Multivessel Coronary Artery Disease. Surgical Treatment versus Angioplasty

Agonist

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THE QUESTION OF THIS CONTROVERSY

The current technical step forwards in metallic stents (MS), bare metal stents (BMS) and drug-eluting stents (DES) respectively led interventional cardiologists to a rude therapeutic attitude, that even the most complex coronary lesions are being treated with angioplasty plus stents (TCA). About a third of all the patients with multivessel disease (MVD) in Europe are being treated with TCA instead of revascularization surgery (MRS), although the guidelines suggest this one as a superior treatment. (1)

DIFFERENCES BETWEEN MRS AND TCA

TCA only treats the guilty lesion and it is mini-invasive; MRS it is not, but treats the guilty and future guilty lesions of any complexity, by the graft anastomosis in the middle or distal vessel, with less impact in the long-term results. (2) TCA is an incomplete revascularization. Of 22000 TCA in the New York Register, 69% were incomplete. (3) We already know that in MRS, the higher complete arterial revascularization, the longer survival at long term. (4-6)

PROBLEMS OF RANDOMIZED STUDIES

One of the problems to take into account is that the number of randomized patients with MVD was low; for example, in ARTS trial (7) only one third of the patients had MVD. Globally, surgery proved that it is superior in terms of repeated revascularization at 3 years (6.6% vs. 26.7%; $p < 0.001$). In most trials, according to including and excluding criteria, the number of enlisted patients was very low. Due to this rigorous sieving, the analyzed population of patients with MVD was not representative of the global population with such disease (selection bias). The results in patients predominantly of one or two vessels should not be applied to the majority of patients with MVD. If only low risk patients are included and those with more severe disease are excluded, who are benefited with MRS, an equivalent survival for both interventions is "built". (8) If the sample is not enough (low power study), even the most meticulous researcher can be wrong while answering the question, the study should be considered unfinished and no negative. An analysis of the real world as it was suggested by Navia should be done, (9) through a review of great registers and the new study SYNTAX. (10) We have to add the problem of crossover: the results of most of the studies come from their methodology based on the principle of intention to treat, and in the studies there were some crosses, analyzing for example randomized patients to TCA group and then operated. SoS study (Stent or Surgery) communicated a crossover of 9% for TCA group and 4% for MRS group. (11) For al long time Taggart emphasized that in most of the comparative studies there was no equal distribution in relation to the disease extension. (2, 12, 13) When a considerable number of patients for a long period were studied, a significant benefit of survival in favour of MRS emerged. (14) In 2003, in a meta-analysis which included 13 randomized studies reaching 8000 patients with disease of one or more vessels, a benefit in survival in favour of MRS at 5 years was found. (15)

THE NON RANDOMIZED REAL WORLD: GREAT REGISTERS

The one of the University of Duke examined 18481 patients with stenosis >75%, of which 6292 underwent TCA and 5327 MRS. Patients were categorized according to the severity of the lesions and were assessed prospectively. Those patients with severe disease had a reduced survival with TCA compared to those with MRS. (16)

The cardiological register of New York City analyzed in 2005 by Hannan et al. (17) showed a 31% of reduction in the risk of death with MRS over TCA at 3 years in MVD (89.3% of survival for MRS vs. 84.4% with stents). The severity of the disease was statistically adjusted with a propensity model. MRS was associated with a significantly higher survival probability in all the anatomical groups. MS; Are BMS superior? If we analyze BASKET study, which compared 746 randomized patients to BMS or MS, after suspending clopidogrel at 6 months, the combined point death and infarction was 4% for BMS over 1.3% for MS ($p = 0.01$). (18) In 2006, Guyton concluded that BMS do not have survival advantages over MS and data from real world registries showed that MVD usual therapeutic had as result an excess of relative mortality of up to 46% in patients who initially received stents. (19)

In another register of the real world of 6033 patients (TCA n= 872 vs. MRS n= 5161), Brenner

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and Lytle, in Cleveland, (20) observed a significantly higher mortality in patients treated with TCA (incidence of adjusted risk 2.1, HF 95% 1.7-2.6; p< 0.0001). The percentage of complete revascularization was higher for MRS (82% vs. 74%; p < 0.0001). The last great register published is the one of Hannan et al. in 2008, (21) which included 7437 patients who underwent MRS and 9963 patients treated with BMS. At 18 months the MRS was associated with lower mortality or AMI or repeated revascularization than TCA. The adjusted survival was of 94% for MRS vs.92.7% for TCA (p = 0.03). The free infarction adjusted survival was of 92.1% for MRS vs. 89.7% for TCA (p < 0.001). Those patients treated with MRS had worst ventricular function, more recent AMI and higher prevalence of predictive factors of percentages of mortality and AMI more elevated, so they were adjusted with the use of multivariate methods and propensity analysis.

HOW LONG OF FOLLOW-UP WOULD WE NEED TO FIND A DIFFERENCE IN THE RESULTS?

We already know from ARTS study that the difference between TCA and MRS tends to be in favour of MRS. In order to clarify the advantage or disadvantage of MRS compared with TCA in terms of mortality, the follow-up should be at least of 4-5 years. (22) With SYNTAX study differences at 24 months appeared.

WHAT IS THE INFLUENCE OF THE COMPLETE REVASCULARIZATION?

Numerous articles have stressed the importance of the complete revascularization. (6, 23) This cannot be achieved in many cases with TCA, among other causes due to chronic obstructions and non critical stenosis with no possibilities of intervention. In ARTS study, complete revascularization was of 84% for MRS vs. 70.5% for TCA. Hannan coincides in that those patients with stents with no complete revascularization have lower results than those patients with complete revascularization. (3)

IF PATIENTS TREATED WITH TCA ARE OPERATED, DO THEY HAVE THE SAME PERIOPERATIVE RISK AS IF THEY HAD BEEN OPERATED WITH NO TREATMENT?

There is a relative excess of mortality of up to 46% in patients with angioplasty with stent after a MRS in comparison to those who received MRS. (20) Authors that investigated this topic suggest that stents inhibit protective collateral and force to insert the anastomosis more distally in the surgery, where the vessel has a smaller diameter, compromising the runoff and the permeability. (24, 25)

ARE THERE MORE COMPLICATIONS WITH MORE NUMBER OF STENTS?

The higher number of stents can produce higher number of future re-stenosis. The real-world average is 1.5 stent per patient, in SYNTAX study 48% of the patients received 5 or more stents (4.6 ± 2.3). There is a MACCE (major cardiovascular or cerebrovascular event) lineal increase due to number of stents in SYNTAX that was of 5.6% for one and 19.8% for eight. (26) This was described by Colombo in 2004 with up to 24-32% of thrombosis for 3-4 stents. (27) For this reason, ACC/AHA guidelines recommend 12 months of clopidogrel instead of 6. In the real world of BMS, in 2007, 60% were off label, that is to say, implanted in types of lesions that had been excluded of the main studies. That circumstance led the Food and Drug Administration (FDA) let the others know the problem. (28, 29)

IS THERE ANY DIFFERENCE WHEN A STENT IS THROMBOSED AND WHEN A BYPASS IS OCCLUDED?

While a thrombosis of a stent produces an AMI in 80% of the cases, with a mortality of between 30% and 45%, (30) the occlusion of a bypass becomes apparent with recurrent angina that leads to a re-revascularization. This effect is well known, as it is demonstrated in the bibliography, and is repeated in SYNTAX study.

APPROPPRIATE CRITERIA FOR CORONARY REVASCULARIZATION: ACC/AHA GUIDELINES

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) together with other seven societies join expert opinion to review 180 common clinical settings, what led to write the Appropriateness Criteria of Coronary Revascularization. (31) MRS was judged as appropriate for patients with disease of two and three vessels and coronary artery disease, when revascularization was considered necessary. TCA was considered as appropriate in acute myocardial infarction and in patients with disease of one or two vessels with proximal AD lesion, but assessed as uncertain for all the patients with MVD.

PRESENT: SYNTAX STUDY

In 2009, the results at 12 months of SYNTAX (Clinical Trials.gov number, NCT00114972) were published, (10) controlled prospective study in which 1800 patients with coronary artery disease or MVD were randomized to MRS or TCA with Taxus stent in order to determine which revascularization strategy is the best. It has several strong points to show the real world: prospective, multicenter (85 centers in the United Stated and Europe), all comers with MVD or coronary artery disease were included. Percentages of enlisted and randomized were very high: 71% and 58.5% 81800 of 3075), respectively. The data of each patient was analyzed by a cardiovascular team, a score was established (32, 33) and an agreement was reached on what action to take. Patients for only one treatment were included in the register. The follow-up has now been 36 months. The primary end-point is MACCE, percentage of cardiovascular or cerebrovascular events, including all causes of death, cerebrovascular

accident (CVA), documented infarction (AMI), and every repeated revascularization (TCA or MRS).

Global MACCE at 3 years for MVD was significantly higher for TCA than for MRS: 28.8% Taxus vs. 18.8% MRS ($p < 0.001$), mainly due to repeated revascularization; thus the primary point of non inferiority proposed was not reached. There was also a significant increase of AMI in TCA cohort in comparison to MRS (7.1% vs. 3.3%; $p = 0.005$), with the result of an important increase in death due to cardiac cause (9.5% vs. 5.7%; $p = 0.02$). This was motivated by a higher percentage of AMI in the group of TCA after the first year. (34, 35)

Regarding repeated revascularization, TCA was clearly lower to MRS at 24 months, with 17.4% of the patients needing reintervention, in comparison to 8.6% in MRS ($p< 0.001$). Even when the results with TCA were better than others previously informed, the advantage for MRS is still significantly high.

This advantage is more visible while increasing the anatomical complexity documented by SYNTAX score. In TCA group, the incidence of MACCE was significantly higher in the intermediate tertile and excessively elevated in the high score. In the corresponding groups of MRS, MACCE percentage decreased even with high scores, perhaps due to a lower competitive flow that occurs when arteries with stenosis received bypass, with greater permeability.

Considering the results according to SYNTAX score, (34) MACCE was not very different between MRS and TCA at three years for low scores, but for patients with intermediate or high scores continues increasing. For a score equal or higher than 33, MACCE was of 31.4% for Taxus over 17.9% for MRS ($p < 0.004$). For intermediate scores it was of 29.4% for TCA vs. 16.8% for MRS ($p= 0.03$). Thus, MRS is the standard treatment for patients with intermediate and complex disease.

For diabetic patients, the difference of MACCE was more visible with the increase of severity of the disease. Another study published in 2010 showed similar results. (36) TCA is an acceptable alternative for patients with low scores.

CAN MRS HAVE BETTER RESULTS IN THE FUTURE? THE PROBLEM OF THE CEREBROVASCULAR ACCIDENT

Considering the percentage of CVA, there was an incidence of 2.8% for MRS over 1.4% for TCA ($p= 0.03$) at 24 months, favouring this last group, but at 3 years no significant difference appears: 2.9% vs. 2.6% ($p= 0.64$). (35) Some of the CVA occurred during the surgery or after it, probably due to atheroembolism of the ascendant aorta. However, 50% of them occurred after the 30th day of the MRS.

There was a noticeable difference in the postoperative medication, especially in the number of patients treated with aspirin (TCA 91.2% vs. MRS 84.3%; $p < 0.001$), statins (74.5% MRS and 86.7% Taxus; $p < 0.001$) or clopidogrel (TCA 71.1% vs. MRS 15%). These secondary factors could be the responsible for this difference. The appearance of postoperative transient atrial fibrillation, which does not occur after the TCA, may have had an important role. These complications can be reduced improving the postoperative medication, adopting the technique of surgery off-pump (EC) with multiple arterial ducts, (37, 38) up to 0.25% of CVA, equated with TCA. (29) The detection of ill aortas and the performance of the surgery with no aorta clamping are very important. (39)

CONCLUSIONS

If we want to have an adequate scene, the Aristotelian point of view is a combination of randomized all comers studies and observational studies with a great number of patients, considering the bias already mentioned in the interpretation of the results.

1. The superiority of MRS over TCA in MVD has been already commented in the great registers.
2. The criteria of convenience for revascularization of the American College of Cardiology give us new and excellent tools to help in the decision making regarding revascularization strategies in MVD.
3. For SYNTAX, the most significant of the randomized studies, MRS should be the standard of treatment for MVD with intermediate and high scores, since the objective of non inferiority has not been achieved by TCA. TCA should be recommended in MVD in cases of low SYNTAX scores and in patients to whom MRS is associated with high risk due to comorbidities.
4. How should be done the final approach of a patient with MVD? All the data, including the angiography, should be checked by the surgeon and the interventional cardiologist and they should decide taking into account the "local" results. In order to guarantee quality, coronary revascularization should not be performed in patients with MVD at the moment of the diagnostic angiography, (40) to give enough time to the team to reach a consensus and discuss the findings with the patient. Without the opinion of the surgeon, it is impossible to take a rational decision.

BIBLIOGRAPHY

1. Kappetein AP, Dawkins KD, Mohr FW, et al. Current percutaneous coronary intervention and coronary artery bypass grafting practices for three vessel and left main coronary artery disease. Insights from the SYNTAX run-in-phase. Eur J Cardiothorac Surg 2006;29;486-91.

2. Taggart DP, Ferguson TB. Coronary artery bypass grafting is still the best treatment for multivessel and left main, but patients need to know [Lecture]. Ann Thorac Surg 2006;82:1966-75.

3. Hannan EL, Racz M, Holmes DR, et al. The impact of completeness of percutaneous coronary intervention revascularization on long term outcomes in the stent era. Circulation 2006;113:2406-12.

4. Lytle BW, Blackstone EH, Loop FD, et al. Two internal thoracic artery grafts are better than one. J Thorac Cardiovasc Surg 1999;117:855-72.

5. Taggart DP. Bilateral internal mammary artery bypass grafts. Lancet 2001;358:870-5.

6. Scott R, Blackstone EH, Mc Carthy PM, et al. Late consequences of incomplete revascularization. Isolated bypass grafting of the left internal mammary artery to the left anterior descending. J Thorac Cardiovasc Surg 2000;120:173-84.

7. Legrand VM, Serruys PW, Unger F, et al. Three year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. Circulation 2004;109:1114-20.

8. Taggart DP. Coronary artery stents [Letter to the Editor]. N Engl J Med 2006;354:2077.

9. Navia D. Enfermedad coronaria de múltiples vasos. Tratamiento quirúrgico versus angioplastia [Controversia (Agonista)]. Rev Argent Cardiol 2006;74:136-40.

10. Serruys PW, Morice MC, Kappetein EP and Syntax investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72. Datos suplementarios accesibles en http:// content.nejm.org/cgi/data/NEJMoa0804626/DC1/1

11. The SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomized controlled trial. Lancet 2002;360:965-70.

12. Taggart DP. Coronary revascularization. Br Med J 2007;33:593-4.

13. Taggart DP. PCI or CABG in coronary artery disease? Lancet 2009;373:1150-2.

14. Daemen J, Boersma E, Flather M, et al. Long term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease. Circulation 2008;118:1146-54.

15. Hoffmann SN, Tenbrook JA, Wolf MP, et al. A metaanalysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 2003;41:1293-304.

16. Smith PK, Califf RM, Tuttle RH, et al. Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. Ann Thorac Surg 2006;82:1420-9.

17. Hannan EL, Racz MJ, Walford G, et al. Long term outcomes of coronary artery bypass grafting versus stent implantation. N Engl J Med 2005;352:2174-83.

18. Pfisterer M, Brunner-LaRocca HP, Buser PT, et al. BASKET-LATE investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of DES vs. BMS. J Am Coll Cardiol 2006;48:2584-91.

19. Guyton RA. Coronary artery bypass is superior to drug-eluting stents in multivessel coronary artery disease. Ann Thorac Surg 2006;81:1949-57.

20. Brenner SJ, Lytle BW, Casserly IP, et al. Propensity analysis of long term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high risk features. Circulation 2004;109:2290-5.

21. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med 2008;358:331-41.

22. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA Guideline update for coronary artery bypass surgery: summary article. J Am Coll Cardiol 2004;44:1146-54, e213-310.

23. Jones EL, Weintraub WS. The importance of completeness of revascularization during long term follow up after coronary artery operations. J Thorac Cardiovasc Surg 1996;112:227-37.

24. Thielmann M, Neuhäuser M, Knipp S, et al. Prognostic impact of previous percutaneous coronary intervention in patients with diabetes mellitus and triple-vessel disease undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 2007;134:470-6.

25. Tran HA, Barnett SD, Hunt SL, et al. The effect of previous coronary artery stenting on short and intermediate term outcome after surgical revascularization in patients with diabetes mellitus. J Thorac Cardiovasc Surg 2009;138:316-23.

26. Hamm CW. Stents or CABG. Latest Techniques in Cardiac Surgery, Leipzig, Alemania, diciembre 4-5 2009.

27. Iakovov I, Schmidt T, Bonizzoni E, et al. Incidence, predictors and outcome of thrombosis after successful implantation of DES. JAMA 2005;293:2126-30.

28. Farb A, Boam AB. Stent thrombosis redux-the FDA perspective. N Engl J Med 2007;356:984-7.

29. Vallely MP, Potger K, Mc Millan D, et al. Results in beating heart coronary artery anaortic surgery. Heart, Lung and Circulation 2008;17;299-304.

30. Mauri L, Hsieh WH, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug eluting stents. N Engl J Med 2007;356:1020-29.

31. Patel MR, Dehmer GJ, Hirschfeld JW, Smith PK, Spertus JA. ACCF /SCAI /STS/ AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation. Circulation 2009;119:1330-52.

32. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. Eurointervention 2005;1:219-27. SYNTAX score online:www.europcronline.com/email/090602-bsci/moviepage.php

33. Serruys PW. Syntax score. Eurointervention 2007;3:450-9.

34. Kappetein EP. Results of the SYNTAX trial at 24 months. Latest techniques in cardiac surgery. Leipzig, Diciembre 2009.

35. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Staehle E, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three vessel disease: 3-year follow up of the SYNTAX trial. Eur Heart J 2011,32:2125-34.

3**6.** Banning AP, Westaby S, Morice MC, et al. Diabetic and nondiabetic patients with left main and or 3-vessel coronary artery disease. Comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. J Am Coll Cardiol 2010;55:000-000 March 16, expedited publication.

37. Puskas JD, Williams WH, Mahoney EM, et al. Off pump vs conventional coronary artery bypass grafting: early and 1 year graft patency, cost and quality of life outcomes: a randomized trial. JAMA 2004;291:1841-9.

38. Navia D, Vrancic M, Vaccarino G, et al. Total arterial off-pump coronary revascularization using bilateral internal thoracic arteries in 3-vessel disease; surgical technique and clinical outcomes. Ann Thorac Surg 2008;86:524-30.

39. Bittner HB, Battellini RR, Rastan AJ, Mohr FW. Intraoperative detection of porcelain aorta remains a challenging dilemma in coronary artery bypass surgery. Circulation. Abstract 13609. World Congress of Cardiology 2008.

40. Califf RM. Stenting or surgery: an opportunity to do it right. JACC 2005; 46:589-91.

Antagonist

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"Probably, the most interesting period in medicine has been the one of the last decades. This step forward has been so fast that as new findings emerge they make the truth of each year modified by the new evidence, so truth becomes a changeable factor."

CHARLES H. MAYO (4)

Since its introduction in 1968, myocardial revascularization surgery (MRS) was the only available revascularization method until 1977, year in which Andreas Gruentzig performed the first coronary balloon angioplasty (TCA). (1) Since that moment, there were great step forwards in the field of interventional cardiology including the improvement of TCA materials, the introduction of

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bare metal stents (BMS) in 1986 and the development of adjuvant pharmacological agents. These, added to the experience of the operators and the performance of clinical trials building the evidence, established the safety and effectiveness of the TCA, becoming an essential tool in the treatment of patients with atherosclerotic coronary disease.

The treatment of patients with multiple vessel disease (MVD) is based on an adequate medical treatment in order to decrease symptoms and modify coronary risk factors, and a revascularization strategy at the right time.

MRS has demonstrated that improves survival at long term in patients with coronary disease of three vessels and disease of the left main coronary artery (LMCA) in comparison to medical treatment. (2) The effectiveness of TCA in patients with disease of one and two vessels has stimulated the indication of this procedure as an alternative to MRS in some patients with MVD.

Multicenter studies that compared balloon angioplasty (TCA) or BMS vs. MRS have demonstrated similar rates of mortality and infarction at long term; but, traditionally, the performance of TCA in patients with multiple vessel compromise was limited due to the high revascularization, as the result of the development of restenosis, in 30-40% with balloon angioplasty (TCA) and in 20-25% with BMS. (3, 4) Most of them are outdated regarding their application in contemporary practice. This is the result of the improvement in both revascularization strategies, as the introduction of drug eluting stents (DES) in the field of interventional cardiology and the increased use of arterial bridges, the better postoperative of the patients and the possibility of performing minimally invasive surgeries or off-pump surgeries, in the case of MRS.

So, based on these studies, MRS is nowadays considered the revascularization treatment of choice in patients with MVD and/or LMCA and, according to the new revascularization guidelines published recently; TCA is considered inappropriate in this type of patients. (5)

CURRENT EVIDENCE DES VERSUS MRS

The practice of the interventional cardiology has changed with the advent of the BMS, born from a TCA limitation, restenosis. Randomized studies which compared BMS with MS showed a significant reduction in the rate of new revascularizations, first in simple lesions and stable patients. (6, 7)
This led to expand the use of TCA in patients with more complex coronary anatomy, among them patients with MVD.

Several registers showed an association between the introduction of BMS and the increase of TCA performances in patients with indications of MRS. Frutkin et al. analyzed 265028 procedures in stable patients and with acute coronary syndrome (ACS) who fulfilled the indications of class I for MRS in three periods: pre-BMS (before April 2003), spreading of BMS (April 2003-December 2004) and BMS (January 2005- September 2006). They demonstrated that thanks to the use of BMS, TCA as an initial way of revascularization in patients with indication of class I of MRS significantly increased, from 29.4% in the first period to 33.4% and 34.7% in the second and this period respectively; this increase was parallel to a decrease in patients referred to MRS. (8)

This tendency was maintained in more selected subgroups, as in those 25068 patients with ACS with no ST elevation and MVD, where during the CRUSADE register development an increase in the use of TCA of 51.5% to 60.1% together with a decrease of NRS indication (48.9% to 39.9%) was observed, while the percentage of patients to whom only medical treatment was indicated was stable (27.8% to 25.5%). (9) With the increase in the use of BMS in these patients observational studies emerged which were compared with MRS with disparate results; on the one hand, Park et al., (10) in a retrospective study, did not demonstrate differences in adjusted mortality at 3 years in 1547 and 1495 patients who underwent TCA and MRS respectively, but there was a higher rate of revascularization with TCA. Contrary to this, Hannan et al. using patients from the New York State database, referred that those patients with MVD who underwent a TCA with BMS had a survival of less than 18 months in comparison to patients who underwent a MRS. (11)

Given these contradictory results and the lack of updated evidence, TCA is the alternative in the revascularization of patients with MVD. In this context SYNTAX study is carried out with the objective of assessing in1800 patients the hypothesis that TCA with Taxus paclitaxel-eluting stent is not inferior to MRS in patients with disease of three vessels or LMCA. (12)

The conclusions of the authors regarding SYNTAX study were: *"Surgical strategy is still being the revascularization procedure of choice in patients with disease of three vessels or LMCA since, compared with TCA, resulted in a lower rate of the combined primary objective of adverse cardiac and cerebrovascular events at one year of follow-up."*

If we only read the last lines of the summary, the final message would be that MRS is the best treatment of revascularization for these patients, but implications are more complex than the final message.

When analyzing a randomized study that compares two types of treatment we must assess if the events involved in the primary end-point are "hard" (those impacting in the life of the patients, as death, AMI, CVA), indicating safety of the treatment, or if they are "soft", as revascularization.

In this study, although TCA was inferior to MRS regarding the primary objective at one year (death, AMI, CVA or revascularization: 17.8% TCA vs. 12.4% MRS; $p=0.002$), mortality in both groups of treatment was similar (4.4% TCA vs. 3.5% MRS; $p= 0.37$). This difference was due to a higher need of revascularization in patients of TCA group (13.5% vs. 5.9%; $p< 0.001$),

with no differences in the secondary objective (death, AMI, CVA: 7.7% TCA vs. 7.6%; p= 0.99).

In this way, TCA would be as safe as surgery according to the same rate of "hard" events, but during the follow-up patients would need new revascularizations more frequently. Although the difference in revascularization rates at one year between both procedures in this study was of 7.6%, is almost 50% lower than the result showed in a meta-analysis of the studies ARTS, SoS, ERACI-2 and MASS-2 (13.5%) showing the impact of BMS in these results.

On the other hand, although MRS had less combined events, CVA rate was significantly higher during the first year of follow-up (2.2% vs. 0.6%; p <0.003), finding that coincides with the results of a meta-analysis of 23 studies that compared MRS with TCA, where CVA related with the procedure were significantly higher in the MRS group (1.2% vs. 0.6%; p< 0.001), with no concomitant decrease of survival. (14)

Although MRS demonstrated a lower rate of events than TCA, when stratifying patients according the complexity of their coronary anatomy by SYNTAX score, those patients with low (≤ 22) and intermediate (23-32) score did not present significant differences in the primary objective between TCA and MRS, while those patients with high score (≥ 33), the surgery showed a lower rate of events at one year (Table 1).

Should all patients with MVD and/or LMCA be revascularized with MRS?

The answer for this question seems to be No and this is, basically, because patients with MVD are a very heterogeneous group, with a varied risk profile regarding basal features and associated comorbidities, clinical setting and, mainly, to the extension and severity of the coronary lesions.

This should be taken into account when deciding the revascularization treatment in the daily practice, since TCA results are more dependant on the complexity of the lesions, while for MRS, in the majority of the cases, is not so important.

TCA must face not only against restenosis and intrastent thrombosis (sub-acute and late), but also with the difficulty of treating total chronic occlusions and small vessels with diffuse disease, especially in diabetic, obtaining in this way less complex revascularizations than with MRS. This can be seen in the results according to the categories of SYNTAX score in each group of patients. In the MRS group, the incidence of the primary objective was similar in patients with low, intermediate and high SYNTAX (14.7%, 12% and 10.9%, respectively), while in the TCA group was significantly higher in patients with high score (23.4%) in comparison with low (13.6%) or intermediate (16.7%) scores.

Unfortunately, as we cannot demonstrate the inferiority of TCA with respect to MRS, the results in subgroups of patients that were not specified in the study should be considered as observational and hypothesis-generating. Among the different subgroups, we can mention two important ones that affirm the previous concept: diabetics and patients with LMCA.

Diabetic patients, who are characterized by having more extensive and diffuse coronary disease, had a similar incidence of death, AMI and CVA with MRS 10.3% vs. TCA 10.1% with a greater rate of primary objective in the TCA group at the expense of greater revascularization (14.2% MRS vs. 26% TCA). These events were greater than in non diabetic (11.8% MRS vs. 15.1% TCA). We must wait for the results of FREEDOM study in order to confirm these findings.

In the case of all patients of SYNTAX study with LMCA disease, there were no significant differences in the primary objective between MRS and TCA (13.7% and 15.8%, respectively; p= 0.44), but patients of TCA group had significantly greater revascularization (11.8% TCA vs. 6.5% MRS, p= 0.02) and less incidence of CVA than those of MRS group (0.3% TCA vs. 2.7% MRS; p= 0.01).

CONCLUSION

Given that not all patients with MVD are the same, their treatment should be done through a multidisciplinary and individualized approach, where the clinical cardiologist, the interventional cardiologist and the cardiovascular surgeon assess in each case in particular the patient surgical risk, the extension and the severity of the coronary disease, perhaps through the implementation of SYNTAX score, giving the patient the best revascularization strategy.

It seems that nowadays TCA with BMS in patients with MVD is a valid alternative as it is as safety as MRS, especially in patients with low and intermediate SYNTAX score, in whom it was not inferior to surgical strategy. Its role in subgroups of patients as diabetic and those with LMCA lesions is still to be confirmed.

On the other hand, only the future could demonstrate if the use of BMS with more antiproliferative power than Taxus stent could decrease the effectiveness that MRS and TCA with BMS have in patients with MVD.

Table 3. Sensitivity, specificity and predictive value of exercise stress testing in each group.

SYNTAX Score	MRS	TCA	p
Low	14.7%	13.6%	0.71
Intermediate	12%	16.7%	0.10
High	10.9%	23.4%	<0.001

BIBLIOGRAPHY

1. Grüntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978;1:263.

2. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994; 344:563-70.

3. Hoffman SN, TenBrook JA, Wolf MP, Pauker SG, Salem DN, Wong JB. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one to eight-year outcomes. J Am Coll Cardiol 2003; 41:1293-304.

4. Hannan EL, Racz MJ, Walford G, Jones RH, Ryan TJ, Bennett E, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med 2005; 352:2174-83.

5. Patel, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: A Report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology. J Am Coll Cardiol 2009;53;530-53.

6. Morice MC, et al; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773-80.

7. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al; TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004; 350:221-31.

8. Frutkin AD, Lindsey JB, Mehta SK, et al. NCDR (National Cardiovascular Data Registry) Drug-eluting stents and the use of percutaneous coronary intervention among patients with class I indications for coronary artery bypass surgery undergoing index revascularization: analysis from the NCDR (National Cardiovascular Data Registry). J Am Coll Cardiol Intv 2009;2:614-621.

9. Gogo Jr. PB, Dauerman HL, Mulgund J, et al. Changes in patterns of coronary revascularization strategies for patients with acute coronary syndromes (from the CRUSADE Quality Improvement Initiative). Am J Cardiol 2007;99:1222-6.

10. Park DW, Yun SC, Lee SW, et al. Long-term mortality after percutaneous coronary intervention with drug-eluting stent implantation versus coronary artery bypass surgery for the treatment of multivessel coronary artery disease. Circulation 2008;117:2079-86.

11. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. N Engl J Med 2008;358:331-41.

12. Serruys, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.

13. Mercado, et al. One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: A meta-analysis of individual patient data from randomized clinical trials. J Thorac Cardiovasc Surg 2005; 130:512-9.

14. Bravata DM, Gienger AL, McDonald KM, et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007; 147:703-16.

AGONIST'S REPLY

Dr. Jorge Belardi led the final discussion to the study by subgroups; let's analyze them in this way. In order not to leave aside an important percentage of the reality, we must remember SYNTAX register, from which hemodynamics have excluded themselves more than surgeons: in 1077 cases MRS was performed vs. TCA 198. Here, the results were better than for randomized cohort MRS: at 12 months death 2.5% vs. 3.5% in randomized; MACCE 8.8% register vs. 12.4% randomized, the latter lower for higher scores, as when operating occluded arteries the permeability of bridges is better due to competitive fluid absence.

In randomized groups, MACCE for MVD at 3 years (1) was of 28.8% for TCA vs. 18.8% for MRS (p= 0.001). There was a significant increase of infarctions in TCA compared with MRS after a year. Considering that perioperative mortality is early, but then stents thromboses occur, the divergent tendency increased and it would be a significant advantage for MRS.

Analyzing the results by SYNTAX score, in those low (0-22) there was no significant difference of MACCE between both treatments, though more revascularizations in TCA group. It is less invasive, although its effect at long term is unknown.

What happens in intermediate scores? MACCE was at 12 months for TCA of 16.6% vs. 11.7% for MRS (p= 0.97), at 24 months was of 22.8% vs. MRS 16.4% (p= 0.06), but at the third year it was of 29.4% vs. MRS 16.8%, with p= 0.003%, with the appearance of the surgery advantages. Besides, myocardial infarction at 2 years was of 2.8% for MRS vs. 6.2% for TCA (p= 0.05) and at 3 years was of 7.1% vs. 3.3% with p= 0.005. If we surgeons want to make the curves diverge at long term, we must perform more complete arterial MRS.

For high scores the advantage of MRS over TCA was more notable with the increase of anatomical complexity of lesions and our antagonist coincides in that for them MRS is better. The results at three years show that MRS is also better for intermediate results.

In conclusion, for low scores we accept TCA, although with more reinterventions. For high and intermediate scores, surgery. For intermediate it must be considered that MACCE was not equal for different centers: individual experience has a role. We conclude that the approach should be multidisciplinary and individualized.

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BIBLIOGRAPHY

1. Kappetein AP, Feldman TE, Mack MJ, Morice MC, Holmes DR, Staehle E, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three vessel disease: 3-year follow up of the SYNTAX trial. Eur Heart J 2011,32:2125-34.

ANTAGONIST'S REPLY

The evidence supporting both percutaneous and surgical treatment was already mentioned by each of the participants of this controversy. Likewise, there is no doubt that evidence always may have different interpretations. In the therapeutic treatment of patients with MVD, the reason of choosing one of the three options (medical, percutaneous or surgical) is due to the considerable variation of clinical, anatomical and functional features (degree of myocardial ischemia). For example, in patients wit MVD that have acute coronary syndrome percutaneous treatment of the guilty lesion is frequent and the rest of the lesions are assessed lately. On the other hand, is undeniable the importance of the coronary tree features, estimated by SYNTAX score. This one combined with EuroScore, allows am adequate stratification of risk of both type of treatments (percutaneous or surgical) in order to guide the selection. A high SYNTAX score is the frequent reason to choose surgical treatment.

Percutaneous treatment has two advantages over the

surgical one: 1) lower morbidity and 2) lower variability of results among different operators, centers, or countries. For example, the range of surgical mortality in the State of New York varies from 0% to 6% and it is probable that this variability would be more marked in our media. In order to guarantee excellent surgical results (≤ 1% of mortality), each center need to perform at least 350 cardiac surgeries annually. Thus, an appropriate selection of revascularization strategy needs, besides an adequate interpretation of the anatomy and the clinical features of the patient, a thorough knowledge of the intervening equipment and of results (Percutaneous treatment: intrastent thrombosis rate or perioperative infarction; Surgical treatment: mortality rate, cerebrovascular accident or reintervention).

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