Diabetes is the most important cause of chronic kidney failure. The usual recommendations for the treatment of diabetic nephropathy are control of hyperglycemia and hypertension, use of renin angiotensin system inhibitors or antagonists, and, more recently, use of gliflozins or sodium/glucose cotransporter 2 inhibitors. Despite all these measures, the risk of diabetic nephropathy progression is high. The role played in this context by the activation of mineralocorticoid receptors is well known. Aldosterone promotes a state of inflammation and fibrosis, which is characteristic of the pathology. The use of mineralocorticoid receptor antagonists slows the progression of the condition in preclinical models, in which the anti-inflammatory and antifibrotic effect of finerenone, a non-steroidal antagonist, appears superior to that of steroid antagonists such as spironolactone. The FIDELIO DKD study was designed to evaluate the effect of finerenone in patients with diabetic nephropathy, under the hypothesis that its use would result in a slowdown of renal dysfunction and an improvement in cardiovascular prognosis.

This was a phase 3, multicenter, randomized, placebo-controlled study, including patients with type 2 diabetes and renal failure defined in two ways: microalbuminuria (urinary albumin-to-creatinine ratio between 30 and <300 mg/g) with a glomerular filtration rate estimated by the CKD-Epi formula between 25 and <60 ml/min/1.73 m2; or macroalbuminuria (urinary albumin-to-creatinine ratio between 300 and 5000 mg/g) with an estimated glomerular filtration rate between 25 and <75 ml/min/1.73 m2. In all cases, patients had to be treated with renin angiotensin system inhibitors or antagonists, and their plasma potassium had to be ≤ 4.8 meq/L. After a run-in period to adjust the baseline medication and achieve the maximum tolerated dose of the renin angiotensin system inhibitors/antagonists, and if the inclusion criteria were maintained, the patients were assigned in a double-blind manner to finerenone or placebo. Those with glomerular filtration between 25 and <60 ml/min/1.73 m2 received a daily dose of 10 mg and those with glomerular filtration between 60 and <75 ml/min/1.73 m2, 20 mg daily. After one month of treatment, the 10 mg dose could be increased to 20 mg per day if the plasma potassium maintained the established levels. If in any case potassium reached values >5.5 mEq/l, the treatment was suspended, and could only be restarted with values ≤ 5 mEq/l.

The primary endpoint was a composite of a sustained reduction in glomerular filtration rate ≥40% in 4 weeks, a glomerular filtration rate <15 ml/min/1.73 m2, need for dialysis for at least 3 months, kidney transplantation, or death of renal origin. The main secondary endpoint was a composite of cardiovascular death, non-fatal acute myocardial infarction, non-fatal stroke, or hospitalization for heart failure. Hierarchically, all-cause death, all-cause hospitalization and a renal endpoint that included, in addition to those already mentioned, a fall in glomerular filtration rate of at least 57%, which implies doubling creatinine levels, were also analyzed. It was an event-driven study: it was estimated that with 1,068 primary endpoint events there would be 90% power to detect a reduction of 20% in the incidence of diabetic nephropathy with finerenone.

Between 2015 and 2018, 13,911 patients were considered in 48 countries, 5,734 of which were included in the study and 5,674 were actually analyzed. Mean age was 65.6 years, slightly over 70% were men, mean duration of diabetes was 16.6 years, and mean glycated hemoglobin 7.7%. Mean glomerular filtration rate was 44.3 ml/min/1.73 m2 (only 11.6% of the patients had a glomerular filtration rate ≥60 ml/min/1.73 m2), and median urinary albumin-to-creatinine ratio was 852 mg/g (only 12.5% had a ratio ≤300 mg/g). More than 98% of the patients were treated with a renin-angiotensin system inhibitor or antagonist at the maximum tolerated dose, slightly more than 74% with statins, 64.1% with insulin and only 4.6% with gliflozins.

In a median follow-up of 2.6 years, the incidence of the primary endpoint was 17.8% in the finerenone group and 21.1% in the placebo group (HR 0.82, 95% CI 0.73-0.93, p=0.001). This implies an annual incidence of 7.6% vs. 9.1%, and a number needed to treat of 29 patients in 3 years (95% CI 16-166) to avoid an event. There was a trend towards a reduction in the incidence of each of the components of the primary endpoint, especially a significant reduction in the decrease of glomerular filtration rate ≥40%. The main secondary endpoint occurred in 13% of patients in the finerenone group and 14.8% in the placebo group (5.1% vs. 5.9% per year, HR 0.86, 95% CI 0.75-0.99, p=0.001). There was a trend towards a reduction in each of the components of the secondary endpoint (without statistically significant reduction in any of them) except for non-fatal stroke, with the same incidence in both groups. The HR for cardiovascular death was 0.86 (95% CI 0.68-1.08) and for all-cause death 0.90 (95% CI 0.75-1.07). There was no differ-
ence in the incidence of acute renal failure. There was a higher incidence of hyperkalemia (18.3% vs. 9%) and hyperkalemia that led to study discontinuation (2.3% vs. 0.9%) in patients receiving finerenone; conversely, the incidence of hypokalemia was lower (1% vs. 2.2%).

Regarding the treatment of diabetic nephropathy, in 2019 we learned about the results of the CREDECE study, which explored the effect of canagliflozin in this context. It should be recalled that in this study the primary endpoint was a composite of end-stage renal disease (dialysis for at least 30 days, kidney transplantation or a drop in glomerular filtration to <15 ml/min/1.73 m² sustained for at least 30 days), sustained doubling of creatinine for at least 30 days, or death from renal or cardiovascular causes. That is, unlike the FIDELIO DKD study, the primary endpoint included cardiovascular death. There was a significant reduction in the annual incidence of the primary endpoint in the CREDECE study, and specifically the difference was significant for end-stage renal disease (HR 0.68; 95% CI, 0.54 to 0.86), doubling of creatinine levels (HR 0.60; 95% CI, 0.48 to 0.76) and the exploratory endpoint of dialysis, kidney transplantation or renal death (HR 0.72; 95% CI, 0.54 to 0.97). A significant reduction was also demonstrated in a composite endpoint of cardiovascular death or hospitalization for heart failure (HR 0.69; 95% CI, 0.57 to 0.83), and hospitalization for heart failure (HR 0.61; 95% CI, 0.47 to 0.80). Moreover, there was a trend towards a decrease in cardiovascular death (HR 0.78; 95% CI, 0.61 to 1.00) and overall death (HR 0.83; 95% CI, 0.68 to 1.02).

As we can see, the effect achieved in the FIDELIO DKD study with finerenone seems inferior to that achieved in the CREDECE study with canagliflozin. Beyond outlining pathophysiological hypotheses on the differential effect of an antialdosterone agent and a gliflozin, we must recall some baseline differences between the populations: the FIDELIO DKD patients had lower glomerular filtration rate than those of the CREDECE study (means of 44 and 56 ml/min/1.73 m²), although their albumin-to-creatinine ratio was somewhat better (medians of 852 and 927 mg/g, respectively). The annual incidence of creatinine doubling in the placebo groups did not differ significantly between the two studies: 3.5% in FIDELIO DKD, 3.4% in CREDECE; but the annual incidence of end-stage renal disease was higher in CREDECE: 2.9% vs. 1.9% in FIDELIO DKD. This illustrates how difficult is the attempt to establish comparisons between diverse therapeutic agents in studies with different populations. In CREDECE and FIDELIO DKD, the annual all-cause mortality was similar; 3.5% and 3.2%, respectively. Although in neither case was there a reduction in total mortality, the effect appears to have been greater with canagliflozin (17% reduction) than with finerenone (10% reduction). It is possible that in a population treated with the maximum tolerated doses of renin-angiotensin system inhibitors or antagonists, the effect of a drug, such as finerenone, that runs through the same pathophysiological pathway is somewhat lower than that of another drug that acts on other mechanisms. The evident prognostic improvement after one year suggests an effect on renal antifibrotic and anti-inflammatory remodeling. It seems clear that both agents, finerenone and a gliflozin, have the merit of offering prognostic improvement in the course of diabetic nephropathy, a pathology that, left to conventional treatment, has an ominous evolution.

The LoDoCo2 Study; colchicine and its role in chronic coronary disease.


Inflammation has been shown to play a fundamental role in the pathophysiology of chronic coronary artery disease. Different anti-inflammatory agents have been explored to evaluate their effect in this clinical condition. The CANTOS study demonstrated that the use of canakinumab, a selective interleukin-1 β inhibitor, in patients with a history of acute myocardial infarction and elevated C-reactive protein is associated with a decrease in recurrent events. In contrast, in another study with methotrexate, the results were not satisfactory. Colchicine is an anti-inflammatory agent that combines inhibition of tubulin polymerization with impaired leukocyte response. The COLCOT study associated the use of colchicine at a dose of 0.5 mg per day, in patients within 30 days of having an acute myocardial infarction, with a reduction in a composite endpoint of cardiovascular death, re-suscitated cardiac arrest, acute myocardial infarction, stroke, or hospitalization for unstable angina requiring revascularization. The LoDoCo trial was an open-label study of 532 participants with chronic coronary artery disease, in which the use of colchicine at the same dose resulted in a reduction in the incidence of acute coronary events; however, the results were considered non-confirmatory; consequently, the LoDoCo2 study was proposed.

Patients between 35 and 82 years of age, with evidence of coronary artery disease in a coronary angiography or coronary computed tomography, or with a calcium score >400 Agatston units and clinically stable within the last 6 months, were included in the study. Conversely, patients with moderate or severe renal dysfunction, severe heart failure or valve disease, or colchicine intolerance were excluded. After a 1-month run-in phase in which potentially eligible patients received 0.5 mg of colchicine daily, those who demonstrated good tolerance and adherence to the program were randomly assigned to receive double-blind colchicine at the aforementioned dose
or placebo. The primary endpoint was a composite of cardiovascular death, spontaneous non-fatal acute myocardial infarction, non-fatal stroke, or ischemia-induced revascularization. The main secondary endpoint was a composite of the first three components of the primary endpoint and then, the occurrence of paired combinations of the four events mentioned, each one separately, all-cause death and cardiovascular death were hierarchically tested.

A minimum sample size of 331 primary events was required during at least 1 year follow-up. It was assumed that with the inclusion of 6,053 patients in the run-in period, a loss of 10% of patients, a drug or placebo discontinuation of 10% during follow-up, and an annual incidence of the primary end point of 2.6% in the placebo group, there would be a power of 90% to demonstrate 30% reduction with the drug, with a two-tailed p value of 0.05.

A total of 6,528 patients were included in the run-in phase; 15.4% (1,006 patients) did not pass it, mainly due to gastrointestinal discomfort, so 5,522 patients were randomly assigned to colchicine or placebo and constituted the population subjected to intention-to-treat analysis, although 5,478 finally received some treatment. Mean age was 66 years, almost 85% were men and 84.4% had a history of acute coronary condition, though in 68.2% of cases it had occurred more than two years before inclusion. They were extremely well-treated patients: 99.7% received antiplatelet or anticoagulant treatment (23.2% had double antiplatelet therapy), 94% statins, 62.1% beta-blockers and 71.7% a renin-angiotensin system inhibitor or antagonist.

At a median follow-up of 28.6 months, the primary endpoint occurred in 6.8% of patients in the colchicine group and 9.6% in the placebo group (annual incidence of 2.5% vs. 3.6%; HR 0.69, 95% CI 0.57-0.83, p <0.001). The secondary endpoint occurred in 4.2% of patients in the colchicine group and 5.7% in the placebo group (annual incidence of 1.5% vs. 2.1%; HR 0.72, 95% CI 0.57-0.92). There was a reduction in all secondary endpoints considered, but not in stroke, cardiovascular death, or all-cause death. The incidence of atrial fibrillation, deep vein thrombosis, or diabetes was similar in both groups. Even the incidence of non-cardiovascular death was higher in the colchicine group, with a strong trend towards statistical significance (0.7% vs. 0.5% per year, HR 1.51, 95% CI 0.99-2.31). However, there was no difference in the incidence of cancer, infection, hospitalization for pneumonia, or gastrointestinal disease. No differences were seen in subgroup analyses according to age, gender, risk factors, baseline treatment, or renal function.

The LoDoCo2 study is part of the list of clinical trials that target inflammation as a therapeutic objective in the context of coronary heart disease. These studies seem to offer a proof of concept in this regard. In the CANTOS and COLCOT trials, and now in the LoDoCo2 trial, there is evidence of the beneficial effect of canakinumab or colchicine, mainly for the reduction of composite endpoints. However, none of the studies managed to reduce cardiovascular or total mortality. Is it utopian to achieve a reduction of this endpoint with anti-inflammatory therapy when there is already an adequate treatment with antiplatelet agents, beta-blockers and statins? Is pathophysiology running along another pathway, or is it necessary to treat more patients to achieve a favorable effect in that sense? The lack of dosage of inflammation markers (C-reactive protein, leukocytes) in LoDoCo2 is regrettable, since it would contribute to support the inflammatory hypothesis.

Interestingly, different studies with the same drug often offer contradictory results. In the COLCOT study, for example, the reduction of a composite cardiovascular endpoint was due to a reduction in the incidence of stroke, but not of acute myocardial infarction. In the LoDoCo2 study, the exact opposite occurred. A warning to avoid hypotheses and conclusions based on individual components of composite endpoints. Finally, the increase in the limit of significance for non-cardiovascular death deserves some clarification. It may be a chance effect. The lack of differences in the most frequent causes of death of this origin (cancer or infection) seems to support this idea, which should be clarified in future randomized studies, or registries.

Should we change the time of administration of antihypertensive medication? Everything is better at night: the Hygia Chronotherapy Study


Lack of adequate decrease in blood pressure during the night (at least 10% compared to daytime) is defined as a non-dipper pattern, which is associated with worse cardiovascular prognosis. The idea of dispensing the medication at night instead of in the morning could improve blood pressure levels during sleep, and therefore the evolution of patients, would proceed naturally. Traditionally, antihypertensive medication is administered after waking up, in the morning with breakfast, or distributed between morning and night. Although in some clinical trials there was night-time administration of the studied medication (ramipril in the HOPE study and nitrendipine in the Syst-Eur study), and this was associated with a prognostic improvement compared with placebo, in these studies there was no comparison between morning and night-time administration schedules. The MAPEC study actually compared both strategies, and found advantages for night-time administration, but it included only 2,156 patients, and therefore, it was considered unable to definitively dispel the doubts. The Hygia de Cronoterapia study, carried out in the context of a
Between 2008 and 2018, the study included data from 19,084 hypertensive patients who, in a 48-hour ambulatory blood pressure monitoring (ABPM), presented at least one of the following criteria: mean daytime systolic blood pressure (SBP) $\geq 135$ mmHg or night-time $\geq 120$ mmHg; or mean daytime diastolic blood pressure (DBP) $\geq 85$ mmHg or night-time $\geq 70$ mmHg; or had previous antihypertensive therapy. Patients were randomly assigned in a 1:1 ratio to receive their treatment in the morning, after waking up, or at night, after going to bed and before turning off the light to sleep. Considering an annual incidence of 2% major cardiovascular events (death, acute myocardial infarction, ischemic or hemorrhagic stroke, heart failure, or coronary revascularization) in patients without significant comorbidities, and 4% in patients with kidney failure or diabetes, a sample size of 18,300 patients (10,700 without comorbidity, 3,600 with diabetes, and the same number with kidney failure) was considered necessary to demonstrate a significant reduction of 20% in this incidence with the night-time scheme compared with the morning one.

Mean age was 60.5 years; 55.6% were men, 24% diabetic, and 29% had impaired renal function. Average hypertension duration was 8.8 years, but with high dispersion; 57.4% were already medicated with at least one antihypertensive drug. At the beginning of the study, mean office SBP was 149 mmHg and mean DBP 86 mmHg. In the ABPM, mean SBP was 131 mmHg (136 mmHg for daytime and 123 mmHg for night-time) and mean DBP was 77 mmHg (81 mmHg for daytime, 70 mmHg for night-time). The average fall of night-time compared with daytime blood pressure was 9±7.8% and 49.3% of patients presented a non-dipper pattern.

Median follow-up was 6.3 years (4.1-8.3 years). At the end of the study, the mean number of medications used was 1.8 in the morning group and 1.7 in the night-time group (p <0.001). The use of angiotensin II antagonists was the same in both groups (53%); in the night-time group, fewer angiotensin-converting enzyme inhibitors (23% vs. 25%), diuretics (39% vs. 46%) and beta-blockers (17% vs. 22%) were used, but more calcium antagonists (37% vs. 33%).

At the end of the study, mean office-based SBP were significantly lower in the night-time group (140 vs. 143 mmHg) and DBP (81 vs. 82 mmHg). In ABPM, blood pressure levels were also lower in the night-time group [mean SBP (124.3 vs. 125.6 mmHg) and DBP (72.2 vs. 73.1 mmHg)]. This was achieved by reducing the night-time means of SBP (114 vs. 118 mmHg) and DBP (64 vs. 66 mmHg), with no difference in the diurnal SBP or DBP (129 mmHg and 76 mmHg in both groups). Night-time blood pressure decrease was greater in the night-time administration group (15% vs. 13%), and the proportion of non-dipper pattern was lower (37.5% vs. 50.3%).

But the most striking thing is that in the night-time group there was a significant decrease in the risk of major cardiovascular events compared with the morning group (HR 0.55; 95% CI 0.50-0.61, p <0.001). A reduction in the risk of all-cause mortality of about 45%, of cardiovascular mortality of 56%, and of each of the individual endpoint components was demonstrated, from a reduction of 34% for the risk of acute myocardial infarction to 61% for hemorrhagic stroke. It is worth noting that this reduction was significant adjusting for age, gender, risk factors, mean SBP, and night-time blood pressure drop. In the night-time group, the LDL cholesterol levels were also lower and renal function somewhat better.

In 2017, three chronobiologists were awarded the Nobel Prize in Medicine for their discoveries in the field of circadian rhythms and their molecular keys. Effectively, the importance of these phenomena is increasing but generally not taken into account despite their ability to define the fate of patients. Examples abound, although the key to the intimate mechanism is often elusive. We all know the peak of sympathetic nervous system activity and the elevation of cortisol during the early hours of the morning, and how this coincides with increased risk of infarction, stroke, acute lung edema, and sudden death. Different treatments have shown uneven results when taking time into account. The flu vaccination generates more antibodies if given in the morning. Valve replacement surgery seems to have better results in the evening. Night burns take longer to heal. Some of these examples (valve replacement) may be attributed perhaps not to what happens in the patients, but to organizational reasons or the state of the treating physicians; others (influenza vaccination) clearly respond to biological reasons.

The Hygia study (the daughter of Asclepius, the god of medicine, and from whose name the word hygiene comes) is inscribed in this line. Why would it be better to administer antihypertensive medication at night? Perhaps because the morning administration often fails to prevent (due to the time frame) the phenomenon of lack of adequate fall in blood pressure during the night. Increased activation of the renin angiotensin system and aldosterone production has been reported at night. This is associated with a higher incidence of night-time hypertension, which has a strong prognostic value. Here is one reason to prefer taking medication before bedtime. Another explanation may be that the increased risk of serious events in the early hours of the day is not prevented if medication that can regulate it is administered in the morning, rather than the night before. If the risk is higher at 6 AM, is it reduced with medication taken at 8 or 9 AM?

The study has some limitations. There is no random administration of medication; the time frame coincides with some difference in the utilization rate of the different agents. Is it just the schedule, then,
or certain agents at certain hours? Another point to take into account is related to the basal pathology and concomitant treatment. The administration of nighttime diuretics can cause sleep disturbances for obvious reasons. In elderly patients with prostate disease, administering antihypertensive treatment and tamsulosin at the same time may be responsible for more than one fall and orthostatic syncope if they wake up in the middle of the night. But, admittedly, the evidence for a marked reduction in cardiovascular risk (by half or more!) is too strong to dismiss. It will be necessary, at least, to take into account the information, and use it, if possible, according to the patient.

**Lowering LDL cholesterol: as imperative in patients above 75 years old as in younger ones. A meta-analysis**


Different meta-analyses have demonstrated the beneficial effect of lowering LDL cholesterol in primary and secondary prevention. However, guideline recommendations are not so strict when referring to patients over 75 years of age as in younger ones. Thus, for example, the 2018 ACC/AHA guidelines consider the use of statins as a grade 1 indication in patients ≥75 years at moderate risk, and the addition of ezetimibe as grade IIb if, despite statin treatment, LDL cholesterol level remains ≥70 mg/dL. Conversely, in patients ≥75 years in the same situation, statin is a IIa indication and there is no recommendation for ezetimibe. Probably, these differences lie in that patients ≥75 years, although they correspond to approximately 20% of the registries’ population, represent a markedly lower proportion of cases in clinical trials, and to the coexistence of different comorbidities in this age range (cancer, malnutrition, kidney failure) which sometimes generate doubt on the benefit of lowering its levels. A recently published meta-analysis condenses all the information available on elderly patients in clinical trials with LDL-cholesterol lowering drugs.

It includes the Cholesterol Treatment Trialists’ Collaboration (CTTC) meta-analysis, which considered 24 studies comparing statins vs. placebo, or high-intensity vs. lower-intensity statin regimens; the TST study, evaluating statin treatment by comparing an objective LDL cholesterol of 70 mg/dL vs. 90-110 mg/dL; the open-label EWTOPIA 75 study, assessing ezetimibe vs. usual treatment; the IMPROVE IT study, comparing ezetimibe vs. placebo in patients treated with simvastatin; the FOURIER study, with evolocumab vs. placebo, and the ODYSSEY OUTCOMES study, with alirocumab vs. placebo, the last two studies in patients treated with statins. Overall, these 29 studies included 244,090 patients, 8.8% (21,492) of which had at least 75 years. The meta-analysis was focused on this population segment.

In 54.7% of cases patients came from statin studies, 28.9% from ezetimibe trials and 16.4% from PCSK9i studies. Median follow-up extended between 2.2 and 6 years. Age and gender data on patients ≥75 years was found in non-statin drug studies (mean age 79 years, 49.2% women). Mean baseline LDL cholesterol was between 77.8 mg/dL and 162 mg/dL. Final LDL cholesterol ranged between 40 mg/dL and 123.8 mg/dL. A total of 16.4% patients presented some major cardiovascular event; among them, 77.8% in secondary prevention. The annual incidence of major cardiovascular events was 5.7% in patients ≥75 years compared with 4.1% in those <75 years in the same studies. In patients ≥75 years the effect of active or more intensive treatment resulted in a RR for major events of 0.74 (95% CI 0.61-0.89) per each mmol/L (38.67 mg/dL) decrease in LDL cholesterol; a RR of 0.82 (95% CI 0.73-0.91) in statin studies and a RR of 0.67 (95% CI 0.47-0.95) in studies with non-statin drugs. No significant difference was encountered with effect measures in patients <75 years (global RR 0.85; RR 0.77 in studies with statins and 0.90 in studies with other drugs, per each mmol/L of LDL cholesterol reduction). The decrease in individual events was 15% for cardiovascular mortality, 20% for acute myocardial infarction and revascularization and 27% for stroke. There was heterogeneity among studies (I2 67%), which disappeared when the EWTOPIA 75 study was excluded from the analysis (I2 <0.01%). No evidence of increased risk of diabetes or cancer was found.

Previous analyses had demonstrated the benefit of reducing LDL cholesterol in patients ≥65 years; this meta-analysis expands it to a higher cut-off value. Up to now, recommendations in patients over 75 years of age have varied in different guidelines, from not even considering it, to postulating lipid-reducing therapy independently of age. Nevertheless, all these studies admitted that the evidence was less solid in this age group. Some of these concerns should disappear after this publication. There are, however, some limitations: short follow-up in some studies, the fact that only 25% of events occur in primary prevention, lack of safety data in statin studies, that the ODYSSEY OUTCOMES study reports safety in patients ≥65 years, not over 75 years, and in addition, the primary endpoint is not the same in all studies. Last, but not least (rather, the contrary) there is surely an inclusion bias when we refer to elderly patients: certainly, those with less comorbidities enter randomized studies, and hence have greater chance of drawing more benefit with the treatment and lower risk of adverse effects. But even taking into account these limitations, the information here presented invites at least to actively consider LDL cholesterol lowering when deemed necessary, without age being a factor for not doing so.
The AFFIRM AHF study: confirmation of the prognostic value of iron deficiency in heart failure

In the context of heart failure, we have learnt that iron deficiency is a significant comorbidity which is present in 50% of patients, independently of anaemia. It is classified as absolute (when plasma ferritin levels are <100 µg/mL) or functional (when ferritin levels range between 100 µg/mL and 300 µg/mL and transferrin saturation is <20%). The causes of iron deficiency are manifold, from nutritional deficit and malabsorption due to bowel edema, to increased iron loss caused by digestive microhemorrhages owing to nonsteroidal anti-inflammatory drugs. A fundamental mechanism is the activation of inflammatory phenomena, with increased hepcidin production, which interferes with ferroportin action (a transmembrane protein ensuring bowel iron absorption and its transfer to transferrin from the liver or the reticuloendothelial system, which in turn transports it to the bone marrow, skeletal or cardiac striated muscle and other tissues. Iron deficiency has been shown to have prognostic value in heart failure, associated with excess risk of cardiovascular death and hospitalization. Oral iron administration has not been shown to improve patient evolution, and among intravenous iron preparations most of the evidence comes from trials with ferric carboxymaltose in patients with reduced ejection fraction. A meta-analysis of four studies with ferric carboxymaltose (the CONFIRM HF study is the most important) demonstrates 45% reduction in the composite endpoint of cardiovascular death and hospitalization for heart failure, 58% decrease in hospitalization for heart failure and 39% in cardiovascular hospitalization, without evidence in the reduction of cardiovascular or all-cause mortality.

Considering the role of iron deficiency in hospitalization for heart failure, we speculated on the value of treating it in this context. The AFFIRM AHF trial, a multicenter, randomized, double blind, placebo-controlled study, was designed for this purpose. It included patients hospitalized for heart failure (with signs, symptoms and elevated natriuretic peptides), left ventricular ejection fraction <50% and absolute or functional iron deficiency. Patients were randomly assigned in a 1:1 ratio to receive ferric carboxymaltose or placebo. The first dose was administered before discharge and the second, 6 weeks later. The administration of a third or even fourth dose in weeks 12 and 24 was limited to those patients with hemoglobin values between 8 g/dL and 15 g/dL which remained with iron deficiency. The primary endpoint was a composite of cardiovascular death and all hospitalizations for heart failure at one-year follow-up. It was estimated that with 500 patients per group, there would be 80% power to detect a RR of 0.75 for the primary endpoint in the treated group with respect to placebo with a two-tailed p < 0.05. Assuming 9% loss, the final number of patients estimated for the study was 1,100.

Even though 1,132 patients were randomly assigned, the analysis included 1,108 patients (558 in the active treatment group) who received at least one dose and had at least one follow-up visit. Mean age was 71 years and 55.5% were men. Mean left ventricular ejection fraction was 32.6% and 71% had a history of hospitalization for heart failure. Seventy-six percent of patients were treated with renin-angiotensin system inhibitors or antagonists or sacubitril/valsartan, slightly over 65% with antialdosterone agents and 82% with betablockers. Almost 55% had anemia, 71% absolute iron deficiency and the rest functional iron deficiency. Median NT pro-BNP was around 4,700 pg/mL in both groups.

During the one-year follow-up period, the primary endpoint occurred in 57.2% of patients in the ferric carboxymaltose group and 72.8% in the placebo group (RR 0.79; 95% CI 0.62-1.01, p = 0.059). If the composite of cardiovascular death and total hospitalizations of cardiovascular cause (not only heart failure) was considered, the incidence was 76% in the treated group and 95.1% in the placebo group (RR 0.80; 95% CI 0.64-1, p = 0.05). The specific incidence of hospitalizations for heart failure was 31.7% and 43.1%, respectively (RR 0.74; 95% CI 0.58-0.94, p = 0.013). The average days lost in the year due to hospitalizations for heart failure or cardiovascular death was 369 days per 100 patient-years in the treated group and 548 in the placebo group (RR 0.67; 95% CI 0.47-0.97). There were no differences in cardiovascular (14% in each group) or total mortality. In subgroup analyses, there was greater trend for a more marked effect in men and in those <67 years, but also in those with absolute iron deficiency.

As follow-up coincided in many patients with the COVID 19 pandemic, a specific analysis was performed considering follow-up exactly until the date in which the first case of SARS COV2 infection was reported in each country. This obies to the fact that the viral infection conspired against adequate patient follow-up, face-to-face-visits were replaced by virtual ones, and on the other hand fear of contagion generated a striking reduction of visits to the emergency room, even when the clinical condition made it necessary. Also, admission criteria changed markedly, favoring viral conditions in detriment of those of other origin. In this study, values were similar to those of the principal analysis, but there was statistical significance for the primary endpoint (RR 0.75; 95% CI 0.59-0.96, p = 0.024).
Iron is a cofactor of several enzymes, and plays a key role in oxidative metabolism (mitochondrial respiratory chain), oxygen storage (myoglobin) and transportation (hemoglobin), and other processes, as fatty acid β-oxidation. Its deficiency has strong prognostic value and different cohort studies have demonstrated its association with higher risk of mortality and hospitalization in the context of heart failure and other chronic diseases. Effectively, intravenous iron replacement therapy decreases the incidence of this composite endpoint and specifically of hospitalization for heart failure. The AFFIRM AHF study has some merits. In essence, it demonstrates in the setting of hospitalization for heart failure with reduced ejection fraction and iron deficiency, a high rate of events when it is not corrected (an annual incidence >70% of cardiovascular death, 95% of all-cause cardiovascular hospitalizations and over 40% hospitalizations for heart failure as isolated endpoint in the placebo group). It stresses that we must not wait for the presence of anemia to assume iron deficiency (45% of patients did not have anemia). It repeats in acute patients what had already been observed in chronic cases regarding the capacity of intravenous ferric carboxymaltose iron replacement to improve the prognosis of hospitalization for heart failure and “is on the verge” of demonstrating reduction of the composite endpoint of cardiovascular death and hospitalization for heart failure (p=0.059) or all-cause cardiovascular hospitalizations (p=0.05). This could be due to the null effect on cardiovascular mortality and, as the authors suggest, to the COVID 19 pandemic which hindered protocol development, monitoring and confused the interpretation of the endpoints and event adjudication. The analysis should be interpreted in this sense, taking into account the results achieved until the pandemic, which, logically, is a post-hoc analysis. Nevertheless, and integrating these results with those of chronic studies, we do not consider the study as negative. Undoubtedly, there is prognostic improvement with the therapy, mainly in reducing hospitalization. Does this mean that ferric carboxymaltose should be used in all patients with reduced ejection fraction hospitalized with iron deficiency? We wish to emphasize that more than 70% of study patients had absolute iron deficiency, and that in the subgroup analysis there was a trend to more striking results in these patients (RR 0.68; 95% CI 0.57-0.92) than in those with functional iron deficiency (RR 1.09; 95% CI 0.69-1.73), p=0.096. Even though there is no strict interaction because p is >0.05, we cannot disregard this fact from a clinical viewpoint at the time of decision making, which for many sectors is still costly and poorly accessible. Finally, it should be highlighted that same as in chronic patients, there is no treatment effect on mortality. Shall we then continue speaking of iron deficiency as a predictor of a composite endpoint, or shall we focus on its specific relationship with hospitalization?

Omecamtiv mcearbil, a different inotropic; better? The GALACTIC HF Study

The traditional view of heart failure with reduced ejection fraction entails a reduction in contractility, a concept that preceded in time that of neurohormonal activation. Over time, the treatment of the disease was tested with various inotropic agents, generally linked to the movement of intracellular Ca2+: they increase its concentration (dependent or independent of cAMP) or favor its binding to troponin C. As we know, Ca2+ initiates the contraction cycle by binding, in the thin filament, to troponin C. This triggers a series of phenomena that involve troponin C, troponin T and tropomyosin, finally leading to the interaction of the actin and myosin contractile proteins. The interaction of myosin heads with actin filaments is called cross-bridge cycling. The energy for contraction is provided by ATP hydrolysis (myosin is an ATPase). Cross bridges can be strong or weak. During diastole, myosin molecules dynamically oscillate between two states: binding to ATP, which generates weak cross-bridges, and binding to the product of ATP hydrolysis, ADP plus inorganic phosphate (Pi), which generates strong cross-bridges. Molecules permanently pass from one state to the other. The greater the number of myosin molecules involved in strong cross-bridges, the greater the force of contraction. Cross-bridges push tropomyosin deeper into the actin groove improving actin-myosin interaction in the closest neighboring sites. This allows the activation to propagate along the myofilaments.

When the cross-bridge is strong, the energy stored in myosin-ADP-Pi is used to generate rotation of the actin-bound myosin head, producing the so-called “power stroke”, releasing Pi. The cross-bridge remains in a strong-bound state until a new ATP molecule binds to myosin, causing a return to the weak-bound state and cross-bridge separation. Each cross-bridge cycling consumes one ATP molecule, and this myosin ATPase activity generates the major consumption of ATP in the heart.

Omecamtiv mcearbil is an inotropic drug with a totally different mechanism of action than traditional calcitropic drugs. It stabilizes the myosin molecule in its binding state to ADP-Pi, and therefore increases the number of strong cross-bridges, preventing the transition to weak states. In animal models of heart failure, the drug was shown to improve fractional shortening, wall thickening, and increase systolic ejection time, stroke volume, and cardiac output. In humans, omecamtiv mcearbil was tested in several phase 1 and 2 studies, many of them with a low number of patients, with the purpose of defining safety,
tolerance, pharmacodynamics and effect on different hemodynamic parameters. The COSMIC HF and ATOMIC HF phase 2b studies demonstrated the ability of omecamtiv mectarbil to improve hemodynamic parameters, without generating significant adverse effects. A small increase in troponin, not linked to the incidence of ischemic symptoms was seen coinciding with a series of initially beneficial changes. But the evidence of a favorable clinical effect to justify the use of the drug in the context of chronic heart failure with low ejection fraction was lacking. The search for this effect occurred in the GALACTIC-HF study.

This multicenter, randomized, double-blind, placebo-controlled study was designed to evaluate the efficacy, safety, and tolerance of omecamtiv mectarbil in chronic heart failure patients with reduced EF. The inclusion criteria were an EF $\leq 35\%$ within the previous year, or within 30 days of an event or intervention that was suspected of having significantly modified it. They had to be in FC II to IV, with standard medical treatment for their heart failure, and could be patients hospitalized for heart failure (at least 25%) or outpatients, but with a history of hospitalization or urgent visit to the emergency room for heart failure in the last year. A pro-BNP NT value $\geq 400$ pg/mL was required in sinus rhythm and a triple level in atrial flutter or fibrillation. Systolic and diastolic blood pressure should be between 85 mmHg and 140 mmHg, respectively, and glomerular filtration rate $\geq 60$ mL/min/1.73 m$^2$. Hospitalized patients should not be receiving inotropic agents within the previous 3 days, and intravenous diuretics or vasodilators within the previous 12 hours. Patients were randomly assigned to 25 mg of drug or placebo every 12 hours. In order to achieve plasma concentrations of omecamtiv mectarbil between 200 ng/mL and 1000 ng/mL, blood dosages were performed in the first weeks to blindly titrate the medication dose up to a maximum dose of 50 mg every 12 hours. The primary endpoint was the time to a composite of cardiovascular death or heart failure (urgent and unplanned emergency room visit, or hospitalization for heart failure). It was established that the study should conclude when it reached 1,590 cardiovascular deaths, which would represent a power of 90% to detect 20% reduction of cardiovascular death, considering an annual incidence of 10% in the first year and 7% in subsequent years. An interim analysis was established when two-thirds of the expected deaths had occurred. The efficacy analysis was done by intention-to-treat, and the safety analysis considered only patients who had received at least one dose.

Between January 2017 and July 2019, 8,232 patients were included in the study, 4,120 in the active treatment group. Mean age was 64 years, nearly 21% were women, 25.3% were hospitalized at the time of randomization, 53% were in FC II and almost 44% in FC III. In 53.6% of cases, patients presented with an ischemic etiology, 40.2% had diabetes, and 27.2% had atrial fibrillation. Mean systolic blood pressure was 116 mmHg and heart rate 72 beats/min, mean left ventricular ejection fraction was 26.6% and median NT-proBNP was around 2000 pg/mL in both groups. In 87% of cases, patients were medicated with renin angiotensin system inhibitors or antagonists or sacubitril/valsartan (between 19% and 20% with sacubitril/valsartan in each of the groups), 94.3% with beta-blockers, 77.7% with antialdosterone agents and 2.7% with gliflozins. Fourteen percent had undergone resynchronization therapy and about 32% had received a cardioverter defibrillator.

In a median follow-up of 21.8 months, the primary endpoint occurred in 37% (24.2% per year) of treated patients and 39.1% (26.3% per year) of the placebo group (HR 0.92; 95% CI 0.86-0.99, p=0.03). The effect did not differ in general between the different subgroups analyzed, with a propensity to better results in patients in sinus rhythm than in atrial fibrillation or flutter: HR 0.86 (95% CI 0.79-0.94) vs. HR 1.05 (0.93-1.18), and a significant difference according to the ejection fraction: HR 0.84 (95% CI 0.77-0.92) was found in those with ejection fraction $\leq 28\%$ vs. HR 1.04 (0.94-1.16) in those with a value $>28\%$. There was no significant difference in the annual incidence of cardiovascular death (10.9% vs. 10.8%) or all-cause death (14.4% annually in both groups). There was also no significant difference in the quality-of-life scale, and a reduction in the limit of significance for the incidence of heart failure events (18.7% vs. 20.3% per year; HR 0.93, 95% CI 0.86-1). There was a non-significant decrease in pro-BNP NT in both groups; the median proBNP NT at 24 weeks was 10% lower with omecamtiv mectarbil. Troponin I at week 24 was only 4 ng/L higher in the treated group. The incidence of ischemic events in general (less than 5%) and of acute myocardial infarction in particular (in the order of 3%) was similar in both groups as well as the incidence of ventricular tachyarrhythmia.

The GALACTIC HF study tested an original drug within the inotropic family, whose effect is not based on the intracellular movement of calcium or on the affinity of troponin C for calcium, but on its action at the level of the actin myosin cross-bridge. If we judge drugs by their adverse effects, there is clearly an advantage of this agent compared with traditional adrenergic agents: there was no excess ventricular arrhythmia or mortality with its use. The increase in troponin release was poor, and this coincided with the lack of increase in ischemic events. But let us go now to the positive effects, beyond the lack of harm.

It is true that an absolute reduction of 2% per year in the risk of cardiovascular death or event of emergency room consultation or hospitalization for heart failure was verified in the GALACTIC HF study, but the effect on mortality was minimal when considering the cases in which cardiovascular death was the first event of the primary endpoint (a difference of less than 0.4% per year), infinitesimal if all cardiovascular death is considered and null when we speak of all-cause mortality. The benefit then passed specifically through the
effect on heart failure events, and not even significantly for hospitalization. And all this in a population in which less than 20% receive sacubitril/valsartan and less than 3% are treated with a gliflozin, two of the four drugs that are known to improve the prognosis in heart failure with reduced ejection fraction. It is appropriate to conclude that these results do not lead to a liberal use of the drug but, quite the contrary, and when available, to be administered in very specific situations.

How to interpret the results of studies in which patients do not receive the best available treatment? The inclusion of patients in GALACTIC HF was concluded when the DAPA HF results were released. The PARA-DIGM study results were known since 2014; however, and similarly to what happens in the real world, the use of sacubitril/valsartan did not reach 20%. Gliflozins and sacubitril/valsartan show a greater reduction in hospitalization, and a significant decrease in mortality, compared to the poor effects described for omecamtiv mecarbil. Does this have to do with the fact that, despite its better profile, this drug carries the original sin of inotropic drugs, and it is not possible to expect a radical change in prognosis from them? Does omecamtiv end up looking like digoxin, which in the DIG study lowered hospitalization, but not mortality? Is it a much more expensive digoxin? The truth is that, with the available information, we initially assume for this agent a niche drug fate as, for example, in patients with markedly reduced ejection fraction and optimal treatment despite which the clinical course is unfavorable.

Complete revascularization in ST-segment elevation myocardial infarction reduces cardiovascular mortality. A meta-analysis.


An old dilemma that arises when considering the best course of action in the face of ST-segment elevation acute myocardial infarction (exclusive revascularization of the culprit vessel vs. a procedure that also treats the rest of the vessels with significant lesions) has been partly settled with the publication of the COMPLETE study. Until this study, there were 5 randomized trials (a study by Politi et al., and the PRAMI, CULPRIT, DANAMI-3-PRIMULTI and Compare-Acute studies), with a total of 2,487 patients, comparing both strategies, with non-culprit vessel angioplasty performed during the index procedure, deferred but during the same hospitalization, or at any time before discharge (immediately or deferred) depending on the study. The indication to treat non-culprit vessels was guided by the angiographic finding of lesions ≥50%, >70% or by measurement of fractional flow reserve in the different designs. The primary endpoint (composite of different events) was significantly reduced with complete revascularization in these trials. Basically, there was a decrease in the need for repeated revascularization and in some of them in the incidence of non-fatal acute myocardial infarction. None of them demonstrated a reduction in cardiovascular mortality or all-cause mortality.

The COMPLETE study, published at the end of 2019, compared both strategies in similar patients. Randomization was carried out within 72 hours of having performed the primary angioplasty and was performed in a stratified manner, taking into account the decision to carry out the revascularization of the non-culprit arteries during hospitalization or after discharge (not beyond 45 days), regardless of the presence of symptoms or ischemia in an evocative test. Angioplasty was decided if the lesion was >70% and according to the result of the fractional flow reserve if it was between 50%-69%. The complete revascularization strategy demonstrated more than 30% reduction in a composite of cardiovascular death and acute myocardial infarction, basically due to a reduction in infarction, with no effect on mortality. There was also a significant reduction in the need for new revascularization and heart failure up to 3 years of follow-up, with no difference between the revascularization of the non-culprit arteries before or shortly after hospital discharge. No reduction in cardiovascular or all-cause mortality was demonstrated in the COMPLETE study.

We now know of a meta-analysis that involves the 6 studies mentioned. It includes 6,528 patients, with a mean age of 63 years and a median follow-up of 2 years. The incidence of cardiovascular death during follow-up was 2.9%, and a reduction of almost 40% was achieved with the complete revascularization strategy (HR 0.62, 95% CI 0.39-0.97). The number needed to treat to prevent one cardiovascular death was 70 (95% CI 36-150). There was also a significant reduction in the incidence of reinfarction (HR 0.65, 95% CI 0.53-0.80), and that of repeat revascularization was 11.7% (HR 0.29, 95% CI 0.22-0.38). The number needed to treat was 45 to prevent reinfarction and only 8 to prevent a new revascularization episode. No reduction could be demonstrated in all-cause mortality (HR 0.81, 95% CI 0.60-1.10).

This meta-analysis, by increasing the number of observations, allows demonstrating a reduction in cardiovascular mortality with complete revascularization that none of the separate studies had been able to demonstrate. It is an expected finding, taking into account the reduction in the incidence of reinfarction and the need for repeated revascularization that we already knew about. Why was a meta-analysis necessary to show this reduction, and even so, a reduction in all-cause mortality was not achieved? Firstly, as in...
all randomized studies, it is a lower risk population than the one we see in daily practice: relatively young, with mean age around 63 years, with a low prevalence of diabetes (peri-20%) and renal dysfunction (between 1 and 2% in the studies with a higher number of patients). It is also a very well-treated population (use of statins in nearly 100% of patients, beta-blockers in almost 90%), more than 90% of cases in Killip and Kimball I, and at most, a third of patients with a 3-vessel injury, (but only 23% in the largest study, the COMPLETE trial). To this we must add a relatively short follow-up, with a median of only 2 years.

Some questions still have no definitive answer. What is the best way to define which non-culprit injuries should be treated? All of them or only those that are hemodynamically significant? Should one rely merely on visual estimation or resort to fractional flow reserve assessment? In the FAME study, 20% of lesions >70% were not hemodynamically significant. What would have happened in these studies if such a measurement had been routinely used? Would it have modified the results? On the other hand, in the COMPLETE study, the protocol established that patients randomly assigned to receive only angioplasty in the culprit artery did not undergo an additional procedure even when there was evidence of ischemia in an evocative test. This may have biased the results in favor of the complete revascularization group. And, on the other hand, the optimal moment for intervention has not yet been defined. Should it be before discharge (and if so, in the same procedure or on the following days) or after? Lastly, this meta-analysis considers the aggregated data of the studies; it is not a meta-analysis of individual data, which could have helped to clarify some of these questions. Ongoing studies may include a population more representative of the current profile of patients with acute infarction, and finish defining the feasibility and results of complete revascularization in the real world. In the meantime, the results of this meta-analysis force, at least, to actively consider the possibility of moving forward in this regard.