JORGE THIERER MTSAC

Bariatric surgery versus intensive medical treatment in obese diabetics: better metabolic outcomes at 5 years

Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes- 5-year outcomes. **N Engl J Med 2017;376:641-51. http://doi.org/b4z2**

Observational studies and some randomized, controlled trials in obese and diabetic patients have suggested that bariatric surgery is associated with better outcomes compared with conventional medical treatment in achieving adequate glycemic control, evidenced by a significant reduction in glycated hemoglobin levels (HbA1c). The outcome at 5 years of the STAMPEDE trial has just been published and supports these assumptions.

The STAMPEDE trial was a randomized, controlled, non-blinded, single-center study that included diabetic patients with body-mass index (BMI) of 27 to 43 kg/m2 and HbA1c >7%. Patients were randomly assigned in a 1:1:1 ratio to gastric bypass (GB), sleeve gastrectomy (SG) or intensive medical therapy (MT) alone. The primary outcome was a HbA1c level of 6% at 5 years. Among the 150 patients included, 134 received the treatment assigned and completed follow-up. Mean age was 49 years and 66% were women; mean BMI was 37 kg/m2, mean HbA1c was 9.2% and the mean duration of diabetes was greater than 8 years.

After a 5-year follow-up period, a HbA1c level of 6.0% was achieved in 5% of the patients in the MT group, 29% in the GB group and 23% in the SG group ($p = 0.07$ compared with the MT group). Duration of diabetes of less than 8 years and treatment with GB were the only significant predictors of achieving the primary outcome at multivariate analysis. None of the patients in the MT group could achieve a HbA1c level of 6% or less without use of diabetes medications, compared with 22% of patients in the GB group and 15% in the SG group. A less ambitious target of HbA1c level ≤7% was achieved by 21% of the patients in the MT group, 51% in the GB group and 49% in the SG group, with $p < 0.05$ in both cases compared with MT. Mean reduction of HbA1c level at 5 years was 0.3% with MT and 2.1% with GB and SG. Mean reduction in body weight was above 5 kg with MT, 23 kg with GB and 18.6 kg with SG. At 5 years, 40% of the patients with MT required insulin compared with 12% in the GB group and 11% in the SG group. Only 2% of the patients in the MT group did not require any medication at 5 years versus 45% in the GB group and 25% in the SG group. Surgery was associated with a better metabolic profile, higher HDL cholesterol levels and reduction in triglyceride levels compared with MT. The advantage of surgery over MT was not different among patients with a BMI > or <35.

This study confirms the beneficial effect of a significant reduction of body weight on the outcome of diabetes, even achieving diabetes remission. Probably, the primary outcome (HbA1c level ≤6%) could have been ambitious; a target HbA1c level ≤7% consistent with that recommended by the treatment guidelines was achieved by more than half of the patients undergoing surgery. It is clear that the indication should be done when routine management of obesity (starting with diet and physical activity) has failed. Although surgery is recommended for patients with BMI >40 or >35 with additional risk factors, it may be indicated in patients with lower BMI in the context of diabetes with poor response to medication, as it happened with more than one third of the participants in this study. Higher insulin sensitivity associated with a reduction in BMI and increased production of incretins are some (but not all) of the mechanisms explaining why surgery acts as a metabolic modulator. Obviously, surgery does not cure diabetes, and there are no long-term studies revealing what happens 10 or 15 years after the intervention. In the same way, gaining weight will be an evidence of disease relapse. Limitations of this study include the low number of patients and that the follow-up period was not long enough to detect differences in the clinical outcomes (coronary artery disease, stroke and blindness). Further studies would contribute to clarify this issue.

Coronary artery bypass grafting with bilateral internal-thoracic-artery grafts does not seem to offer benefits compared with traditional surgery

Taggart DP, Altman DG, Gray AM, Lees B, Gerry S, Benedetto U, et al; ART Investigators. Randomized trial of bilateral versus single internal-thoracic-artery grafts. **N Engl J Med 2016;375:2540-9. http://doi.org/b4zz**

The standard surgical approach of coronary artery bypass grafting is anastomosis of the left internal thoracic artery (LITA) to the left anterior descending coronary artery and the use of saphenous-vein or radial-artery grafts to bypass other coronary arteries. The superiority of the internal-thoracic-artery graft over saphenous-vein grafts has stimulated some surgeons to use a bilateral internal-thoracic-artery (BITA) ap-

proach, i.e. both the left and right internal thoracic arteries, to improve the outcomes. In fact, pooled analyses of observational studies suggest that BITA grafting is associated with better outcome and lower long-term mortality than single internal-thoracic-artery (SITA) grafting. However, BITA grafting has not been widely adopted because it is a more complex procedure, associated with a higher risk of sternal wound complications, and there is lack of randomized evidence of benefit. In this sense, the ART trial tries to give an answer to this concern. The study was initiated in 2004 and assigned patients with multivessel disease not requiring concomitant valve surgery to undergo SITA or BITA grafting. The primary outcome was mortality at 10 years. The authors of the study calculated that 2,928 patients would need to be enrolled in order for the trial to detect an expected difference in mortality of 20% with BITA and 25% with SITA with 90% power and a p value <0.05. The results at 5 years have been recently published.

Between 2004 and 2007, 3,102 patients were enrolled in the study (1,554 with SITA and 1,548 with BITA). Mean age was 63 years, 85% were men and 42% had previous myocardial infarction. In the SITA group, 96.1% of the patients assigned received a SITA graft, and 16% of the patients assigned to BITA grafting did not receive the treatment assigned. Off-pump procedures were performed in 40% of patients. There were no differences in the use of concomitant medication throughout the follow-up period: aspirin and statins were used in 89% of patients, beta-blockers in 76% and angiotensin-converting–enzyme inhibitors in 73%.

There were no differences in mortality at 5 years: 8.4% in the SITA group versus 8.7% in the BITA group. The outcome was also similar for the composite endpoint of death, myocardial infarction, or stroke: 12.7% versus 12.3%, respectively. Sternal wound complication was the only relevant difference between both groups (3.5% with BITA vs. 1.9% with SITA) with higher incidence of sternal wound reconstruction (1.9% vs. 0.6%). There were no differences in subgroups according to age, sex, use of radial-artery graft, number of grafts or diabetes. A post hoc analysis suggested that more careful dissection of the internal thoracic artery (the "skeletonized" technique) was associated with lower risk of sternal wound complications.

Some observational studies had suggested that BITA grafts might have up to 20% better prognosis than SITA grafts. This randomized trial argues this assumption. Some of the reasons that could explain the lack of differences between both strategies up to the present depend on the surgeons. Several configurations, (Y graft, in situ graft, use of the second thoracic artery as free graft) may be associated with different long-term success rates. However, we prefer other explanations. Firstly, the adequate use of medication can attenuate the differences expected between SITA and BITA. The life span of venous grafts may increase with a more adequate control of risk factors. Half of the follow-up period planned (10 years) has been accomplished. In addition, one sixth of the patients in the BITA group did not receive the treatment assigned. Undoubtedly, all these factors reduce the power of the study to find the difference expected. The curves should separate in the following 5 years to achieve the goal of the study.

Prediabetes predicts greater risk of cardiovascular events and mortality: a meta-analysis

Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. **BMJ 2016;355:i5953. http://doi.org/b4zx**

Prediabetes (PD) is a clinical condition between normoglycemia and diabetes, and is defined by two conditions that do not always coexist: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Impaired glucose tolerance is defined as a 2-hour plasma glucose concentration of 140-200 mg/dL during an oral glucose tolerance test and IFG is defined as elevated fasting plasma glucose <126 mg/dL. There is not a single definition of IFG: while the World Health Organization (WHO) defines it as fasting plasma glucose between 110 and 126 mg/dL, the American Diabetes Association (ADA) recommends a cut-off value between 100 and 126 mg/dL. Some societies also consider glycated hemoglobin levels (HbA1c), though with different values: the AAD suggests values between 5.7% and 6.4%, while the National Institute for Health and Care Excellence (NICE) suggested using a higher cut-off point of 6-6.4%. It is clear that all these conditions predict the development of diabetes, emphasizing the need of lifestyle changes, particularly increasing physical activity and modifying dietary habits to prevent the consequences of progression to diabetes. Although the risks of diabetes are well known, with higher incidence of all-cause mortality, cardiovascular disease, cerebrovascular disease, renal disease, amputation and blindness, there is no precise information about the prognostic value of hard end points of the different conditions comprised under the term PD.

We present a large-scale meta-analysis that clarifies many of these matters. Prediabetes was considered using any of the definitions previously mentioned, and it included prospective cohort studies in which this condition (in any of its definitions) had been considered at baseline, exploring its association with events. The study finally included 53 studies comprising 1,611,339 participants. All the studies excluded patients with fasting plasma glucose concentration >126 mg/dL, except for one.

Twenty five studies reported data for the association between PD with all-cause mortality. Impaired glucose tolerance and IFG (as defined by WHO and ADA) were associated with an increased risk of all-cause mortality (RR 1.32 and 1.13, respectively). The

sensitivity analysis showed greater risk of mortality with PD as defined by ADA IFG (cut-off value of 100 mg/dL) only in participants with mean age <55 at study entry, but not in those aged ≥55 (p=0.009). In general, the risk was significantly higher with IGT than with IFG (p <0.001). On the contrary, the definitions based on HbA1c levels were not associated with greater mortality.

Thirty five studies reported data for the association between any definition of PD (IFG, IGT or elevated HbA1c) and risk of cardiovascular disease, with RR between 1.13 and 1.30 and no significant differences. Twenty four studies reported data for the association between PD and risk of coronary heart disease, and the findings were similar; and in 18 studies evaluating the association with stroke, IGT and IFG were associated with an increased risk of stroke (RR between 1.06 and 1.20), but, as in the case of all-cause mortality, this association was not observed with elevated HbA1c levels. The prognostic value of PD still remained high after adjusting for smoking.

The main merit of this study lies in the great number of observations and in the fact of having explored all the definitions of PD. A reasonable emerging doubt is how much of the highest risk is due to PD and how much to diabetes progression. In fact, blood glucose levels were not measured during follow-up and we lack this information. How can we manage PD? Undoubtedly, with lifestyle and nutrition interventions. The ADA also recommends pharmacological intervention in individuals with both IGT and IFG and at least one of the following conditions: age <60 years, BMI >35, high triglyceride levels or, reduced HDL cholesterol levels, family history of diabetes mellitus in first degree relatives or HbA1c >6%. In any case, it is clear that elevated blood glucose levels below the cutoff values for diabetes indicate a population that should be carefully monitored. The greater risk associated with IGT compared with IFG emphasizes the importance of performing an oral glucose tolerance test to characterize the patient. Considering that a cut-off value of 100 mg/dL for IFG has prognostic value in subjects <55 years would mean that we must be more active in this age group in case of apparently "minor" abnormalities.

Genetics, lifestyle and their association with cardiovascular events

Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. **N Engl J Med 2016;375:2349-58. http://doi.org/f9fv94**

Coronary artery disease is a multicausal condition. Over the past decade, apart from the traditional risk factors, the presence of 50 genetic determinants, single-nucleotide polymorphisms, has been associated with higher risk of coronary artery disease. If coronary artery disease is, at least in part, determined genetically, will lifestyle modifications make sense? The study here presented helps to answer this question.

Three cohort studies starting 25 to 30 years ago were considered: the ARIC study (in the United States, which incorporated adults between 45 and 64 years), the WGHS (derived from the WHS, which incorporated health care professional women), and the MDCS (which included participants between 44 and 73 years in Malmö, Sweden). It also considered participants of The BioImage study, which enrolled participants between 55 and 80 years who were at risk for cardiovascular disease and were subjected since 2008 to imaging studies, including coronary calcium score. Genetic material was available for each study. A risk score was created by considering the effect matched by each allele of each polymorphism. In this way, each participant had an individual risk score, defining the risk of coronary events genetically determined. The score was divided into quintiles: the highest quintile corresponded to high genetic risk, the lowest quintile to low genetic risk and the remaining quintiles to intermediate risk. A healthy lifestyle was defined according to the presence of four criteria: no current smoking, no obesity (body-mass index <30), physical activity at least once weekly, and a healthy diet pattern (defined by at least half of the following characteristics: consumption of an increased amount of fruits, nuts, vegetables, whole grains, fish and a reduced amount of processed meats or unprocessed red meats, refined grains, sugar-sweetened beverages, trans fats and sodium). A healthy lifestyle was defined as the presence of at least three criteria, an intermediate lifestyle as the presence of two, and an unhealthy lifestyle as the presence of only one or no healthy lifestyle criteria.

The primary end point was a composite of acute myocardial infarction (AMI), coronary revascularization or cardiovascular mortality. The population considered for follow-up included 7,814 participants of the ARIC study, 21,111 of the WGHS cohort and 22,389 of the MDCS cohort. Median follow-up ranged from 18.8 to 20.5 years, depending on the study. After adjusting for age, sex, education level, and family history, a risk gradient of coronary events was noted across quintiles of genetic risk: the participants in the top quintile of the genetic score were at an excess risk of 91% (HR, 1.91; 95% CI, 1.75-2.09) compared with those in the lowest quintile, while those in the intermediate risk quintile had lower HR but with statistical significance. A high genetic score was associated with a modest increase of LDL cholesterol that was independent of the other traditional risk factors,

In turn, each of the healthy lifestyle factors was associated with a reduction in the risk of events: 44% with no current smoking, 34% with no obesity, 12% with physical activity and 9% with a healthy diet pattern. An unhealthy lifestyle was associated with a HR of 1.71 to 2.27 according to the cohort. Of importance, within each category of genetic risk, adherence to a healthy lifestyle, as compared with an unhealthy life-

style, was associated with a significant and similar risk reduction, between 45% and 47%. For example, in the ARIC study, among participants in the highest quintile of genetic risk, the 10-year coronary event rates were 10.7% among those with an unhealthy lifestyle and 5.1% among those with a healthy lifestyle. Conversely, among participants at the lowest genetic risk quintile, a healthy lifestyle was associated with an event rate of 3.1% at 10 years, while an unhealthy lifestyle was associated with an event rate of 5.8%. Therefore, the rate of events was similar among participants with high genetic risk and healthy lifestyle and low genetic risk and unhealthy lifestyle.

The BioImage study showed an association between higher calcification score and higher genetic score, but, again, a healthy lifestyle was associated with lower risk of calcification in each category compared with an unhealthy lifestyle.

This elegant study confirms the value of genetics in determining the incidence of coronary events, beyond the traditional risk factors. But, at the same time, it opens an optimistic pathway: beyond the genes, it seems to be that our lifestyle habits hold a significant place to define our future heath. No smoking, an adequate diet and weight and physical activity are associated with 50% reduction in genetic risk. Why do we say "it seems to be"? Simply because the healthy lifestyle was not randomly assigned. We might reason that there are other unknown factors beyond healthy lifestyle that may act as confounders and are the real cause of risk reduction. There is evidence suggesting that our behavior also has genetic determinism, and that genes have to do with addiction to tobacco or with obesity. In the meantime, the evidence here presented is convincing. It is biologically reasonable; it is repeated in each of the three cohorts and coincides with the findings in the imaging studies. Genetics and behavior, the keys to approach our future. We cannot change genetics. But because we can modify our behavior, even when genes push us in one direction, recommending a healthy lifestyle is still imperative.

Elevation of troponin levels in outpatients implies greater risk of coronary events, but statins contribute to its reduction. An analysis of the WOSCOPS trial

Ford I, Shah AS, Zhang R, McAllister DA, Strachan FE, Caslake M, et al. High-sensitivity cardiac troponin, statin therapy, and risk of coronary heart disease. **J Am Coll Cardiol 2016;68:2719-28. http://doi.org/f9p325**

The WOSCOPS trial was one of the first studies to demonstrate that treatment with statins reduces the risk of coronary events in patients with elevated cholesterol levels. The study randomized 6,595 patients between 45 and 64 years, LDL cholesterol concentrations of 152 to 228 mg/dL and no prior history of acute myocardial infarction (AMI) to receive placebo or pravastatin 40 mg/day. As we know, after a mean follow-up of almost 5 years, there was a reduction in the incidence of hard end points (AMI or death from coronary heart disease) in the intervention group, with a HR of 0.45. This benefit persisted after an extension of the follow-up period to 15 years, with a HR of 0.68. Determinations of high-sensitivity cardiac troponin I (hs-cTnI) were available at baseline and after one year in 3,318 patients, which constitute the population of this sub-study.

Median hs-cTnI at baseline was 4 ng/L. Patients were divided into quartiles of hs-cTnI levels. The lowest quartile corresponded to those with hs-cTnI value <3.1 ng/L and the highest to those with values >5.2 ng/L. Compared to the lowest quartile, participants in the upper quartile were older and were more likely to have higher blood pressure levels, symptoms of angina, and minor abnormalities on the electrocardiogram. Compared to the lowest quartile, patients in the highest quartile were at the highest risk for nonfatal AMI or death from coronary heart disease at 5 (HR 2.27) and 15 years (HR: 1.54). At 1 year, participants taking pravastatin had greater reduction of hs-cTnI levels than those receiving placebo (19% vs. 6%, p <0.001). Change in troponin concentration correlated weakly with change in LDL cholesterol (r=0.20, yet with p <0.01).

After adjustment for multiple variables, including baseline hs-cTnI concentration, and baseline and change in LDL cholesterol, change in hs-cTnI concentration at 1 year was an independent predictor of AMI or death from coronary heart disease. Participants were divided into quintiles based on the change in hs-cTnI levels in the placebo group. The top quintile corresponded to an increase in hs-cTnI levels >26% and the lowest quintile corresponded to >27% decrease. The risk of hard end points at 5 years was 5-fold lower in those in the lowest quintile compared to the highest, and this reduction was independent of the change in LDL cholesterol. The lowest risk associated with the highest reduction in hs-cTnI was seen both with pravastatin and placebo, but in those taking pravastatin twice as many participants were in the lowest quintile and 30% less were in the highest. The highest rate of events occurred in those treated with placebo, with an increase in hs-cTnI of more than 25% at one year (11.6% over 5 years) and the lowest rate was seen in those treated with pravastatin, whose hs-cTnI concentration fell more than 25% at one year (1.4% over 5 years).

This study confirms the prognostic value of troponin in outpatients, in agreement with many publications we have commented in this section, and which point out the same findings in the general population, patients with peripheral artery disease, elderly population, etc. The fact that the effect of treatment with statins is independent of the effect on LDL cholesterol is remarkable. Of interest, the prognostic value of the reduction in hs-cTnI was also seen in the placebo

group which did not show changes in LDL cholesterol. Would this have something to do with the pleiotropic effects of statins, so defended as rejected? The antioxidant effect of statins and their effect on endothelial function can attenuate the myocardial lesion that releases troponin. The authors of this study propose that the effect of troponin can be a new approach to evaluate the effect of statins. However, a change of 25% in such low values can correspond to 1 ng/L, too small a value to have clinical significance in the individual patient, considering the variability of the method.

Prognostic value of serum potassium levels in hypertensive patients: the safety range narrows

Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, et al. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. **Eur Heart J 2017;38:104-12. http://doi.org/b5jm**

The prognostic vale of hypokalemia (serum potassium level <3.5 mEq/L) and hyperkalemia (serum potassium level >5 mEq/L) in hypertensive patients is well-known. We know that many antihypertensive agents modify potassium values. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) beta blockers (BB) and aldosterone antagonists (AAs) increase potassium levels, while thiazides decrease them. Little is known about the optimal range of serum potassium in hypertensive patients and which combinations of drugs affect them most.

Denmark has a universal, and permanent registry of information about all hospital admissions, prescriptions and dispensed prescriptions in pharmacies. Date of birth, date of death, vital status and electronic registries of laboratory data are also available. This data was used by the authors of the study to answer these questions. Hypertension was defined by the use of at least two antihypertensive drugs in two consecutive trimesters. Baseline serum potassium measurement was taken within 90 days of the antihypertensive treatment selected. Patients under the age of 30 years and those with potassium levels <2.9 mmol/L or >5.8 mmol/L were excluded. The outcome of the study was 90-day mortality from the date of serum potassium measurement.

Between 1995 and 2012, 44,799 hypertensive patients with a potassium measurement within 90 days from diagnosis were identified. Mean age was 67±12 years and median serum potassium level was 4.2 mEq/L. Values below the median were more common in women and in those treated with thiazides. Values above the median were more common in men and with the use of drugs that increase potassium levels. Overall, 75% of the patients received diuretics and 70% ACEIs or ARBs. The major antihypertensive drug combinations were ACEIs or ARBs combined with thiazides and potassium supplement, ACEIs or ARBs with BB and ACEIs or ARBs with thiazides.

The lowest 90-day mortality risk was observed in the interval of 4.1–4.4 mEq/L: 1.5%. Considering this group as reference, mortality was higher in patients with the lowest potassium level: 4.5% in patients with potassium <3.5 mEq/L (HR 3.1; p <0.01), 2.7% in those with potassium 3.5-3.7 mEq/L (HR 1.8; p <0.01), and 1.8% for potassium between 3.8 and 4 mEq/L (HR 1.2; p=0.06). Mortality was also higher in patients with potassium level >4.4 mEq/L: 1.7% in patients with potassium between 4.5 and 4.7 mEq/L (HR 1.16; p =0.17), 2.7% for values between 4.8 and 5 mEq/L (HR 1.83; p <0.01) and 3.6% in patients with potassium >5 mEq/L (HR 2.47; p <0.01). As we see, a real U-shaped curve was configured, with mortality rates progressively higher at both sides of the central range. After adjusting for age, sex, co-morbidities, and treatment, mortality remained significantly increased for all potassium ranges outside the interval of 3.8–4.7 mEq/L. Considering the different antihypertensive drug combinations, ACEIs or ARBs combined with thiazides and potassium supplement seemed to be a safe option, while BB with thiazides were associated with higher risk.

This study shows that the "safe" potassium range is lower than we supposed. We realize that the normal range between 3.5 and 5 mEg/l we usually consider is narrower. As measurement of potassium level is a recommended practice but not mandatory, we can understand that only 45,000 patients were included during 15 years (around 3,000 per year), which undoubtedly implies a selection of the total number patients in whom hypertension is diagnosed every year. The characteristics of the patients who have their serum potassium measured may be different from the patients who do not have a potassium measurement or have a different treatment. As with every observational study, higher mortality could be attributed to factors that were not considered and associated with higher or lower potassium levels. We do neither know the mechanisms associated with mortality in each case, although arrhythmias could have an important role. Nevertheless, the message of this study is that electrolytes should be routinely controlled in our hypertensive patients and that we must remember the effect of drugs on renal function and electrolyte balance.

Percutaneous coronary intervention vs. surgery in left main coronary artery disease: two contemporary and contradictory trials

Stone GW, Sabik JF, Serruys PW, Simonton CA, Généreux P, Puskas J, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. **N Engl J Med 2016;375:2223-35. http://doi.org/b4zw**

Makikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treat-

ment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. **Lancet 2016;388:2743-52. http://doi.org/f3vjgk**

In patients with left main coronary artery (LMCA) disease, coronary artery bypass grafting (CABG) is still the standard treatment. Over the past years, a growing number of studies have been published on the feasibility and efficacy of percutaneous coronary intervention (PCI) in patients with LMCA disease. In fact, the SYNTAX trial, which compared PCI with CABG, reported similar results with both procedures in patients with LMCA disease and coronary artery disease of low or intermediate anatomical complexity (SYNTAX score <33).

In the SYNTAX trial, patients assigned to PCI received paclitaxel-eluting stents. Later, different studies demonstrated the superiority of everolimus-eluting stents over paclitaxel. At the same time, CABG has evolved, with greater use of arterial grafts, off-pump surgery and better techniques for myocardial protection. Moreover, patients with LMCA disease represented only a subgroup of the population included in the SYNTAX trial and the results were the effect of subgroup analysis. All these reasons justified the design of the EXCEL trial. EXCEL was an open-label randomized trial that included patients with LMCA stenosis ≥70%, or 50% to 69% stenosis if determined by means of testing to be hemodynamically significant. Participants were required to have a SYNTAX score <33. Patients were randomly assigned to PCI with everolimus-eluting stent or CABG. The goal of PCI was revascularization of all the ischemic territories, intravascular ultrasonographic guidance was strongly recommended during the procedure and dual antiplatelet therapy was continued for a minimum of 1 year. The goal of CABG was revascularization of all vessels with diameter ≥1.5 mm, the use of arterial grafts was recommended, and aspirin was indicated. The trial was designed to determine that PCI was non inferior to CABG. The primary end point was a composite of all-cause death, acute myocardial infarction (AMI) or stroke at 3 years. The authors assumed an 11% event rate at 3 years and defined a non-inferiority margin of 4.2%, which means that non-inferiority of PCI would be accepted if the result of PCI was up to 4.2% worse in absolute terms. Secondary end points were death, AMI or stroke at 30 days and death, AMI, stroke or repeat revascularization at 3 years. The sample size was estimated in 2,600 patients to provide 90% power; however, the inclusion of patients was slower than expected and the authors decided to reduce the number to 2,000, accepting 80% power. Randomization was performed with stratification according to diabetes and SYNTAX score (≤22 vs. 23-32).

A total of 1,905 patients were included in the study (948 to PCI and 957 to CABG). Mean age was 66 years and 77% were men. Twenty-nine percent had diabetes, 53% had stable angina, 7% presented silent ischemia and 40% was admitted due to AMI or unstable angina. The SYNTAX score according to assessment at local sites was low (≤22 in 60.5% of patients and 23 to 32 in the remaining 39.5%. However, the SYNTAX score according to the central laboratory analysis was ≥22 in 35.8% of the patients, 23-32 in 40.0%, and ≥33 in 24.2% (patients that should not have been included according to the inclusion criteria). Distal LMCA disease was present in 80.5% of the patients and two-vessel or three-vessel coronary artery disease in 51%. A mean of 2.4 stents with a mean total stent length of 49 mm were implanted in the PCI group. A mean of 2.6 grafts were implanted and internal thoracic artery graft was used in 99% of the patients in the CABG group.

After a median follow-up of 3 years, the primary end point occurred in 15.4% of the cases with PCI and 14.7% with CABG, fulfilling the non-inferiority criterion. Death from all cause was 8.2% with PCI and 5.9% with CABG (p=ns). Percutaneous coronary intervention was also non inferior to CABG for the secondary end point at 30 days (4.9% vs. 7.9%). In fact, at 30 days PCI was superior to CABG (HR 0.61; 95% CI=0.42-0.88) due to fewer periprocedural AMI (3.9% vs. 6.2%) which was prospectively defined as a rise in the level of CPK-MB to more than 10 times the upper reference limit of the assay or more than 5 times if additional evidence was present. Periprocedural mortality was similar (1.1% vs. 1%). The incidence of periprocedural adverse events was higher with CABG than with PCI (23% vs. 8%) mainly due to more arrhythmias, infections and need of blood transfusion. A post hoc analysis demonstrated higher incidence of events in the PCI group after 30 days, which explains that finally the rate of events was similar at 3 years. For the secondary end point at 3 years (23.1% vs. 19.1%), PCI was also non inferior to CABG. However, repeat revascularization due to ischemia was more frequent after PCI than after CABG (12.6% vs. 7.5%; p <0.001), although symptomatic graft occlusion occurred more frequently than stent thrombosis (5.4% vs. 0.7%; p <0.001).

The EXCEL trial revealed a balanced scenario between both strategies, with lights and shadows for each of them. The immediate outcome is favorable for PCI, with fewer hard events and complications. However, the advantage is for surgery in the long-term, with less need of repeat revascularization. The low incidence of acute stent thrombosis, lower than that of the SYNTAX trial with paclitaxel-eluting stent, is worth mentioning. Among the limitations of the study, we should mention that 24% of the patients should not have been included and that the follow-up period could be short to show real differences between both procedures.

The NOBLE trial performed in Northern Europe (Nordic and Baltic countries, the UK and Germany) also compared PCI with CABG in patients with LMCA

disease and, as the EXCEL trial, was designed as a non-inferiority study. Patients with LMCA stenosis ≥50% or fractional flow reserve ≤0•8 in the LMCA, and no more than three additional noncomplex lesions in the rest of the coronary arteries were included in the study. Randomization was done with stratification by gender, presence of distal LMCA lesion, and presence of diabetes. Similiar to the EXCEL trial, patients were treated with the intention of achieving complete revascularization and use of DES was mandatory (biolimus-eluting stent was recommended). The primary endpoint was a composite of death, stroke, AMI and revascularization at 5 years (two differences with the EXCEL study were the inclusion of repeat revascularization in the primary end point and longer follow-up). A non-inferiority margin of 1.35 was established, which means that the upper limit of the 95% CI of the HR of PCI compared with CABG should not exceed 1.35, i.e. the occurrence of the primary end point with PCI could not exceed 35% in relative terms. A median follow-up of 2 years was required, but was changed to 3 years because the inclusion of patients was slower than expected.

A total of 1,184 patients were included (592 in each group). Mean age was 66 years and 78% were men; 15% had diabetes, 82% had stable angina and 18% acute coronary syndromes. Median SYNTAX score was 22.5. Distal LMCA disease was present in 81% of the patients. A first-generation stent was implanted in 11% of PCI cases and complete revascularization was achieved in 92% of the cases. Grafting with the left internal thoracic artery was done in 93% of the patients in the CABG group.

At the 5-year follow-up, the primary end point occurred in 29% of the patients in the PCI group and in 19% in the CABG group. Thus, the HR was 1.48 (95% CI 1.11–1.96), exceeding the limit for non-inferiority expected. There were no significant differences in all-cause mortality (12% vs. 9%) and cardiac death (3% in both groups), but significant differences were seen in the incidence of non-procedural AMI (7% vs. 2%; p = 0.004), repeat revascularization (16% vs. 10%; p = 0.032) and a trend toward higher incidence of stroke (5% vs. 2%; p = 0.07). At 30 days, the incidence of adverse events was higher in the CABG group as in the EXCEL trial: greater need for blood transfusion (28% vs. 2%) and re-operation due to bleeding (4% vs. <1%). Unlike the EXCEL trial, the authors of the NOBLE trial did not make a prospective definition of periprocedural AMI. This end point was retrospectively analyzed in less than half of the cases, with an incidence of 5% for PCI and 7% for CABG (p=ns). There was also a minimal difference in the incidence of stroke (0% vs. <1%, with p=0.04). An analysis of events at 1 year did not show significant differences for the primary end point or any of its components.

The conclusions of the EXCEL and NOBEL trials are different: in the EXCEL trial PCI is non inferior to CABG at 3 years and in the NOBLE trial PCI is inferior to CABG at 5 years. Truly, the primary end point is not the same: death, AMI and stroke in the EXCEL trial, while the NOBLE trial adds repeat revascularizaiton. If the EXCEL trial had also considered revascularization as a primary end point and the follow-up period had been longer, would the results of both trials have been similar? The definition of periprocedural AMI considered in the EXCEL trial may not be correct, but we may also question that the NOBLE study did not take into account this event prospectively. Yet, periprocedural AMI does not seem to have influence in the final outcome: mortality at 30 days and long-term mortality do not differ in the EXCEL trial or in the NOBLE trial. Some doubts persist: why is there a trend toward higher incidence of stroke at 5 years in the PCI group than in the CABG group in the NOBLE study, if the incidence at one year is similar? This finding may be due to chance. Nevertheless, we emphasize some similar findings: CABG is associated with more complications in the short term, and PCI with more complications and repeat revascularization in the long term. And it its particularly important to bear in mind that randomized studies recruit patients in whom it is a priori assumed that receiving one strategy or procedure or the other will make no difference. They do not represent the patients in whom we would indicate one particular treatment for some reason or another.