JORGE THIERER

## Differences in cardiovascular health in men and women. An analysis of the PURE registry

Walli-Attaei M, Joseph P, Rosengren A, Chow CK, Rangarajan S, Lear SA, et al. Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. **Lancet. 2020;396(10244):97-109.**

It has traditionally been thought that cardiovascular risk assessment and access to diagnostic and therapeutic procedures are much less frequent in women than in men. The PURE study was an epidemiological study including persons aged 35 to 70 years, from urban and rural areas of 27 high, moderate, and low-income countries. We know a publication providing revealing data on cardiovascular health differences between men and women.

Between 2005 and 2009, 202,072 persons, 59.3% women, were included in the registry. Cardiovascular risk factors, incidence of cardiovascular disease and all-cause death were assessed and measured. Mean age was 50.8±9.9 years in women and 51.7±10.9 years in men, and median follow-up was 9.5 years (interquartile range 8.5-10.9 years). Less than half of the participants lived in rural communities (43.2% of women and 44.2% of men). Women more frequently lived in mid-income (72.1% vs. 67.7%) and less frequently in high-income (8.1% vs. 10.3%) or low-income (19.8% vs. 22%) countries. Compared with men, women were less frequently current smokers and exhibited lower rate of high levels of physical activity or alcohol consumption. Conversely, a probable depression condition and low-educational level was more prevalent.

Total cholesterol, LDL and HDL-cholesterol and ApoA1 were higher in women than in men, but triglyceride concentration, ApoB and ApoB/ApoA1 ratio and total cholesterol/HDL cholesterol ratio was lower. Body mass index was higher in women, but blood pressure and fasting blood sugar levels were lower. A history of cardiovascular disease was reported by 5.3% of women and 6.5% of men. The INTERHEART risk score was lower in women: 8.44 (95% CI 8.43-8.66) vs. 11.44 (95% CI 11.41-11.46) in men; p <0.0001. The lower burden of cardiovascular risk factors in women was seen even in participants with cardiovascular disease. This burden was higher for both women and men in high-income countries.

During follow-up, 8,332 participants without history of cardiovascular disease had a major cardiovascular event (cardiovascular death, myocardial infarction, non-fatal stroke or heart failure); 47% corresponded to women, which, let us recall, represented 59.3% of participants. Also, during follow-up, all-cause death was verified in 10,244 participants, 45% in women. The incidence of major cardiovascular events standardized by age was lower in women: 4.1 vs. 6.4/1000 person-years. This lower incidence was observed in all regions except Africa, and in all socioeconomic strata. The risk of a major cardiovascular event was 38% lower in women without adjusting by the INTERHEART score and 25% lower after adjustment. Risk was lower for each separate event: 41% lower for myocardial infarction, 14% lower for stroke, 14% lower for heart failure and 41% lower for cardiovascular death. The incidence of all-cause death standardized by age, was also lower in women: 4.1 vs. 6.4/1000 person-years. The lowest difference was seen in high-income countries (0.8/1000 person-years incidence difference) and the highest in low-income countries (4.4/1000 person-years incidence difference). Women presented 44% lower risk of all-cause death without adjusting by the INTERHEART score and 38% lower risk after adjustment.

Thirty-day mortality after a major cardiovascular event was 22% higher for women and 28% for men (p <0.0001). The difference was more marked in mid-income (18% in women vs. 24% in men) and low-income (38% in women and 44% in men) countries. Among the 190,414 participants without cardiac or vascular disease at the beginning of the study, use of anti-platelet agents, betablockers, renin-angiotensin system inhibitors and antagonists, diuretics, statins and hypoglycemic drugs was significantly greater in women after adjusting by the INTERHEART score and socio-demographic characteristics, but the differences in proportions were small. Women were more prone to have controlled hypertension and having abandoned smoking.

Conversely, when considering the 11,658 participants with previous cardiovascular disease, and after adjusting by socio-demographic characteristics and the INTERHEART score, use of the above-mentioned drugs was significantly lower in women. They also had less probability of undergoing echocardiography, exercise-stress tests, angiographies or coronary revascularization procedures. Despite this, the risk of a new major cardiovascular event was lower in women with prior coronary heart disease. This pattern was observed in low- and mid-income countries, but not in high-income countries, where the risk of new events was similar between men and women.

*This analysis of the PURE registry confirms some already known epidemiological data about cardiovascular health differences between men and women. It confirms that the prevalence of traditional risk factors*

*is lower in women, except for cholesterol, and hence, the incidence of major cardiovascular events in them is lower, mainly acute myocardial infarction and cardiovascular death. It corroborates that this reduced incidence, which is accompanied by lower annual all-cause mortality, is preserved even after adjusting for risk factors, leading us to think about the presence of protective factors in females. In this sense, and even with some discordant information, the role of estrogens stands out. There are specific risk factors for middle-aged women which are not taken into account in traditional risk scores: preeclampsia, gestational diabetes, early menopause and ovarian insufficiency. But it is clear they are not extended pathologies and, therefore, beyond considering them in individual cases, they do not seem to weigh in the prognosis of the global population. Surprisingly, due to the extended idea of less access in women to cardiovascular care, the use of recommended medication in primary prevention is more frequent in women than in men, and blood pressure and smoking control is more successful. Therefore, biological factors and those associated with treatment whenever necessary seem to explain this better prognosis of women in primary prevention.*

*It is in the case of secondary prevention where known and surprising facts interchange in the analysis. In principle, after adjusting by risk factor burden and socioeconomic factors, the prognosis after a major cardiovascular event is better in women, despite a lower access in women to diagnostic and therapeutic measures. This leads to assume a less severe index condition, or less extended prior cardiovascular disease. If cardiovascular disease were similarly extended and severe in both sexes, a worse outcome would be expected in women, worse studied and treated. However, the opposite situation is encountered. Could lower use of some therapeutic alternatives recommended for secondary prevention in women be explained by less access to the healthcare system or underestimation of risk, or that they more frequently present with non-obstructive heart disease and heart failure with preserved ejection fraction, entities in which it is less imperative the use of some drugs and procedures? Will the explanation lie in a combination of causes? The data from the present analysis do not provide an answer, but welcome making a deeper analysis, in order to remove anything that might entail an avoidable inequity.*

## Quadruple therapy. A new standard of care for heart failure with reduced ejection fraction?

Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. **Lancet. 2020;396(10244):121-8.**

Usual treatment for patients with heart failure and reduced ejection fraction (EF) (EF <35% to 40% depending on studies) include betablockers and renin-angiotensin system inhibitors or antagonists, with Class IA recommendation in all treatment guidelines. Mineralocorticoid receptor antagonists, such as spironolactone, tested in the RALES study and eplerenone in the EMPHASIS HF study, have the same level of recommendation, but with a lower widespread use. In the last years, we have known the results of two studies adding two drugs to the therapeutic battery capable of improving the prognosis of this condition: the PARADIGM HF study with sacubitril-valsartan, which reduced total and cardiovascular mortality compared with enalapril, and the DAPA HF study, in which dapagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i), reduced cardiovascular death, hospitalization for heart failure and total mortality compared with placebo. The analysis here presented sought to answer the question about the effect on all-cause mortality of the combination of sacubitril-valsartan, a SGLTi drug, an anti-aldosterone agent and a betablocker (quadruple therapy) versus only a betablocker and a renin-angiotensin system inhibitor or antagonist.

The study included patients with reduced EF from the placebo branch of the EMPHASIS trial as control group. These patients, who according to protocol should receive betablockers and renin-angiotensin system inhibitors or antagonists, were treated with eplerenone to explore its effect on prognosis. Using an indirect comparison method with information from the three studies (EMPHASIS HF, PARADIGM HF and DAPA HF) it was possible to quantify the effect of quadruple therapy versus conventional therapy with betablockers and a renin-angiotensin system inhibitor or antagonist.

The HR for the primary endpoint of cardiovascular death or hospitalization for heart failure was 0.38 (95% CI 0.30-0.47), for cardiovascular death 0.50 (95% CI 0.37-0.67), for hospitalization for heart failure 0.32 (95% CI 0.25-0.43) and for all-cause death 0.53 (95% CI 0.40-0.70). Patients from the EMPHASIS HF control group, with a median follow-up of 20.5 months, had an annual incidence for the primary endpoint of 16.4% and for total mortality of 8.9%. Use of the quadruple therapy in these patients would result in 18%-25% absolute risk reduction in three years, with a number needed to treat of 4-6 patients to prevent an event. A reduction of 6%-13% total mortality was estimated in three years with the quadruple therapy, with a number needed to treat of 8-16 patients to prevent one death. At 55 years of age, 6.4 years of free-of-event survival for the primary endpoint was estimated with the combination of betablockers and renin-angiotensin system inhibitors or antagonists, and 14.7 years for the quadruple therapy, with an estimated 8.3-year gain (95% CI 6.2-10.7 years). At the same age, a survival of 11.4 years

was estimated for conventional therapy and 17.7 years for the quadruple therapy, with a 6.3-year gain (95% CI 3.4-9.1 years). At 65 years, a 4.4-year and at 80 years a 1.4-year survival gain was estimated with the quadruple therapy compared with conventional therapy.

If the control group consisted of patients treated with betablockers, renin-angiotensin system inhibitors or antagonists and mineralocorticoid receptor antagonists, rotating to sacubitril-valsartan and adding gliflozin would translate in 0.8-1.3 more years of life

*Two studies published in the last years (PARADIGM HF and DAPA HF) have come to alter the traditional plan proposed as sine qua non for the treatment of heart failure with reduced EF. For a long time, the combination of 3 neurohormonal antagonists (betablockers, renin-angiotensin system inhibitors or antagonists and anti-aldosterone agents) exhibited the unbeatable condition to successfully treat this pathology, keeping the validity of the pathophysiological model. The emergence of sacubitril-valsartan did not imply, despite the name of the study which demonstrated its virtues, a true change of the neurohormonal paradigm; in any case, it extended its reach, by evidencing that a dual action (adding to angiotensin II antagonism the promotion of natriuretic peptide effects) is better than simply blocking the effects of the former. Conversely, the demonstration of the beneficial effects of SGLT2i is a pathophysiological novelty, as it involves mechanisms beyond the current model. It will be necessary to unravel the modes of action truly responsible for the favorable impact; many are known, but none can be said to bear the supremacy.*

*This analysis tries to put into numbers the effect achieved with the quadruple therapy, and the figures are really impressive: a reduction by half for risk of cardiovascular death and to one third for hospitalization for heart failure; 6 years more of survival at 55 years and more than 4 at 65 years. Of course, these data emerge from indirect comparisons and should be seen more as indicators of powerful effects than as absolute numerical certainty. We must bear in mind that the group used as control is the placebo group of the EMPHASIS study, which started enrolling patients in 2006, while the DAPA HF study started in 2017. This temporal difference might imply discrepancies in the conditions and concomitant interventions, beyond the specific heart failure treatment. Nevertheless, quadruple therapy appears as a new standard of care in the treatment of heart failure with reduced EF. Two reflections emerge spontaneously:*

*The first, linked to costs and access issues. In different publications, one of the most important determinants of treatment with sacubitril-valsartan is medical coverage. The addition of SGLT2i implies another expensive medication. Economical analyses suggest that both interventions are cost effective, but who effectively pays for it is not a minor topic. Decisions should progress towards measures ensuring patients the real possibility of receiving the best treatment. The second refers to the different alternatives for treating heart failure with reduced EF. In this sense, for patients with EF >55%, no neurohumoral antagonist has proved to be beneficial, and the effect for EF between 45% and 55% is favorable, but lower than with more reduced EF values. In the case of SGLT2i, we await the results of ongoing studies, which will define if these drugs add to previous failures, or if, for the first time, we have access to a medication able to turn the course of this disease.*

## Early discontinuation of aspirin after coronary angioplasty: Heresy?

O'Donoghue ML, Murphy SA, Sabatine MS. The Safety and Efficacy of Aspirin Discontinuation on a Background of a P2Y12 Inhibitor in Patients After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. **Circulation. 2020;142(6):538-45.**

The addition of a P2Y12 inhibitor to aspirin in the context of non-ST-segment elevation acute coronary syndrome has been shown to reduce the incidence of major adverse cardiovascular events, but at the expense of a higher rate of bleeding. After coronary angioplasty, dual antiplatelet therapy (DAPT) is the rule. The optimal duration of the double scheme has been the subject of a large number of trials and analyses, and it is recognized that, the longer its use, the higher the incidence of bleeding events. If the indication for anticoagulation is also required (for example, in the context of atrial fibrillation), after one month of DAPT plus the anticoagulant, it is recommended to suspend aspirin and maintain the P2Y12 inhibitor and the oral anticoagulation. However, when only DAPT is indicated, there is greater doubt about the behavior of suspending aspirin and persisting exclusively with the P2Y12 inhibitor. A recently published meta-analysis evaluates this conduct and its consequences.

The meta-analysis consisting of 5 randomized studies (GLOBAL LEADERS, SMART CHOICE, STODAPTPT 2, TICO and TWILIGHT) which included patients after coronary angioplasty due to acute coronary syndrome or stable coronary heart disease, explored aspirin discontinuation after 1 to 3 months of DAPT vs. remaining with a double scheme. Overall, 32,145 patients were considered, 56.1% after an acute coronary syndrome. The average age ranged between 61 and 68.6 years; 70% of patients were hypertensive, 64% dyslipidemic, 30% diabetic, and 20% had had a previous infarction. The P2Y12 inhibitor used was clopidogrel in 16.5% of cases and ticagrelor or prasugrel in the remaining 83.5%.

Aspirin discontinuation 1-3 months after coronary angioplasty reduced the risk of bleeding by 40% compared with persistent DAPT (HR 0.60, 95% CI

0.45-0.79, p <0.001). When the analysis was restricted to BARC 3 or 5 bleeding only, risk reduction was similar. It should be considered that BARC 3 bleeding can be type 3a bleeding (decrease in hemoglobin between 3-5 g/dL or some transfusion), type 3b bleeding (decrease in hemoglobin ≥5 g/dL, bleeding that requires compression, surgical intervention or tamponade) or type 3c bleeding (intraocular or intracranial bleeding); and that BARC 5 bleeding is fatal bleeding, and may be probable type 5a bleeding (without confirmation but with clinical suspicion), or definitive type 5b bleeding, (confirmed by autopsy or imaging study).

It should be noted that the heterogeneity in the results of the 5 studies was very high ($I^2$ 64%), but the tendency of the effect was consistent. Aspirin discontinuation did not appear to increase the risk of major adverse cardiovascular events (HR 0.88; 95% CI 0.77-1.02, p= 0.09) or the risk of all-cause mortality (HR 0.85; 95% CI 0.70-1.03, p=0.09), acute myocardial infarction (HR 0.85, 95% CI 0.69-1.06, p=0.14) or stroke (HR 1.08; 95% CI 0.67-1.74, p=0.74). The results did not vary when considering only patients with acute coronary syndrome.

*This meta-analysis confirms the lower risk of bleeding when aspirin is discontinued 1 to 3 months after a DAPT scheme has been established following a coronary angioplasty. Previous analyses had already shown a similar effect if the P2Y12 inhibitor is suspended under the same conditions and aspirin is maintained. And this effect is not surprising: less bleeding is expected with a single antiplatelet agent rather than with two. It is in the safety endpoint where the most reasonable doubts lie. Does the risk of ischemic events increase with a single antiplatelet agent in the period close to an angioplasty procedure? Does it especially occur when we abandon the "sacred cow", and leave everything to the P2Y12 inhibitor? In this sense, different results could be expected: possibly, the use of a single agent might increase the risk of ischemia, due to less protection; or, on the contrary, the reduction in the risk of bleeding could be accompanied by a reduction in ischemic events, since in the case of bleeding events the tendency to abandon antiplatelet treatment is greater, and in this context the risk of a thrombotic event increases.*

*Fine, the meta-analysis points in this last direction, but it does not confirm it definitively: there is a reduction in the incidence of cardiovascular events greater than 12%, with a trend towards significance (p=0.09). Approximately, a 2% increase in risk cannot be excluded. Let us remember that the design of the 5 studies showed some differences: the only double-blind study was TWILIGHT (which we discussed in detail in RAC 2019 vol. 87 no.6). GLOBAL LEADERS evaluated ticagrelor monotherapy at 1-month post-angioplasty; TWILIGHT and TICO monotherapy with ticagrelor at 3 months; SMART CHOICE monotherapy with any P2Y12 inhibitor at 3 months; and STOPDAPT 2 monotherapy with clopidogrel at 1 month. It is not defined which P2Y12 inhibitor we should prefer: we know from previous studies that ticagrelor and prasugrel reduce the incidence of ischemic events compared with clopidogrel in patients who also receive aspirin; there is no head-to-head comparison in the absence of aspirin. In the context of a trend to discuss the role of aspirin in primary and secondary prevention, it is expected that we will see studies of this type in the future.*

## The presence of cardiac amyloidosis does not appear to worsen the results of percutaneous aortic valve implantation

Scully PR, Patel KP, Treibel TA, Thornton GD, Hughes RK, Chadalavada S, et al. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. **Eur Heart J. 2020; 41 (29): 2759-67.**

Aortic stenosis and transthyretin amyloidosis are two conditions whose prevalence increases with age and is higher in male patients. In recent years, the coexistence of both conditions has been emphasized in a non-negligible proportion: up to 15% of patients who will undergo a surgical replacement procedure or a percutaneous aortic valve implantation (TAVI) present with cardiac amyloidosis. Doubts have been raised that such procedures would be futile in its presence. An observational study carried out in two British centers (in London and Oxford) seems to contradict this belief.

Two-hundred patients with a diagnosis of severe aortic stenosis were recruited and referred for TAVI. In all of them, a light chain assay was performed to rule out blood dyscrasia and a bisphosphonate scintigraphy to confirm the diagnosis of transthyretin amyloidosis. Mean age was 85±5 years and 50% of patients were men. Mean aortic valve area was 0.73±022 cm2, with mean gradient of 41±14 mm Hg and mean peak velocity of 4.1±0.6 m/s. In 13% of patients, a diagnosis of amyloidosis was confirmed. Treatment decision was blinded to the scintigraphy result. TAVI was decided in 75% of the cases, surgery in 1% and medical treatment in 24%. Patients with amyloidosis were 3 years older (88.1±5 vs. 84.7±5 years, p=0.001) with a somewhat higher prevalence of men (62% vs. 48% in the group without the disease). The quality of life score as well as the 6-minute walk (mean 94 vs. 138 m, p=NS due to the low number of cases) were lower. There was no difference in comorbidities and similar severity of valve involvement. The ECG revealed lower QRS voltage, and greater incidence of right bundle branch block (36% vs. 13%). Echocardiographic wall thickness was 1 to 2 mm greater, and there was no difference in the prevalence of low-flow, low-gradient aortic stenosis with reduced (12% vs. 9%) or normal (19% vs.

15%) ejection fraction. Left ventricular ejection fraction, longitudinal deformation, left atrial size, right ventricular function, and diastolic function measurements did not differ either. The ECG voltage/mass ratio in the echocardiogram was lower in patients with amyloidosis (0.017 ± 0.007 vs. 0.025 ± 0.012, p=0.03). NT pro-BNP values were significantly higher (median of 3702 pg/mL vs. 1254 pg/mL, p=0.001) and the same occurred with high-sensitivity troponin T (median of 41 pg/mL vs. 21 pg/mL, p <0.001). In the multivariate analysis, age, troponin, voltage/mass ratio, and right bundle branch block were associated with the presence of amyloidosis. The rate of TAVI complications was similar in patients with and without amyloidosis. In a median follow-up of 19 months, mortality was similar in patients with and without amyloidosis (23% and 21%, respectively).

*Cardiac amyloidosis coincides with significant aortic stenosis in a not inconsiderable proportion of patients with valve disease. A high prevalence of low-flow, low-gradient aortic stenosis has been described, in most cases with preserved ejection fraction. The coexistence of both pathologies increases chamber stiffness and, therefore, the presence of heart failure. Reports with a limited number of patients suggest that the evolution of patients undergoing TAVI may be worse in the context of amyloidosis. Obviously, we have no data from randomized trials, but the fear of therapeutic futility limits the treatment of aortic stenosis when the diagnosis of cardiac amyloidosis is made.*

*This observational study data confirms some previous assumptions. Patients with amyloidosis are older and have higher values of biomarkers and mass/voltage ratio. It is worth mentioning that there has been no difference in the prevalence of low-flow, low-gradient aortic stenosis or in the degree of hypertrophy, diastolic dysfunction or reduction of longitudinal deformation, characteristics that are usually cited as typical of amyloid involvement. We understand that the small number of patients may have conspired against statistical power to find significant differences. Although it is true that TAVI decision was taken blinded to the diagnosis of infiltrative pathology, we cannot rule out the indication bias: decision-making was not randomized, and it is possible that the most seriously ill patients may have been assigned to medical treatment, and patients with less marked amyloidosis to TAVI. Specifically, in the population evaluated, the use of TAVI did not appear to be futile, which opens the possibility of performing the procedure in patients with a combination of both diseases. More observational data, and ideally from randomized studies, will be able to finish defining the population that obtains real benefit from percutaneous implantation*.

## The saga of the ISCHEMIA study

Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. **N Engl J Med. 2020;382(15):1395-407.**
Spertus JA, Jones PG, Maron DJ, O'Brien SM, Reynolds HR, Rosenberg Y, et al. Health-Status Outcomes with Invasive or Conservative Care in Coronary Disease. **N Engl J Med. 2020;382(15):1408-19**.
Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, et al. Management of Coronary Disease in Patients with Advanced Kidney Disease. **N Engl J Med. 2020;382(17):1608-18.**

In the context of chronic coronary syndromes, the choice between medical treatment and a revascularization procedure is raised daily in decision-making. Different randomized studies have explored this issue. A meta-analysis (Stergiopoulos et al, JAMA Intern Med 2014; 174: 232-40) which included 5 studies, among them, the COURAGE, BARI 2 D and FAME 2 studies, with a total of 5,286 patients reported no advantage for invasive treatment relative to the reduction of death, acute myocardial infarction (AMI) or need for unplanned revascularization.

Different reasons have been put forward to explain the lack to demonstrate effect in these studies. It has been suggested that, since the coronary anatomy is known, the most seriously ill patients and, therefore, with a greater probability of benefiting from an invasive procedure, may have been excluded and referred directly to it. Similar patients, randomly assigned to medical treatment, with an assigned prognostic improvement in the intention-to-treat analysis to pharmacological treatment, may also have been crossed over to invasive treatment. At the other end of the spectrum, it has been suggested that patients with mild ischemia, assigned to revascularization procedures, are not those in whom benefit is expected and may, therefore, have diluted the beneficial effect of the intervention. Lastly, it has been suggested that with the latest advances in fractional flow reserve (FFR) measurement, it is possible to properly select patients in whom revascularization offers advantages. In fact, the 5-year follow-up of the FAME 2 study indicated that treatment with coronary angioplasty guided by FFR measurement was capable of reducing the need for a new revascularization procedure and spontaneous AMI. And a meta-analysis of individual data published in 2019 points to a reduction in the incidence of death and AMI when an angioplasty is done taking FFR data into account.

In this context, the ISCHEMIA study was carried out to define the effect of performing an angiography and, eventually, angioplasty in patients with stable coronary artery disease and moderate to severe ischemia. Initially, it included patients with moderate or severe ischemia on imaging studies; later, it was accepted to include patients with severe ischemia in a stress test without images. The criteria of moderate or severe ischemia in the gamma camera study were

ischemia in ≥10% of the left ventricle; in the echocardiogram ≥3 segments of moderate or severe hypokinesia or stress-induced akinesia; in cardiac magnetic resonance stress perfusion imaging ≥12% of ischemic myocardium; or ≥3/16 segments with severe stress-induced hypokinesia or akinesia; on exercise testing, at least 1.5 mm ST-segment depression in >2 leads or > 2 mm ST-segment depression in a single lead at <7 METS, with angina.

Patients with glomerular filtration rate <30 mL/min/1.73 m2, with acute coronary syndrome in the last 2 months, heart failure in FC III-IV, left ventricular ejection fraction (LVEF) <35%, lesion of unprotected left main coronary artery >50%, or with unacceptable angina despite optimal medical treatment were excluded from the study. A coronary CT angiography was carried out to define if the anatomy met the inclusion and exclusion criteria, with the purpose of excluding patients with a left main coronary artery lesion and those with non-obstructive coronary artery disease. The study was not carried out in patients with glomerular filtration rate between 30 and 60 mL/min/1.73m2, and in those with known coronary anatomy. The results of the CT angiography were used to decide if the patients could be included, but they were blinded to the treating physicians or the patients so as not to influence decision-making (study participation, group crossover after random allocation).

Patients were randomly assigned to an invasive strategy, based on angiography and revascularization if indicated, carried out within 30 days of random assignment, or a conservative strategy with optimization of drug therapy and lifestyle modification, with angiographic study only in case of medical treatment failure. Fractional flow reserve measurement was suggested to optimize angiography results in both study groups. The primary endpoint was a composite of cardiovascular death, AMI, hospitalization for unstable angina, heart failure, or resuscitated cardiorespiratory arrest. The secondary endpoint was the composite of cardiovascular death or AMI. The diagnosis of AMI not related to the procedure corresponded to types 1, 2, 4b and 4c of the third definition of AMI. To diagnose periprocedural AMI, higher cut-off values than those considered for types 4 to 5 of the third definition were required.

A sample size of 8,000 patients and a 4-year follow-up were initially defined to assess the effect of both strategies on the 5-component primary endpoint. Before initiating the study, the secondary endpoint was turned into the primary endpoint, with the open possibility of reversing the change, if necessary, to maintain statistical power. Given the low recruitment and that the incidence of events was lower than expected, it was decided to return to the 5-component endpoint and from a predicted event rate of 20% in the conservative group, with an expected reduction of events of 18% in a 4-year follow-up with the invasive strategy, to an expected rate of 14% in the conservative group at 4 years, with a reduction of 18.5% in a 3-year follow-up.

Between July 2012 and January 2018, 8,518 patients were enrolled with 5,179 effectively randomized in 320 sites in 37 countries, while 434 patients due to left main coronary artery lesion >50%, 1,218 for non-obstructive coronary disease; and 1,350 for insufficient ischemia were excluded from the study. Median age was 64 years and 77% were men. Seventy-three percent of patients were hypertensive, 42% diabetic, 12% current smokers and 45% ex-smokers. Median LDL cholesterol was 83 mg/dL at the beginning, and 64 mg/dL at the end of the study; 19% had a history of AMI, 20% of coronary angioplasty and 4% of revascularization surgery. Median LVEF was 60%. Almost 90% had a history of angina, but 35% had not presented it in the last month. In 26% of the cases angina had started or had progressed in the last 3 months and in 17% it had specifically started in that period.

The degree of baseline ischemia was nil or mild in 12% of patients, moderate in 33%, and severe in 55%. There was 2-vessel and at least 3-vessel lesion in 31% and 45% of cases, respectively. There was a proximal lesion of the anterior descending artery in 47% of cases.

Median follow-up was 3.2 years. In the invasive group, angiography was performed in 96% of patients, and a revascularization procedure was carried out in 79% (angioplasty in 75% of cases). In the conservative group, 26% of the patients received an angiography study, and 21% underwent a revascularization procedure. In 75% of cases, this crossover was done prior to the occurrence of any primary endpoint event.

At follow-up, the incidence of the primary endpoint was similar in both groups, with a HR of 0.93; 95% CI 0.80-1.08, p=0.34. At 6 months there was a higher rate of events in the invasive group (5.3% vs. 3.4%) with an excess of 1.9%; but at approximately 2 years the incidence curves crossed over and the invasive group began to present a lower rate of events than the conservative one, reaching values of 16.4% vs. 18.2% at 5 years, with an excess of 1.8% for the conservative group. Regarding the secondary endpoint, the results were similar, with 4.8% vs. 2.9% of events for the invasive and conservative groups at 6 months, but with values of 14.2% vs. 16.5% at 5 years. There were also no differences in all-cause mortality; however, there were more hospitalizations for heart failure (HR 2.23, 95% CI 1.38-3.61) and less for unstable angina (HR 0.50, 95% CI 0.27 -0.91) in the invasive group throughout the study. There was no interaction of treatment with ischemia severity, diabetes, or number of vessels involved.

The difference in the incidence of the primary and secondary endpoints in the first 6 months was specifically based on the higher prevalence of peri-

procedural AMI. Furthermore, when the secondary definition of AMI was used, the incidence of the primary endpoint was 10.2% in the invasive group and 3.7% in the conservative group. Throughout follow-up, the invasive group presented an adjusted HR for periprocedural AMI of 2.98 (95% CI 1.87-4.74) and for spontaneous AMI of 0.67 (0.53-0.83).

The other secondary endpoint considered in the study was quality of life, which took into account 3 items, the Seattle angina questionnaire, the Rose dyspnea scale and the visual analog scale of the EQ-5D-questionnaire. The central analysis relied on the variation of the Seattle questionnaire, which in each case considers 3 scores: anginal frequency, functional limitation and quality of life in the month prior to being administered. The three scores vary between 0 and 100, with higher scores indicating better results: less frequent angina, less limitation and better quality of life. The Rose dyspnea scale score ranges from 0 to 4, with higher scores indicating dyspnea with lighter activities, and the EQ5D score ranges from 0 to 100 (from worst to best quality of life). The questionnaires were administered before randomization, at 1 month and a half, at 3 and 6 months and then every 6 months. The analysis included 4,617 patients for whom all data was available. In baseline conditions, the average frequency score was around 81 points, that of functional limitation was 79, and that of quality of life was 61 points; the dyspnea scale score averaged 1.2 points, and the EQ5D score 69 points. It should be recalled that at the beginning of the study, 21% of patients had daily to weekly angina; 44% 3 or less times per month; and 35% had had no angina in the previous month.

Quality of life always improved in both groups during follow-up, but more in the invasive than in the conservative group. At 3 months, the Seattle questionnaire averaged 85 vs. 82 points, at 1 year 87 vs. 84 points and at 3 years 88 vs. 86 points. Throughout the study, patients in the invasive group had an OR ≥1.5 for better score than those in the conservative group. At the beginning of the study the more frequent the angina the greater the differences: at 3 years, 5.3 points for patients with daily to weekly angina, 3.1 points for those with angina 3 or less times per month, and only 1.2 points for those without angina in the month prior to inclusion. For a patient with weekly angina, the probability of being angina-free at 3 months was 45% in the invasive group and only 15% in the conservative group.

A population at increased risk of events is that of patients with severe renal dysfunction, excluded from the ISCHEMIA study. With a similar protocol although with some modifications, the ISCHEMIA CKD study was carried out in patients with advanced chronic kidney disease (glomerular filtration rate <30 mL / min/1.73 m2 or dialysis). The rest of the inclusion and exclusion criteria were similar to those of the ISCHEMIA study, but in this study coronary CT angiography was not performed before randomization to avoid the risk of contrast nephropathy. A strict hydration protocol was used to perform coronary angiography in the invasive or conservative group, with controlled administration of contrast adjusted to weight and renal function and with the indication to restrict the amount of contrast if angioplasty was necessary.

The primary endpoint was the composite of all-cause death or non-fatal acute myocardial infarction. Initially, a sample size of 1,000 patients was proposed, but due to the slow recruitment it was reduced to 650 (between 500 and 700). As in the ISCHEMIA study, the assumptions changed over time. A sample of 500 patients per group had been assumed and a 4-year incidence of 60% to 75% events in the conservative group, with a mean follow-up of 3 years, and a power of more than 81% to detect 23% to 27% reduction in the incidence of the primary endpoint in the invasive group. The low inclusion rate and a lower than expected incidence of events led to recalculation of the sample size and the final inclusion of 802 patients, with 777 randomly assigned. It was understood that with this number of patients a power of 80% was ensured to detect 22% to 24% reduction with the invasive strategy, assuming an event rate of 41% to 48% in the conservative group at 4 years.

Median age was 63 years, 69% were men, 92% were hypertensive, 57% diabetic, 17% had previous AMI, and 17% had heart failure. Median left ventricular ejection fraction was 58%, and 53% were on dialysis (hemodialysis in over 80% of cases). Among non-dialysis patients, median glomerular filtration rate was 23 m min/1.73 m2. About 48.5% of patients presented no angina at the beginning of the study; in 39.1% the frequency of angina was monthly, and in only 12.4% it was daily or weekly. In the admission evocative test, ischemia was moderate in 61.4% of patients and severe in 37.8%.

In the invasive group, coronary angiography was performed in 85% of patients. Multiple vessel injury was verified in 51.3% of patients and anterior descending artery involvement was present in 57.2%. In 26% of cases, there was no obstructive coronary artery disease. Revascularization was carried out in 50% of patients (85% angioplasty, and 15% surgical). Over a 3-year period, angiography was performed in 31.6% and a revascularization procedure in 19.6% of the conservative group patients.

At a median follow-up of 2.2 years, there was no significant difference in the incidence of the primary endpoint: 36.4% in the invasive group vs. 36.7% in the medical treatment group (HR 1.01, 95% CI 0.79-1.29, p=0.95). There was also no difference in the incidence of AMI, unstable angina, or death. The invasive strategy was associated with a higher risk of stroke (HR 3.76, 95% CI 1.52-9.32, p=0.004), most of the time not related to the procedure. The incidence of death/initiation of dialysis was also higher in this

group (HR 1.48 95% CI 1.04-2.11 p=0.03). The incidence of contrast nephropathy in non-dialysis patients who underwent coronary angiography was low (7.9%).

*The ISCHEMIA study provides a lot of material for analysis. In principle, patients were selected to enter the trial due to moderate to severe ischemia in an evocative test, and after undergoing a coronary angiography scan that made it possible to rule out patients with left main coronary artery injury (who could not be adjudicated to medical treatment) and to patients with non-obstructive coronary artery disease (in whom revascularization is irrelevant). The inclusion and exclusion criteria allowed to define a population with a low risk of events, with a median LVEF of 60%, far from an acute coronary syndrome, with 35% of the patients with no angina in the last month, and only 55% with severe ischemia, acceptably managed with medical treatment. This selection of patients may have contributed to the absence of differences between the invasive and the conservative strategy. The fact that in the conservative group finally one in 5 patients ended up undergoing a revascularization procedure may also have contributed to dilute a possible difference. The message we have heard is that these results allow patients with the characteristics of those in the study to remain in medical treatment since the invasive strategy did not offer advantages.*

*But does ISCHEMIA reproduce everyday practice? Let us take for example a patient with severe and extensive ischemia. Do we request a CT angiography to know the coronary anatomy and consider the alternative of invasive vs. conservative treatment? Or do we order a coronary angiography straight away? And, in this case, having demonstrated the presence of a 3-vessel lesion with proximal involvement of the anterior descending artery, is it usual to indicate medical treatment or progress to a revascularization procedure? It could be said that the study suggests that there are no differences between the two conducts, but, as already stated, the decision is not reached by the way outlined in the study design.*

*Different modifications were made throughout the trial, and have been the subject of criticism. It went from a primary endpoint of five components to one of the two hardest and from there again to five, as there was a low inclusion rate and fewer events than expected. The idea of including only patients based on the result of an evocative imaging test was abandoned to accept patients undergoing conventional exercise stress testing. A different cut-off value was established for the severity of lesions detected by imaging studies (>50%) and by exercise stress testing (>70%). To adjust to reality, the expected event rate and the follow-up time were reduced. And lastly, the need for approval of study results by a central imaging laboratory for study entry was eliminated. All these modifications reveal a pragmatic adaptation criterion and the desire to preserve the conduct of the study, and reflect a new way of approaching randomized trials, in which the initial criteria are changed to sustain its framework. However, the inclusion of such a low number of patients per center (5,179 in 320 centers in 6 years implies 2.7 patients per center per year) allows for well-founded doubts about the representativeness and the conclusions. Perhaps this low inclusion rate reflects that treating physicians prefer to adopt a certain conduct in each situation, and it is unusual to leave decision-making to chance. And that decisions about invasive or conservative behavior are made knowing the coronary anatomy.*

*The demonstration reporting the same results in the long-term follow-up, but with an increased risk for the invasive group in the period close to the intervention and for the conservative group later, seems to go hand in hand with having considered a population that is not so ill. Presumably, with more compromised patients, the advantage of the invasive group would have been more evident.*

*The analysis on quality of life does show favorable results with the initial revascularization strategy. We can, however, ask ourselves how much, beyond statistical significance, a difference of 2 or 3 points on a scale of 100 represents, taking into account that, as it is a subjective assessment, it is more frequent that patients undergoing an invasive procedure experience symptomatic improvement due to the widespread belief that this will be more effective than continuing with the pharmacological treatment that, in fact, they had been receiving before entering the study. The placebo effect of the intervention (ORBITA study) should not be overlooked.*

*Finally, the ISCHEMIA CKD study is worth at least as much for what it reveals about kidney failure and its relationship with cardiovascular risk as for the comparison between both strategies. Thus, in the ISCHEMIA study 35% had no angina in the previous month compared with 48.5% in the ISCHEMIA CKD study. In the ISCHEMIA study, baseline ischemia was moderate in 33% and severe in 55% of cases; in ISCHEMIA CKD it was moderate in 61.4% and severe in 37.8%, respectively. This implies a less severe and less symptomatic ischemia in patients with renal failure. Based on these findings, in the invasive group of the ISCHEMIA study, 79% of the patients underwent revascularization compared with 50% in the ISCHEMIA CKD study. However, the incidence of cardiovascular death or AMI at 3 years in the ISCHEMIA study was 9.7% in the invasive group and 11% in the conservative group, whereas the ISCHEMIA CKD study values were more than 3 times higher: 36.4% and 36.7%, respectively, which highlights the adverse prognostic effect of renal failure, beyond the evident ischemia and disease of the epicardial coronary arteries.*

*In conclusion, the saga of the ISCHEMIA study and its derivatives confirm that in low-risk patients, but also in the context of renal failure and a markedly higher risk, optimized medical treatment can globally compete on equal terms with an initial invasive strat-*

*egy. Choosing the best treatment for the individual patient remains an art, one of the most complex.*

## Weight loss in diabetes, and its relationship with an adverse prognosis

Doehner W, Gerstein HC, Ried J, Jung H, Asbrand C, Hess S, et al. Obesity and weight loss are inversely related to mortality and cardiovascular outcome in prediabetes and type 2 diabetes: data from the ORIGIN trial. **Eur Heart J. 2020;41(28):2668-77.**

Being overweight and obese are risk factors for the development of diabetes and cardiovascular disease. The recommendation of weight loss to improve metabolic control is usual for patients with diabetes. However, the effect of weight loss on cardiovascular and total mortality in the context of diabetes is less clear. The LOOK AHEAD study failed to show that an intensive control and weight loss strategy in obese patients with type 2 diabetes (14% with established cardiovascular disease) was beneficial. And, in the DGCP study in patients with diabetes (26% to 30% of them with cardiovascular disease) followed up for 19 years, weight loss, intentional or not, was associated with a worse vital prognosis. The ORIGIN study evaluated the use of insulin glargine and omega 3 acids in a 2 x 2 factorial design in prediabetic and type 2 diabetic patients. We now know of a subsidiary analysis of this study, which evaluates the effect of body mass index (BMI) and weight variations across the study on all-cause mortality. Sustained weight loss was understood as a reduction of at least 1 kg in 2 years, without an increase of ≥0.5 kg in the interim; and for sustained weight gain an increase of at least 1 kg in 2 years without a decrease of ≥0.5 kg in that period.

A total of 12,521 patients were included in the study (99.9% of the total ORIGIN study participants), with mean age of 63.5 years and 35% women. In 3.8% of cases patients had BMI <22 kg/m2, 12.5% had a BMI considered normal (22-24.9 kg/m2), 40.3% were overweight (BMI 25-29.9 kg/m2) and the remaining 43.4% were obese (BMI ≥30 kg/ m2). Overweight and obese patients were younger, with higher blood pressure and LDL cholesterol values, but a lower prevalence of cardiovascular events.

In a median follow-up of 6.2 years, 15.3% of the patients died, 9.2% due to cardiovascular causes. An inverse relationship between BMI category and the incidence of events was verified for total mortality, cardiovascular mortality, and a composite of cardiovascular death, non-fatal acute myocardial infarction, and non-fatal stroke. Regarding all-cause mortality, and considering as reference patients with BMI 22-24.9 kg/m2 (adjusting for age, sex, risk factors, duration of diabetes, branch of treatment in the study and use of drugs with cardiovascular effect) the HR for patients with BMI <22 kg/m2 was 1.29 (95% CI 1.01-1.65); for overweight patients 0.79 (95% CI 0.68-0.91); for patients with BMI between 30 and 34.9 kg/m2 0.75 (95% CI 0.61-0.93), for those with BMI between 35 and 39.9 kg/m2 0.65 (95% CI 0.46-0.92), and only among patients with a BMI of 40 kg/m2 or more the trend stopped, with a HR of 0.81 (95% CI 0.50-1.32). The same phenomenon was evident when considering the other endpoints mentioned.

Weight gain during the first year of follow-up was associated with a better outcome. For every 5% increase in body weight in the first year (after adjusting for the variables already mentioned) there was a reduction of 14% in total mortality, 8% in cardiovascular mortality, 9% in the incidence of major cardiovascular events, 10% in stroke, 6% in non-fatal infarction, 10% in need for revascularization, and 14% in hospitalization for heart failure. In contrast, the decrease in weight in the first year pointed to patients with a worse prognosis: for every 5% decrease in body weight, there was an increase of 17% in total mortality, 9% in cardiovascular mortality, 10% in major cardiovascular events, 11% in the incidence of stroke, 11% in revascularization procedures and 16% in hospitalization for heart failure. In the first 2 years of the study, sustained weight gain did not impact the prognosis in a favorable or unfavorable way compared to not presenting it, but sustained weight loss implied a HR for total mortality of 1.31 (95% CI 1, 18-1.46) and for cardiovascular mortality of 1.17 (95% CI 1.02-1.35).

*This publication adds more evidence to the controversial topic of the obesity paradox, the fact that in primary prevention overweight and obesity entail an adverse prognosis, but, on the other hand, in patients with various pathologies (cardiovascular, kidney failure, acquired immunodeficiency syndrome, chronic obstructive pulmonary disease) the same conditions are associated with a better outcome. The availability of greater energy reserve and less inflammatory and catabolic activation have been indicated as reasons to explain this phenomenon. In this sense, this analysis of the ORIGIN study replicates previous information from meta-analyses of observational studies in diabetes. The favorable prognostic weight in these studies for overweight and obesity is concentrated in diabetic patients with additional risk factors (as were all those included in the ORIGIN study), and not in those free of these factors. It is usually pointed out that the presence of other diseases (such as cancer) that explain a reduced weight can help explain that those with overweight have a better evolution. In this context, it can be thought that patients who have normal weight, in many cases, are obese who have been losing weight and, therefore, are patients whose prognosis is worse than those who maintain a high weight. But what is striking is that the excess risk is not only for all-cause death (which would include the risk of death from different pathologies that occur with catabolism or activated inflammation, such as cancer, col-*

*lagen diseases and kidney failure), but specifically for cardiovascular death and the incidence of coronary events.*

*A notable contribution of the study is to assess the prognosis of changes in weight, beyond a specific determination. As in ORIGIN there was no precise recommendation of weight loss nor was a strategy in this sense tested, we do not know in how many cases weight loss was intentional or spontaneous; and, therefore, it is not possible to differentiate between the two situations. And a point to discuss is whether it is the BMI that allows better discrimination, since it expresses information on fat and muscle mass without differentiating between the two: will it be the same to lose fat mass and maintain or gain muscle mass, than the reverse situation?*

## Conflicts of interest

JT is Deputy Director of the Argentine Journal of Cardiology.