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Is long-term dual antiplatelet therapy advisable in patients with previous myocardial infarction? The Pegasus-TIMI 54 trial

Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. **N Engl J Med 2015;372:1791-800. http://doi.org/6md.**

Currently in vogue acute myocardial infarction (AMI) treatment guidelines recommend the use of sustained aspirin administration with the addition of a P2Y12 receptor antagonist (clopidogrel, prasugrel, ticagrelor) during the first year after AMI. It is unclear whether the extension of dual antiplatelet therapy beyond one year may provide additional benefit or not. To answer this question the PEGASUS TIMI 54 study was performed.

It included patients of at least 50 years of age who had suffered AMI between 1 and 3 years before entering the study, and had one additional risk factor (age ≥65 years, diabetes treatment, a second previous AMI, coronary multivessel disease or creatinine clearance <60 mL/min) treated with aspirin and other usual medication for the disease. They were randomly assigned in a 1:1:1 ratio to placebo, ticagrelor (T) at a dose of 60 mg bid (120 mg per day, T120) or at a dose of 90 mg bid (180 mg per day, T180). Patients with anticoagulation indication, history of bleeding, ischemic or hemorrhagic stroke or other intracranial pathology, and those who had presented with gastrointestinal bleeding in the previous 6 months or had undergone major surgery within the last 30 days were excluded from the study. The primary efficacy endpoint (EP) was the composite of cardiovascular death, nonfatal AMI and nonfatal stroke, and the secondary EP was cardiovascular and all-cause mortality. The incidence of other events was studied in an exploratory fashion. The primary safety EP was major bleeding according to TIMI classification, while intracranial and fatal bleeding was considered as secondary safety EP. Efficacy analysis was performed with intention-to-treat and the safety analysis was performed considering those who had received at least one dose of the assigned treatment.

Approximately 7,000 patients per group were included, with an average age of 65 years, 76% male, with a median index AMI- study entry time of 1.7 years. ST-segment elevation AMI was considered for inclusion in nearly 54% of AMI cases. In 83% of cases patients had history of angioplasty, and baseline treatment was impeccable: almost 100% were receiving aspirin, over 90% statins, more than 80% beta-blockers, and 80% renin-angiotensin system antagonists or inhibitors.

Median follow-up was 33 months. The incidence of the primary efficacy EP at 3 years was 9.04% with placebo, 7.77% with T120 (HR vs. placebo 0.84, 95% CI 0.74-0.95, p=0.004) and 7 85% with T180 (HR vs. placebo 0.85, 95% CI 0.75-0.96 p=0.008). This implies an absolute event reduction of 0.40% yearly with T180 and of 0.42% with T120 with no significant difference between the two groups. There was a tendency but no significant difference in cardiovascular death as isolated EP; with both doses of T there was significant AMI reduction and with 60 mg stroke was significantly reduced. All-cause mortality reduction was not seen with active treatment.

Regarding major bleeding, the incidence at 3 years was 1.06% with placebo, 2.32% with T120 (HR vs. placebo 2.32, 95% CI 1.68-3.21, p <0.001) and 2, 60% with T180 (HR vs. placebo 2.69, 95% CI 1.96-3.70 p <0.001). This implies, almost mirroring ischemic event reduction: an absolute increase of major bleeding of 0.41% annually with T180 and of 0.31% with T120. With the use of T there was also higher incidence of minor bleeding and transfusion requirements, but not of fatal bleeding or intracranial hemorrhage, with figures at 3 years between 0.6% and 0.7% in the 3 groups. The use of T was also associated with higher incidence of dyspnea (6.4% with placebo, 15.8% with T120 and 18.9% with T180, p <0.001 for both doses compared with placebo) and gout.

The use of T is associated with reduction of just above 1 major event (cardiovascular death, AMI or stroke) for every 100 patients treated in 3 years. This event is primarily AMI. There is no significant reduction of cardiovascular death and even less of overall death. To achieve this benefit an increased risk of major bleeding of little more than 1 event in 3 years is met, albeit not fatal or intracranial bleeding. As we can see, there is some balance and we are actually talking about low incidence of events (most likely because they are properly treated patients). In this sense, the decision should be individual: in patients with increased risk of ischemic events and low bleeding risk, we prefer a dual antiplatelet therapy beyond one year of AMI; if the situation is the opposite we will probably interrupt dual antiplatelet therapy earlier. Note that the conclusions are very similar to those expressed when referring to prolonged dual antiplatelet therapy or not in the context of coronary angioplasty.

Radial versus femoral access is preferable in patients with acute coronary syndromes undergoing coronary angioplasty. The MATRIX trial

Valgimigli M, Gagnor A, Calabró P, Frigoli E, Leonardi S, Zaro T, et al. Radial versus femoral access in pa-

tients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. **Lancet 2015;385:2465-76. http://doi.org/6mf**

One of the most frequent and deleterious complications of percutaneous coronary intervention (PCI) is periprocedural bleeding. Several randomized studies and registries have shown that the incidence of bleeding is associated with poor prognosis, and point out that the risk is greater with femoral access (FA) than with radial access (RA). However, in the context of acute coronary syndrome (ACS) and although comparative studies have been conducted, there has been so far no real evidence that any access is associated with better outcomes.

The MATRIX study, conducted in 78 centers in the Netherlands, Italy, Spain and Sweden, included patients with ST-segment elevation ACS or non-ST-segment elevation ACS, who were to undergo angiography and PCI when indicated. Participating physicians were required to have expertise of at least 75 interventions, and at least 50% of them via RA during the previous year. Patients were randomly allocated in a 1: 1 ratio to either access. Exclusion criteria were the use of low molecular weight heparin in the previous 6 hours, IIb IIIa inhibitors in the previous 3 days and any PCI performed in the previous 30 days. The 30-day coprimary endpoints were major adverse cardiovascular events (MCE), defined as death, acute myocardial infarction (AMI) or stroke, and net adverse clinical events (NAE), defined as the combination of MCE and type 3 or 5 BARC classification major bleeding unrelated to cardiac surgery. A rate of 6% was expected for MCE and of 9% for NAE with FA, and of 4.2% and 6.3% with RA with a RR of 0.70 in both cases. The necessary prespecified p value to demonstrate superiority of RA over FA was 0.025.

This study included 8,404 patients, 4,197 in the RA group and the rest in the FA group. The average age was 65 years, 74% were men and 47.7% had ST-segment elevation ACS. After angiography, 80.1% of cases underwent PCI, 3.7% coronary artery bypass graft surgery and the rest medical treatment. There was more use of unfractionated heparin in the RA group (49.9% vs. 45.5%, p <0.01) with no significant differences in the use of IIb/IIIa inhibitors (about 13%) or bivalirudin (about 40%). Only in 13.7% of cases two or more vessels were treated with PCI. One or more drug-eluting stents were used in 66% of cases and one or more bare-metal stents in 24%. There was no difference in the primary success rate between the two groups, which was close to 94%.

The incidence of MCE was 8.8% with RA and 10.3% with FA (p=0.031, above the prespecified value to accept superiority). The incidence of NAE was 9.8% vs. 11.7%, p=0.009. Considering endpoints separately, there was a slight reduction of total death with RA (1.6% vs. 2.2%, p=0.045) with no significant difference in AMI or stroke. The incidence of 3 or 5 BARC bleeding (1.6% vs. 2.3%, p=0.013) was lower with RA, mainly that related to puncture site (0.4% vs. 1.1%, p <0.001). There was no difference between subgroups (type of ACS, diabetes, renal failure, employed thienopyridine), but in centers that routinely use RA in 80% or more of the interventions, the benefit was clearly higher.

Previous randomized studies comparing RA and FA had provided conflicting results. The RIFLE STEACS study performed in 1,001 ST segment-elevation ACS patients, reported advantage in the use of RA with reduced bleeding and mortality. In contrast, in a similar population of 707 patients, the RADIAL STEMI trial revealed bleeding but not mortality. The RIVAL study in ST-segment-elevation and non-ST-segment elevation ACS patients showed no difference in the outcome, and even suggested a tendency to higher mortality in RA patients with non-ST-segment elevation ACS. In the RIVAL study the requirement of prior experience in the use of RA was lower than in the MATRIX study. This last study has undoubtedly the largest number of randomized patients and of expertise levels in the use of RA. A meta-analysis of all RA vs. FA randomized studies in ACS, with no heterogeneity in the results, shows a reduction of 42% in bleeding unrelated to surgery (p <0.0001) and of 28% in total mortality (p=0.001) implying a mechanistic link between the two events. The RA appears as the one that should be preferred, with better results the more experienced the center is.

Dysglycemia in coronary artery disease patients: which is the best way to diagnose it?

Gyberg V, De Bacquer D, Kotseva K, De Backer G, Schnell O, Sundvall J, et al. Screening for dysglycemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV- a survey from the European Society of Cardiology. **Eur Heart J 2015;36:1171-7. http://doi.org/6mg**

Many patients with coronary artery disease have alterations in carbohydrate metabolism, including impaired fasting glucose (IFG), decreased glucose tolerance (DGT), the so-called high-risk glycated hemoglobin (HR HbA1c) and diabetes mellitus (DBT). The tests used for diagnosis include fasting plasma glucose (FPG), 2 hour glucose (2hPG) in an oral glucose tolerance test (OGTT) and HbA1c. Practice guidelines encourage use of these tests to diagnose dysglycemia, but it is known that the overlap of results between them is low, and that a negative result of any of them does not preclude an abnormal result in another.

EUROASPIRE IV was an observational study conducted in 79 centers in 24 European countries, which enrolled patients between 18 and 80 years of age with evidence of coronary artery disease between the 6 and 36 previous months (angioplasty or coronary surgery,

myocardial infarction or acute myocardial ischemia). The 3 mentioned tests were performed in all those who denied being diabetic and in those where studies could be conducted with at least 10 hours fasting (5,395 out of the initial 7,998 respondents). Data from the 3 studies was obtained from 4,004 patients and they constitute the basis of this report.

For the diagnosis of abnormal carbohydrate metabolism, definitions of the American Diabetes Association (ADA) and the World Health Organization (WHO) were used. According to ADA, DBT was diagnosed with FPG 126 mg/dL and/or HbA1c 6.5%; or else 2hPG 200 mg/dL according to WHO. Impaired fasting glucose according to ADA was diagnosed with FPG between 101 and 125 mg/dL and HbA1c <6.5%; and according to WHO with FPG between 110 and 125 mg/dL, HbA1c <6.5% and 2hPG <140 mg/dL. Decreased glucose tolerance was diagnosed with FPG <126 mg/dL, HbA1c <6.5% and 2hPG between 140 and 199 mg/dL according to WHO; and with HR HbA1c between 5.7% and 6.4% according to ADA.

In 1,158 (29%) out of the 4,004 patients included in the study, a diagnosis of previously unknown DBT was performed with at least one of the tests. Thus, in 606 of cases (52%), diagnosis was made only by FPG, 218 (19%) only by 2hPG; 49 (4%) only by HbA1c; and in the remaining 25% there was agreement of at least two tests. Only in 7.2% of cases there was agreement in the three tests. Of all diagnosed diabetics, FPG was positive in 75%; 2hPG in 40%; HbA1c in 17%; OGTT (combining FPG and 2hPG) in 96%, and the combined FPG with HbA1c in 81% of cases.

Using the ADA criteria, prevalence of DBT was 23.5%, of normality 10.5%, and in 66% of cases there was high risk of developing DBT: IFG or HR HbA1c. With the WHO criteria the figures were 26.6% for DBT, 27.7% for normality and 45.7% for high risk of DBT (IFG or DGT).

The profusion of figures should not hide the essential: in chronic coronary patients undiagnosed DBT prevalence is high. Different tests and definitions can take us through different paths. However, OGTT combining FPG with 2hPG appears as the most beneficial diagnostic test. However, its complexity level should be considered with regard to FPG (not requiring glucose overload or 2 hour determination) or HbA1c (it can be done at any time of the day).

Not only statins reduce cardiovascular events by lowering cholesterol. The IMPROVE IT trial

Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. **N Engl J Med 2015;372:2387-97. http://doi.org/6mh**

Statins lower LDL cholesterol levels and the rate of cardiovascular events. Ezetimibe reduces the intestinal absorption of cholesterol. When associated with statins it produces a further reduction of LDL cholesterol in the range of 23% to 24%. It was not clear so far whether adding ezetimibe to statins, beyond the effects on the lipid profile, would result in an additional reduction of events. The IMPROVE IT study devoted itself to answer this question.

It included patients of at least 50 years of age, who had been hospitalized for an acute coronary syndrome (ACS) within the preceding 10 days, and who were stable, with a value of LDL cholesterol level measured within the first 24 hours after disease onset of 50 to 100 mg/dL if they were already receiving statins, or 50 to 125 mg/dL if they were not. Patients with planned coronary surgery, those with creatinine clearance <30 ml/min, active liver disease, or use of statin therapy that had LDL cholesterol-lowering power greater than 40 mg of simvastatin were excluded. All were receiving simvastatin 40 mg/day and were assigned in a dual blind fashion to ezetimibe 10 mg or placebo. At protocol initiation it was established that if a patient had two consecutive LDL measurements of 80 mg/dL or higher, the dose of simvastatin should be increased to 80 mg daily. Since 2011, the FDA warned against that dose of simvastatin, therefore, all the patients who had been receiving 80 mg/dL up to 1 year returned to 40 mg daily. If the value of LDL cholesterol was greater than 100 mg/dL with the new regime, then the study drug could be discontinued and a stronger therapy initiated. The primary efficacy end point was a composite of death from cardiovascular disease, nonfatal acute myocardial infarction (AMI), unstable angina requiring hospitalization, need of coronary revascularization within 30 days after inclusion or nonfatal stroke. Secondary endpoints were different combinations of the primary endpoint components. The study continued until each patient had been followed up for at least 2.5 years and 5,250 events were estimated to give the study 90% power to detect a risk reduction of 9.375% for the primary endpoint. Three interim efficacy analyzes were prespecified after 46%, 76% and 87% of participants were recruited.

Between 2005 and 2010, 18,144 patients from 1,147 centers in 39 countries were included. The average age of patients was close to 64 years, 75% were men, and nearly 20% had previous AMI. Almost 29% were admitted for ST-segment elevation AMI, 47% for non-ST segment elevation AMI and the rest for unstable angina. Time between ACS and inclusion had a median of 5 days (interquartile range from 3 to 8 days). Seventy per cent of patients underwent coronary angioplasty in the hospital and 34% were receiving statins at the time of inclusion. Mean baseline LDL cholesterol was 93.8 mg/dL; at 1 year mean LDL cholesterol level had dropped to 69.9 mg/dL in the simvastatin-placebo group and to 53.2 mg/dL (an additional reduction of 24%; p <0.001) in the simvastatin-ezetimibe group. In the drug combination group the values of total cholesterol, HDL cholesterol, triglycerides and C-reactive protein were also significantly lower. Median follow-up was 6 years.

The incidence of the primary endpoint at 7 years was 34.7% with simvastatin monotherapy and 32.7% with the combination therapy (HR 0.936, 95% CI 0.89 to 0.99; p=0.016). There was no difference in the overall and cardiovascular or coronary artery mortality rate. There was a reduction in the incidence of AMI (13.1% vs. 14.8%; p=0.002) at the expense of non-fatal AMI and stroke in the borderline significance (4.2% vs. 4.8 %; p=0.05). Similarly the need for urgent revascularization was reduced within 30 days from 8.6% to 7% (p=0.001). The benefit was particularly pronounced in patients with diabetes mellitus and in patients aged 75 years or older.

There was a similar incidence of adverse events in both groups. At the end of the study, 42% of patients in each group had abandoned the assigned treatment, 10% as a consequence of adverse events.

The rate of event reduction with the simvastatin-ezetimibe combination was that expected according to the achieved reduction of LDL cholesterol in the meta-analysis of statin monotherapy: approximately 20% for each reduction of 1 mmol/L (38.67 mg/dL). The IMPROVE IT study leaves two significant messages: a) it confirms that in coronary artery patients, the greater the reduction in cholesterol levels, the better the prognosis; b) it challenges the hypothesis of statins, which claims that only with these drugs LDL cholesterol reduction results in a better outcome: in patients with probability of suffering acute coronary syndrome with not so high LDL cholesterol levels (remember that there was a relatively low "ceiling" as inclusion criterion), a non-statin drug is able to improve the prognosis and with a mechanism of action different from that of statins.

How to interpret the value of cardiac troponin in patients with kidney failure

Twerenbold R, Wildi K, Jaeger C, Gimenez MR, Reiter M, Reichlin T, et al. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. **Circulation 2015;131:2041-50. http://doi.org/6mj**

It is known that in patients with renal dysfunction (RD) the incidence of acute myocardial infarction (AMI) is higher, with more frequent atypical presentation. Renal dysfunction is also associated with left ventricular hypertrophy, with less specific ECG findings. A fundamental diagnostic tool, cardiac troponin elevation, has also its weakness in this context. A value of cardiac troponin above the 99th percentile of a healthy reference population is generally assumed for the diagnosis of AMI; however, in patients with RD those values are often found in the absence of AMI. What is then the diagnostic yield of cardiac troponin in patients with RD? What are the optimal cutoff levels for diagnosing AMI?

The APACE study is a prospective multicenter study including 3,030 patients (excluding those on dialysis) who consulted the emergency service for symptoms compatible with AMI within 12 hours of symptom onset. The analysis includes 2,813 patients in whom complete data are available. Two independent cardiologists reviewed all available medical records: pain characteristics and hours since symptom onset, medical history, ECG, laboratory data (including cardiac troponin) and chest X-ray, including in-hospital outcome and the results of coronary angiography if any were performed. In patients with RD (creatinine clearance <60 ml/min/1.73 m2) even previous cardiac troponin values were taken into account. The final diagnosis of AMI was made with all the information reviewed, considered as the evidence of myocardial necrosis (cardiac troponin above the 99th percentile in healthy subjects, with a significant fall or increase) in a clinical context of ischemia.

Different cardiac troponin assays were used in the participating centers: 6 cardiac troponin I (3 sensitive and 3 highly sensitive) and 1 highly-sensitivity cardiac troponin T (hs-cTnT). Among 2,813 unselected patients, 447 (16%) were diagnosed with RD with a higher prevalence of risk factors, previous AMI and ECG abnormalities. In them, cardiac troponin levels, irrespective of the assay used, were higher than in the rest. AMI was the final diagnosis in 36% of patients with RD and in 18% of patients without RD (p <0.001). Among patients without AMI, troponin values were also significantly higher in those with RD. Between 12% and 71% (the latter value corresponding to hs-cTnT) of patients with RD without AMI had levels above the cutoff value. In patients without RD or AMI that figure was much lower: it ranged between 7% and 21% (15% in the case of hs-cTnT). Troponin values were inversely correlated with renal function in patients without AMI. There were no differences in the diagnostic yield of the various assays. In patients with RD, troponin was more sensitive (between 77% and 98%) and less specific (between 32% and 89%) than in those without RD to diagnose AMI. In patients with RD, the ROC area ranged between 0.87 and 0.89 in the baseline measurement, slightly lower than in patients without RD: from 0.91 to 0.94. The worse the renal function, the lower the ROC area. The optimal cutoff value for the diagnosis of AMI was in patients in whom RD had similar values to those of usual sensitive assays, but clearly higher with high sensitivity assays: in the case of hs-cTnT 2.1 times higher: 29.5 ng/L vs. the usually considered value of 14 ng/L. Optimal cutoff levels for sensitivity and specificity derived from ROC curves, were finally 2-3 times higher in patients with RD.

This observational study provides important information on an issue that raises questions every day: how to interpret cardiac troponin data in patients with RD. It should be noted that each assay has its own characteristics, and especially in this group of patients the properties or cutoff levels of one assay should not be extrapolated to the properties or cutoff levels of an-

other. Everyone should be making its own experience with the tool at his disposal. Most importantly, troponin, although with higher cutoff levels, does not lose its diagnostic and prognostic value in patients with RD: according to the assay used, between 45% and 80% of cases above the reference values corresponded to AMI. This implies not to rule out a priori the diagnosis of AMI in patients when high levels of troponin are found, under the pretext that the patient has RD, but at the same time to be careful with the diagnosis, especially when a patient with these characteristics presents with not so marked elevation.

Mendelian randomization, a new demonstration of diabetes and coronary heart disease association

Ross S, Gerstein HC, Eikelboom J, Anand SS, Yusuf S, Pare G. Mendelian randomization analysis supports the causal role of dysglycemia and diabetes in the risk of coronary artery disease. **Eur Heart J 2015;36:1454-62. http://doi.org/6mk**

Numerous observational studies have established a firm connection between various expressions of dysglycemia, including impaired fasting glucose (IFG), elevated glycosylated hemoglobin (HbA1c) and diabetes mellitus (DM), and coronary heart disease (CHD) in its various manifestations, from angina and myocardial infarction, to coronary angioplasty or surgery and death. However, randomized studies evaluating the effect of an intensive glucose-lowering treatment have shown only a modest effect on the incidence of CHD. This has led to question whether the alleged relationship between dysglycemia and CHD is as strong as assumed. Mendelian randomization is based on the principle that genetic information variants related to the occurrence of various conditions or events are randomly distributed in the general population, regardless of confounding factors. Therefore, genetic information significantly associated with dysglycemia can be further studied to assess whether it is also linked to the existence of CHD. While this does not exclude that this genetic material may associate with other coronary risk factors, the adjustment for these factors can "clean" dysglycemia and CHD association. The authors based their work on these concepts.

The data that establish the statistical association of single nucleotide polymorphisms (SNP) with the different expressions of dysglycemia, CHD, dyslipidemia and anthropometric alterations were obtained from repositories of genetic material from tens of thousands of people with these diseases or without them. To avoid considering weak associations, a significant p value $<5 \times 10\text{-}8$ was established for SNP associated with dysglycemia. Once these SNP were chosen a linear regression analysis was performed, considering as independent variable its effect on dysglycemia and as dependent variable its effect on CHD, adjusting for the effect of these SNP on lipid values and body mass index.

Finally, 30 SNP related to IFG, 9 with HbA1c and 59 with DM were selected. The SNP associated with HbA1c were also significantly associated with CHD risk (OR 1.53, 95% CI 1.14-2.05 for every 1% increase in HbA1c). Similarly, SNP associated with DM were also significantly associated with CHD risk, with an OR of 1.57, 95% CI 1.16-2.05. Conversely, SNP linked with IFG were not associated with increased risk for CHD. When the effect on CHD was adjusted by the effect on lipid levels and body mass index, only the SNP related with DM remained independently associated with the occurrence of CHD, with an OR of 1.63, 95% CI 1 23-2.07. It is interesting to point out that when considering a meta-analysis of 102 prospective studies with almost 700,000 individuals there is an association between DM and CHD, with an OR of 2, 95% CI 1.83-2.19, quite similar to that obtained with genetic information.

There is no statistically significant difference ($p=0.16$) between the OR considered in this meta-analysis and that obtained in the Mendelian randomization presented in this study. This study definitively confirms the association between DM and CHD. The advantage of Mendelian randomization over traditional observational studies is that it excludes residual confounding and reverse causality. As they are genetically determined relations, hypoglycemic interventions may require longer follow-up than that provided by a randomized study, in order to demonstrate reduction of coronary events. It should be noted that the association of genes related with CHD and DM was evidenced both for those related to decreased function of the beta cells in the pancreatic islets (decreased insulin secretion) as for those related to increased insulin resistance, suggesting that both aspects should be addressed.

Not only increase in body weight should be considered in heart failure: unintentional decrease also implies risk.

Rossignol P, Masson S, Barlera S, Girerd N, Castelnovo A, Zannad F, et al. Loss in body weight is an independent prognostic factor for mortality in chronic heart failure: insights from the GISSI-HF and Val-HeFT trials. **Eur J Heart Fail 2015;17:424-33. http://doi.org/6mm**

Although the increase in body weight is a phenomenon taken into account in the context of heart failure because it represents hydrosaline retention in most cases, weight loss (WL) is a phenomenon much less considered, and which is often even seen as a manifestation of successful congestive treatment. However, as seen in the present study, WL may be an adverse prognostic marker.

The subanalysis of two randomized studies, the GISSI-HF (exploring the use of rosuvastatin in patients with HF) and Val-HeFT (exploring the same with valsartan) trials, considered a WL ≥5% between programmed visits, and in the case of GISSI-HF an

additional intentional or not WL ≥2 kg during the course of the first year follow-up. The prognostic consequence of this phenomenon was evaluated, adjusting for baseline conditions, treatment, biomarkers and in the GISSI-HF trial the change in plasma volume (calculated from the equation using hemoglobin and hematocrit changes during the same time interval in which WL was verified, to isolate the effect due to relief from the congestive condition).

Weight loss ≥5% was found in 16.4% of patients included in the GISSI-HF trial and in 15.7% of those included in the Val-HeFT trial. Patients were older and more severely ill than those without WL, they were less likely to be treated with beta-blockers and had greater presence of comorbidities. In the GISSI-HF trial, WL ≥5% was predictor of overall and cardiovascular mortality with a HR of 1.20 and 1.23, respectively ($p < 0.01$ in both cases). In the same study, unintentional WL ≥2 kg (present in 18.9% of cases) was predictor of overall, cardiovascular and non-cardiovascular mortality with a HR of 1.22, 1.17 and 1.39, respectively ($p=0.002$, 0.003 and 0.01, respectively). In the Val-HeFT trial, WL ≥5% was predictor of overall, cardiovascular and non-cardiovascular mortality with a HR of 2.52, 2.23 and 4.12, respectively ($p<0.0001$ in all cases).

In the GISSI-HF trial, the increase in plasma volume was associated to higher overall and cardiovascular mortality, independently of WL of 5% or an unintentional decrease of at least 2 kg, indicating the prognostic value of congestion.

This observational study in the context of two large randomized trials confirms the poor prognostic outcome associated with weight loss in chronic heart failure. As patients had to be compensated at study inclusion, it is understood that WL was in general unintentional, and was not the result of successful diuretic treatment in patients with congestive heart failure. This WL denotes from a decrease in food intake, passing through malabsorption, to increase of catabolic phenomena. In all cases there is underlying activation of inflammatory phenomena and elevated cytokine levels. We should bear in mind that a WL of 5% as cut-off point is used to define cardiac wasting. The fact that we should be attentive to even lower weight losses is denoted by the adverse prognosis implicated in WL of only 2 kg in less than 1 year. The reverse association with use of betablockers confirms previous information, and adds another mechanism of action to those postulated to explain the favorable effect of these drugs.

How much of what is published in cardiovascular journals is then cited? Little encouraging data from over 164,000 articles

Ranasinghe I, Shojaee A, Bikdeli B, et al. Poorly cited articles in peer-reviewed cardiovascular journals from 1997 to 2007: analysis of 5-year citation rates. **Circulation 2015;131:1755-62.**

As another expression of the growing complexity of the world, the number of journals and publications has also increased exponentially, and even if we had the intention, we could not thoroughly read and analyze all that is published, not only about medicine or a specialty, but even about a specific topic. We face an explosion of production and publication of data, because medicine has been industrialized and so has scientific literature. Publishing has become important; a doctor or an institution is judged not only by the healthcare provided, but also by its teaching and research undertakings, and every day new journals appear, and existing ones increase the frequency of publication. This remarkable increase in quantity is not always accompanied by comparable quality, and the truth is that much of what is published "passes by", has no impact on the medical community, repeats already known information, and is not cited in other publications.

The authors of this work identified in Scopus (the largest database of medical peer-reviewed articles worldwide, with more than 50 million registries in more than 21,000 journals, including 100% of those indexed in Medline and Pubmed) all the cardiovascular journals edited between 1997 and 2007 . They selected articles with original research, excluding reviews, letters, editorials, etc., and established the number of citations for each article in the 5 years following publication. They defined poorly cited articles as those with 5 citations or less. In turn, journals were classified as poorly cited when more than 75% of its content was poorly cited, moderately cited if poor citation was between 26% and 75%, and well cited if only up to 25% of articles were poorly cited.

The authors identified 222 cardiovascular journals. In 1997, the number was 113 and in 2007, 198, representing an increase of 75%. Among the journals edited in 2007, 52% were already edited in 1997 and 48% had appeared thereafter. The analysis considered 164,377 articles. Among them, 46% was poorly cited in the 5 years following publication (15.6% was never cited). Ninety one percent of articles published in 1997 and poorly cited between 1997 and 2001 were also poorly cited between 2002 and 2007. Regarding the journals, 44% were poorly cited, 47 moderately cited and the rest highly cited. In-between the extremities of the period considered, the number of poorly cited journals fell by 10.8%, but due to the increase in the number of journals, the absolute number increased from 45 to 63. Journals with basic research content were more cited: among them, only 14% had a low citation rate, compared to 63% of clinical journals and 40% of those with mixed content. There was a higher rate of poor impact in open access journals.

As we see, almost half of all that is published in indexed cardiological journals ends being poorly cited afterwards and one out of seven articles is not cited at all. What can be the cause of this phenomenon? Several explanations can be given, and certainly not always the same. On the one hand, the increase in the number of journals implies greater possibility of publication.

But, in turn, the excess of articles published conspires against reading each of them individually. The articles cited in a review have greater probability of being cited in subsequent articles and reviews. It is possible that poorly cited articles are those with lower scientific quality, but it is no less true that access to a higher impact journal guarantees more reading and greater citation index, and that sometimes high-quality articles are not acknowledged, or do not refer to trendy topics at a certain moment, threatening its publication or its citation in case of being published. The subject is hard and complex, and does not admit univocal interpretations. And to conclude, a question: how many times will this article be cited in the next years?