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Finerenone in patients with diabetic nephropathy. FIDELITY, joint analysis of the FIDELIO-DKD and FIGARO-DKD studies

Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. **Eur Heart J 2022;43:474-84. https://doi.org/10.1093/eurheartj/ehab777**

Diabetic nephropathy (DN) is an entity clearly associated not only with renal but also poor cardiovascular prognosis. Metabolic alterations, neurohormonal activation, inflammation and fibrosis are the pathophysiological basis that explains its torpid evolution. A basic treatment is the use of renin angiotensin system (RAS) inhibitors or antagonists, either angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs); nevertheless, the incidence of serious events remains high. The association of ACEI and ARBs was tested in the NEPHRON-D study, with poor outcome due to a higher incidence of adverse events, mainly hyperkalemia and acute kidney failure. In the ALTITUDE study, the addition of aliskiren, a direct renin inhibitor, to an ACEI or ARB in patients with type-2 diabetes and high risk of renal or cardiovascular events, was associated with an increased risk of hyperkalemia and hypotension, without improving prognosis. As a better alternative, it was thought of adding, to the maximum tolerated dose of a RAS inhibitor/antagonist, the use of an anti-aldosterone agent. The largest research program in this regard was FIDELITY, a pooled analysis of the FIDELIO-DKD and FIGARO-DKD studies, in which the use of finerenone, a non-steroidal mineralocorticoid receptor antagonist, was tested.

The results of the FIDELIO-DKD study were published in 2020, and we commented on them in Rev Argent Cardiol 2020; 88:591-600. Briefly, in patients with DN and microalbuminuria (urinary albumin-creatinine ratio, UACR, between 30 and <300 mg/g) with a glomerular filtration rate (GFR) estimated by the CKD Epi formula between 25 and <60 mL/min/1.73 m^2; or macroalbuminuria (UACR between 300 and 5000 mg/g) with an estimated GFR between 25 and <75 mL/min/1.73 m^2, finerenone, compared with placebo, produced a significant reduction in a renal primary composite endpoint (sustained GFR drop ≥40% in 4 weeks, reaching a GFR <15 mL/min/1.73 m^2, need for dialysis for at least 3 months, kidney transplant or death of renal origin). The annual incidence was 7.6% vs. 9.1%, HR 0.82 (95% CI 0.73-0.93). There was also a significant reduction in a cardiovascular secondary composite endpoint (cardiovascular death, nonfatal acute myocardial infarction, nonfatal stroke, or hospitalization for heart failure, HHF), with an annual incidence of 5.1% vs. 5.9%, HR 0.86 (95% CI 0.75-0.99). No reduction in cardiovascular death or all-cause death was demonstrated.

The FIGARO-DKD study was published in 2021 and was discussed in Rev Argent Cardiol 2021;89:372-381. It included patients with DN, microalbuminuria with a GFR between 25 and 90 mL/min/1.73m^2, or macroalbuminuria with a GFR ≥60 mL/min/1.73m^2. In this study the primary endpoint was the cardiovascular composite of the previous study. Its annual incidence was 3.9% in the finerenone arm and 4.5% in the placebo arm, with HR 0.87 (95% CI 0.76-0.98), a decrease driven by the reduction in HHF, without significant reduction of the other composite components. The incidence of a renal composite secondary endpoint presented a reduction in the limit of statistical significance: 9.5% vs. 10.8%, HR 0.87 (95% CI 0.76-1.01).

The results of the combined analysis of both studies in the FIDELITY program are now published. According to the admission criteria, a total of 13 026 patients with DN, GFR ≥25 mL/min/1.73 m^2, plasma potassium ≤4.8 mEq/L, and free from HF with reduced left ventricular ejection fraction were included in the analysis. Two composite endpoints were taken into account: the aforementioned cardiovascular endpoint and a renal endpoint with the aforementioned components, except for the fact that a drop in GFR ≥57% and not ≥ 40% was considered, equivalent to doubling the baseline creatinine values, to achieve more robust results. Mean age was 65 years, and 70% of patients were men. Mean duration of diabetes was 15.4 years, and mean HbA1c 7.7%. In 45% of cases patients had a cardiovascular history, but only 7.7% had HF. Mean GFR was 57.6 ml/min/1.73m^2, (60% had GFR <60 ml/min/1.73m^2), median of UACR was 515 mg/g (67% had macroalbuminuria). Patients were almost universally treated with ACEI/ARBs, and 72% with statins. Almost 60% were receiving insulin, but only 7.2% GLP-1 receptor agonists and just 6.7% gliflozins, a fact to be taken into account.

In a median follow-up of 3 years, the annual incidence of the cardiovascular composite endpoint was 4.3% with finerenone and 5% with placebo (HR 0.86; 95% CI 0.78-0.95, p=0.0018). The reduction in HHF

was notable (HR 0.78, 95% CI 0.66-0.92) and there was a tendency to reduce cardiovascular death (HR 0.88, 95% CI 0.76-1.02). The number needed to treat (NNT) to reduce a cardiovascular event in 3 years was 46 (95% CI 29-109). Regarding the renal endpoint, the annual incidence was 2% with finerenone and 2.5% with placebo (HR 0.77, 95% CI 0.67-0.88, p=0.0002). Each of the renal endpoint components was significantly reduced. The NNT to reduce a renal event in 3 years was 60 (95% CI 38-142). The reduction in events was also significant when considering a drop in GFR ≥40%. Annual total mortality was 2.76% with finerenone and 3.1% with placebo, with HR 0.89, 95% CI 0.79-1.001, p=0.051). The increase in plasma potassium with finerenone was 0.2 mEq/L and 0.02 mEq/L with placebo. The incidence of adverse events related to hyperkalemia was higher with finerenone, 14% vs 7%, but the annual rate of treatment abandonment for this reason was only 0.66% with finerenone, and 0.22% with placebo. Logically, there was less hypokalemia in the finerenone arm.

Diabetic nephropathy is one of the most feared complications of diabetes; it is expected in 40-45% of patients with type I diabetes, and in 30% of those with type II diabetes. Its prevention involves strict control of blood glucose and blood pressure levels. Beyond the already known RAS activation, that of the mineralocorticoid receptors is an integral part of the disorder, which justifies adding an anti-aldosterone agent to ACEI/ARBs. In different animal and human studies, the use of drugs from this family is associated with a reduction in microalbuminuria, a delay in renal function impairment, and a reduction of fibrosis. But a certain risk is that of hyperkalemia, a condition to which patients with diabetes are more prone due to the frequent presence of hyporeninemic hypoaldosteronism. Finerenone is a nonsteroidal mineralocorticoid receptor antagonist, unlike spironolactone and eplerenone steroids; its half-life is shorter and its anti-inflammatory, antiproteinuric and antifibrotic effect is at least as potent as, and in many studies, superior to, that of the steroids mentioned. In a recent meta-analysis, it was shown that its addition to ACEI or ARBs in patients with ND does not increase the risk of hyperkalemia, compared to significant increases with eplerenone and especially with spironolactone. Unlike eplerenone and spironolactone, which tend to accumulate more in the kidney than in the heart, the distribution of finerenone is balanced between both organs. All these are reasons that could justify the preference for this agent over its analogue in the treatment of DN.

With these data in mind, the results of the FIDELITY program are not unexpected. Renal and vascular protection must necessarily translate into a better prognosis. Therefore, we have a therapeutic agent that is added to RAS inhibitors/antagonists for the treatment of DN. We must surely admit that, beyond statistical significance, in absolute terms the reduction in events is modest. We must treat almost 140 patients for a year to reduce a cardiovascular event, almost certainly an episode of heart failure with preserved ejection fraction; and 180 patients for 1 year to prevent an event of severe kidney function worsening. As is always the case, the more committed the patients, the greater the profit with the treatment. Consequently, the annual NNT to prevent a cardiovascular event was 125 in FIDELIO-DKD, and more than 170 in FIGARO-DKD; and to prevent a renal event, 66 in FIDELIO-DKD, but more than 250 in FIGARO-DKD. Perhaps these figures could help make the right decisions when access to medication is problematic.

And, of course, we cannot fail to mention gliflozins, the sodium-glucose cotransporter 2 inhibitors, which have long demonstrated beneficial effects in the field of diabetes and kidney failure, as we have already discussed several times thanks to the different studies known in recent years. Specifically in the field of DN, it is necessary to bring up the CREDENCE study. In CREDENCE,, canagliflozin, in patients with DN (mean GFR 56 ml/min/1.73m², median UACR 927 mg/g; GFR somewhat better, UACR somewhat worse than in FIDELIO-DKD) generated a reduction in the renal composite endpoint, in HHF (annual reduction of 1% vs. 0.3% in FIDELIO-DKD) and a reduction in cardiovascular death at the very limit of statistical significance. As these are not strictly similar populations, we cannot establish a reliable comparison between finerenone and the gliflozin, but the effects of the latter seem somewhat more notable. It is unfortunate that a very small proportion of patients in the FIDELITY study were also treated with a sodium glucose cotransport 2 inhibitor to be able to draw conclusions about the synergism between both interventions. We will certainly know in the future comparative and combination studies between both drugs. Meanwhile, it is to celebrate that we have more tools to deal with an entity as complex and ominous as DN.

Sacubitril valsartan stumbles with advanced heart failure. The LIFE study

Mann DL, Givertz MM, Vader JM, Starling RC, Shah P, McNulty SE et al. Effect of Treatment with Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. **JAMA Cardiol 2022;7:17-25. https://doi.org/10.1001/ jamacardio.2021.4567**

The PARADIGM-HF study enthroned sacubitril valsartan (SV) as the first-choice drug for the treatment of heart failure with reduced left ventricular ejection fraction (HFrEF), by demonstrating a significant reduction in hospitalization for heart fail-

ure, cardiovascular mortality and total mortality compared with enalapril. Almost all the patients in this study were in FC II-III with those in FC IV representing less than 1% of the total number of patients. It is true that the PIONEER-HF study demonstrated in hospitalized HFrEF patients that SV generates a greater reduction of NT-proBNP values than enalapril, and that this may be linked to a better clinical outcome during follow-up, but we know that we cannot equate the moment of HF decompensation with a persistent FC IV. For this reason, until now we did not have accurate data on the usefulness of SV in patients with advanced HFrEF. The LIFE study sought to clarify this point.

It included patients with left ventricular ejection fraction (LVEF) ≤35%, who had HF symptoms in FC IV at presentation or in the last 3 months, with a minimum of 3 months of HF treatment according to guidelines, with a BNP dosage ≥250 pg./mL, or NT- proBNP ≥800 pg./mL and at least one additional manifestation of advanced HF (current inotropic therapy or use of inotropic drugs within the previous 6 months, ≥1 hospitalization for HF in the last 6 months , LVEF ≤25% in the past 12 months, decreased peak VO2 consumption in the past 12 months, and 6-minute walk distance <300 meters in the last 3 months). Patients underwent an initial run-in phase with SV at a dose of 50 mg every 12 hours for 3 to 7 days. Those who tolerated SV were subsequently randomized to SV or valsartan, with a target dose of 200 mg every 12 hours or 160 mg every 12 hours, respectively. In each arm, a placebo of the drug corresponding to the other arm was also administered, in what constitutes a double dummy design. In all patients, NT-proBNP was assessed at baseline, and then at weeks 2, 4, 8, 12, and 24. The primary endpoint of the study was the area under the curve for the ratio of NT-proBNP values at follow-up compared with baseline. As a secondary endpoint, the number of days alive and free from hospitalization, inclusion into the transplant list or heart transplantation, need for inotropic drugs for 7 or more days, ventricular assistance, or 2 or more hospitalizations for HF during follow-up were considered. As safety endpoints, hyperkalemia, hypotension, and renal function worsening were taken into account. It was considered that 400 patients would provide 88% power to demonstrate a difference of 20% in the area under the NT- proBNP curve in favor of SV.

The study started in March 2017. Enrollment was suspended in March 2020 due to the advent of the COVID-19 pandemic. It was established that all those patients who had been randomly assigned until December 7, 2019, and whose 12-week visit had been prior to March 1, 2020, would be considered for the analysis. Among 409 patients initially considered, 18% did not pass the run-in phase. This restricted the analysis to 335 patients actually assigned to randomization, 167 to the SV arm. Median age was 60 years, and 73% were men. Mean LVEF was 20.4% and 39% had been hospitalized for HF in the last 6 months. At the time of inclusion, 25% of the patients were in FC II, 41% in FC III and 34% in FC IV. Mean systolic blood pressure was just over 112 mm Hg, median NT- proBNP close to 1900 pg. /mL and mean glomerular filtration rate 64 ml/min/1.73 m^2. In 78% of cases patients were receiving beta-blockers, 57% aldosterone antagonists, and 65% had a cardioverter-defibrillator implanted, alone or associated with cardiac resynchronization therapy. At 24 weeks, the median ratio of NT- proBNP with respect to baseline was 1.08 (IQR 0.75-1.60) in the SV arm and 1.19 (IQR 0.91-1.64) in the valsartan arm, which implies that there was no significant change in the concentration of the natriuretic peptide in each arm, nor was there a significant difference between the two. Neither did clinical events considered in the secondary endpoint differ during follow-up. The incidence of hyperkalemia was higher in the SV arm: 17% vs. 9% (p=0.04). There was no difference in the discontinuation rate, which was around 30%, and only 35% of patients reached the SV target dose of 400 mg daily.

The LIFE study seems to put a limit to the triumphal march of SV in the treatment of HFrEF. The comparison with the PARADIGM-HF study is necessary if we want to understand the causes.

In the PARADIGM-HF study, 20% of the patients initially considered did not pass the two successive run-in phases with enalapril and SV, in which, let us remember, the doses used were up to 20 mg of enalapril and 400 mg of SV. Among the 8442 patients finally included, just over 70% were in FC II, 24% in FC III, and 0.7% in FC IV. Mean LVEF was 29%; systolic blood pressure 122 mm Hg; glomerular filtration rate 70 ml/min/1.73 m2 and median NT-proBNP was around 1600 pg/mL. In the SV arm, discontinuation throughout the study was almost 18%, and the mean final dose achieved was 375 mg daily.

According to the data presented, in the LIFE study18% of the patients did not pass a run-in phase with only 100 mg of SV, and only 25% of the patients were in FC II. Left ventricular ejection fraction was almost 10 points lower, systolic blood pressure 10 mm Hg lower, NT- proBNP value was higher and the glomerular filtration rate was lower. All this constitutes firm evidence about much more compromised patients. And it should be emphasized, as already described, that in patients with more advanced HF, the beneficial effect of natriuretic peptides declines, due to different mechanisms: decreased receptor response capacity due to a reduction in their number and uncoupling with intracellular cascades that generate a biological response (phenomenon similar to that of beta receptors), in addition to overactivation of va-

soconstrictor systems (renin-angiotensin-aldosterone and endothelin). For this reason, the addition of sacubitril to valsartan, which generates an increase in natriuretic peptides, may not demonstrate an advantage over using valsartan alone. The full dose of SV could only be achieved in slightly more than a third of the patients. Lower blood pressure and worse renal function surely have some effect, also explaining the higher incidence of hyperkalemia. And, to conclude, a fact that due to the much-criticized subgroup analysis and the imperative of considering only global results is usually overlooked: in PARADIGM-HF, the effect of SV on the composite endpoint of cardiovascular mortality/ hospitalization for HF was much more marked in patients in FC I-II than in those in FC III-IV, with a p-value for interaction=0.03. Perhaps in that difference the results of the LIFE study were beginning to be outlined.

A recent network meta-analysis of heart failure with reduced ejection fraction treatment

Tromp J, Ouwerkerk W, van Veldhuisen DJ, Hillege HL, Richards AM, van der Meer P et al. A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction. **JACC Heart Fail 2022;10:73-84. https://doi.org/10.1016/j.jchf.2021.09.004**

Over the last 35 years we have witnessed a true revolution in the treatment of heart failure with reduced ejection fraction (HFrEF). Different drugs or drug families have successively been shown to improve patient prognosis by reducing the incidence of total and cardiovascular death, and/or hospitalization for heart failure. Thus, angiotensin-converting enzyme (ACEI), angiotensin II receptor blockers (ARBs), beta-blockers (BB) and aldosterone antagonists (AA) were gradually incorporated into the therapeutic arsenal. In general, each new addition was tested against the background of what was already established. An exception is sacubitril/valsartan, a dual angiotensin II receptor and neprilysin inhibitor (ARNI), which in the PARADIGM-HF study was directly compared with an ACEI, enalapril. In recent years, drugs with other mechanisms of action have been added to this plethora of neurohormonal antagonists: a vasodilator, vericiguat (V), which stimulates soluble guanylyl cyclase and increases cGMP levels; a novel-acting inotrope, omecamtiv mecarbil (OM), and sodium glucose cotransporter 2 inhibitors (SGLT2i). Logically, this profusion of drugs leads us to wonder what the ideal combination is, what is the sum of agents that offers the best results. To answer this question, a network meta-analysis of all randomized studies that tested a pharmacological intervention in the context of HFrEF and were published between 1987 and early 2021 was carried out. As we have already pointed out in previous comments, the network meta-analysis considers drug vs. placebo and drug vs. drug/s comparisons from different studies. If one study compared one drug vs. a placebo, and another study this drug vs. another drug, the network meta-analysis allows, from the effect measures of each study, to estimate the effect of the latter vs. placebo, even though that comparison had never been carried out. The same occurs for estimating the effect of one drug over another with which it was never compared head-to-head. The results then depend on direct evidence (comparisons actually carried out in clinical trials) and indirect evidence (results inferred from successive comparisons of different study branches, without actually having such a comparison in a trial).

Studies in which another condition affected the entire population and was life threatening, beyond HFrEF (for example, post-infarction ventricular dysfunction, or diabetes) were excluded, and only outpatient studies were considered. Treatment prior to random assignment of the investigation product in at least 50% of the included population was considered baseline treatment. In the case of sacubitril/valsartan, this has not yet occurred (in no recent study has the use of this drug reached this percentage in baseline conditions), despite which the main analysis, when taking into account the studies of vericiguat, omecamtiv mecarbil, and gliflozins, was carried out considering the use of ARNI as a substrate, and alternatively that of ACEI. The primary endpoint of the analysis was all-cause mortality, as the composite endpoint of cardiovascular death/ hospitalization for heart failure came into use more recently. To define confidence in the results, the presence of biases inherent to the design, reporting bias, imprecision (when the 95% CIs are very wide), heterogeneity in the results and incoherence (when the results obtained by direct evidence differ significantly from those arising from indirect evidence) were considered.

The analysis included 75 studies with 95 444 patients (the majority in FC II) and 199 978 patient/years of follow-up. Median follow-up was 11 months. Overall, the studies provided reliable results when taking into account the mentioned parameters. Compared with a real or hypothetical placebo, ARNI (HR 0.75; 95% CI 0.66-0.85) and AA (HR 0.76; 95% CI 0.67-0.85) were associated with the largest reduction of all-cause mortality, followed by BB (HR 0.78; 95% CI 0.72-0.84), ACEI (HR 0.89; 95% CI 0.82-0.96), SGLT2i (HR 0.88; 95% CI 0.78-0.99) and ARBs (HR 0.95; 95% CI 0.88-1.02). Vericiguat (HR 0.94; 95% CI 0.79-1.11) and OM (HR 1.0; 95% CI 0.92-1.09) did not reduce this risk.

Regarding the association of drugs compared with a hypothetical placebo, the best combination was ARNI-BB-AA-SGLT2i (HR 0.39; 95% CI 0.31-0.49), followed by ARNI-BB-AA-V (HR 0.41; 95% CI

0.32-0.53) and ARNI-BB-AA-OM (HR 0.44; 95% CI 0.36-0.55), with no significant differences between the three. The ARNI-BB-AA combination was also associated with an HR of 0.44; CI 95% 0.37-0.54; the addition of SGLT2i to this triple therapy implied a significant improvement (HR of the quadruple with respect to the triple therapy, 0.88; 95% CI 0.78-0.99). When in each combination case the ARNI was replaced by an ACEI, the significant reduction in mortality was maintained, but less than that achieved with the former. It is interesting to note that the ACEI-BB-digoxin-hydralazine-nitrates combination was associated with a HR of 0.46; CI 95% 0.35-0.61; and the ACEI-BB-AA-ivabradine combination was associated with an HR of 0.48; CI 95% 0.39-0.58. When analyzing cardiovascular death (results available from 43 studies) or cardiovascular death/hospitalization for heart failure (16 studies), the results were generally similar in magnitude and direction.

To define the benefit to be achieved in the real world, the results of the meta-analysis were applied to 7376 patients with HFrEF from 2 observational studies: BIOSTAT-CHF and ASIAN-HF, with 77% using ACEI/ARBs, 82% BB and 55% AA. Compared with the absence of treatment, it was estimated that the use of ARNI-BB-AA-SGLT2i would extend life by 7.9 years in 50-year-old patients and by 5 years in 70-year-old patients; compared with the treatment actually received, the gain would be 4.9 and 3.3 years, respectively.

This network meta-analysis condenses the results of randomized pharmacological intervention studies conducted in HFrEF over the last 35 years. It offers no surprises in the most important conclusions: the quadruple therapy (ARNI-BB-AA-SGLT2i), which from an analysis that considered the EMPHASIS-HF, PARADIGM-HF and DAPA-HF studies, discussed in Rev Argent Cardiol 2020;88:401-411, Vaduganathan et al., defined as the standard of care in HFrEF, is corroborated here in a much broader context, where other combinations and classic and recent drugs are also taken into account. It is confirmed that the addition of SGLT2i to the triple ARNI-AA-BB therapy improves the results of the latter. The combination of ARNI-AA-BB with V or OM is slightly less effective than with SGLT2i (a striking fact, if we consider that in the VICTORIA studies, with vericiguat, and GALACTIC-HF, with OM, there was no reduction in mortality). The results of the ACEI-BB-digoxin-hydralazine-nitrates combination are challenging. The authors of the meta-analysis call for tempering optimism (finally an economic combination, and with noticeable effect!), noting that the reduction in mortality with hydralazine-nitrates stems from a single study, A-HeFT, in African-American patients. Regarding the years of life gained, the data also repeat the message of what was reported in Vaduganathan's study.

Some reflections must however be formulated. The meta-analysis presented is of studies considered as patient aggregates. It is not a meta-analysis of individual data, so the precision in the estimation of the effects is somewhat lower, although the direction of the described associations is not discussed. It is clear, because it is in the nature of the design, that we are in many cases in the presence of estimates, not real results of a comparison actually carried out. For example, it should be remembered that, in the case of ARNI, their use in the studies with V, OM and SGLT2i did not exceed 20%; patients treated with ARNI are not similar to those who do not receive them; and there are, without a doubt, patients in whom the quadruple therapy or the combination of triple therapy with OM or V is not feasible. The same is true for the rest of the drugs. We are citing in each case the expected effect if the combination is applied, but it may not always happen. In some patients, hypotension can limit the use of ARNI or BB, in others bradycardia or conduction disorders, that of BB, and in many with significant renal dysfunction, that of AA, ARNI, or SGLT2i. And it is necessary to recall that the information from the meta-analysis comes from randomized studies, which, as we will see in the following commentary, are not always a true reflection of reality, since they include patients free from significant comorbidities and hemodynamically stable, in whom achieving optimal doses and combinations is more feasible than in the so-called "real world".

Another point to note is that the comparisons presented indicate the power of a combination with respect to a placebo, not that of one with respect to another; this translates into risk reductions that are undoubtedly more striking; we must bear in mind that in general we do not deal with patients who are completely new to medication, except in cases of very recent onset or diagnosis of the disease, so it is useful to know in each case how much we can expect to improve the prognosis with the introduction of a new agent with respect to what the patient has already been receiving. And, on the other hand, remember that the figures presented to us refer to the relative risk reduction, and that it would be very informative to also know the expected absolute risk reduction (which is what defines the number needed to treat), and how much a new agent added to a baseline combination prolongs life compared to the latter. Especially, when expensive medications with marginal benefit are proposed, although the reduction in HR is accompanied by a $p < 0.05$.

And finally, we must recall the generally neglected issue of access. As a counterpart of the results achieved in the world of randomized studies, in which the availability of the most expensive drugs is not a problem for the patients included, in the office and care centers we collide frontally with inequity in

the distribution of resources and with the economic limitations of patients and coverage, so the benefit of multiple therapies seems restricted for many patients to the world of literature, medical, of course, but literature nonetheless.

Differences between randomized studies and the real world. Examples from the DAPT study and cardiogenic shock

*Butala NM, Faridi KF, Tamez H, Strom JB, Song Y, Shen C et al. Estimation of DAPT Study Treatment Effects in Contemporary Clinical Practice: Findings From the EXTEND-DAPT Study. C***irculation 2022;145:97-106. https://doi.org/10.1161/CIRCULATIONAHA.121.056878**

Megaly M, Buda K, Alaswad K, Brilakis ES, Dupont A, Naidu S et al. Comparative Analysis of Patient Characteristics in Cardiogenic Shock Studies: Differences Between Trials and Registries. **JACC Cardiovasc Interv 2022;15:297-304. https://doi.org/10.1016/j.jcin.2021.11.036**

When the evidence used to formulate recommendations in clinical practice guidelines is classified, the greatest force of evidence, termed A, is the one corresponding to data resulting from at least 2 randomized controlled trials (RCT) or meta-analysis. Evidence B stems from a single randomized study or large non-randomized studies (cohort, case control), and C corresponds to experts' opinion consensus, case reports or standard of care. Thus, from their classification, the preeminence of randomized interventional studies is installed over observational studies. Some doubts naturally arise when examining the implementation logic of randomized studies. It is certainly true that randomization eliminates selection bias. Bur it is not less true that the population participating in the trial is selected. And that selected population is doubtless the one in which the intervention has greater probability of demonstrating its beneficial effect, if this were the case. Control procedures and close follow-up, patients attending all visits and free from comorbidities that threaten the evolution and compliance beyond the disease of interest, frequent analyses, etc. Daily life centers, procedures, physicians and patients generally do not ensure such perfection. Two recent publications illustrate on the differences between randomized studies in two different clinical situations, and their observational counterpart.

The first refers to the DAPT study. As recalled, the DAPT international, multicenter, randomized, placebo-controlled trial evaluated the safety and efficacy of continuing dual antiplatelet therapy (DAPT) beyond a year in patients with drug-eluting stent (DES) implantation. If after being treated with open-label DAPT during one year, they had not presented major cardiovascular or cerebrovascular events, repeat revascularization or moderate-severe bleeding, they were randomly assigned to continue with DAPT until completing 30 months or to only continue with aspirin and placebo of the P2Y12 inhibitor. Once the 30 months were concluded, patients were observed during 3 additional months to see the effect of thienopyridine discontinuation in those receiving prolonged DAPT. The final coprimary efficacy endpoints were stent thrombosis (ST) and the incidence of major events: death, acute myocardial infarction (AMI) or stroke within 12 and 30 months; and the primary safety endpoint was the incidence of moderate or severe bleeding. A total of 9961 patients were included in the study, with mean age slightly below 62 years, 75% men and 31% presenting diabetes. Primary percutaneous intervention was performed in 26% of cases in the context of AMI, and almost an additional 17% due to unstable angina. Sixty-five percent of patients received clopidogrel and the rest prasugrel. In 47.2% of cases, the stent released everolimus and in 26.7%, paclitaxel; in the remaining cases, sirolimus or zotarolimus.

At the 18-month follow-up, the group that continued with DAPT presented a lower incidence of ST (0.4% vs.1.4%; HR 0.29, 95% CI 0.17-10.48) and major events (4.3% vs. 5.9%; HR 0.71, 95% CI 0.59-0.85). The incidence of AMI was lower, associated or not with ST. The reduction of major events seemed more marked when DES contained paclitaxel rather than everolimus, although it should be recalled that the choice of DES was not randomized. The incidence of cardiac death, vascular death and stroke did not differ significantly between both groups. The incidence of all-cause mortality was greater in the prolonged DAPT group (2% vs. 1.5%; HR 1.36, 95% CI 1-1.85; p=0.05). In the secondary analysis considering follow-up until 33 months (including the 3 months after thienopyridine discontinuation), mortality was 2.3% vs. 1.8%; p=0.04. Non-cardiovascular deaths were responsible for the differences observed, especially those due to mortal bleeding (11 vs. 3, mostly in the context of trauma) and those due to cancer (31 vs.14). A post-hoc analysis showed that despite randomization, the number of cancer patients between both groups was unbalanced, with a larger number in the prolonged DAPT group. When these patients were excluded, the differences in mortality disappeared. The incidence of at least moderate bleeding was higher in the prolonged DAPT group (2.5% vs.1.6%; HR 1.61, 95% CI 1.21-2.16; p=0.001), without difference in the incidence of severe or mortal bleeding.

It should be emphasized that the population selected was low-risk: it had a first year after stent placement without complications or major events. Patients who might have benefited for presenting a major event in the first year were not included.

In the analysis we are commenting now, the EXTEND-DAPT study, 8864 patients of the DAPT study enrolled in USA between 2009 and 2011 were selected. In a second step, the 568 541 patients enrolled in the USA NCDR CathPCI registry between mid-2016 and mid-2017, who received DES and were discharged with a P2Y12 inhibitor, were considered. As 5743 patients of the EXTEND-DAPT study presented a covariable pattern (age, gender, risk factors, comorbidities, cardiovascular history, and stent and procedure characteristics) similar to that of the registry, they could be linked with it. The probability of each participant to form part of the study was weighted according to the resemblance with registry patients. The representation of participants more similar to those of the registry was increased, and that of those less similar to the real world was decreased. Compared with the initial 8864 initial patients, the 5743 of this weighted cohort were 3 years older, with greater prevalence of female sex, cardiovascular and cerebrovascular disease, and history of coronary artery bypass grafting. Acute coronary syndrome at presentation and left main coronary artery disease were more common, and they had greater probability of receiving a second-generation stent (100% vs. 58%).

In DAPT study, prolonged use of DAPT was associated with a significant 71% reduction (1% in absolute terms) in the incidence of ST. When the effect seen in the study was applied to the weighted cohort akin to that of the registry, this significant reduction was lost. Something similar happened with the incidence of major cardiovascular and cerebrovascular events. It passed from an absolute reduction of 1.6% in the original study to an absence of effect when considering the cohort related to the registry. Conversely, excess risk of bleeding did not change when considering the weighted cohort. The exclusion of the type of stent as associated variable did not modify the findings regarding the lack of effect on the composite of cardiovascular and cerebrovascular events and the maintenance of excess bleeding with extended DAPT, but, on the contrary, the effect seen in the study concerning the reduction of ST and the incidence of AMI was recovered.

The other example refers to cardiogenic shock (CS) studies in the context of AMI. As we know, CS is the most severe AMI presentation, and entails an ominous prognosis. The inclusion of patients with CS in RCT is difficult, due to hemodynamic instability and the danger of poor immediate evolution, which hinders the physician, patient and family decision to participate, as well as taking the informed consent. We all suspect that this favors the selection of less compromised patients and hence contrives against the representativeness of studies in real-world patients. A recently published meta-analysis confirms these misgivings.

It included studies published in English, 14 RCT published between 2005 and 2020 (n=21 549) and 12 registries published between 2012 and 2021, so that patients were nearer the current reality (n=133 617, most of them from the already mentioned CathPCI registry). Compared with registry patients, RCS patients were more frequently men (73% vs. 67.7%), with less prevalence of coronary risk factors, peripheral vascular disease and history of coronary artery bypass graft surgery. They presented less frequently with ST-segment elevation AMI (72.4% vs. 79.3%), and on admission lactate was lower (mean of 4.7 vs. 5.9 mmol/L) and systolic blood pressure was higher (mean of 73 vs. 62.5 mmHg). There was a notable difference in the treatments established. Patients from RCT underwent more frequently percutaneous coronary intervention, PCI, (95.8% vs. 58.4%), multi-vessel PCI (31% vs. 27.4%) and use of extracorporeal membrane oxygenation (ECMO) (11.6% vs. 3.4%). Patients in the RCT group had lower in-hospital mortality23.9% (95% CI 18-29.9%) vs. 38.4% (95% CI 29.2-47.5%), p<0.001. They also presented lower 90-day mortality: 39.9 % (95 % CI 33.1 -46.6 %) vs. 45.9 % (95 % CI 33-58.9 %), p<0.001.

Both studies point out the clear differences between the world of RCT and the real world, and question whether the benefits of an intervention, expected from the results of a clinical trial, are the same when applied to "everyday" patients. Are observational studies the solution? Observational studies, comparing patients effectively treated with a different approach, but in whom the indication has not been randomized, in turn, deserve a series of criticisms. They are subject to a great number of biases: selection, observation and immortality biases (to start receiving the medication it is necessary to be alive; if the time from incorporation into a cohort until treatment initiation is assigned to this intervention, its benefit is overestimated). In these studies, there is confounding by indication (a certain conduct or treatment is indicated in those who can receive it, and therefore have conditions associated with the evolution beyond what is done) and residual confusion (factors influencing the prognosis and that are not taken into account in the analysis of baseline characteristics). Obviously. in the case of observational studies there are economical limitations: it is not simple to maintain a lubricated registry and demands great efforts. The association between different administrative bases is a form of implementing an adequate patient follow-up, but due to its nature there can be mistakes in the way of labeling different events.

We then confront a dilemma which seems insoluble. It is getting clearer that we cannot exclusively rest on studies including selected patients, and it is equally clear that blindly accepting "what we see" can lead us to erroneous conclusions. What can be done in the face of this contradiction? The perfor-

mance of pragmatic RCT, which preserve randomization, but with a simple design and with more lenient inclusion and exclusion criteria, and which reproduce the normal follow-up conditions of patients with the usual frequency of visits and practices is an option. Another option is the performance registry-based RCT, where in principle, all the included patients could be subjected to the study with wide external validity. It seems excessive to understand as "evidence" only what arises from RCT. In reality, Evidence Based Medicine was, in its origins, the idea of basing our conduct on the best available evidence. This information can derive from randomized or observational studies. And one and the other can be of better or worse quality, more or less acceptable, with conclusions that can be more or less extrapolated to all our patients. The PRECIS and GRADE tools point in that direction. According to the words of Sir Michael Rawlins, head of NICE (National Institute for Health and Care Excellence): "Individual and collective experiment, observation and mathematics have a crucial role in providing the basis of evidence for modern therapeutics. Arguments on the relative importance of each are an unnecessary distraction. Evidence hierarchies should be replaced by accepting and even embracing a diversity of approaches."