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El value of definitions: a post-hoc analysis of the ISCHEMIA trial

Chaitman BR, Alexander KP, Cyr DD, Berger JS, Reynolds HR, Bangalore S, et al. Myocardial Infarction in the ISCHEMIA Trial: Impact of Different Definitions on Incidence, Prognosis, and Treatment Comparisons. **Circulation. 2021;143(8):790-804. https://doi.org/10.1161/CIRCULATIONAHA.120.047987.**

As we recall, the ISCHEMIA study (which we commented in the Argentine Journal of Cardiology 2020, vol. 88: n° 4) was carried out in patients with stable coronary artery disease and moderate to severe ischemia in an evocative test, to define the effect of performing an angiography and, eventually, a revascularization procedure, compared with a conservative strategy. It excluded patients with glomerular filtration rate <30 mL/min/1.73m², acute coronary syndrome in the last two months, heart failure in FC III-IV, left ventricular ejection fraction (LVEF) <35%, unprotected left main coronary artery lesion >50%, or unacceptable angina despite optimal medical treatment. A coronary computed tomography angiography was performed to rule out patients with main left coronary artery lesion and those with non-obstructive coronary artery disease. The study was not carried out in patients with glomerular filtration rate between 30 and 60 mL/min/1.73 m², and in those with known coronary anatomy. The results served to decide whether patients could be included, but were not revealed to the treating physician or the patients, in order not to influence decision making. Patients were randomly assigned to a complete invasive strategy, based on angiography, and revascularization in case this was indicated [by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)], within 30 days of random assignment, or a conservative strategy with optimization of the pharmacological therapy and lifestyle modifications, with an angiographic study only in case of medical treatment failure. The primary end point was a composite of cardiovascular death, acute myocardial infarction (AMI), hospitalization for unstable angina, hospitalization for heart failure or resuscitated cardiorespiratory arrest. The secondary end point was a composite of cardiovascular death or AMI. A total of 5179 patients were randomly assigned between July 2012 and January 2018. Mean age was 64 years and 77% of patients were men. Nineteen percent of cases has a history of AMI and median LVEF was 60%. There was no or mild baseline ischemia in 12% of patients, moderate in 33% and severe in 55%. Two-vessel lesion was present in 19% of patients, and at least three-vessel lesion in 45%.

Median follow-up was 3.2 years. Effective coronary angiography was performed in 96% of patients in the invasive group, and in 79% a revascularization procedure was carried out (PCI in 75% of cases). In the conservative group, 26% of patients underwent angiography and 21% received a revascularization procedure. In 75% of cases, this crossover was produced before a primary end point event had occurred

During follow-up, the incidence of the primary end point was similar in both groups (HR 0.93, 95% CI 0.80-1.08). At 6 months, there was a higher rate of events in the invasive group (5.3% vs. 3.4%), with an excess of 1.9%, but approximately at 2 years, the incidence curves crossed over and the invasive group started to present lower rate of events than the conservative group, reaching at 5 years values of 16.4% and 18.2%, with an excess of 1.8% for the conservative group. The secondary end point results were similar, with 4.8% and 2.9% rate of events for the invasive and conservative groups, respectively, at 6 months, but 14.2% vs. 16.5%, respectively, at 5 years. Neither were differences found in all-cause mortality, but there were more hospitalizations for heart failure in the invasive group throughout the study (HR 2.23, 95% CI 1.38-3.61) and less hospitalizations for unstable angina (HR 0.50, 95% CI 0.27-0.91). There was no interaction of treatment with ischemia severity, diabetes or the number of vessels affected.

An analysis of the ISCHEMIA trial that goes deeper into the results according to the definition of AMI used has just been published. To diagnose peri-procedural AMI (types 4a and 5) a *primary definition* based on CPK-MB dosage and a *secondary definition* taking into account elevated cardiac troponin (cTr) were considered. Biomarker levels >5 times the normal upper limit in the case of PCI and >10 times in the case of CABG were required, adding ECG changes and angiographic evidence within 48 hours of the procedure. But if there was no clinical or ECG manifestation, the biomarker levels required to diagnose peri-procedural AMI were much higher: >10 times the upper normal limit for CPK-MB and 70 times for cTr for PCI and >15 and >100 times the upper normal limit, respectively, for CABG. Acute myocardial infarction unrelated to the procedure was that which occurred more than 48 hours later, and corresponded to types 1, 2, 4b and 4 c of the third definition of AMI. CPK-MB was preferred to diagnose peri-procedural AMI, and cTr was used when this was not available; the situation was reversed in the case of AMI unrelated to the procedure.

Using the primary definition (based on CPK-MB), 8.6% (n=443) of patients presented AMI, which was peri-procedural in 20.1% of cases. When the secondary definition was used, 11.5% (n=593) presented AMI, which was peri-procedural in 40.6% of cases. What is

interesting is the different incidence of AMI according to the definition used. Taking into account the primary definition, there was more AMI in the conservative group (8.9% vs. 8.1% in the invasive group), and considering the secondary definition, the reverse took place (9.6% vs. 13.2% in the invasive group). In each case, the accumulated incidence of type 1 AMI during follow-up was clearly lower in the invasive group than in the conservative one (35.7% vs. 63.1% of the total number of AMI with the primary definition; 21.6% vs. 60.4% with the secondary definition), regardless of the revascularization procedure employed. Conversely, the peri-procedural incidence of AMI was greater in the invasive group (32.9% vs. 8.6% of the total number of AMI with the primary definition; 60.4% vs. 13.6% with the secondary definition). Considering the primary definition, there were no differences in the incidence of the primary end point at 5 years between both groups, but, considering the secondary definition, the incidence was lower in the conservative group, due to the greater incidence of peri-procedural AMI. The difference in the incidence of the primary and secondary end points in the first 6 months rested specifically in the higher incidence of peri-procedural AMI. Moreover, when the secondary definition of AMI was used, the incidence of the primary end point was 10.2% in the invasive group and 3.7% in the conservative one. Throughout follow-up, the invasive group presented an adjusted HR of 2.98 (95% CI 1.87-4.74) for peri-procedural AMI and 0.67 (95% CI 0.53-0.83) for spontaneous AMI. In the survival analysis, peri-procedural AMI was not a predictor of cardiovascular or all-cause mortality. Conversely, type 1 AMI was a strong predictor of cardiovascular mortality (HR between 3 and 4 with both AMI definitions) and all-cause mortality (HR between 2 and 3 with both definitions), in all cases with $p < 0.001$.

This analysis highlights the crucial importance of definitions, and why one should be rigorous at the time of formulating them, analyzing the results and drawing conclusions. With the primary definition, based on CPK-MB, and less sensitive, there is no difference in the primary end point; with the secondary, as the incidence or peri-procedural AMI increases, a difference in favor of the conservative group logically arises. It is also interesting to notice the messages that implicitly emerge from the different analyses. This publication emphasizes that with the conservative strategy, type 1 AMI is much more frequent, and is just associated with higher mortality. At first, we could ask ourselves about the cause of reduction in the incidence of this type of AMI with the invasive strategy. The reduction is due to the procedure itself, to the dual antiplatelet therapy, or to unknown causes? Regarding this point, it has been postulated that in the case of CABG, complete revascularization distal to significant lesions could reduce the consequences of a future plaque accident in the bridge area, leading to smaller AMI, or even become unnoticed. In turn, a PCI implies the use dual antiplatelet therapy or strong individual antiplatelet agents, which would translate not only in a reduction of stent thrombosis in the treated vessel, but also in that of thrombotic events in the rest of the coronary circulation. The explanation, however, is far from being completely satisfactory, and mechanisms not taken into account must play a role. Regarding the concomitant mortality, it is clear that peri-procedural AMIs are controlled AMIs, in general secondary to events such as dissection, temporary occlusions, etc., that occur in the setting in which the intervention was performed, and can be treated at the moment. Conversely, type 1-AMIs respond to different mechanisms. In them, coronary thrombosis plays a key role; they occur outside the hospital, the possibility of immediate treatment is lower, they are extensive, etc. All these might explain their higher mortality. But what we would like to emphasize, if we limited ourselves to consider that the invasive strategy is associated with lower type 1-AMI, which is the one responsible of higher mortality, the prognosis with this strategy should have been better……, and nevertheless, it was not so. Mortality was similar in both groups. Undoubtedly, the prognosis at follow-up does not depend only on the incidence of AMI, or its type. Other complications associated with surgery, the incidence of bleeding due to the procedure, either PCI or CABG, are also prognostic factors. However, follow-up was slightly more than 3 years. A more prolonged follow-up could make us think differently in the future. Reality is multidimensional, its accurate interpretation, complex.

Should we choose directly catheter ablation in paroxysmal atrial fibrillation? The EARLY-AF trial

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The treatment of choice for paroxysmal atrial fibrillation (AF), according to clinical practice guidelines, is pharmacological therapy. However, antiarrhythmic drugs have limited efficacy: the rate of recurrence is high, as well as the incidence of adverse events. Catheter ablation is usually reserved for cases where pharmacological treatment of symptomatic paroxysmal AF has failed. The EARLY-AF trial, carried out in 18 Canada centers was presented in the recent 2020 AHA Congress and its results have been published. It included patients who had presented symptomatic AF, and at least one episode recorded in an ECG, in the previous 24 months. It excluded patients regularly receiving class I or III antiarrhythmic drugs. This was an open-label study where patients were randomly assigned to AF cryoablation with pulmonary vein isolation or pharmacological treatment. This was left at the discretion of the treating physician, recommending in each case, the administration of the maximum tolerated recommended dose without significant adverse events (propafenone at

doses >300 mg/day, sotalol >160 mg/day, flecainide >100/day or dronedarone 800 mg/day). All patients received an implantable cardiac loop recorder within 24 hours of pharmacological treatment onset or undergoing ablation. The primary end point was atrial tachyarrhythmia recurrence lasting at least 30 seconds. The first 90 days after ablation or drug treatment were deemed as "blanking" period and the incidence of arrhythmias was not considered during this interval, so arrhythmia occurrence was taken into account from day 91 to 365. Secondary end points were the emergence of symptomatic atrial arrhythmia, arrhythmia burden (defined as percentage of time in AF), quality of life and the incidence of serious adverse events. Taking into account a freedom from recurrence of 70% in the ablation group and a rate of 15% loss or crossover, it was estimated that 88 events, would be sufficient, with 90% power and a two-tailed p <0.05, to demonstrate 20% event reduction with the invasive therapy. This implied 149 patients per group. It was established that to crossover from the medical treatment group to the ablation group, a sufficiently severe AF should occur after day 90 to justify the procedure, despite the therapeutic doses of the drug used. Similar temporal and severity criteria were considered to justify the crossover in the opposite direction.

Between the beginning of 2017 and the end of 2018, 154 patients were included in the ablation group (the procedure was effectively carried out in 152, with median duration of 106 minutes) and 149 in the medical treatment group. Mean age was 58 years; 70% were men and mean monthly AF episodes was 3. During follow-up, 26 patients (16.8%) received an antiarrhythmic drug due AF recurrence, and among these patients, 17 underwent a second ablation at a median of 21 days. In the medical treatment group, 36 patients (24.2%) underwent an ablation during follow-up, at a median of 192 days. At one year follow-up, the incidence of the primary end point was 42.9% in the ablation group and 67.8% in the medical treatment group (HR 0.48, 95% CI 0.35-0.66; p <0.001). The incidence of symptomatic atrial tachyarrhythmia was 11% vs. 26.2%, respectively (HR 0.39, 95% CI 0.22-0.68). Median AF burden was 0% vs. 0.13% and the incidence of serious adverse events was 3.2% in the ablation group (including 3 cases of phrenic nerve palsy) vs. 4% in the medical treatment group (including 2 cases of tachyarrhythmia with broad QRS, one syncope and one heart failure worsening).

New evidence suggests that in patients with recent AF, an active rhythm control strategy is superior to the traditional approach. In the EAST AFNET 4 study, patients with diagnosed AF in the previous year, and several combinations of advanced age, risk factors and history of cerebral embolic events, were randomly assigned to early rhythm control or standard care. Early rhythm control included use of drugs or ablation. The primary end point was a composite of cardiovascular death, stroke or hospitalization with heart failure worsening or acute coronary syndrome, and the secondary end point was the number of nights spent in the hospital per year. A total of 2789 patients with median interval since AF diagnosis of 36 days were included in the study. The trial was stopped after a median follow-up of 5.1 years, with an annual incidence of the primary endpoint of 3.9% in the rhythm control group vs. 5% in the control group (HR 0.79, 95% CI 0.66-0.94). There was no difference in the number of hospitalization days, and the incidence of serious adverse events related with the rhythm control therapy was higher (4.9% vs. 1.4%). It is important to point out that the rhythm control strategy involved AF ablation in only 8% of cases initially, and 19% at 2 years; in the rest different antiarrhythmic drugs were used.

Assuming the that the rhythm control strategy can be superior to that of frequency control, the following question is with what weapon. Up to here, guidelines postulate that the advantage of ablation over pharmacological treatment is specifically due to greater symptomatic relief, without evidence of event reduction. That is why ablation is reserved for cases where drug therapy has failed. The EARLY-AF trial recommends an initial aggressive treatment of catheter ablation in patients with paroxysmal AF, without drug failure. In this sense, it goes a step ahead of most available evidence and guideline recommendations. It shows reduction in the incidence of AF events, but with scarce difference in overall arrhythmia burden. However, it does not evidence difference in the frequency of serious events: it was not the primary end point of the study, the number of patients included was low and follow-up was short to pretend such demonstration. It is also true that the patients included had relatively good prognosis, with low rate of comorbidities (<10% of patients with heart failure), with mild heart disease (mean atrial diameter of 39 mm and mean left ventricular ejection fraction of 60%), and low AF burden in the control group: only 0.13% (less than 2 minutes per day). Therefore, it does not seem that their results are going to change the strength and sense of recommendations, but open a door for studies with larger number of patients and longer follow-up which may define which is the best treatment for paroxysmal AF, the most helpful in terms of patient outcome and cost-effectiveness.

Current status of smoking cessation therapy: a systematic review

Patnode CD, Henderson JT, Coppola EL, Melnikow J, Durbin S, Thomas RG. Interventions for Tobacco Cessation in Adults, Including Pregnant Persons: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. **JAMA. 2021;325(3):280-98. https://doi.org/10.1001/jama.2020.23541**

Different strategies, from various pharmacological interventions to behavioral therapy and use of electronic cigarettes, have been proposed to quit smoking. However, the proportion of smokers who use these strategies is low. In 2015, the United States Preventive Services Task Force (USPSTF) conducted a systematic review and made a set of recommendations. Now the agency publishes an update of the available information and the conclusions derived from it.

It considered all the systematic reviews with relevant and non-repeated information on the subject published since 2014, focused on the general population of smokers or specific subgroups, and on each of the interventions cited. In order to generate recommendations for adults in general, the authors identified 32 primary reviews and another 21 focused on specific subgroups, after reviewing 210 articles. Three questions of interest were asked.

The first one was whether there is evidence about a reduction in morbidity and mortality with the implementation of these therapies. There is only one randomized study, with 1,445 patients, in which the use of a behavioral intervention did not lead to a reduction in total or cardiovascular mortality or lung cancer, in a population of male smokers at high risk for respiratory disease. And it dates from 1978!

The second was whether various interventions render greater abstinence in active smokers. It considered 52 studies of drug therapy associated with different procedures of behavioral support vs. usual care or minimal support, with a total of 19 488 participants. At 6 months, an average cessation incidence of 15.2% was demonstrated with the various interventions (between 2% and 50%) vs. 8.6% (between 0% and 36%) in the control group (RR 1.83, 95% CI 1.68-1.98). With another type of design, there were studies in which all patients received behavioral support, and were assigned to different drugs vs. placebo or no drug. In this case, both nicotine replacement therapy (133 studies, 64 640 participants, RR 1.55), as well as bupropion (46 studies, 17 866 participants, RR 1.64) and varenicline (27 studies, 12 625 participants, RR 2.24) were effective. The use of dual nicotine replacement therapy (short and long-acting therapies) was superior to single therapy. There was no difference in replacement therapy studies comparing nicotine vs. bupropion; but varenicline was superior to both in direct comparisons: RR 1.25 vs. nicotine therapy, RR 1.40 vs. bupropion, in both cases with $p < 0.05$, although there were few studies (8 and 6 respectively, with little more 8000 and 6000 patients). Absolute differences in smoking cessation averaged 6.4% for nicotine replacement therapy, 8.2% for bupropion, and 14.5% for varenicline. Physician (RR 1.76) or nurse (RR 1.29) advice as well as participation in groups, telephone calls, and interventions via the Internet, also showed a positive short-term effect. There was a clear lack of benefit for acupuncture, exercise, hypnosis, assessment of biomedical risk, etc. No difference in effect was evidenced in specific subgroups. Five studies, with a total number of 3117 participants, evaluated the use of the electronic cigarette. Cigarette type, nicotine content, co-intervention (none, behavioral support, nicotine replacement therapy), and design differed between studies, rendering (successful or not) varied and inconsistent findings.

The third question was whether any of the mentioned drugs is associated with a significant increase in cardiovascular or neurological risk. There was no evidence of a higher risk than that of the comparator in 9 systematic reviews. In conclusion, there is strong evidence that a variety of drugs and behavioral interventions, both individually and in combination, are effective in increasing smoking cessation in adults. Data on the efficacy and safety of e-cigarettes are limited, and the results are inconsistent.

A special chapter was reserved for pregnant women. Evidence suggests that behavioral interventions are effective to quit smoking, but data on the use of drug therapy are limited. There is no firm evidence on health status effects.

The evidence on the harmful effect of smoking is overwhelming and undeniable. In this regard, we would like to recall a meta-analysis that we discussed in Rev Argent Cardiol 2018; vol. 86, no. 1. It was based on 55 publications (141 cohorts, more than 5 million people included). The RR of coronary heart disease in men was 1.48 for those who smoked 1 cigarette, 1.58 for those who smoked 5 cigarettes and 2.04 for those who smoked 20 cigarettes per day. Smoking a cigarette per day implied a median 46% of the risk associated with smoking 20 cigarettes per day; and smoking 5 cigarettes implied a median 57% of the rik involved in smoking 20 cigarettes per day. In the studies that reported the risk in women, smoking 1, 5, or 20 cigarettes a day represented an RR of 1.57, 1.76, and 2.84 respectively. The risk of smoking 1 or 5 cigarettes was 31% and 46% of the risk involved in smoking 20 cigarettes a day. In the studies that did not discriminate risk between men and women, the consumption of 1 or 5 cigarettes a day represented 53% and 61%, respectively, of the risk caused by smoking 20 cigarettes a day. So there seems to be no doubt about the imperative of quitting smoking. And, to achieve this, it is clear that implementing various strategies delivers better results than not doing so. In this sense, the systematic review that we present emphasizes their usefulness, without specifying doses or preferable schedules, although in the specific comparison between drugs there seems to be a certain advantage for varenicline. The truth is that due to the variety of interventions, the diversity of options and their respective combinations, it seems difficult to establish clear superiorities, and perhaps it is possible to consider choosing a strategy adjusted to the characteristics and preferences of the patients. But, and

in this we would like to put an emphasis, unfortunately getting them to quit the habit does not seem an easy task. All the studies considered included those smokers who, at least, had some interest in quitting. A considerable number of smokers who postponed the issue "for later" were left out. And even so, with those who a priori seemed more motivated, the average abandonment rate was only 15%. Frequently, the smoker finally assumes abstinence when he becomes a patient: when he has a heart attack, when he must undergo revascularization surgery, or when he begins with heart failure. And then it is too late. Waiting to get sick does not seem like the best strategy to quit smoking. There is still a long way to go with essential policies and measures that go beyond the individual case if concrete results are to be expected to reduce the risk associated with smoking. As with other addictions, if one seeks to reduce the number of those affected, it certainly seems best to ensure that they do not start.

Two studies with sotagliflozin: early suspension, poor results.

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Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med. 2021;384(2):129-39. https://doi.org/10.1056/NEJMoa2030186

In recent years, we have witnessed the publication of various studies with gliflozins in the context, first of diabetes, then of heart failure (HF) and kidney failure, in patients with and without diabetes. In some, there has been a reduction in all-cause mortality, in others of cardiovascular mortality, in all reduction of hospitalization for HF and progression of kidney dysfunction. Studies have been carried out with empagliflozin, canagliflozin, dapagliflozin and ertugliflozin. All of them block the sodium glucose cotransporter-2 (SGLT2), present in the kidney, thus increasing renal sodium and glucose excretion. Now 2 studies are added to the body of evidence with another agent of the family, sotagliflozin, which, in addition to being a SGLT2 inhibitor, also inhibits the sodium glucose cotransporter-1 (SGLT1), present in the intestine, thus adding to kidney excretion the intestinal excretion of glucose and sodium. On the other hand, it should be reminded that SGLT1, unlike SGLT2, is found in the myocardium, so an additional advantage when using sotagliflozin could be speculated.

The SOLOIST study was carried out in patients with type 2 diabetes, hospitalized for HF. It excluded patients with end-stage HF, recent hospitalization for acute coronary symptoms or revascularization procedure, or with glomerular filtration <30 mL/min/1.73 m^2. They should be stable, with systolic blood pressure of at least 100 mm Hg, without need for inotropic or intravenous vasodilators agents (except nitrates) and with oral diuretic treatment. They should have a BNP value ≥150 pg/mL or NT-proBNP ≥600 pg/mL (≥ 450 pg/mL and 1,800 pg/mL, respectively, in the case of atrial fibrillation). Patients were randomly assigned and stratified according to left ventricular ejection fraction (LVEF) < or ≥50%, to sotagliflozin (first 200 mg, and, if well tolerated, 400 mg daily) or placebo, during hospitalization or within 3 days after discharge. The primary end point of the study was initially a composite of cardiovascular death or hospitalization for heart failure. It was estimated that 947 events in patients with LVEF <50% would give the study a power of 85% to detect 19% reduction in that group, with p <0.05. Similarly, 1341 events would be necessary to have the same power to detect a similar reduction in the total group. This implied including more than 4000 patients. But in March 2020, when 1222 patients had been included (only 256 with LVEF ≥50%), the sponsor decided to withdraw support. This entailed a notable loss of statistical power and led to a change of the primary end point to a composite of cardiovascular death, hospitalizations for heart failure, and urgent ER visits (the first and subsequent visits). Median age was 70 years, one third were women; median LVEF was 35% (almost 80% had LVEF <50%), and that of glycosylated hemoglobin 7.1%. Forty-nine percent of patients started treatment before discharge and the remaining 51% in a median of 2 days after it. More than 90% of the patients were treated with renin-angiotensin system inhibitors or antagonists (including sacubitril valsartan in almost 17%), and the rest with beta-blockers. More than 60% of patients received an anti-aldosterone agent.

Median follow-up was just over 9 months. The annual incidence of the new composite primary end point was 51% in the sotagliflozin group and 76.3% in the placebo group (HR 0.67, 95% CI 0.52-0.85, p <0.001). When considering only cardiovascular death and total number of hospitalizations for HF, leaving aside emergency room (ER) visits, the result was similar: HR 0.68, 95% CI 0.53-0.88. There was no interaction with LVEF. No reduction in cardiovascular death or total death could be demonstrated. The most frequent adverse effects with the use of sotagliflozin were hypotension and diarrhea, both about 6%. The incidence of hypoglycemia was 1.5%, compared with 0.3% in the placebo group.

The SCORED study focused on patients over 18 years of age, with type 2 diabetes, chronic kidney failure (glomerular filtration rate between 25 and 60 mL/min/1.73m^2) and additional cardiovascular risk factors (in all of them a major risk factor, and in

those over 55 years of age, at least two minor risk factors). The study initially planned two co-primary end points: major adverse cardiovascular events (MACE, including cardiovascular death, and non-fatal acute myocardial infarction and stroke), and a composite of cardiovascular death and hospitalization for HF. It was designed in order to demonstrate non-inferiority for the first primary end point (with an upper 95% CI limit of HR that should not exceed 1.3), and superiority for the second end point. As in the case of the SOLOIST study, patients were randomly assigned to sotagliflozin or placebo. It was estimated that for 10 500 enrolled patients, 1189 events from the first and 844 from the second primary end points would be required to meet the study objectives. When 10 584 patients had been included, what we have already mentioned regarding the SOLOIST study happened: the sponsor withdrew the financial support. This made it necessary to shorten the times and adopt the same strategy as in the SOLOIST study: to consider a composite of cardiovascular death and all hospitalizations for HF and urgent ER visits as an end point.

Median age was 69 years and almost 45% were women. Median glycosylated hemoglobin was 8.3%, median glomerular filtration rate 44.5 mL/min/1.73m^2 and median urinary albumin creatinine index 74 mg/g. A third of the patients had microalbuminuria (index between 30 and <300 mg/g) and another third macroalbuminuria (index ≥ 300 mg/g). Twenty percent of the patients had LVEF ≤40% or had been hospitalized for HF in the last 2 years. In 64% of cases, patients were receiving insulin and 55% metformin. In a median follow-up of 16 months, the incidence of the modified primary end point was 5.6% in the sotagliflozin group and 7.5% in the placebo group (HR 0.74, 95% CI 0.63-0.88, p <0.001). The effect was mainly due to the decrease in the composite of hospitalizations for HF and urgent ER visits (HR 0.67, 95% CI 0.82), without being able to demonstrate a reduction in cardiovascular or total death, or of a renal end point (sustained fall in glomerular filtration rate, dialysis, kidney transplantation). The most common adverse events with sotagliflozin were diarrhea (8.5%), genital fungal infections, diabetic ketoacidosis (0.6%), and volume depletion.

These studies with sotagliflozin confirm what is the main and indisputable class effect of gliflozins, which has already been shown in every context in which it was explored (patients with and without diabetes, with risk factors, cardiovascular disease, or established heart failure or kidney failure): the ability to reduce hospitalization for HF. Perhaps in this sense, the novelty is provided by the SOLOIST study, by focusing on peri-hospitalization for HF patients, compared to the "stable" patients included in previous studies. To be honest, did we expect a different result in this regard? Now, beyond this final end point, the rest of the results seem to be poor. There is no evidence of a reduction in total or cardiovascular mortality (as we saw in several of the studies discussed in previous issues), and not even evidence of kidney protection (a finding as universal as the reduction in hospitalization for HF, in patients with and without diabetes). It is clear that the early suspension of the studies influenced in a notable loss of power to demonstrate reduction of hard events, and in fact forced to modify the primary end point (a situation that always motivates discussion, but which seems justified not to jeopardize all the effort made). With regard to kidney function, it is also true that initially gliflozins generate a fall in glomerular filtration rate greater than that of placebo (because they precisely attenuate hyperfiltration), and that it is after approximately one year that the renal protective effect manifests; therefore, the end point of renal protection would also have required a longer follow-up than the one that could be established for reasons beyond the researchers´ wishes. The consequence is that finally the results of these studies only make us turn our attention to others with the drugs already mentioned, and that the hope for the eventual advantage of inhibiting not only renal SGLT2 but also intestinal SGLT1 fails: no strong effect on hard endpoints or kidney function could be demonstrated, and the incidence of hypoglycemia and diarrhea was higher than with SGLT2 inhibitors. Some authors have pointed out that the fact that there was no interaction with LVEF in the SOLOIST study is an encouragement for the use of gliflozins in patients with preserved LVEF. The small number of patients with LVEF ≥50%, only 256, hinders drawing final conclusions and makes it necessary, in this context, to wait for the results of the studies with empagliflozin and dapagliflozin, currently underway.

Machine learning: a tool to amplify our ability to know and predict

D'Ascenzo F, De Filippo O, Gallone G, Mittone G, Deriu MA, Iannaccone M, et al. Machine learning-based prediction of adverse events following an acute coronary syndrome (PRAISE): a modelling study of pooled datasets. **Lancet. 2021;397(10270):199-207. https://doi.org/10.1016/S0140-6736(20)32519-8**

Verdonschot JAJ, Merlo M, Dominguez F, Wang P, Henkens M, Adriaens ME, et al. Phenotypic clustering of dilated cardiomyopathy patients highlights important pathophysiological differences. **Eur Heart J. 2021;42(2):162-74. https://doi.org/10.1093/eurheartj/ehaa841**

Scores and traditional prediction rules are generally made using logistic regression models, which imply a linear relationship between each predictor variable of those selected by the researchers, and the natural logarithm of the OR. In recent years, artificial intelligence techniques have been developed with the capacity of dealing with a large amount of data, and of finding between different variables relationships

unsuspected in a traditional approach, by considering, in addition to linear relationships, non-linear relationships between predictor variables, and of them with the response variable. These techniques include "machine learning" or automatic learning. Machine learning focuses on building automated clinical decision systems that help clinicians make more accurate predictions, rather than simple estimated scoring systems. Machine learning can be classified into 3 learning types: supervised; without supervision, and reinforcement. In supervised learning, algorithms use labeled data set to predict a known outcome. Supervised learning is ideal for classification and regression problems, but it is data-intensive and time-consuming because the data has to be labeled by humans. Unsupervised learning seeks to identify new mechanisms, genotypes or phenotypes of diseases from hidden data, discovering patterns present in the data that go unnoticed by human understanding. For example, teaching doctors before they see patients can be called supervised learning; getting them to see patients and then allowing them to learn from their mistakes and make their own plans (optimize) can be called unsupervised learning. The reinforcement technique is a hybrid between the two previous models. The limitation of unsupervised learning is that the cluster pattern must be corrected without bias; therefore, the study must be validated in other cohorts.

The first study presented here refers to patients with acute coronary syndrome (ACS). As we know, they face a high risk of ischemic and hemorrhagic events at 1-year evolution that condition their prognosis. An essential part of ACS treatment is the use of a dual antiplatelet scheme with aspirin and a P2Y12 inhibitor, clearly associated with the aforementioned risks. The choice of antiplatelet agent and the dual antiplatelet therapy period depend on the balance between both risks. A high risk of ischemic events favors a more intensive and prolonged treatment; a high hemorrhagic risk puts a brake on this claim. Different prognostic scores and prediction rules have been developed to favor decision making, among them the PARIS and PRECISE DAPT scores. But their ability to predict and discriminate is far from ideal.

An Italian collaborative group has developed a model called PRAISE, to predict ischemic and hemorrhagic events in the context of ACS. The derivation cohort came from 2 ACS registries (BleeMACS, with 15 401 patients from America, Europe, and Asia, treated with clopidogrel, prasugrel, or ticagrelor; and RENAMI, with 4425 patients treated with prasugrel or ticagrelor). The validation cohort considered 3444 ACS patients followed up for 2 years, the vast majority from Italian registries, and the rest from other European countries. The end points to predict in the 1-year follow-up period were three: all-cause death, acute myocardial infarction (AMI), and major bleeding (type 3 or 5 of the BARC classification). The variables considered to build the models were 25: 16 clinical, including gender, age, risk factors, cardiovascular history, left ventricular ejection fraction (LVEF), ST-segment elevation, kidney function, and cancer; 5 pharmacological treatment (neurohormonal antagonists, statins, anticoagulants and proton pump inhibitors); 2 angiographic (multiple vessel injury and complete revascularization) and 2 pertaining to the procedure (vascular access and use of pharmacological stent). The derivation cohort was randomly divided into a training cohort (80% of the observations) to generate the initial models, and an internal validation cohort (with the remaining 20%) to fine-tune them. The models were validated in the external validation cohort, and in turn, the complete cohort (derivation and validation, with a total of 23 720 patients) was again divided into a training cohort (70% of the observations) and a final model test cohort (with the remaining 30%). For each final event, the scores of the entire cohort were divided into risk deciles, and then grouped into low, medium and high-risk categories.

The derivation and validation cohorts presented different characteristics: the mean derivation cohort age was 4 years younger (64 vs. 68 years), with a higher prevalence of risk factors, but better LVEF (55% vs. 50%). Use of clopidogrel predominated in the derivation cohort, and prasugrel and ticagrelor in the validation cohort. Use of statins and neurohormonal antagonists was greater in the derivation cohort. In this cohort, the incidence of all-cause death, AMI, and major bleeding was 3.3%, 3.1%, and 2.8%, respectively, while the corresponding values in the validation cohort were 1.7%, 1.7%, and 0.8%, at 1-year follow-up. The most important predictors of events were LVEF, age and hemoglobin in all cases, and in the highest range, use of statins for the prediction of all-cause death, and kidney function for the prediction of AMI and major bleeding were added.

The area under the ROC curve for predicting total death within the derivation cohort, was 0.91 in the training cohort and 0.82 in the internal validation cohort, and in the external validation cohort, 0.92. In the case of AMI 0.88, 0.74 and 0.81, respectively, and in the case of major bleeding, 0.87, 0.70 and 0.76, respectively. The observed incidence of all-cause mortality was 0.5% in the low-risk category, 2.9% in the moderate-risk category, and 29.4% in the high-risk category; that of AMI 0.7%, 2.8% and 19.4%, respectively, and of major bleeding 0.6%, 2.6% and 19.6%. As the risk of bleeding increased, that of AMI increased in parallel, and vice versa. Thus, for example, among patients with a low risk of major bleeding (60% of the total), only 4% had high risk of AMI, while among patients at high risk of major bleeding (10% of the total), 28% had high risk of AMI.

The second study to which we are going to refer was carried out in patients with dilated cardiomyopathy (cardiomyopathy of non-ischemic or valvular

origin). As we know, in these cases we face a high degree of etiological, genetic, clinical and functional heterogeneity, and a variable response to therapy. Only 40% to 50% of patients present reverse remodeling with the use of neurohormonal antagonists. Defining subgroups of patients with common characteristics can then be useful to choose the most effective treatment in each case. Again, artificial intelligence seems to come to our aid. In this study, patients with a diagnosis of dilated cardiomyopathy, with LVEF <50% and absence of significant coronary artery disease (>50% obstruction in any significant branch) were selected. The derivation cohort consisted of 795 patients from the Maastricht Cardiomyopathies Registry, Netherlands. Forty-seven variables were considered with data from the physical examination, clinical history, genetic endowment, laboratory tests, echocardiogram, ECG Holter, MRI and endomyocardial biopsy. Fourteen variables were excluded because data were missing in more than 25% of the cases, and 5 because the information they provided was redundant. Thus, 28 variables were defined, of which late gadolinium enhancement in nuclear magnetic resonance was maintained despite missing data in almost 30% of cases, due to its clinical importance. Through the use of complex artificial intelligence algorithms that defined in an unsupervised manner the relationships between the variables and the main factors that made it possible to group observations, 4 mutually excluding phenogroups with specific characteristics were established. Phenogroup 1 (42% of patients) was characterized by mild to moderate systolic function impairment (mean LVEF 43%), a net predominance of FC I-II (90%), scarce ventricular dilation, and low NT-proBNP values. At the other end, phenogroup 4 (27% of observations) included patients with marked systolic function impairment (mean LVEF 23%), notable ventricular dilation, and a high prevalence of FC III-IV. Phenogroups 2 and 3 presented a certain characterization beyond their LVEF. Phenogroup 2 (10% of patients) predominantly included women, with autoimmune etiology and worse kidney function; and phenogroup 3 (21% of patients) predominantly consisted of men with a high prevalence of atrial fibrillation and non-sustained ventricular tachycardia (in both cases, more than 60%), genetic etiology, and late gadolinium enhancement (fibrosis) on cardiac magnetic resonance imaging. From the point of view of the different biomarkers and molecules involved in different intracellular pathways, phenogroup 4 was characterized by an increase in glycolytic pathways and a decrease in fatty acid consumption, phenogroup 2 by the activation of inflammatory pathways, with higher expression of cytokines, and phenogroup 3 by the activation of profibrotic pathways.

The validation cohort included 789 patients from 2 cohorts from Madrid, Spain, and Trieste, Italy. Considering the 4 phenogroups derived from the Dutch cohort, a different rate of severe events (potentially fatal arrhythmia, transplantation, circulatory assistance and death) was verified in the Italian and Spanish cohorts according to the phenogroup: 1.1% per year in phenogroup 1, 4.2% in phenogroups 2 and 4, and 6.5% in phenogroup 3. After adjusting for age, sex, FC, LVEF, renal function, late gadolinium enhancement, atrial fibrillation and NT-proBNP, considering phenogroup 1 as reference, phenogroup 2 presented a HR of 2.3 (95% CI 0.9-5.7), phenogroup 4 a HR of 2.6 (95% CI 1.1-6.2) and phenogroup 3, a HR of 5.1 (95% CI 2.3-11.2) for severe events.

Faced with the explosion of studies and publications on artificial intelligence applied to medicine, it is impossible not to think in the analogy with other moments in its history. As the Dutch cardiologist A J Dunning points out in his book Broeder Ezel (Brother Donkey) , the invention of the stethoscope involved an enormous qualitative leap: the doctor went from listening to the patient's complaint to listening to the voice of the disease hidden in his body. Thus, for example, in the case of pneumonia, the stethoscope made it possible to listen to it; decades later, X-rays would allow it to be seen. Each of us has, in his daily medical practice, and for each of the necessary operations, a certain capacity. We are ourselves instruments with distinctive sensitivity and specificity for diagnosis (visual, auditory, tactile and finally intellectual), going through the stages that we learned in our earliest training (interrogation, inspection, palpation, percussion, auscultation), adding the adequate interpretation of each of the diagnostic methods we use. When we talk about the sensitivity and specificity of a sign or symptom for a certain condition, that value is the aggregate of the sensitivity and specificity of the findings of a group of doctors to discover it. Accepting this point, any diagnostic instrument designed by man serves to amplify his natural detection capacity.

It has been rightly said, that reality is only known by those who can predict it rather than by those capable of describing it. And we add, by those who can accurately predict it. The development of the first predictive diagnostic and prognostic models, the generation of scores and rules, represented a great advance at the time. But individual prediction is still deficient. We build the models with the variables that we judge a priori to be related to the diagnosis and prognosis, and we ignore the relationships among variables with which we feel there is no association. In this sense, artificial intelligence amplifies our ability to unravel the present to diagnose and the future to forecast, as an MRI allows us to see what is hidden and as electron microscopy places the ultrastructural in front of us. The database analysis with millions of structured and unstructured data (big data), often apparently unrelated to each other, allows the detection of unrecognized patterns. In this sense, the two studies that we present are small-scale samples of what we are referring to and constitute the first step towards the desired personalized or precision medicine. It is fair

to recognize that they are limited models because they are based on retrospective analyses, with data that, because they are often incomplete, forced to discard variables. On the other hand, as with each new tool, its capacity for implementation in daily practice, its acceptance by the medical community and its benefits in different contexts should be assessed. For example, does recognizing 4 phenogroups in the context of dilated cardiomyopathy translate into a different approach in each case? Does it tend to a greater or lesser use of certain resources? Does it influence long-term prognosis? Could the use of an implantable cardioverter defibrillator be specifically recommended in phenogroup 3, and anti-inflammatory therapy in phenogroup 2? Finally, we must remember that, still, these systems require human interpretation for correct data labeling and, many times, to define among several algorithms the most useful one from the clinical point of view.