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In patients with pulmonary arterial hypertension treatment initiation with two drugs is associated with better outcome than with monotherapy: the AMBITION trial

Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. **N Engl J Med 2015;373:834-44. http://doi.org/74f**

The specific treatment of Group 1 pulmonary hypertension or pulmonary arterial hypertension (PAH) in its different forms (idiopathic, inherited, associated with connective tissue disease, repaired congenital heart defects, drugs, toxins or HIV) consists in the use of three types of drugs with different action: endothelin receptor antagonists (such as bosentan, ambrisentan or macitentan), phosphodiesterase type 5 inhibitors (as sildenafil or tadalafil), and prostanoids (as iloprost or treprostinil). Treatment guidelines accept initiation with any of them, and it is accepted that if the goals are not met (clinical, imaging, and laboratory) a second and then a third drug with other mechanisms of action should be added. A point of discussion is whether simultaneous treatment with two drugs of different action should be considered from the beginning. The AMBITION study evaluated this hypothesis.

It included patients with PAH in FC II-III, with mean pulmonary pressure ≥25 mm Hg, who had either not received specific treatment until study initiation or had received it for less than 14 days, and not in the last 7 days prior to enrollment. They were randomized to receive in a 2:1:1 ratio the combination of ambrisentan (A)-tadalafil (T), A with T placebo, or T with A placebo. A and T target doses were 10 and 40 mg daily, respectively. The primary endpoint was a composite of a) death from any cause, b) PAH hospitalization (including those due to procedures such as lung transplant or septostomy), c) disease progression, when the patient was in FC III-IV and there was >15% decrease of the distance measured in the six-minute walk test (6MWT) between 2 visits separated by at least 14 days, and d) unsatisfactory long-term response when the patient was in FC III, with any decrease in the 6MWT in 2 visits separated by at least 6 months. It was estimated that the annual incidence of the composite endpoint would be 20% with monotherapy, and 10% with combination therapy. At 6 months of study initiation, the high prevalence of hypertension, diabetes and coronary heart disease led to protocol modification to prevent the incorporation of patients with pulmonary hypertension secondary to left ventricular diastolic failure (group 2).

Although 605 patients receiving medication were enrolled, the primary analysis focused on 500 (253 A-T, 126 A and 121 T) who met the amendment criteria. Mean age was 54.4 years, 78% were women, 53% of the cases were idiopathic and 69% were in FC III. Average mean pulmonary pressure was 48 mmHg, and mean 6MWT was 352 meters. Forty percent of patients were hypertensive, 10% diabetic and only 4% had coronary heart disease. The primary endpoint occurred in 18% of cases with A-T therapy and in 31% with monotherapy (HR 0.50, 95% CI 0.35-0.72), with no significant difference with A (34%) and T (28%). The benefit was mainly reduced hospitalization for PAH (4% with A-T, 14% with A, 10% with T), with no significant difference in the other endpoint components. The combined therapy was associated with higher increase in the 6MWT and greater NT-proBNP decrease at 24 weeks.

The idea of an initial combined therapy in PAH treatment replicates what occurs in other diseases, such as heart failure or hypertension, in which we often begin treatment with more than one agent. Furthermore, there is theoretical justification since as it is a disease with high mortality, the most "complete" treatment should be implemented as quickly as possible. The pursuit of specific objectives adequately quantified is an additional reason: theoretically, they will be easier to achieve using more than one drug. Until now, the experience with initial combined therapy has been tested in studies with small number of patients and different outcomes. In the AMBITION study, initial combined A-T therapy seems to be associated with better outcomes in PAH patients without prior treatment than any single monotherapy. We may wonder what would happen if patients were able to bridge from one component to the other, and whether the results are specifically due to the tested drugs or the combination concept is global. To accept the first hypothesis, a study for each drug combination in use would be necessary; alternatively, it can be interpreted, that beyond the drugs studied in this trial, what the results emphasize is a more aggressive treatment initiation.

Is bridging from oral to subcutaneous anticoagulation necessary in perioperative patients with atrial fibrillation? The BRIDGE trial

Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. PerioperativeBridging Anticoagulation in Patients With Atrial Fibrillation. **N Engl J Med 2015; 373: 823-33. http://doi.org/74g**

In patients with atrial fibrillation (AF) receiving oral anticoagulation (OAC) the question frequently posed

is what to do at the time of surgery. The most common behavior is the interruption of OAC for a few days before the procedure, its replacement by low molecular weight heparin (LMWH) until a few hours before surgery, and the continuation of OAC one to two days after surgery. However, this behavior is empirical, and it is unclear whether it is actually the most correct. The authors of the BRIDGE study decided to assess the hypothesis that OAC interruption before surgery and then its continuation without use of LMWH, was non-inferior to perioperative bridging with LMWH for the prevention of arterial thromboembolism and even decreased the risk of major bleeding

The study included patients with chronic AF (paroxysmal or permanent) with a CHADS2 score of at least 1 and correct anticoagulation (INR between 2 and 3) with warfarin at least 3 months prior to study entry, who were to undergo surgery or another invasive procedure requiring OAC interruption. It excluded patients with history of systemic embolism or stroke in the previous 12 months, major bleeding in the previous 6 months, mechanical valve prosthesis, creatinine clearance <30 ml/kg/min, and platelet count <100000/mm3, or when cardiac surgery or neurosurgery was planned. Oral anticoagulation was interrupted five days before the procedure and patients were randomly allocated to receive, 3 days and up to 1 day before the procedure, subcutaneous dalteparin or placebo (the last injection 24 hours before the intervention). Within 24 hours after the procedure OAC administration was resumed, and also within 24 hours, dalteparin or placebo were resumed in the case of minor or low bleeding risk procedures, while in case of major surgery or of high bleeding risk, subcutaneous anticoagulation or placebo was restarted 48 to 72 hours post-intervention. In any case, dalteparin or placebo was interrupted when an INR of 2 was achieved; thereafter, patients resumed open-label OAC. The primary efficacy endpoint (EP) was arterial thromboembolism at 30 days, assuming an expected event rate of 1% in each arm and a non-inferiority analysis. The primary safety EP was major bleeding at 30 days, assuming an expected event rate of 1% in the placebo arm and 3% in the dalteparin arm and a superiority analysis.

Between 2009 and 2014, 1,884 patients were included in the study. Mean age was 71.7 years and 73% were men. The average CHADS2 score was 2.3 and nearly 40% of patients had a score ≥3. Forty-four percent of the procedures were gastrointestinal and 17% were cardiothoracic. In 89% of the procedures bleeding risk was low, although the investigators only treated as such 69%. The incidence of the primary efficacy EP was 0.4% in the placebo arm (no bridging) and 0.3% in the dalteparin arm (bridging), confirmed by the non-inferiority analysis with p=0.01. The incidence of the primary safety EP was 1.3% with placebo and 3.2% with dalteparin, with p=0.005 for superiority. The incidence of minor bleeding (12% vs. 20.9%; p <0.001) was also lower with placebo.

In a meta-analysis of observational studies and in the RE-LY study (dabigatran vs. warfarin in non-valvular AF) similar results to those of the BRIDGE study had already been found. The randomized design of the latter study provides stronger power evidence. Possibly, the risk of embolic event in a programmed OAC interruption is overrated, and depends mainly on the type of procedure and blood pressure variations during the intervention. Embolism rate was lower than expected (0.3% to 0.4% vs. 1% considered in the study design), and this may be related with the low risk of most interventions. The low rate of bleeding can be associated with the careful control inherent to a research study. Even with these limitations, the findings are important, and could help to simplify diagnostic and surgical procedures in patients with AF. Finally, let us remember that in the BRUISE CONTROL study [Rev Argent Cardiol 2013; 81 (5)] in patients with OAC and planned pacemaker implantation, lower risk of pocket hematoma was associated with the maintenance of OAC rather than its interruption and periprocedural substitution with subcutaneous heparin. Perhaps bridging from one to another form of anticoagulation would be a more important risk factor for bleeding than the fact of maintaining OAC (as in the BRUISE CONTROL study) or interrupting it (as in the BRIDGE study), when this is possible.

Diabetes: The TECOS trial, one as many others.....

Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. **N Engl J Med 2015;373:232-42. http://doi.org/74h**

In the treatment of type 2 diabetes (T2DM), lowering of glycosylated hemoglobin (HbA1c) using oral hypoglycemic (OHG) agents or insulin results in decreased risk of microvascular events. Emerging data with some OHG drugs suggest increased risk of cardiovascular events, as for example myocardial infarction (AMI) with some thiazolidinediones. Therefore, the regulatory authority requires that each OHG agent should demonstrate, beyond its specific effect, that it does not generate increased cardiovascular risk. Dipeptidyl peptidase 4 (DPP-4) inhibitors are drugs that prolong the action of incretins such as GLP 1, inhibiting their degradation, and therefore increasing endogenous insulin secretion. Previous DPP-4 inhibitor studies suggested increased risk of heart failure. This clearly occurred with saxagliptin in the TIMI SAVOR study, and there was also a trend in the EXAMINE study with alogliptin. The TECOS multicenter, randomized, double-blind, placebo-controlled study explored cardiovascular risk associated with the use of sitagliptin (S).

It included patients with T2DM, under 50 years of age, with established cardiovascular disease (coronary artery, cerebrovascular, peripheral vascular), and

HbA1c between 6.5% and 8%. They could be treated with 1 or 2 OHG agents (sulfonylureas, metformin, pioglitazone) or insulin with or without metformin. Creatinine clearance had to be ≥30 ml/min/1.73 m2, without DPP-4 inhibitor, GLP-1 agonist or thiazolidinedione (except pioglitazone) treatment in the previous 3 months, nor with more than 2 severe hypoglycemic events in the last 12 months. They were randomly assigned to receive S (at a dose of 100 mg daily, 50 mg if creatinine clearance was between 30 and 50 ml/min/1.73 m2) or placebo. Increased doses of OHG agents or the initiation of a new open-label treatment was allowed if the glycemic targets sought for each patient were not met. The primary endpoint (EP) was a composite of cardiovascular death, nonfatal AMI, nonfatal stroke or hospitalization for unstable angina. The secondary EP was similar, but without considering unstable angina. A sequential statistical analysis was planned: a) the non-inferiority primary EP analysis projected a HR of 1 between drug and placebo, with 95% CI upper limit of 1.3, (which means that an increased cardiovascular risk of up to 30% was enough to consider the drug non-inferior to placebo, i.e. it did not significantly increase risk), and per-protocol (it considers the patients who effectively comply with the treatment to which they were randomly assigned) and then supported by an intention-to-treat analysis; b) non-inferiority and per-protocol secondary EP analyses; and c) superiority and intention-to-treat EP analyses.

Between 2008 and 2012, 14,735 patients were enrolled, 14,671 of whom were included in the intention-to-treat analysis and 14,523 in the per-protocol analysis. Median follow-up was 3 years and almost 95% of patients completed the study. Mean HbA1c at baseline was 7.2±0.5%; at 4 months it had decreased an average of 0.4% in the S group, but throughout the whole follow-up period the decrease compared with placebo was only 0.29%. It is true that in the S group the need to increase the dose or the number of other OHG agents, or to start insulin treatment was 30% lower. The annual incidence of the primary EP was similar in both arms: 4.06% with S and 4.16% with placebo ($p<0.001$ for non-inferiority, $p=0.65$ for superiority). Also, when considering the secondary EP, S was non-inferior to placebo, but it was not superior. The incidence of hospitalization for heart failure was the same: 3.1% in both groups. There was a slight excess of pancreatitis (0.3% vs. 0.2%, $p=0.07$) with S, and a minimal decrease in glomerular filtration rate (a difference throughout the study of 1.34 ml/min/1.73 m2, $p<0.001$). There was no difference in the incidence of severe hypoglycemia.

The TECOS trial shows that the use of S allows achieving a minimum difference in HbA1c, with less need for other agents, without excessive hypoglycemia or increased risk of either exacerbating or generating heart failure. The authors mention as an achievement that the drug is non-inferior to placebo: it allows achieving the minimal expressed advantage, without worsening the patients' prognosis. And, as added interest, unlike previous studies with gliptins and a meta-analysis of 50 studies (n=55,141 patients) with these drugs showing no difference in cardiovascular events, but 16% increase in heart failure incidence (although not correlated with excess mortality), in the TECOS study the use of S does not increase this risk: a safety study, which means that between DPP-4 inhibitors S might be the preferred choice in view of the objections which the FDA has recently raised on its direct competitors, saxagliptin and alogliptin, considering precisely this adverse effect. Although debatable, the fact is that what has been achieved does not seem enough: at best, a small reduction in HbA1c, no excess of adverse events, and no change in cardiovascular or vital prognosis. Another example of non-inferiority, and there are ...

Diabetes: ... and a clinical trial different from all others: the EMPA-REG trial

Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. **N Engl J Med 2015 [Epub ahead of print] http://doi.org/748**

Empagliflozin (E) is a drug belonging to the family of sodium-glucose cotransporter 2 inhibitors. It basically inhibits renal glucose reabsorption and lowers HbA1c levels; however, other actions have also been described: it reduces weight and blood pressure, and decreases albuminuria, uric acid levels, rigidity and vascular resistance, and at the same time it may increase LDL and HDL cholesterol values. The EMPA-REG randomized, multicenter, double-blind study tested the ability of the drug to improve the prognosis of patients with type 2 diabetes (T2DM) and established cardiovascular disease. Patient body mass index had to be ≤45 and glomerular filtration rate ≥30 ml/min/1.73 m2. They could enter the study with HbA1c between 7% and 9% if they had not received hypoglycemic therapy in the last 12 weeks or between 7% and 10% if they had been treated. After a 2-week placebo run-in period, if the above conditions were preserved, patients were randomly allocated in a 1:1:1 ratio to receive E 10 mg daily, E 25 mg daily or placebo. The primary endpoint (EP) was the composite of cardiovascular death, nonfatal AMI or nonfatal stroke. The secondary EP was the primary EP plus hospitalization for unstable angina. A non-inferiority sequential analysis was planned (as in the TECOS study, a HR of 1, with 95% CI upper limit of 1.3, i.e. admitting up to 30% excess events) for the primary and secondary EP, followed by a superiority analysis for the same EP.

The study was performed in 590 centers of 42 countries, including 7,020 patients (4,687 with E). Average age was 63 years and slightly over 70% of patients

were men. Mean HbA1c was 8%. Seventy- six percent of patients had history of coronary heart disease (46% AMI) and 23% had history of stroke. Almost half were receiving insulin, 95% anti-hypertensive therapy and 80% hypolipidemic drugs. At median follow-up of 3.1 years, the primary EP occurred in 10.5% of patients with E and 12,1% with placebo (HR 0.86, 95% CI 0.74-0.99, p <0.001 for non-inferiority and p=0.04 for superiority). Empagliflozin decreased cardiovascular death (3.7% vs. 5.9%, p <0.01) and total mortality (5.7% vs. 8.3%, HR 0.68, 95% CI 0.57-0.82, p <0.001). There was no significant reduction in AMI or stroke, but a significant reduction was found in hospitalization for heart failure (9.4% vs. 14.5%, p=0.002). There were no EP differences between E doses. At 12 weeks, the adjusted mean HbA1c reduction compared with placebo was 0.54% with E 10 mg, and 0.6% with E 25 mg; at 94 weeks of 0.42% and 0.47%, and at 2 years of 0.24% and 0.36%, respectively. There was no difference in the incidence of hypoglycemia, ketoacidosis (0.1%), kidney failure or urinary tract infection; however, genital tract infections were present (5% vs. 1.5% in men, 10% vs. 2.6% in women).

The results of this study can well be described as historical: for the first time in a randomized study a hypoglycemic drug has been shown to reduce mortality. And interestingly, glycosylated hemoglobin reduction apparently is not responsible for this finding: similar reductions to that achieved in this study have been observed with the use of other drugs vs. placebo, without ever having achieved this result, and higher reductions in studies comparing intensive glucose lowering treatment vs. standard treatment have ranged from excessive risk to neutral effect on mortality. Moreover, the separation of the survival curves (almost from the beginning for cardiovascular death and at one year for total mortality) suggests precisely that the responsible mechanism goes far beyond reducing blood glucose. In this regard, it should be remembered that the effects of E also include a slight decrease in weight and blood pressure, attenuation of arterial stiffness, albuminuria and uric acid reduction, decreased myocardial oxygen demand, etc. Is it possible that the results arise from this combination? In the case of the decrease in heart failure incidence, the osmotic diuretic effect appears to play a role (if so, it suggests that glucosuria in patients treated with E ceases to be a manifestation of more severe disease). The results of the study (was it expected by the authors whose initial analysis was of non-inferiority?) are extremely remarkable and promising, and invite to intensify the research of the involved mechanisms.

Muscle strength and cardiovascular prognosis

Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A Jr, Orlandini A, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. **Lancet 2015;386:266-73.http://doi.org/749**

Grip strength (GS) is an expression of muscular strength. In different observational studies its decline has been associated with poor prognosis, but none had the number of observations or reached the information range of the PURE study. We have already referred to the PURE study in former publications. This was a longitudinal and prospective epidemiological cohort study, conducted between 2003 and 2009 in 17 countries of varying income levels, where unbiased households with at least one household member between 35-70 years old was selected. Different analyses allowed to link baseline variables, including diet, income, and urban or rural housing, with the evolution of those included. As part of the initial evaluation, baseline GS was measured with a dynamometer in each of the subjects enrolled, with 3 determinations only in the non-dominant hand and then in both, considering an average of the highest values in both hands and adjudicating a linear regression value when it was not available. Grip strength prognostic value for different cardiovascular and non-cardiovascular adverse events was determined adjusting for age, gender, cardiovascular risk factors, medical history, income level of the country, caloric intake and its protein proportion.

The study included 139,691 participants, with an average age of 50 years, 58% of whom were women. Mean GS was 30.6±11.1 kg. Greater GS was associated with male gender, younger age, higher level of national income, and higher protein and calorie intake. However, history of hypertension, heart failure, coronary or cerebrovascular disease or emphysema (but not cancer) revealed people with lower GS. In a median follow-up of 4 years and adjusting for all these characteristics, GS was an independent predictor (inversely correlated) of total cardiovascular and non-cardiovascular mortality, myocardial infarction (AMI) and stroke. Every 5 kg reduction in GS was associated with adjusted excess risk of overall cardiovascular and non-cardiovascular mortality between 16% and 17%, 9% risk of stroke and 7% risk of AMI. Decreased GS was a stronger predictor of total and cardiovascular mortality than systolic blood pressure, but a lower predictor of cardiovascular disease.

The loss of muscle strength appears in this study as a predictor of cardiovascular events and overall mortality independent of traditional risk factors. Why does it seem part of the cascade of events leading to a fatal or non-fatal coronary event? The average age of only 50 years appears to attenuate the effect that "aging" can play; but on the other hand, the prognostic value is independent of age. Different mechanisms can be postulated: endothelial dysfunction or autonomic imbalance. We are inclined to assume greater activation of inflammatory phenomena. In fact, in several prospective cohort studies inflammatory activation predicts major cardiovascular events, and it is known that the decrease in muscle mass is one of its clinical manifestations. Probably, GS reduction expresses, among oth-

er things, this phenomenon in a more marked manner than measurement of plasma cytokines or C-reactive protein; new studies may help clarify the relationship.

Takotsubo cardiomyopathy: an international registry

Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. **N Engl J Med 2015;373:929-38. http://doi.org/75b**

Takotsubo syndrome or stress cardiomyopathy, first described in 1990, is increasingly diagnosed. Although often initially suspected by its presentation (especially in older women, after an emotional stress), in other cases it is confused with an acute coronary syndrome, and only coronary angiography clarifies its nature. There is, moreover, little information about its natural evolution, beyond acknowledging that most patients experience clinical improvement with recovery of ventricular function. We present recently published data of an international registry led by the University Hospital Zurich, with the participation of 26 centers from 8 European countries and the United States. Between 2011 and 2014, records from all hospitalized patients with diagnosis of Takotsubo between 1998 and 2014 were reviewed according to generally accepted criteria: transient abnormal left ventricular contraction that does not correspond to a coronary artery perfusion territory; new ECG abnormalities or biomarker elevation; absence of obstructive coronary heart disease; and absence of pheochromocytoma or myocarditis. Presence of coronary heart disease that did not coincide with the contraction disorder, contraction disorder coincident with the perfusion territory of an artery in a patient who met the other criteria, and death before recovery of ventricular function could be verified were accepted as exceptions.

Data of 1,750 patients were included; 89.8% were women, and 79.1% of women were over 50 years of age. The predominant symptoms on admission were chest pain (75.9%), dyspnea (46.9%) and syncope (7.7%). The most common trigger (36%) was a physical event (acute respiratory failure, post-surgical, infection, and nervous system disease), followed by emotional trigger (27.7%). In nearly 8% of cases both triggers were coincident, but in 28.5% there was no detectable trigger. The most frequent form of presentation was apical (81.7%); midventricular involvement occurred in 14.6% of cases and the remaining cases had focal or baseline involvement. In 87% of cases there was troponin elevation at the beginning, and in 83% elevation of natriuretic peptides was verified. Mean left ventricular ejection fraction (LVEF) was 40.7%; and accompanying coronary heart disease was confirmed in 15% of cases by coronary angiography. In 46.8% of patients history of an acute episode of psychiatric or neurological disease was obtained. Ten percent of patients presented with cardiogenic shock on admission, and in-hospital mortality was 4.1%. In the multivariate analysis, advanced age and emotional trigger were associated with better hospital evolution, whereas the organic trigger, higher levels of troponin and LVEF <45% predicted worse outcome. At 10-year follow-up, annual mortality was slightly higher than 5%, and the incidence of major cardiovascular and cerebrovascular events was 10% annually. The recurrence rate of Takotsubo syndrome was 1.8% per year, with a time to onset ranging from 25 days to 9 years. The incidence of complications was significantly higher in men. Despite what is commonly accepted, use of angiotensin-converting enzyme inhibitors but not of beta-blockers at discharge was associated with better prognosis.

In the subsidiary study, 455 patients of this registry were compared with 455 patients hospitalized for acute coronary syndrome in a Zurich registry, matched for age and gender. In this comparison, Takotsubo patients presented more frequently with dyspnea, similar troponin elevation on admission but lower maximum elevation (14 vs. 50 times the maximum normal value), higher natriuretic peptide levels (6 vs. 3 times the maximum normal value), and in the evolution, somewhat less frequent incidence of ST-segment elevation (44% vs. 51%), significantly less frequent ST-segment depression (8% vs. 31%), and the prevalence of neurological and psychiatric history was higher (55% vs. 25%). Left ventricular ejection fraction was lower (40.7% vs. 51.5%) and there was no difference in in-hospital prognosis.

A number of points should be highlighted. This is a retrospective analysis of 1,750 patients with no available information of the evolution at 30 days in 468 of cases, and in 632 patients medication at discharge could not be analyzed. Nevertheless, information on the presentation and in-hospital evolution is very rich. Despite the belief that Takotsubo syndrome responds mainly to an emotional stimulus, the number of secondary syndromes that respond to a physical and organic stress is greater. The relationship with neurological and psychiatric conditions leads to consider the possible neurological origin of many of the episodes and another link in the chain that associates heart and brain. The presence of coronary heart disease (in 1 out of 7 patients) does not exclude Takotsubo diagnosis if coronary heart disease cannot explain the location and extent of the involved territory. Finally, lower LVEF and higher natriuretic peptide in an acute coronary syndrome support Takotsubo identification as acute heart failure. The lack of data on the usefulness of beta-blocker therapy should be viewed with caution, given its non-randomized assignment and data loss in more than a third of cases.

Embolic risk in patients with heart failure and sinus rhythm: a new utility of theCHA_2DS_2-VASc score?

Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA_2DS_2-VASc score in predicting ischemic stroke,

thromboembolism, and death in patients with heart failure with and without atrial fibrillation. **JAMA 2015;314:1030-8. http://doi.org/76c**

The CHA_2DS_2-VASc score is a widely used tool to define the risk of ischemic stroke and systemic embolism in patients with atrial fibrillation (AF) and the need for oral anticoagulation (OAC). It considers the presence of heart failure (HF), high blood pressure, diabetes, age between 65 and 74 years, history of vascular disease (myocardial infarction, peripheral vascular disease, aortic plaque) and female gender as variables that, when present, add one point each, while age ≥75 years and a history of stroke add 2. Heart failure, in turn, is an entity in which thromboembolic risk is increased. The triad alteration already described by Virchow is met: dilation of the cardiac chambers with motility disorders, rheological abnormalities with increased blood viscosity, coagulation disorders with increased levels of fibrinogen and neurohormonal activation and endothelial dysfunction with release of thrombogenic substances. All these factors, therefore, favor thrombus formation in the heart chambers and intravascular thrombosis. It is clear that in HF patients, the presence of AF increases the risk of systemic embolism or stroke, but can the CHA_2DS_2-VASc score define the same risk in patients in sinus rhythm (SR)? To answer this question, the authors of this work relied on three sources of information in Denmark: the National Patient Registry, which since 1977 records all the country's hospitalizations, with their diagnoses; the National Prescription Registry, which since 1994 stores the information about all the prescriptions dispensed in the pharmacies; and the Civil Registry, which gathers vital information on the Danish population status. The combined information of the three sources allows defining for each hospitalization in- hospital and long-term prognosis, and outpatient treatment received.

From early 2000 to late 2012, patients older than 50 years who were discharged from hospital with a diagnosis of HF were selected. The presence or not of AF was defined for each patient. Those treated with OAC 6 months prior to the index event, those who were diagnosed with cancer in the previous 5 years and patients with chronic obstructive pulmonary disease were excluded. The primary endpoint (EP) was defined as the incidence of embolic events (including pulmonary embolism and myocardial infarction) and ischemic stroke after discharge from hospitalization for heart failure.

The study included 42,987 patients, 33,592 (78.1%) of whom were in sinus rhythm (SR). Among these patients, 7% had a CHA_2DS2-VASc score of 1 (implying they had only HF); 35.6% had scores of 2 or 3 and 57.4% had a score ≥4. Among patients with AF, 6.5% had a score of 1 (only HF) and in them the prevalence of high scores was greater: 65% with score ≥4. The annual incidence of ischemic stroke was 1% with SR and 2% with AF.

In patients in SR, the incidence of ischemic stroke increased progressively with increasing CHA_2DS_2-VASc: from 0.4% with a score of 1 to 2.6% with score ≥6. The area under the ROC curve to predict ischemic stroke at 1 and 5 years ranged between 0.67 and 0.69. The annual incidence of death also increased: from 2.1% with a score of 1 to 12.9% with score ≥6. The area under the ROC curve for predicting death at 1 and 5 years ranged between 0.64 and 0.68. In patients with AF, the incidence of ischemic stroke and mortality was higher for each score, but the discrimination ability evaluated by the ROC curve was similar.

This work shows that in patients with HF and SR the risk of ischemic stroke is not negligible: although lower to that occurring in the presence of AF, it is about 5% at 5 years. In this context, the CHA2DS2-VASc score shows a moderate discrimination ability, but not different from that seen in patients with HF and AF. Some questions are not answered by the study. Is risk similar in HF patients with preserved or impaired ventricular function? Some reports suggest that risk is focused in those with impaired ventricular function, but in the CHA_2DS_2-VASc or $CHADS_2$ score, "C" is worth one point, regardless of function. Would that be correct? On the other hand, should we use the score to define the need of OAC in patients with SR? So far, randomized clinical trials (WARCEF was the last of importance,) do not justify the use of OAC in these patients. Could a selection of higher risk patients using the CHA_2DS_2-VASc score criterion define a population with OAC indication? Questions that can be answered by future studies.

Does chloride substitute sodium as a prognostic marker in acute heart failure?

Grodin JL, Simon J, Hachamovitch R, Wu Y, Jackson G, Halkar M, et al. Prognostic role of serum chloride levels in acute decompensated heart failure. **J Am Coll Cardiol 2015;66:659-66. http://doi.org/76d**

In the context of acute heart failure (AHF) different international registries and observational studies have long shown that hyponatremia is an adverse prognostic factor. An expression of congestion, with increased extracellular fluid, higher neurohormonal activation (mainly of the renin-angiotensin system and antidiuretic hormone), and also due to the excessive use of diuretics, hyponatremia implies bad in-hospital prognosis and, when present at discharge, also in the long term. Sodium movements are closely linked to those of chloride, given that sodium chloride is its main source of admission to the body; and perhaps this relationship has been responsible for traditionally considering chloride a partner to which little attention is paid. An observational study of the Cleveland Clinic challenges this view.

The study included 1,318 consecutive patients admitted between mid-2008 and late 2013, with a dis-

charge diagnosis of chronic decompensated heart failure. To increase the specificity of the selection and include indisputable cases, all patients should have evidence of defibrillator or biventricular pacemaker implantation. Patients with heart transplant or in dialysis were excluded. The prognostic value of clinical, laboratory and treatment variables was assessed in all of them. The role of plasma chloride on admission was considered.

Median (interquartile range) chloremia was 101 (97-104) mEq/L. Patients were divided into tertiles according to chloremia: <99, 99-103, and >103 mEq/L. Chloride values were positively correlated with sodium (r=0.61) and negatively with bicarbonate (r=0.39). Higher chloride levels were associated with increased left ventricular ejection fraction, better renal function and use of angiotensin-converting enzyme inhibitors and beta blockers, and also with lower values of natriuretic peptide, urea and bilirubin. At median follow-up of 1.47 years, annual mortality was significantly higher for the lowest tertile of chloride with respect to the intermediate and high: 22% vs. 14% vs. 10%. In the univariate analysis, each increase of 1 mEq/L chloride on admission resulted in a decrease of 6% (95% CI 3%-8%) in long-term mortality. Similarly, each increase of 1 mEq/L of the sodium value on admission resulted in a decrease of 5% (95% CI 3-7) mortality. But in the multivariate analysis (considering age, sodium, urea, etiology and use of neurohormonal antagonists) chloride maintained its prognostic value (for each increase of 1 mEq/L, a decline in mortality of 7%, 95% CI 3%-10%) whereas sodium lost it (for each increase of 1 mEq/L, increased mortality of 3%, with 95% CI crossing 0, implying possible increase or decrease in mortality).

The results of this analysis were validated in a cohort of the University of Pennsylvania Hospital in patients discharged with the same condition between 2004 and 2009. The results, in both sodium and chloride, were repeated.

The reason that explains why the prognostic value of chloride appears superior to that of sodium is unclear; chloride acts as a cation buffer, including sodium and acids; it is possible that its homeostatic role is more important than that of sodium. Moreover, the causes leading to a decrease in chloride levels are very similar to those that generate hyponatremia. Is chloride really a prognostic factor or just a marker that speaks of another condition? On the other hand, will it maintain this role in a multivariate analysis including other covariates, different from those taken into account here? In the interim, we can say that a new actor appears to join the heart failure scenario. And we can reflect on what we understand as unwavering truth, and how it changes the minute we look aside.