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Should transcatheteraortic valve implantation be extended to lower surgical risk patients? The PARTNER 2 Trial

Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. **N Engl J Med 2016;374:1609-20. http://doi.org/bff4**

Transcatheter aortic valve implantation (TAVI) was initially tested in randomized studies in high surgical risk patients vs. surgical replacement, and in patients considered inoperable vs. best medical treatment. In real life, its use in intermediate surgical risk patients has consistently increased. However, no study had evaluated until now its performance in this context.

The PARTNER 2 trial included patients with symptomatic severe aortic stenosis and intermediate surgical risk (STS score between 4% and 8%, equivalent to similar values of surgical mortality), who were randomly assigned to TAVI or surgery. If patients had STS score <4% but conditions not considered by the model to involve intermediate risk, they could also be included, and similarly if they suffered from non-complex coronary artery disease requiring revascularization. The system used for TAVI was the second-generation SAPIEN XT, which compared with the first-generation SAPIEN, presents a series of improvements in the hemodynamic profile and the implantation procedure. After evaluating the peripheral arteries, patients were allocated, according to their characteristics, to one of 2 access routes: transfemoral or transthoracic, and within each cohort, they were randomly assigned to TAVI or surgery in a 1:1 ratio. In the group allocated to transthoracic implantation, transapical or transaortic pathways could be used. The primary endpoint was the composite of death or disabling stroke, defined by a score ≥2 in the Rankin scale, after 2 years of follow-up. An intention-to-treat study was the primary analysis, and a per treatment analysis was also performed including patients in whom the procedure had at least been started. The rate of events at 2 years was assumed as 30% for both branches. The aim was to demonstrate non-inferiority of TAVI vs. surgery, with a margin corresponding to the upper RR 95% CI limit of 1.20 (which implies accepting that the risk of TAVI could be up to 20% higher than with surgery).

Between 2011 and 2013 2,032 patients were enrolled in 56 centers of the United States and Canada; 76.3% (n=1,550) in the transfemoral cohort and 23.7% (n=482) in the transthoracic cohort. Among the latter, the 236 patients assigned to TAVI received transapical implantation in 174 cases and transaortic in the remaining 62 cases. Mean STS score was 5.8%, and although most patients had 4% and 8% , 6.7% of cases had score <4% and 12% a score >8%. Mean age was 81.6 years; 54.5% were men and 67.8% had concomitant coronary heart disease. Periprocedural mortality was 0.9%, without significant difference between TAVI and surgery. A second prosthesis was implanted in 2.2% of TAVI patients due to moderate or severe aortic regurgitation, and in 3.9% of patients it was necessary to perform coronary angioplasty. Among surgical patients, 9.1% underwent additional procedures, such as aortic root enlargement or mitral or tricuspid valve surgery, and in 14.5% of cases revascularization surgery.

At 2 years, there was no difference in the primary endpoint, with RR 0.92 (95% CI 0.77-1.09) in the intention-to-treat analysis and RR 0.90 (95% CI 0.75-1.08) in the as treated analysis. It can be seen, that in neither case the upper 95% CI limit reached the non-inferiority margin of 1.20, thus meeting the presumptive non-inferiority condition of TAVI compared with surgery ($p<0.01$ in both cases). Specifically, in the transfemoral access group, the primary endpoint decreased compared with surgery, with HR 0.79 in the intention-to-treat analysis ($p=0.05$) and 0.78 in the as treated analysis ($p=0.04$).

Mortality at 2 years was 16.7% with TAVI and 18% with surgery, and the incidence of disabling stroke was 6.2% and 6.4%, respectively. The incidence of adverse events differed according to the procedure: more vascular complications at 30 days with TAVI (7.9% vs. 5%), and less severe bleeding (10.4% vs. 43.4%), kidney injury (1.3% vs. 3.1%) or atrial fibrillation (9.1% vs. 26.4%), in all cases with $p<0.01$. There were no significant differences in the need for permanent pacemaker within 30 days (8.5% vs. 6.9%). The echocardiographic finding of at least mild aortic regurgitation was significantly greater in the TAVI branch at 30 days (22.5% of mild regurgitation, and 3.7% of moderate to severe regurgitation, respectively) and at 2 years. Conversely, the improvement in valve area and gradient was also higher with TAVI than surgery. Mean hospital stay was lower with TAVI: 6 vs. 9 days ($p<0.001$).

The PARTNER 1 trial had already demonstrated non-inferiority of TAVI compared with surgery for the treatment or high surgical risk severe aortic stenosis. This study extends this finding to lower risk conditions (with periprocedural and long-term mortality clearly lower than those of the previous study). The different incidence of complications according to the procedure confirms the PARTNER 1 findings: more vascular injury with percutaneous implant, and more bleeding and atrial fibrillation with surgery. It is nonetheless surprising that severe bleeding is reported in more than 40% of surgeries, doubtless because the need for transfusion is one of the definition components. Better results with transfemoral implantation relative to

surgery is a challenging finding, in the limit of significance (p values =0.05) , but should be confirmed with future prospective studies.

In the meantime, some considerations can be expressed. As technique progresses it is possible that better results will be obtained; in fact, the system used in this study has already been replaced by another, the SAPIEN 3. Use of TAVI in patients at lower surgical risk and hence with less systemic and vascular disease also implies higher probability of employing the transfemoral pathway, where it might achieve better performance. Lower hospital stay is another factor to consider. However, we should be careful. To begin with, studies with adequate follow-up are necessary to know durability and need for reintervention during long-term follow-up. In this sense, it is clear that we have information concerning surgery, and for obvious reasons, not with TAVI. Cost-effectiveness studies are also lacking justifying a more liberal indication of the procedure. The participation of multidisciplinary teams (heart teams) in decision-making seems the most adequate approach to indicate the best option in each case.

This is the way obesity and diabetes grew worldwide in the last 40 years: results of two large collaborative studies

Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. **Lancet 2016;387:1377-96. http://doi.org/bd2d**

Obesity and diabetes are increasingly extending cardiovascular risk factors, to the point of being considered epidemics. The aim of the World Health Organization (WHO) is to stop their increase in the population, to achieve in 2025 similar levels to 2010. Will this be possible? Two very large recently published collaborative studies conducted by the same group, (NCD-RisC), allow knowing what happened in the last 40 years, and the expectations of its future evolution.

Regarding obesity, they considered 1,698 population studies performed between 1975 and 2014, assessing body mass index (BMI) through weight and height of each participant. A total of 19.2 million persons (9.9 million men and 9.2 million women) from 186 countries were included in the study, and using statistical models taking into account local data, income, socioeconomic status, rate of urban population and food consumption, BMI could be estimated in 200 countries and territories.

In the male population, mean BMI increased from 21.7 kg/m2 in 1975 to 24.2 kg/m2 in 2014, with a mean increase of 0.63 kg/m2 per decade. In 2014, the lowest BMI (21.4 kg/m2) corresponded to Central Africa and Southeastern Asia, and the highest (29.2 kg/m2) to Polynesia and Micronesia. The prevalence of low BMI (<18.5 kg/m2) fell from 13.8% in 1975 to 8.8% in 2014. Conversely, the prevalence of obesity (BMI > 30 kg/m2) increased from 3.2% to 10.8%; in 2014, the prevalence of morbid obesity was 0.64%. Around 266 million obese men were estimated for 2014, 58 million with severe obesity (BMI >35 kg/m2). In 1975, the 5 countries with highest prevalence of obese men were the United States (22.5% of global figures), Russia, Germany, the United Kingdom and France. In 2014, China displaced the United States to a second place, followed by Brazil, Russia and India. Argentina moved from the 9th to the 16th place, and in 2014 contributed with 1.4% of the world's obese men. The countries with the highest proportion of men with low BMI had not changed: India, China, Indonesia, Bangladesh and Pakistan.

In women, mean BMI increased from 22.1 kg/m2 in 1975 to 24.4 kg/m2 in 2014, with a mean increase of 0.59 kg/m2 per decade. In 2014, the lowest BMI (21.8 kg/m2) corresponded to Southeastern Asia, and the highest (32.2 kg/m2) to Polynesia and Micronesia. The prevalence of low BMI (<18.5 kg/m2) fell from 14.6% in 1975 to 9.7% in 2014. Conversely, the prevalence of obesity increased from 6.4% to 14.9%; in 2014, the prevalence of morbid obesity was 1.6%. Around 375 million obese women were estimated for 2014, 126 million with severe obesity. In 1975, the 5 countries with highest prevalence of obese women were Russia (17% of global figures), the United States, Ukraine, Germany and Italy. In 2014, the 5 countries with the highest proportion of obese women were China, the United States, India, Russia and Brazil. Argentina did not appear among the first 20 countries. The countries with the highest proportion of women with low BMI were the same as those cited for men.

If this trend continues, the probability of meeting the WHO target is less than 10% for men in 194 countries and for women in 174 countries. Rather, by 2025, the prevalence of obesity will reach 18% in men and surpass 21% in women.

Different definitions have been used over time to report the prevalence of diabetes in different population studies in the last decades: from self-report or fasting blood sugar levels (generally 126 mg/dl, but before 140 mg/dl), to results of oral glucose tolerance test or glycosylated hemoglobin (HbA1c) values. This does not allow having a clear notion of the temporal evolution of disease prevalence. The same collaborative group reporting the study on obesity conducted a similar study on diabetes, taking into account population studies performed worldwide addressing the prevalence of diabetes between 1980 and 2014. Presence of diabetes was defined as fasting blood sugar of 126 mg/dl. Using complex regression procedures which considered individual and environmental factors in studies that had employed other cited criteria (38% of cases), it was possible to establish the expected prevalence according to the criteria selected in this review. In all cases, age-adjusted prevalence was used.

Seven hundred and fifty one studies were included, with 4,372,000 participants ≥18 years from 146 countries. Based on regional data and population composition, the expected prevalence of diabetes was estimated in 54 countries without real data. According to the

estimation, diabetes-adjusted prevalence grew worldwide from 4.3% to 9% in men and from 5% to 7.9% in women between 1980 and 2014. More than half of the world's diabetics live in 5 countries: China, India, the United States, Brazil and Indonesia. Countries with low to middle income levels as Egypt, Pakistan and Mexico displaced European countries (Germany, Italy, the United Kingdom, and Ukraine) from the first 10 places in the list. The lowest prevalence values in 2014 for both men and women (less than 5% for women, 5.8% for men) were found in Northwestern Europe, and the highest (above 20% for both sexes) in Polynesia and Micronesia. No country decreased its prevalence during the study period; on the contrary, values at least doubled in 120 countries for men and in 87 for women. If the current trend is preserved, the prevalence of diabetes in 2025 will be 12.8% (95% CI 8.3%-19.6%) for men and 10.4% (95% CI 7.1%-15.1%) for women, resulting in more than 700 million diabetics. The probability of meeting WHO targets for diabetes by 2025 is below 1% for men and 1% for women.

In the last 4 decades we have been witness to an explosive increase in the prevalence of obesity and diabetes. These highly complex and transcendental collaborative studies have the huge merit of not being based on self-reporting data, of providing a universal prospect of what happened with both pathologies and what awaits us if current trends are not modified, and of offering data even from those countries where they are scarce or absent. In this line, it is now difficult to speak of individual efforts to stop the epidemic. The growth of obesity is a social problem that is associated with access to healthy food, available time and space to perform physical activity, and overcrowding. Although some consider that BMI is not the most adequate measure of obesity to address prognosis, the differences with other prevalence estimations in epidemiological studies are not relevant. Regarding diabetes, its marked increase worldwide can be attributed to a series of factors: population ageing, growth of obesity and sedentary lifestyle, and food consumption factors. Notably, the countries with more obesity are also those with greater proportion of diabetes; it calls to attention that a faster growth of the disease has been verified in countries with lower economic development, as a result of a less healthy lifestyle and richer food in fats and flours.

Endgame for aliskiren in the treatment of heart failure.The ATMOSPHERE trial.

McMurray JJ, Krum H, Abraham WT, Dickstein K, Køber LV, Desai AS, et al. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. **N Engl J Med 2016;374:1521-32. http://doi.org/bjhk**

In the renin-angiotensin system (RAS) antagonizing/inhibiting model in the context of heart failure (HF), angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) have separately shown their ability to improve diagnosis. Their association has shown dissimilar results in different randomized studies, but we can conclude that in the best scenario this is associated to a certain reduction in hospital stay at the expense of higher incidence of adverse events. Aliskiren (A) is a direct renin inhibitor offering another way of modulating the effects of RAS activation.

The international, randomized, double blind and double dummy (when comparing two drugs, patients receive one active drug and placebo of the other drug) ATMOSPHERE trial compared A, enalapril (E) and the combination of both (C) in the treatment of patients with chronic HF. Inclusion criteria were functional class II-IV, left ventricular ejection fraction (LVEF) ≤35% and BNP values ≥150 pg/ml or NT-pro BNP ≥600 pg/ml, or in case of hospitalization for HF in the previous year, values ≥100 pg/ml or 400 pg/ml, respectively. At the moment of allocation to the different branches, systolic blood pressure had to be ≥90 mmHg, glomerular filtration rate ≥35 ml/min/1.73 m2 and blood potassium levels <5.2 mEq/L. Treatment with E, at a dose of at least 10 mg daily or equivalent dose of another ACEI, was a necessary condition to enter the study. First, patients had to undergo a run-in phase receiving E, at a dose of 5 mg twice daily, during 1 to 4 weeks, and if well tolerated, 10 mg twice daily for the following 2 weeks. In the second run-in phase, patients received A, at a dose of 150 mg daily, in addition to E. If this second drug was well tolerated, they were randomly assigned to receive E (at the dose they had tolerated) and A placebo; A, at a dose of 150 mg daily and E placebo, or C of both drugs (with E, at a dose of 10 or 20 mg daily, according to tolerance). At two weeks, the dose of A was increased to 300 mg daily in the corresponding branches. The study tested two hypotheses: superiority or at least non-inferiority of A with respect to E, and the superiority of C compared with isolated E. The primary endpoint was the composite of cardiovascular death or hospitalization for HF.

Between March 2009 and December 2013, 2,336 patients were included in the E branch, and 2,340 patients in each of the other two branches. During the course of the study, data from another two trials with aliskiren were reported, which we have already commented in this Journal: the ALTITUDE trial (Argentine J. Cardiol. 2013;81:91-94), specifically in diabetic patients, that had to be discontinued due to excess of adverse events, and the ASTRONAUT trial (Argentine J. Cardiol. 2013;81:289-293), in patients included at discharge of hospitalization for decompensated HF, with neutral results, due to apparently favorable effects in non-diabetic patients and deleterious results in diabetic ones.This led to protocol discontinuation in diabetic patients and their data were censored at the time of amendment.

Mean age was slightly over 63 years and LVEF just above 28%. At median follow-up of 36 months (46 in non-diabetic and 24 in diabetic patients) no differences were found in the incidence of the primary endpoint: 12.4% annually in the E branch, 12.1% in the A branch and 11.7 % in the C branch. The trial was un-

able to demonstrate superiority of C over E, and neither superiority nor inferiority of A over E. The rate of events was uniformly superior in diabetic patients, but, despite hypotheses emerging from previous studies, there were no differences between the C and E branches in diabetic and non-diabetic patients. Hypotension, renal dysfunction and hyperkalemia were more frequent with C than with E.

This study seems to be the swan song for aliskiren as individual drug, for the inhibition of renin as a project that deserves to be further investigated, and for the hypothesis that associating two drugs for the inhibition of the renin-angiotensin system is better than employing a single drug in adequate doses. Moreover, the argument that the poor results obtained until now with aliskiren were due to its use in diabetic patients is refuted by the ATMOSPHERE trial data: different from findings in the ASTRONAUT trial (perhaps by chance) a different effect was not evidenced between diabetic and non-diabetic patients. This success of ACEI drugs with respect to a possible competitor paradoxically arrives when a new dual-effect compound, sacubitril-valsartan, comes to dispute their supremacy in the treatment of heart failure.

Was there need for more time? A more prolonged follow-up of the STICH trial seems to put an end to the ambiguity of results at 5 years

Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. **N Engl J Med 2016;374:1511-20. http://doi.org/bjhm**

The STICH trial, published in 2011, attempted to determine whether in patients with left ventricular dysfunction of coronary etiology (left ventricular ejection fraction <35%), cardiac surgery was superior to medical therapy alone. It compared isolated revascularization and revascularization associated to ventricular reconstruction surgery and medical therapy in patients with adequate vascular beds, and in different strata according to the feasibility of performing the different types of surgery.

Six hundred and two patients were assigned to medical therapy in one study branch and 610 to medical therapy plus revascularization surgery in the other branch. Mean age was 60 years, most patients were men, almost 80% had previous infarction, 40% were diabetic, 37% were in FC III-IV heart failure and the rest in FC I-II. Average LVEF was 28% and almost 20% of patients had moderate to severe mitral regurgitation. Among patients assigned to medical therapy, 17% ended undergoing surgery during follow-up, with a mean of 142 days after randomization. Among patients assigned to surgery, 91% was operated on and 9% finally remained in medical therapy.

Median follow-up was 56 months. The primary endpoint was all-cause death and no significant difference was found between medical therapy and revascularization surgery. Mortality with medical therapy was 41% and 36% with revascularization surgery, with 14% risk reduction, which was not significant in the intention-to-treat analysis. Within 30 days of surgery, mortality was higher in the surgical group due to risks inherent to the intervention. The secondary endpoint of cardiovascular death was reduced from 33% to 28%, in the limit of statistical significance.

The authors of this work performed two other analyses. The first was a per-protocol analysis: it considered patients assigned to surgery who were effectively operated on and patients assigned to medical therapy who effectively remained in medical therapy. In this analysis, revascularization surgery improved prognosis: the HR was 0.76, with a statistically significant risk reduction of approximately 24%. The other was an as treated analysis, which considered patients assigned to surgery that were effectively operated on together with those assigned to medical therapy that finally underwent surgery, compared with all those who remained in medical therapy: the ones assigned to medical therapy that remained in medical therapy, plus those assigned to surgery that were transfered to medical therapy. In this as treated analysis, a clearly significant difference was found in favor of surgery, with 30% mortality reduction.

The criticism that can be made to these two analyses is that they were post hoc, and hence should be regarded conservatively. In general, when a randomized study is made, it is understood that the analysis is valid as intention-to-treat, understanding that it compares strategies: the strategy of offering surgery vs. the strategy of medical therapy.

We now know that before the 5-year results were reported it was decided to extend the study for another 5 years. The results of this extended follow-up (in a study called STICHES) are the ones we know now. In the intention-to-treat analysis, the primary endpoint occurred in 58.9% of cases in the surgery branch and 66.1% in the medical therapy branch (HR 0.84, 95% CI 0.73-0.93, p=0.02). Median survival was 7.7 years with surgery and 6.3 years with medical therapy. The necessary number needed to treat was 14 to prevent one death. There was also reduction of cardiovascular death and of the composite of death or hospitalization for heart failure. Per protocol and as treated analyses were also favorable for surgery.

For many, the initially published results of the STICH trial were disappointing or scarcely believable regarding their external validity: the rate of patient inclusion was low, it took a long time to recruit the required number of patients, making it necessary to decrease the number of patients and follow-up duration. Patients included in the study represented only a small part of the total number treated in the centers; only those in whom the doctor effectively understood that one treatment or the other was the same. In many patients with advanced heart failure this does not happen; there is clear preference for a certain therapy, considering the individual characteristics of patients, presence of comorbidities, quality of vascular beds, etc.

Moreover, the transfer of patients from one branch to the other significantly influences study results. That is why revascularization surgery, when feasible, seemed to most, a better option than medical therapy. But the truth is that the randomized study in the most pure intention-to-treat analysis did not agree with this belief.

The extension to 10 years seems to put things in the place most assumed. It is true that this was not the initially planned follow-up, that few knew about the study extension, that this prolongation appears as an intent to sustain the initial hypothesis (in how many interventional studies concluding with "almost significant" differences could not the same conduct be applied?), and that concerns about the included population representativeness persist. It is also true that these patients were enrolled between 2002 and 2007 and that some things have changed in surgical practice and medical therapy. Regardless, we still believe that, if feasible, we can assume that in centers able to operate this kind of patients (and with adequate life expectancy), surgical revascularization associated to medical therapy seems to offer better outcome than medical therapy alone.

Primary prevention with statins and antihypertensives in intermediate-risk patients. The HOPE 3 Trial

Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. **N Engl J Med 2016;374:2009-20. http://doi.org/bjht**

Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. **N Engl J Med 2016;374:2021-31. http://doi.org/bjhv**

Yusuf S, Lonn E, Pais P, Bosch J, López-Jaramillo P, Zhu J, et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. **N Engl J Med 2016;374:2032-43. http://doi.org/bjhw**

Antihypertensive and statin therapy has shown significant reduction of cardiovascular and cerebrovascular events in people at high risk of their occurrence. The benefit of primary prevention with these drugs in intermediate-risk subjects is less clear. The international, multicenter, randomized, 2 × 2 factorial, placebo-controlled HOPE 3 trial was conducted to explore this hypothesis.

This study included ≥55-year old men and ≥65 year-old women who also had at least one of the following risk factors: elevated waist-to-hip ratio, current or recent smoking, low HDL cholesterol, abnormal fasting glucose levels or glucose intolerance, early diabetes, hypertension, family history of early coronary heart disease or early renal dysfunction. In addition, 60-year old women or older with at least 2 risk factors could be enrolled in the study. They had to be free of clinically evident vascular disease, presenting with an annual risk of cardiovascular events of approximately 1%, and with no express indication or contraindication for statin, candesartan or hydrochlorothiazide use. Although baseline blood pressure and laboratory values were measured at study onset, and in some patients during follow-up, no specific values were defined to decide patient inclusion or as treatment objective.

Patients initially underwent a 4-week single-blind run-in period, in which they received rosuvastatin 10 mg/daily, candesartan 16 mg/daily and hydrochlorothiazide 12.5 mg/daily. Patients who showed good adherence (≥80% of tablets) and tolerated the treatment were randomly assigned to four groups: a) combination therapy (CT, n=3,180): active treatment with the three drugs in the prescribed doses; b) rosuvastatin and placebo of antihypertensive drugs (R, n=3,181); c) candersartan and hydrochlorothiazide with rosuvastatin placebo (CH, n=3,176) and d) placebo of all the drugs mentioned (P, n=3,168). The factorial design allowed to establish specific comparisons between CT vs. P, treatment with rosuvastatin (CT and R groups) vs. placebo (CH and P groups), and antihypertensive treatment (CT and CH groups) vs. placebo (R and P groups). There were two co-primary endpoints (EP): 1) a composite of cardiovascular death, nonfatal acute myocardial infarction (AMI) or nonfatal stroke; and 2) the former plus resuscitated cardiac arrest, heart failure or revascularization.

Average age was slightly over 65 years, with small differences between the four groups, 46% were women, approximately 38% were hypertensive, 6% diabetic, 13% with glucose intolerance, 36% with low HDL, 26% with family history of the heart disease, 28% smokers or recent ex- smokers and 87% with elevated waist-hip ratio. Nearly 46% had 2 risk factors and 24% had 3 or more. The average INTERHEART score was 14.5 (a score between 10 and 15 corresponds to intermediate risk). Mean systolic blood pressure (SBP) was 138.1 mmHg and average LDL 127.8 mg/dl.

Average follow-up was 5. 6 years. Systolic blood pressure decreased 6.2 mm Hg and diastolic blood pressure 3.2 mm Hg in groups with active antihypertensive treatment vs. placebo; LDL cholesterol level was 33.7 mg/dL in the rosuvastatin groups vs. placebo.

In the comparison between the groups receiving candesartan and hydrochlorothiazide (CH and CT, total n=6,356) vs. placebo (R and P, total n=6,349), the former presented lower follow-up systolic and diastolic blood pressure values of 6±13 and 3±8 mm Hg, respectively. There were no differences in the incidence of the first co-primary EP (4.1% vs. 4.4%) or second co-primary EP (4.9% vs. 5.2%). Following the performance of a prespecified analysis according to tertiles of baseline SBP, the highest tertile (SBP>143.5 mmHg, with a mean of 154 mm Hg) revealed a significant reduction of the first co-primary EP (4.8% vs. 6.5%, HR 0.73, 95% CI 0.56-0.94) and of the second co-primary EP (5.7% vs. 7.5%, HR 0.76, 95% CI 0.60-0.96). However, the middle tertile (SBP between 131.6 and 143.5 mm Hg) showed no difference in the incidence of events with active treatment (HR 1.08 for the first

co-primary EP and 1.02 for the second co-primary EP) and the lower tertile (SBP<131.6 mm Hg) evidenced an increasing trend in the incidence of events, without reaching statistical significance (HR 1.16 and 1.25 for co-primary 1 and 2 EP, respectively).

Although the incidence of hypotension and dizziness which led to treatment discontinuation was higher in those who had active treatment (3.4% vs. 2%), discontinuation rate was similar in both groups, around 25%, with no difference in the incidence of renal dysfunction or hyperkalemia.

In the comparison between the groups receiving rosuvastatin (CT and R, total n=6,361) vs. placebo (CH and P, total n=6,344), the former presented lower follow-up LDL cholesterol, triglyceride and C-reactive protein values (reductions of 34.6 mg/dl, 21.2 mg/dl and 0.19 mg/L, respectively). The incidence of the first co-primary EP was 3.7% and 4.8%, respectively (HR 0.76, 95% CI 0.64-0.91; p=0.002), which implies a number needed to treat (NNT) of 91 to prevent one event. The incidence of the second co-primary EP was 4.4% and 5.7%, respectively (HR 0.75, 95% CI 0.64-0.88; p<0.001), with a NNT of 73 to prevent one event. There was no significant reduction of cardiovascular death (2.4% vs. 2.7%, HR 0.89, 95% CI 0.72-1.11), but decrease of fatal or nonfatal AMI (0,7% vs. 1.1%, HR 0.55, 95% CI 0.32-0.93) and fatal or nonfatal stroke (1.1% vs. 1.6%, HR 0.70, CI 95% 0.52-0.95). There was also less need for revascularization at follow-up (0.9% vs. 1.3%, HR 0.68, 95% CI 0.48-0.95). There was no difference in overall mortality or incidence of diabetes (about 4% in both groups). Among patients treated with rosuvastatin there was only 1 case of rhabdomyolysis and 1 of myopathy. There was increased incidence of cataract surgery with statin therapy (3.8% vs. 3.1%; p=0.02).

Finally, when comparing TC vs. P groups, the incidence of the first co-primary EP was 3.6% and 5%, respectively (HR 0.71, 95% CI 0.56-0.90; p=0.005), which implies a NNT of 72 to prevent one event. The incidence of the second co-primary EP was 4.3% and 5.9%, respectively (HR 0.72, 95% CI 0.57-0.89; p=0.003), which implies a NNT of 63 to prevent one event. There was no significant reduction in cardiovascular death (2.4% vs. 2.9%, HR 0.82, 95% CI 0.60-1.11), but reduction of fatal or nonfatal myocardial infarction (0, 7% vs. 1.2% HR 0.55, 95% CI 0.32-0.93) and of fatal or nonfatal stroke (1% vs. 1.7%, HR 0.56, 95% CI 0, 32-0.93). The need for revascularization at follow-up was also lower with CT (0.8% vs. 1.4%, HR 0.59, 95% CI 0.37-0.95).

A post hoc analysis with baseline SBP divided into tertiles showed that CT was associated with a more marked effect for the first co-primary EP in the highest tertile (SBP >143.5 mm Hg, HR 0.59, 95% CI 0.40-0.85) than in the two lower tertiles (HR 0.82, 95% CI 0.59 -1.12). Although the incidence of muscle weakness and dizziness was higher with CT than with P (excess of 0.9% and 2.2%, respectively), the rate of permanent discontinuation was similar in both groups: 26.3% vs. 28, 8%, respectively. There were no differences in the incidence of diabetes, cancer, and kidney or liver dysfunction.

The HOPE 3 trial explored the effect of statins and antihypertensive drugs in primary prevention based on the calculated 1% annual risk of cardiovascular events, 10% at 10 years. Interestingly, HOPE-3 had no LDL cholesterol or SBP thresholds for enrollment or as study goals. In this sense, HOPE 3 was based on clinical criteria (age and risk factors), which seems to be destined to favor the indication of patient treatment and follow-up. Perhaps that is also why tested doses of each of the therapeutic agents were not high.

Regarding the use of statins, the 2014 ACC/AHA guideline recommends its use for primary prevention in 40 to 75 year-old, non-diabetic patients, with LDL of 70-189 mg/dl, and an estimated risk of events of 7.5% at 10 years. The study results confirm the indication accuracy, demonstrating a significant reduction of events. Although the decrease of the first co-primary EP is only 1.1% at 5 and a half years (2 events per 1,000 patients per year, with no reduction in cardiovascular mortality), the simple administration schedule, the lack of need for laboratory controls, the very low incidence of serious adverse events and the projected benefit are all factors that favorably impact on the indication when judging in terms of public health.

The case of antihypertensive treatment is different. The idea of using it regardless baseline SBP is novel. We do not remember any guideline postulating its use in normotensive subjects. And in fact, the analysis by tertiles of baseline SBP points a benefit in hypertensive patients (SBP>143 mm Hg) and tendency to damage in those with normal SBP. It is worth mentioning that in the SPRINT study, discussed in this section (Rev Argent Cardiol 2016; 84: 102-8), mean SBP was barely higher than in the HOPE 3 trial (139.7 vs. 138.1 mm Hg), but patients had higher risk of events at 10 years (effectively, with standard treatment, the annual rate of events was above 2%). In this context, intensive treatment was clearly helpful. Would the results have been the same in lower risk patients in the HOPE 3 trial? Or the incidence of more adverse events would have weakened the alleged advantage?

Finally, due to the combined use of three drugs in fixed dose and the simplicity and lack of complex or costly determinations, some have seen in this study an argument for the use of a polypill. We consider this is not so. The drugs were administered separately, allowing a small percentage of patients assigned to CT to take some of them and not others. Moreover, the results presented can justify the use of statins in all patients, but antihypertensives only in hypertensive ones.