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A GLP 1 analog improves the prognosis of type 2 diabetes with and without vascular disease. The REWIND trial

Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. **Lancet 2019;394:121-30**

Different GLP 1 agonists have been tested in the treatment of type 2 diabetic patients with established cardiovascular disease, and some of them have been shown to improve the prognosis: liraglutide demonstrated reduced all-cause mortality in the LEADER study; semaglutide was associated with a reduction in the incidence of non-fatal stroke in the SUSTAIN study; and albiglutide was shown to reduce the incidence of fatal or non-fatal acute myocardial infarction (AMI) in the HARMONY study. We now know the results of the REWIND trial with dulaglutide, a drug that arises from the fusion of 2 modified human GLP1 molecules, covalently bound to an IgG4 heavy chain molecule. It is administered subcutaneously; its half-life is 5 days and can therefore be injected every 7 days, unlike liraglutide that requires daily administration. The weekly dose can be 0.575 or 1.5 mg. The REWIND trial was a randomized, double-blind, multicenter, placebo-controlled study comparing dulaglutide with placebo in type 2 diabetic patients ≥50 years of age, with HbA1c ≤5%, glomerular filtration rate of at least 15 ml/min/1.73 m2, and body mass index (BMI) >23 kg/m2. If they were ≥50 years, they should have established cardiovascular or cerebrovascular disease (AMI, stroke, previous coronary revascularization, previous hospitalization for unstable angina or evidence of ischemia), as well as evidence of myocardial ischemia or coronary heart, carotid or lower limb arterial disease >50%, left ventricular hypertrophy, and glomerular filtration rate <60 ml/min/1.73 m2; and if they were ≥60 years, it was enough to have at least 2 of the following 4 risk factors: smoking, hypertension, dyslipidemia or abdominal obesity. The primary endpoint (PE) was a composite of major adverse cardiovascular events (MACE): death of cardiovascular origin, non-fatal AMI or non-fatal stroke. The secondary endpoints were a clinical composite of microvascular disease (retinopathy or nephropathy), hospitalization for unstable angina, each of the components of the PE separately, death and hospitalization for heart failure. After a 3-week run-in phase in which patients were instructed to inject a prefilled placebo syringe weekly, those who showed perfect adherence to this regimen were randomly assigned to either dulaglutide or placebo in a double-blind regimen. The study was initially proposed as a superiority trial, assuming an annual incidence of 2% in the placebo group. It was estimated that, with 9,600 patients followed-up for a maximum of 8 years, and with an incidence of 1,200 events, there would be a power of 90% to demonstrate statistical significance ($p < 0.05$) with a HR of 0.82 in the dulaglutide group compared with placebo; and a power of 80% with a HR of 0.85.

Between 2011 and 2013, 12,133 patients were evaluated in 371 centers in 24 countries; 10,917 entered the run-in phase and finally 9,901 were randomly assigned to dulaglutide (n=4,949) or placebo (n=4,592). Mean age was 66.2±6.5 years; 46.3% were women, median duration of diabetes was 9.5 years and median HbA1c was 7.2%. Only 31.5% had established vascular disease, whereas the rest had risk factors. Median follow-up was 5.4 years and, at the last visit, 73.2% of those assigned to dulaglutide and 71.1% of those assigned to placebo continued taking their medication. The PE occurred in 12% in the dulaglutide group (2.4% annually) and 13.4% in the placebo group (2.7% annually), with HR of 0.88, 95% CI 0.78-0.99, p=0.026. There was no heterogeneity among the 3 components of the PE, but only a significant reduction of non-fatal stroke (HR 0.76-0.91) was demonstrated, while the HR for nonfatal AMI was 0.96, 95% CI 0, 79-1.16; and for cardiovascular mortality 0.91, 95% CI 0.78-1.06. There was a trend to reduce total mortality (2.06% vs. 2.29% per year, p=0.067) and a significant reduction in the incidence of microvascular disease, due to the effect on nephropathy, but not on the incidence of retinopathy. Risk reduction was similar in patients with HbA1c above or below the median level, and in patients with established vascular disease or only risk factors. Use of dulaglutide was associated with 0.6% reduction in HbA1c, 0.53 kg/m2 in BMI, 1.7 mm Hg in systolic blood pressure and an increase in heart rate of 1.87 beats/min compared with placebo. There were no differences in the incidence of hypoglycemia, cancer or pancreatitis, but there was a higher incidence of gastrointestinal disorders (47.4% vs. 34.1%). As in other studies and meta-analyses, the lack of effect of GLP 1 analogues on heart failure became clear.

The REWIND trial differs from other studies with GLP 1 agonists for a number of reasons. First of all, it included less compromised diabetic patients, since almost 70% had only risk factors, and the average HbA1c was clearly lower. Hence, the incidence of MACE in the placebo group was 2.7% per year, compared with 3.4% in the LEADER study and 5.8% in the HARMONY study. On the other hand, it broke the inertia of designing non-inferiority studies in the incidence of cardiovascular events when testing a new hypoglycemic drug, following FDA directives dating back 10 years, when the analyses that assigned rosiglitazone excess risk

of AMI and mortality were published. The REWIND trial sought to demonstrate superiority over placebo when added to baseline therapy, and it is possible that from now on other studies will adopt the same behavior. It is difficult to attribute a prognostic improvement to a particular reason, and it is possible that several combined actions (metabolic, anti-inflammatory, anti-atherosclerotic, and renal protective) have contributed to these results. It is true that the most marked effect was on the incidence of stroke, but it is also true that, since it was a population with lower baseline risk, it was more difficult to expect a significant reduction in cardiovascular mortality. What is clear is that their results open the door to a more widespread use of GLP 1 agonists in patients with only risk factors. Another factor that may contribute to a greater dissemination of its use is the weekly and not daily administration. Undoubtedly, economic factors will strongly influence their incorporation into the usual therapy of type 2 diabetic patients.

Is there a reason to continue using bare-metal stents? A meta-analysis of individual data

Piccolo R, Bonaa KH, Efthimiou O, Varenne O, Baldo A, Urban P, et al; Coronary Stent Trialists' Collaboration. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. **Lancet. 2019;393:2503-10**

In the practice of percutaneous coronary intervention (PCI), the introduction of drug-eluting stents (DES) meant a decrease in the incidence of restenosis, with respect to the use of bare-metal stents. The use of first-generation DES (with sirolimus or paclitaxel) was nevertheless associated to a certain excess risk of stent thrombosis, which results in acute myocardial infarction (AMI) and frequently death. With the emergence of new generation DES with other drugs, there was a marked reduction in this occurrence, with an almost exclusive increase in the use of these stents. Some clinical practice guidelines (such as that of the European Society of Cardiology), have directly proposed abandoning the use of bare-metal stents, and only using DES in all PCI practices. Other guidelines, such as the AHA/ACC, are not as definite, and in fact 20% of the stents used worldwide are still bare-metal. Is this behavior justified? We found the answer in a recently published meta-analysis.

This is a meta-analysis of individual data from 20 randomized studies that compared head-to-head new generation DES with bare-metal stents. A total of 26,616 patients were considered, 53% of which were assigned to DES. Mean age was 66 years, and 25% were women. In 71% of cases PCI was motivated by some type of acute coronary syndrome and in 29% of cases by stable coronary disease. Bare-metal stents tended to have larger diameter and shorter length than DES. In the case of DES, 53.5% corresponded to everolimus, 19.3% to biolimus, 17.1% to zotarolimus and 2.8% to sirolimus. The use of double anti-platelet therapy was on average 292 days with DES and 244 days with bare-metal stents. Clopidogrel was the P2Y12 inhibitor used in almost 90% of cases. The primary endpoint was the incidence of a composite endpoint of cardiac death or AMI. In a median follow-up of 2.1 years, the primary endpoint occurred in 14.5% of patients with DES and 16.7% with bare-metal stents (HR 0.84, 95% CI 0.78-0.90). The effect occurred specifically in the incidence of AMI, since the incidence of cardiac death was not significantly different between the two groups. There was interaction of the treatment with the follow-up time (reduction of events with DES with respect to bare-metal stents during the course of the first year, but not later) and with the treated artery: only a clear advantage for DES was seen for the anterior descending coronary artery (HR 0.76, 95% CI 0.68-0.85) and not for any other artery (HR 0.92, 95% CI 0.83-1.03). There was, however, no interaction with PCI or with the presence of diabetes. Clearly, the use of DES was associated with lower risk of stent thrombosis: 1.2% vs. 1.7% (HR 0.63, 95% CI 0.50-0.80). Also in this case the difference was in the first year, and not later. The use of DES reduced the need for repeated revascularization of the treated vessel, again in the course of the first post procedural year.

This meta-analysis of individual data confirms the advantage of new generation DES over bare-metal stents, with a reduction in the incidence of AMI, stent thrombosis and the need for repeated revascularization, especially during the first year. Beyond that, after that first year there is no evidence of an increase in the incidence of events in the DES group, and this explains why the difference achieved in the first year determines an advantage that is sustained in a longer follow-up. With these data in mind, only economic reasons can justify the adoption of bare-metal stents today. And if that condition were inexorable, at least the artery that will be operated should be considered, and preserving the use of DES for the anterior descending coronary artery seems a way to mitigate the risk. The non-diabetic condition does not seem to be a reason to rule out the use of DES. The meta-analysis does not allow defining if a specific type of DES offers better outcome compared with the others. It is regrettable that the influence of concomitant medication in the outcome could not been assessed, and that a longer follow-up was not carried out in order to confirm the durability of the advantage obtained.

What is the best antiplatelet and anticoagulant combination to treat patients with atrial fibrillation and percutaneous coronary intervention or acute coronary syndrome? The AUGUSTUS study

Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. **N Engl J Med 2019;380:1509-24.**

The use of oral anticoagulation (OAC) in patients with atrial fibrillation (AF) significantly reduces the risk of stroke and peripheral embolic events. In patients undergoing percutaneous coronary intervention (PCI), the use of dual antiplatelet therapy (DAT) with aspirin and a P2Y12 inhibitor reduces the incidence of major cardiovascular and stroke events, as well as stent thrombosis. In patients with AF undergoing PCI, a triple regimen (TR) with OAC and DAT may theoretically offer maximum anti-ischemic protection, but at the expense of an increased risk of bleeding. This fact has led us to investigate whether the use of a dual regimen (DR) with OAC and a single antiplatelet agent may preserve the protective capacity of the TR, but with a reduced risk of bleeding. The WOEST study (n=563) compared a TR with warfarin, aspirin and clopidogrel vs. a DR with warfarin and clopidogrel in anticoagulated patients (almost 70% with AF) with PCI indication. The DR was associated with lower bleeding, without evidencing excess of ischemic events (although there was not enough power to find it). In the PIONEER AF PCI study (n=2,124), including patients with AF undergoing PCI, a DR with rivaroxaban (15 mg daily) and a P2Y12 inhibitor, as well as a TR with rivaroxaban (5 mg daily) plus DAT, were superior to a conventional TR with a vitamin K antagonist (VKA) plus DAT to reduce major bleeding, without excess of ischemic events. It is worth noting that the doses of rivaroxaban used in the study (5 or 15 mg daily) were lower than the recommended dose (20 mg) to prevent stroke in the context of AF. In the RE-DUAL PCI study (n=2,725), patients with paroxysmal, persistent or permanent AF, in whom a successful PCI had been performed, were randomly assigned to 3 strategies: dabigatran 110 mg every 12 hours plus a P2Y12 inhibitor (branch D 110), dabigatran 150 mg every 12 hours plus a P2Y12 inhibitor (branch D 150), or a TR with warfarin (with an INR target between 2 and 3), aspirin and a P2Y12 inhibitor. The incidence of major bleeding was significantly lower with the DR for any dose of dabigatran with respect to the TR. Regarding the TR, it was impossible to demonstrate non-inferiority in the incidence of ischemic events for each DR group separately; however this was possible when combining both groups. Non-inferiority could not be demonstrated for a composite endpoint of thromboembolic events and mortality. Thus, these studies showed that low or standard doses of direct-acting oral anticoagulants (DOAC) combined with a P2Y12 inhibitor are associated with lower bleeding than the combination of VKA with DAT. But, how to explain this reduction? To the use of DOAC vs. VKA, or to the non-use of aspirin? Which is, definitely, the best combination in patients who require OAC and anticoagulant therapy?

The answer seems to come from the hand of the AUGUSTUS study, a prospective, randomized, multicenter study that included patients with paroxysmal, persistent or permanent AF (and should therefore receive OAC), with a recent acute coronary syndrome or a planned PCI, or both conditions, who should then receive a P2Y12 inhibitor for the next 6 months. Apixaban was compared with VKA and aspirin with placebo in a 2×2 factorial design. Four groups were then defined, all with the P2Y12 inhibitor: apixaban-aspirin, apixaban-placebo, VKA-aspirin and VKA-placebo. The aspirin groups then received TR, and the placebo groups DR. The primary endpoint (PE) was the incidence of major or clinically relevant non major bleeding at 6 months. Major bleeding was considered when it resulted in death, occurred in a critical organ (intracranial, intraocular, intraspinal, retroperitoneal, intraarticular, intramuscular or pericardial), or was associated with a hemoglobin drop ≥2 g/dl or the need to transfuse at least 2 units of red blood cells. Clinically relevant non major bleeding was considered when it caused hospitalization, the need for a medical or surgical intervention, an unplanned visit, or a change in the therapeutic regimen. The secondary endpoints were the composite of death or hospitalization, and death or ischemic event of significance (stroke, AMI, stent thrombosis or urgent revascularization).

The dose of apixaban was 5 mg every 12 hours or 2.5 mg every 12 hours in patients≥80 years, with creatinine ≥1.5 mg/dl or weight ≤60 kg. The dose of VKA was adjusted to achieve an INR between 2 and 3. The dose of aspirin was 81 mg daily. The comparison between VKA and apixaban was planned as an initial non-inferiority analysis, which if positive was followed by a superiority analysis. The comparison between aspirin and placebo was designed as a superiority analysis of the use of a single antiplatelet agent (P2Y12 inhibitor-placebo) with respect to DAT (P2Y12 inhibitor-ASA)

Between 2015 and 2018, 4,614 patients from 492 sites in 33 countries were included in the study. Median age was 70.7 years, and 29% were women. The median time between the index event and the random assignment was 6 days. In 37.3% of cases, patients were admitted to the study for acute coronary syndrome undergoing PCI, 23.9% for acute coronary syndrome undergoing medical treatment, and 38.8% for elective PCI. Ten percent of patients treated with apixaban received a dose of 2.5 mg every 12 hours. The time in the average therapeutic range of those treated with VKA was 59%. The P2Y12 inhibitor used was clopidogrel in 92.6% of cases. Before completing the study, 12.7% of those treated with apixaban, 13.8% with VKA and 16.9% with aspirin, and 14.8% of those assigned to placebo discontinued treatment.

At 6 months, 10.5% of patients treated with apixaban presented the PE as well as 14.7% of those treated with VKA (HR 0.69, 95% CI 0.58-0.81, p <0.001 for non-inferiority and for superiority). The number needed to treat to avoid one primary event was 24 with apixaban vs. VKA. The incidence of the PE was 16.1% in those treated with aspirin and 9% in those assigned to placebo (HR 1.89, 95% CI 1.59-2.24). The

number needed to treat to generate an additional event with aspirin with respect to placebo was 14. The highest incidence of the PE was seen among patients who received TR with VKA and DAT (18.7%), and the lowest incidence among those who received DR with apixaban and a P2Y12 inhibitor (7.3%). There was no interaction between the two randomization factors, nor were there significant differences in subgroup analysis based on baseline characteristics.

Deaths and hospitalizations at 6 months were 23.5% in patients receiving apixaban and 27.4 % in those taking VKA (HR 0.83, 95% CI 0, 74-0.93). The difference was specifically found in the incidence of hospitalization (22.5% vs. 26.3%, respectively), with no difference in mortality. There was no significant difference in the incidence of this secondary endpoint between aspirin and placebo (26.2% vs. 24.7%). The highest incidence of the secondary endpoint was among those who received TR with VKA and DAT (27.5%) and the lowest was among those receiving DR with apixaban and a P2Y12 inhibitor (22%). There was no significant difference in the incidence of death or ischemic event in any of the 2 comparisons: 6.7% with apixaban vs. 7.1% with VKA, 6.5% with aspirin vs. 7.3% with placebo. But specifically regarding stroke, there was a significant reduction with apixaban vs. VKA: 0.6% vs. 1.1% (HR 0.50, 95% CI 0.26-0.97).

The AUGUSTUS study confirms three facts in patients who, due to the presence of AF, must be anticoagulated, and who due to acute coronary syndrome must also receive antiplatelet therapy: a) that a regimen that uses apixaban rather than VKA is associated with a lower incidence of major or relevant bleeding; b) that DAT is associated with a higher rate of major or relevant bleeding than using a P2Y12 inhibitor alone; c) as corollary, that a TR with VKA, aspirin and a P2Y12 inhibitor is the most risky combination, and a DR with only apixaban and a P2Y12 inhibitor is the safest, not only for bleeding but also for the incidence of hospitalization in the first 6 months after the index event. As with previous studies, there is not enough power to assess the effect on ischemic events, and in this regard a lower incidence of these must be reported in patients treated with aspirin, compared with those who were not (6.5% vs. 7.3%), although this finding (0.8% less ischemic events) seems to be surpassed by the clear increase in major or relevant bleeding associated with its use (16.1% vs. 9%, an excess of 7.1%).

A recently published network meta-analysis (Lopes et al, JAMA Cardiol 2019, doi 10.1001/jamacardio.2019.1880) helps to summarize the information derived from the WOEST, PIONEER AF PCI, RE DUAL PCI and AUGUSTUS studies. With regard to major bleeding, compared with a TR of AVK and DAT, the OR for TR with DOAC and DAT is 0.70 (95% CI 0.38-1.23, p NS), for DR with AVK and a P2Y12 inhibitor is 0.58 (95% CI 0.31-1.08, p NS) and for DOAC with a P2Y12 inhibitor it is 0.49 (95% CI 0.30-0.82, p <0.05). On the other hand, there is no difference in the incidence of ischemic events: compared with a TR with VKA and DAT, none of the tested regimens is associated with significant excess of major cardiovascular events (cardiovascular death, non fatal AMI or non fatal stroke), with ORs which vary between 0.94 and 1.02 (in all cases p=NS). In conclusion, a DR with DOAC and a P2Y12 inhibitor is the safest combination in patients such as those included in these studies.

TAVI in low-risk patients: two randomized studies and one registry

Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. **N Engl J Med 2019;380:1695-705.**

Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. **N Engl J Med 2019;380:1706-715.**

Bekeredjian R, Szabo G, Balaban Ü, Bleiziffer S, Bauer T, Ensminger S , et al. Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results from the German Aortic Valve Registry (GARY). **Eur Heart J 2019;40:1323-30**.

Transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis and at high and moderate surgical risk has shown to be superior or at least non-inferior to valve replacement surgery. However, a high proportion of patients with this pathology has low surgical risk according to the assessment with different scoring tools. What will their behavior be with TAVI compared to surgical replacement? Two randomized studies and a real-world registry on the subject have been recently published to address this question.

The PARTNER 3 study enrolled patients with severe calcific aortic stenosis and STS score <4% to be treated with conventional replacement with a biological valve or TAVI with transfemoral implantation of a balloon-expandable Edwards SAPIEN 3 valve. Patients with clinical frailty, bicuspid aortic valve or other anatomical conditions that increased the risk of complications were excluded. Patients who received TAVI were treated with aspirin and clopidogrel before and up to one month after the procedure. The primary endpoint (PE) was a composite of all-cause death, stroke or rehospitalization within the year. The study was planned as a non-inferiority analysis and to demonstrate this, the 95% upper confidence limit of the difference in the PE between TAVI and surgery should be <6%. If non-inferiority was demonstrated, superiority could be tested. A per protocol analysis of the results was carried out, considering in each group the patients in whom the assigned procedure had been carried out effectively.

Assuming an expected PE incidence of 14.6% in the TAVI group and 16.6% in the surgery group, the calculated necessary sample size was 1000 patients. The study was carried out in the United States, Australia, New Zealand, Canada and Japan.

Between 2016 and 2017, 503 patients were assigned to TAVI and 497 patients to surgery and the procedure was carried out in 496 and 454 patients, respectively. Mean age was 73.4 years and 68.3% were men. Mean STS score was 1.9±0.7, mean valve area 0.8 cm2, and mean gradient 49 mmHg. Twenty-eight percent of patients had coronary heart disease, 3% left bundle branch block, and there was a higher proportion of patients in functional class III-IV in the TAVI group (31.2% vs. 23.8%). Concomitant procedures were performed in 7.9% of patients in the TAVI group and 26.4% in the surgical group (6.5% and 12.8% coronary revascularization, respectively). After the first follow-up year, the PE occurred in 8.5% of patients in the TAVI group and 15.1% in the surgical group (absolute difference -6.6%, 95% CI -10.8% to -2.5%, p <0.001 for non-inferiority; HR 0.54, 95% CI 0.37-0.79, p=0.001 for superiority). At one year the incidence of all-cause death was 1% with TAVI and 2.5% with surgery (HR 0.41, 95% CI 0.14-1.17); 1.2% vs. 3.1% for stroke (HR 0.38, 95% CI 0.15-1) and 7.3% vs. 11% for rehospitalization (HR 0.65, 95% CI 0.42 -1), respectively. The incidence of major bleeding was also significantly lower with TAVI: 3.6% vs. 24.5%, as well as the 30-day incidence of stroke (0.6% vs. 2.4%), death or stroke (1% vs. 3.3%), atrial fibrillation (5% vs. 39.5) %) and hospital stay (3 vs. 7 days). Conversely, at one year, the incidence of new onset left bundle branch block was greater with TAVI (23.7% vs. 8%, HR 3.43, 95% CI 2.32-5.08). Echocardiographic results at 30 days were similar: mean gradients of 12.8 mmHg and 11.2 mmHg with TAVI and surgery and valve areas of 1.7 and 1.8 cm2, respectively. At one year, the incidence of mild paravalvular regurgitation was higher with TAVI. There were no differences in other complications which in previous studies had been more frequent with TAVI, such as vascular complications or the need for permanent pacemakers.

The EVOLUT study included patients with severe aortic stenosis and risk of death with surgery <3% at 30 days, who were randomly assigned to TAVI with one of 3 models of self-expanding bioprostheses (CoreValve, Evolut R or Evolut PRO) or surgical replacement with biological valve. The PE was death or disabling stroke at 2 years. An initial non-inferiority analysis was postulated (with a margin similar to that of the previous study, i.e., that the upper confidence limit of the difference in events between TAVI and surgery should be <6%). Only if this and also other 7 secondary endpoints (related with echocardiographic and quality of life criteria, in some cases with a claim of non-inferiority level and in other cases of superiority) were demonstrated, the search of superiority for PE could be addressed.

Between 2016 and 2018, 1,468 patients were included, and were equally and randomly assigned to either of the two procedures. TAVI was effectively performed in 725 patients and surgery in 678 patients, constituting the basis of the primary analysis. Mean age was 74 years, 35% were women, and the average STS score was as in the previous study 1.9±0.7. In the recently published analysis, median follow-up was 12 months, with only 72 patients in the TAVI group and 65 in the surgery group who had reached the 2 years of the stipulated follow-up. The incidence of the PE at 24 months was 5.3% in the TAVI group and 6.7% in the surgery group. The non-inferiority of TAVI with respect to surgery for the PE was demonstrated, and non-inferiority or superiority was also shown for the 7 secondary endpoints, including greater valve area and lower gradient with TAVI; but it was not possible to demonstrate superiority of TAVI over surgery for the PE.

At 30 days there was a significant difference in favor of TAVI in the incidence of death or disabling stroke (0.8% vs. 2.6%) mainly at the expense of stroke; and of a secondary safety endpoint of death, disabling stroke, life-threatening bleeding, major vascular complication or acute renal failure (5.3% vs. 10.7%). The incidence of atrial fibrillation was significantly lower with TAVI (7.7% vs. 35.4%), but the need for permanent pacemaker implantation and the incidence of aortic regurgitation were higher (17.4% vs. 6.1% and 3.5% vs. 0.5%, respectively).

At 12 months, the difference in the incidence of the PE was no longer statistically significant: 2.9% vs. 4.6%, and the difference in the incidence of atrial fibrillation and need for pacemakers was maintained. The estimation of death at 24 months was similar in both groups: 4.5%. In contrast, the incidence of stroke was significantly lower with TAVI: 1.1% vs. 3.5%.

As a complement to the information derived from these two randomized studies, we present recently published data from the German GARY registry. It is a registry initiated in 2010 that includes all patients undergoing TAVI or aortic valve surgery in 78 German centers. In 2014 and 2015, 45,567 patients were included. Patients with STS score <4%, submitted to TAVI and isolated aortic valve replacement were included for this publication, whereas those with myocardial revascularization by catheterization or associated surgery were excluded. Thus, 20,549 patients were defined, 14,487 (70.5%) treated with surgery and the rest (29.5%) with TAVI. (During the same period, 82.5% of 7,744 patients with an STS score between 4% and 8% underwent TAVI and 92.2% of 2,934 patients with an STS score >8% were also treated with TAVI).

Among the 20,549 patients with an STS score <4%, those treated with TAVI were significantly older (mean age of 78.9 vs. 67.5 years, p <0.001), had a higher STS score (mean of 2.9 vs. 1.8, p <0.001), and more frequently previous cardiac surgery and pulmonary hypertension. The most frequently considered reasons for choosing TAVI were: clinical frailty

(49.1%), porcelain aorta (7%), concomitant tumoral pathology (2.7%) and Euro SCORE ≥20%, which in those years justified the reimbursement of TAVI expenses in Germany (14.6%). A transvascular implantation approach was chosen in 84.3% of cases, (almost all of them were transfemoral) and in the remaining 15.7%, they were transapical. There were vascular complications in 2.2% of cases, and the need for permanent pacemaker was greater with TAVI than with surgery: 15.1% vs. 4.4%, p <0.001. There was lower transvalvular gradient with TAVI, but higher presence of aortic regurgitation.

When comparing the evolution of patients, and given the baseline differences between those subjected to TAVI or surgery, a propensity score was built based on independent predictors of TAVI use. This score was used as a covariate to adjust the survival analysis. Adjusting then for the propensity score, in-hospital survival and 30-day survival were better with TAVI (98.5% vs. 97.3%, p=0.003 and 98.1% vs. 97.1%, p=0.014, respectively); however, the difference disappeared at 1 year (90% vs. 91.2%, p NS). The figures were similar when TAVI with transfemoral approach was compared with surgery. However, when TAVI with transapical approach was compared with surgery, there was no difference in in-hospital survival (96.9% vs. 97.2%) or at 30 days (96.9% vs. 96.8%), but at 1 year survival was lower with TAVI: 87.6% vs. 90.9%, p=0.04.

Practice guidelines have traditionally recommended the use of TAVI in patients with severe aortic stenosis considered inoperable or in those at high surgical risk. The indication has been expanding towards patients with moderate surgical risk; however, in patients at low surgical risk the indication is still valve surgery. However, as in any procedure, the idea to extend the indication to the rest of the spectrum arises. And, as we see in the GARY registry, many patients are operated beyond the indications of the guidelines, and even of the evidence of randomized studies. Note that the registry data refer to 2014-2015, and that the first adequate size randomized studies in this type of patients have just been published.

The excellent results obtained in the PARTNER 3 study are striking: a reduction of 50% in the composite endpoint of death, stroke or hospitalization and a markedly low mortality rate at one year: 2.5% with surgery, but only 1% with TAVI. It is true that these are low-risk patients, but even so, a reduction of 1.5% mortality in absolute terms is still achieved with TAVI. The difference in the incidence of stroke and major bleeding certainly plays a role in these results. The use of TAVI appears as superior to surgery when considering this combination of adverse events. The unexpected result is that with a higher incidence of left bundle branch block as expression of conduction disorder, this study has not analyzed a greater need for permanent pacemaker, a general rule in this type of procedure. A limitation of this study is the short follow-up period: because patients are low risk and the event rates are so low a much longer follow-up might be useful to demonstrate the equivalence or superiority of any of the procedures.

In this sense, the EVOLUT study is somehow incomplete. We know the results when little more than half of the patients have completed one year of follow-up, and less than 10% have reached the stipulated 2 years. The analyzed publication is that of a pre-specified interim analysis, carried out when 850 patients had reached one year of follow-up. Undoubtedly, reasons that go beyond what is purely medical underlie the decision to publish the interim analysis of a study that is being carried out: the fast development of technology, the need not to be relegated to competition between brands, etc. Nevertheless, what do we have up to now? An initial outcome that is more beneficial with TAVI, which loses significance as time passes, but with an incidence of stroke that is still lower than that of the surgical group. Here the rule of a greater need for pacemakers is fulfilled, and the significantly lower incidence of atrial fibrillation, evidenced in the PARTNER 3 study is confirmed, probably related to the lower incidence of stroke. In conclusion, with the data available to date, TAVI appears as non-inferior to surgery in the 24-month follow-up (although this conclusion arises from only 137 patients who achieved this goal!)

Finally, the GARY registry provides real-world evidence, initially without the rigid inclusion and exclusion criteria of a randomized study. In its own way, however, the evidence is also curtailed: all patients requiring a combined treatment are excluded; among more than 45,000 patients included, just over 20,000 end up being part of the publication. The use of the propensity score is an attempt to adjust the outcome to the different baseline conditions, but it is clear that it cannot be adjusted by unknown confounders. With these caveats, the results of the GARY study differ in the magnitude of the events compared with those seen in randomized studies: for 1% mortality at one year with TAVI and 2.5% with surgery, the GARY figures in both groups are around 10%, once again evidencing the difference between both sources of information. But the sense of the findings is similar: we can assume at least equivalent survival with both forms of treatment also in the real world.

All the conclusions we can draw seem temporary in a field that shifts under our feet. The general impression is that the progress of TAVI as treatment of severe aortic stenosis is unstoppable; and that factors other than surgical risk will be those that end up helping to decide in each case the best strategy, including a consideration of events and situations that differentiate TAVI from surgery (less hospitalization time, less stroke, bleeding and atrial fibrillation, and more need for pacemaker). Economic reasons are clearly associated with the choice of treatment in the real world. As with all technology, costs will decrease over time. New randomized studies and registries, but also health economic studies will finish defining the horizon.

Low risk of sudden death in patients with heart failure after 5 years of resynchronizer implantation

Barra S, Duehmke R, Providencia R, Narayanan K, Reitan C, Roubicek T, et al. Very long-term survival and late sudden cardiac death in cardiac resynchronization therapy patients. **Eur Heart J 2019;40:2121-7**

Cardiac resynchronization therapy (CRT) has shown to improve the prognosis in patients with heart failure and depressed ejection fraction (HFdEF). In general, the devices used also offer defibrillator function (CRT-D) but sometimes CRT is limited specifically to the pacemaker function (CRT-P). A topic of permanent discussion is whether CRT-D improves the prognosis compared with CRT-P. In 2015, the results of the CeRtiTuDe cohort study, showed that in patients with CRT-P excess mortality at the 2-year follow-up was due to an increase in non-sudden death, adding fuel to the controversy. We now know the data of a European cohort study that sheds light on the outcome of patients who have survived 5 years to cardiac resynchronization implant, and focuses specifically on the form of death.

This is a CRT registry in French, British, Czech and Swedish patients undergoing the intervention between 2002 and 2013, and who completed at least 5 years of follow-up after implantation. This cut-off point was chosen as it corresponds to the median battery life of a CRT-D device. Among the 1,775 patients considered, 1,241 (69.9%) received CRT-D and the rest CRT-P. The primary end point was overall mortality and long-term sudden cardiac death, defined as unexpected death of cardiac origin that occurred within the hour of onset of an acute heart condition or 24 hours after the patient was last seen in stable conditions.

Patients who received CRT-D were on average 6 years younger, with a higher prevalence of men, a lower prevalence of QRS >150 ms and FC III-IV than those treated with CRT-P. In these patients there was a tendency to higher prevalence of ischemic etiology, and a somewhat lower EF (means of 25.5% vs. 26.8%, p <0.01). Mean follow-up after completing the first 5 years post-implantation was 23 months. The standardized annual mortality rate by age was 4.04% in patients with CRT-D and 9.7% in those with CRT-P. The cause of death was progression of heart failure in 52.6% of patients with CRT-D and 42.8% of those with CRT-P. In 33.1% of patients with CRT-D and 33.3% with CRT-P death was of non-cardiovascular cause. The incidence of sudden death was very low: it represented 5.8% of deaths among those treated with CRT-D and 8.5% in those with CRT-P. In the multivariate analysis, the type of device was not an independent predictor of mortality. The incidence of defibrillation therapy in patients with CRT-D was lower after the 5-year post-implantation period than during it.

The evidence on the ability of CRT to reduce the incidence of sudden death is age-old: the CARE HF study had already demonstrated it. However, the fact that one third of deaths in the CRT group in that study were due to sudden death led to support the need of a CRT-D joint therapy. The authors of this study emphasize that the incidence of sudden death is very low in patients who have survived 5 years to a CRT implantation, with or without associated defibrillator, and that the vast majority of deaths are due to the progression of heart failure. We had already commented on RAC 2017 vol 85 n° 4 a review of randomized studies, encompassing from the RALES study (1999) to the PARADIGM study (2014) a significant reduction in the annual incidence of sudden death, from 6.6% to 3.3%. The period covered by that review coincides with the one considered in this study. At that moment we mentioned that a more aggressive approach to coronary heart disease, having abandoned antiarrhythmic agents with a proarrhythmic effect, and fundamentally the increasingly widespread use of neurohormonal antagonists, were reasons that could explain this phenomenon. However, it would be wise to make a proviso: patients included in the study we are presenting are those who survived the cardiac resynchronizer implant for 5 years; we do not know the causes of death of those who died in that period. The fact that the incidence of defibrillation therapy has been greater in the first 5 years than in the average 23 months of subsequent follow-up in the group of patients with CRT-D leads us to question what the real incidence of sudden death will have been in those who died in the years immediately after the implant. In other words, this is a population selected by the passage of time, a clear example of survival bias. And, since it is an observational study, there are confounding factors that may not have been considered. Therefore, we understand that the discussion about whether it is essential to associate a defibrillator to CRT, or that only the latter is enough, is not settled. And it is surely possible that the decision is individual, based on the age, the degree of ventricular function impairment, the functional class, the presence of comorbidities and even, why not, the presence of myocardial fibrosis, which increases the risk of sudden death. Younger patients, in less advanced functional class, with no excessive elevation of natriuretic peptides, absence of significant comorbidities and verifiable myocardial fibrosis could be the best candidates for double therapy. At present two ongoing European studies are attempting to clarify the questions raised.

Prognostic value of pulmonary pressure values usually considered normal

Strange G, Stewart S, Celermajer DS, Prior D, Scalia GM, Marwick TH, et al. Threshold of Pulmonary Hypertension Associated With Increased Mortality. **J Am Coll Cardiol 2019;73:2660-72.**

Pulmonary hypertension (PHT), defined by a mean pulmonary pressure >25 mmHg is a universally recognized adverse prognostic factor. The so-called borderline pulmonary hypertension (mean pulmonary pressure between 21 and 25 mmHg) is also associated with an adverse prognosis, but practice guidelines do

not yet recommend specific treatment in this context. Although the diagnosis of certainty arises from right catheterization, in most cases the assessment is made with echocardiography. An Australian cohort study suggests that traditionally accepted values of pulmonary pressure are associated with adverse prognosis.

NEDA is a registry that collects prospective and retrospective echocardiographic and clinical data throughout Australia. The study here presented considered all patients >18 years in whom at least one echocardiogram had been performed between 1997 and 2017, and had tricuspid regurgitation velocity (TRV) data to enable the estimation of right ventricular systolic pressure (RVSP), as pulmonary systolic pressure surrogate. The formula RVSP=4 (TRV)2 + 5 mmHg was used. This value was associated with mortality in the follow-up period. Among 313,492 individuals, 157,842 (50.3%) had TRV data, of whom 52.9% were women. Normal RVSP was <40 mmHg; mild between 40 and 49.9 mmHg, moderate between 50 and 59.9 mmHg and severe ≥60 mmHg. The population was divided into quintiles according to RVSP: ≤24.36; 24.37 to 28.04; 28.05 to 32.04; 32.05 to 38.82 and ≥38.83 mmHg. Median follow-up was 4.2 years.

In 81.3% of cases patients presented normal RVSP (28.6% between 30 and 39.9 mm Hg). Among the remaining cases, 11.4% presented mild elevation, 4.4% moderate and 2.9% severe elevation. An increase in RVSP was verified with age, with a mean of 25.9 mmHg in those under 25 years and up to 39.3 mmHg in those over 85 years. If all cases in whom the TRV data could not be obtained had normal RVSP, its elevation prevalence would be 9.4%

During follow-up, RVSP elevation was associated with higher mortality. Mortality at 1 and 5 years for the group with normal RVSP was 6.8% and 20.3%, respectively, compared with values of 44.2% and 78% in those with severe RVSP increase. Taking as reference patients with normal RVSP, the HR for mortality at 5 years was 2.8, 4.9 and 9.7, respectively for those with mild, moderate and severe elevation. Adjusting for age, sex and echocardiographic evidence of left heart disease, there was an increased risk of mortality for those in the third, fourth and fifth quintile of RVSP (HR of 1.4, 1.9 and 4.4, respectively, in all cases with $p<0.001$). Therefore, a threshold value to indicate a higher risk of mortality was evident around 30 mmHg, in men and women and in the entire age range.

Practice guidelines consider that TRV >3.4 m/sec implies high probability of PHT. If TRV is between 2.9 and 3.4 m/sec and there are other suggestive signs of PHT, the probability is high; If there are none, it is moderate. And if TRV is ≤2.8 m/sec, the probability is moderate in the presence of other signs of HTP, but low if there are none. The main finding of this study with more than 150,000 patients is that "acceptable" values of TRV already involve risk, adjusting for the presence of left heart disease. In fact, using the formula RVSP=4 (TRV)2+5, a value of 30 mmHg corresponds to a TRV of only 1.58 m/sec. It is true that people who have an echocardiography generally have a reason to undergo this study; there may therefore be a selection bias, due to symptoms, signs, ECG, etc., that partly explain the worst prognosis of those included in the registry; and it is also true that, as we said, the certainty diagnosis is hemodynamic. But the strength of the number of patients included, and the homogeneity of the findings suggest that the echocardiogram may be at least a screening tool to define a population at higher risk, in which a deeper search for causes and consequences allows to adopt an earlier behavior, or maintain at least an alert expectation.