Current options for treatment of chronic coronary artery disease

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ABSTRACT The primary issues must be discussed regarding the decision making of treating a patient with chronic coronary artery disease (CAD), are the appropriateness of revascularization and the method which will be applied. The criteria will be the symptoms, the evidence of ischemia and the anatomical complexity of the coronary bed. Main indications are persistence of symptoms, despite oral medical treatment and the prognosis of any intervention. The prognosis is based on left ventricular function, on the number of coronary arteries with significant stenosis and the ischemic burden. For patients with symptoms and no evidence of ischemia, there is no benefit from revascularization. If ischemia is proven, revascularization is beneficial. If revascularization is decided, the next important issue must be taken under consideration is the choice of the appropriate method to be applied, surgical or interventional approach. Current treatment options will be presented.

KEYWORDS Coronary artery disease (CAD); heart failure; minimal invasive techniques; surgical techniques

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The effect of Coronary Artery ByPass Graft (CABG) surgery on survival has been proven in an overview of 10-year results from randomized trials, two decades earlier (1). The advantages of CABG versus Percutaneous Coronary Intervention (PCI) in a relation to the place of intervention are based on fact that atheroma is mainly located in the proximal coronary arteries. Placing ByPass grafts to the mid coronary vessel, we overcome the culprit lesions of any complexity over the long term, while the method offers prophylaxis against future culprit lesions. On the other hand, PCI with stents treats suitable localized proximal culprit lesions, but has no prophylactic benefit against new disease, proximal to, within or distal to the stent.

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Based on registries and randomized trials, Task Force Members for Guidelines on Myocardial Revascularization, ESC Committee for Practice Guidelines and EACTS Clinical Guideline Committee suggest, for better prognosis, the surgical treatment for cases with Left Main Disease and any proximal Left Anterior Descending (LAD) stenosis >50% (Class I, Level A), for two or three-vessel disease with impaired Left Ventricular (LV) function (Class I, Level B) and for single remaining patent vessel stenosis >50% (Class I, Level C). PCI is suggested only for single vessel disease without proximal LAD (Class III, Level A). Additionally, the evidence that CABG is still the best therapy for severe chronic coronary artery disease (CAD) is indicated by a series of other Pre-Syntax publications. Hlatky *et al.* (2), in a collaborated analysis from ten randomized trials—including 7,812 patients with median follow up of six years—proved lower overall CABG mortality, which was significantly lower in diabetic patients or patients over 60 years old—and lower re-intervention for CABG *vs.* PCI, which was 10% for CABG versus 25% for PCI. Also, other authors as Hannan *et al.* (3,4), Bair *et al.* (5) and Javaid *et al.* (6), in trials of more than 100,000 patients, in total—follow up

three to five years, proved that PCI decreases absolute survival by around 5% and increases absolute re-intervention five times, comparing to CABG. Nowadays, the Syntax Trial is the most important trial ever, comparing PCI *vs.* CABG. Designed to look at five year outcomes, death and MACCE, this trial has become a landmark trial. After four of the five years completed, the Syntax Trial proved that CABG is superior to PCI, in almost 80% of all three vessel disease cases with Syntax Score >22 and in almost 65% of all Left Main Disease (LMD) cases with Syntax Score >32. Cerebral vascular accident (CVA) was higher for LMD cases only.

Considering that CABG is chosen, the next issue to be discussed is: classical CABG operation, off pump coronary artery bypass grafting (OPCABG) or other alternative surgical techniques? The use of extracorporeal circulation is of technical convenience to the surgeon, but leads to a general inflammatory reaction, the systemic inflammatory response syndrome (SIRS), which has been studied extensively and is mainly related with contact between the blood and the biological surfaces, its dilution and the absence of pulsatile flow. The negative pathophysiological consequences of the phenomenon are associated with postoperative dysfunction of many organs, as well as the blood (7). Various drug protocols, methods and clinical approaches, such as the use of a leukocyte filter (8), extracorporeal circulation with pulsatile flow (9), the use of heparinized surfaces (10), and the others that have been suggested from time to time have been able to mitigate the phenomenon but never to eliminate it. Fortunately, in clinical practice especially in a patient who is well-monitored preoperatively, it is not related with clinical morbidity. However, high risk patients often pay a price for using extracorporeal circulation in the perioperative period. In a series of studies of low or medium risk patients, the early outcome from the use of extracorporeal circulation was the same as for the OPCAB technique (11). Nathoe *et al.* (12) found similar long-term results regarding survival, incidence of cardiac events, need for reoperation and one-year graft patency—93% for On Pump versus 91% for OPCAB.

A landmark study of Puskas *et al.* (13) indicates that OPCAB disproportionately benefits high risk patients. Comparing 7,083 OPCAB cases versus 7,683 on-pump coronary artery bypass grafting (ONCABG) cases proved that the survival benefit of OPCABG technique appears when predicted mortality risk was greater than 2.5% and increases while predicted mortality increases. In acute coronary syndromes with progressing infarction and myocardial deterioration, the use of extracorporeal circulation is disadvantageous, since it imposes and additional burden on the myocardium and myocardial protection is compromised (14). OPCAB is also associated with a better outcome in patients who undergo operation soon after a myocardial infarction (15), as well as in those with a low injection fraction (16). The same applies to aged patients, where OPCAB is associated with significantly lower mortality, incidence of stroke, duration of mechanical ventilation and hospitalization in general (17). In low and medium risk patients with chronic respiratory problems, the outcome is independent of the use of extracorporeal circulation (18). If other risk factors are present, however, the outcome of OPCAB surgery is clearly better (19). It is significant that in specific patients keeping the pleural space closed, leads to fewer respiratory complications (20). OPCAB also offers better protection of renal function in comparison with classical surgery (21), and the recommendation to treat renal patients with OPCAB is generally accepted. OPCAB is associated with better results and fewer strokes in patients with carotid artery disease or peripheral vascular disease (22).

Although, OPCAB has proved superior in high risk patients, the diffusion of the technique is relatively limited. In USA and Europe, almost 20-25% of surgeons use the technique, while in Asia more than 60%. The less invasive techniques, such as minimally invasive direct coronary artery bypass (MIDCAB), left anterior small thoracotomy (LAST), endoscopic atraumatic coronary artery ByPass (Endo-ACAB), also have their place nowadays, but are performed by a small number of qualified surgeons. The use of The Da Vinci Robotic system has so far, either found similar applications to those of Endo-ACAB, replacing the endoscope of the preparation of the internal mammary arteries (IMA), or has achieved reperfusion of one or two targets on the anterior wall or perhaps also the right coronary artery. The future will prove the capabilities of the Robotic system for multiple vessel myocardial reperfusion.

Next issue must be discussed is the choice of grafts that will be used. The patency of venous grafts at ten years is unsatisfactory, since 40% of grafts are occluded, 30% are stenotic and only 30% function well. Dion *et al.* (23) increased the good percentage of good patency to 76% at eight years, only for cases with sequential use of venous graft. Although, the use of venous grafts in cases of moderate obstruction of the target vessel seems to be associated with a lower probability of graft occlusion than when arterial grafts are used, as was demonstrated by Shimizu *et al.* (24). Finally, venous grafts are goldmine in patients with an urgent need for reperfusion, in cases of acute perioperative dysfunction of an arterial graft or in cases where the surgeon prefers them based on greater experience in their use, especially for the right coronary artery.

As indicated in a historic study by Loop *et al.* (25), in 1986, the use of at least one mammary artery graft, significantly

improves the expected 10-year survival. Equally important is a second study, 13 years later, in 1999, by Lytle *et al*. (26), who proved that the use of both IMA is associated with better long term results than the use of just one, while also improving survival and reducing cardiac events. Many other techniques have been described for maximizing the use of the IMA, such as bilateral direct use, sequential use, use as a free graft, composite grafts and other. All these, were aimed at total arterial revascularization with exclusive use of the two IMA or the supplementary use of another arterial graft. At the same time, the technique of skeletonized IMA proved to lead to an increase in automatic flow (27) and reduction in sternal wound complication. Coronary ByPass is the treatment of choice for the coronary patient with diabetes mellitus. The Bari Study and others recommend the use of total arterial revascularization in diabetic patients, since the 5 -year mortality is lower than in patients who receive venous grafts or who undergo PCI. The use of skeletonized mammary arteries in those patients, even in insulin dependent, gives results similar to the use of a single IMA (28). Skeletonizing the mammary arteries also seems to be particularly beneficial to the other high risk groups, while it is associated with less blood loss during the preparation of the graft. Concerning the phenomenon of hypoperfusion, in the case of composite grafts, it must be remarked that the flow reserve of a pedicled IMA is similar to the peripheral outflow and approaches three times the flow necessary for complete myocardial reperfusion. A series of studies has demonstrated the good long term patency of the T-graft, using a free mammary end-laterally in the pedicled. Finally, the long term results from the use of the mammary arteries continue to be exceptionally good.

Suma *et al*. (29), Pym *et al*. (30) and Carter *et al*. (31) were the first to report the use of the right gastroepiploic artery (RGEA) in coronary artery surgery. At the beginning of the 90s, the RGEA was the third most used arterial graft, after the two IMA, but it later fell into disuse, because of the wide acceptance of the radial artery. The radial artery is used for coronary artery surgery as a free graft and nowadays, has largely replaced the venous grafts that are used in a similar fashion. Good long-term results were reported from the revival of its use by Acar *et al.* (32). Tatoulis *et al.* (33) proved 94% patency after the first year and 89% after four years. In the conclusion of the same study, apart from the type of graft, the patency was also associated with the target vessel, as well as with the degree of stenosis of the vessel. In the latter case, the four year patency of the radial artery, when the vessel stenosis was >80%, was 92%. Otherwise, it was 83%. The poorest patency was seen in anastomoses of a moderately stenotic right coronary artery with a pedicled or free right IMA, or with a radial artery. This observation could provide justification for the recommendation of Suma *et al.* (29) to use a venous graft in such cases. In these days of drug eluting stents, it might be preferable to carry out supplementary angioplasty after reperfusion of the left system in cases with a moderately diseased right coronary artery.

Atheromatous lesions of the ascending aorta in patients who are undergoing coronary ByPass surgery are seen in about 13% of cases (34). Additionally, given that one third of patients who undergo coronary ByPass nowadays, are aged over 70 years and fraction that is tending to increase the problem of manipulating, the ascending aorta is likely to become even greater than at present (*Data Analysis of the Society of Thorac Surgeons National Cardiac Surgery Database*). The avoidance of any manipulation of the ascending aorta, using the technique of OPCAB and the aorta-non-touch technique, leads to excellent results, minimizing or eliminating the incidence of stroke or aortic dissection (35).

Based on the points made by the studies mentioned above, we have arranged in clinical practice to combine three principles. Complete arterial revascularization, avoidance of extracorporeal circulation through the use of OPCAB and avoidance of manipulations of ascending aorta. We were thus lead to create the arterial "Π-Circuit-Greek Pi-Circuit", which is based on the flow though one or two pedicled IMA, that, as the basis of composite grafts, acquire the ability of multiple connections with the coronary net via peripheral anastomoses, single or sequential, with the diseased vessels. During the last 12 years [2001-2013], we have implemented the "Π-Circuit-Greek Pi-Circuit" in combination with OPCAB, in 2,803 cases, with excellent results. Namely, 0.32% seven days mortality and no cases of stroke. A fraction of the above number, 1,077 patients were operated with the exclusive use of both IMA's, using compositions and sequential grafting. In the pre-operative analysis 84.5% were male patients, 6.7% diabetics, 7.2% had renal insufficiency, 1.1% were on dialysis, 146 patients had injection fraction 25-45% and 114 patients below that 25%. The average age of the patients was 66 years old. The total number of the performed sequential anastomoses was 1,454 in 569 patients. The 30 days mortality was 7 to 1,077 (0.64%) and the total cumulative 10 years survival 91.6%. Other complications, perioperatively, were post-operative bleeding 1.3%, hemodynamic instability 0.3%, sternal wound complications 1.2%, gastrointestinal complications 1.6% and post-operative atrial fibrillation 206 to 1,077 (21.2%). Pre-operative IABP was used in 19 patients and post-operative use in 14 patients. In a three months period, postoperatively, five patients had acute CVA (<0.5%), three of them with a history of atrial fibrillation and two with history of carotid disease. The above results were presented at the 62th Congress of ESCVS, which was held in Germany, March 2013.

In conclusion, combining literature with personal experience, I could summarize as follows: the use of extracorporeal circulation is well tolerated by patients of low or medium risk and facilitates surgical procedures. In experienced surgical hands, OPCAB is the method of choice in high risk patients. The use of at least one mammary artery in the LAD, and even better two pedicled IMA, is the cornerstone of coronary artery surgery nowadays, while the use of skeletonized grafts offers only advantages. In patients with three-vessel disease, the choice of third graft should be based on age, target, degree of stenosis of the coronary vessel and the surgeon's experience. The main aim in younger patients should be complete arterial reperfusion. In the aged and in patients with an atheromatous ascending aorta, the aorta-non-touch technique should be used. Reperfusion of the left-sided bed with arterial grafts is associated with a better long-term outcome, while reperfusion of the right bed is based on the degree of stenosis. The choice of minimally invasive access, for reperfusion of the LAD, alone or in combination with PCI for the remaining vessels, is a safe procedure and one that may well predominate in the future. Robotic surgery and the use of automatic anastomoses, still have some way to go, before they are proved to be safe, effective and widely applicable. The use of the arterial "Π-Circuit-Greek Pi-Circuit" combines the advantages of OPCAB surgery, use of total arterial grafting and the avoidance of manipulation of the aorta. In experienced surgical hands and in a team devoted to the method, the early and medium-term results are excellent and seem to eliminate the occurrence of stroke.

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