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## CANVAS and CVD REAL: a randomized and observational study confirming the beneficial effect of glifozins in diabetes treatment

Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. **N Engl J Med 2017;377:644-57. http://doi.org/gbs57w**

Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, et al. Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). **Circulation 2017;136:249-59. http://doi.org/gbqk98**

Sodium glucose-2 cotransporter inhibitors (SGLT2) are a new family of drugs that has appeared for diabetes treatment. Its basic action favors osmotic diuresis, generating renal elimination of sodium and glucose. In the EMPA-REG study, which we discussed in Rev Argent Cardiol 2015; 83: 5, the use of one of these agents, empagliflozin, in type 2 diabetic patients with established cardiovascular disease or risk factors for its development resulted in reduced hospitalization for heart failure and, more importantly, in decreased cardiovascular and total mortality. We now know the results of two studies, a randomized study and a large registry that provide more understanding about these drugs.

The CANVAS program integrated data from two studies (CANVAS and CANVAS R) independently planned to define the safety and efficacy of canagliflozin, a SGLT2 inhibitor in the treatment of type 2 diabetic patients at high cardiovascular risk. Both studies evaluated the effect of treatment on cardiovascular events, and the CANVAS R study added the effect of treatment on renal function.

Patients with glycosylated hemoglobin between 7.5% and 10%, aged ≥30 years with established cardiovascular disease, or aged ≥50 years and at least two of the following conditions were included in the study: diabetes for ≥10 years, systolic blood pressure (SBP) >140 mmHg under treatment, HDL cholesterol <38.7 mg/dl, current smoking, and macro or microalbuminuria. The glomerular filtration rate had to be >30 ml/min/1.73m2. In the CANVAS program, patients were assigned to canaglifozin 100 mg or 300 mg daily or placebo. In the CANVAS R study, they were assigned to canaglifozin 100 mg daily (with the possibility of increasing it to 300 mg daily at week 13) or placebo. In both cases, the allocation was double blind. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction (AMI) and non-fatal stroke. Secondary endpoints were: total mortality, cardiovascular death, progression of albuminuria (an increase >30%, and the change from normoalbuminuria to micro or macroalbuminuria, or from micro to macroalbuminuria) and a composite of cardiovascular death and hospitalization due to heart failure. The primary hypothesis was one of non-inferiority, accepting, for active treatment, a value for the HR 95% CI upper limit of 1.3 with respect to the primary endpoint (which implies accepting results up to 30% worse with the drug than with placebo). If non-inferiority is met, superiority will be tested, seeking, as usual, a HR 95% CI upper limit <1.

The CANVAS and the CANVAS R studies were started in 2009 and 2014, respectively. The joint monitoring of both studies ended in 2017. A total of 10,142 patients were included (4,330 of them in CANVAS, and the rest in CANVAS R). Mean follow-up was 188 weeks (296 in CANVAS and 108 in CANVAS R). Mean age was 63.3±8.3 years, and 36% were women. In 72% of cases patients had history of atherosclerotic vascular disease and almost 66% of cardiovascular disease, 69.8% had normoalbuminuria, 22.6% microalbuminuria and the remaining 7.6% cases macroalbuminuria. Mean glycosylated hemoglobin (HbA1c) was 8.2± 0.9%, and the duration of diabetes was 13.5 years. During follow-up, canagliflozin produced a mean reduction of 0.58% HbA1c, 1.6 kg weight and 3.9 mmHg SBP compared with placebo; use of other hypoglycemic drugs was 9.3% lower in the active treatment group.

During follow-up, canagliflozin showed a significant reduction in the primary endpoint from 3.15% to 2.69% per year (HR 0.86, 95% CI 0.75-0.97), hospitalization due to heart failure from 0.87% to 0.55% per year (HR 0.67, CI 95% 0.52-0.87), progression of albuminuria from 12.8% to 8.9% per year (HR 0.73, 95% CI 0.67-0.79) and a combined decrease of 40% or more in the glomerular filtration rate, need for dialysis or death from renal cause from 0.9% to 0.55% per year (HR 0.60, 95% CI 0.47-0.77). Unlike EMPA-REG, there was no significant reduction in cardiovascular death (1.16% vs. 1.28% per year with placebo, HR 0.87, 95% CI 0.72-1.06) or total death (1.73% vs. 1.95% per year with placebo, HR 0.87, 95% CI 0.74-1.01).

Although the rate of serious adverse events was higher with placebo than with drugs (12% vs. 10% per year), there was a trend towards greater discontinuation due to adverse events with canagliflozin (3.5% vs. 3.3% per year), and attention was particularly drawn for an excessive need of distal amputation in the lower limbs (especially fingers or metatarsals): 0.63% vs. 0.34% per year (p <0.001). The incidence of fractures (1.54% vs. 1.19%) and of urinary and genital tract infections was also significantly higher.

The other study to which we refer is CVD REAL, an observational study that took data from multicenter or national registries from 6 countries: USA, United Kingdom, Germany, Sweden, Norway and Denmark. Between the end of 2012 and mid-2013 type 2 diabetic patients who had begun the treatment of their disease with a new drug were selected. They should not have a prescription of this drug for 6 months (in Germany) or the previous year (in the rest of the countries) prior to entering the study to assume that it was the first treatment with this therapeutic agent. It included a total of 1,392,254 patients, of which 166,033 were prescribed glifozins and the rest another agent, alone or in combination. The patients treated with gliflozins were younger, with less renal failure or cardiovascular complications, but more microvascular damage. Most often they were treated with statins and antihypertensive drugs, and less with diuretics. Similarly, they had more frequently prior treatment with hypoglycemic agents. In order to adequately compare the evolution of the two groups with respect to the primary endpoint of hospitalization due to heart failure, and the secondary end point of total mortality and a composite of these two, a propensity score was generated for the use of glifozins based on the independent predictors of this prescription. Patients were matched on a 1: 1 ratio based on that score, and 154,528 new gliflozin users were thus compared with the same number that had started another treatment.

The selected patients had an average age of 57 years, slightly more than 55% were men, and only 13% had an established cardiovascular disease. Only 2.5% had history of myocardial infarction, and 3% had heart failure. Almost 80% were already treated with metformin, 38% with sulfonylureas, 33% with inhibitors of dipeptidyl peptidase 4, 19% with GLP1 agonists and 29% with insulin. Among glifozin users, the drug used was canagliflozin in 53% of cases, dapagliflozin in 42% and empagliflozin in the remaining 5%. In a follow-up that lasted, according to the country, from the end of 2015 to the end of 2016, the annual incidence of hospitalization for heart failure was 0.5% per year. The risk of hospitalization was much lower in glifozin users compared to those who started another treatment: HR 0.61, 95% CI 0.51-0.73, p<0.001.

In 107,811 pairs of patients it was possible to determine the incidence of all-cause mortality. In this case, glifozin users received canagliflozin in 42% of cases, dapagliflozin in 51% and empagliflozin in the remaining 7%. The annual incidence of mortality was 0.87%, and the risk was again lower in glifozin users compared to those who initiated another treatment: HR 0.49, 95% CI 0.41-0.57, p<0.001.

To rule out differences not due to a protective effect of gliflozins but to a detrimental effect of some of the comparison drugs, a sensitivity analysis in in which the families of drugs employed were individually removed, and glifozin users were compared with those treated with the rest of the hypoglycemic agents. The results continued to favor glifozin users in all cases.

*Gliflozins are a family of drugs with diverse actions: as they generate glycosuria glycosylated hemoglobin decreases, but no more than other agents which in no way produce the prognostic improvement that is observed with its use. Is that consistent with the other effects that have been shown? They promote a negative caloric balance, decreasing body fat mass and epicardial fat, and inducing weight loss; they attenuate arterial stiffness and generate a slight decrease in blood pressure; they have anti-inflammatory and anti-fibrotic action and increase the levels of HDL cholesterol; they have, as we have seen, nephroprotective action (decreasing intraglomerular filtration pressure and therefore hyperfiltration) and decrease the progression of albuminuria. Added to this, it has a natriuretic effect, which translates into decreased plasma volume and is undoubtedly linked to the decrease in the incidence of heart failure, the most consistent of all the results presented. It is difficult to attribute the decrease in mortality to only one of these effects, and it is most likely that their combination is responsible for the prognostic improvement.*

*Some remarks can be made concerning the publications we present. Considering that in the EMPA-REG study the use of empagliflozin had caused a decrease in total mortality this did not occur in the CANVAS program with canagliflozin, can we therefore make a difference in the action of both drugs? We do not believe so. The EMPA-REG population had a higher prevalence of cardiovascular disease, with, for example, coronary artery disease in 75% of patients compared to 55% in the CANVAS program; and an annual all-cause-mortality of almost 3% compared to 2% in the CANVAS program. It is therefore possible that it would be easier to demonstrate a significant reduction in mortality in the empagliflozin study. Let us recall that the reduction of mortality in the CANVAS program was at the limit of significance (the HR 95% CI upper limit for total mortality is 1.01), so we understand that the results of both drugs can be seen as similar in the context of a class effect. The excess of amputation with canagliflozin in the CANVAS program has generated concern. It is of small magnitude (3 amputations more per 1000 patients per year, and in general of the more distal part of the foot, in patients with severe vasculopathy and previous amputations). There is no true explanation so far, and a chance effect cannot be ruled out in the context of multiple comparisons.*

*The CVD REAL study demonstrates the benefits of continuous registration. Only in countries with a long tradition in registering can the capacity to generate an observational study like this one, by the magnitude in the number of observations and the generation of relevant information, be understood. And, again, reduction of hospitalization due to heart failure and total mortality is confirmed with the use of these agents, now in a much lower risk population than in randomized studies: only 13% of cardiovascular disease, less than 1% annual mortality. It is not a randomized study, and although a propensity score has been used to adjust for the different baseline characteristics of glifozin and other drug use, residual confounders cannot be completely ruled out: variables not considered, linked to the use of these drugs and also the different outcome. However, the weight of the effect is such that it is very difficult to deny that, even with a lower magnitude than the one presented, there is a real prognostic improvement. And it should be noted that the glifozins mainly used here are the ones with which there is less evidence in randomized studies, confirming the idea of a class effect.*

*We seem to be witnessing the birth of a new era in which diabetes treatment targets will be different from the traditional ones: from focusing on laboratory data, to aiming for a clear improvement in clinical endpoints.*

## Decrease in the incidence of sudden death in patients with heart failure and reduced ejection fraction: an analysis of 12 randomized studies over 20 years

Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, et al. Declining Risk of Sudden Death in Heart Failure. **N Engl J Med 2017; 377: 41-51. http://doi.org/gbvvrd.**

Patients with heart failure have two polar forms of death: sudden death and death due to disease progression. Usually, sudden death is proportionally more frequent in patients with better functional class. The use of implantable cardioverter defibrillators (ICD) has been shown to significantly reduce the incidence of sudden death and in randomized studies has reduced all-cause-mortality. This is the basis to justify their indication in primary prevention in patients with reduced ejection fraction, below 35% (HFrEF). Practice guidelines emphasize the appropriate selection of patients for the indication to be cost effective. It is not so if patients have a very low risk of total mortality and sudden death in particular; nor if the risk of death by disease progression is very high and the main contributor to total mortality.

In this sense, we present an interesting recently published analysis taking into account 12 large randomized studies of patients with HFrEF, carried out between 1995 and 2014, in which different therapeutic agents were tested: beta-blockers (BEST, CIBIS II and MERIT HF), antialdosterone agents (RALES and EMPHASIS), angiotensin II antagonists (CHARM Alternative, CHARM Added, Val HeFT), statins (GISSI HF and CORONA), ICD (SCD HeFT) and sacubitril valsartan (PARADIGM). The incidence of sudden death was considered the primary endpoint of the study. Patients who had an ICD and a subgroup of patients with EF >40% from the GISSI HF study were excluded.

A total of 40,195 patients, with mean age of 65 years, 77% men, and 95% in FC II-III were included in the analysis. Mean EF was 28% and coronary artery etiology was present in 62% of cases. The patients who presented sudden death at follow-up in each of these studies were older, more frequently men, with worse EF and renal function, lower systolic blood pressure and higher heart rate, higher prevalence of diabetes and coronary heart disease. In these patients there was less use of beta-blockers and greater use of diuretics, digitalis and mineralocorticoid-receptor antagonists. The annual incidence of sudden death decreased over time, from 6.5% in the RALES trial, completed in 1998, to 3.3% in the PARADIGM study, completed in 2014 (p-trend=0.02). The only study in which this progression was not verified was the CORONA study, concluded in 2007, in which sudden death was 5.2% per year. The proportion of sudden death with respect to total death was similar over the years, which implies that total mortality also had a progressive decrease. In almost all studies, the incidence of sudden death was lower in the treated group than in the control group. There was a reduction of 44% in the incidence of sudden death (HR 0.56, 95% CI 0.33-0.93, p=0.03) over the 19 years considered. An additional adjustment for baseline characteristics and treatment significantly attenuated this reduction (HR 0.90, 95% CI 0.61-1.32, p NS). The risk of sudden death was higher the longer the follow-up, the longer the time elapsed from the diagnosis of HF until inclusion in the study, and the lower the EF within each trial.

*The assessment of the incidence of sudden death is subject to a series of methodological problems. The first one is the definition, that is, the time elapsed from the onset of symptoms (there have been definitions that only consider 15 minutes, others extending to 1, 6 or 24 hours), the presence or not of witnesses, and the coexistence with other manifestations of heart failure. Each of these points can vary in different definitions used in clinical trials and in observational studies. It is easier to attribute sudden death to a patient in FC II than to one in FC IV, as it is also easier to attribute sudden death to the subject who dies in his home compared to the one who dies in the hospital. Another important issue is who defines the type of death: the attending physician or an external committee of endpoints. For all these reasons, there may be diversity in the values reported in different trials, beyond which, logically, the clinical and paraclinical baseline differences play a fundamental role.*

*Further than these considerations, this study demonstrates a consistent reduction over time in the incidence of sudden death in patients with HFrEF. What has changed? Undoubtedly, there are several factors that we can mention: a more aggressive approach of the underlying coronary heart disease, either pharmacological or non-pharmacological, in a large numbers of patients; the identification of factors that can increase risk: excessive use of diuretics, sympathomimetic drugs, etc,; and doubtless, the increasingly widespread use of neurohumoral antagonists. If the use of spironolactone, which was shown to reduce the incidence of sudden death, was tested in the RALES study (the first on the list), was it not logical to find a lower-than-expected risk in subsequent studies in which antialdosterone drugs were already commonly used among hospitalized patients,? If beta-blockers significantly reduce sudden death, was it not reasonable to observe a higher-than-expected risk in studies which were just exploring its use compared to other studies where about 90% already used them? It is true then that the correct treatment of heart failure significantly reduces the risk of sudden death. How to properly select patients who despite the best pharmacological approach can benefit from the implantation of an ICD remains a challenge. Large observational studies, subgroup analyses carried out with extreme methodological rigor, may perhaps provide the answer that randomized studies conducted in the traditional way seem not to offer.*

## Increasing diet quality improves the prognosis. Follow-up results of two cohorts

Sotos-Prieto M, Bhupathiraju SN, Mattei J, Fung TT, Li Y, Pan A, et al. Association of Changes in Diet Quality with Total and Cause-Specific Mortality. **N Engl J Med 2017; 377:143-53. http://doi.org/cg4v**

The relationship between food quality and prognosis has been demonstrated in numerous epidemiological studies and some randomized studies. How do changes in diet influence people's long-term evolution, and how does it specifically affect cardiovascular and total mortality? The authors of the here presented work answer this question based on two well-known studies: the Nurses' Health Study, which started in 1976 enrolled 121,700 nurses between 30 to 55 years of age, and the Health Professionals Follow-up Study, which began in 1986 and prospectively followed-up 51.529 professionals aged between 40 and 75 years. At baseline and then every 2 years the participants in each of these studies had to answer questionnaires about medical data and lifestyle. At baseline and every 4 years they reported their eating habits with a structured questionnaire.

This analysis considered the information collected in 1986; 1998 was taken as follow-up initiation and 2010 as the end of the study. Those who were diagnosed cardiovascular disease or cancer in 1998; those on whom complete information about diet and lifestyle was not obtained, and those who had a markedly hypocaloric (<800 daily cal. in men, <500 daily cal. in women) or hypercaloric (>4.200 cal. daily in men, >3.500 cal. per day in women) diet were excluded from the study. To assess the diet, 3 recommended scores were used: a) the Alternative Index of Healthy Eating, which considers 11 components of the diet and according to the frequency and quantity of each component and its relation to the risk of chronic disease ranks them with a score that goes from 0 (not healthy) to 10 (the healthiest), so that the total score can range between 0 and 110; b) the Alternative Mediterranean Diet Score, which considers 9 components and awards each one 0 or 1 point, according to whether its consumption is above or below the median population, so that the score can vary between 0 and 9, indicating higher scores for healthier behavior; c) the DASH score (Dietary Approach to Stop Hypertension), which includes 8 components and gives 1 (unhealthy) to 5 (the healthiest) points according to consumption, so that the total score ranges from 8 to 40 points . It has already been demonstrated with the use of these scores that adherence to healthier eating is associated with a reduction in total mortality ranging between 8% and 22%, cardiovascular mortality between 19% and 28%, and mortality due to cancer between 11% and 23%.

The score values were then considered for each cohort in 1986 and in 1998. The difference between the two scores allowed defining for each participant whether food quality had worsened (lower score in 1998 than in 1986), remained the same or improved (score increase). Five quintiles were then defined according to the difference achieved, the lowest corresponding to those with the highest level of decline in scores, and the highest to those who had achieved the greatest increase. The association of the 5 quintiles with cardiovascular and global prognosis was defined taking as index date 1998 and extending the follow-up until the occurrence of the event or 2010, in which the planned follow-up was concluded.

As different feeding patterns are logically associated with other baseline characteristics, physical activity and treatment, the relationship between diet change and prognosis was adjusted by age, calendar year, initial diet, body mass index, menopause, use of hormone replacement therapy, family history of cardiovascular disease, hypertension, diabetes and dyslipidemia, alcohol consumption, cigarette consumption and changes during follow-up, baseline physical activity and during follow-up, and use of statins and antihypertensive medication. In both cohorts, those who improved food quality over time started with a poorer initial quality, were younger, consumed less alcohol and performed more physical activity. Food quality change consisted primarily in increasing whole grain, vegetable and omega-3 acid consumption, and in decreasing sodium

consumption. In multivariate analysis, an inverse relationship was demonstrated between diet changes between 1986 and 1998, and the prognosis thereafter. Compared with those who did not show significant change (increase between 0% and 3%) in the scores between 1986 and 1998, those with the greatest improvement in diet quality (between 13% and 33% increase in the scores) had a reduction of 9% and 16% in the risk of total mortality; in contrast, in those with the greatest worsening of diet quality, risk increased between 6% and 12%. All these differences were significant. A 20% increase in scores was associated with a reduction in total mortality between 8% and 17%. In the subgroup of participants with the worst baseline score but the greatest increase in follow-up, there was a reduction in the risk of total mortality between 15% and 28%. The longer the sustained increase in scores, the greater the benefit in terms of mortality reduction. Different adjusted analyses considering the manifest smoking or alcohol consumption yielded similar results.

*Different publications have confirmed the favorable prognostic value of a healthy diet. In the Argentine Society of Cardiology Journal 84: 4, 2016 we discussed the Aune et al. meta-analysis, which shows a reduction in cardiovascular events and total mortality with the high intake of whole grain cereals, and in the Argentine Society of Cardiology Journal 84: 5, 2016 we noted in the Stewart et al. study that a diet rich in components of the so-called Mediterranean diet is a predictor of good evolution, and that the benefit of the healthy components weighs more than the damage that is caused by the undesirable ones. It is true that perhaps the consumption of whole grains points to a population more concerned with its health status, with greater care of itself, more physical activity and better socioeconomic level; however, many of the studies considered adjusted for these variables and the association with better prognosis persisted. It is also true that in observational studies such as the one presented here, variables underlying dietary patterns (e.g., medical treatment, lifestyle, physical activity, comorbidities not taken into account) may be at least partly responsible for the best evolution. But the authors have adjusted for a large number of baseline variables, and an essential data is the demonstration of a dose response gradient: the more the diet improves over time, the more the long-term prognosis does, and in contrast, worsening of the diet is associated with worse evolution. Nevertheless, it is clear that these changes may be associated with others that are responsible for the observed response (perhaps subjects that for different reasons worsen their diet and cease to take care of themselves due to the presence of organic disease or depression or that suffer deterioration of their economic situation, which, as we know, also overshadows the forecast). But in certain situations we cannot expect randomized trials. In the light of what we already know, could anyone assign study participants to abandon "prudent" eating patterns, as the INTERHEART study says, to eat animal fats in an excessive way?*

*Be it really because of the diet effect, be the diet the expression of other factors, the truth is that this publication confirms that nothing is irreversible in the field of cardiovascular disease; and that there is always time to twist the course of events.*

## Positive pressure: more neutral than positive in the treatment of sleep apnea. A meta-analysis

Yu J, Zhou Z, McEvoy RD, Anderson CS, Rodgers A, Perkovic V, et al. Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea: A Systematic Review and Meta-analysis. **JAMA 2017;318:156-66. http://doi.org/cg4w**

Sleep apnea has been linked to a series of adverse factors from the cardiovascular point of view: increased sympathetic tone, endothelial dysfunction, increased insulin resistance, increased incidence of hypertension, diabetes, stroke, ventricular arrhythmia, and sudden death. However, treatment with positive airway pressure has not consistently demonstrated a reduction in the rate of events. We reviewed in the Argentine Society of Cardiology Journal 84: 5, 2016 the SAVE study, which could only show improvement in quality of life. We now have a meta-analysis that includes 10 randomized studies with 7,266 patients (5,683 with obstructive apnea, the rest with central apnea), in whom positive pressure treatment was compared with conventional treatment, or sham positive pressure (fictitious, false). Nine of the 10 studies were published during or after 2010, the number of participants ranged from 83 to 2,717, the follow-up varied between 6 and 68 months and the average adherence between 1.4 and 6.6 hours per day.

There was no association of active treatment with significant reduction of cardiovascular events, death (total, cardiovascular or non-cardiovascular), acute coronary syndrome, stroke or heart failure. In meta-regression analysis, there was neither relationship with adherence, length of follow-up or baseline apnea-hypopnea index. There was no clear effect of positive pressure on blood pressure, body mass index, blood glucose, or lipid levels. However, some association was found with improvement in drowsiness and quality of life. A post hoc analysis suggested that in those studies in which adherence to treatment was reached for at least 4 hours daily, there was a reduction in the risk of major cardiovascular events (RR 0.58, 95% CI 0.34-0.99).

*This meta-analysis provides results similar to those reached by the SAVE study with almost 2,700 patients. Doubts are raised. The association between sleep apnea and metabolic, endocrine and neurohormonal disorders is true from the physiopathological point of view. However, treatment with positive pres-*

*sure does not improve many of these conditions or impacts in the prognosis. Is sleep apnea then a risk marker, an innocent observer of something that goes on outside that association? Or is it that this form of treatment is inadequate, and hence the failure? The decrease in events in those with longer daily treatment is a posteriori finding that is not enough to make a firm recommendation, but leaves an open gap in a predominantly negative scenario. However, the beneficial effect on daytime sleepiness and quality of life should not be forgotten. For now it is the only true data to avoid relegating positive night pressure to the chest of memories.*

## Natriuretic peptide-guided therapy: end of the illusion? The GUIDE IT trial

Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of Natriuretic Peptide-Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. **JAMA 2017;318:713-20. http://doi.org/cg4x**

Heart failure patients have increased plasma levels of natriuretic peptides in response to enhanced wall stress. The elevation of peptide levels is important to diagnose the disease (especially due to their sensitivity and negative predictive value) and contributes to predict prognosis. It has also been postulated that plasma levels may be useful to guide treatment: persistently elevated levels would indicate failure of adopted measures favoring the modification of the diuretic treatment and the increase of neurohormonal antagonist doses. Different randomized trials have compared a conventional treatment strategy (guided by the presence of congestive signs) versus one based upon reducing peptide plasma levels. Different meta-analyses of these studies have suggested reduced total mortality and hospitalization for heart failure with peptide-guided therapy. However, no single clinical trial was able to demonstrate marked benefit and, in fact, most studies had shown a neutral result.

Therefore, great expectations had been placed on the GUIDE IT trial, the largest study designed so far to evaluate the effect of peptide-guided therapy in patients with heart failure and reduced ejection fraction (HFrEF). The study included patients with EF <40%, clinical heart failure, and history of hospitalization or visit to the emergency room for that cause, or intravenous diuretic treatment during the last year. Patients should have NT pro BNP >2,000 pg/ml or BNP >40 pg/ml in the last 30 days to be included in the study. Participants were randomly assigned in a 1:1 ratio to conventional treatment of NT pro BNP-guided values, with the aim of achieving values <1,000 pg/ml. Physicians in both study arms were encouraged to privilege the use of neurohormonal antagonists over that of diuretics, except in cases of clear congestive signs. A sample of 1,000 participants was calculated, taking into account a combined primary endpoint of cardiovascular death or hospitalization for heart failure, 40% annual incidence of this endpoint in the conventional treatment group, a relative 20% reduction in the guided treatment group, 90% power and alpha error of 0.05.

A total of 894 patients (446 in the NT pro BNP-guided group) were finally included in the study between 2013 and 2016. Median age was 63 years, median EF 35% and median NT pro BNP 2,653 pg/ml. Ninety-three percent of these patients were treated with beta blockers, but with a mean dose of only 34% of the target dose according to treatment guidelines, 75% were receiving a mean dose of renin-angiotensin system inhibitors/antagonists that was 42% of the target one and 49% were treated with antialdosterone agents (mean dose, 96% of the target one). Forty percent of patients had an implantable cardioverter defibrillator and 19% a resynchronizer. After a median 15-month follow-up, the study was discontinued by the Data Monitoring and Safety Committee, because the interim analysis showed futility to continue the trial. At that moment more than half of the predicted events had taken place. Patients assigned to guided therapy had more visits to the doctor's office (median of 12 vs. 10, p=0.002) and more treatment adjustments (median of 6 vs. 4, p<0.001), but finally there was no difference in the treatment intensity reached. Thus, for example, the mean dose of beta blockers attained with respect to the target dose in the peptide-guided and conventional treatment groups was 48% and 45%, respectively (p=ns) and something similar occurred with renin-angiotensin system inhibitors/antagonists: 55% vs. 53%, p=ns. Neither were there differences in the final furosemide mean final dose: 86 vs.77 mg per day, p=ns.

In agreement with this lack of difference in medication, there was no variation in the NT pro BNP attained at the end of the study: it decreased from an average of 2,658 pg/ml to 1,209 pg/ml in the peptide-guided group (53% decrease) and from 2,678 pg/ml to 1,397 pg/ml (48% decrease) in the conventional treatment group (p=ns). The primary endpoint occurred in 37% of patients in both groups, and adjusted for age, sex, EF, diabetes and NT pro BNP, the HR for the primary endpoint was 0.98 (95% CI 0.79-1.22). Neither were there significant differences in hospitalization due to heart failure and total and cardiovascular mortality.

*The GUIDE IT trial is a hard blow for advocates of the peptide-guided therapy. It shows that when recommended guideline measures are implemented for the use of neurohormonal antagonists, there is no need to routinely assess NT pro BNP. It is worth noting that if the goal in peptide-guided therapy was to attain a value <1,000 pg/ml, this was only achieved in 46% of cases versus 40% in the conventional treatment group.*

*This trial is not an example of the maximum treatment that can be provided: the mean dose of betablockers and renin-angiotensin system inhibitors/antagonists was only half the therapeutic dose. The patients' outcome could have been better if higher doses had been used. Yet, knowing the NT pro BNP value as part of the follow-up studies was not enough, perhaps in some cases due to limitations imposed by the patient's condition (low blood pressure, reduced heart rate, conduction abnormalities, renal dysfunction, etc.) and in others due to lack of physician indication.*

*How should the results of the GUIDE IT study be read? "Previous positive studies were those showing greater use of neurohormonal antagonists in the guided treatment group. J. Januzzi, one of the greatest supporters of guided therapy and author of this study, had already pointed out that previous trials had shown no difference with conventional therapy in patients in which medical care in the treatment group had been of high quality." A confession of parts….If things are done right, serial peptide assessment is not essential. Does this mean that we should never know its value? Neither. Early injury detection (for example in patients undergoing chemotherapy), the differential diagnosis in unclear cases of dyspnea, and patient evaluation with poor response to treatment are situations in which its use is welcome. An approach based on careful examination, laboratory control, thorough echocardiographic study and close contact to improve treatment in each patient visit are still the key in the vast majority of cases.*

## An early invasive strategy could decrease mortality in subgroups of patients with non-ST-segment elevation acute coronary syndrome. Results of a meta-analysis

Jobs A, Mehta SR, Montalescot G, Vicaut E, Van't Hof AWJ, Badings EA, et al. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. **Lancet 2017;390:737-46. http://doi.org/gbvvxg**

An invasive strategy (angiography and coronary angioplasty when indicated) for the treatment of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is the routine recommendation for all moderate to high risk disorders. In patients with refractory angina, hemodynamic or electrical instability (all conditions associated with worse in-hospital prognosis), the invasive conduct should be as early as possible. In patients without this presentation but with elevated biomarkers, ECG changes or high GRACE score (>140 points predicts in-hospital mortality >3%), it is accepted to implement the invasive conduct within the next 24 hours. The most recent information comes from the TIMACS study, in which a global early invasive strategy (within 24 hours, median of 14 hours) was associated with a significant reduction in the combined final endpoint of death, acute myocardial infarction (AMI) or stroke compared with a delayed intervention (more than 36 hours, median of 50 hours) only in patients with GRACE score >140. And different meta-analyses suggested that the clear benefit of the early invasive strategy mainly consisted in the reduction of refractory or recurrent ischemia.

Until now, the effect of early invasive strategy on each separate endpoint was not clear, and neither whether beyond the already mentioned GRACE score subgroup, there are other subgroups which might specially benefit. The meta-analysis here presented was carried out to answer these questions. It included all studies comparing an early vs. a delayed strategy of coronary angiography in NSTE-ACS patients, reporting events at 30 days and providing, thanks to the collaboration of each study author, with individual data or lists of data prepared to that effect. The primary endpoint was all-cause death. A global analysis and a specific analysis in 4 subgroups were made: age ≥75 years, diabetes, positive biomarkers and GRACE score >140. Eight studies were included: ABOARD, ELISA, ELISA-3, ISAR-COOL, LIPSIA-NSTEMI, RIDDLE-NSTEMI, the one from Sciahbasi et al. (individual data from each patient were obtained from all of them) and the TIMACS study which presented ad hoc listed data. A total of 5,324 patients were included, 3,031 from the TIMACS study. Essential information is the heterogeneity of definitions used. Thus, for example, in three studies, the early strategy consisted in the immediate performance of the hemodynamic study and in the rest its accomplishment within the first 24 hours. Therefore, in those with immediate intervention, the later performance of the study but within the first 24 hours was already considered a delayed approach, whereas in those considering as early the intervention accomplished within the first 24 hours, only the one achieved later (even up to 108 hours in the ISAR-COOL study) was considered delayed.

Median follow-up was 180 days. During this period, there was a trend but not significant decrease of total mortality with the early strategy (HR 0.81, 95% CI 0.64-1.03, p=0.088). Neither were there differences in the incidence of AMI (HR 0.91, 95% CI 0.57-1.46). In the subgroup analysis, however, the results were different. Patients aged ≥75 years represented 24% of the total, but provided 49% of deaths during follow-up. In them, the HR for total mortality in the early vs. the delayed strategy was 0.65, 95% CI 0.46-0.93. Diabetic patients were 27% of the total, but supplied 37% of deaths, and in them the HR of the early strategy was 0.67, 95% CI 0.45-0.99. Seventy-nine percent of patients had positive biomarkers and provided the same proportion of deaths; in them, the HR of the early strategy was 0.76, 95% CI 0.58-0.99. Finally, in patients with GRACE score >140 (defined only in 4 of the 8 studies, though including 80% of the total number of patients) the HR of the early strategy was 0.70, 95% CI 0.52-0.95). A meta-regression analysis could

not establish an association between the variable time to perform the study within each strategy and the incidence of mortality, but it could do so with the incidence of AMI: the earlier the intervention, the greater the reduction.

*This meta-analysis suggests that although, globally, an early reperfusion strategy compared with a delayed reperfusion strategy does not decrease NSTE-ACS mortality, there is a trend that should be taken into account, based on the benefit afforded to patients at greater risk (elderly, diabetic, increased GRACE score). Some consideration should be stated. Almost 60% of data come from only one study, the TIMACS trial, which carries significant weight on the total result. A notable heterogeneity was found in the times considered to define one strategy or another, even with overlapping between what is defined as early in one study and delayed in another. And finally, the tests for interaction in each of the subgroups have not been positive. Thus, for example, although it is true that in diabetics the HR was 0.67 (95% CI 0.45-0.99), in non-diabetics the HR was 0.92 (95% CI 0.67-1.23). To accurately state that the intervention in diabetics generated a different effect than that achieved in non-diabetic patients, both HR should be significantly different. This does not occur, and the same situation is encountered in the other three groups. Therefore, the benefit exhibited should be seen as something possible, generator of hypotheses, but without achieving a condition of certainty. Nevertheless, and until confirmed, the data presented can help us pay more attention to certain patient characteristics and make decisions in specific cases.*

## A Swedish registry suggests that phosphodiesterase 5 inhibitors reduce mortality in patients after acute myocardial infarction

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Erectile dysfunction (ED) is a risk marker for cardiovascular disease, preceding its onset by 3-5 years, and in patients with established disease is a marker of worse outcome. A common concern among doctors and patients is whether drugs used to treat ED impose greater risk of events to patients having suffered a recent acute myocardial infarction (AMI). The answers are often based on preconceptions or in a defensive attitude ahead of possible harm. An observational Swedish study provides interesting data that deserve to be discussed.

Using the national and compulsory registry of patients and of prescribed and dispensed medication, the study authors included all men from 18 to 80 years of age, who had been hospitalized due to a first AMI between January 2007 and December 2013. Patients with prior AMI or some revascularization procedure, history of prostatectomy or colorectal cancer surgery before their AMI, and those who had received medication due to ED between 2005 and AMI occurrence were excluded from the study. Exposed patients were those who had received at least one prescription of the drugs used in Sweden for ED (sildenafil, vardenafil, and tadalafil, which are phosphodiesterase-5 inhibitors and alprostadil, which has prostaglandin E1). The final endpoints were major events (hospitalization for AMI, heart failure or revascularization), all-cause death and cardiovascular or non-cardiovascular death. The incidence of prostatectomy and colorectal cancer surgery was also investigated. Follow-up started 30 days after AMI occurrence and concluded upon presentation of the endpoint events, or on December 31 2013 if no events had taken place.

Among a total of 43,145 patients, 3,068 (7.1%) were treated with ED medication after AMI. Compared with the rest of the patients, they were younger (mean of 61 vs. 64 years) and with lower prevalence of comorbidities. At a mean follow-up of 3.3 years, the annual incidence of all-cause mortality was 1.43% vs. 3.45% in the other group (HR adjusted for age, comorbidities and concomitant medication was 0.67, 95% CI 0.55-0.81). There was a significant reduction of cardiovascular and non-cardiovascular death. No significant differences were encountered in the incidence of AMI or revascularization procedures, but a significant difference was found for heart failure (adjusted HR 0.60, 95% CI 0.44-0.82) and major events (adjusted HR 0.79, 95% CI 0.68-0.92).

Although the age group between 70 and 80 years was the one receiving less frequently prescription for ED (3.5% vs. 9.2% in patients <60 years of age and 8.5% in those between 60 and 69 years), it was the one which derived the highest benefit. Effectively, only in this subgroup a significant reduction of mortality was verified, compared with a certain trend between 60 and 69 years and the absolute lack of difference among the younger ones. The group above 70 years also presented significant reduction of hospitalization for heart failure. Reduced mortality was verified with phosphodiesterase-5 inhibitors but not with alprostadil, and was more marked the higher the number of prescriptions (81% mortality reduction in patients receiving more than 5 prescriptions vs. 53% in those receiving between 2 and 5 and 34% in those receiving only one prescription).

*There are various physiopathological reasons for the eventual benefit of phosphodiesterase-5 inhibitors in post AMI patients: anti-ischemic effect, improved hemodynamic conditions, reduction of arterial stiffness. However, before falling in an exaggerated enthusiasm, we must mention the potential limitations of the study. There is no diagnosis of ED in the patients, only that the treatment is considered as a sign of its presence. Firstly, it should be assumed that not all patients with*

*ED received treatment: a prevalence of at least 20% is considered for a population >60 years, and the proportion which received treatment in this study was 7%. It is known that in general, patients with ED receiving specific treatment are of higher sociocultural and economic level than those who do not receive it. Although the HR was adjusted for age and comorbidities, many factors of residual confusion, among them cited ones, can be responsible for the better prognosis. Neither do we know the AMI characteristics, nor the blood pressure at the onset of treatment. Perhaps patients with ED, more extensive AMI, and lower blood pressure are not treated, and it is the hypotension or poor ventricular function the factor that predicts worse outcome. It is the inherent risk of every observational study. Another point of interest is that, as we see it, the data presented are not sufficient to support a definitive conclusion. Will they suffice to perform a randomized study?*