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Is there room for the specific treatment of inflammation in cardiovascular disease? The CANTOS Trial

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The pharmacological treatment intended to slow the atherosclerotic process aims primarily to reduce plasma cholesterol levels. However, we know that the complex physiopathology of atherosclerosis does not rest exclusively on lipid levels. Inflammatory activation, expressed for example by the elevation of C reactive protein (CRP) or interleukin-6 (IL-6) values, plays a fundamental role in disease progression. In addition to their cholesterol-reducing property, statins attenuate inflammation, but it has been debated whether this effect plays an independent role from the lipid-lowering capacity in their ability to reduce cardiovascular and cerebrovascular events. Until now there has been no clear evidence that the reduction of inflammation, without associated cholesterol decrease, results in prognostic improvement. Canakinumab (Can) is a monoclonal antibody targeting IL-1β (which triggers the inflammatory pathway of IL-6). Use of Can is associated with CRP and IL-6 reduction without modifying cholesterol levels. Its use has been approved to treat rheumatologic diseases.

The recently published CANTOS trial explored the effects of Can in coronary artery disease patients, with history of acute myocardial infarction (AMI) and stable with intensive medical treatment despite a CRP value ≥2mg/l, under the hypothesis that it would improve cardiovascular prognosis. Patients with chronic or recurrent infection, tuberculosis, HIV carriers, cancer (except basal cell skin cancer) or those receiving treatment with another anti-inflammatory agent were excluded from the study. The comparison of placebo vs. active treatment with 150 mg or 300 mg doses was initially postulated. A 50 mg group was subsequently included. For the 50 and 150 mg doses, the administration scheme was subcutaneous injection every 3 months, and in the case of the 300 mg dose, the first two injections were separated by only two weeks, and then a scheme was continued every 3 months. The primary endpoint (PEP) was a composite of cardiovascular death, nonfatal AMI, and nonfatal stroke. A secondary endpoint included the PEP components plus hospitalization for unstable angina leading to a revascularization procedure and other endpoints were the incidence of diabetes and all-cause death. Patients were assigned to placebo or each of the 3 doses in a 1.5:1:1:1 ratio. A total incidence of 1,400 events was assumed for the primary endpoint; and estimating a power of 90% to detect a reduction of 20% for any of the doses compared with placebo, a total of 17,200 patients followed up for 5 years were estimated. Difficulties in recruiting that number of patients reduced the required number to 10,000 patients, extending follow-up for another year. As each of the groups would be compared with the placebo, a necessary p value of 0.01058 was considered to establish the superiority of the 300 mg dose compared with placebo, and a value of p=0.02115 for the other two doses. It was established that only if superiority for the PEP was demonstrated, the effect on the secondary endpoints would be explored for the corresponding dose.

The patients were enrolled between 2011 and 2014, and the follow-up was completed in June 2017. A total of 10,061 patients, with mean age of 61 years, 25.7% women and 40% diabetics were included in the study. Almost 67% of patients had undergone coronary angioplasty, and 14% revascularization surgery. Median CRP was 4.2 mg/l, and LDL-cholesterol was 82.4 mg/dl. These were very well treated patients, with more than 90% of them receiving antiplatelet, lipid-lowering and anti-ischemic drugs. At 48 months, treatment with 50, 150, and 300 mg Can led to 26%, 37%, and 41% CRP reduction, respectively, compared with the placebo group. There was no reduction in LDL-cholesterol values. A dropout rate of approximately 18% was similar for Can and placebo. In a median follow-up of 3.7 years, the annual incidence of the PEP was 4.5% per year in the placebo group; 4.11% with the 50 mg dose (p=NS vs. placebo); 3.86% with the 150 mg dose (HR 0.85, p=0.02075) and 3.9% for the 300 mg dose (HR 0.86, p=0.0314). Although there was a tendency to reduce events with increasing doses of Can, according to the rules established a priori on the necessary p value, it was understood that the difference was significant for the 150 mg dose, but not for the 300 mg dose. Therefore, the secondary endpoint was analyzed only for the 150 mg dose, with a significant difference vs. placebo. No dose reduced cardiovascular or total mortality. The difference between Can at a dose of 150 mg and placebo was mainly due to the lower annual incidence of AMI (1.9% vs. 2.4%, p=0.005) and hospitalization for unstable angina leading to a revascularization procedure (0.44% vs. 0.69%, p=0.02). There was, as expected, an increased incidence of thrombocytopenia and neutro-

penia with Can, and the incidence of death due to infection or sepsis was slightly higher (0.31% vs. 0.18% per year), but the incidence of gout, osteoarthritis and death due to cancer, especially lung cancer, was lower.

Interleukin-1β promotes the acceleration of the atherosclerotic process by different mechanisms: it is procoagulant, and induces monocyte and leukocyte adhesion to endothelial cells and vascular smooth muscle growth. Different stimuli (tissue hypoxia, cholesterol crystals and reduced flow) lead to increased levels of this interleukin, which in turn stimulates the IL-6 pathway, strongly linked in observational studies with atherothrombotic phenomena. Until now there had been no evidence that a specifically anti-inflammatory intervention could improve the fate of known coronary patients. In this sense, the CANTOS trial is extremely interesting from the physiopathological point of view: it demonstrates for the first time that targeting inflammation in adequately treated patients according to standards, but with persistent inflammatory activity (high CRP) generates an additional prognostic improvement. Let us recall that the rate of major events was more than 20% at 5 years in the placebo group.

However, some objections can be formulated. The reduction of major events was no more than 3% per 100 patients treated during the 5-year follow-up, and it consisted of a reduction in coronary syndromes, not of stroke or mortality. We may wonder whether a more intensive lowering of LDL-cholesterol levels would not have achieved similar results. In fact, in the FOURIER trial, the use of evolocumab reduced a final endpoint similar to the CANTOS trial PEP in 1.5 events per 100 patients at a mean follow-up of 26 months: half the events in almost half the time. Will the beneficial effect of targeting inflammation be maintained in the presence of a strong decrease in LDL-cholesterol levels? And two other questions: should the interleukin-1β pathway be targeted, or will there be other more relevant ones? Is this a cost-effective intervention? It seems at first difficult to sustain it. The cost of Can is very high for any health system that considers its routine use in a disease as widespread as cardiovascular disease. Therefore, more than seeing in the trial an indication of treatment, we recognize in it a remarkable advance in the understanding of the disease and its mechanisms, and a stimulus for research aimed at pragmatically linking the physiopathology with patient outcome.

Direct-acting anticoagulants knock at the door of cardiovascular prevention. The COMPASS trial

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Use of antithrombotic drugs is an essential part of the treatment of patients with cardiovascular disease. In the field of secondary prevention, aspirin has been shown to reduce cardiovascular and cerebrovascular events and mortality. The use of a P2Y12 inhibitor associated with aspirin has shown dissimilar results with respect to aspirin alone: in the CHARISMA trial, the combination of clopidogrel and aspirin was not better than aspirin alone in reducing a primary endpoint of cardiovascular death, myocardial infarction (AMI) or stroke; in the PEGASUS trial, the combination of ticagrelor and aspirin was superior to aspirin alone in the reduction of this final endpoint, but without a clear effect on mortality and with excess bleeding episodes. Regarding anticoagulant treatment with vitamin K antagonists, its association with aspirin has shown an excess risk of cerebral bleeding, which is why it is not recommended for secondary prevention in patients with vascular disease. More recently, the ATLAS-TIMI 51 trial demonstrated that the use of a direct-acting oral anticoagulant, rivaroxaban associated with aspirin after an acute coronary syndrome, at doses of 2.5 or 5 mg every 12 hours, decreased the incidence of major events, and that even the 2.5 mg dose every 12 hours, reduced cardiovascular mortality.

We now know the result of the COMPASS trial, which attempted to answer the question of whether the use of rivaroxaban in stable patients with coronary or peripheral vascular disease is capable of improving the prognosis versus conventional treatment. This is a randomized, double blind and double dummy trial, with a 3 x 2 factorial design, in which two comparisons were tested: one with rivaroxaban alone or associated with aspirin vs. aspirin, and the other pantoprazole vs. placebo. The results we know are those of the first comparison.

Stable patients with coronary artery disease, peripheral vascular disease, or both, were included in 602 centers in 33 countries. In the case of coronary arterydiseasepatients below 65 years of age, they should have additional involvement of two other vascular beds, or two risk factors for cardiovascular events (smoking, diabetes, renal dysfunction, heart failure, or lacunar stroke of more than 1 month evolution). Patients with high bleeding risk, history of hemorrhagic stroke, double antiplatelet therapy, use of anticoagulants, or glomerular filtration rate <15 ml/min were excluded. Eligible patients were initially included in a run-in phase with aspirin and rivaroxaban placebo, to verify whether they would be able to adhere to the treatment scheme. Only patients between 4 and 14 days after coronary artery bypass grafting were left out of the run-in phase, because as they are at high risk of initial thrombotic events, it was deemed necessary to lose no time before randomization. The patients of this subgroup, and all those who passed the run-in phase were randomly assigned to 3 groups: rivaroxaban 2.5 mg every 12 hours and aspirin 100 mg daily; rivaroxaban 5 mg every 12 hours and aspirin placebo; aspirin 100 mg once daily and rivaroxaban placebo twice daily. The primary efficacy endpoint was

a composite of cardiovascular death, non-fatal AMI, and non-fatal stroke. The primary safety endpoint focused on bleeding, and considered fatal bleeding, symptomatic bleeding in a critical organ, perioperative bleeding requiring reoperation, and bleeding leading to hospitalization. Considering an incidence of 3.3% events per year in the aspirin and rivaroxaban placebo group, an expected decrease of 20% in each of the other two groups, a power of 90% and a two-tailed test with p=0.05, sample size was estimated as 27,400 patients. Rules were established to stop the trial if at 50% and 75% anticipated event occurrence there were clear differences in favor of a group with respect to control.

A total of 27,395 patients were included between 2013 and 2016. Mean age was 68 years, and 22% were women. Slightly more than 90% of patients had coronary heart disease and 27% peripheral vascular disease. In 90% of cases they were treated with statins, 70% with beta-blockers and the same percentage with renin-angiotensin system inhibitors or antagonists. When 50% of the events were reached and the first interim analysis was carried out, it was decided to interrupt the trial due to a clear superiority of the rivaroxaban-aspirin group versus aspirin alone. The annual incidence of the primary endpoint was 4.1% with aspirin and rivaroxaban 2.5 mg every 12 hours vs. 5.4% with aspirin and rivaroxaban placebo (HR 0.76, 95% CI 0.66-0.86, p <0.0001). The incidence of all-cause mortality was 3.4% vs. 4.1% (p=0.01). The incidence of major bleeding was higher with double therapy: 3.1% vs. 1.9% (HR 1.7, 95% CI 1.4-2.05, p<0.0001). The combined risk of ischemic events and bleeding was lower with double therapy: 4.7% vs. 5.9% (HR 0.80, 95% CI 0.70-0.91, p<0.0001).

The comparison between rivaroxaban at doses of 5 mg every 12 hours with aspirin placebo, vs. aspirin and rivaroxaban placebo did not show significant difference for the primary efficacy endpoint, but evidenced excess bleeding: 2.8% vs. 1.9% (HR 1.5, p<0.0001).

This trial shows results in chronic patients similar to the ones of the TIMI 5.1 trial in acute patients: that the association of anticoagulation with low doses of rivaroxaban (2.5 mg every 12 hours, a quarter of the recommended dose in atrial fibrillation) and aspirin is able to significantly improve the prognosis, including a significant reduction in cardiovascular death and all-cause mortality. In this context no dual antiplatelet therapy has achieved the same results. Even a meta-analysis of secondary prevention in more than 33,000 patients with prior AMI showed that dual antiplatelet therapy versus aspirin alone can reduce cardiovascular but not overall mortality.

However, the early interruption of the trial, although according to previously established rules, may exaggerate the benefit of the intervention. In absolute terms, the reduction of the primary endpoint was similar to the excess of major bleeding (1.3 vs. 1.2 per 100 patients per year) but the reduction in mortality and the net clinical benefit argue in favor of the intervention. It is true that in the context of current medicine, earnings in terms of events are usually limited, and that is why the cost-effectiveness analysis is fundamental when deciding the introduction of a new drug in the therapeutic arsenal. Preliminary studies suggest that in developed countries the association would be cost-effective, especially in patients with peripheral vascular disease. An adequate selection of patients looking for those subgroups in which the potential benefit is maximized and the risk of bleeding is minimized could guarantee better results. More real world data will be necessary to finally define the scope of an intervention that at least looks promising.

The DETO2X-AMI trial: the routine administration of supplemental oxygen does not improve the prognosis in the context of acute myocardial infarction.

Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. **N Engl J Med 2017; 377: 1240-9. http://doi.org/gbvvps**

Oxygen administration (O2) in the first hours of an acute myocardial infarction (AMI) is a routine procedure, generally recommended by clinical practice guidelines, motivated by the idea of limiting the ischemic area to decrease infarct size. It should be noted that there is no firm evidence for the usefulness of this practice, which is even questioned by a meta-analysis of the Cochrane Collaboration. In order to achieve greater certainty on the subject and taking advantage of SWEDEHEART, the national registry of acute coronary syndromes in Sweden, a group of researchers from the Karolinska Institute designed the open-label, randomized DETO2X-AMI trial. Patients with suspected AMI within 6 hours of onset of symptoms, and with oxygen saturation by pulse oximetry ≥90%, were randomly assigned to receive supplemental oxygen at a flow rate of 6 l/min via a face mask, or ambient air for 6 to 12 hours. Patients with a clear indication of oxygen therapy and those who presented with cardiorespiratory arrest were excluded. If patients had received oxygen for less than 20 minutes, this could be discontinued and after 10 minutes proceed with the randomization. The primary endpoint was all-cause mortality at 1 year, and among the secondary endpoints were mortality at 1 month and re-hospitalization due to AMI or heart failure. An expected mortality rate f 14.4% per year and a reduction of 20% in the oxygen therapy group were postulated

Between 2013 and 2015, 6,629 patients, assigned in a 1:1 ratio to oxygen therapy or ambient air were included in the study. Median age was 68 years, 69% were men, and the median time from the onset of symptoms to randomization ranged from 245 to 250 minutes. Median O2 saturation in both groups was 97% at the beginning of the trial; it reached 99% with oxygen therapy, and it remained the same in the group

with ambient air. The protocol was completed by 91% of patients assigned to oxygen therapy and 97% of the ambient air group. The final diagnosis was AMI in 75.6% of the patients, angina in 5.6%, another heart disease in 7.7%, respiratory disease in 0.5%, non-characteristic pain in 7.4% and non-cardiovascular pathology in the remaining 3.2%. In 4.8% of cases patients received O2 supplementation for hypoxemia of different causes, 1.7% in the oxygen therapy group and 7.7% in the ambient air group.

At 1 year, the mortality rate was 5% with oxygen therapy and 5.1% with ambient air. In those who fully complied with the protocol, the mortality rate was 4.7% and 5.1%, respectively. Rehospitalization for AMI was 3.8% and 3.3%, respectively. None of these differences was statistically significant.

Another blow to the former routine treatment of AMI! For years we have assisted to the defeat of the usual use of lidocaine, nifedipine, and opioids in this disease, thanks to the results of observational studies and meta-analyses. Now a simple, pragmatic randomized trial, based on a registry (a way of generating studies that significantly increases the representativity and external validity) comes to question even oxygen therapy. Because that which seems indisputable from the physiopathology or common sense point of view (how not try to increase the oxygen supply in a tissue that suffers its acute interruption?, how not keep the patient adequately oxygenated at a time when the pump that precisely ensures the arrival of oxygen to the entire body fails?) does not finally find a foothold in the pure and hard facts. The DETO2X-AMI trial confirms what was already suggested by a previous meta-analysis: the lack of usefulness of the intervention that on the other hand, and as mere consolation, does not harm either. It is true that 24% of patients finally had no AMI, but the results of both groups are so similar that it is practically impossible to think there will be a benefit even without considering them. It is important to note that because it was a randomized trial, only those in which the administration of supplemental oxygen was not considered essential by the treating physicians were included: 22% of the total number of patients registered in SWEDEHEART in the study period. In fact, during the trial, the mortality of patients who were not included was greater than that of selected patients. i.e., we cannot recommend from now on the universal administration of oxygen in the context of AMI. We should neither reject its use if we judge it necessary according to the patient's condition.

Antiaggregation-Anticoagulation in patients with atrial fibrillation and coronary angioplasty: when less is more. The RE-DUAL PCI trial

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In patients with atrial fibrillation (AF), oral anticoagulation significantly reduces the risk of cerebral and peripheral embolic events. In patients undergoing coronary angioplasty, the use of dual antiplatelet therapy with aspirin and a P2Y12 inhibitor reduces the incidence of major cardiovascular and cerebrovascular events, as well as stent thrombosis. Therefore, in patients with AF who undergo coronary angioplasty, a triple scheme (TS) of treatment will be necessary: oral anticoagulation and double antiplatelet therapy. But TS is also associated with an increased risk of bleeding. This fact has led to investigate whether the use of a dual scheme (DS) with an oral anticoagulant and a single antiplatelet agent may preserve the protective capacity of TS against cardiovascular and cerebrovascular events, but with a reduced risk of bleeding. The WOEST trial compared in patients with indication for angioplasty who had to be anticoagulated (almost 70% with AF), TS with warfarin, aspirin and clopidogrel vs. DS with warfarin and clopidogrel. The DS was associated with a significantly lower incidence of bleeding, without evidence of excess ischemic events (although there was not enough power to detect it). In the PIONEER AF PCI trial, in patients with AF who underwent coronary angioplasty, DS combining rivaroxaban 15 mg daily and a P2Y12 inhibitor, as well as DS combining rivaroxaban 5 mg daily plus dual antiplatelet therapy, were superior to conventional TS with a vitamin K antagonist plus dual antiplatelet therapy for the reduction of major bleeding, without excess of ischemic events.

Now the larger RE-DUAL PCI trial explores the same problem. It included patients with paroxysmal, persistent or permanent AF, in whom a successful coronary angioplasty with conventional or drug-eluting stent had been performed in the last 5 days. Patients were randomly assigned to 3 strategies: DS combining dabigatran 110 mg every 12 hours plus a P2Y12 inhibitor (D 110 group), DS with dabigatran 150 mg every 12 hours plus a P2Y12 inhibitor (D 150 group), or TS combining warfarin (with an INR target between 2 and 3), aspirin and a P2Y12 inhibitor. In the latter case, aspirin was discontinued after the first month in the bare-metal stent cases, and after 3 months in cases with a drug-eluting stent. The P2Y12 inhibitor was maintained for at least 12 months in all cases and in the 3 groups. Randomization was made by stratifying patients according to their age into two categories elderly and non-elderly. In Japan, 70 years was considered as the cut-off value and in the rest of the participating countries 80 years. In the United States, all patients, regardless of age, were randomly assigned to any of the 3 strategies. Outside the United States and for regulatory reasons, only the non-elderly patients could be assigned to any of the 3 strategies, while the elderly could only be assigned to DS with dabigatran 110 mg every 12 hours, or TS. For that reason, the DS group with dabigatran 150 mg every 12 hours was compared with similar age patients on TS.

This was planned as a noninferiority trial. The primary endpoint was safety. It sought to demonstrate that any DS was not inferior to TS for major bleeding or clinically relevant non-major bleeding. The upper limit of the HR 95% CI assumed as noninferiority margin was 1.38, i.e. up to 38% worse results were accepted with DS than with TS. Assuming an expected major or relevant bleeding rate of 14%, 2,500 patients were considered sufficient to demonstrate non-inferiority with a power of almost 84%. A secondary efficacy endpoint was also considered: embolic or ischemic events, unplanned revascularization or death. Finally, 2,725 patients were included: 981 in the DS group with D 110, 763 in the DS group with D 150 and 981 in the TS group. Mean age was 70.8 years and more than 75% were men. The reason for angioplasty was acute coronary syndrome in 50.5% of cases, and a drug-eluting stent was used in 82.6% of patients. In 88% of cases, clopidogrel was theY2P12 inhibitor. In the TS group, the time in therapeutic range (INR between 2 and 3) was 64%. Mean treatment duration was 12.3 months, and mean follow-up 14 months.

In the comparison between DS with D 110 and TS, the incidence of the primary endpoint was 15.4% vs. 26.9% (HR 0.52, 95% CI 0.42-0.63, p <0.001 for noninferiority and p <0.001 for superiority). The incidence of the secondary endpoint was 15.2% vs. 13.4% (HR 1.13, 95% CI 0.90-1.43, p=0.30).

In the comparison between DS with D 150 and TS, the incidence of the primary end point was 20.2% vs. 25.7% (HR 0.72, 95% CI 0.58-0.88, p<0.001 for noninferiority and p=0.002 for superiority). The incidence of the secondary endpoint was 11.8% vs. 12.8% (HR 0.89, 95% CI 0.67-1.19, p=0.44).

Although each DS strategy could not separately demonstrate noninferiority for the secondary efficacy endpoint compared with TS, this was possible with the combination of both DS, with an incidence of 13.7% vs. 13.4% with TS (HR 1.04, 95% CI 0.84-1.29, p=0.005 for non-inferiority). The incidence of stent thrombosis in the comparison of DS with D 110 vs. TS was 1.5% vs. 0.8%, and in DS with D 150 vs. TS it was 0.9% in both groups.

The RE DUAL PCI trial confirms what WOEST and PIONEER AF PCI trials had already demonstrated: DS ensures greater safety and reduced bleeding compared with TS. It is worth remembering that the TS lasted 3 months, enough time for the difference to be noticeable. The advantage for decreased bleeding is greater with D 110.

Nevertheless, a point to be considered is the incidence of thromboembolic events. We said that the joint consideration of both DS ensured noninferiority with respect to TS for a broad endpoint. But if we consider a combined endpoint of thromboembolic events and death (leaving aside unplanned revascularization), the incidence was 9.6% with both DS vs. 8.5% with TS, with a HR of 1.17 (95% CI 0.9-1.53, p=NS for noninferiority). This means that for harder endpoints we cannot even exclude an excess risk of 53%. And if we focus on the group with the greatest decrease in bleeding, that of DS with D110, it is not surprising that it was also the one which appeared associated with an increased risk of thromboembolism or death: 11% vs. 8.5% (HR 1.30, 95% CI 0.98-1.73, p=0.07).

In conclusion, the decrease in bleeding is promising. But a less ambiguous result would be expected regarding the excess risk of a significant thromboembolic event. A very strong reason to select the best individualized strategy according to the risk of bleeding and thromboembolism in each patient. Another point to consider: what will be the best combination of anticoagulant and antiaplatelet agent in a DS scheme? Presumably, we will see in the future studies aimed at answering this question.

Patent foramen ovale and cryptogenic stroke: a closed case?

Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L et al. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. **N Engl J Med 2017;377:1011-21. http://doi.org/gbxbns**

Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS et al. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. **N Engl J Med; 2017;377:1022-32. http://doi.org/gbw5z8**

Sondergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE et al. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. **N Engl J Med; 2017;377:1033-42. http://doi.org/gbw87k**

More than 25% of strokes are cryptogenic. In patients with cryptogenic stroke and patent foramen ovale (PFO) the best therapeutic strategy is unclear. Traditionally, there are three options: percutaneous PFO closure (PFOC), antiplatelet therapy (AP) or anticoagulation therapy (AC). Three randomized trials (CLOSURE, PC and RESPECT) could not individually show the advantage of any of these strategies over the others. Although a meta-analysis of these three studies suggests advantage of PFOC on the reduction of the combined endpoint of transient ischemic attack and stroke, the question seems far from being solved, and different guidelines and consensuses suggest a therapeutic decision based on patient characteristics and resource availability. Recently, three publications add relevant information.

The CLOSE trial was an open-label, randomized study carried out in 32 centers in France and 2 in Germany between 2007 and 2016. It selected patients aged between 16 and 60 years with ischemic stroke in the last 6 months, with defined PFO anatomical and functional criteria: presence of interatrial septal

aneurysm (IASA) with >10 mm septum primum excursion and/or right to left shunt which, in an echocardiogram with agitated saline solution, generated more than 30 microbubbles to the left atrium after 3 cardiac cycles from right atrial opacification. Three randomized groups were designed. In the first group, patients were assigned to PFOC with concomitant AP, AP alone or AC alone. Patients with contraindication to receive AC entered group 2, where they were assigned to PFOC and AP or AP alone. And the few patients with PFOC contraindication were allocated to group 3, where they were randomized to either AP or AC. Patients assigned to PFOC had to receive double AP therapy (aspirin and clopidogrel) for 3 months and thereafter only one agent, aspirin, clopidogrel or aspirin-dipiridamol. Patients assigned to AC, could receive vitamin K antagonists or direct AC.

The primary efficacy endpoint was the incidence of fatal or nonfatal stroke. The primary safety endpoint was the incidence of procedure complications or major bleeding. The initial sample size was 900 patients to demonstrate with 80% power, 50% reduction in the incidence of stroke with PFOC and AP compared with AP alone during a 5-year follow-up. As it was not possible to incorporate the predicted number of patients, follow-up had to be extended. The comparison having greatest interest was that of PFOC and AP vs. AP alone, considering patients of both randomized 1 and 2 groups. Secondarily, AP and AC were compared, with patients of both 2 and 3 groups. Finally, 663 patients were included: 524 in group 1 (173 patients assigned to PFOC and AP, 180 to AC and 171 to AP); 129 in group 2 (65 to PFOC and AP and 65 to AP); and 10 in group 3 (7 to AC and 3 to AP). In two-thirds of patients, PFO presented a significant shunt without IASA. The remaining cases evidenced IASA with shunt of diverse severity. Mean age was almost 44 years and women represented slightly above 40% of cases.

In the PFOC-AP group, 11 different devices were used. Implant was successful in 99.6% of patients, and effective PFO closure was achieved in 88.6% of cases. In the groups with AP, aspirin was administered in almost 87% of cases and clopidogrel in an additional 10%. In patients allocated to AC, more than 90% were treated with vitamin K antagonists. During a mean follow-up of about 5.3 years, there was a clear difference in the incidence of stroke: no cases in the PFOC-AP group, vs. 14 cases (4.9% at 5 years) in the AP alone group (HR 0.03, 95% CI 0-0.26, p<0.0001). Also, the incidence of a combined endpoint of stroke, transient ischemic attack or systemic embolism was lower: 3.4% vs. 8.9%, p=0.01. The prevalence of stroke was higher in patients with IASA than in those without it: 12.2% vs. 3.1%. In a per protocol analysis, considering only patients who fulfilled the treatment indicated in the randomized allocation, the difference favoring PFOC-AP was preserved for the incidence of stroke (HR 0.04, 95% CI 0-0.27). Conversely, the prevalence of atrial fibrillation (AF) was greater with PFOC-AP: 11 vs. 2 patients (4.6% vs. 0.9%, p=0.02), most AF cases occurring during the first month of the procedure. In the comparison between AP and AC, no differences could be verified in the incidence of stroke due to the number of patients and the low occurrence of events.

The RESPECT trial was a randomized, open-label trial conducted between 2003 and 2011 in 69 centers of the United States and Canada. It included 980 patients with cryptogenic stroke within the previous 9 months and the presence of PFO considered as the only possible cause of stroke. Patients were assigned in a 1:1 ratio to PFOC with Amplatzer device or medical treatment (MT) with AP or AC. In 48.8% of cases, patients had a significant right to left shunt, and 35.7% had IASA. The PFOC group received double AP therapy with aspirin and clopidogrel during the first month, aspirin alone during the following 5 months, and thereafter therapy at the discretion of the treating physician. The MT group received aspirin, clopidogrel, aspirin-dipiridamol or warfarin. The primary endpoint was a composite of new fatal or nonfatal ischemic stroke and early death (within 45 days of randomization or 30 days after device implantation). A diagnostic algorithm allowed classifying the incident stroke at follow-up as due to a defined or undefined cause, as well as to a cryptogenic or non-cryptogenic origin. Initial results are part of the body of information known to date, to which an extension of the follow-up period has been added, reaching a median of 5.9 years. Patient dropout during follow-up was 20.8% in the PFOC group vs. 33.3% in the MT group. Therefore, follow-up was more extended in the first group.

The annual incidence of new ischemic stroke was 0.58% in the PFOC group and 1.07% in the MT group (HR 0.55, 95% 0.31-0.99, p=0.046). Stroke was considered to be due to a defined cause in 28.3% of patients and to an undefined cause in 71.7%. Percutaneous PFO closure generated a significant reduction of undefined stroke (0.32% vs. 0.86% per year, p=0.007), but not of that associated to defined mechanisms (0.19% vs. 0.25%, p=NS). The benefit of PFOC was higher in patients with IASA, significant shunt and among those treated with AP rather than AC. At the same time, the incidence of pulmonary embolism was greater with PFOC (0.41% vs. 0.11% per year, p=0.04) but without increased AF occurrence.

The last is the REDUCE trial, a randomized, open-label study performed in 63 centers in the United States, Canada, the United Kingdom and the Scandinavian countries. In this case, patient age had to be between 18 and 59 years, with cryptogenic stroke and PFO with right-left shunt. Patent foramen ovale severity was defined according to the echocardiographic right to left passage of microbubbles with agitated saline solution: small if 1 to 5 microbubbles, moderate if 6 to 25 microbubbles and large if more than 25 microbubbles passed in 3 cardiac cycles. An initial imaging study, mostly with magnetic resonance imaging, was

performed in 99.8% of cases. Patients were randomly assigned in a 2:1 ratio to PFOC with one or two devices (HELEX or GSO) combined with AP therapy (aspirin, aspirin-dipiridamol or clopidogrel), or exclusively to AP. Follow-up was extended between 2 to 5 years. Two co-primary endpoints were considered. The first was freedom from clinical evidence of new ischemic stroke. The other endpoint was new brain infarction, clinically defined or due to an imaging study 2 years after inclusion in the study. Sample size was calculated estimating a freedom from new ischemic stroke of 92% at 2 years in the AP group. It was assumed that PFOC-AP would be superior to AP alone if 55% reduction was verified. During the course of the study, other trials showed that the incidence of stroke was lower than expected in this population; therefore, it was decided to establish an endpoint that also considered the incidence of silent brain infarction.

Six-hundred and sixty-four patients were included between 2008 and 2015 (441 in the PFOC-AP group), 81% with moderate or large shunts. Complete PFO closure was completed in 73.2% of patients assigned to the PFOC-AP group. Median follow-up was 3.2 years. A total 6.6% of cases passed from the AP to the PFOC-AP group. The trial was dropped out by 8.8% of patients in the PFOC-AP group and 14.8% of the AP alone group. The annual incidence of new clinically evident stroke was 0.39% in the PFOC-AP group and 1.71% in the AP group (HR 0.23, 95% CI 0.09-0.62). The incidence of clinically evident brain infarction or found in an imaging study was 5.7% vs. 11.3%, respectively (RR 0.51, 95% CI 0.29-0.91). The difference in this endpoint was due to the incidence of the clinical event, as there were no differences in silent infarctions. This study showed no difference in the incidence of pulmonary embolism or deep vein thrombosis but the incidence of AF was higher in the PFOC-AP group (6.6% vs. 0.4%, p <0.001), especially in the first 45 days after the procedure.

These three studies (two new ones, and the other a follow-up extension from an already known trial) seem to put an end to the discussion about the relative usefulness of the different therapeutic alternatives in cases of cryptogenic stroke and PFO. Percutaneous PFO closure seems the best option: in the three studies there is a significant reduction in the incidence of stroke with this intervention. Some characteristics seem to indicate the population which most benefits: that with presence of IASA, a significant right-left shunt. Why is there now and not before evidence of PFOC superiority? Except for the RESPECT trial, the other two studies incorporated patients up to 2015 and 2016. We can therefore assume a learning curve and improvement in the devices used. But it is also clear that they selected patients in whom IASA prevalence and shunt was significantly high, which implies greater probability that the percutaneous intervention gets ahead of a purely pharmacologic treatment. None of the three studies made a prolonged ECG follow-up to rule out AF as the cause of new stroke, but it is interesting to point out that despite in two of the three studies PFOC was associated with greater incidence of AF (especially in the initial stage), this did not translate into excess stroke. The 5-year incidence of new stroke was between 5% and 8% with MT, and the reduction with PFOC varied between 45% and 97%. It should be taken into account that this is a young population in whom stroke implies a significant loss of economically active years. A meta-analysis considering the results of these new studies will probably be enough to establish the superiority of invasive therapy in clinical practice guidelines.

Increased mortality after hospitalization for heart failure might be an unwanted consequence of the program to reduce readmissions

Fonarow GC, Konstam MA, Yancy CW. The Hospital Readmission Reduction Program Is Associated With Fewer Readmissions, More Deaths: Time to Reconsider. **J Am Coll Cardiol 2017;70:1931-4. http://doi.org/gbw87k**

It is unusual that we introduce in this section an opinion letter, but we decided to do it given the importance of the data and the reputation of the persons who endorse it.. Gregg Fonarow, Marvin Konstam and Clyde Yancy sign a letter in the page of invited editor in JACC. They point out that in the last decade several initiatives were taken to reduce readmission in the first 30 days after hospitalization for heart failure in Medicare patients. Thus, the Hospital Readmission Reduction Program was established, including the public report of standardized readmission rates of the hospitals involved, as well as economic penalties for those centers presenting worse than expected indicators. The report was initiated in 2010 and penalties are applied since 2012, starting with 1% withdrawal of the corresponding reimbursement to the center, which later increased to 3%. Since model adjust is based on administrative data, there are complaints because factors associated with severity and complexity of the disease might not be duly taken into account. Academic centers and those who work with the most compromised population from a socioeconomic point of view are more exposed to suffer penalties. Straightforward determinants of access to the health care system, medication, intervention and adequate follow-up, as ethnics, social condition and knowledge of the disease are not contemplated. And as the process is centered in preventing readmissions during the first month, it is possible that even with the best intention of achieving good results, necessary readmissions are postponed, keeping the patient in ambulatory status or with visits to the emergency room where the necessary treatment cannot be implemented. Between 2008 and 2014, the 30-day-adjusted rate of readmissions in hospitals ascribed to the Program decreased from 23.5% to 21.4%. But simultaneously, in these hospitals, 30-day-adjusted mortality after discharge

increased from 7.9% to 9.2%, 16% in relative terms. It is worth pointing out that in the decade prior to the implementation of the Program, a slow, sustained decrease in 30-day post-discharge mortality was being registered. The authors cannot clearly indicate that the Program is responsible for the increased mortality, but they remark the temporal coincidence and the fact that these values are already adjusted for age, sex, comorbidities and length of hospital stay.

The data presented are striking but not unexpected. We could even ask ourselves if a readmission rate at one month above 20% is not reflecting an initial hospitalization that could have been shorter than recommended. We are still thinking that one or more days of "excess" hospitalization destined to complete the congestion treatment and adjust the medication are the key to prevent early readmissions. Hospitalization should be seen as an opportunity to improve medical care. To avoid it for a fundamentally economic reason can be deceivingly profitable; but it is clear that what is earned spuriously is what the system ends paying sooner or later, and, as we see, what the patient pays, and not only with money. As the authors conclude: Primum non nocere.