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Surprising result, or not so much? In frail elderly people with atrial fibrillation, the routine switching of vitamin K antagonists to direct oral anticoagulants is not advisable. FRAIL-AF Study

Joosten LPT, van Doorn S, van de Ven PM, Kohlen BTG, Nierman MC, Koek HL et al. Safety of Switching From a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients With Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial. **Circulation 2024;149:279-89. https://doi.org/10.1161/CIRCULATIONAHA.123.066485**

The incidence and prevalence of atrial fibrillation (AF) increase with increasing age and the presence of comorbidities. It is well known that AF is a risk factor for the occurrence of stroke, heart failure (HF), kidney failure, cognitive impairment, and cardiovascular and all-cause mortality. Specifically, in patients with AF, stroke prevention is a primary objective, and oral anticoagulant treatment aims to achieve this. Oral Vitamin K antagonists (VKAs) have been surpassed in the last two decades by direct oral anticoagulants (DOACs), which in large clinical trials were shown to be more effective in preventing stroke, with a decrease in the rate of bleeding attributable to anticoagulation. DOACs also offer the advantage of their use not requiring periodic coagulation tests, and greater stability in the therapeutic range. However, a high proportion of elderly patients continue to use VKAs instead of DOACs. The causes are varied, but the presence of frailty (a condition that involves biological vulnerability, dependence on care and a diminished capacity to resist stressors) is one of marked importance. We know that frailty is a condition that, like AF, increases with age, and that the coexistence of both conditions obscures the prognosis. The prevalence of each one increases in the presence of the other; frail patients have been underrepresented in large DOAC trials, and therefore there is no conclusive evidence regarding the superiority of these agents in frail patients with AF.

The FRAIL-AF clinical study, multicenter, randomized, open-label, pragmatic, was designed to demonstrate the superiority of DOACs over VKAs in elderly, frail patients with AF, already anticoagulated with VKAs, and in which a strategy of switching to treatment with DOAC was compared to remaining on usual anticoagulation. They had to be at least 75 years old and have a Groningen Frailty Indicator (GFI) value ≥ 3. This indicator includes 4 questions on mobility limitations, 2 on visual or hearing impairment, one on unintentional weight loss, 6 on cognitive impairment and psychosocial limitation and one on global physical fitness. Each question answered positively adds one point, the maximum is 15, and a higher score means greater frailty. Patients with AF of valvular origin and those with glomerular filtration rate <30 mL/Min/1.73m^2 were excluded. In the crossover arm to a DOAC, it was proposed that after suspending the VKA, the new treatment could be started with an international normalized ratio (INR) value < 2, but when certain excess bleeding was verified, it was decided that the DOAC could be started with an INR <1.3. In the VKA arm, a target INR between 2 and 3 was set. The primary end point was the occurrence of major bleeding or non-major but clinically relevant bleeding (NMCR). Major bleeding was defined as fatal bleeding, bleeding that occurred in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular that led to a compartment syndrome), bleeding which generated a drop in hemoglobin ≥ 2 g. /dL or required a transfusion of at least 2 units of blood or red blood cells. NMCR bleeding was defined as bleeding that required an in-person medical consultation, an intervention by health personnel, hospitalization, or an increase in the level of care. It was assumed that with an annual incidence of major bleeding or NMCR between 11% and 15% in the VKA arm, for a two-tailed p value < 0.05 and a power of 80%, 1250 patients in each arm would be necessary to demonstrate a risk reduction of 20% to 30% in the DOAC arm. The analysis was done by intention to treat.

Between 2018 and 2022, 2621 patients underwent screening, but 662 were finally included in the DOAC arm and 661 in the VKA arm. The mean age of the patients was 83 years, and the median GFI was 4; 38.7% were female, just over 50% of the cases were permanent AF and almost 30% were paroxysmal AF; the median CHA_2DS_2-VASc score was 4. The DOAC used was at the discretion of the general practitioner: in just over one half of the cases it was rivaroxaban, and the rest was mainly divided between apixaban, edoxaban and dabigatran.

During a mean follow-up of 344 days, 6.7% of the DOAC arm and 7% of the VKA arm patients died. The incidence of the primary endpoint was 15.3% in the DOAC arm and 9.4% in the VKA arm (HR 1.69, 95% CI 1.23-2.32; p= 0.0011). In the DOAC arm

there was more gastrointestinal (2.6% vs 0.6%) and urogenital (3% vs 1.7%) bleeding. There was no difference in intracranial bleeding. The significant difference in the incidence of bleeding between both arms was verified after 100 days of follow-up: HR 1.17 (95% CI 0.79-1.96) until day 100, and 2.10 (95% CI 1.40-3.16) then. The difference between both arms was in the incidence of NMCR bleeding: 12.7% vs 7.4%. On the other hand, the incidence of major bleeding was similar: 3.6% vs 2.4%. The incidence of thromboembolic events was also similar: 2.4% vs 2%.

When deciding anticoagulant treatment in an elderly patient with AF, we often lean towards DOACs. The reduction in embolic events and hemorrhagic stroke compared to the use of VKAs is a compelling reason. To this we add that it is not necessary for the patient to undergo frequent tests to control the INR, which facilitates anticoagulation and makes transfers unnecessary in patients who often lack adequate family support, or with mobility limitations. In the 4 large, randomized trials of DOACs vs warfarin (RELY with dabigatran, ARISTOTLE with apixaban, ROCKET-AF with rivaroxaban and ENGAGE AF with edoxaban), with 71 683 patients included, the use of DOACs was associated with a decreased risk of major bleeding or NMCR regardless of age. However, older patients had a higher risk of major bleeding with DOACs than younger patients: each 10-year increment marked an increase of 10.2% with the standard dose and 17.6% with the reduced dose (although it could seem like a contradiction, let us remember that patients with a reduced dose per se have more comorbidities and risk than patients with a usual dose). In both ROCKET-AF and ARISTOTLE trials, polypharmacy entailed a greater risk of bleeding. Why do we emphasize these aspects? Because age and comorbidities are generally considered the greatest predictors/indicators of frailty. Frail patients were underrepresented in the trials we mentioned, as is generally the case across the spectrum of clinical research. In FRAIL-AF, however, there was a decision to focus on this type of patient, and the criteria for considering frailty (included in the GFI) were much broader, as corresponds to an entity with multiple layers of meaning. We must remember that the included population consisted of patients who were already treated with VKAs and had tolerated them. So, there was undoubtedly an initial advantage for patients who remained on VKA: the chance of experiencing significant bleeding was lower, because they were already treated and there had been no indication to stop treatment until now. The results of the FRAIL-AF study go against the general indication. They demonstrate, in an increasingly large subgroup of patients with a high prevalence of AF (elderly, with a high rate of comorbidity) an increased risk of non-major, but clinically relevant, bleeding. A more detailed analysis of the data would be necessary to detect higher risk groups, but with the information available, caution is necessary when deciding to cross from a VKA to a DOAC in this population. Each case must be analyzed individually. It should be clear, however, that these results do not automatically apply to anticoagulation-naïve patients in whom initial treatment must be decided, and that frail elderly patients with VKA intolerance were not represented in the study.

Combination of non-steroidal mineralocorticoid receptor antagonists, gliflozins and glucagon-like peptide-1 receptor agonists (GLP-1 RA) in diabetes with albuminuria: the new standard of care?

Neuen BL, Heerspink HJL, Vart P, Claggett BL, Fletcher RA, Arnott C et al. Estimated Cardiovascular Lifetime, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria. **Circulation 2024;149:450-62. https://doi.org/10.1161/CIRCULATIONAHA.123.067584**

The presence of albuminuria in the context of diabetes indicates renal compromise and endothelial dysfunction. The prognostic impact of this combination is fearsome: accelerated deterioration of renal function, need for dialysis, marked increase in cardiovascular morbidity and mortality and mortality from all causes. For a long time, therapeutic alternatives in this context were scarce: demanding control of risk factors, reduction of sodium intake, and meeting strict glycemic goals were postulated. Regarding specific pharmacological treatment, there was only room for inhibitors or antagonists of the renin-angiotensin system. In the last decade, new therapeutic agents have appeared: sodium-glucose cotransporter 2 inhibitors (SGLT2i, or gliflozins), glucagon-like peptide-1 receptor agonists (GLP-1 RA) and non-steroidal mineralocorticoid receptor antagonists (nsMRA), mainly finerenone. Each of these drugs has been shown to improve vital prognosis in patients with diabetes and albuminuria. Very few patients in these trials were treated with the combination of at least 2 of the families, and until now we do not know the results of ongoing clinical trials that explore these combinations. Until these results arrive, we can ask ourselves if, with the data from the studies that evaluated each drug separately, there is sufficient reason to use a treatment in which the three families of drugs coincide.

To answer this question, an actuarial analysis was carried out that took into account a) the individual data from two trials with SGLT2i, both with canagliflozin: CREDENCE, in patients with type 2 diabetes, renal failure and albuminuria, and CANVAS, in patients with diabetes and established cardiovascular disease or multiple risk factors; in total 14 543 patients; b) data from a meta-analysis of 8 studies with GLP-1 RA in the context of type 2 dia-

betes with or without established cardiovascular disease: ELIXA with lixisenatide, LEADER with liraglutide, SUSTAIN-6 and PIONEER-6 with semaglutide, EXSCEL with exenatide, Harmony Outcomes with albiglutide, REWIND with dulaglutide, and AMPLITUDE-O with efpeglenatide; in total 60 080 patients; and c) combined data from 2 studies with finerenone in type 2 patients, renal failure and albuminuria, FIDELIO-DKD and FIGARO-DKD, in total 13 026 patients. The primary endpoint was considered the incidence of major adverse cardiovascular events (MACE), but also the incidence of hospitalization for heart failure (HHF), progression of renal failure, cardiovascular mortality (CVM), and all-cause mortality. The placebo arm of CANVAS and CREDENCE was taken as the control group (patients with type 2 diabetes and urinary albumin-creatinine ratio > 30 mg/g), and the effect of the combination of 2 of the three families, and of the 3 combined (which we call triple therapy, TT), on those end points was defined through indirect comparisons.

In a median follow-up of 2.5 years, among patients in the placebo arm of CANVAS and CREDENCE trials, incidence of MACE was 12.6%, HHF 5.8%, progression of renal failure 7.2%, CVM 6.7% and all-cause death 9.5%. Regarding MACE, each of the treatments in isolation implied HR between 0.83 and 0.90; the combination of two of them, depending on the case, HR between 0.72 and 0.77; and TT an HR 0.65 (95% CI 0.55-0.76). For HHF, isolated interventions had HR between 0.64 and 0.78; the combinations of two of the three, HR between 0.50 and 0.69; TT an HR 0.45 (95% CI 0.34-0.58). For the progression of renal failure, one intervention was associated with HR between 0.63 and 0.67, two interventions with HR between 0.49 and 0.66, and TT, an HR of 0.42 (95% CI 0.31-0.56). For CVM, the HR ranged between 0.84 and 0.88 for one treatment, between 0.74 and 0.77 for two, and the HR was 0.64 (95% CI 0.51-0.80) for TT. Finally, for all-cause death, the HR of one intervention varied between 0.85 and 0.89, those of 2 interventions between 0.76 and 0.78, and TT implied an HR of 0.67 (CI 95 % 0.55-0.80). In terms of absolute risk reduction, 3-year TT involved 4.4% for MACE, 3.4% for HHF, 4.4% for progression of renal failure, 2.4% for CVM, and 3.1% for all-cause death. This implied for a 50-year-old patient an event-free survival gain of 3.2 years for MACE and HHF, 5.5 years for the progression of renal failure, 2.2 years for CVM and 2.4 years for all-cause death. The benefits were greater the younger the patients.

The combination of diabetes and albuminuria (a condition we usually call diabetic nephropathy) is, as we said, one of the most ominous in the context of cardiovascular disease. The appearance in the last 10 years of various therapeutic alternatives undoubtedly implies a renewed hope for these patients. Perhaps the simultaneity of the emergence of these drugs has caused that, in the clinical trials of each of them, the others were underrepresented or directly absent. Thus, for example, in the FIGARO study (finerenone vs placebo) only 7.5% of patients were treated with GLP-RA and 8.4% with SGLT2i. The different mechanisms of action (which include, but are not limited to, promotion of autophagy and attenuation of glomerular hyperfiltration in the case of SGLT2i, anti-inflammatory action and correction of metabolic alterations for GLP-1 RA and the antifibrotic action of nsMRA) allow us to understand an additive action when two of these drugs are combined. It has already been demonstrated in animal models or in mechanistic studies. This synergistic effect remains to be verified when considering randomized trials with clinical endpoints, which are being carried out. In this sense, the analysis we present seems to predict what will happen. But certain limitations must be considered: adherence to the combined treatment is assumed, which must be verified in practice; It is understood that the clinical effect represents a sum of what was achieved with each drug separately, when it is possible that there is some overlap (since some biological effects are coincident) and the magnitude of the observed reduction in risk is less than predicted. On the other hand, the issue of tolerance also arises, and the possible appearance of adverse effects due to the various combinations. In any case, a quadruple therapy for diabetic nephropathy (TT plus the use of inhibitors or antagonists of the renin-angiotensin system) appears on the horizon, as there is a quadruple therapy in heart failure with reduced ejection fraction... and let's note the similarity of the components in both cases. And, as we have said so many times, it is impossible to forget the issue of access to the best treatment, so that what we discuss can actually be good news for the majority of patients.

Women obtain greater prognostic benefit than men from physical activity, and with less effort

Ji H, Gulati M, Huang TY, Kwan AC, Ouyang D, Ebinger JE et al. Sex Differences in Association of Physical Activity With All-Cause and Cardiovascular Mortality. **J Am Coll Cardiol 2024;83:783-93. https://doi.org/10.1016/j.jacc.2023.12.019**

Although clinical practice guidelines emphasize the importance of physical activity (PA), with at least 150 minutes of moderate PA or 75 minutes of vigorous PA per week, without differentiating between sexes, it has been reported that participation and commitment of women with PA are lower than those of men. Reasons range from differences in tolerance to PA, to different physiological responses and, of course, sociocultural factors. This gender gap should be closed, especially in light of the findings of a recent observational study.

For more than 20 years, the Centers for Disease Control and Prevention (CDC) has been collecting data in the USA, in a health survey that is carried out

in all 50 states and the District of Columbia. For this study, data from 646 279 participants surveyed between 1997 and 2017 were considered. Those with a previous diagnosis of cardiovascular disease, stroke, respiratory disease, or cancer, those unable to perform PA, data not available and those with who had presented events within 2 years of being surveyed were excluded. This finally left a sample of 412 413 participants available. All of them provided data on the PA they developed, its frequency, type, and duration. In this way, the number of weekly minutes of PA could be calculated, and how much of it corresponded to moderate to intense PA. We examined the association of PA with cardiovascular and all-cause mortality in men and women, adjusting for age, ethnicity, body mass index (BMI), cardiovascular risk factors, alcohol consumption, socioeconomic factors, access to the health system, marital status, self-perceived health status and chronic health conditions. Participants were considered inactive when moderate/vigorous PA did not reach 150 minutes per week, and active when it was at least 150 minutes. Similarly, they were considered inactive if PA involved less than 2 weekly muscle strengthening sessions, and active if it involved at least 2.

The average age of the participants was 44 years, 54.7% were women. Compared to men, they were slightly older, had a lower BMI, had a lower prevalence of smoking and alcohol consumption, and had a worse socioeconomic status. Among men, 43.1% practiced aerobic PA regularly, compared to 32.5% of women; 15.2% of men and 10.3% of women carried out moderate PA for at least 150 minutes weekly, and 38.9% of men and 28.3% of women carried out intense PA for at least 75 minutes weekly. The average follow-up was almost 12 years. In women, carrying out regular moderate/vigorous PA was associated, compared to being inactive, with a reduction in all-cause mortality of 24% (HR 0.76; 95% CI 0.73-0. 80) Among men, the same behavior was associated with a 15% reduction in all-cause mortality (HR 0.85; 95% CI 0.82-0.89), p< 0.001 compared to the reduction in women. Among men, the maximum benefit was achieved with 300 minutes of moderate/intense PA per week, with a reduction in total mortality of 18%; Among women, this reduction was achieved with 140 minutes per week, and with moderate/vigorous PA for 300 minutes per week the reduction was 24% (p= 0.002 compared to men). Regarding vigorous PA, in men the maximum benefit (a 19% reduction in the risk of overall mortality) was achieved with 110 minutes per week. In women, this reduction was achieved with 57 minutes per week, and with 110 minutes the reduction was 24%. Regarding moderate PA, the maximum benefit in men (20% mortality risk reduction) was seen with 90 minutes per week; In women, the same reduction was achieved with 50 minutes per week. Regular PA also decreased cardiovascular mortality more in women (36%) than in men (14%), and the same thing happened specifically with muscle strengthening activities (30% vs. 11%).

Regarding muscle strengthening exercises, 27.8% of men and 19.9% of women reported actively carrying them out. This translated into a reduction of 11% in men and 19% in women in the risk of all-cause mortality (p= 0.005). Men achieved the greatest reduction, 14%, with 3 weekly muscle-strengthening PA sessions; women achieved the same reduction with just one weekly session.

When it comes to doing PA, men and women have differences. The effort capacity is greater in men, hand in hand with greater muscle mass, heart size, diameter of the airways, and gas diffusion capacity in the alveolus-capillary membrane. In men the ability to do strength exercises is greater, in women those linked to flexibility. However, women have a greater possibility of improving their performance: they have greater capillary density per unit of skeletal muscle mass and a greater supply of oxidative muscle fibers. For the same dose of PA focused on increasing muscle strength, the increase achieved is greater in women, and it is known that muscle strength is a better predictor of survival than mass. So it is that PA seems to offer more advantage in women than in men.

The findings of this large observational study are not unexpected. A meta-analysis of 33 prospective cohort studies demonstrated that PA generates a greater reduction in the incidence of coronary artery disease in women (RR 0.66) than in men (RR 0.79). The current data add up to a reduction in global and cardiovascular mortality. What could be the reason for this different decrease in the risk of coronary artery disease and death? It may be that women start from a more disadvantaged physical condition, so the opportunity for improvement with training is greater. We should not rule out that the difference in the physiological response to PA also implies more favorable changes in women, with greater repercussions. It is striking that this difference in the beneficial effect of PA tends to attenuate with increasing age, suggesting interaction with the estrogenic effect.

The exclusion of events recorded in the first 2 years of follow-up aims to attenuate the effect of reverse causality: a present illness that will trigger an upcoming death may be responsible for lower PA, and not the other way around. Because it is an observational study, there may be, as always, residual confusion: factors unequally distributed between men and women, truly responsible for the observed phenomenon. In any case, the large number of observations and follow-up time (more than 4 million person-years) seems to exclude this possibility. In summary, the evidence presented strongly impels us to advise women to engage in PA, traditionally understood as an area of male domain. As in so many other things, the gender gap must be closed. Women have an advantage that they should not waste.

Microvascular dysfunction and a change in the

diagnostic yield of exercise electrocardiographic stress testing.

Sinha A, Dutta U, Demir OM, De Silva K, Ellis H, Belford S et al. Rethinking False Positive Exercise Electrocardiographic Stress Tests by Assessing Coronary Microvascular Function. **J Am Coll Cardiol 2024;83:291-9. https://doi.org/10.1016/j.jacc.2023.10.034**

For decades, the exercise electrocardiographic stress testing (EST) was considered the fundamental test for diagnosing obstructive coronary artery disease in patients who reported angina pectoris or equivalents. The gold standard to define its sensitivity and specificity was, then, coronary angiography, which certified the presence or absence of significant coronary artery disease. Little by little, EST was displaced by other imaging methods (exercise echocardiography, pharmacological stress testing, nuclear cardiology studies) that exhibit greater diagnostic yield. But in recent years we have witnessed notable progress in the pathophysiological understanding of angina pectoris and its substrate, myocardial ischemia. We learned that up to a third of patients with angina present the condition called ANOCA (angina with non-obstructive coronary artery disease), and that a coronary angiography without significant lesions in no way excludes the presence of ischemia. Coronary microvascular dysfunction (CMD) assumes a predominant role in ANOCA, and is also present as a contributing mechanism in angina with obstructive coronary artery disease. If this is so, the concept of a "false positive" when an EST is positive due to ST segment depression in a patient without significant coronary obstruction is called into question. The authors of the article we present dedicated themselves to exploring this concept.

Patients with ANOCA, defined by a fractional flow reserve (FFR) > 0.80, were included; with left ventricular ejection fraction (LVEF) > 50%. Patients with glomerular filtration rate <30 mL/min/1.73 m², significant valvular disease, history of acute coronary syndrome, left bundle branch block, poor quality or uninterpretable ECG tracings, limitation due to non-anginal symptoms, and patients with pacemaker rhythm were excluded. Coronary angiography was performed, and distal coronary pressure and average peak flow velocity (APV) were measured in the left anterior descending artery. Microvascular function was defined in two forms: a) endothelium- independent, with intravenous infusion of adenosine, and b) endothelium-dependent, with intracoronary infusion of acetylcholine. Coronary flow reserve was defined as the ratio between the APV with adenosine and the baseline APV: the presence of endothelium-independent CMD was established if this ratio was < 2.5. The presence of endothelium-dependent CMD was explored with acetylcholine infusion: a flow reserve with acetylcholine (AFR), ratio between coronary flow with acetylcholine and in basal conditions ≤ 1.5, was considered an expression of CMD. After a median of 29 days, an EST with Bruce protocol was performed in all patients, and sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) for the development of ECG changes in the presence of endothelium-dependent, endothelium-independent CMD or any of them interchangeably were defined.

Of 262 patients initially considered, after excluding those free of symptoms, those who did not have angina, and those who presented some of the aforementioned exclusion criteria, 102 patients were finally included. Of them, 32 developed ischemia in the EST (ischemic group, IG) and 70 did not (non-ischemic group, NIG). There was no difference between them in age, sex, coronary risk factors or functional class. IG patients had a higher prevalence of typical angina (91% vs 73%, p= 0.04) and lower hemoglobin values (13 vs 13.7 g/dL, p= 0.008). There was no difference between both groups in the development of angina during EST, the prevalence of risk factors, exercise time or mean FFR. All patients in the IG had CMD, compared to 66% in the NIG (p < 0.001). The difference was mainly based on the AFR (ratio of 1.2 in the IG and 1.5 in the NIG, p < 0.001), the maximum heart rate in the EST (mean of 145 bpm in the GI vs 136 bpm in the GNI, p=0.015) and the product of heart rate and maximum systolic blood pressure (27 662 vs 24 678, p= 0.039). Ninety seven percent of the IG patients had AFR ≤ 1.5, and therefore endothelium-dependent CMD, compared to 56% in the NIG, p< 0.001. Regarding endothelium-independent CMD, it occurred in 63% of the IG versus 43% of the NIG, p= 0.066. In multivariate analysis, AFR (OR 0.82; 95% CI 0.72-0.93), hemoglobin (OR 0.93; 95% CI 0.89-0.89) and maximum heart rate (OR 1.03; 95% CI 1.00-1.06) were independent predictors of positive EST due to changes in the ECG.

EST had low Sn for detecting endothelium-independent (40%), dependent (44%) or any of them (41%) CMD, hence its poor NPV for any of these forms of CMD. On the other hand, although Sp was also poor for endothelium-independent CMD (77%, with PPV 63%), it was on the contrary very high for endothelium-dependent CMD (97%, with PPV 97%) and absolute for the indistinct diagnosis of one form or another of CMD: 100%, with PPV 100%.

This interesting study allows us to advance in the pathophysiological understanding of the ECG changes evidenced in an EST. Up to this point, in the absence of coronary artery disease, a positive ECG response in EST is interpreted as a false positive. In this specific case, of the 102 patients without obstructive coronary artery disease finally selected, 32 (31%) presented ischemic changes. According to the traditional criterion, they are false positives, and this indicates a specificity of 69%, poor for a stress test. If the true criterion is no longer the presence of obstructive coronary disease, but

of endothelium-independent CMD, the specificity rises to 77%, but if we consider a decreased AFR, expression of endothelium-dependent CMD, we are on the verge of a specificity of 100 %, which is achieved when we accept any form of CMD. What changes, then? What we want to demonstrate. Specificity increases because our true criterion for accepting ischemia is no longer the presence of macrovascular disease but that of CMD. And the gold standard is no longer coronary angiography alone but accompanied by acetylcholine infusion.

Very rich from a pathophysiological point of view, at the moment these findings add little to the usual therapy. It should be made clear that the aforementioned specificity is achieved in a selected group of patients: those with coronary angiography that excluded obstructive coronary disease, and in whom the usual sources of false positive EST results were previously ruled out. Therefore, the interpretation that can be made when these conditions are present is not as precise.