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Another scenario for the aspirin swan song? The TWILIGHT study

Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. **N Engl J Med 2019; 381:2032-42. http://doi.org/ggdq9p**

The use of dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor vs. aspirin monotherapy in the context of acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) has been shown to significantly reduce the incidence of ischemic events, at the expense of increased risk of bleeding. Several studies have evaluated different schemes regarding the duration of DAPT to achieve the optimal balance of safety and efficacy between both phenomena. Traditionally, the interruption of DAPT consists in the abandonment of the P2Y12 inhibitor, while maintaining aspirin. In recent years, the usefulness of aspirin has been questioned in terms of its role in primary and secondary prevention. The TWILIGHT study proposes a twist on how to implement DAPT cessation. What if instead of suspending the P2Y12 inhibitor it was maintained and aspirin was suspended?

TWILIGHT was a multicenter, randomized study, including patients undergoing a successful PCI with placement of at least one drug-eluting stent. Patients should have at least one clinical and one angiographic criteria of high risk ischemic event or bleeding. Clinical criteria were age ≥65 years, female gender, diabetes, renal failure and positive troponin, while angiographic criteria included multi-vessel damage, main left coronary artery or proximal anterior descending artery injury, thrombotic lesion, calcified lesion treated with atherectomy, or stent length >30 mm. Patients with ST-segment elevation, cardiogenic shock or oral anticoagulant treatment were excluded. These were patients in whom the attending physician planned to use DAPT with aspirin and ticagrelor. After three months of open treatment with aspirin (80-100 mg daily) and ticagrelor (90 mg every 12 hours), if the patients had not presented with stroke, acute myocardial infarction (AMI), a revascularization procedure or major bleeding, they were randomly assigned to receive double-blind aspirin or aspirin placebo for the following 12 months, keeping ticagrelor as open treatment. The primary end point was the incidence of bleeding 2, 3 or 5 according to the Bleeding Academic Research Consortium (BARC).

As we know the BARC scale considers five groups:

Type 0: No bleeding.

Type 1: Bleeding that does not lead to patient consultation, hospitalization or studies.

Type 2: Any bleeding that does not meet type 3, 4 or 5 criteria, but with at least one of the following: 1) requires non-surgical medical intervention, 2) leads to hospitalization or 3) requires immediate evaluation.

Type 3: it can be 3a (3-5 g/dl hemoglobin drop or transfusion), 3b (hemoglobin decrease ≥5 g/dl, bleeding requiring compression, surgical intervention or tamponade) or 3c (intraocular or intracranial bleeding).

Type 4: Bleeding associated with coronary artery bypass surgery.

Type 5: Deadly bleeding. It can be 5a: Probable (without confirmation but with clinical suspicion), or 5b: Definitive (confirmed by autopsy or image).

The study assumed a superiority hypothesis for the primary endpoint. Assuming an annual BARC 2, 3 or 5 bleeding rate of 4.5% with DAPT, a sample size of 8,200 patients was considered to demonstrate with a power of 80% and $p<0.05$ a 28% reduction in the ticagrelor branch with aspirin placebo. The secondary endpoint was a composite of all-cause death, nonfatal AMI or nonfatal stroke. In this case a non-inferiority hypothesis was considered. Assuming an annual incidence of 8% with DAPT, it was assumed that 8,200 patients allowed, with a power of 80%, to rule out an absolute excess risk of 1.6% in the ticagrelor-aspirin placebo branch, with one-tailed $p=0.025$.

The study enrolled 9,006 patients of which 7,119 were effectively randomized 3 months after PCI to DAPT or ticagrelor with aspirin placebo. Mean age was 65 years, 23.8% were women and 36.8% had diabetes. In almost 65% of cases PCI was indicated for ACS, and in the rest, predominantly due to stable angina. Adherence to ticagrelor in the study year was around 86.5% in both branches. The annual incidence of the primary endpoint (BARC 2, 3 or 5 bleeding) was 4% in the ticagrelor-aspirin placebo group versus 7.1% in the DAPT group (HR 0.56; 95% CI 0.45-0.68, $p<0.001$). The annual incidence of BARC bleeding 3 or 5 was 1% in the ticagrelor-aspirin placebo group versus 2% in the DAPT group (HR 0.49; 95% CI 0.33-0.74, $p<0.001$). The incidence of the secondary endpoint was evaluated in a per protocol analysis in the 7,039 patients who received the medication and did not deviate from the protocol, and it was similar in both groups, 3.9%, p=NS. There were no differences in the incidence of death, AMI or stent thrombosis.

The TWILIGHT study seems to indicate that the use of aspirin could be significantly limited after performing a PCI. In the open GLOBAL LEADERS study, one month of DAPT followed by ticagrelor monotherapy for 23 months was not better than conventional DAPT. The differences with the TWILIGHT study may be due to the fact that the population of the GLOBAL LEADERS study included all patients and not only those at

high risk, that it was open and not double blind, to the manner of event adjudication and to follow-up duration. As limitations it should be noted that the patients included were in principle at high risk of events according to the inclusion criteria, and in them the use of ticagrelor had been planned. Therefore, the conclusions cannot be extrapolated to different patients or to the use of another P2Y12 inhibitor. But, on the other hand, despite the calculated risk, the incidence of ischemic events was lower than expected, and there was not enough power to detect an increase in the incidence of stroke (0.5% with ticagrelor, 0.2% with DAPT). It is logical to have lower bleeding with a single antiplatelet agent than with two. Are the conclusions about the absence of excess risk of ischemic events definitive? We can discuss it; with a similar incidence of 3.9% in each group, it is difficult to assume a significant difference with a greater number of patients; but, on the other hand, it could be argued that perhaps in patients at higher ischemic risk the conclusions would not be the same. It is true, however, that after decades of reigning in primary and secondary prevention, the universal use of aspirin seems to be losing ground.

Effect of antihypertensive treatment in almost 5 million patients. The LEGEND HTN study

Suchard MA, Schuemie MJ, Krumholz HM, You SC, Chen R, Pratt N, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. **Lancet 2019, 394:1816-26. http://doi.org/ggbsxn**

In antihypertensive treatment, the practice and consensus guidelines recognize thiazide diuretics (TD), angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), and calcium antagonists (CA) as first-choice drugs. The evidence on the use of these drugs comes from long-standing randomized trials (mostly prior to the year 2000) that tested not classes but individual agents. We do not have recent evidence on the comparative effectiveness of these drugs in the real world. In this sense, the LEGEND HTN study constitutes an outstanding contribution. This was an observational study that considered 9 large databases, 6 administrative databases and 3 electronic health record systems, from 4 countries (6 from the United States, 1 from Germany, 1 from Japan and 1 from South Korea). In each case, new users of each of these therapeutic agents were retrospectively individualized (patients diagnosed with hypertension who began to use any of these drugs as monotherapy, after at least 1 year of not using them). A total of 4,893,591 patients included in the study. Among new users, 48% received ACEI, 17% TD, 16% dihydropyridine CA, 15% ARBs and 3% non-dihydropyridine CA. The most used individual agent among ACEI was lisinopril, hydrochlorothiazide as TD, losartan as ARBs, amlodipine as dihydropyridine CA, and diltiazem as non-dihydropyridine CA. The highest baseline blood pressure was seen among TD users (median 142/88 mm Hg) and the lowest among those using non-dihydropyridine CA agents (median 133/80 mm Hg). New ACEI users were more frequently men, diabetics, with atherosclerotic disease and heart disease compared with new TD users. Atrial fibrillation was more frequent among new non-dihydropyridine CA users. The study compared different therapeutic agents in pairs and their influence on 9 points of effectiveness, the most important being acute myocardial infarction (AMI), stroke and hospitalization for heart failure (HHF), and 46 safety points, from the most common adverse effects to the most unusual. In each database the different agents were compared. As the baseline characteristics of each drug user were obviously different, which may influence the evolution beyond the agent used, comparable cohorts were generated by propensity score, taking into account age, comorbidities and cardiovascular and general treatment) when contrasting each pair of agents. Thus, considering 5 classes of drugs, 10 comparisons of each pair of drugs, 55 endpoints between those of effectiveness and safety, and 9 databases, more than 22,000 comparisons were generated between cohorts matched by propensity score, which were subsequently meta-analyzed.

Thiazide diuretics consistently demonstrated to be associated with better evolution than ACEI, evidencing between 16% and 17% AMI, stroke and intracranial hemorrhage (ICH) reduction in all cases ($p=0.01$). Both TD as ACEI, ARBs and dihydropyridine CA were associated with better evolution than non-dihydropyridine CA, with a lower incidence of AMI, stroke and ICH, with statistically significant differences in all cases. The rest of the comparisons did not show differences. Regarding the incidence of adverse effects, new TD use was associated with an increased risk of hypokalemia (with HR 2.8 to 2.9 compared with ACEI and ARBs, and 1.8 to 1.9 compared with various CA) and hyponatremia, while ACEI use was associated with excess risk of angioedema, gastrointestinal disorders and renal dysfunction.

The LEGEND HTN study once again focuses the discussion on the difference between randomized and observational studies. For example, so far, we knew a meta-analysis of 3 randomized studies that, with almost 30,000 patients, showed no difference in the incidence of AMI between the use of TD or ACEI. In this case, with close to 2,300,000 new ACEI users and 800,000 new TD users, the difference in favor of TD becomes evident. It may be argued that in the absence of randomization certain baseline differences not considered may be the real ones responsible for the phenomenon. In fact, it should be noted that when adjusting for baseline blood pressure in the available databases (which is perhaps the point that should be most regretted, the absence of blood pressure measurements in some of the administrative databases), the risk ratio

for AMI in the aforementioned comparison loses only slightly statistical significance, with HR 0.85, 95% CI 0.70-1.03. But the large number of observations and the wide and comprehensive inclusion of the covariates taken into account when generating propensity scores make the conclusions of this study difficult to refute. Their results are an invitation to consider TD when selecting the initial hypertension treatment, contemplating the risk of electrolyte alterations that should be periodically investigated.

A cluster study demonstrates the effectiveness of a simple strategy to treat high blood pressure. The HOPE study 4

Schwalm JD, McCready T, Lopez-Jaramillo P, Yusoff K, Attaran A, Lamelas P, et al. A community-based comprehensive intervention to reduce cardiovascular risk in hypertension (HOPE 4): a cluster-randomised controlled trial. **Lancet. 2019 ;394:1231-42. http://doi.org/dg74**

Although we have several options when choosing an antihypertensive treatment, the truth is that less than 20% of hypertensive patients have their condition controlled. Different barriers of all kinds (from the awareness of the importance of diagnosing and treating hypertension, to cultural and socioeconomic access factors) contrive against the goal of achieving normal blood pressure. A similar reality can be acknowledged regarding dyslipidemia. Randomized studies are generally focused on the therapeutic impact of a particular agent, and traditionally, randomization considers individuals. There is a specific type of randomized studies, which considers clusters when assigning an intervention. In this case, these are groups (hospitals, schools, health units, locations) which are randomly assigned to receive a specific intervention that usually involves a series of actions that apply to all members of the cluster.

The HOPE 4 study was an open study that randomly assigned hypertensive patients of urban and rural communities in Colombia and Malaysia to the usual care vs. a strategy based on knowledge of local barriers, the action of non-medical health workers (NMW) supported by doctors, with free provision of antihypertensive medication and statins, and simple treatment guidelines that were accessed on a tablet. Different strategies (from door-to-door visits to public events) were useful to recruit participants. They should be at least 50 years old, with any of these conditions: an average systolic blood pressure (SBP) ≥160 mmHg in one visit; or average SBP between 140 and 159 mmHg in one visit, with diagnosis of hypertension or treatment for this condition; or average SBP between 140 and 159 mmHg on two visits separated by at least one day; or average SBP ≥130 mmHg in diabetic patients. The communities were randomly assigned in a 1:1 ratio, stratifying by country and by urban or rural category, with hypertensive patients assigned to receive either the standard or the strategy treatment. In both groups, the NMW were responsible for diagnosing and recruiting the participants; however, in the control group the hypertension treatment was the usual one, while in the intervention group the action of the NMW, guided by simple algorithms exposed in the tablet to diagnose and suggest the treatment then prescribed by the physicians, was supplemented with the free provision of pills that combined two antihypertensive agents (angiotensin converting enzyme inhibitors with diuretics or calcium antagonists) and a statin (10 mg rosuvastatin or 20 mg atorvastatin). Added to this procedure was the action of a family member or friend who favored adherence to healthy lifestyle habits and compliance with indications. The strategy was tested for 1 year and the primary end point was the change in the Framingham cardiovascular risk score at 10 years at the end of the intervention. The secondary endpoints were changes in the values of SBP, cholesterol, triglycerides and glycemia.

Thirty communities were included (15 from each country) and randomly assigned as follows: 16 of them (with 727 patients) to the control group and 14 (644 patients) to the intervention group. Mean age was 65 years; 69% were illiterate or had primary education and only 4% were university students. More than half of those included were women, 9% were smokers and 36% were diabetics. Mean blood pressure was 151/85 mmHg; mean cholesterol 208 mg/dl and mean LDL cholesterol 131 mg/dl. In 73.5% of cases the patients were known to be hypertensive with poor response to medication, and the rest was diagnosed as hypertensive in the context of the study.

At 1 year, there was a significantly greater proportion of patients taking 2 or more antihypertensive agents (84% vs. 65%) and a statin (84% vs. 38%) in the intervention group. The Framingham risk score reduction was 6.4% in the control group and 11.2% in the intervention group ($p<0.0001$). There was a significant reduction of 11.4 mm Hg in systolic blood pressure, 17 mg/dl in total cholesterol and 16 mg/dl in LDL cholesterol in the intervention group compared with the control group at 12 months.

This pragmatic cluster study provides several teachings. It demonstrates that community-centered interventions allow active detection of hypertensive patients; that the intervention of non-medical health workers guided by simple and accessible algorithms can play an important role in the diagnosis and treatment of the disease; that the administration of combined and economic treatment can have a more favorable impact on the control of risk factors than the usual prescription of medication, achieving greater scope and better results. It does not mean in any way leaving doctors out of patient care; in fact, the non-medical activity consisted of diagnosis and suggestion, but it was the doctor who signed the indication. Simple measures, involvement of medical and non-medical staff,

input from family members, access to medication. A message to listen in this day and age.

Metformin and its effect on the regression of left ventricular hypertrophy.

Mohan M, Al-Talabany S, McKinnie A, Mordy I, Singh J, Gandiy S, et al. A randomized controlled trial of metformin on left ventricular hypertrophy in patients with coronary artery disease without diabetes: the MET-REMODEL trial. **Eur Heart J 2019;40:3409-17. http://doi.org/dg9j**

Left ventricular hypertrophy (LVH) is a condition that adversely affects the evolution of patients with or without arterial hypertension. In different publications its presence has been associated with an excess risk of acute myocardial infarction, stroke, renal failure, cognitive impairment and mortality. The most important factors linked to its development are hypertension, obesity and increased insulin resistance. Metformin occupies a privileged position among the drugs that reduce this resistance. Studies in laboratory animals and some non-randomized observational studies have indicated the ability of metformin to generate reduction in left ventricular mass. A randomized study that provides new information in this regard has just been published.

It included 68 patients with known coronary heart disease, with pre-diabetes or increased insulin resistance and LVH defined as a ventricular mass value (g)/height $^{1.7}$ (m) >95th percentile for sex and age. Increased insulin resistance was considered as a fasting value (glucose x insulin/25) >2.7. A glycosylated hemoglobin value between 5.7% and 6.4% was defined as pre-diabetes. Patients could be hypertensive, but with current blood pressure values ≤140/85 mmHg. Left ventricular mass was evaluated with nuclear magnetic resonance imaging. Patients were randomly assigned in a double-blind scheme to receive prolonged-release metformin or placebo at a dose of 500 mg every 12 hours for two weeks, and if tolerated, at 1000 mg every 12 hours to complete one year of treatment.

Patients included had an average age of almost 65 years; 79% were pre-diabetic, 70% had increased insulin resistance and 51% shared both conditions. Seventy per cent of the patients were medicated with angiotensin-converting enzyme inhibitors, 81% with beta blockers and 91% with statins. At 1 year, the metformin-treated group experienced, a ventricular mass reduction of 1.37 g/m $^{1.7}$ (p=0.033) compared with placebo, without difference in ventricular volumes or left ventricular ejection fraction. The use of metformin was also associated with a significant reduction of 9 mmHg systolic blood pressure, 3.6 kg body weight, 6.4% subcutaneous adipose tissue, and an oxidative stress marker with respect to placebo.

At a time when the use of metformin in the treatment of diabetes is discussed by the limited evidence of a randomized study to support it, and its unclear indication in previous stages of the disease, this study confirms that in prediabetic patients or with increased insulin resistance, metformin exerts a number of beneficial effects: weight and blood pressure reduction and a discrete regression of LVH. The mechanisms involved may have an effect on weight and blood pressure, on insulin resistance reduction, oxidative stress relief and specific effects on protein synthesis, fibrosis, apoptosis and nitric oxide availability. Studies with a larger number of patients and clinical endpoints may help defining the role of metformin in these patients.