out, the decision is generally taken in the presence of symptoms, it can be inferred that most patients were symptomatic. Half of these patients presented fibrosis. If the patient

undergoes surgical intervention when a scar has already been developed, and without denying that the patient has benefitted from the treatment (there is no control population where surgical or percutaneous valve replacement has not been performed), it is clear that the presence of fibrosis implies an adverse prognosis. Corollary: We should act before the development of fibrosis.

The conclusion on the prognostic value in asymptomatic patients is an inference. What is the prevalence of fibrosis in asymptomatic patients? How much does the emergence of fibrosis precede symptoms? These are questions that can only be answered with new studies. Because it is the population of asymptomatic patients the one in which the demonstration of fibrosis seems more feasible of imposing the adoption of a surgical decision. Once the patient becomes symptomatic, does the finding of myocardial fibrosis change the decision? Even acknowledging that its presence obscures the prognosis, would we discourage valve replacement? New studies with the value of serial echocardiographic, biomarker and cardiac magnetic resonance imaging analyses, will help to define the role of myocardial fibrosis in this condition.

Two randomized studies on the use of MitraClip in secondary mitral regurgitation with contradictory results. What is the explanation?

Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. **N Engl J Med 2018;379:2297-306. http://doi.org/gfj3wd**

Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. **N Engl J Med 2018;379:2307-18. http://doi.org/gfj3wf**

In patients with ventricular dilatation and heart failure, regardless its etiology, severe mitral regurgitation (MR) secondary to mitral annular dilation and subvalvular apparatus dislocation is associated with increased risk of hospitalization and mortality. Surgical treatment (valve replacement or repair), so successful in case of primary valve disease, has not shown to substantially improve the prognosis in secondary MR. In the last years, a percutaneous implant device (MitraClip) is a new interventional option which reduces the valve area through coaptation of the anterior and posterior leaflets, markedly decreasing regurgitation. Practice guidelines suggest its use in patients with severe primary MR, in whom surgical risk is high. Nevertheless, its indication prospers in patients with secondary MR. In this context, two randomized trials have been recently published with dissimilar results, which allow us to draw some conclusions on the usefulness of this device in patients with secondary MR.

The MITRA-FR study evaluated the efficacy and safety of MitraClip in patients with severe secondary MR and clinical heart failure condition. This was a multicenter, randomized, open-label, phase 3 study, sponsored by the Ministry of Health of France. It was conducted in 37 French centers with previous experience of having performed at least 5 valve implantations. The manufacturing company provided the devices and supervised the procedures. Patients with left ventricular ejection fraction (LVEF) between 15% and 40%, in functional class (FC) II to IV of the NYHA, with regurgitant volume (RV) >30ml/beat and effective regurgitant orifice area (ERO) >20 mm2 were included in the study. Patients considered candidates for valve surgery were excluded. All patients underwent a transthoracic and a transesophageal echocardiography. They were assigned in a 1:1 ratio to device implantation plus medical treatment according to the heart failure European guidelines, or exclusively to medical treatment. The primary efficacy endpoint was a composite of all-cause death or unplanned hospitalization for heart failure at one year. Secondary endpoints were the components of the primary endpoint, cardiovascular death and a composite of major cardiovascular events (death, acute myocardial infarction, stroke or hospitalization for heart failure). It was assumed that with an expected annual incidence of 50% for the primary endpoint in the medical treatment group and an absolute 17% reduction with the use of the device, 144 patients per group would be necessary to achieve with 80% power and an expected loss to follow-up of 10%, a p value <0.05. The primary analysis was by intention-to-treat, but a per-protocol analysis was also planned, in which patients in whom the device had not been effectively implanted, those with protocol deviation or patients suffering from events in the first 21 days post implantation were not considered.

Between 2013 and 2017, 452 patients were considered for the study, and among them, 152 were finally included in each group. Mean age was 70 years and 74% were men. Almost 60% of patients had ischemic heart failure etiology, and history of myocardial infarction was unbalanced (49% in the intervention group vs. 34% in the control group). Sixty-three percent of patients was in FC II-IV in the intervention group compared with 71% in the medical treatment group. Average LVEF was 33%, mean ERO was 31 mm2 and mean RV was 45 ml/beat. Eight out of the 152 patients in the device group, did not receive device implantation. In the remaining 144 patients, device implantation was initially successful in 95.8% of cases. Only one device was necessary in 45.7% of cases; in the rest, two or more devices were used. The severity of MR in the intervention group was reassessed at discharge: in 95% of cases, MR was reduced in at least one degree; in 92% it was mild to moderate or minor and in 75% it was absent or only mild.

In the intention-to-treat analysis, the annual incidence of the primary endpoint was 54.6% in the MitraClip group and 51.3% in the control group (p=0.53). At one month, mortality was 3.3% in the device group and 2.6% in the control group. The annual incidence

of mortality was 24.3% and 22.4%, and that of hospitalization for heart failure was 48.7% and 47.4%, respectively, without significant differences between both groups. The incidence of severe adverse events was higher with device implantation, with a rate of 4.6% vs. 0.7% for stroke and 7.2% vs. 3.9% for severe hemorrhage. The authors regret not having a large amount of clinical parameter, echocardiographic and lab test data during follow-up (lost or not recorded), so a formal analysis of available data could not be performed. Therefore, a trustworthy evaluation of the initial success durability is not available. They report that at least 48 out of the 93 patients in whom mild or absent MR was achieved after the procedure, this had evolved to mild-moderate or above at one year.

The COAPT study was similar. It was a multicenter, randomized, open-label study also comparing MitraClip implantation plus the best medical treatment vs. medical treatment alone in ambulatory patients with moderate to severe or severe MR and heart failure in FC II to IV, under optimal medical treatment and with LVEF between 20% and 50%. Patients should not be candidates to mitral valve replacement or repair, and they were randomly assigned to either strategy. A follow-up of at least one year was established and no cross-over between groups was allowed during the first two years. The primary efficacy endpoint was the total number of admissions for heart failure during the first two follow-up years, including recurrent events. The primary safety endpoint was freedom from procedure-related events during the first 12 months, including mitral stenosis, endocarditis, embolism, need for ventricular assist devices or heart transplantation. Estimating an annual 60% incidence of hospitalization for heart failure and 27% mortality in the device group and 42% and 22%, respectively, in the control group, a total of 610 patients would be necessary to achieve with 80% power and 7% expected annual loss of patients, a p value <0.05. At the same time, the 305 patients in the device group would detect freedom from adverse events above 88% with 95% power, postulated as initial objective. In this case, the study was supported by the manufacturing company, also responsible for data management and analysis.

Six hundred and fourteen patients (302 in the MitraClip group) were included in 78 centers of the United States and Canada between 2012 and 2017. Mean age was 72 years, 64% were men and 36.5% had an implanted resynchronizer. Forty percent of patients had history of myocardial revascularization surgery. Average STS core was 8.2% and mean ERO was 41 mm2. Also in this study, patients had heart failure of ischemic etiology in 60% of cases and mean LVEF was 31%., Mitral regurgitation was moderate-severe in 52.2% of cases and severe in 47.8%. A total of 60.7% of patients was in FC III-IV. Device implantation was attempted in 293 of the 302 patients in the device group (97%) and was effectively implanted in 288. An echocardiogram was performed in 260 patients after the procedure, verifying absent or mild MR in 82.3% of cases, moderate in 12.7% and moderate-severe or severe in the remaining 5%.

In August 2018, the last of the included patients completed the first follow-up year. Median follow-up was 22.7 months in the MitraClip group and 16.5 months in the control group. The total number of hospitalizations for heart failure in 24 months was 160 in the device group and 283 in the control group, corresponding to an annual rate of 35.8% and 67.9%, respectively (HR 0.53, 95% CI 0.40-0.70). The number needed to treat to prevent a rehospitalization at 24 months was 3.1. Freedom from complications at 12 months was 96.6%, significantly higher than the pre-specified objective performance goal of 88%. The 2-year mortality was lower with the device (29.1% vs. 46.1%, HR 0.62, 95% CI 0.42-0.82) and clinical, functional capacity and echocardiographic parameters were clearly better during follow-up. No differences in results were found according to sex, age, etiology, functional capacity or LVEF. During the 2-year follow-up among survivors, MR was moderate or major in 22.8% of patients and moderate-severe or severe in only 0.9%.

It is infrequent that two randomized studies seeking to answer the same question are reported in such a short time span and with contradictory results. The search for an explanations needs to contemplate different factors.

In principle, we may consider the patients included and the severity of their MR. In both studies, patients received medical treatment according to clinical practice guidelines, but the MITRA-FR protocol, different from the COAPT study, did not establish their non-inclusion if they improved symptoms as treatment was optimized. We may assume that the COAPT patients were truly refractory to treatment. However, the proportion of patients in FC III-IV was slightly inferior in the COAPT study. The LVEF was similar, but MR of patients in the COAPT study seems to have been more severe than that of MITRA-FR patients (ERO was larger, 41 vs. 31 mmm2 and the NT proBNP levels were higher, but with a lower left ventricular volume (around 110 vs. 135 ml/m2). This allows to assume that MR played a more marked role in symptom determination in the COAPT study than in the MITRA-FR study.

In line with the same argument, the incidence of hospitalization for heart failure in the control group at one year was much higher in the COAPT study (68% vs. 47%), confirming the greater severity of MR (since FC and LVEF were similar). It is true that because they are open-label studies there may be bias when deciding hospitalization, with greater tendency to indicate it in patients without intervention, but this is valid for both studies. One-year mortality in the control group was similar in both studies: 22% in the MITRA-FR study and 23% in the COAPT study. The longer follow-up in the COAPT study (2 years vs. 1 year in the MITRA-FR study) was able to demonstrate a significant reduction of mortality, not evidenced in the French study. Is

this difference simply explained because the more prolonged follow-up allowed to demonstrate the beneficial effect on mortality? In the MITRA-FR study, the one-year follow-up does not exclude the possibility that the intervention will reduce mortality (the HR was 1.11, but the 95% CI was 0.69-1.77, so that a 31% reduction is possible), but in the COAPT study results are more convincing (the survival curves start to separate before one year). The loss to follow-up was somewhat greater in the control group, which may have exaggerated the differences in favor of the treated group, but not to a degree justifying that the reduction in mortality was due to this factor.

This leads us to consider another line of discussion: the effectiveness of the treatment adopted. At the end of the procedure, MR was mild or absent in 75% of patients in the MITRA-FR study and 82% in the COAPT study. It is regrettable the poor quality of follow-up in the MITRA-FR study, but even so we may state that in more than half of the cases in which an initial success was achieved, the results were not preserved at one year. Conversely, in the COAPT study, MR continued to be less than moderate in almost 80% of cases at 2 years.

In summary, it seems that the use of MitraClip is not a strategy that can be used indiscriminately in patients with heart failure and secondary MR. We must continue to consider secondary MR as a predominantly ventricular disease, in which the prognosis depends mainly on LVEF and systemic conditions. Nevertheless, it seems that in a group of selected patients, in whom beyond ventricular function, MR plays an important role in symptom determination, if they are adequately treated (including intensive use of diuretics, vasodilators, neurohormonal antagonists and even ventricular resynchronization therapy), a percutaneous procedure performed by expert hands, able to ensure sustained results over time, may guarantee prognostic improvement. A more certain answer will come from new randomized studies, among them the RESHAPE-HF 2 trial.

Important news in the treatment of dyslipidemia: ODDISEY OUTCOMES and REDUCE IT studies

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Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N **Engl J Med 2019;380:11-22. http://doi.org/gfj3w9**

Proprotein convertase subtilisin-kexin type 9 inhibitors (PCSK9I) are a new family of lipid-lowering drugs that in recent years have shown to be potent reducers of LDL cholesterol levels and in some studies improve the prognosis of patients with established cardiovascular disease, beyond the benefit conferred by treatment with statins. So far the available evidence focused on patients with chronic disease. We now know the results of the ODDISEY OUTCOMES study (a multicenter, randomized, placebo controlled study) that tested the efficacy and safety of a PCSK9I, alirocumab, in patients who presented with acute coronary syndrome within the year preceding their incorporation into the study.

Patients at least 40 years old, who had presented acute myocardial infarction (AMI) or hospitalization for unstable angina between 1 and 12 months previously, who were in high intensity treatment with statins (atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily), or with the maximum tolerated dose, and with or without added ezetimibe, were included in the study. They should have a value of LDL cholesterol ≥70 mg/dl, or non-HDL cholesterol ≥100 mg/dl, or apolipoprotein B ≥80 mg/dl after at least 2 weeks of stable statin therapy. After a run-in period in which the patients were instructed to administer the injection (with placebo), they were randomized in a 1:1 ratio to receive every two weeks a subcutaneous injection of alirocumab at a dose of 75 mg or placebo. An objective of LDL cholesterol between 25 and 50 mg/dl was postulated, and sustained values below 15 mg/dl in a patient were avoided. The dose adjustments were made blindly for patients and researchers and in case of sustained values below 15 mg/dl the drug was switched to placebo. The primary endpoint was a composite of death of coronary origin, non-fatal AMI, fatal or non-fatal ischemic stroke and hospitalization for unstable angina. The secondary endpoints were any coronary event (adding revascularization procedures to the previous ones), only major coronary events (death or AMI), any cardiovascular event, and specifically coronary, cardiovascular or all-cause death. Events were analyzed by intention to treat. Likewise, the effect on LDL cholesterol was analyzed by intention to treat, but in the alirocumab group it was also done by actual treatment, excluding those who had discontinued the drug prematurely or had to replace it by placebo. Sample size was calculated assuming an incidence of the primary endpoint of 11.4% at 4 years, an initial median LDL cholesterol of 90 mg/dL, and a LDL value due to treatment 50% lower than placebo, which would translate in 15% reduction in the rate of events. It was estimated that with a population of 18,000 patients, the occurrence of 1,613 events with a follow-up of at least 3 years would be necessary to demonstrate the difference expected with a power of 90% and a value of $p<0.05$.

The study included 18,924 patients from 1,315 sites in 57 countries. The great majority was incorporated between 2012 and 2015. Due to regulatory reasons, 642 patients from China entered the study between 2016 and 2017 and therefore did not have the expected follow-up. Average age was 58.5 years, 75% were men; 83% were admitted for AMI and the rest for unstable angina. Ninety-two percent of patients met the LDL cholesterol ≥70 mg/dl criterion, and in the

rest of patients, the majority met the non-HDL cholesterol criterion ≥100 mg/dl. In 89% of patients there was high intensity treatment with statins, which remained close to 85% in both treatment groups until the end of the 3-year follow-up. Median follow-up was 2.8 years, discontinuation not due to death occurred in 14.2% of patients in the alirocumab group and 15.8% in the placebo group. Baseline mean LDL cholesterol was 92±31 mg/dl. At 4 months, 1 and 4 years, mean values of LDL cholesterol in the alirocumab group were 40, 48 and 66 mg/dl (and if one considers those who were effectively under treatment at any time, 38, 42 and 53 mg/dl, respectively). In the placebo group, the corresponding values were 93, 96 and 103 mg/dl. The primary endpoint occurred in 9.5% of patients in the alirocumab group and 11.1% in the placebo group (HR 0.85, 95% CI 0.78-0.93, p <0.001). There were similar reductions for the secondary endpoints, but not for death of coronary origin (HR 0.92, 95% CI 0.76-1.11). Since a hierarchical analysis of the endpoints from the least to the most relevant had been proposed, when the incidence of death from coronary origin was not significantly different, a formal analysis of all cause death was not made, even though its incidence was lower with alirocumab (3.5% vs. 4.1%). Regarding the primary endpoint, a number needed to treat (NNT) of 49 patients (95% CI 28-164) was calculated over 4 years to prevent an event. The reduction in events was greater the higher the baseline LDL cholesterol, so that among those with LDL ≥100 mg/dl, the NNT was 16 (95% CI 11-34). The incidence of adverse events was similar in both groups, including neurocognitive deficit (1.5% with drug, 1.8% with placebo); the only exception was the reaction at the injection site, which was more frequent with alirocumab (3.8% vs. 2.1%, p<0.001).

Let us analyze the other study. Although high levels of triglycerides have shown to be predictors of ischemic events in both epidemiological and Mendelian randomization studies, randomized studies with the use of medications that lower these values, such as niacin, fibrates or omega 3 acids, have not shown improvement of cardiovascular prognosis in patients under statin treatment. Recently, the results of the Japanese JELIS study revealed that the use of eicosapentaenoic acid, added to statins in low intensity treatment, generated a 19% reduction in the incidence of major coronary events compared to isolated treatment with statins in patients with plasma triglycerides ≥500 mg/dl. This led to the design of the multicenter, randomized, double-blind, placebo-controlled REDUCE IT study that tested the use of icosapent ethyl (IE), a highly purified eicosapentaenoic acid ethyl ester. Patients with triglyceride levels between 150 and 499 mg/dl were included in this study. Although initially the protocol allowed a value up to 10% lower than stipulated, which in the practice could include patients with values of 135 mg/dl, a second amendment took the lower limit of 150 to 200 mg/dl, without admitting variability. Patients should also have an LDL cholesterol value between 41 and 100 mg/dl, under a stable dose of statins in the last 4 weeks. They could be patients in primary prevention (at least 50 years old, diabetic and with an additional vascular risk factor) or secondary prevention (at least 45 years old, with established cardiovascular disease). It was established that patients in primary prevention should not exceed 30% of the total. Patients with advanced heart failure, severe liver disease, glycosylated hemoglobin >10%, planned coronary intervention or history of pancreatitis were excluded from the study. In the placebo group, a "mineral oil" was used to achieve the same color and consistency of the active treatment. The primary endpoint was a composite of cardiovascular death, non-fatal AMI, non-fatal stroke, coronary revascularization and hospitalization for unstable angina. There was a main secondary endpoint, which resulted from the composite of cardiovascular death, non-fatal AMI, and non-fatal stroke and other secondary endpoints considering either isolated or combining some components of the primary endpoint, and also all-cause death. It was established that 1,612 events in 7,990 patients would be necessary to detect with a power of 90%, 15% reduction in the incidence of the primary endpoint. If this difference was demonstrated with a p value of 0.0437, it would be possible to proceed with the hierarchical analysis of the secondary endpoints, up to all-cause death, so that statistical significance could only be sought for the difference in the incidence of any event, if in the order established a priori, a statistical significance was found for the immediate prior event.

Among 19,212 patients considered, 8,179 were finally included in the study. Median age was 64 years, and 71.2% were men. In 70.7% of cases patients were in secondary prevention and the rest in primary prevention. Median LDL cholesterol was 75 mg/dl and that of triglycerides was 216 mg/dl, with 60.6% of patients with values ≥200 mg/dl. At the end of the first year, triglyceride levels had decreased by a median of 39 mg/dl (18.3%) in the IE group and increased 4.5 mg/dl (2.2%) in the placebo group (p <0.001). Regarding LDL cholesterol there was an increase in both groups, but lower with IE (3.1% vs. 10.2%, p<0.001).

At a median follow-up of 4.9 years, the incidence of the primary endpoint was 17.2% in the IE group and 22% in the placebo group (HR 0.75, 95% CI 0.68-0.83), with NNT of 21 (95% CI 15-33) to avoid an event in that period. The incidence of the main secondary endpoint was 11.2% and 14.8%, respectively (HR 0.74, 95% CI 0.65-0.83), with a NNT of 28 (95% CI 20-48). The use of IE was associated with a significant decrease in AMI, stroke, and hospitalization due to unstable angina on an individual basis. Use of IE resulted in cardiovascular death reduction of 4.3% vs. 5.2% (HR 0.80, 95% CI 0.66-0.98) and only a trend to reduce total mortality (HR 0.87, 95% CI 0.74-1.02). There was no difference in the effect according to the levels of triglycerides or baseline LDL cholesterol, and neither did it influence that a triglyceride value above

or below 150 mg/dl was achieved at one year. In general, there was no difference in the incidence of adverse events, but a higher incidence of non-fatal atrial fibrillation (5.3% vs. 3.9%), peripheral edema (6.5% vs. 5%), and serious bleeding (2.7% vs. 2.1%, p=0.06) was verified with IE. On the other hand, there was a lower incidence of anemia, diarrhea and gastrointestinal disorders.

Regarding the results of the ODDISEY OUTCOMES study, we understand that more than conforming a novelty, they confirm an already known trend. In 2017 we had learned about the results of the FOURIER study, with evolocumab, in ambulatory patients. In this study there was no objective LDL cholesterol value. The starting point was a median LDL cholesterol value of 92 mg/dL; and after one year, evolocumab had reached a median value of 30 m/dL. In the ODDISEY study, involving patients after acute coronary syndrome (but between 1 and 12 months, which brings many to the conditions of a chronic ambulatory patient), the LDL cholesterol value was similar to that of the previous study (mean of 92 mg/dl) and, despite it is emphasized that an objective value was sought, in the group treated with alirocumab the mean value of LDL cholesterol was somewhat higher than in the FOURIER study (48 mg/dl by intention to treat, 42 mg/dl in real treatment) after 1 year. The follow-up was somewhat longer in the ODDISEY OUTCOMES study (2.8 years vs. 2.17 years in the FOURIER study). FOURIER patients were almost 4 years older, with a higher prevalence of hypertension (80% vs. 64%) and diabetes (36% vs. 29%). In both studies, the primary endpoint occurred in just over 11% of cases in the control group and slightly more than 9% in the active treatment group. In fact, in both cases the HR was similar, 0.85. There was coincidence between both studies on the capacity of active treatment to reduce the incidence of AMI, stroke and revascularization. In neither of the two studies was it possible to demonstrate reduction in mortality of cardiovascular origin. In the ODDISEY study, all-cause mortality was slightly higher (considering the proximity of an acute episode, which implies a somewhat higher risk, and a somewhat longer follow-up), and a reduction not evidenced in the FOURIER study was verified with the active treatment, that, nevertheless and for the reasons stated in the protocol, cannot be considered formally, but that does not sound extemporaneous. Beyond similarities and differences, both studies with PCSK9I confirm that achieving greater LDL cholesterol reduction is associated with a better prognosis. The greatest benefit in patients with LDL cholesterol ≥100 mg/dl is in line with the meta-analysis of Navarese et al., which we discussed in the Argentine Journal of Cardiology 2018; vol. 86 number. 2. Perhaps the final confirmation on the reduction of cardiovascular and total mortality will come from randomized studies with longer follow-up.

On the other hand, the results of the REDUCE IT study do introduce a novelty. For the first time, a therapeutic agent aimed at reducing triglycerides demonstrates a reduction of cardiovascular mortality and a tendency to reduce total mortality. The IE treatment succeeds where niacin, fibrates and other polyunsaturated fatty acids had failed. It is true that a meta-analysis of 45,058 patients from 18 studies with fibrates had suggested a 10% reduction in major cardiovascular events, but without showing reduction in coronary or all-cause mortality. And it does so in a population with median LDL cholesterol lower than the studies recently discussed, in which more than 90% had treatment with moderate to high intensity statins. The study extends the benefit of lowering triglycerides in a population with a median value of 216 mg/dl, clearly lower than those in which it is usually indicated to intervene. What is the explanation for these effects? It is logical to assume that part of the effect is due to the agent itself and part to the dose. In the REDUCE IT study, an individual, highly purified omega 3 acid was used in high doses. This contrasts with other studies that used a combination of acids, or at lower doses. It is possible that a specific molecular arrangement achieves what heterogeneous molecules do not; and it is also possible that having used high doses has played a role. Some voices have raised the possibility that the "mineral oil" placebo has had a damaging effect, helping to magnify the difference between drug and placebo, but there is no firm evidence in this regard. And, as usual when a completely convincing explanation is not found, the always handy "pleiotropic effects" can also be considered. In this sense, it is worth remembering that IE is attributed, as other omega 3 acids, anti-inflammatory, membrane stabilizer and antiplatelet effects. The membrane stabilizing effect is questioned by the higher incidence of atrial fibrillation; the antiplatelet therapy, on the other hand, seems to be confirmed with the higher incidence of bleeding, and may contribute to the lower incidence of ischemia. Probably, also in this case, new studies will contribute to consolidate these findings, of which it would also be appropriate to ask how they will influence in the treatment guidelines.

The decline in respiratory function predicts cardiovascular events: an analysis of the ARIC study

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There is known interaction between cardiac and respiratory function. Coronary heart disease and heart failure are more prevalent in patients with pulmonary disease, even after adjusting for common risk factors, such as smoking. Impaired pulmonary function is associated with an increased risk of cardiovascular mortality. The decline of pulmonary function begins already in youth. The forced expiratory volume in the first second (FEV1) drops at a rate of 20 ml/year from the age of 25; and forced vital capacity (FVC) also declines with age, reaching approximately 75% of

the best value. Over the years, then, respiratory function declines and the risk of cardiovascular disease increases. Is there a statistical association between both phenomena? Does the worsening of respiratory function predict a worse cardiovascular prognosis? A secondary analysis of the ARIC study provides us with an answer.

ARIC was a prospective cohort study that recruited 15,792 persons aged 45 to 64 years, in 4 different centers of the United States, in order to define the association of different clinical and paraclinical variables with the prognosis. The initial visit took place between 1987 and 1989, and there were subsequent follow-up visits. On the first and second visit (between 1990 and 1992) the participants underwent a spirometry test, and only those in whom both tests were performed were included in the analysis. As it is possible that a heart failure condition generates a drop of ventilatory parameters, due to the expected phenomenon of reverse causality (heart failure worsens pulmonary function, which in the short-term follow-up then appears predicting heart failure) those who presented heart failure, coronary disease or stroke in the second visit were excluded from the analysis. Neither were those patients with studies of poor or non-reproducible quality considered, nor those for whom data were not available during follow-up.

A cohort of 10,351 subjects (mean age 54 years, 56% women) was defined exploring the rate of change in the predicted percentages of both determinations (adjusted for age, sex, race and height) between the first and second spirometry, and the long-term cardiovascular prognosis. For each determination of FEV1 and FVC, the change between the first and the second spirometry was divided into quartiles. The quartile with the highest difference between both spirometries (the highest decrease) was called rapid decline (RD); the other three quartiles, taken as reference, non-rapid decline (nRD). By definition, then, 25% of participants presented RD for FEV1 (defined as a drop >1.9% per year), and 25% RD for FVC (defined by a drop >2.1% per year); in 16% of cases the RD coincided for both measurements.

Regarding FEV1, those with RD, compared with those of nRD, were somewhat older, with a higher proportion of men and smokers. At visit 2, the values of NT-pro BNP and high sensitivity C reactive protein (CRP) were higher in these subjects. The drop of FVC and FEV1 was also greater. At a mean follow-up of 17±6 years, persons with RD showed an increased annual incidence of cardiovascular disease: 16.7 vs. 12.9 ‰ (adjusted for age, gender, race, vascular risk factors and baseline FEV1) (HR 1.15, 95% CI 1.04-1.26). The incidence of heart failure (HR 1.17), stroke (HR 1.25) and all-cause mortality (HR 1.18) was higher in all cases, with $p < 0.05$. In the case of stroke, the HR for RD was significant throughout the follow-up period. For heart failure, the HR was higher in the first year of follow-up, and remained statistically significant for 10 years, but not thereafter. On the other hand, this association was only evident in those with FEV1 <80% of that predicted in baseline conditions.

In the case of FVC, those with RD were older, with a greater proportion of hypertension and smoking. At visit 2, the values of NT-pro BNP and high sensitivity CRP were higher. The drop of FEV1 was also greater. In the mean follow-up mentioned, persons with RD showed an increased annual incidence of cardiovascular disease: 16.6 vs. 12.6 ‰ (adjusted for age, gender, race, vascular risk factors and baseline FEV1) (HR 1.19, 95% CI 1.08-1.32). In them, the incidence of heart failure and total mortality was greater (in both cases the adjusted HR was 1.27) but not that of stroke. There was no influence of baseline FVC on the incidence of any of the mentioned endpoints.

The association between respiratory and cardiac dysfunction has been attributed to a number of factors. Among them, smoking is undoubtedly an important link. In this study, the association between the decline over time of pulmonary function and the incidence of heart failure was maintained after adjusting for the presence of current or past smoking. Two equally remarkable points are the following: The RD of FEV1 or FVC was not associated with a higher incidence of coronary heart disease as an isolated endpoint; and the relationship with the incidence of heart failure was still maintained even after adjusting for coronary risk factors, the incidence of coronary heart disease and specifically acute myocardial infarction (AMI). I.e., a higher incidence of coronary artery disease does not explain the association of respiratory function impairment and heart failure, and this leads us to seek other explanations. Ischemia secondary to decreased arterial oxygen level is a key; the higher incidence of inflammatory activation, with endothelial dysfunction, another. In fact, in subjects with RD, CRP levels were higher. Although there was no discrimination between heart failure with reduced or preserved ejection fraction, the association with inflammatory parameters and the lack of association with AMI suggest that principally the latter should be the predominant form.

The RD in FEV1 showed very strong association with the incidence of heart failure especially in the first year of follow-up, with a HR >4, although with very few events in that period (only 22). In this sense it cannot be ruled out that part of this association is due to reverse causality, but the fact that the association of RD for FEV1 and heart failure was maintained until 10 years of follow-up (and independently of the traditional risk factors) are enough to demonstrate a possible true association. In the case of RD in FVC, the association with heart failure can be justified by common factors of inflammation and loss of elasticity at the pulmonary and cardiac levels. We should not forget that the decline in pulmonary function parameters predicts the occurrence of chronic obstructive pulmonary disease, which includes among its many manifestations the increase in hemoglobin levels, with higher blood viscosity and risk of heart failure.

This study has indisputable value from the phys-

iopathological point of view, but what is the practical conclusion we can draw? We do not routinely perform a spirometry to our patients. We generally resort to the study if they are heavy smokers, or we seek to rule out lung disease when they report dyspnea that we cannot explain from a cardiological point of view. And we certainly do not repeat the study at two years if the clinical conditions have not changed and the baseline study was normal. Perhaps spirometry should be considered at least in patients with more baseline risk of events, regardless of the conditions already described. And values close to the normal lower limit or below it should alert us to an increased risk of cardiovascular events. It is not clearly defined yet if specific behaviors, beyond maximizing usual measures, can contribute to improve the prognosis.

Is it safe to stop specific treatment for heart failure in patients who have normalized the ventricular function? The TRED-HF Study

Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. **Lancet 2019;393:61-73. http://doi.org/gfkkbb**

A significant proportion of patients with heart failure and reduced left ventricular ejection fraction (LVEF) improve it over time. Part of this improvement may be spontaneous, due to reversibility of inflammatory, autoimmune or toxic phenomena, and partly due to the treatment instituted. In fact, practice guidelines recently recognize the heart failure entity with recovered LVEF, referring to those cases that started with LVEF<40% and now consistently have values above that level. A question that is often repeatedly asked is whether in these cases the treatment instituted when the LVEF was low should be maintained. And it is usually answered that there is no firm evidence to advise a conduct.

We now know the results of a pilot study with a small number of patients, but which provides highly revealing data. It is an open-label, randomized, crossover trial of treatment withdrawal for heart failure with reduced LVEF (HFrEF) vs. maintenance thereof. It was carried out in a center of the United Kingdom and included patients with history of dilated heart disease, heart failure and LVEF≤ 40%, who were currently asymptomatic, treated with diuretics, inhibitors or antagonists of the renin angiotensin system, beta blockers, antialdosterone drugs or a combination of these agents; and had normal ventricular volumes assessed by cardiac magnetic resonance imaging, LVEF ≥ 50% and NT-pro BNP <250 pg/ml. They were randomly assigned to a supervised program of reduction or discontinuation of the treatment they had been receiving, or its maintenance during an initial phase of 6 months, after which they were crossed-over to the other study branch with the same follow-up duration. During the treatment discontinuation phase, diuretics were first withdrawn followed by neurohormonal antagonists. If the patients were receiving a dose of furosemide ≤40 mg/day or a dose of neurohormonal antagonists ≤25% of the maximum dose recommended by the treatment guidelines, they were directly discontinued. If the doses were greater, they were initially reduced by 50% and then continued with larger reductions until complete discontinuation. Visits were made every 4 weeks, and the first 16 weeks were devoted to this reduction of medication, after which the clinical, imaging and laboratory determinations described were repeated. In the non-intervention group, the treatment that was being received continued. The study was open-label, that is, patients and physicians knew in each case the actions that were adopted. The primary endpoint was the recurrence of dilated cardiomyopathy manifestations at 6 months: clinical symptoms of heart failure, LVEF reduction >10% and to a value <50%, increase in ventricular volumes by at least 10%, or an increase of twice or more in NT-pro BNP, reaching a value >400 pg/ml. If any of these manifestations appeared during the reduction/discontinuation phase, treatment was restored. After the first 6 months, the control group was crossed-over to discontinuation and the same protocol was followed. Because it was a pilot, exploratory study, no sample size estimation was done.

Fifty-one patients (25 in the discontinuation group) were included in the study. Median age was 55 years and 67% were men. Median LVEF at the time of heart failure (median of 57 months earlier) had been 25%. Median current LVEF was 60%; and a value >50% dated from a median of 24 months earlier. The predominant etiology, in almost 70% of cases, was idiopathic dilated cardiomyopathy and the rest was divided into familiar forms, mutations and the action of toxic or environmental agents. At the time of admission to the study, all patients were receiving inhibitors or antagonists of the renin angiotensin system, 88% beta blockers, and 47% antialdosterone agents. Of the 25 patients who underwent initial discontinuation, 44% presented the primary endpoint in the first 6 months compared to no case in those who continued with the treatment. And of the latter, when crossed-over to the discontinuation branch at 6 months, 36% presented the same event at follow-up. Thus, 40% (n=20) of patients with LVEF >50% in a median of the last 2 years presented significant clinical and paraclinical worsening upon discontinuation of treatment for HFrEF. Sixty per cent presented a fall of LVEF, 55% increase in volumes and 45% increase in NT-pro BNP. Only 5% presented symptoms of heart failure. In 10 of the 20 patients who resumed treatment, 85% had LVEF >50% at the next visit. The low number of patients included did not allow defining independent predictors of relapse with medication withdrawal.

This study offers interesting data. Almost half of the patients with HFrEF in whom we could expect an established improvement in LVEF due to having spent

substantial time with values >50%, worsened after stopping treatment. This implies that where we expected healing there had been only transient remission attributable to the medication. What can we assume as an underlying mechanism? That in a large part of patients there is genetic predisposition, neurohormonal activation or persistent inflammatory phenomena that require indefinite treatment. And that another group of patients, not less substantial, can present sustained improvement beyond the treatment. However, some objections and comments can be made. The study was open-label, and therefore the determinations were not blinded to the strategy used. And although the difference between the two groups is overwhelming, the ideal would probably have been a study in which the active medication was progressively replaced by placebo, or one in which the studies were evaluated by researchers blinded to the treatment branch. Another point is that related with the time that was allocated to assess the response to the evaluated strategy. Had the observation time been extended, would the proportion of patients with relapse have been even greater? And, on the contrary, if the discontinuation had been made progressively, taking months for each change, advancing more slowly, would that ratio have been lower? Regarding the origin of heart failure, we must remember that the patients included were not of ischemic etiology, so we cannot extrapolate the conclusions to this population.

Can we then discontinue the treatment in patients with recovered LVEF? For the moment, this study suggests that it would be a mistake to do. so, in a high proportion of cases. If there are very strong reasons for the reduction/discontinuation of medication (intolerance, change of clinical conditions, adverse effects) perhaps we could try it, although forced to make very frequent controls. A larger study could help to define worsening predictors, to better delineate the group of patients in which we can carry out the change more safely.