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Cancer and cardiovascular disease: a bidirectional relationship

Bertero E, Robusto F, Rulli E, D'Ettorre A, Bisceglia L, Staszewsky L et al. Cancer Incidence and Mortality According to Pre-Existing Heart Failure in a Community-Based Cohort. **JACC: CardioOncology 2022;4:98-109.**

Paterson DI, Wiebe N, Cheung WY, Mackey JR, Pituskin E, Reiman A et al. Incident Cardiovascular Disease Among Adults With Cancer. **JACC: CardioOncology 2022;4:85-94.**

For a long time, cardiovascular disease and cancer, the two main determinants of mortality in the adult Western population, were understood as entities of a different nature, two different pathways, although with the same destiny. In the last decade, cohort studies that illuminated the deep relationship that exists between the two, a relationship with a common history and bidirectional nature, began to proliferate. However, some publications questioned this association. We present two recent studies that confirm it, and add new data of interest.

The first is a retrospective cohort study carried out in the region of Puglia, in southern Italy, based on different kinds of administrative health records: outpatient consultations, hospital discharges, medication prescriptions, tax exemptions related to health costs and death certificates. Patients aged ≥50 years, included in the registries between 2003 and 2015, which at the time of inclusion had no history of cancer in the previous 3 years and in whom there was follow-up data for at least 5 years, unless they had died before, had been diagnosed with cancer or moved to another region, were selected. Cases of heart failure (HF) were defined as those diagnosed in the last 12 months, in an outpatient clinic, at hospital discharge or in a certificate to obtain a discount on medication. Patients without a diagnosis of HF were chosen as controls, matched with the cases by gender and age, within each of Puglia districts (urban, industrialized or rural, to ensure similar socioeconomic conditions), a medication complexity index, follow-up duration and, in the case of hospitalized patients, also by the Charlson comorbidity index.

A total of 104 020 patients diagnosed with HF and as many controls were included. Mean age was 70±10 years, and median follow-up was 5 years. Patients with HF logically had a higher prevalence of cardiovascular disease, and a higher prescription of drugs administered for its treatment. The annual incidence of cancer during follow-up was 2.13% in the HF arm and 1.24% in the control arm (HR 1.76; 95% HF 1.71-1.81). Excess risk of cancer in the HF arm was observed regardless of age, with HR of 1.66 in patients <70 years, 1.69 in those between 70-79 years, and 2.07 in those ≥80 years, evident in both men and women. Specific risks for solid organ cancer were particularly high: lung (HR 4.49), pancreas (HR 4.64), liver (HR 3.78), and central nervous system (HR 3.85). But the increased risk of oncohematological disease was also striking: multiple myeloma (HR 2.33), leukemia (HR 2.17) and lymphoma (HR 1.84). There were no differences in the incidence of breast cancer, melanomas, or endocrine tumors, and the risk of prostate cancer was lower (HR 0.90).

Patients with HF presented death attributable to cancer more frequently than controls (HR 4.11; 95% CI 3.86-4.38). Excess risk was greater in younger patients: HR 7.54 in those <70 years, 3.80 in those between 70-79 years and 3.10 in those ≥80 years, and remained present after considering the competing risk of death from other pathologies. The increased risk of mortality attributable to cancer was more significant in the case of lung cancer (HR 7.41) among solid organ tumors and myeloma (HR 4.70) among oncohematological diseases. The association of HF with risk of death from cancer was seen in men (HR 3.79) and women (HR 4.86). The specific cause of death could be determined in 74.5% of cases. The increased risk of death attributable to cancer among HF patients persisted even when all deaths of unknown cause were attributed to HF. As it is possible that the higher incidence of cancer among patients with HF is due to the fact that these patients are frequently subjected to laboratory and imaging studies, in which some oncological disease can be detected (surveillance bias), a stratified analysis by number of hospitalizations was performed revealing that the relationship of HF with the higher incidence of cancer was maintained.

The second study explores the relationship between cancer and cardiovascular disease in the opposite direction. The database of the Ministry of Health of Alberta, Canada, which provides health coverage to more than 99% of patients in that region, was retrospectively analyzed, and the records were linked with data from clinical laboratories and vital statistics. The study included the information of 4 519 243 Alberta residents between 2007 and 2018, free from cancer diagnosis in the 3 years prior to registry onset. The 224 016 patients with cancer diagnosis between 2007 and 2018 were compared with 4 295 227 who were cancer free. Cancer association in a generic manner and in each of its locations, stages and time since diagnosis (compared with its absence), was evaluated with dif-

ferent endpoints: all-cause mortality, cardiovascular mortality, and incidence (new cases) of acute myocardial infarction (AMI), heart failure (HF), stroke or pulmonary embolism (PE). The relationship was explored through multivariate analysis, adjusting for age, gender, socioeconomic status, distance from the center and treating physician, and 31 comorbidities.

Patients who developed cancer at some point during follow-up were older at baseline (median age 56 vs. 34 years), and with a higher prevalence of women (57% vs. 49%), cardiovascular comorbidities (for example, hypertension 31.7 % vs. 10.7%; diabetes 10.1% vs. 3.6%), and non-cardiovascular comorbidities (including chronic pain 15.1% vs. 7.9% and chronic obstructive pulmonary disease 10.1% vs. 3.5 %). The most frequent cancers were gynecological (20%), genitourinary (19%), gastrointestinal (17%), breast (13%), thoracic (10%) and hematological (9%).

In a median follow-up of 11.8 years and after adjusting for baseline covariates, cancer patients presented a HR of 1.33 (95% CI 1.29-1.37) for cardiovascular mortality, 1.01 (95% CI 0.97-1.05) for AMI, 1.44 (95% CI 1.41-1.47) for stroke, 1.62 (95% CI 1.59-1.65) for HF and 3.43 (95% CI 3.37-3.50) for PE. Among cancer patients, the highest incidences of cardiovascular events and their relationship with location corresponded to cardiovascular death in patients with hematological cancers (3.7 ‰ per year), AMI in patients with genitourinary cancer (2.4 ‰ per year), stroke in patients with cancer of the central nervous system (16.4 ‰ per year), HF in hematological cancers (12 ‰ per year) and PE also among patients with cancer of the central nervous system (16.5 ‰ per year). The greatest increase in risk for cardiovascular mortality, stroke and PE corresponded to central nervous system neoplasms and for AMI and CHF to thoracic and hematological cancer. Results did not differ when patients younger than 50 years, or cancers in situ, were removed from the analysis. There was no difference between men and women. Excess cardiovascular risk was always higher in the first year after cancer diagnosis (with HR for the different events between 1.24 and 8.36) after which it began to decline; but it remained significant for cardiovascular mortality, HF, and PE up to 10 years after diagnosis.

Remarkably, while anemia, kidney failure and chronic obstructive pulmonary disease have a secure place when listing the comorbidities of cardiovascular disease, cancer is systematically left out. As if it were an entity completely divorced from the former. The only situation in which they are considered together is when exploring the cardiotoxicity phenomena of oncological drugs. That is, cancer treatment as generator of heart disease, and heart disease as a limitation for the administration of antitumor medication.

Actually, cancer and cardiovascular disease have a much deeper link, which we are learning to unravel. To begin with, common conditions that favor their concomitant occurrence: aging, obesity, smoking. Low-grade inflammation and neurohormonal activation, present in heart failure, can favor the emergence of cancer, and the specific production of oncogenic factors has been postulated in its context, as well as those that depress cardiac function and prothrombotic factors as a result of cancer. On the other hand, it is clear that there may be a detection bias. In patients with heart failure, periodic evaluations (physical examination, laboratory tests, chest X-rays) can favor the discovery of cancer, although it is no less true that in any case, they promote its early detection, not its generation. Use of diuretics can unmask a prostate cancer;, that of anticoagulants, an intestinal tumor. And the idea remains that certain treatments for cardiovascular disease may be associated with an increased risk of cancer, although it is worth clarifying that until now the targeted agents (statins, digoxin, and angiotensin-converting enzyme inhibitors) have been exonerated by the most thorough studies. In turn, by generating asthenia and reduced exertion capacity, cancer can, on the one hand, favor the detection of cardiovascular disease (if an alternative explanation for the symptoms is sought) or postpone it (if it is decided to attribute the entire condition to the oncological situation). And it is clear that each condition and its treatment can conspire against the proper treatment of the other. Asthenia, digestive intolerance, electrolyte disorders secondary to nausea and vomiting, and hypotension, often lead to the abandonment of specific cardiovascular treatment (diuretics, digoxin, neurohormonal antagonists, other antihypertensive agents). In turn, we have already pointed out how baseline cardiological conditions (low left ventricular ejection fraction) or adverse effects (decreased ejection fraction, ischemic or electrocardiographic phenomena, among others) can hinder or delay cancer treatment. And note that throughout this comment we have said "cancer" when it would be more appropriate to refer to "cancers" as each one, in type and location, is different in terms of repercussion and specific treatment. In this sense, for example, it is striking that the cancer most linked to stroke is that of the nervous system (chance or expression of local paracrine or prothrombotic phenomena?)

The two studies that we are commenting on share a series of virtues: they are population-based, collected from universal records of a large number of patients, with long-term follow-up, and the relationship with the incidence of the disease emerges after performing multivariate analysis or matching by large number of baseline variables of proven biological and epidemiological significance. The observational and retrospective nature of both studies can, of course, be pointed out, which always raises the question of residual confusion (factors not taken into account in the analysis, linked with the supposed independent predictor condition and with the event, which are really responsible for the appearance of the latter). But it is no less true that the number of observations, follow-up time and robustness of the relationships found (with more than

one cancer in heart failure, with different cardiovascular events in patients with cancer) render improbable that a factor not taken into account may dismiss published data.

In conclusion, the association of cardiovascular disease and cancer must always be taken into account so that, the facts that we have been unraveling and the investigation in a timely manner, once embarked on the treatment of the pathology first detected, prevents us from an unpleasant surprise due to the untimely occurrence of the other.

Is a low-sodium diet useful in heart failure? The SODIUM-HF Study

Ezekowitz JA, Colin-Ramirez E, Ross H, Escobedo J, Macdonald P, Troughton R et al. Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial. **Lancet 2022;399:1391-1400.**

Sodium and water retention, and increased total body sodium are essential features of heart failure (HF). The restriction of sodium intake is one of the first indications that every patient with HF receives; but there seems to be no agreement on the daily amount that can be ingested. Some practice guidelines simply state that intake should be limited, but do not clearly quantify the recommended reduction; others do so, but end up suggesting the same restriction in mild hypertension as in heart failure. And, to further complicate matters, the evidence is scarce and not always consistent: although in observational studies a high-sodium intake is associated with a higher risk of hospitalization for heart failure (and, in fact, in our daily practice food transgression is one of the most frequent causes of admission), it is also true that patients with low-sodium intake have greater activation of the renin-angiotensin system; and in randomized studies, all of small sample size, and with different protocols, low-sodium diet has been associated with worse evolution. All of this justified performing the SODIUM-HF study, recently presented at the ACC 2022 congress, whose results have just been published.

SODIUM-HF was a randomized study that included patients with HF in FC II-III, regardless of left ventricular ejection fraction (LVEF) or natriuretic peptide values. Patients had to be treated in accordance with clinical practice guidelines. Patients who consumed less than 1500 mg of sodium daily, who had natremia <130 meq/L or glomerular filtration rate <20 mL/min/1.73 m^2, and those hospitalized for HF in the last month were excluded from the study. In an open-label manner, they were randomly assigned in a 1:1 ratio to the usual treatment for their HF, with dietary advice to restrict sodium intake; or to an intervention branch, in which they were given 6 menus so that each day, at their choice, they would consume a normocaloric diet compatible with most of the usual nutritional indications (15 to 20% protein, 50 to 55% carbohydrates, 25 to 30% fat and 7% saturated fat), and a sodium quantity <1500 mg. The intervention lasted 12 months, and follow-up was extended for an additional 12 months. Sodium intake was assessed by recording what was eaten for 3 days (including 1 weekend day) at baseline, at 6 and 12 months in both groups, and in the intervention arm also at 3 and 9 months to monitor and support adherence to dietary prescription. The food records were analyzed by trained personnel, with a computer program that allowed defining the amount of sodium intake in each case. The primary endpoint was a composite of hospitalization for cardiovascular causes, emergency consultations for the same cause, and all-cause mortality at 12 months after inclusion in the study. Secondary endpoints were the individual components of the primary endpoint at 12 and 24 months, and changes in quality of life assessed with the Kansas Questionnaire (KCCQ), the 6-minute walk distance, and FC. An incidence of the primary endpoint of 25% per year, 30% reduction in the intervention arm and a sample size of 992 patients were estimated to demonstrate this difference, with 80% power and two-tailed $p < 0.05$.

The results of an interim analysis planned for the time when 500 patients with a follow-up of at least 1 year had already been enrolled, and the COVID-19 pandemic that made enrollment and follow-up visits difficult, led to the early termination of the study, when 806 patients, 397 of them in the low sodium diet group, had been enrolled. Median age was 67 years, 67% were men, and 68% had HF of at least 1-year evolution, 33% with hospitalization in that period. Median left ventricular ejection fraction was 36%. Natriuretic peptides were measured in 325 patients, and in those in which NT-proBNP was assessed, its median value was 801 pg/mL. A total of 81% of patients received angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or sacubitril valsartan; 87% beta-blockers and 57% an anti-aldosterone agent. At study onset, median sodium intake in the control arm was 2119 mg daily and 2286 mg daily in the low-sodium diet arm. In the usual care arm, median intake was 2021 mg/day at 6 months, and 2073 mg/day at 12 months (a 4% reduction from baseline). In the low-sodium diet group, the corresponding values were 1649 mg/day at 6 months and 1658 mg/day at 12 months (28% reduction from baseline). The median difference between groups was 415 mg/day at 12 months. There was no significant difference between groups in weight, systolic blood pressure, or calorie or fluid intake. At 12 months, the primary endpoint occurred in 15% in the low-sodium diet arm and 17% in the control arm (HR 0.89; 95% CI 0.63–1.26, p=0.53). All cause mortality occurred in 6% and 4%, hospitalization for cardiovascular causes in 10% and 12%, and a visit to the emergency room in 4% of both groups. None of these comparisons showed a statistically significant difference. There was also no difference in the distance covered in the 6-minute walk. On the other

hand, the probability of improving at least one FC was greater in patients with a low-sodium diet, and the quality of life score was better after 12 months.

The prescription of a low sodium diet is an expression of "common sense" in the treatment of heart failure. As we pointed out, the evidence from observational and randomized studies is controversial, and practice guidelines acknowledge this problem. The 2021 European Society of Cardiology Heart Failure guideline calls for avoiding excessive salt intake (not >5 g daily, that is, no more than 2 g sodium daily), without giving this indication strength of recommendation or grading the evidence. The 2022 AHA/ACC guideline establishes as a 2a recommendation with level of evidence C LD (limited data) avoiding excessive sodium intake to reduce congestive symptoms, without stipulating a defined amount. The SODIUM-HF study is the largest randomized study that has tested the effect of a low-sodium diet in a population with HF. How should its results be read? It is tempting to conclude that the low-sodium diet does not improve the outcome of patients. But… weren't the patients in the control group on a low sodium diet? Let's see: at the beginning of the study, the daily intake of sodium in this group was 2.1 g, very close to the recommendation of the European Society guideline, and to some of the examples cited by the AHA/ACC guideline. That is, the prescription of sodium restriction was already made in the control group patients; and they maintained that intake until the end of the study (median of 2.07 g of sodium per day). By comparison, patients in the intervention arm started at a median of 2.28 g per day, and after 12 months reached 1.66 g per day. The difference between both branches, of only 415 mg/day, exempts us from further comment. Can anyone expect significant differences in the evolution of 2 groups of patients, due to the mere difference in daily sodium intake of just over 400 mg? Above all, with such a high use of neurohormonal antagonists, and, despite a depressed ejection fraction, with natriuretic peptide values (when measured) similar to those seen in studies of patients with preserved left ventricular ejection fraction. In fact, the annual incidence of events in the control arm was well below expectations, and was even lower than those in the treatment arm of several clinical trials in patients with reduced ejection fraction. Very well treated patients, low event rate, an intervention that had actually been already implemented in the control arm, and had only slightly greater implementation in the treatment arm, render not unexpected results. As a study merit we must cite its pragmatic approach (menus so that patients can choose what to cook, instead of delivering prepared meals; assessment of intake from records, instead of, for example, the measurement of urinary sodium) that facilitated its implementation. As a minor criticism, it is noteworthy that diuretics are not mentioned when baseline medication is reported, when it is precisely a study on sodium restriction and its effects. In conclusion, we do not believe that SODIUM-HF fully answers the question that motivated its performance. We suppose that it would have been another story if more compromised patients had been included, with more congestion, with a higher incidence of events and, fundamentally, with higher salt intake in daily life.

Coronary flow reserve: a meta-analysis confirms its prognostic relevance

Kelshiker MA, Seligman H, Howard JP, Rahman H, Foley M, Nowbar AN et al. Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis. **Eur Heart J 2022;43:1582-1593.**

Coronary flow reserve (CFR) describes the relationship by which this flow can increase in response to exercise, stress or vasodilation of the microcirculation. Its reduction reflects the severity of coronary heart disease and the pathological processes affecting from the epicardial territory to the distal coronary arteries, small vessels and capillaries. Different diagnostic methods can be used to measure it, either non-invasively [echocardiography, positron emission computed tomography (PET) and cardiac magnetic resonance imaging (CMR)], or invasively, through Doppler flow velocity determination, and thermodilution. Guidelines recommend its assessment in conditions of suspected microvascular angina, but it is true that CFR is decreased in several cardiovascular diseases. A recently published meta-analysis considers all studies which, under slightly different names (CFR, coronary flow velocity reserve, myocardial blood flow reserve, myocardial flow reserve, quantitative myocardial perfusion reserve) and using in each case one of the above-mentioned methods, explored the relationship between CFR and prognosis, specifically all-cause mortality and major adverse cardiovascular events (MACE). The studies which evaluated the index of microcirculatory resistance associated with fatal outcomes were separately analyzed.

The meta-analysis included 79 studies with 59 740 persons, most with proven or suspected ischemic heart disease (58 studies, 57 613 patients). Heart failure (7 studies, 647 patients), heart transplantation (8 studies, 784 patients) and type 2 diabetes without symptoms of coronary heart disease (3 studies, 541 patients) were also represented in the meta-analysis. Fifteen studies were identified including 10 848 patients with isolated microvascular coronary dysfunction (abnormal CFR with coronary angiography without obstructive disease, or a negative stress test for ischemia, without history of heart transplantation, cardiomyopathy or aortic stenosis). Mean age was 64.7 years, 45.1% were women, 71.2% had hypertension and 26.8% diabetes.

Mean follow-up was 35.7 months, with a wide range (1-150 months). The diagnostic methods were echocardiography in 39 studies, PET in 18, CMR in 4 and invasive measurement in 18. Most studies di-

vided patients into normal or impaired CFR, from a prespecified cut-off point, with a median of 2 (with lower values corresponding to altered CFR). Mean normal or abnormal CFR in all studies was 2.70±0.6 and 1.70±0.32, respectively. All-cause mortality was clearly higher in patients with abnormal CFR (in 16 studies reporting it, HR 3.78, 95% CI 2.39-5.97), same as the incidence of MACE (60 studies, HR 3.42, 95% CI 2.92-3.99). The presence of abnormal CFR implied worse evolution in all the conditions considered (acute and chronic coronary syndromes, aortic stenosis, heart failure, transplantation, systemic diseases as sepsis and collagen diseases), though with high heterogeneity in many cases. In studies of patients with isolated microvascular dysfunction, an abnormal CFR was also associated with excess risk for mortality and MACE. Adjusting for age, sex and coronary risk factors did not change the relationship of reduced CFR and poor prognosis. The prognostic value of abnormal CFR for mortality was not very different between studies with invasive measurement or echocardiography (HR 4.98 and 4.19, respectively) and somewhat less in the case of PET studies (HR 2.35).

Other studies considered excess risk for each 0.1 change up to 1 in CFR assessment. In the meta-analysis of studies reporting evolution, each 0.1 unit decrease in CFR was associated with 16% excess risk of mortality (95% CI 4-29%) and 8% risk of MACE (95% CI 4-11%). Eight separately analyzed studies in which the microcirculatory resistance index was invasively measured confirmed the prognostic value of its alteration, with 15% excess risk of MACE, although with variable results according to the condition considered.

The relevant point of this study is the demonstration of the prognostic value of decreased CFR, beyond angina with normal coronary arteries, where its assessment is most frequent and recommended. Different entities where decreased CFR may be suspected from a pathophysiological point of view (due to inflammatory substrate, hypertension, dyslipidemia, diabetes, heart failure with neurohormonal activation, heart transplantation, and aortic valve disease with or without left ventricular hypertrophy) but is usually not explored, confirm that its presence entails a poor outcome, not only from a higher incidence of angina or ischemia, but from greater occurrence of hard endpoints, such as AMI and mortality, with 3 and 4-fold excess risk in both cases! One condition, then, of enormous clinical value. And it is important to bear in mind that its repercussion goes above the definition and method. Regardless of which, reduced RFC indicates patients with worse vital prognosis. The question now is, why.

It is clear that microvascular dysfunction implies greater risk of ischemia, indisputable cause of adverse events. But decreased CFR, is only a risk factor or is also a risk marker? It would have been interesting to know in the meta-analysis the baseline characteristics of patients with normal and abnormal CFR. We would surely have seen greater prevalence of risk factors among the latter or, among those with the same underlying condition, greater severity. Therefore, the multivariate analysis that could indicate the prognostic weight of CFR per se, adjusted by the rest of the conditions is missed. Heterogeneity in the always present association of decreased CFR with evolution, of different magnitude according to the condition, could imply greater or lower pathophysiological weight, or being sometimes more a risk marker than a factor, and sometimes the opposite. In any case, this great analysis seems to suggest that, perhaps, CFR assessment could be extended to other pathologies where it is usually not performed. Nevertheless, what remains unclear is whether any specific treatment, beyond that of predisposing factors, can change the adverse prognosis.

Coronary artery bypass grafting vs. percutaneous coronary intervention in three-vessel or left main coronary artery disease: does the number of arterial grafts influence the results? A subanalysis of the 10-year follow-up of the SYNTAX study

Davierwala PM, Gao C, Thuijs D, Wang R, Hara H, Ono M et al. Single or multiple arterial bypass graft surgery vs. percutaneous coronary intervention in patients with three-vessel or left main coronary artery disease. **Eur Heart J 2022;43:1334-1344**.

As we will recall, the SYNTAX study compared percutaneous coronary intervention (PCI) with drug-eluting stent (DES) vs. coronary artery bypass grafting (CABG) in patients with left main coronary artery disease (LMCAD) or three-vessel disease (3VD) . Overall, at the 12-month follow-up, CABG was associated with a lower incidence of a composite endpoint of death, nonfatal acute myocardial infarction (AMI), nonfatal stroke, and need for repeat revascularization. The difference was based fundamentally in the need for reintervention, with excess risk of stroke in the CABG arm. Taking into account the complexity and extension of the lesions evaluated, the analysis showed similar results between both interventions, with low (≤22) or intermediate (23-32) SYNTAX score values. The difference in favor of CABG was evident with SYNTAX score values ≥33 . Similarly, in patients with 3VD, results with CABG were superior to PCI, with a lower incidence of the primary endpoint, at the expense of reduced rate of repeat revascularization, while in patients with LMCAD lesions there was no difference in the incidence of this endpoint, with a greater need for reintervention in the PCI arm, but higher rate of stroke in the CABG arm. In the 5-year follow-up, the lower incidence of the primary endpoint was maintained in the CABG arm, due to less need for revascularization, but also due to a lower incidence of non-fatal AMI. The differences occurred in patients with 3VD and intermediate or high SYNTAX score; however, in patients with 3VD and a low score, or in patients with LMCAD, no significant difference was found. In the 10-year follow-up (Extended SYNTAX,

or SYNTAXES study) there was an overall trend towards lower mortality with CABG, due to a significant result in its favor in patients with 3VD, with no difference in patients with LMCAD. This means that in patients with 3VD, CABG was associated with a better prognosis than PCI with DES, being more marked as follow-up was longer.

An analysis that has just been published delves deeper into the difference between both study arms. The SYNTAX study initially included 1800 patients, 1766 of which were effectively treated with CABG or PCI. In this publication, patients who exclusively received saphenous venous grafts (VG) were excluded; 1743 patients were considered, 901 (51.7%) treated with PCI, and 842 (48.3%) with CABG. Among the latter, 532 (30.5% of the total) received only 1 arterial graft (1AG) and the rest VG, and the remaining 310 (17.8% of the total) were treated with at least 2 arterial grafts (≥2AG), with or without additional VG. Compared with PCI patients, patients with 1AG presented a slightly lower left ventricular ejection fraction (LVEF) (mean 56% vs. 59%) and a slightly higher EuroSCORE, with median (interquartile range) of 4 (2-6) vs. 4 (2-5), while those with ≥2AG had a somewhat higher LVEF (mean 61%) and a lower EuroSCORE, 3 (1-5). There were no differences between groups regarding age, or the SYNTAX score; the number of lesions was similar between PCI and 1AG groups (mean 4.3) and somewhat higher in the ≥2AG group (mean 4.6). There was also no significant difference in the type of injury: isolated LMCAD in PCI, 1AG and ≥2AG groups, 4.8%, 5.3% and 4.5%, respectively; 3VD without LMCAD in 59%, 55% and 64%, and combined conditions in the rest.

In the PCI arm, a median of 4 stents per patient was used. In the CABG arm, there was no difference in the average number of grafts (2.8) between 1AG and ≥2AG groups. In the 1AG group, the arterial graft used was the left internal mammary artery in 99.6% of cases, and VG in 98.3% of cases. In the ≥2AG group, the left internal mammary artery was used in 98.4% of cases; the right mammary artery in 72.9%, both mammary arteries in 71.3% and the radial artery in 38.1% of cases. Venous grafts were also used in 46.1% of patients. Complete revascularization was achieved in 55.7% of patients with PCI, 66% in the group with 1 AG (p vs. PCI, <0.001) and 61.9% with ≥2AG (p vs. PCI 0.065). Off-pump surgery was used in 12.8% of patients with 1AG, and 19.7% with ≥2 AG.

At a median follow-up of 11.9 years, all-cause mortality was 33.9% in the PCI arm, 32.9% in the 1AG group, and 22.6% in the ≥2AG group (adjusted p value <0.001). There was no significant difference between PCI and 1AG, but the risk was significantly lower with ≥2AG (adjusted HR 0.66, 95% CI 0.49-0.89). In a subsidiary analysis using a propensity score, with patients matched according to covariates associated with greater or lesser probability of receiving 1AG or ≥2AG, regardless of the treatment they had actually received, the observed differences were maintained. Among patients with LMCAD lesion, there was no significant difference in mortality between patients with PCI, 1AG, or ≥2AG; In contrast, in patients with 3VD, the risk of mortality was significantly lower for CABG, with HR with respect to PCI of 0.68 for 1AG and 0.55 for ≥2AG. Interestingly, the differences between CABG and PCI were seen in patients without diabetes, not in those with this pathology.

Based on the results of the SYNTAX study, corroborated by later trials and meta-analyses, it is an accepted criterion, and clinical practice guidelines make it explicit, that CABG and PCI have similar indications in patients with LMCAD when the SYNTAX score is low. In patients with an intermediate score, there is a slight preference for CABG (indication I for CABG, IIa for PCI), while in patients with a high SYNTAX score, there is a precise indication of CABG. Among patients with 3VD, only in those without diabetes and low SYNTAX score, both procedures are even; in the rest (without diabetes with an intermediate or high score, or with diabetes) the indication is again CABG.

The analysis here presented indicates that, when considering patients in the SYNTAX study globally, the advantage of CABG over PCI was specifically attributable to the use of more than one arterial graft; 1 single arterial graft supplemented by VG did not offer differences with PCI. And, in fact, there was an interaction between the number of AG and the benefit obtained with respect to PCI: mortality when 3 myocardial territories had to be revascularized was 34.2% when PCI was used; 31.3% with 1 AG and 2 VG, 23.1% with 2 AG and 1 VG, and 21.9% with 3 AG. The advantage of AG over VG is usually attributed to the release of vasoactive substances, including nitric oxide and anti-inflammatory and antithrombotic mediators, by the arterial endothelium, in addition to the ability to better accommodate distal coronary flow, reducing turbulence. The results then suggest a dose-response gradient: the greater the number of AG, the better the prognosis, specifically in 3VD, and fundamentally with more complex lesions. Should these results inevitably guide conduct? The decision to use 1 or more AG was not casual: chance determined whether the patient received CABG or PCI, but the surgical strategy depended on the intervening surgeon. Therefore, this analysis is still an observational study in the context of a randomized clinical trial. It is possible that, beyond the multivariate analysis, there are certain conditions related to the choice of procedure that influences the evolution, from patient baseline characteristics to the surgical teams involved. Can we presume differences in experience, skills, context or means between the teams that use more than one arterial conduit with respect to those that continue with the conventional treatment of internal mammary artery and vein? Could the somewhat greater use of surgery without extracorporeal circulation in the group with ≥2AG have had an

influence? In general, all observational analyses consider patient characteristics; it is much more difficult to take into account the centers, or the intervening physicians, even when different interventions are carried out by operators that also differ.

In summary, this analysis of the long-term follow-up of the SYNTAX study suggests an advantage in the treatment of 3VD with CABG with more than 1 arterial conduit compared with PCI (not so in the case of LMCAD); it seems then that, if possible, this should be the behavior of choice. The fact that patients have been included until 2007 (when much progress has been made since then in the field of PCI, but also in that of CABG), and that data of the comparison between CABG (with 1 AG or ≥2 AG) vs. PCI are presented, but not a direct comparison between both surgical arms, are two conditions that may limit the power of the conclusions