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**Is an intensive vasodilation strategy effective in the context of acute heart failure? The GALACTIC trial**

Kozuharov N, Goudev A, Flores D, Maeder MT, Walter J, Shrestha S, et al. Effect of a Strategy of Comprehensive Vasodilation vs Usual Care on Mortality and Heart Failure Rehospitalization Among Patients With Acute Heart Failure: The GALACTIC Randomized Clinical Trial. *JAMA*. 2019;322:2292-302. <https://doi.org/10.1001/jama.2019.18598>

The pathophysiology of acute heart failure (AHF) is complex, with peripheral vasoconstriction, redistribution of extracellular volume, acute fall in contractility, and neurohormonal and inflammatory activation among others. The agents commonly used for its treatment are diuretics, vasodilators and inotropic drugs. In the context of acute pulmonary edema, treatment with vasodilators and non-invasive ventilation has revealed to be superior to high doses of diuretics. Although this evidence has been extrapolated to the rest of the signs and symptoms with which AHF presents, there is no firm proof in this regard. In fact, in randomized trials with different vasodilators (serelaxin, ularitide, nesiritide) it has not been possible to demonstrate their superiority over conventional treatment. Nonetheless, the idea that an intensive vasodilator treatment can ensure better evolution persists in the pathophysiological interpretation.

The GALACTIC trial tested this hypothesis. It included patients over 18 years of age hospitalized for AHF (clinically defined by the presence of FC III-IV dyspnea and BNP  $\geq 500$  pg./ml or NT pro-BNP  $\geq 2000$  pg./ml), in all the range of left ventricular ejection fraction (LVEF). Patients with acute coronary syndrome, systolic blood pressure (SBP)  $< 100$  mm Hg or creatinine  $> 2.8$  mg/dl were excluded. Patients were randomly assigned to receive conventional treatment (with the choice of drugs to be used by the attending physician) or an intensive vasodilator treatment defined on SBP levels and with previously established daily increments. In this branch, aerosol or sublingual nitrites were used on the first day, followed by the administration of transdermal nitrites (with increasing doses according to SBP) and hydralazine. On the second day, transdermal nitrites (with increasing doses according to SBP), hydralazine, and treatment with angiotensin converting enzyme (ACEI) inhibitors, angiotensin II receptor blockers (ARB) or sacubitril valsartan (SV) were administered. On the third day a gradual decrease in the dose of nitrites began and the dose of ACEI, ARB or SV was increased, all in accordance with the values of SBP, and this management continued until discharge or on day 7, whichever came first. The aim in the intensive branch was

to reach the dose of ACEI, ARB or SV recommended in large clinical trials. The primary endpoint of the study was all-cause mortality or rehospitalization due to heart failure at 180 days. Secondary endpoints were the components of the primary endpoint, plus evolution of SBP and dyspnea. As an open-label study, the endpoint adjudication was carried out by researchers blinded to the therapy received. In the calculation of the sample size, the occurrence of the primary endpoint was expected in 48% of the patients in the usual treatment branch, and a 20% reduction in the intensive treatment branch. Three hundred and eighty-five patients per group was calculated to achieve a power of 80% and an alpha error of 0.05; taking into account a potential loss of 1 to 2% in the follow-up, a sample size of 785 patients was defined. The analysis was done by intention to treat.

Between 2007 and 2018, 788 patients were included in 10 centers of 5 countries, of which 781 were eligible for the analysis, 382 of them in the intervention branch and 399 in the usual treatment branch. Median age was 78 years, 37% were women; median BP at admission was 130/75 mmHg, and median LVEF was 36%. Between days 1 and 5 the dose of nitrites was significantly higher in the intensive treatment branch; the same occurred with the dose of hydralazine between days 1 to 3. In contrast, the dose of diuretics was lower (on day 4 the average dose of furosemide or equivalent was 80 mg in the usual treatment branch and 60 mg in the intensive treatment branch). Therefore, weight loss was slower in the intensive treatment branch. At 180 days, the target dose of ACEI, ARB or SV was attained by 22% of patients in the intensive treatment branch and by 16% in the usual treatment branch ( $p=0.04$ ). The incidence of the primary endpoint at 180 days was 30.6% in the intensive treatment branch and 27.8% in the usual treatment branch (HR 1.07; 95% CI 0.83-1.39,  $p=NS$ ), and the mortality rate was 14.4% and 15.3%, respectively ( $p=NS$ ). There was no significant difference in dyspnea relief or in the decrease of pro-BNP NT; SBP was only significantly lower in the intensive treatment branch on day 2, but not on day 1 or from day 3 onwards. In the intensive treatment branch, the incidence of headaches (26% vs. 10%), dizziness (15% vs. 10%), hyperkalemia (11% vs. 7%) and hypotension (8% vs. 2%) were higher.

*The ASCEND HF (nesiritide), TRUE HF (ularitide) and RELAX (serelaxin) studies had already shown that the use of specific vasodilators does not improve the prognosis of AHF. The GALACTIC study tested the vasodilators that we use every day, and suggested that an early and intensive use of them could be beneficial. This strategy, which implicitly generated a lower use*

*of diuretics, was not successful, and was even accompanied by a higher incidence of adverse events. And perhaps because it was precisely accompanied by less use of furosemide and similar drugs, there was not even variation in dyspnea or in the level of natriuretic peptides. Diuretic therapy, very rejected a few years ago, seems to gain ground again in achieving the primary objective, the relief of congestion. Are the results of the studies we have cited, including the GALACTIC study, the definitive proof of vasodilator failure? We do not believe so, because AHF is a proteiform condition, with varied etiology, pathophysiology and forms of presentation. Can we assume the same usefulness for vasodilators in a patient with chronic heart failure, low LVEF, poor adherence to diet and a considerable hydrosaline overload (in which diuretics appear as the preferred choice) than in a patient with preserved LVEF, hypertensive acute lung edema or acute mitral regurgitation, where vasodilators seem to be the best option? Unfortunately, we do not have a subgroup analysis according to etiology, and also the number of patients does not allow carrying out some other analyses with enough power. It does seem that, globally, an intensive vasodilator strategy is not a panacea (in the sense of universal remedy) for AHF. A final comment has to do with the dose reached for ACEI, ARB or SV: only 22% of the intensive treatment branch achieved the goal. Having excluded patients with low filtration rate, and with a mean SBP of 130 mmHg, therapeutic inertia seems to be a reason to consider.*

### **Usefulness of abdominal aortic aneurysm screening in asymptomatic persons over 50 years of age.**

#### **Analysis of the evidence.**

Guirgis-Blake JM, Beil TL, Senger CA, Coppola EL. Primary Care Screening for Abdominal Aortic Aneurysm: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2019;322:2219-38. <https://doi.org/10.1001/jama.2019.17021>

An abdominal aortic aneurysm (AAA) is a dilation  $\geq 3$  cm of the abdominal aorta. To avoid the catastrophic consequence of rupture, endovascular surgery or repair is indicated when the diameter reaches 5.5 cm dilation. The risk factors for the development of AAA are age, male gender, smoking and family history of the disease. In 2014, after a thorough analysis of the available literature, the United States Preventive Services Task Force (USPSTF) recommended screening AAA in men aged 65-75 years who had smoked at some stage of their lives, and with lower indication strength, in men of the same age who had not smoked. It was advised not to seek AAA in non-smoking women aged 65-75 years and it was established that there was scarce evidence to do the same in smoking women of the same age. To update these recommendations, the USPSTF conducted a search of new studies reporting evidence on the subject published between 2013 and

2018. Nine new studies (4 randomized, 2 cohort and 3 registries) were found, which were added to the 24 studies (13 randomized, 8 cohort, 1 case control and 2 registries) that were the basis of the 2014 recommendations.

Four randomized studies (n=124,929) served to answer the question of whether one screening in asymptomatic subjects  $\geq 50$  years improves evolution. A significant reduction in mortality associated with AAA was demonstrated at 12 to 15 years of follow-up (OR 0.65, 95% CI 0.57-0.74). There was also a significant reduction in the risk of rupture with screening (OR 0.62; 95% CI 0.55-0.70). The benefit was demonstrated specifically in men, with 305 men needed to screen to prevent one AAA death. It could not demonstrate a reduction in all-cause mortality (OR 0.99, 95% CI 0.98-1), nor was there evidence of positive results in women, although their number was very low and the prevalence of AAA much lower.

Another question that needed to be answered was whether in patients in whom the initial screening had not shown AAA, a new screening every 1 to 5 years would have a favorable effect. Seven cohort studies and a control case showed very low AAA-related mortality (<3% in 5 to 12 years). In any case, the data was heterogeneous and did not allow a definitive conclusion to be drawn.

Routine screening was associated with a higher rate of AAA surgery: five studies showed 1.1% to 2.9% surgery rate in those undergoing monitoring vs. 0.6% to 1.4% in the control group (OR 1.75; 95% CI 1.65-1.90). This means an excess of 8 elective surgeries for every 1000 men studied routinely.

Four studies revealed the effect of early intervention in AAA of 4 to 5.4 cm dilation, with respect to strictly monitoring with control every 6 months and intervention in case of accelerated growth ( $\geq 1$  cm/year), onset of symptoms or if AAA reached a size of 5.5 cm. No difference between the two strategies could be evidenced.

Smoking indicated a higher risk of mortality associated with AAA and all-cause mortality; age did not seem to have a distinctive effect and female gender appeared associated with lower prevalence, but higher operative mortality.

*This review of the available evidence suggests that it makes no sense to lower the traditionally cited screening age for AAA from 65 years to 50 years. Although the incidence of associated mortality and rupture decreases, this does not translate into an improvement in the overall prognosis, and it also implies an excess of programmed AAA surgeries. Other questions (usefulness of new studies if the first one was negative, logic of intervening in smaller AAA) cannot be answered at the moment due to lack of sufficient evidence. We may think that perhaps it would be more effective to comply strictly with the screening measures in the population at greater risk (men >65 years of age smoking at some stage of their life), and, of course, to continue with the*

*campaigns and measures that promote a significant reduction in smoking and strict control of blood pressure values.*

### **Asymptomatic very severe aortic stenosis: does surgery improve the prognosis?**

Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, et al. Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis. *N Engl J Med.* 2020;382:111-9. <https://doi.org/10.1056/NEJMoa1912846>

Severe aortic stenosis (AS) is defined as that in which peak aortic velocity is  $>4$  m/sec., corresponding to an average aortic gradient  $>40$  mmHg. Under these conditions the aortic valve area is usually  $<1$  cm<sup>2</sup> or  $<0.6$  cm<sup>2</sup>/m<sup>2</sup>. If the condition is accompanied by symptoms, the indication of valve replacement (AVR) is clear, because they indicate a poor prognosis in the short and mid-term. Traditionally, it has been considered that when severe AS is asymptomatic, expectant behavior can be adopted. This is due to the fact that in a truly asymptomatic severe AS, the annual risk of sudden death does not exceed 1%, a percentage that is lower or matches the risk of mortality associated with the AVR procedure. However, risk markers have been recognized in asymptomatic severe AS, such as left ventricular ejection fraction (LVEF)  $<50\%$ , elevation of natriuretic peptides or the development of pulmonary hypertension that do not admit another cause, or an abnormal stress test due to the onset of symptoms or the drop in blood pressure, which justify earlier invasive management. Similarly, practice guidelines recommend replacement when severe asymptomatic AS accompanies another cardiac condition that requires surgery. Another situation in which AVR is recommended is when asymptomatic AS is very severe (with peak velocity  $>5$  to  $5.5$  m/sec). It is worth noting that in all these cases the recommendation is B, based on cohort studies, or C, derived from expert consensus, and that there is no firm evidence arising from randomized studies. A Korean study is now considering a progress in the surgical indication of asymptomatic advanced AS.

The RECOVERY trial was an open-label, randomized, parallel group study, which included patients between 20 to 80 years of age with very severe AS, defined by a valve area  $\leq 0.75$  cm<sup>2</sup>, with peak velocity  $\geq 4$ ,  $5$  m/sec or mean transvalvular gradient  $\geq 50$  mmHg. Patients should be asymptomatic for angina, dyspnea or syncope, with LVEF  $\geq 50\%$ , and should not present aortic regurgitation or significant mitral valve disease. Patients with previous cardiac surgery were excluded. Patients with nonspecific symptoms were subjected to a stress test, and if positive, they were also excluded. Participants were randomly assigned to AVR (which should be carried out within the indicated months) or medical follow-up, until the onset of symptoms or risk markers led to the intervention. The primary endpoint was a composite of surgical mortality and

cardiovascular mortality at follow-up (up to 4 years after the last inclusion). It was considered that, with a power of 80% and a p value  $<0.05$ , 144 patients would be necessary to demonstrate a primary endpoint incidence of 16% in the conservative treatment group and 2% in the early surgery group. The primary analysis was done by intention to treat.

Among a total of 273 patients recruited for the study between 2010 and 2015, 145 were randomly assigned as follows: 72 to the surgical group and 73 to the conservative group. Mean age was 64.2 years, 49% were men and mean LVEF was 64.8%. The etiology of AS was bicuspid valve disease in 61% of patients, degenerative disease in 33% and rheumatic disease in 6%. Mean valve area was  $0.63 \pm 0.09$  cm<sup>2</sup>, with a mean left ventricular outflow tract velocity of  $5.1 \pm 0.5$  m sec.

In the 72 patients assigned to early surgery, this was carried out after a median of 23 days post randomization. The AVR was performed with a mechanical valve in 50% of cases, and with a biological valve in the other 50%. There was no operative mortality. In the 73 patients of the conservative group, AVR was necessary at follow-up (at a median of 700 days) in 53 patients (74%), in 52 cases by surgery and in one case by percutaneous implantation. In 9 of these cases the procedure was urgent. There was also no operative mortality in this group.

Median follow-up was 6.2 years in the early surgery group and 6.1 years in the conservative group. Cardiovascular mortality was 1% in the early surgery group and 15% in the conservative group (HR 0.09; 95% CI 0.01-0.67), which implies treating 20 patients to prevent one cardiovascular death in 4 years of follow-up. The cumulative incidence of cardiovascular mortality at 4 years was 1% vs. 6%, and at 8 years 1% vs. 26%, in the early AVR group and the conservative group, respectively. The corresponding incidence of all-cause mortality was 7% vs. 21% (HR 0.33; 95% CI 0.12-0.90,  $p=0.033$ ), with values of 4% vs. 10% at 4 years and 10% vs. 32% at 8 years. The incidence of hospitalization for heart failure was 0% in the early AVR group vs. 11% in the conservative treatment group.

After randomization, 2 patients crossed from the conservative group to early surgery, and 4 in the opposite sense. A per protocol analysis, considering patients according to the treatment actually received, showed similar results to the intention-to-treat analysis.

*The RECOVERY study has undisputable merit: it is a randomized study. Before so much observational recommendation based on case-control or cohort studies, we are here faced with a randomized intervention study. Another point of interest is that precisely the cases in which better evolution is expected with surgery, according to the cited observational studies (low LVEF, natriuretic peptide elevation, positive stress test), are excluded. We are then in principle before cases in which expectant behavior is feasible. In almost half of the cases transvalvular velocity is less than 5 m/sec*

which many consider surgical indication. And the difference in evolution is striking, with much lower cardiovascular and all-cause mortality that extends to 8 years. This coincides with the lower incidence of heart failure. It is remarkable that surgical mortality is zero, not only in the scheduled surgeries of the early intervention group, but also in the scheduled and emergency surgeries of the conservative group, in which since they were carried out a median of almost 2 years later, worse baseline conditions were to be expected.

Among the limitations of the study we can mention that the population is undoubtedly selected: they are young patients, with low surgical risk (average EuroSCORE of 0.9%); therefore, the indication for surgery can be easily performed. The stress test was not done in all patients: were there oligosymptomatic patients within the population considered? The number of patients is still low to make a definitive indication or to promote changes in the practice guidelines, but it certainly represents an important step in this regard. And a question that will certainly be evaluated in future studies: does the observation extend to percutaneous aortic valve implantation in patients such as those considered in the RECOVERY study?

### Colchicine in acute myocardial infarction; in search of a new indication

Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med.* 2019;381:2497-505. <https://doi.org/10.1056/NEJMoa1912388>

Inflammatory etiology plays a fundamental role in the development of atherosclerotic disease and different therapies have been explored in this regard. In the CANTOS randomized study, canakinumab, a monoclonal antibody that inhibits interleukin 1, showed a 15% decrease in the incidence of cardiovascular events but also generated excess fatal infections. On the other hand, its high cost excludes the possibility of using it regularly in the treatment of coronary heart disease. On the other hand, in the CIRT study, methotrexate, another anti-inflammatory agent, was not effective in reducing events.

Colchicine is a potent drug that inhibits tubulin and the generation of microtubules in the inflammatory response, and probably adhesion molecules. It is used regularly in the treatment of gout, familial Mediterranean fever and for the past years, pericarditis. In a non-randomized study with 532 patients, its use was associated with reduction in the incidence of cardiovascular events. This led to the design of the COLCOT study, a randomized, multicenter, double-blind, placebo-controlled trial that tested the use of colchicine in this context.

It included patients with myocardial infarction (AMI) within the previous 30 days, who had completed any planned percutaneous revascularization procedure and were treated according to standards, includ-

ing intensive use of statins. Exclusion criteria were severe heart failure, left ventricular ejection fraction (LVEF) <35%, stroke in the previous 3 months, type 2 AMI, coronary bypass graft surgery, planned or performed within the 3 previous years, history of non-cutaneous cancer in the 3 previous years, inflammatory bowel disease or chronic diarrhea, neuromuscular disease or a persistent CPK value greater than three times the normal upper limit (unless due to AMI), clinically significant hematologic abnormalities, serum creatinine greater than twice the normal upper limit, severe liver disease, drug or alcohol abuse, current or expected long-term use of glucocorticoids, and history of colchicine hypersensitivity.

The primary endpoint was a composite of cardiovascular death, resuscitated cardiac arrest, AMI, stroke, or urgent hospitalization for angina leading to coronary bypass graft surgery. Secondary endpoints were the components of the primary endpoint; a composite of cardiovascular death, resuscitated cardiac arrest, AMI, stroke and overall mortality. There were also additional pre-specified exploratory endpoints, which included the variation in high sensitivity C-reactive protein (CRP) levels between treatment onset and 6 months, and the change in white blood cell count since treatment onset to 12 months.

It was estimated that with a sample size of approximately 4,500 patients randomly assigned to colchicine or placebo (2,250 patients in each group), 301 patients in which the primary endpoint occurred would be necessary to demonstrate with 80% power and  $p=0.05$  an event reduction of 27% (HR 0.724) in the colchicine group.

An event rate of 7% was estimated in the placebo group at 24 months, with a recruitment period of 18 months and a minimum follow-up of 24 months, with an annual loss of 1%.

Between 2015 and 2018, 4,745 patients were included in the study (2,366 randomized to the colchicine group in doses of 0.5 mg daily, and 2,379 to placebo). Mean age was 60 years and 81% were men; 98 to 99% were medicated with aspirin and statins and almost 90% with beta blockers. In 93% of cases, a percutaneous revascularization procedure was performed. The randomized allocation was carried out at an average of 13.5 days post AMI. Median follow-up was 22.6 months, during which the primary endpoint occurred in 5.5% of patients in the colchicine group, and 7.1% in the placebo group (HR 0.77; 95% CI 0.61-0.96;  $p=0.02$ ). When considering the components of the primary endpoint, there was only a significant difference for stroke (HR 0.26; 95% CI, 0.10-0.70) and urgent coronary revascularization (HR 0.50; 95% CI, 0, 31-0.81). There were no differences in cardiovascular mortality, AMI, resuscitated cardiac arrest or overall mortality (1.8% in both groups).

Baseline and 6-month CRP measured in a small subgroup of patients showed decreased levels in both groups. Adjusting for changes in the placebo group there was no significant decrease in the colchicine

group. Similarly, there were no differences in the values of white blood cells, in the incidence of gastrointestinal adverse events (between 17 and 18% in both groups) or in the incidence of diarrhea, whereas nausea was slightly greater with colchicine (1.8% vs. 1%). The incidence of pneumonia was also higher with colchicine (0.9% vs. 0.4%,  $p = 0.03$ ).

*The COLCOT study shows some benefit with the use of colchicine in a group of AMI patients excellently treated, which could imply a boost for anti-inflammatory therapy in the context of atherosclerotic disease. We say "a certain benefit" because it reduces the incidence of stroke and urgent revascularization, but does not achieve a reduction in mortality, AMI, stroke or total mortality, nor in leukocyte or PCR. So, what is the mechanism of action? Can we postulate an anti-inflammatory effect? Is it perhaps a restricted effect that fails to reduce the incidence of hard endpoints? In the presence of revascularization and high rate of aspirin, beta blockers and statins, is the inflammation antagonism contribution small? Until these questions are answered by future studies, we see the COLCOT study as an initial step, but not as support for colchicine addition to the usual treatment of patients with coronary heart disease.*

### **Has the implementation of the Fourth Definition of Acute Myocardial Infarction changed the treatment or evolution of patients with myocardial injury or infarction? An analysis of the High-STEACS study**

Chapman AR, Adamson PD, Shah ASV, Anand A, Strachan FE, Ferry AV, et al. High-Sensitivity Cardiac Troponin and the Universal Definition of Myocardial Infarction. *Circulation*2020; 141: 161-71. <https://doi.org/10.1161/CIRCULATIONAHA.119.042960>

The Fourth Universal Definition of Acute Myocardial Infarction (AMI) establishes the use of high sensitivity cardiac troponin for its diagnosis. Values above the 99th percentile diagnose myocardial injury. It can be acute (when increase or decrease is verified in consecutive measurements, or chronic (when the elevation is persistent, with variation <20%). When the injury appears in the clinical context of acute myocardial ischemia (with at least one clinical manifestation, ECG, imaging study or demonstration of thrombus in coronary angiography), the diagnosis of AMI is made. Type 1 AMI corresponds to the condition due to atherosclerotic disease, with plaque disruption. Type 2 AMI is secondary AMI, in which the injury appears as a consequence of an imbalance between the provision and the demand of myocardial O<sub>2</sub>, excluding coronary thrombosis, and with at least one of the aforementioned manifestations of ischemia. Type 3 AMI is the one that causes sudden death, and in which troponin is often unable to be dosed. Type 4 AMI is associated with an angioplasty revascularization procedure. It may be 4a when it occurs in the context of an angioplasty (with an increase of >5 times the normal upper limit), 4 b (when it occurs in the context of acute

stent thrombosis) or 4 c (in the context of restenosis). Type 5 AMI is the one that occurs as a complication of myocardial revascularization surgery. The Fourth Definition has served to highlight the use of high sensitivity troponins, which increase diagnostic certainty. It has clearly established the different categories of AMI, and above all it has clearly differentiated the difference between the concept of AMI and injury, and emphasized the value of the latter in cardiac and non-cardiac conditions. But has it significantly changed the therapeutic strategies and prognosis of affected patients? A sub-analysis of the High STEACS study questions this issue.

This randomized controlled study was conducted in 10 centers of Scotland. Consecutive patients admitted to the emergency department with suspected acute coronary syndrome, in whom cardiac troponin I was measured with a conventional reagent and one with high sensitivity (hsTnI) were included in the study. During a validation phase of 6-12 months, only the results of the conventional measurement were used to guide treatment. Five hospitals were randomly assigned to the early implementation (immediately after the validation phase) and another 5 to late implementation (6 months later) of results with the high sensitivity reagent and the diagnostic criteria of the Fourth Definition. The primary endpoint was AMI or cardiovascular death during the follow-up year.

A total of 48,282 patients with suspected acute coronary syndrome were included in the study, with a mean age of 61 years, 47% women in 10 sites, and 39% in the validation phase. Twenty-one percent of patients ( $n = 10,360$ ) had hsTnI values above the 99th percentile. In 88% of cases ( $n = 9,115$ ) a diagnosis could be achieved: type 1 AMI in 55%, type 2 AMI in 12%, type 4a AMI in <1%, type 4b in <1%, acute myocardial injury in 18% and chronic injury in 14%. Compared with the Third Universal Definition and the use of a conventional reagent to measure TnI, the use of the Fourth Universal Definition reclassified 15% of patients, in the majority of cases with chronic injury. Use of hsTnI diagnosed type 1, type 2, type 4a and type 4b AMI in 11%, 22%, 10% and 10%, respectively, but in 36% of cases of acute myocardial injury and 43% of chronic myocardial injury. The diagnostic agreement was higher in patients with type 1 AMI or injury than in cases of type 2 AMI. Compared with type 1 AMI patients, those with type 2 AMI were older, with a higher prevalence of female gender and more cardiovascular history. Patients with acute or chronic myocardial injury were similar in age and gender to patients with type 2 AMI. The values of hsTnI were higher in type 1 AMI than in the other diagnoses.

At discharge, patients with type 2 AMI received less antiplatelet, neurohormonal antagonist or statin treatment than those with type 1 AMI; and patients with acute or chronic injury, even less. The primary endpoint of AMI or cardiovascular death occurred in 17% of patients with type 1 AMI, 14% with type 2 AMI, 16% with acute myocardial injury, and 16%

with chronic myocardial injury. Compared with those without pathological troponin elevation, the adjusted HR was 5.6 in type 1 AMI; 3.5 in type 2 AMI; 4.4 in acute myocardial injury and 3.9 in chronic myocardial injury. And the most striking fact: although the implementation of the Fourth Definition and the use of hsTnI increased the diagnosis of type 1 AMI and the use of antiplatelet agents and revascularization procedures in this context, there was no improvement in the prognosis. In the case of type 2 AMI and injury cases, the treatment and evolution did not vary with the implementation of the Fourth Definition.

All-cause death occurred in 9% of patients. Compared with patients without TnI elevation, the risk of non-cardiovascular death was higher in patients with acute myocardial injury, type 2 AMI and chronic myocardial injury (with adjusted HR of 2.6, 1.7 and 2, respectively) and lower in patients with type 1 AMI (adjusted HR of 0.8).

*This High STEACS study analysis provides data of interest. When the traditional reagent was used to measure TnI, 59% of the values above the 99th percentile corresponded to type 1 AMI, 12% to type 2 AMI, and 28% to acute or chronic myocardial injury. The use of hsTnI increased by 15% the number of patients with pathological values with a decrease in the proportion of type 1 AMI to 55% and an increase of cases with injury to 32%. Despite the increase in the diagnosis of type 1 AMI in absolute values, the increase in revascularization procedures was modest and the prognosis did not change. Perhaps because the cases reclassified with the use of the high sensitivity reagent were those in which the benefit of implementing invasive measures is more doubtful.*

The main usefulness of hsTnI was to diagnose more cases of myocardial injury. And the basic problem is that in general these cases occur in the context of elderly patients, with a high rate of comorbidities, inflammatory activation, sepsis, cerebrovascular or respiratory disease and kidney dysfunction. In them, hsTnI elevation indicates myocardial distress and most likely underlying coronary heart disease, but due to its chronic nature and context or myocardial involvement without obvious coronary heart disease, it will not be explored or treated. That is, injury is diagnosed, but the lack of ischemia contrives against the active search for coronary heart disease. It is understood that troponin elevation involves risk, but there are no specific measures that may be taken; and in fact, the excess risk of non-cardiovascular death implies that myocardial injury often indicates that the myocardium suffers, in the manner of an innocent bystander, but that it will not be responsible for death. In other situations, it will be responsible for death of cardiac origin, but the patient's general condition, age and comorbidities will have sterilized any attempt of a more thorough study. We have advanced in the ability to diagnose injury and type 2 AMI; in many cases we lack unraveling its exact meaning, and knowing what (as in the case of type 1 AMI) are the measures that

must be adopted to improve the prognosis of patients. Perhaps, in many cases, effects on "non-cardiological" mechanisms may be necessary.

### **Cardiovascular disease and its burden as a cause of death in cancer patients. A population study of more than 3 million patients.**

Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J* 2019;40:3889-97. <https://doi.org/10.1093/eurheartj/ehz766>

It is already known that cancer patients have an increased risk of cardiovascular disease. This is due, among other causes, to age, the prevalence of cardiovascular risk factors, the inflammatory substrate common to both pathologies and the cardiotoxic effects of cancer medication. A recent epidemiological study helps to define the risk of death for neoplasia or cardiovascular disease according to the age of the patients, the year of diagnosis and the type of cancer. It is based on the analysis of a network of registries associated with invasive cancer diagnosed between 1973 and 2015, which covers 28% of the population of the United States of America.

A total of 3,234,256 cancer patients from 28 different locations were included in the study. In 49.3% of cases patients died from index cancer or cardiovascular disease in the study period, and 76.3% of all cardiovascular deaths were specifically cardiac. With increasing age at the time of diagnosis, the percentage of patients who died from cancer or cardiovascular disease increased. Patients diagnosed in the most recent years are in general still alive. The average risk of cardiovascular death at follow-up was 11.3%. Patients with bladder (19.4%), larynx (17.3%), prostate (16.6%), uterine body (15.6%), colorectal (13.7%) and breast (11.7%) cancer presented higher than average risk of cardiovascular death. Those with the lowest risk of cardiovascular death (<10%) were carriers of lung, liver, brain, stomach, gallbladder, multiple myeloma, pancreas, esophageal and ovarian cancer. All of them were cancers associated with high mortality from index cancer, and in which the prognosis has been relatively stable in recent decades. As the prognosis of cancers improves (soft tissues, nasopharynx, anus, oropharynx, colorectal, non-Hodgkin lymphoma, kidney and cervix), there seems to have been a concomitant increase in deaths from cardiovascular causes, although cancer death remains >10% higher than cardiovascular death. In fact, in 2012, death from index cancer was the leading cause of death among the majority of patients (24 of 28 sites studied). The four cancer sites where patients presented cardiovascular disease as the main cause of death were prostate, thyroid, Hodgkin lymphoma and testicles.

Cancer patients diagnosed at ≤85 years of age or younger had generally a higher risk of death from heart disease than the general population. The young-

er a cancer survivor was diagnosed, the greater the risk of cardiovascular death. However, the prevalence of death from heart disease in cancer survivors between 15 and 35 years was very low. For survivors diagnosed before 55 years of age, the risk of cardiovascular death was more than 10 times higher than in the general population. The incremental risk of cardiovascular death in cancer survivors gradually decreased as age increased at the time of cancer diagnosis (between 55–64 years, a standardized risk of 7.5%; between 65–74 years, 3.8%, and between 75–84 years, 2.4%) This was due to the fact that the risk of cardiovascular death increased in the general population as age increased. The highest risk of cardiovascular mortality occurred in the first year after cancer diagnosis. In relation to the average risk for the 28 cancer sites, endometrial cancer presented the highest risk of death from heart disease at all times after diagnosis. Compared with the first year after cancer diagnosis, patients with breast, melanoma and prostate cancer presented a constant high risk of cardiovascular mortality.

*This population study highlights the importance of cardiovascular disease as a cause of death in cancer patients. The causes are varied. In principle, a common inflammatory substrate which is expressed in cancer activation and in parallel with cardiovascular disease may be considered. To this is added that many times cardiac patients, when starting chemotherapy treatment, due to the digestive intolerance, nausea, diarrhea, dehydration, electrolyte disorders and arterial hypotension it generates, abandon their cardiovascular disease medication, and therefore remain more exposed to a sometimes fatal manifestation. And, of course, we must remember the consequences of cancer treatment. The improvement in the prognosis of cancer allows the underlying heart disease to be expressed in elderly patients; and, of course, cancer treatment often generates cardiotoxicity, and may change one cause of death for another. Patients up to 74 years of age, those in the first year of cancer diagnosis, and due to the high frequency and the importance of cardiovascular disease as a cause of death, those with breast, endometrial, prostate and colorectal cancer appear as the most firm candidates for an intensive search for cardiac and coronary heart disease, to avoid an unexpected pathology truncating life when the fear of cancer and its consequences absorb all efforts and thoughts.*

*Cancer and cardiovascular disease are the two most frequent causes of death. They present competitive risks; the reduction of one implies the increase of the other. The challenge is to achieve a decrease in both, so as to succeed in extending survival.*

### **Prognostic value of atrial fibrillation at 1 year of non-cardiac surgery. Doubts and certainties**

Conen D, Alonso-Coello P, Douketis J, Chan MTV, Kurz A, Sigamani A, et al. Risk of stroke and other adverse outcomes in patients with perioperative atrial fibrillation 1 year after non-cardiac surgery. **Eur**

**Heart J** 2020;41:645-51.<https://doi.org/10.1093/eurheartj/ehz431>

It is well known that atrial fibrillation (AF) outside the perioperative setting imposes a significantly higher risk of death and stroke. Similarly, it is accepted that AF in the context of cardiac surgery is also a predictor of short- and mid-term adverse events. But in principle things are not so clear when we refer to AF as a complication of non-cardiac surgery. Several studies suggest an increased risk of stroke and other adverse effects up to 30 days after surgery. In the POISE study, the OR adjusted for stroke at 30 days in patients with postoperative AF was 3.51%, 95% CI 1.4–8.5. Few studies have evaluated whether the increased risk persists over time. An administrative data registry suggested that in non-cardiac surgery, the risk of stroke at one year was 1.5% in patients with postoperative AF and 0.4% in those without this complication.

We now know the joint analysis of the cohorts included in the POISE 1 and POISE 2 studies. Both studies included patients with or at risk of cardiovascular disease undergoing non-cardiac surgery. The POISE-1 trial evaluated the effects of metoprolol versus placebo in 8,351 patients. The POISE-2 trial compared the effect of aspirin versus placebo, and clonidine versus placebo in 10,010 patients. Postoperative AF was defined as a new AF that occurred within 30 days after surgery, and that required pharmacological treatment or electrical cardioversion, or that resulted in angina, congestive heart failure, or symptomatic arterial hypotension in a patient without history of AF before surgery. The primary endpoint was stroke at 1-year. Secondary endpoints within the follow-up year were all-cause death, vascular mortality, acute myocardial infarction (AMI), and a composite of vascular mortality, myocardial infarction and stroke. The prognostic impact of postoperative AF adjusted for age, gender, smoking, history of hypertension, diabetes, heart failure, coronary heart disease, peripheral artery disease, previous stroke, type of surgery, urgent/emergency surgery, and treatment branch in the randomized trial was analyzed. The 244 patients who had AF before surgery were excluded from this analysis.

Among 18,117 patients, 404 (2.2%) developed postoperative AF. Compared with those without this complication, they were older (mean of 74 vs. 68 years,  $p < 0.001$ ), with a greater prevalence of stroke or previous transient ischemic attack, heart failure, and higher CHADS2 score (averages of 1.9 vs. 1.7,  $p < 0.001$ ). Regarding the type of intervention, thoracic surgery (14% vs. 4%) and vascular surgery (30% vs. 22%) were more frequent in patients with postoperative AF. During the 1-year follow-up, the incidence of stroke was 5.58% (95% CI 4.1%–7%) in patients with postoperative AF, compared with 1.54% (95% CI 1.4%–1.6%) in those without this complication (adjusted HR 3.4, 95% CI 2–5.9;  $p < 0.001$ ). They also presented with higher risk of vascular mortality (adjusted HR 2.7, 95% CI

1.9–3.9;  $p < 0.001$ ), AMI (adjusted HR 5.1, 95% CI 3.9–6.6;  $p < 0.001$ ) and all-cause death (adjusted HR 2.5, 95% CI 2–3.1;  $p < 0.001$ ). The annual incidence of stroke increased significantly as the CHADS2 score increased, from 0% in patients with a score  $< 2$ , to 8.2% in those with a score between 2 and 3 and 11.6% in those with a score  $> 3$  ( $p = 0.01$ ).

*The analysis we present indicates the adverse prognosis associated with the incidence of new AF in the context of non-cardiac surgery, a situation that is often poorly taken into account, on the grounds that it is simply due to transient disorders, including neurohormonal or inflammatory activation, stress, electrolyte abnormalities or the effect of drugs used in the perioperative period. The incidence of stroke at 1 year in patients with postoperative AF is high enough to focus more seriously on this complication. Is the need to anticoagulate all patients with postoperative AF then obvious? We dare not formulate this statement. Theoretically, the patients included in both studies were patients with a high risk of vascular event, with a prevalence of 75% hypertension, 34% diabetes, and 14% previous neurological event. On the other hand, it is not clear*

*how many of the patients had previous history of an AF episode, nor do we know what happened to the AF considered in the study: How many of them reversed? How many persisted? How many recurred in the follow-up year? We do not have the necessary data to dissect the prognostic value of postoperative AF episodes, or to formulate a recommendation that takes into account the aforementioned factors. In addition, the AF considered were those that required some type of intervention, so we may presume longer duration and more florid clinical manifestations. What about transient or not very evident AF? Would they have the same prognostic implication? On the other hand, the relationship between AF and the incidence of AMI is not surprising. In this context, we may ask ourselves if AF did not indicate patients with more atherosclerotic disease and more unstable in different situations of cardiovascular stress. Would implementing anticoagulant therapy be enough? Or may we regard postoperative AF in non-cardiac surgery as a manifestation of underlying cardiovascular disease that requires a comprehensive approach? Certainly, new cohort and randomized studies are necessary to unravel these dilemmas*