JORGE THIERER

The ASPREE study: more evidence that questions the usefulness of aspirin in primary prevention

McNeil JJ, Woods RL, Nelson MR, Reid CM, Kirpach B, Wolfe R, et al. Effect of Aspirin on Disability-free Survival in the Healthy Elderly. **N Engl J Med 2018;379:1499-508. http://doi.org/ct5g**

McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. **N Engl J Med 2018;379:1509-18. http://doi.org/ct5f**

McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. **N Engl J Med 2018;379:1519-28. http://doi.org/ct5h**

The use of aspirin is indisputable in secondary prevention of cardiovascular and cerebrovascular events. In contrast, in primary prevention, a favorable balance between the prevention of ischemic events and the incidence of bleeding attributable to medication has provided controversial data. The indications in the treatment guidelines are not uniform. Recently, the ARRIVE study could not demonstrate a significant reduction in ischemic events but a higher incidence of hemorrhagic events in patients with 10 to 20% estimated risk of events at 10 years (although the actual incidence was less than 10%). In the same line, in the ASCEND study in diabetic patients, use of aspirin in primary prevention showed reduction of cardiovascular and cerebrovascular events but a similar increase in bleeding episodes. We now know three publications of the ASPREE study, which question even more the usefulness of aspirin in primary prevention.

The ASPREE study was a randomized, double-blind, placebo-controlled study that included ≥70 year-old patients (≥65 years old if black or Hispanic), in apparent good health, with a life expectancy of at least 5 years., free from cardiovascular and cerebrovascular disease, dementia-free and with adequate physical capacity to perform daily activities (bathing, dressing, going to the bathroom, moving, walking and feeding). Patients with systolic blood pressure ≥180 mm Hg or diastolic ≥105 mm Hg, with high risk of bleeding, anemia, indication or contraindication for the use of aspirin, or anticoagulants were excluded. Based on the events of interest (death, dementia and marked disability in at least one of the mentioned activities) a composite endpoint of dementia-free survival and disability was defined. The participants, after a run-in period in which a placebo was administered for one month, were admitted to the study if they demonstrated an intake of at least 80% of the pills administered. They were randomly assigned, in a 1:1 ratio, to 100 mg of enteric coated aspirin or placebo. A total of 19,114 participants were included between 2010 and 2014 (9,525 in the aspirin arm). Median age was 74 years, and 56.4% were women, Eighty-seven percent of participants were recruited in Australia, and the rest in the United States. A little over 74% were hypertensive, almost 11% diabetic and 64% dyslipidemic. Nineteen percent had history of cancer, and 11% were using aspirin before entering the study.

In June 2017, the study was terminated, since the available data made it extremely difficult to demonstrate a reduction in the incidence of the primary endpoint. By then, the median follow-up was 4.7 years. In the last follow-up year, 62.1% of patients in the aspirin arm and 64.1% in the placebo arm continued taking the allocated medication. The annual incidence of the composite endpoint of death, dementia or disability was 21.5 ‰ in the aspirin arm, and 21.2 ‰ in the placebo arm (p NS). There were no differences in various subgroups defined by age, gender, body mass index, risk factors, etc. Of the three components of the primary endpoint, the most frequent was death (50% of cases), followed by dementia (30%) and disability (20%). There was no difference in the onset of dementia or disability. The incidence of major bleeding was highest with aspirin: 3.8% vs. 2.8%, HR 1.38 (95% CI 1.18-1.62). The incidence of hemorrhagic stroke was similar in both arms: 0.5% vs. 0.4%.

However, the specific analysis of mortality yielded unexpected information: the annual incidence of all-cause mortality was 12.7 ‰ in the aspirin arm and 11.1 ‰ in the placebo arm (HR 1.14, 95% CI 1, 01-1.29). The difference was mainly in death from cancer, which accounted for 49.6% of all deaths: 6.7 ‰ per year in the aspirin arm vs. 5.1 ‰ per year in the placebo arm. The curves of total mortality and cancer mortality began to differ in the third follow-up year. There was no tendency for a specific location of cancer, but the contribution of gastrointestinal cancer was substantial. There was also no difference in the subgroup analyses. In the general population matched by age, gender, country and race, the annual mortality was much higher than in the placebo arm of the study population: 34.9 ‰ vs. 11.1 ‰. Similarly, the incidence of death from cancer was higher in the general population: 10.5 ‰ vs. 5.1 ‰ in the study.

Another specific analysis was carried out on the incidence of cardiovascular events and bleeding. And again the news was not favorable to aspirin. A pre-specified secondary endpoint of cardiovascular disease (fatal coronary disease, non-fatal myocardial infarction, fatal and non-fatal stroke, and hospitalization due to heart failure) had a similar annual incidence in both

groups: 10.7 ‰ vs. 11.3 ‰. And the incidence of major cardiovascular adverse events (fatal or non-fatal myocardial infarction, fatal or non-fatal stroke), those in which the role of thrombosis is supposed to be essential and therefore where a beneficial effect of aspirin may be expected, also did not differ significantly: 7.8 ‰ vs. 8.8 ‰. On the other hand, there was a marked difference in the incidence of major bleeding: 8.6 ‰ per year with aspirin vs. 6.2 ‰ with placebo (HR 1.38, 95% CI 1.18-1.62). The incidence of gastrointestinal bleeding (HR 1.87) and intracranial hemorrhage (HR 1.50) was also significantly higher with aspirin.

What is important

The use of aspirin in primary prevention has been questioned in recent years. A 2009 meta-analysis with 95,000 patients established a relative reduction in a composite endpoint of cardiovascular death, acute myocardial infarction (AMI) and stroke of about 12%, at the expense of 30% increased risk of bleeding. The risk reduction was significant only for the incidence of AMI, not for stroke or cardiovascular or all cause mortality. Another meta-analysis performed in 2012, with more than 100,000 patients confirmed the reduction of events, especially of AMI, but again with a significant increase in bleeding. Therefore, the indication of aspirin in this context differs among practice guidelines, and it is generally assumed that it depends on the balance between ischemic and hemorrhagic risk. The Prevention Guideline of the European Society of Cardiology considers the indication of aspirin in primary prevention as class III (it should not be carried out). The 2016 update of the SAC prevention guideline takes into account the risk of events and the risk of bleeding. Only when the risk of events at 10 years is>20% and the risk of bleeding is low does the guideline consider aspirin as II a indication in primary prevention. With a lower risk of events and/or a higher risk of bleeding, the indication is IIb or III.

Recently, the results of the ARRIVE study helped to calm the enthusiasm for the use of aspirin in primary prevention. The results of these three publications of the ASPREE study shed another shovel of earth on the well in which for decades has been an indisputable indication. In this sense, the data are more conclusive: in a population with good cardiovascular health, but exposed to risk simply by virtue of advanced age, the use of aspirin not only does not improve the cardiovascular prognosis, but overshadows the overall prognosis. This excess of total mortality must be viewed with caution because it is a secondary endpoint in a study in which the sample size was not calculated according to it. But due to the number of patients involved and the consistency of the findings in different subgroups, it is not a negligible data. It is deeply interesting that this excess is due to a higher incidence of death from cancer, since until now the available information had gone from a certain preventive effect to a neutral effect. This is the first time that an increase in the incidence of fatal and non-fatal cancer has been attributed to aspirin. One might think of a chance effect, but the data are concordant for different forms of the disease, with greater or lesser significance according to the number of recorded cases.

It will be necessary to study in detail what intrinsic mechanisms underlie this increase. We also understand the need of new cohort or randomized studies that confirm this risk. And there remains, as a defense wielded by lovers of aspirin, the doubt about whether a more extensive follow-up could have resulted in a decrease in the incidence of cancer, as if the drug had a dual action: an increase in the incidence of cancer by certain earlier phenomena, a decrease in its incidence by mechanisms that require more time to manifest.

Beyond these speculations, the whole body of available information strongly suggests that the use of aspirin is not a strategy that we should understand as universal. In low-risk patients such as those of the ASPREE or ARRIVE studies there is more to lose than to gain with an indiscriminate indication. Perhaps, in patients at higher risk, which equals or at least approaches them to secondary prevention, and with adequate measures to reduce bleeding, there is still a place under the sun for aspirin in primary prevention. But it is clear that the range of treatable patients has narrowed significantly.

And an extra data, which reveals how patients who are included in randomized studies often do not represent the general population: in a simulated cohort matched to the study by age, gender, country of origin and race, annual all-cause mortality was 34.9 ‰, and the annual cancer mortality 10.5 ‰, compared to figures of 11.1 ‰ and 5.1 ‰ in the study population.

New failure of anticoagulant therapy in patients with heart failure and low ejection fraction: the COMMANDER HF study

Zannad F, Anker SD, Byra WM, Cleland JG, Fu M, Gheorghiade M, et al. Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. **N Engl J Med 2018;379:1332-42. http://doi.org/gfdg5d.**

In patients with heart failure and reduced ejection fraction (HFrEF) there is activation of the coagulation cascade. The indication of anticoagulant therapy is indisputable when these patients present atrial fibrillation (AF); however, there is no firm evidence to indicate it when they are in sinus rhythm. In fact, in the last decade several studies were carried out that tested the use of warfarin in patients with HFrEF and sinus rhythm, none of which demonstrated a beneficial effect of the intervention. In recent years we have learnt about a new class of anticoagulant agents, direct-acting oral anticoagulants, which demonstrated superior efficacy to warfarin in the context of AF, and a beneficial effect in the treatment of deep vein thrombosis and pulmonary thromboembolism. One of them, rivaroxaban, in lower doses than those used in AF and combined with aspirin, demonstrated in the COMPASS study the ability to reduce the inci-

dence of death and acute myocardial infarction (AMI) or stroke in patients with stable coronary or peripheral vascular disease. And in the ATLAS study, rivaroxaban, also in low doses and associated with dual antiplatelet therapy, reduced the same endpoint in patients with an acute coronary syndrome. In both studies, the subgroup of patients with history of heart failure presented a higher rate of events, and obtained greater absolute benefit with the use of rivaroxaban. The aforementioned facts constitute the substrate for conducting the COMMANDER HF study.

This multicenter, randomized, double-blind, placebo-controlled study included patients with a history of HFrEF of coronary etiology (left ventricular EF ≤40%) of at least 3 months duration, who had been treated for decompensation of their condition within 21 days prior to their incorporation in the study. They should be in sinus rhythm, with glomerular filtration rate ≥20 ml/min/1.73 m2 and no indication or precise contraindication for anticoagulation. Patients were randomly assigned in a 1:1 ratio to receive rivaroxaban at a dose of 2.5 mg. twice daily or placebo. The primary efficacy endpoint was a composite of all-cause death, non-fatal AMI or nonfatal stroke. The primary safety endpoint was a composite of fatal bleeding or bleeding in a critical space with the potential to cause permanent disability (e.g., intracranial, intraspinal or intraocular).

Between 2013 and 2017, 5,022 patients (2,507 in the rivaroxaban arm) were included in 628 centers in 32 countries. Seventy-seven percent of patients were men, almost 41% diabetic, 75% hypertensive, and 75.7% had history of AMI. The median left ventricular EF was 34%; the usual NYHA FC was II in 44% and III in 49% of cases. More than 90% of patients were treated with diuretics, beta-blockers and renin-angiotensin system antagonists or inhibitors, and almost 77% with anti-aldosterone drugs.

At a mean follow-up of 21.1 months (interquartile range 12.9-32.8 months), the incidence of the primary efficacy endpoint was 25% in the rivaroxaban arm and 26.2% in the placebo arm (p=NS). The most frequent event of the composite endpoint was death (21.8% in the rivaroxaban arm and 22.1% in the placebo arm). The incidence of non-fatal AMI was 3.9% and 4.7%; and of non-fatal stroke of 2% and 3%, respectively. None of these differences were statistically significant. There was also no difference in the secondary endpoint of cardiovascular death or hospitalization due to heart failure (37.2% vs. 36.9%). The incidence of the primary safety endpoint was similar in both groups (0.7% vs. 0.9%) but higher bleeding was more frequent in the rivaroxaban arm (3.3% vs. 2%), mainly due to a drop in hemoglobin >2 g/dl.

Heart failure is a thrombogenic entity: it promotes thrombi formation and thromboembolic events. The alteration of the triad already described by Virchow is fulfilled: there is cardiac chamber dilatation with motility disorders, rheological abnormalities with increased blood viscosity, altered coagulation with increased levels of fibrinogen, neurohormonal activation and endothelial dysfunction with release of thrombogenic substances. At the same time, the decrease in the formation of nitric oxide and vasoconstriction specifically favor the existence of thrombotic vascular phenomena, and finally platelet abnormalities related with increased volume, decreasing their survival and increasing their adhesiveness. All these factors promote, then, the formation of thrombi at the level of the cardiac chambers and intravascular thrombosis.

However, studies such as WATCH and WARCEF failed to demonstrate the beneficial effect of oral anticoagulation. Was it expected that the results would be very different with rivaroxaban? A large part of the answer resides in a not minor detail: more than 90% of major events were deaths, and more than 70% of all major events were specifically deaths of cardiovascular origin. Let us compare these data with those of the COMPASS study, where in patients with stable coronary or vascular peripheral disease cardiovascular death represented only slightly more than 40% of major events. We know that death in the context of heart failure recognizes most of the time a mechanism linked to the progression of the disease or the occurrence of arrhythmic events, and that the use of neurohormonal antagonists and in selected cases electric therapy is associated with a decrease in mortality. Therefore, if the primary endpoint is reached primarily at the expense of death, and anticoagulant therapy is not capable of diminishing this event in this context, the result of the COMMANDER HF study is not at all unexpected.

The ATTR-ACT Study: A hope for patients with transthyretin amyloid cardiomyopathy.

Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. **N Engl J Med 2018;379:1007-16.**

Transthyretin (TTR) is a protein synthesized by the liver transporting thyroxine and vitamin A. Its structure is usually tetrameric, but pathologically it can dissociate into "misfolded" oligomers and monomers that deposit as amyloid fibrils in different body structures, including the heart, giving origin to amyloid cardiomyopathy (AC). The origin of TTR amyloidosis (TTRA) may be an inherited autosomal dominant mutation in the TTR gene (mTTRA), or the "wild type" deposition of TTR (wtTTRA) determined by the presence of the most extended allele, called normal, wild or natural, that is traditionally called senile amyloidosis. Transthyretin AC predominates in men >60 years, and its most frequent manifestations are heart failure, hypotension, syncope, arrhythmias and conduction disorders. The prognosis is poor in the short term and the average survival does not exceed 3 and a half years. The prevalence is greater than that presumed, with wtTTRA being found in 10 to 15% of the cases of aortic stenosis and heart failure with preserved ejection fraction (PEF) and 5% of the cases diagnosed as

hypertrophic cardiomyopathy. Recently, a compound has been developed, tafamidis, which is able to stabilize TTR by preventing its dissociation, and which has shown beneficial effects in amyloid polyneuropathy.

The multicenter, double-blind, placebo-controlled ATTR-ACT study randomly assigned patients with TTRA to tafamidis at doses of 80 or 20 mg daily, or placebo in a 2:1:2 ratio. They should have amyloid substance in cardiac or non-cardiac biopsy, and in the case of wtTTRA, immunohistochemical confirmation or by nuclear medicine or mass spectrometry studies. The inclusion criteria were history of heart failure, echocardiographic interventricular septal thickness >12 mm, NT proBNP >800 pg/ml and >100 meters in the 6-minute walk. Patients in FC IV, with glomerular filtration <25 ml/min/1.73 m2 or with light chain amyloidosis were excluded. Four hundred participants were required to demonstrate with 90% power a reduction in mortality of 30%, and an average reduction of 2.5 to 1.5 cardiovascular-related hospitalizations per person in the 30-month follow-up. In the analysis, mortality followed by cardiovascular-related hospital admission was hierarchically considered.

The study included 441 patients between 2013 and 2015, in 48 centers in 13 countries, 264 of them in the tafamidis arm. Median age was 75 years, and 90% were men. Seventy-six percent presented with wtTTRA and the rest mTTRA; 68% of the patients were in FC I-II, and 32% in FC III. Mean supine blood pressure was 115/70 mm Hg, without variation when standing upright. Average supine heart rate was 70 beats/min, and it increased 3 to 4 beats/min standing upright. At the 30-month mean follow-up, mortality was 42.9% in the placebo arm and 29.5% in tafamidis arm (HR 0.70, 95% CI 0.51-0.96), and hospital admission decreased from 0.70 to 0.48/patient/year (RR 0.68, 95% CI 0.56-0.61). The difference in mortality was ostensible following 18 months of treatment. There were already differences in the quality of life score and in the 6-minute walk at 6 months, and in the incidence of hospitalization at 9 months. The mortality results were similar in different subgroups; however in the case of hospitalization, there was interaction with FC, as the use of tafamidis was associated with a reduction of hospitalization in FC I-II and in contrast an increase in FC III. There were no differences in the incidence of adverse effects.

Finding cardiac amyloidosis is becoming more frequent in clinical practice. The development of imaging methods with the possibility of making a non-invasive diagnosis has undoubtedly contributed to this fact. As happens every time the diagnosis is facilitated, or that some therapeutic alternative appears, the pathology is further considered contributing to a more frequent diagnosis. The ATTR-ACT study confirms the poor prognosis the pathology entails: more than 40% mortality at 2 and a half years in the placebo arm, and even almost 30% in the active treatment arm. And we are talking about a population that is not the one we usually see when it comes to diagnosing AC! Let us see: 70% of patients in FC I-II, and without evidence of orthostatism (the same blood pressure in supine or standing position, and almost no change in heart rate). It is clear that in the usual practice we are late most of the time, because we usually make the diagnosis with patients in worse condition.

One point that deserves further investigation is the increase in the incidence of hospitalization with tafamidis in patients in FC III. The authors argue that the absence of a beneficial effect on hospitalization in this subgroup demonstrates that treatment should be instituted early, because when the disease is advanced, the ability to turn the tide is less. But if it were merely that, we would expect the drug to have a neutral effect, not unlike the placebo. Conversely, in the study, a damaging effect has been seen, which should be studied in more detail. In conclusion, we must celebrate the appearance of a specific therapy in a surely deadly pathology in the short and mid-term, which we must learn to search more frequently. Careful analysis of baseline characteristics associated with a higher response rate will allow adequate selection of candidates for treatment in the future.

Telemedicine is associated with prognostic improvement in heart failure: the TIM-HF 2 study

Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomized, controlled, parallel-group, unmasked trial. **Lancet 2018;392:1047-57. http://doi.org/gfcdgr**

One of the many consequences of the progress and dissemination of digital media is the development of telemedicine systems, which facilitate the remote care of patients with chronic pathology, improving diagnostic and therapeutic procedures. In the specific context of heart failure there have been several studies which have not allowed to draw definitive conclusions.

We now know the results of the German study TIM-HF 2, a prospective, randomized, controlled, open study, which explored the effect of telemedicine in patients with FC II-III heart failure and a hospitalization history for this cause in the last 12 months. They should have left ventricular ejection fraction (LVEF) ≤45%, but patients with LVEF >45% were accepted if they were treated with diuretics. Patients with major depression or hemodialysis were excluded. They were randomly assigned to receive conventional treatment for heart failure, or a strategy that added to this treatment remote management of the pathology. This management consisted in the provision of telemonitoring systems to obtain electrocardiographic, blood pressure, peripheral capillary O2 saturation and body weight records. Data was transmitted daily through a digital tablet to the coordinating center that worked 24 hours a day, 7 days a week. Each patient in the telemonitoring group received a cell phone to communicate with the coordinating center in case of emergency. In both

groups patients had an initial medical visit followed by others at 3, 6 and 9 months, and a final visit between 12 and 13 months, towards the end of the follow-up period. In addition, the telemonitoring group received also a medical education program run by nurses through structured monthly telephone interviews. Every 3 months a measurement of pro-adrenomedullin was made, and based on this value and the daily data, patients were classified as high or low risk. The primary endpoint of the study was the percentage of days lost to follow-up owing to death or hospitalization due to heart failure. To calculate the percentage of days lost due to death, days from the occurrence of death until the end of the planned follow-up were divided by the days of planned follow-up since the beginning of the study. For example, in a planned follow-up of 365 days, a death that occurred 73 days before the end implied a loss to follow-up of 20%. In order to determine the percentage of days lost due to hospitalization, the number of hospitalization days was divided by the number of follow-up days planned. In a follow-up of 365 days, an admission of 15 days implied a loss of 4%.

Between 2013 and 2017, 1,571 patients were included in the study. Data of 765 patients were finally used in the telemonitoring group and 773 in the usual treatment group. Average age was 70 years, and 70% were men; 28% of patients lived alone, and 60% lived in urban areas. Slightly over half of the patients were in FC II and the rest in FC III. Mean LVEF was 41%, and 35% had LVEF >45%. Ischemic etiology occurred in 40% of cases, and 45% were diabetic. Eighty-three percent of patients were treated with renin-angiotensin system inhibitors/antagonists, 92% with beta-blockers and 55% with antialdosterone drugs.

In the 393-day follow-up, 97% of the patients in the telemonitoring group complied with at least the delivery of 70% of the expected data. A median of 1,421 data were transmitted per patient. A total of 35% of patients in the telemonitoring group and 38% of patients in the usual treatment group presented the endpoint of death or hospitalization due to heart failure. The percentage of days lost for one reason or another was 4.88% in the telemonitoring group and 6.64% in the usual treatment group (p=0.046), which corresponds to means of 17.8 and 24.2 days respectively. In the telemonitoring group there was lower mortality (7.9% vs. 11.2% per year, HR 0.70, 95% CI 0.50-0.96) and lower percentage of days lost due to hospitalization for heart failure: 1. 04% vs. 1.53% (p=0.007).

This study establishes an irrefutable truth: a permanent monitoring of the vital signs, added to a strategy of patient education and the unrestricted access to the healthcare system guarantee a better prognosis than a usual strategy of quarterly consultations in the context of heart failure. It should be noted that the effect on mortality seems to be stronger than on hospitalization: total mortality decreases from 11 to 8% (a difference of 3%), while the composite endpoint of death and re-hospitalization does so from 38% to 35% (also 3%, which allows inferring that the incidence of hospitalization is practically similar in both groups).

The point to discuss is whether this strategy can be imitated or taken as an example to follow. It is doubtless a feasible strategy in a rich society in which everything works. Is it, from an economic point of view, the best? A thorough analysis of the information collected would allow us to define which data led most frequently to changes in treatment, additional medical consultations or even hospitalizations. We could know which data were predictors of unexpected events, or which were evidently futile. And we could even go so far as to prove that so much information might not be necessary; and that between a consultation every 3 months and a daily collection of vital data there could surely be intermediate stages (how about a visit every 2 months, or every month?). How much improved access to the healthcare system influenced the best evolution, and how much the patient's continuing education program? Even when the patients included in the study had an increased risk of events (all with hospitalization in the previous year) and were therefore patients in whom a more active behavior is justified, the considerations formulated aim to find a point of balance between the desirable and the possible, in a situation in which, on the other hand, there must be as many solutions as medical systems and coverage.

Harmony Outcomes and Declare TIMI 58: two new studies demonstrating a favorable effect of GLP 1 analogues and SGLT2 inhibitors on cardiovascular events in type 2 diabetic patients

Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Sr., Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomized placebo-controlled trial. **Lancet 2018;39:P1519-29. http://doi.org/gfb3ss**

Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. **N Engl J Med 2018 http://doi.org/cw4m**

GLP-1 analogues are hypoglycemic drugs that act by stimulating insulin secretion and decreasing that of glucagon. Randomized studies with cardiovascular endpoints have shown inhomogeneous effects. Thus, while exenatide and lixisenatide did not demonstrate superiority over placebo, semaglutide in the SUSTAIN study demonstrated significant reduction in the incidence of stroke, and liraglutide in the LEADER study was associated with significant reduction of a combined endpoint of cardiovascular death, non-fatal acute myocardial infarction (AMI) and non-fatal stroke. Additionally, in this study liraglutide showed reduced all-cause mortality.

We now know the results of the HARMONY Outcomes study, with another GLP 1 analogue, albiglutide, that arises from the genetic fusion of 2 tandem copies of human GLP1 modified with albumin, generating a

protein that can be weekly injected subcutaneously. HARMONY Outcomes was a multicenter, randomized, placebo-controlled, double-blind study. It included type 2 diabetic patients with known cardiovascular, cerebrovascular or peripheral vascular disease, with HbA1c >7% and a glomerular filtration rate of at least 30 ml/min/1.73m2. Patients with risk factors for pancreatitis, history of pancreatitis, medullary thyroid carcinoma or multiple endocrine neoplasia type 2 were excluded from the study. Patients were randomly assigned to receive a weekly injection of albiglutide at an initial dose of 30 mg that could rise to 50 mg in case the goal of glycosylated hemoglobin defined locally for each patient was not met, or a placebo injection. The primary endpoint of the study was a composite of cardiovascular death, AMI or stroke. Secondary endpoints were the primary endpoint plus urgent revascularization for unstable angina and each of the primary endpoint components separately. As in other similar studies, a noninferiority design was postulated, accepting 1.30 as the upper limit of the 95% CI for the hazard ratio when comparing active drug vs. placebo, which implies accepting noninferiority even when the incidence of the primary endpoint was 30% higher in the albiglutide group. If non-inferiority was demonstrated, a test would then be carried out to demonstrate superiority. An initial calculation of 611 events was found to determine with 90% power the non-inferiority of albiglutide, considering an expected event rate of 2% to 3% per year. This implied the need to recruit 9,400 patients and follow them up for 2.2 to 3.2 years. Once the study was started, an event incidence higher than expected was verified, allowing for a mean follow-up of only 1.1 years. A longer exposure time that would ensure certainty regarding the safety of the intervention was decided, extending the follow-up period to at least 1.5 years.

Between July 2015 and November 2016, 9,463 patients were successfully included in the study, 4,731 of them in the albiglutide group. Mean age was 64.1 years and 69% of patients were men. Seventy-one percent of patients had history of coronary heart disease, 25 % of cerebrovascular disease, 25% of peripheral vascular disease and 20% had history of heart failure. The average duration of diabetes was 14 years, and the average HbA1C was 8.7%. Seventy-three percent of patients were treated with biguanides, mainly metformin, 59% with insulin, 28% with sulfonylureas and 15% with gliptins.

In a median follow-up of 1.6 years, 24% of the patients in the albiglutide group and 27% in the placebo group discontinued treatment. The primary endpoint occurred in 7% of the albiglutide group and 9% of the placebo group (4.57% vs. 5.87% per year, HR 0.78, 95% CI 0.68-0.90; p <0.0001 for non-inferiority and 0.0006 for superiority). The difference was the result of a significant reduction in fatal or non-fatal AMI (2.43% vs. 3.26% per year), with no decrease in cardiovascular death (1.6% vs. 1.7% per year) or stroke (1.25% vs. 1.45% per year). There was also no reduction in all-cause mortality (2.44% vs. 2.56% per year). Towards the end of the study a greater reduction of HbA1c (0.52% less) and weight (0.8 kg less) was verified with albiglutide compared with placebo. The only more frequent adverse effect with the drug was a reaction at the injection site.

SGLT2 inhibitors or glifozins are drugs that inhibit sodium-glucose cotransport at the level of the proximal convoluted tube, thus generating natriuresis (with decreased blood pressure, weight and vascular stiffness) and glucosuria (with HbA1C reduction, negative caloric balance and decreased inflammatory activity). Randomized studies with empagliflozin and canagliflozin have demonstrated, in type 2 diabetic patients with established vascular disease, the ability to reduce a composite endpoint of cardiovascular death, non-fatal acute myocardial infarction (AMI) and non-fatal stroke and to significantly decrease hospitalization for heart failure and delay renal function worsening. In the EMPA-REG OUTCOME trial, empagliflozin also showed a specific reduction of cardiovascular mortality and all-cause mortality. Similar results have been found in observational studies, such as the large CVD REAL 1 and 2 registries. In these registries, the most commonly used gliflozins were canagliflozin and dapagliflozin, while the use of empagliflozin did not reach 10% of cases.

The results of the randomized DECLARE-TIMI 58 study were presented at the AHA congress. It was a multicenter, randomized, placebo-controlled study that tested the use of dapagliflozin in type 2 diabetic patients with established cardiovascular atherosclerotic disease or multiple risk factors for its development. Initially postulated as a safety study to demonstrate that it did not increase the incidence of major cardiovascular adverse events (MCAE), the publication of the EMPA-REG OUTCOME trial results led to a protocol amendment, introducing two primary efficacy endpoints: the incidence of MCAE (cardiovascular death, AMI or stroke) and the incidence of a composite endpoint of cardiovascular death or hospitalization for heart failure. The patients included were ≥40 years, with HbA1c ≥6.5% and <12%, with a glomerular filtration rate ≥60 ml/min, established atherosclerotic disease (coronary, cerebrovascular or peripheral vascular), or multiple factors for its development (age ≥55 years in men or ≥60 years in women, and one of the following: hypertension, dyslipidemia or smoking). After a run-in period of 4 to 8 weeks during which all received placebo, those who remained eligible were randomly assigned to receive dapagliflozin at a dose of 10 mg/daily or placebo. The primary safety endpoint was the incidence of MCAE and the two efficacy endpoints were those described above. Secondary efficacy endpoints were significant impairment of renal function and all-cause mortality. The analysis considered was hierarchical. Non-inferiority of the drug should be demonstrated initially with respect to placebo, with a non-inferiority margin of 30%, accepting 1.3 as upper limit of the 95% CI. If non-inferiority was demonstrated, the two primary efficacy endpoints would be tested, demanding a

p value <0.023. If any of the two endpoints was significant with that value of p, the other would be tested again accepting a p value <0.046. If both endpoints were significant, secondary endpoints would be tested, with a significant p value of 0.046.

During the run-in phase, 25,698 patients were screened and 17,160 overcame that phase; 40.6% had already established atherosclerotic disease, and 59.4% had multiple risk factors. Mean age was 64 years and 62.5% were men. Median diabetes duration was 11 years and mean HbA1c was 8.3%. History of coronary heart disease was ´present in 33% of patients, cerebrovascular disease in 7.6% and peripheral vascular disease in 6%. Eighty-two per cent of patients were receiving metformin, 41% insulin, 42.6% sulfonylureas and 16.8% gliptins. In the median follow-up of 4.2 years, 21.1% of the patients in the dapagliflozin group and 25.1% in the placebo group abandoned treatment. The use of active drug with respect to placebo resulted in a drop of 0.4% in HbA1c, 1.8 kg in weight, 2.7 in mm Hg in systolic blood pressure and 0.7 mm Hg in diastolic blood pressure.

The study demonstrated the non-inferiority of dapagliflozin over placebo. Superiority was also verified for the primary endpoint of cardiovascular death or hospitalization for heart failure (1.22% vs. 1.47% per year, HR 0.83, 95% CI 0.73-0.95), specifically due to reduction in hospitalization (0.62% vs. 0.85% per year) with no decrease in cardiovascular death. The effect was similar in the group of patients with established vascular disease and in patients with risk factors (HR of 0.83 and 0.84 respectively), although, logically, with higher figures among patients who presented with vascular disease.

On the other hand, there was no significant difference between the two groups in the MCAE endpoint: 2.26% vs. 2.42% (p=0.17). This happened in both groups, again with higher incidence among patients with vascular involvement. There was a significant reduction of the renal endpoint (although this data is not definitive due to the design of the aforementioned study) and no reduction in total mortality (1.51% vs. 1.64% per year). There was no excess risk of amputation or fractures, but there was more diabetic ketoacidosis (0.3% vs. 0.1%) and genital tract infections (0.9% vs. 0.1%) with dapagliflozin.

The HARMONY Outcomes study demonstrates once again the beneficial effects of a GLP 1 analog, but it also puts forward the question of whether we can really speak of a class effect. We already saw that exenatide and lixisenatide did not show favorable effects in diabetics with cardiovascular disease. In this sense, the HARMONY results are closer to those of the LEADER study. In the LEADER study, the annual incidence of non-fatal cardiovascular death, AMI or stroke was 3.9% in the placebo group and 3.4% in the liraglutide group. In the HARMONY study, the annual incidence of the same endpoint was 5.87% in the placebo group and 4.57% in the albiglutide group. In both cases, the reduction was significant. It can be assumed that the population of HARMONY was more ill; however, the diabetes data and the mean HbA1c were similar, and the annual mortality rate was the same in the placebo group of both studies: 2.5%. There was in both a significant reduction in the incidence of AMI, but only liraglutide managed to demonstrate a decrease in total mortality. In summary, it can be assumed that some GLP 1 analogues have a beneficial effect in diabetics with established cardiovascular disease, focused on what appears to be the reduction in the incidence of AMI. However, there seem to be some differences in the ability to achieve even more remarkable effects: only liraglutide has so far demonstrated the ability to reduce mortality. Is this based on structural differences of the molecules? Is this related to a different profile of the populations included in the studies? Is it simply a chance effect? Did the very short follow-up time conspire against albiglutide, less than half in the HARMONY study than in the LEADER trial? Would a longer follow-up period have helped to demonstrate beneficial effects beyond reducing the incidence of AMI? These are questions that perhaps a meta-analysis of individual data could help to clarify, exploring whether the heterogeneity of the results is real.

Regarding gliflozins, the DECLARE study with dapagliflozin confirms the ability of this drug to reduce the incidence of heart failure and impaired renal function, as did empagliflozin in the EMPA-REG study and canagliflozin in the CANVAS study. In this case, too, empagliflozin seems to be in advantage of its class mates, since it is the only one that in a randomized study showed a reduction in total mortality. However, the situation is different from what happened in the studies with liraglutide and albiglutide (equal annual mortality of the placebo group, differences in the groups of active treatment): the annual mortality of the placebo group in the EMPA-REG study was close to 3%; in the CANVAS study near 2%, and in the DECLARE study close to 1.6%. Should, in this case, a difference be assumed in the effects of drugs or can we think that the lower the baseline risk, the more difficult it is to demonstrate a significant reduction in total mortality? In large observational studies (CVD REAL study 1 and 2, and EASEL registry) no difference has been found in the ability to reduce mortality among the different gliflozins, but confounders could be involved. What is certain is that the DECLARE study, in a population with lower baseline risk and where almost 60% of patients have risk factors and no established vascular disease, confirms the usefulness of these therapeutic agents and allows for an expansion of the indication, prompting to its greater precocity.

It is worth remembering that the recent consensus of the American Association and the European Diabetes Society consider metformin as the first line of treatment in type 2 diabetes; and they urge to use as a second drug a GLP 1 analogue or a glifozin if the patient has evidence of atherosclerotic disease, due to its demonstrated effect on cardiovascular events, showing even a slight preference for glifozins if the patient has heart failure.