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On-pump versus off-pump coronary artery bypass graft surgery. What do the evidences show?

Revascularização cirúrgica do miocárdio com versus sem circulação extracorpórea. O que mostram as evidências?

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Abstract

The main purpose of the off-pump coronary artery bypass surgery is to reduce morbidity and mortality due cardiopulmonary bypass. However, even though many studies have shown that off-pump coronary artery bypass is feasible and provides hospital morbidity and mortality similar to the on-pump coronary artery bypass graft surgery, probably better in some aspects, its long-term results have been questioned, since some trials have shown reduced survival with off-pump coronary artery bypass. It is likely that incomplete revascularization and/or poor graft patency with off-pump coronary artery bypass probably are responsible for such unfavorable outcome.

Descriptors: **Myocardial revascularization. Coronary artery bypass. Coronary artery bypass, off-pump. Evidence-based medicine.**

Resumo

A proposta da revascularização do miocárdio sem emprego da circulação extracorpórea visa à diminuição da morbimortalidade decorrente dos potenciais efeitos deletérios da circulação extracorpórea. Todavia, embora a maioria dos estudos demonstre que a revascularização sem circulação extracorpórea é factível e forneça resultados similares à operação com circulação extracorpórea, no que se refere à morbimortalidade hospitalar, e pode mesmo diminuir a incidência de alguns eventos, sua eficácia a médio e longo prazo tem sido questionada. Alguns estudos demonstram menor sobrevida em pacientes submetidos à revascularização do miocárdio sem circulação extracorpórea, levantando a hipótese de que a revascularização incompleta e/ou a pior evolução dos enxertos realizados na operação sem circulação extracorpórea em comparação à operação com circulação extracorpórea, observadas em alguns estudos, seriam responsáveis por essa evolução desfavorável.

Descritores: **Revascularização miocárdica. Ponte de artéria coronária. Ponte de artéria coronária sem circulação extracorpórea. Medicina baseada em evidências.**

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Abbreviations , acronyms & symbols	
CPB	Cardiopulmonary bypass
CVA	Cerobrovascular accidents
PCT	Prospective clinical trials
EuroSCORE	European System for Cardiac Operative Risk Evaluation

INTRODUCTION

It is undisputed that the advent of cardiopulmonary bypass (CPB) favors the development of cardiac surgery. Despite the continuous evolution, it is undeniable that the CPB has harm potential as a result of pathophysiological processes that are inherent and can result in tissue damage and organ dysfunction [1]. Moreover, there is considerable risk of cerebrovascular accidents (CVA) in cardiovascular surgeries, partly resulting from events related to CPB [2,3].

Vasilii Kolesov [4,5] has been considered one of the pioneers of coronary artery bypass grafting and published in 1967 their clinical series using the internal thoracic artery anastomosed to the coronary arteries without use of CPB [6]. However, his option for OPCAB was not due to lack of apparatus for its performance, but by recognizing its deleterious effects [7], especially in the early stage of clinical use. In one of his articles he had written: "*Although cardiopulmonary bypass is safe and reliable ..., the overall inflammatory response after cardiopulmonary bypass is too intense to justify its use for CABG*" [4].

Although the use of CPB for performing the CABG has gained popularity, driven by the improvement of CPB devices and the publication of the excellent results of revascularization with its use [8,9], some surgeons continued to defend that revascularization surgery could offer even better results without the use of CPB, decreasing the morbidity and mortality associated with CPB [10-12].

As the interest in the use of revascularization without CPB was gradually increasing, especially meeting the challenges posed by the progressive evolution of percutaneous procedures, several issues have emerged:

a) Is the CABG without the use of CPB safe?

b) Does it really reduce hospital morbidity and mortality?

c) Are the results comparable to those of surgery with CPB, especially with regard to security, survival and quality of grafts?

d) Is it possible to perform the full revascularization using the method?

e) It the method reproducible?

Thus, the search for answers to these questions led to the development of several studies, progressively building the body of evidence. It is necessary for surgeons to critically assess the available evidence and know how to employ them in clinical practice.

Hospital morbidity and mortality

The first investigations were retrospective analyzes, especially for large databases, and small observational studies. Most of these studies showed that OPCAB decreased hospital morbidity and mortality [13-15] or had mortality and morbidity similar to CABG with CPB [16]. Thus, the results of prospective clinical trials with random allocation (PCT) began to appear, initially with small samples and low-risk patients. One of the first of these studies was of Gerola et al. [17], which showed that although the hospital mortality in patients undergoing surgery without CPB was lower than that observed in patients undergoing surgery with CPB, the difference was not significant, as well as the differences observed in the incidence of postoperative complications.

In 2009, the results of the first PCT with extensive sampling performed by the research group of Veteran Affairs, North America, the ROOBY Study Group [18], were published. In this study, 2023 patients were randomly assigned to undergo CABG with or without CPB. The results showed that OPCAB provided similar results to surgery with CPB with respect to hospital mortality.

In 2012, the results with 30 days of ECP performed by CORONARY group [19], a multicenter, multinational study that enrolled more than 4,700 patients have been published. This study showed that despite the hospital mortality is similar between surgery with and without CPB, OPCAB significantly reduced the need for transfusion and reoperation for bleeding, in addition to the incidence of acute renal failure and respiratory complications.

Even with regard to hospital mortality, results of recent meta-analyzes [20,21] have shown that apparently the general population of coronary mortality in patients operated with and without cardiopulmonary is similar.

Stroke

The incidence of stroke after cardiac surgery ranges from 3% to 9%, and its effect on postoperative morbidity is significant and can increase mortality from 4% to 19% [3]. Three different mechanisms can cause perioperative stroke: cerebral perfusion deficit, embolic events, and the inflammatory response, which in turn can also magnify the effects of other mechanisms [2]. Thus, as part of the stroke is closely connected to the CPB, it seems logical that its exclusion may decrease the incidence of perioperative stroke.

Recent meta-analyzes that included several PCT [20-23] and analysis of databases [24] shows that OPCAB is associated with lower risk of stroke. But in the last two large prospective trials, ROOBY [18] and the CORONARY groups [19], the incidence of stroke were similar in both surgeries, both in the first month as after one year [25].

The greater statistical power of the meta-analyzes to detect differences may explain this discrepancy in the results, although the meta-analysis may be influenced by selection bias in clinical trials. In recent meta-analysis filtered by the COCHRANE [26] it was observed a lower risk of stroke in OPCAB when considering all selected studies, but when the analysis was restricted to studies with low risk of bias, the difference was not significant. Also, different rules and protocols for the detection of postoperative stroke may also explain the differences between studies.

Moreover, probably the most strokes that occur in coronary artery bypass operations are not directly related to the CPB, but the manipulation of atherosclerotic aorta, especially its clamping. Thus, in off-pump surgeries the manipulation of the ascending aorta for confection of proximal anastomoses is certainly one of the predominant causes of embolic stroke. Thus, some argue that on-pump CABG surgery, but without aortic clamping and/or performing proximal anastomoses of vascular grafts, with the heart beating and/or under fibrillation, may result in a decrease in the incidence of stroke. We should know that the cannulation of the aorta and the femoral vessels and the turbulent flow caused by arterial cannulas may also result in embolization of atherosclerotic material.

Survival

Although many studies show that early mortality of OPCAB is comparable to that obtained with the use of CPB, but lower in some aspects, the results related to medium and long term are controversial.

By assessing the follow-up between six and eight years of 401 patients who participated in two PCT (BHACAS I and II) Angeli et al. [27] observed that survival free of cardiac events, including death, was similar to surgeries with and without CPB. A similar result was observed in the MASS III [28] study after five years of follow-up. Puskas et al. [29] observed a trend toward greater survival in patients undergoing surgery without CPB which reached significance in the fifth year of follow-up, but no significant difference in the seventh year.

Studies of ROOBY and CORONARY groups provided divergent results. In the ROOBY [18] study group, after one year of follow-up the authors observed significantly higher incidence of composite outcomes, including mortality from cardiac causes in patients undergoing surgery with CPB, although when we considered all-cause mortality the difference was not significant. The results with one year follow-up from the CORONARY study group [25] showed no significant difference between patients undergoing surgery with and without CPB in relation to primary compound outcomes, the rate of new coronary revascularization, quality of life or neurocognitive function.

The authors comment that this divergence of results from the ROOBY study is due to important differences between the two studies. The CORONARY study recruited more than twice as many patients in general with more comorbidities, and only allowed the participation of surgeons with experience in OPCAB, which resulted in lower conversion rate (7.9% vs. 12.4%) and need for further revascularization at 30 days and 1 year (0.6 % vs. 3.5%).

Meta-analyzes and systematic reviews of recently published prospective studies [26,30,31] show a higher risk of late mortality for patients undergoing surgery without CPB. It is speculated that this trend may be due to an increased probability of incomplete revascularization in off-pump CABG.

Complete revascularization

Given the potential prognostic implications of incomplete myocardial revascularization [32,33], this has been an important concern in studies comparing CABG with and without CPB, but whose results have also shown contradictory. Several authors have observed that the number of distal anastomoses is significantly lower and/or higher occlusion rate of grafts in patients undergoing OPCAB [18,22,26,28,34-36], others found no significant differences in the evolution of grafts [25,37-40] or quality of the anastomosis [41].

Currently, it is considered that the "index of complete revascularization" (number of grafts divided by the number of grafts needed) is more important than the absolute number of distal anastomoses. Magee et al. [42] assessing the surgical and angiographic data prospectively collected from 945 patients included in a database noted that although the number of grafts in off-pump CABG was lower, the rate of complete revascularization was generally similar between patients undergoing surgery with and without CPB. However, we found that surgeons who performed OPCAB in less than 25% of patients had complete revascularization rate significantly lower.

On- and off-pump CABG surgery in high-risk patients

Considering that the ability to reduce the risk of occurrence of a specific outcome provided by a given treatment may keep constant, when treatment is employed in population with higher risk of this outcome, so the outcome has a higher incidence in this group, the lower the required number of patients to demonstrate that the benefit of treatment [43].

Thus, investigations in order to compare the results of revascularization with and without cardiopulmonary bypass in high-risk groups has emerged, although there are still few ECP and usually with relatively small samples. Two recent PCT [44,45], in which the operation with or without cardiopulmonary bypass were compared in patients aged over 75 years showed no significant difference in hospital mortality and survival at 6 months and 1 year.

Cavallaro et al. [23], when assessing the results of over 80,000 revascularization with and without cardiopulmonary bypass in a group of patients considered of high risk (≥ 85 years, COPD, renal failure, peripheral artery disease and aortic atherosclerosis), observed that the only event with significantly different incidence was stroke, lower in the subgroup of patients aged ≥ 80 years and/or patients with peripheral artery disease or aortic atherosclerosis.

For the patients considered of high risk by EuroSCORE (score>5), Moller et al. [46] found no significant difference in the incidence of major cardiac events, but noted a higher all-cause mortality after three years in the off-pump group. Lemma et al. [47] in a multicenter PCT (on-off study) reported a lower incidence of composite primary outcomes, including hospital mortality in patients operated without CPB, although the difference in the incidence of each event were not considered individually significant. Marui et al. [24], when assessing a multicenter registry in Japan (CREDO-Kyoto), observed that in the substrate of high risk patients (EuroSCORE ≥ 6) the OPCAB was associated with lower risk of short- and long-term stroke. However, no survival benefit was observed regardless of the level of preoperative risk.

In patients with left ventricular dysfunction both prospective trials, with [48] and without random allocation [49] and meta-analyzes [35] or retrospective analyzes of large databases with risk adjustments [50] have shown less morbidity in patients operated without CPB, the same occurring in diabetic patients [51,52].

Critical analysis of outcomes

Although prospective clinical trials with random allocation are at the top of the hierarchical pyramid to provide evidence, such studies are not free of systematic error (bias) caused by inadequately designed and/or performed projects.

Inadequate sample size, selection bias and/or assignment and/or assessment, co-intervention, follow-up loss, lack of external validation and analysis of compound events should be considered in the critical analysis of the studies, and often explain the divergent results. We must also consider that even properly designed and performed projects may produce results that do not reflect reality, the so-called "random error" or "type I error or a" or whose probability of occurrence is given by "*P* value" in statistical tests [53].

Even though it seems counterintuitive when we do not observe significant differences in hospital mortality when it stops using known method that imposes potential damage, such as cardiopulmonary bypass, for example, it should be remembered that the sample size required to observe significant differences in rare events is high. Using the chi-square two-tailed test with correction for continuity (Fisher's exact test) with a "*P*" value of 0.05 and 80% power to detect a 40% reduction in mortality rate, for example, of 2% to 1.2%, a sample of more than 8,000 patients would be required, and reduction of 3% to 1.8% a sample of 5,400 patients (G* Power 3.1.5 software, Heinrich Heine University Düsseldorf). Thus, this difficulty can be called "Pollyanna effect", or that is, there will always be difficulty in demonstrating the possibility of improvement when everything is doing well.

The meta-analysis, although increasing the statistical power by aggregating samples of various studies, are also not exempt from be biased due to the use of inappropriate methodology for the selection of included trials and/or errors in the statistical analysis. Moreover, although there are sophisticated statistical methods aimed at verifying the absence of random assignment (propensity score) in observational studies, these analyzes still carry residual risk of bias caused by not measured "confounding factors", and may underestimate possible deleterious effects with the treatment [26,53].

In a recent filtered systematic review performed by Cochrane Database of Systematic Reviews [26], the authors warned that from the 86 trials included in the review, only 10 had low risk of bias, 26 studies had a high risk of bias observation ("not blinded") despite being considered properly "randomized", and in the other 50 studies, the risk of allocation bias was undefined or had the risk of high or indefinite observation bias. In this review, which did not include the results of a year from the CORONARY study group [25], it was found that when compared to surgery with CPB the OPCAB increased the risk of death from any cause, provided a smaller number of distal anastomoses. And although the risk of stroke was lower in the off-pump surgery, when we assessed only the data from the trials with low risk of bias the difference disappeared.

Importantly, not only in medical practice the best evidence should be considered, but the physician has an obligation to assess each particular clinical situation, considering also the values and expectations of the patient, as well as his clinical experience [53]. It should also be alert to the fact that in general the events that compose the "composite outcomes" do not have all the same "value", especially for patients and they should be considered separately. We should consider that although certain treatment may not be beneficial to the general population, it may be in certain subgroups, and the opposite is also possible, and that the potential harm of treatment should also be considered in assessing the risk/benefit.

CONCLUSION

We can say that, given the available evidence, CABG with CPB remains the standard operation, but that CABG without CPB is feasible with a similar operation with hospital morbidity and mortality similar to on-pump surgery, but with potential to reduce morbidity and mortality in hospital subgroups at higher risk. However, further studies are needed

to assess its use in these subgroups, because although OPCAB may provide benefits, it also has the potential to cause harm, like any treatment.

Considering that the trend toward shorter survival with OPCAB observed in some studies may be related to incomplete revascularization and/or higher rates of grafts with unsatisfactory progress, which seems more likely with less experienced surgeons with the technique, it is prudent to consider that OPCAB is not a surgery that should be performed routinely by any cardiac surgeon, but due to its beneficial potential in specific situations, every surgeon should enable himself to perform it through proper training and use of specific available technology.

Authors' roles & responsibilities	
AJR	Author, review and drafting
PRB	Author, review and drafting
PVA	Coauthor, bibliographic survey, formatting, writing

REFERENCES

1. Warren OJ, Smith AJ, Alexiou C, Rogers PL, Jawad N, Vincent C, et al. The inflammatory response to cardiopulmonary bypass: part 1 - mechanisms of pathogenesis. J Cardiothorac Vasc Anesth. 2009;23(2):223-31.

2. Baufreton C. Role of surgical factors in strokes after cardiac surgery. Arch Cardiovasc Dis. 2010;103(5):326-32.

3. McKhann GM, Grega MA, Borowicz LM Jr, Baumgartner WA, Selnes OA. Stroke and encephalopathy after cardiac surgery: an update. Stroke. 2006;37(2):562-71.

4. Konstantinov IE. Vasilii I Kolesov: a surgeon to remember. Tex Heart Inst J. 2004;31(4):349-58.

5. Berry D. Vasilii Kolesov a surgeon to remember: a pioneer in the field of coronary artery bypass surgery. Eur Heart J. 2010;31(8):898-9.

6. Kolessov VI. Mammary artery-coronary artery anastomosis as method of treatment for angina pectoris. J Thorac Cardiovasc Surg. 1967;54(4):535-44.

7. Kolesov VI, Levin AO, Vinogradov AG, Danilova LD. On changes of morphological and functional properties of the blood and hemodynamics during the use of the Niiekhaii (AIK-59) and Baliuzek's (ISL-2) artificial circulation apparatus. Grudn Khir. 1963;5:34-40.

8. Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: operative technique. Ann Thorac Surg. 1968;5(4):334-9.

9. Favaloro RG. Saphenous vein graft in the surgical treatment of coronary artery disease. Operative technique. J Thorac Cardiovasc Surg. 1969;58(2):178-85.

10. Buffolo E, Andrade JC, Succi J, Leão LE, Gallucci C. Direct myocardial revascularization without cardiopulmonary bypass. Thorac Cardiovasc Surg. 1985;33(1):26-9.

11. Buffolo E, Andrade JC, Succi JE, Leão LE, Cueva C, Branco JN, et al. Direct myocardial revascularization without extracorporeal circulation. Description of the technic and initial results. Arq Bras Cardiol. 1983;41(4):309-16.

12. Trapp WG, Bisarya R. Placement of coronary artery bypass graft without pump oxygenator. Ann Thorac Surg. 1975;19(1):1-9.

13. Li Z, Yeo KK, Parker JP, Mahendra G, Young JN, Amsterdam EA. Off-pump coronary artery bypass graft surgery in California, 2003 to 2005. Am Heart J. 2008;156(6):1095-102.

14. Mack MJ, Pfister A, Bachand D, Emery R, Magee MJ, Connolly M, et al. Comparison of coronary bypass surgery with and without cardiopulmonary bypass in patients with multivessel disease. J Thorac Cardiovasc Surg. 2004;127(1):167-73.

15. Puskas JD, Edwards FH, Pappas PA, O'Brien S, Peterson ED, Kilgo P, et al. Off-pump techniques benefit men and women and narrow the disparity in mortality after coronary bypass grafting. Ann Thorac Surg. 2007;84(5):1447-54.

16. Chu D, Bakaeen FG, Dao TK, LeMaire SA, Coselli JS, Huh J. On-pump versus off-pump coronary artery bypass grafting in a cohort of 63,000 patients. Ann Thorac Surg. 2009;87(6):1820-6.

17. Gerola LR, Buffolo E, Jasbik W, Botelho B, Bosco J, Brasil LA, et al. Off-pump versus on-pump myocardial revascularization in low-risk patients with one or two vessel disease: perioperative results in a multicenter randomized controlled trial. Ann Thorac Surg. 2004;77(2):569-73.

18. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med. 2009;361(19):1827-37.

19. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E; CORONARY Investigators, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med. 2012;366(16):1489-97.

20. Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ. Off-pump vs. on-pump coronary artery bypass surgery: an updated

meta-analysis and meta-regression of randomized trials. Eur Heart J. 2012;33(10):1257-67.

21. Sá MP, Ferraz PE, Escobar RR, Martins WN, Lustosa PC, Nunes EO, et al. Off-pump versus on-pump coronary artery bypass surgery: meta-analysis and meta-regression of 13,524 patients from randomized trials. Rev Bras Cir Cardiovasc. 2012;27(4):631-41.

22. Moller CH, Penninga L, Wetterslev J, Steinbrüchel DA, Gluud C. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: systematic review with meta-analyses and trial sequential analyses. Eur Heart J. 2008;29(21):2601-16.

23. Cavallaro P, Itagaki S, Seigerman M, Chikwe J. Operative mortality and stroke after on-pump vs. off-pump surgery in high-risk patients: an analysis of 83 914 coronary bypass operations. Eur J Cardiothorac Surg. 2013.

24. Marui A, Okabayashi H, Komiya T, Tanaka S, Furukawa Y, Kita T; CREDO-Kyoto Investigators, et al. Benefits of off-pump coronary artery bypass grafting in high-risk patients. Circulation. 2012;126(11 Suppl 1):S151-7.

25. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E; CORONARY Investigators, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. N Engl J Med. 2013;368(13):1179-88.

26. Moller CH, Penninga L, Wetterslev J, Steinbrüchel DA, Gluud C. Off-pump versus on-pump coronary artery bypass grafting for ischaemic heart disease. Cochrane Database Syst Rev. 2012;3:CD007224.

27. Angelini GD, Culliford L, Smith DK, Hamilton MC, Murphy GJ, Ascione R, et al. Effects of on- and off-pump coronary artery surgery on graft patency, survival, and health-related quality of life: long-term follow-up of 2 randomized controlled trials. J Thorac Cardiovasc Surg. 2009;137(2):295-303.

28. Hueb W, Lopes NH, Pereira AC, Hueb AC, Soares PR, Favarato D, et al. Five-year follow-up of a randomized comparison between off-pump and on-pump stable multivessel coronary artery bypass grafting. The MASS III Trial. Circulation. 2010;122(11 Suppl):S48-52.

29. Puskas JD, Williams WH, O'Donnell R, Patterson RE, Sigman SR, Smith AS, et al. Off-pump and on-pump coronary artery bypass grafting are associated with similar graft patency, myocardial ischemia, and freedom from reintervention: long-term follow-up of a randomized trial. Ann Thorac Surg. 2011;91(6):1836-42.

30. Bakaeen FG, Chu D, Kelly RF, Ward HB, Jessen ME, Chen GJ, et al. Performing coronary artery bypass grafting off-pump may compromise long-term survival in a veteran population. Ann Thorac Surg. 2013;95(6):1952-8.

31. Takagi H, Mizuno Y, Niwa M, Goto SN, Umemoto T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. A meta-analysis of randomized trials for repeat revascularization following off-pump versus on-pump coronary artery bypass grafting. Interact Cardiovasc Thorac Surg. 2013;17(5):878-80.

32. Farooq V, Serruys PW, Garcia-Garcia HM, Zhang Y, Bourantas CV, Holmes DR, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. J Am Coll Cardiol. 2013;61(3):282-94.

33. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. Circulation. 2013;128(2):141-51.

34. Hattler B, Messenger JC, Shroyer AL, Collins JF, Haugen SJ, Garcia JA; Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group, et al. Off-Pump coronary artery bypass surgery is associated with worse arterial and saphenous vein graft patency and less effective revascularization: Results from the Veterans Affairs Randomized On/Off Bypass (ROOBY) trial. Circulation. 2012;125(23):2827-35.

35. Jarral OA, Saso S, Athanasiou T. Off-pump coronary artery bypass in patients with left ventricular dysfunction: a meta-analysis. Ann Thorac Surg. 2011;92(5):1686-94.

36. Takagi H, Matsui M, Umemoto T. Lower graft patency after off-pump than on-pump coronary artery bypass grafting: an updated meta-analysis of randomized trials. J Thorac Cardiovasc Surg. 2010;140(3):e45-7.

37. Lingaas PS, Hol PK, Lundblad R, Rein KA, Mathisen L, Smith HJ, et al. Clinical and radiologic outcome of off-pump coronary surgery at 12 months follow-up: a prospective randomized trial. Ann Thorac Surg. 2006;81(6):2089-95.

38. Magee MJ, Alexander JH, Hafley G, Ferguson TB Jr, Gibson CM, Harrington RA; PREVENT IV Investigators, et al. Coronary artery bypass graft failure after on-pump and off-pump coronary artery bypass: findings from PREVENT IV. Ann Thorac Surg. 2008;85(2):494-9.

39. Nathoe HM, van Dijk D, Jansen EW, Suyker WJ, Diephuis JC, van Boven WJ; Octopus Study Group, et al. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. N Engl J Med. 2003;348(5):394-402.

40. Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, 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(15):1841-9.

41. Cerqueira Neto FM, Guedes MA, Soares LE, Almeida GS, Guimaraes AR, Barreto MA, et al. Flowmetry of left internal

thoracic artery graft to left anterior descending artery: comparison between on-pump and off-pump surgery. Rev Bras Cir Cardiovasc. 2012;27(2):283-9.

42. Magee MJ, Hebert E, Herbert MA, Prince SL, Dewey TM, Culica DV, et al. Fewer grafts performed in off-pump bypass surgery: patient selection or incomplete revascularization? Ann Thorac Surg. 2009;87(4):1113-8.

43. Chatellier G, Zapletal E, Lemaitre D, Menard J, Degoulet P. The number needed to treat: a clinically useful nomogram in its proper context. BMJ. 1996;312(7028):426-9.

44. Diegeler A, Börgermann J, Kappert U, Breuer M, Böning A, Ursulescu A; GOPCABE Study Group, et al. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. N Engl J Med. 2013;368(13):1189-98.

45. Houlind K, Kjeldsen BJ, Madsen SN, Rasmussen BS, Holme SJ, Nielsen PH; DOORS Study Group, et al. On-pump versus off-pump coronary artery bypass surgery in elderly patients: results from the Danish on-pump versus off-pump randomization study. Circulation. 2012;125(20):2431-9.

46. Moller CH, Perko MJ, Lund JT, Andersen LW, Kelbaek H, Madsen JK, et al. Three-year follow-up in a subset of high-risk patients randomly assigned to off-pump versus on-pump coronary artery bypass surgery: the Best Bypass Surgery trial. Heart. 2011;97(11):907-13.

47. Lemma MG, Coscioni E, Tritto FP, Centofanti P, Fondacone C, Salica A, et al. On-pump versus off-pump coronary artery bypass surgery in high-risk patients: operative results of a prospective randomized trial (on-off study). J Thorac Cardiovasc Surg. 2012;143(3):625-31.

48. Masoumi M, Saidi MR, Rostami F, Sepahi H, Roushani D. Off-pump coronary artery bypass grafting in left ventricular dysfunction. Asian Cardiovasc Thorac Ann. 2008;16(1):16-20.

49. Caputti GM, Palma JH, Gaia DF, Buffolo E. Off-pump coronary artery bypass surgery in selected patients is superior to the conventional approach for patients with severely depressed left ventricular function. Clinics (Sao Paulo). 2011;66(12):2049-53.

50. Keeling WB, Williams ML, Slaughter MS, Zhao Y, Puskas JD. Off-pump and on-pump coronary revascularization in patients with low ejection fraction: a report from the society of thoracic surgeons national database. Ann Thorac Surg. 2013;96(1):83-8.

51. Emmert MY, Salzberg SP, Seifert B, Rodriguez H, Plass A, Hoerstrup SP, et al. Is off-pump superior to conventional coronary artery bypass grafting in diabetic patients with multivessel disease? Eur J Cardiothorac Surg. 2011;40(1):233-9.

52. Renner A, Zittermann A, Aboud A, Pühler T, Hakim-Meibodi K, Quester W, et al. Coronary revascularization in diabetic patients: off-pump versus on-pump surgery. Ann Thorac Surg. 2013;96(2):528-34.

53. Guyatt G, Rennie D, Meade M, Cook D. Users' guides to the medical literature: a manual for evidence-based clinical practice. 2nd ed: McGraw-Hill Professional; 2008.