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Prediabetes: a condition that should not be underestimated

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In the last years (perhaps as a consequence of emerging treatments that might modify its natural history) type 2 diabetes mellitus (DM2) has gained relevance as a high impact disease in cardiovascular and global health. A previous abnormality in carbohydrate metabolism, called prediabetes (PD), has greater prevalence and is usually disregarded, when it is by itself an adverse prognostic factor. Data from a large British study confirm this assertion. The UK Biobank registry is an observational, prospective, population-based cohort study conducted in the United Kingdom, including more than 500 000 participants between 40 and 69 years of age. Sociodemographic data, history of prior disease, lifestyle and medication were recorded upon inclusion in the study; a physical exam was carried out and blood and urine samples were taken for laboratory tests. The analysis here presented explored the relationship between baseline carbohydrate metabolism abnormalities (exposure) and the incidence of atherosclerotic disease (AD), heart failure (HF) and chronic kidney disease (CKD). Exposure was categorized as DM2 (self-reported, HbA1c ≥6.5% and/or insulin use), PD (non-self-reported DM2, with HbA1c ≥5.7% and <6,5%) or normoglycemia (N), in the absence of self-reported DM2 and HbA1c <5,7%. People with HbA1c >15% and those that presented type 1 DM, AD, HF or CKD at the time of inclusion were excluded from the study. Follow-up was extended until March 2020.

A total of 336 709 subjects were included in the study, 82.3% with N, 13,9% with PD and 3.8% with DM2. Mean age was 56.3 years, 55.4% were women and median HbA1c was 5.36%. Patients with N were younger and those with DM2 had lower prevalence of female gender. In the passage from N to PD, and from this to DM2, a progressive increase in systolic blood pressure (SBP), triglyceride, urinary albumin-to-creatinine ratio and C-reactive protein (CRP) levels was verified, as well as an increase in antihypertensive and lipid-lowering medication. Median follow-up was 11.1 years. During this period, 7.9% of N participants, 13.8% with PD and 23.7% with DM2 presented at least one of the three evolutions of interest. The most common adverse evolution was AD, with accumulated incidences of 5.7%, 10% and 16.8% in N, PD and DM2, respectively, followed by CKF (2%, 4% and 9.3%) and HF (1.5%, 2.9% and 5.2%). Only 14% of patients with PD progressed to DM2 during follow-up, and among all patients with PD who presented any adverse evolution, only 12.4% had progressed to DM2 before its occurrence. In a multivariate model adjusted for baseline characteristics, medication and laboratory data, PD showed greater risk compared with N, with HR of 1.11 for AD, 1.08 for CKF and 1.07 for HF, statistically significant in all cases. Logically, risk was greater in the case of DM2, with HR of 1.44, 1.57 and 1.25, respectively.

Taking into account the HbA1c value, an increased risk was already manifested with a value >5.4% for AD, >6.2% for CKF, but >7% for HF. Due to its higher prevalence, PD was associated to a greater population attributable risk than DM2 for AD (8,1% vs. 5.9%) and HF (9,9% vs. 7.1%). After excluding PD patients who ended developing DM2, the values tended to be similar.

TElevated blood glucose levels, which should draw our attention even though they do not meet a diabetes diagnosis, often go unnoticed or are disregarded in daily practice. A light attitude is assumed in their presence and a quick indication of diet and exercise is made, without definite or explicit definitions. Let us not speak about knowing the HbA1c value! And the truth is that PD is not simply a condition that should warn us about the future development of diabetes, but an entity unto itself, which does not need to progress to be deleterious. The Biobank registry, of huge epidemiological value, deserves some objection as it included healthier subjects and with higher socioeconomic level than the British general population. In fact, the prevalence of DM2 is below 4%, well beneath the acknowledged prevalence in different Western European countries. However, the data suffice to demonstrate a PD incidence 4 times higher than that of DM2, which explains why the proportion of population attributable risk for AD and HF finally overcomes that of DM2. A posterior analysis of this study points out a subgroup of patients with "high risk" PD, in which PD coincides with smoking, elevated SBP, LDL-cholesterol and CRP values. And this subgroup (6% of total PD) has a risk of events similar to DM2 patients, even when only a third of them progresses to DM2 during follow-up.

Different criteria have been used to define PD, not always including HbA1c. In fact, the WHO and ADA diagnostic criteria resort to abnormal fasting blood glucose levels, or glucose intolerance in an oral glucose overload test for its definition. In all cases, PD has implied an independent prognostic factor of cardiovascular events. A meta-analysis of 53 studies with more than 1 600 000 patients, which defined PD as abnormal fast-

ing blood sugar or glucose intolerance, reported excess risk of coronary artery events, stroke and all-cause mortality, confirming the relevance of a timely diagnosis. Older age, family history of diabetes, sedentarism and excess body weight, as well as the presence of other risk factors, should heighten our suspicion, leading to more detailed characterization of carbohydrate metabolism. Lifestyle changes, less fat and carbohydrate intake, lower body weight and regular exercise have demonstrated to reduce the incidence of DM in PD patients. There is evidence of the beneficial effect of metformin, mainly to reduce the progress to DM, but more studies with this and other agents are necessary to complete defining their ability to decrease the incidence of events, independently of the transition to DM2.

The EMPEROR Preserved Study: Another gliflozin show of strength

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Successive randomized clinical trials with different neurohormonal antagonists have been unsuccessful to demonstrate a significant reduction in the primary endpoint of heart failure with preserved ejection fraction (HFpEF). The latest examples are the TOPCAT study with spironolactone, and the PARAGON HF study with sacubitril/valsartan. In both cases, post hoc or subgroup analyses demonstrated a beneficial effect in patients with up to 55% left ventricular ejection fraction (LVEF) in the TOPCAT and 57% in the PARAGON HF studies, specifically on the incidence of heart failure hospitalization (HFH). The demonstration in a large number of type 2 diabetes studies on the beneficial effect of SGLT2 inhibitors or gliflozins in patients with established vascular disease or risk factors, specifically in terms of reducing HFH and preserving renal function, led to the development of studies with these drugs in the context of HF, in patients with or without diabetes. We knew the DAPA HF study with dapagliflozin and the EMPEROR Reduced study, with empagliflozin, in patients with HF and LVEF ≤40%. A meta-analysis of both studies showed a reduction in the composite endpoint of cardiovascular death and HFH, the total number of HFH, cardiovascular and all-cause mortality and progression of impaired kidney function. Similar studies were carried out in HF with LVEF >40%. The results of the EMPEROR Preserved study, with empagliflozin, have just been released.

It included patients in FC II-IV, with a NT-proBNP level >300 pg/mL in sinus rhythm and >900 pg/mL in atrial fibrillation. Patients had to be clinically stable. They were randomly assigned to empagliflozin 10 mg daily, or placebo. The primary endpoint was a composite of cardiovascular death or HFH. Secondary endpoints were total HFH (the first and subsequent) and the slope of glomerular filtration rate drop. After screening 11 583 patients, 5988 were finally included in the study, 2997 in the empagliflozin group. Mean age was 71.8 years and 45% were women. Mean LVEF was 54.4%, and mean NT-proBNP 974 pg/mL. In 82% of cases, patients were in FC II; 49% had diabetes, 51% atrial fibrillation, and 50% kidney failure. Mean glomerular filtration rate was 60.6 mL/min/1.73 m2. In 86% of cases, patients were treated with diuretics, 81% with renin angiotensin system inhibitors/antagonists or sacubitril/valsartan, 86% with beta-blockers and 37% with anti-aldosterone agents.

Median follow-up was 26 months. The annual incidence of the primary endpoint was 6.9% in the empagliflozin group and 8.7% in the placebo group (HR 0.79; 95% CI 0.69-0.90, p=0.0003), with no difference according to LVEF (<50%, ≥50% - <60%, or ≥60%). The effect was similar in patients with and without diabetes. The reduction occurred at the expense of HFH (4.3% vs. 6%; HR 0.71, 95% CI 0.60-0.83), while there was no significant difference in cardiovascular death (3.4% vs. 3.8%). Regarding the secondary endpoints, there was total HFH reduction with empagliflozin: 407 vs. 541 (HR 0.73; 95% CI 0.61-0.88) and lower drop of glomerular filtration rate, with 1.36 ml/min/1.73 m2 per year difference in the slopes in favor of the drug. Despite this result, there was no difference in the incidence of a composite renal endpoint (persistent drop of glomerular filtration rate ≥40% or below 10-15 ml/min/1.73 m2, need for chronic dialysis or kidney transplantation): 2.1% vs. 2.2% annually. Similarly, there was no difference in all-cause mortality (6.6% vs. 6.7% per year). At the end of the study, 0.19% decrease in HbA1c, 1.28 kg weight reduction, 1.2 mm Hg decrease in systolic blood pressure and 2.36% increase in the hematocrit were confirmed with the drug vs. placebo. NT-pro-BNP NT reduction was not significant in both groups, but somewhat greater with empagliflozin.

The incidence of adverse events did not differ according to treatment, but there was a slightly higher incidence of hypotension (10.4% vs. 8.6%) and urinary (9.9% vs. 8.1%) and genital (2.2 % vs. 0.7%) infections in the group with active treatment.

The EMPEROR Preserved study has the merit of being the first study to achieve its primary and secondary endpoints in patients with HF and LVEF >40%. A first comment concerns the definition of the entity considered. Almost 20 years ago, the CHARM program considered preserved LVEF at a value >40%. This was the inclusion criterion in the CHARM Preserved study. But, over the years, it was recognized that the cut-off value to define HFpEF should be higher. In the TOPCAT and PARAGON HF studies, the inclusion cut-off value was 45%, and for the universal classification of HF known this year, HFpEF is defined for an EF of at least 50% and LVEF between 41% and 49% is "slightly depressed" (until recently it was called "midrange"). So, if we stick to the definitions, EMPEROR Preserved

should be "Preserved and mildly Reduced". For this reason, rather than talking about the effects in HFpEF, we prefer to say in HF with LVEF >40%. Beyond this discussion, we repeat, for the first time a study shows prognostic improvement, without need for subsidiary analyses. The gain is mainly at the expense of reduced HFH. An analysis that is not part of the main publication indicates, here, the influence of LVEF on total HFH, with a clear reduction below 60%, and no effect with LVEF ≥60%.

Another point that we want to highlight is the effect on kidney function, which repeats the finding of the EMPEROR Reduced study. But unlike this study, no clinical impact was verified in the EMPEROR Preserved study, with a reduction in the composite renal endpoint, even though the baseline glomerular filtration rate was similar in both trials. And again, a subsequent analysis comes to our aid, considering a more demanding renal endpoint in which the filtration drop is not 40% but 50%, and in which death of renal origin is included. In this case, the interaction with baseline LVEF is verified, and basically patients with LVEF between 40% and 50% do achieve benefit with the drug. Thus, the effect is homogeneous on the primary endpoint, but there is heterogeneity in the secondary endpoints: as LVEF increases, the benefit is less. Does this simply represent a lack of statistical power, or does it point to patients with different etiology and pathophysiology?

The annual HFpEF all-cause mortality in the DAPA HF and EMPEROR Reduced studies was around 10%, 80% of which was attributable to cardiovascular causes. In the EMPEROR Preserved study, the annual all-cause mortality did not reach 7%, and that from cardiovascular causes was less than 60% of the total. This confirms that the evolution of patients in both HF categories is not exactly the same, nor are the mechanisms involved in the prognosis identical. Can we hope to reduce the mortality of patients with HFpEF? So far, it seems that when the same weapons are used as in reduced LVEF this is not possible. Either way, gliflozins are once again proving their usefulness in HF, and are definitely far from being merely "antidiabetic" drugs. The DELIVER study, with dapagliflozin, also in patients with HF and LVEF >40%, will be able to confirm the findings of the EMPEROR Preserved study and add new information.

Towards a short dual antiplatelet therapy: the MASTER DAPT study

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There is evidence that one month with dual antiplatelet therapy (DAPT) is associated with a lower risk of bleeding complications without apparent excessive ischemic complications in patients at high bleeding risk undergoing a coronary percutaneous coronary intervention (PCI) with drug-eluting stent (DES). However, part of this evidence comes from observational studies, or from randomized studies in patients at low ischemic or hemorrhagic risk. This justified the performance of a randomized, multicenter, open-label study, the MASTER DAPT trial, in which patients at high bleeding risk with acute or chronic coronary syndrome, undergoing bioresorbable polymer sirolimus-eluting coronary stent implantation, were assigned to DAPT for one month vs. longer therapy, assessing ischemic and hemorrhagic events during follow-up.

Patients were included if a new coronary event, stent thrombosis, symptomatic restenosis, stroke, or a revascularization procedure had not occurred justifying prolonged antiplatelet therapy during the month following the index PCI, nor a new revascularization procedure had been planned in the future. Patients under DAPT, were selected between 30 and 44 days after the index procedure, and randomly assigned to abbreviated or standard therapy. The abbreviated therapy group immediately suspended DAPT and continued with a single antiplatelet agent until the end of the study. Patients who entered the study with anticoagulant treatment continued with a single antiplatelet agent until month 6 post procedure. Patients assigned to standard therapy continued with DAPT until month 6 post procedure, and if they were receiving anticoagulation, they continued with DAPT until month 3 post procedure, and then with a single antiplatelet agent. In all cases, single antiplatelet therapy could consist either of aspirin or a P2Y12 inhibitor. Three endpoints were considered: net adverse clinical events (a composite of all-cause mortality, myocardial infarction, stroke, or major bleeding), cardiac or cerebral events (a composite of all-cause mortality, myocardial infarction, or stroke) and clinically relevant major or non-major bleeding that occurred between randomization and day 335 (that is, up to one year after the procedure). A non-inferiority analysis was planned hierarchically for net adverse clinical events (the upper limit of the 95% CI for the difference in events between the abbreviated and standard groups should not reach 3.6%), followed by a non-inferiority analysis for cardiac or cerebral events (with a non-inferiority margin exceeding 2.4%) and then by a superiority analysis for hemorrhagic events (with 95% CI for the difference in the incidence between both groups whose extreme upper limit should not reach 0%). A sample size of 4100 patients was estimated to have a power of 90% to demonstrate non-inferiority with respect to net adverse clinical events (estimating an incidence of 12% in each group) and cardiac or cerebral events (estimating 8% in each group), as well as superiority for bleeding episodes (with an estimate of 6.5% in the standard therapy group and 4.2% in the abbreviated treatment group). Estimating a dropout rate of 5%, sample size was brought to 4300 patients. A per protocol analysis was used for non-inferiority analyses, considering in each group patients who complied with

the protocol and an intention-to-treat analysis for the superiority analysis.

A total of 4579 patients were randomly assigned, 2295 to the abbreviated therapy group, with a median of 34 days from the index PCI. Mean age was 76 years, 69.3% were men. 33.6% had diabetes, 19.1% chronic kidney failure, and 18.9% heart failure. In 36.4% of cases, patients were anticoagulated and 48.3% underwent coronary PCI in the context of an acute coronary syndrome. In the abbreviated therapy group, 98% complied with the indication to suspend DAPT at a median of 34 days post PCI. In the standard treatment group, 99.6% continued with DAPT for a median of 157 days (193 from the index procedure). Clopidogrel was used as monotherapy in 53.8% of cases in the abbreviated group, and as a DAPT component in 78.7% in the standard treatment group. There was complete follow-up at 335 days in 99.3% of the patients. The incidence of net adverse clinical events was 7.5% in the abbreviated therapy group and 7.7% in the standard one, with a difference of -0.23% (95% CI -1.8% to 1.33 %, p <0.001 for non-inferiority). The incidence of cardiac and cerebral events was 6.1% in the abbreviated therapy group and 5.9% in the standard group, with a difference of 0.11% (95% CI -1.29% to 1.51%, p=0.001 for non-inferiority). The annual incidence of major or clinically relevant bleeding was 6.5% in the abbreviated group and 9.4% in the standard group, with a difference of -2.8% (95% CI -4.4% to -1.24%, p <0.001 for superiority). There were no significant differences in the incidence of any of the individual components of the composite endpoints.

The MASTER DAPT study meets the three objectives that had been set: it demonstrates the non-inferiority of a short DAPT for the incidence of a composite of ischemic and bleeding adverse events and for cardiac and cerebral adverse events, and superiority with respect to the incidence of bleeding events, mainly due to a reduction in clinically relevant non-major bleeding. It is worth highlighting that it selected patients at high bleeding risk (those in whom a short therapy could offer the greatest advantages in the struggle between ischemia and bleeding), and with both acute (almost half of the cases) and chronic coronary conditions. However, some doubts about the representativeness of the sample (certain data from the screening period indicate low inclusion), and a heterogeneous duration of the assigned treatments in both groups withdraws some certainty from the findings. The bioresorbable polymer stent minimizes the possibility of thrombotic complications, and therefore the results of this study should not be extrapolated to other types of interventions. To this we add that the inclusion of patients was done after having successfully gone through the first month, and excluding those who had already presented significant thrombotic complications. It is interesting to note that the expected incidence of adverse clinical events and cardiac and cerebral events was 12% and 8%, respectively, and that the observed incidence was around 8% and 6%, while that of bleeding events was 50% higher than expected. It will be necessary to refine the strategies and wait for new studies to reach definitive conclusions, but the tendency to shorten times is growing, largely due to the improvement in stent design, which reduces thrombogenicity and thus allows shorter dual antiplatelet therapies.

Finerenone in diabetic kidney disease: the FIGARO-DKD trial

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Diabetic kidney disease is an entity entailing high morbidity and mortality, due to the associated cardiovascular involvement, beyond kidney contribution. Inflammatory activation and fibrosis have a key role in its complex pathophysiology. Different from traditional spironolactone and eplerenone, finerenone is a non-steroidal selective mineralocorticoid receptor antagonist.

Last year, we knew the results of the FIDELIO-DKD trial in patients with diabetic kidney disease, microalbuminuria (urinary albumin-to-creatinine ratio between 30 mg/g and <300 mg/g) and estimated glomerular filtration rate between 25 and <60 mL/min/1.73 m2 by CKD-EPI equation, or macroalbuminuria (urinary albumin-to-creatinine ratio between 300 mg/g and 5000 mg/g) and estimated glomerular filtration rate between 25 and <75 mL/min/1.73 m2. In this study, use of finerenone compared with placebo was associated with a significant reduction of a primary renal endpoint (a composite of sustained glomerular filtration rate drop ≥40% during 4 weeks, attaining a glomerular filtration rate <15 mL/min/1.73 m2, need for dialysis for at least 3 months, kidney transplant or death from kidney failure). The annual incidence was 7.6% vs. 9.1%, with HR=0.82 (95% CI 0.73-0.93). There was also a significant reduction of a secondary cardiovascular endpoint (composite of cardiovascular death, non-fatal acute myocardial infarction, non-fatal stroke or hospitalization for heart failure), with annual incidence of 5.1% vs. 5.9%, and HR=0.86 (95% CI 0.75-0.99). A trend towards reduction of each of the secondary endpoint components was observed, except for stroke. This study did not demonstrate a reduction in cardiovascular or all-cause mortality.

We now have the results of the FIGARO-DKD trial, that together with the FIDELIO-DKD trial constitute the FIDELITY program. FIGARO-DKD included patients with diabetic kidney disease, microalbuminuria and glomerular filtration rate between 25 and 90 mL/min/1.73m2, or macroalbuminuria and glomerular filtration rate ≥60 mL/min/1.73m2. Patients should be treated with maximum tolerated doses of the renin-angiotensin system inhibitor/antagonist not generating unacceptable adverse effects, and serum

potassium should not be >4.8 mEq/L. The endpoints of this study were inverted with respect to the former study. The primary endpoint was the cardiovascular composite of the FIDELIO-DKD trial and the secondary endpoint the kidney composite of that study. It was assumed that 976 events would be necessary to demonstrate 20% reduction in the primary endpoint with 90% power. A target dose of finerenone 20 mg/day was postulated.

After a run-in phase in which the maximum tolerated dose of renin-angiotensin system inhibitors/antagonists was adjusted, and a screening phase, 7352 patients were included and randomly assigned to finerenone or placebo. Mean age was 64.1 years, and 69.4% were men. Mean systolic blood pressure was 135.8 mmHg and glomerular filtration rate 67.8 mL/min/1.73m2. In 61.7% of cases, patients had a glomerular filtration rate ≥60 mL/min/1.73m2, 46.4% had microalbuminuria, 50.7% macroalbuminuria, and the remaining patients a urinary albumin-to-creatinine ratio <30 mg/g. Slightly above 70% of patients were treated with statins and 97.9% with hypoglycemic agents (insulin in 54.3%, SGLT2 inhibitors in 8.4% and GLP-1 agonists in 7.5%, although the use of the last two agents increased to 24.2% and 18.8%, respectively, during the course of the study). As in other cases, the COVID-19 pandemic generated disorders during the course of the trial, with missing visits in 28.5% of patients or temporary suspension in 9.5%.

Median follow-up was 3.4 years. Mean finerenone dose attained was 17.5 mg/day. The primary endpoint was reached in 12.4% of the treated group and in 14.2% of the placebo group (3.87% vs. 4.45% annually), with HR=0.87 (95% CI 0.76-0.98, p=0.03). This reduction was driven by the decrease in hospitalization for heart failure: 3.3% vs. 4.4% [0.96% vs. 1.36% annually; HR=0.71 (95% CI 0.56-0.90)], without significant reduction in the other cardiovascular composite components. This implies a number needed to treat of more than 50 patients during three and a half years to prevent a primary endpoint event. The incidence of the renal composite endpoint: 9.5% vs. 10.8%, HR=0.87 (95% CI 0.76-1.01) almost attained significant difference. The assumption in the renal composite of ≥57% drop in the glomerular filtration rate (which implies doubling creatinine levels) instead of a 40% drop, implied a lower incidence (2.9% vs. 3.8%) but allowed demonstrating a significant reduction, with HR=0.77 (95% CI 0.60-0.99). The incidence of hyperkalemia was greater with finerenone (10.8% vs. 5.3%), with low incidence of treatment discontinuation. (1.2% vs. 0.4%) or hospitalization (0.6% vs. 0.1%). The incidence of hypokalemia and severe pneumonia events was lower.

The population included in the FIGARO-DKD trial was less affected than that of FIDELIO-DKD. Let us analyze some differences: in FIDELIO-DKD, mean glomerular filtration rate was 44.3 ml/min/1.73m2, and in FIGARO-DKD 67.8 ml/min/1.732; median urinary albumin-to-creatinine ratio was 852 mg/g in FIDELIO-DKD and 308 mg/g in FIGARO-DKD; the annual incidence of the cardiovascular endpoint in the placebo group was 5.9% in FIDELIO-DKD and 4.4% in FIGARO-DKD and that of the renal composite was 9.1% and 3.5%, respectively. Certainly, this reflects the inclusion criteria that excluded from the FIGARO-DKD trial patients with glomerular filtration rate <60 ml/min/1.73m2 and macroalbuminuria, and those with worse prognosis, which were the main constituents of FIDELIO-DKD. This also explains that the annual hospitalization rate for heart failure was higher in FIDELIO-DKD (2.21% vs.17.5%). And it is surely the reason of a lower incidence of hypokalemia in FIGARO-DKD (almost 11% vs. 18.3% in FIDELIO-DKD).

Therefore, in a less severe and at lower risk population, finerenone basically generated reduction in hospitalization for heart failure and showed a strong tendency to produce a certain kidney protection. It is clear that in a population with so few therapeutic alternatives any triumph should be celebrated; but the achievement is only in absolute terms and not in magnitude. We should treat slightly over 170 patients per year to prevent a composite cardiovascular event, almost certainly a hospitalization for heart failure, without modifying cardiovascular or all-cause mortality, and more than 250 patients to prevent a renal event. A more adequate patient selection would undoubtedly allow a more cost-effective performance. Perhaps we should approach more severe patients, as in FIDELIO-DKD the results were more promising and the number needed to treat lower, both for the cardiovascular (125) as the renal (66) endpoints. And, of course, we should think of gliflozins. In the CREDENCE trial, canagliflozin showed superior effects to those achieved with finerenone. It is possible that in patients already treated with maximum tolerated doses of renin-angiotensin system inhibitors/antagonists, the additional effect of an anti-aldosterone agent is inferior to that of a drug acting on other pathways and mechanisms (although its antifibrotic action should not be disregarded). The analysis of FIGARO-DKD subgroups indicates that both drugs have an independent effect. Maybe, the first-choice drug in these patients should be the SGLT2 inhibitor and finerenona, an additional measure.

Dilations and aneurysms of the aorta: prevalence and predisposing factors in a population-based study.

Obel LM, Diederichsen AC, Steffensen FH, Frost L, Lambrechtsen J, Busk M et al. Population-Based Risk Factors for Ascending, Arch, Descending, and Abdominal Aortic Dilations for 60-74-Year-Old Individuals. **J Am Coll Cardiol 2021; 78: 201-11. https://doi.org/10.1016/j.jacc.2021.04.094.**

Dilation of the aorta in its different portions tends to go unnoticed, and its detection is most of the time an

incidental finding in the context of the study of another thoracic or abdominal pathology. The presence of aneurysmal dilations clearly carries a risk of complications that can be life threatening. In the case of abdominal aortic aneurysms, there are screening programs in some countries, especially in men over 60-65 years of age. This is not the case with thoracic aortic aneurysms. We do not have universally accepted reference values for the diameters of each portion of the aorta, nor a reliable estimate of the prevalence of dilation and aneurysm of each portion, especially in the case of the thoracic aorta. We now know of a population-based study carried out in Denmark that provides relevant information.

The Danish population DANCAVAS I and II registries prospectively included more than 78 000 people between 60 and 74 years of age. Participants were randomly selected to undergo a cardiovascular examination between 2014 and 2018. Since screening for cardiovascular disease was not cost-effective in women, a final sample of 14 235 men and only 754 women was available. In this study, a non-contrast computed tomography of the thorax and abdomen was carried out in all participants. The anteroposterior diameter of the ascending and descending aorta at the first circular level above the sinotubular junction, the diameter of the aortic arch perpendicular to the intersection of the aorta and the trachea, the anteroposterior diameter of the abdominal aorta above the bifurcation and the diameter of the primitive iliac arteries were defined in each study. Based on previous literature, normal values of 40 mm, 35 mm, 30 mm and 25 mm were considered in the ascending aorta, aortic arch, and descending and abdominal aorta, respectively. Considering the diameters measured in computed tomography, the formula was then defined by linear regression, taking into account age, body surface area and gender, which would allow defining the normal expected value for each of the diameters mentioned in each observation. The presence of aortic dilation was determined when the measured diameter was at least 25% greater than that predicted, and that of aneurysm when the excess was at least 50%. The independent predictors of the presence of dilation in each of the sectors were defined by multiple logistic regression.

Normal values were 37.3 mm for the ascending aorta, 30.6 mm for the aortic arch, 28.3 mm for the descending aorta and 20.3 mm for the abdominal aorta. The prevalence of aortic dilation was 4%, 0.9%, 2.3% and 9.4%, respectively, in men; and 2.1%, 0.3%, 1.1% and 3.9% in women. The prevalence of aneurysm was 0.1%, <0.1%, 0.1% and 3.7%, respectively, in men, and 0.1%, 0%, 0.1% and 0.4% in women. Hypertension (HTN), family history and atrial fibrillation (AF) were independent predictors of dilation in the ascending aorta, with OR between 1.6 and 1.9, while diabetes and history of smoking acted as a protective factor (OR between 0.5 and 0.7). Hypertension was a predictor in the case of the aortic arch, with an OR of 1.5. For the descending aorta, HTN and AF increased risk, with an OR of 1.3 and 1.5, respectively, while diabetes appeared again as a protective factor, with an OR of 0.6. And in the case of the abdominal aorta, smoking, both past (OR 2) and current (OR 4.2), a history of myocardial infarction (OR 2.3) and family history (OR 1.9) increased risk.

But what is most remarkable about the study is that the strongest predictor of dilation in one sector of the aorta was the presence of dilation in another sector. Thus, for example, aortic arch, descending aorta and abdominal aorta dilation were predictors of ascending aortic dilation with OR of 8.4; 3.3 and 1.7, respectively. And ascending aorta, aortic arch, and descending aorta dilation were predictors of abdominal aortic dilation with OR of 1.8, 1.9, and 3.7, respectively. Even the dilation of the primitive iliac arteries was an independent predictor of dilation of the aortic arch onwards, with ORs of 2.2 for the aortic arch, 1.9 for the descending aorta, and 9.9 for the abdominal aorta.

This large observational study has the unquestionable merit of establishing reference procedures to predict the normal diameter of each section of the aorta. It confirms that the prevalence of aortic dilation and aneurysm is higher in the abdominal aorta, followed by the ascending aorta, and that the pathology is more frequent in men, although the evident disproportion in the number of men and women included is regrettable: an equal inclusion would have allowed a better definition of the specific risk factors. With regard to the latter, HTN is still a risk factor for dilation of the entire aorta, although it is more notable the closer to the heart the aortic portion is, with an OR of 1.7; 1.5; 1,3 and 1,2 from the ascending to the abdominal aorta. It confirms smoking as a risk factor for dilation of the abdominal aorta, but offers as a novelty its protective role for dilation of the ascending aorta, something that must be confirmed. The observation of diabetes as a protective factor, already seen in large cohort studies of patients with diabetes, is repeated, and also does not yet have a clear pathophysiological explanation.

However, what motivates the presentation of this analysis is fundamentally the finding that the strongest prediction of dilation in one sector of the aorta is the dilation in another sector, even when we speak of non-adjacent portions. The presence of dilation in the ascending aorta is associated with an excess risk of 70% of having dilation in the abdominal aorta, and this excess increases to 80% when we consider the inverse relationship. The finding of a dilated ascending aorta therefore justifies exploring not only the entire thoracic aorta, but also the abdominal aorta. The diagnosis of dilation or aneurysm of the abdominal aorta should lead us to study the thoracic aorta. This is undoubtedly the most important message of this Registry.

Surgery or percutaneous coronary intervention for extensive coronary disease in patients with heart failure and low ejection fraction? An analysis of the SCAAR Registry

Volz S, Redfors B, Angeras O, Ioanes D, Odenstedt J, Koul S et al. Long-term mortality in patients with ischaemic heart failure revascularized with coronary artery bypass grafting or percutaneous coronary intervention: insights from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). **Eur Heart J 2021;42:2657-2664. . https://doi.org/10.1093/eurheartj/ehab273.**

Ischemic necrosis is the predominant etiology in heart failure with reduced ejection fraction (HFrEF). Traditionally, it was understood that in patients with HFrEF, the presence of coronary artery disease susceptible to revascularization justified resorting to coronary artery bypass grafting (CABG). The STICH study challenged this assumption, as it could not demonstrate an advantage of revascularization surgery over optimal medical treatment in these patients, but its extension (the STICHES study) showed that with longer follow-up, there was a better evolution with invasive treatment. However, this possibility does not appear limited to surgical treatment: percutaneous coronary intervention (PCI) has been a frequently used alternative for years. Patients with HFrEF have been generally excluded from randomized trials comparing CABG with coronary PCI, and there is no study specifically conducted in this population.

The Swedish SCAAR registry is a coronary angiography and PCI registry, forming part of the large SWEDEHEART registry. The analysis we present included patients who underwent an angiographic study in Sweden between 2000 and 2018 for primary HFrEF indication (left ventricular EF, LVEF, <50%), had multi-vessel disease (lesion ≥50% in at least two vessels, or left main coronary artery) and had undergone some revascularization procedure. As the choice of method was influenced by certain baseline characteristics, patients were matched by a propensity score (method in which the use of independent predictors for a diagnostic or therapeutic method are defined by multiple logistic regression, generating a score, which is used to "match" patients with a similar propensity to receive or not the treatment under study, as if they had been allocated on a randomized basis). Nevertheless, as it is not possible to exclude the presence of unknown confounders (residual confounding), an instrumental variable adjustment was carried out. An instrumental variable is related to a certain diagnostic or therapeutic practice regardless of the characteristics of the patients or the physician's decision. Let us assume that a certain center has a diagnostic method on Tuesdays and Thursdays, but not on the rest of the days. Whether to use the diagnostic method or not depends on the day the patient consults. If the use of the method is only influenced by the day, and there is no obvious relationship between the arrival day and the evolution, this day can be considered an instrumental variable to define the use of the method independently of baseline conditions (just as a random assignment is carried out in a clinical trial). In this case, the instrumental variable was the "preference" of the center for the revascularization method (defined from the percentage of surgeries over the number of PCI procedures).

The retrospective analysis included 2509 patients, 82.9% men, 35.8% with diabetes, and 34.7% with previous infarction. Mean age was 68 years, and 65% had left main coronary artery lesion or 3-vessel lesion. Percutaneous coronary intervention was used in 1409 patients (56.2%) and CABG in the rest. Patients in the PCI group were 2 years older, with a higher prevalence of coronary risk factors and some previous revascularization procedure. Those in the CABG group had more frequently left main disease (89.5% vs. 46.7%). In 71.9% of patients with PCI and 75.9% with CABG the LVEF was <30%. Almost 80% of the patients in the PCI group received drug-eluting stents. In both cases, the use of beta-blockers and renin-angiotensin system/inhibitors or antagonists exceeded 85%, and that of anti-aldosterone agents was around 40%. The preference for PCI in the different centers ranged between 27% and 86%, and logically the preference for complementary CABG between 14% and 73%. Until 2008, the preferred treatment was CABG; since then, the use of PCI increased and in 2018 it became 3.4 times more frequent than CABG. Median follow-up was 3.9 years (1 day-10 years) and CABG was associated with a significantly lower risk of mortality (OR 0.62, 95% CI 0.41-0.96, p=0. 03). The advantage of CABG became evident since the fourth year, and in 10 years it was associated with a mean survival rate of 0.59 years longer. The risk of death increased linearly by 27% with the quintiles of preference for PCI. The adjustment for propensity score and for the instrumental variable did not change the strength of the association.

This analysis of the SCAAR registry is a very good example of the weapons that are used when there is no data from randomized trials but there are very good registries. The use of a propensity score to which the instrumental variable analysis is added, attempts to adjust (beyond the traditional multivariate analysis) all known variables (with the propensity score), and even some unknown or not expressly recorded ones (when using the instrumental variable), so that finally the effect found can be attributed with certainty to the intervention. Why was CABG superior to PCI in these patients? Perhaps due to a more complete revascularization, whose effects take time to manifest themselves. In fact, let us note that the survival curves began to separate from the fourth year. The fear of a higher baseline risk associated with CABG does not seem to find support in the data: the same curves were strictly overlapped during the first 3 years. Of course, we are referring to pa-

tients with HFrEF and coronary artery disease amenable to revascularization, whereas patients with coronary artery disease that was deemed non-revascularizable by either method were excluded from this analysis, as well as those in whom any procedure was ruled out due to age, frailty, comorbidities, etc.

The information from this analysis does not agree with a similar one carried out with patients from the New York state, which did not find differences between the two strategies. But the Swedish registry follow-up was longer, perhaps achieving the time necessary for the CABG advantage to manifest itself. Some data to bear in mind: the patients date from the 2000-2018 period. How far away most of them are from recent advances in the practice of PCI, CABG and even more in medical treatment! Just think of the prognostic benefit offered by sacubitril/valsartan and gliflozins in patients with HFrEF; certainly, not to suggest that revascularization should not be carried out, but indeed to ask ourselves whether their prognostic impact is preserved, as well as the marked difference in favor of CABG. The truth is that, until we have randomized studies that compare CABG with PCI in patients with HFrEF (we are not aware of any in progress), the information in this Registry, even assuming some residual confounding that may not have been corrected, prompts us to prefer CABG in this context.

Prediction of in-hospital mortality in percutaneous coronary intervention

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The CathPCI National Cardiovascular Data Registry is an American initiative that gathers data from all coronary percutaneous coronary intervention (PCI) procedures carried out in more than 1600 United States centers, with the aim of improving the quality of care and impact in decision-making. One of its main advantages is to define patient baseline characteristics and establish risk patterns. Researchers of this Registry have released a score that allows to accurately predict the risk of mortality associated with the procedure in the hospital stage. It was built based on data collected in 1608 centers between July 2018 and June 2019, referring to patients, centers and interventions.

Clinical and paraclinical variables chosen by a working group of the ACC were considered, based on their clinical relevance, data from the literature and their influence on the prognostic model of in-hospital mortality. To choose the variables finally included in the model, a bootstrap analysis was performed. It consists in generating, from the initial sample, and using computer tools, successive samples, each of which is constructed from random sampling with replacement of the initial sample. Thus, for example, if the initial sample considers 100 prognostic variables, the next one is built randomly from the first one; thus, 100 variables are randomly selected, some of which may be repeated (otherwise, each sample of 100 variables would include the same 100 as the first one). By allowing replacement, a variable already selected to integrate the second sample can be considered again to be chosen in that same sample). From the initial sample, 1000 random samples were generated. A logistic regression analysis made it possible to define in each of these samples the variables that retained statistical significance to predict mortality. The variables that were chosen in at least 70% of the samples were those used to constitute the final score. New variables were added to the clinical, demographic, laboratory, and PCI-related variables: surgical rejection prior to PCI, the degree of frailty in patients who were not in shock, the severity of aortic stenosis, the response to stimuli after resuscitation from cardiorespiratory arrest prior to PCI; and an ordinal variable that shows clinical instability based on the cardiovascular condition and the procedure to be performed. This variable considers 6 mutually excluding categories of decreasing severity: 1) rescue PCI or refractory shock; 2) cardiogenic shock (non-refractory) without rescue PCI; 3) cardiovascular instability (including hemodynamic instability, symptoms of acute heart failure, and ventricular arrhythmia in the absence of shock) without rescue PCI; 4) emergency PCI in the absence of shock or cardiovascular instability; 5) urgent PCI in the same conditions as the previous one; 6) elective PCI under the same conditions as the two previous ones.

A total of 706 263 patients were considered in this registry; 70% were randomly selected for the development cohort used to build the score and the remaining 30% for the validation cohort. Mean age was 66 years, 30.8% were women, 40.8% had history of diabetes and 41.0% had previous PCI. In 39.2% of cases the procedures were elective; 1.3% were in patients without response to stimuli after cardiac arrest, and 0.5% in patients with rescue PCI or refractory shock. Marked frailty was present in 2.7% of patients in the absence of shock or hemodynamic instability, 1.9% had at least moderate aortic stenosis, and 3.2% had surgical rejection. In-hospital mortality in the development and validation cohorts was the same: 1.9%, but varied markedly according to the category of clinical instability, from 62.01% in rescue PCI or refractory shock and 35.6% in non-refractory shock and non-rescue PCI, to 0.17% in elective PCI with hemodynamic stability. It was also very high in cardiac arrest without response to stimuli (somewhat greater than 50%). Responsive cardiac arrest, advanced frailty, and cardiovascular instability without rescue PCI exhibited approximately 7% mortality.

Based on the analyses, a complete predictive model was built with 22 variables (including gender,

age, history, kidney function, type of acute myocardial infarction and those already mentioned), and a bedside model which considers age, kidney function, the ordinal variable of referred clinical instability and a history of cardiac arrest, with or without response to stimuli in case of occurrence. This more accessible score adds 1 point for each decade of life from 10 years of age, 1 point if the glomerular filtration rate is between 45-60 ml/min/1.73 m2, 2 if it is between 30 and 44, and 3 if it is less than 30 ml/min/1.73 m2. Category 1) of the ordinal variable of clinical instability is assigned 13 points, and it goes down until assigning 0 points to category 6). The history of cardiac arrest with response to stimuli adds 1 point and 5 if there is no response. The predicted mortality increases with each point of the score, from 0.04% with values <5 to 91.67% with values of 29 points. Mean cohort mortality (1.91%) coincides with a score value between 12 and 13. The predicted mortality in 90% of the cohort was <1.6%. The score had excellent calibration (correlation between predicted and observed risk) in both cohorts, and discrimination capacity (area under the ROC curve 0.92).

This is another excellent demonstration of the power of National Registries, with constant updating of data, and the value of statistical techniques that allow the delivery of relevant information. In this case, what deserves to be highlighted is the creation and selection of variables full of information that we often sense and which are part of our comments about a patient or case, but not of the traditional risk scores. To consider frailty beyond a serious hemodynamic condition logically involves it, to take into account that a heart team has rejected a patient for surgery (with all that this implies in terms of age, comorbidity and frailty); to collect data on whether or not the patient responds to stimuli after a cardiac arrest (when in any case only the presence of this situation is taken into account in other predictive models); and the creation of a single variable that integrates the hemodynamic condition and the urgency of the procedure, are all "points in favor" of this predictive instrument in its full version. The most accessible version of use allows an approximation to prognosis with the need to know only two values (age and glomerular filtration rate), the clinical condition, the response after cardiac arrest and the PCI condition. It is clear that calibration and discrimination are excellent, but for the time being the validation is internal: the population in which the score was validated is similar to the development cohort. Studies in other populations would be necessary to aspire to a universal use. The fact of being able to assign (by virtue of the high number of observations) a specific mortality to each score, from 0 to 29, allows a very precise discrimination that each center can consider when evaluating its own results, when comparing centers with each other and, at an individual level, to specify the expected result in each patient.