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CRITICISM TO THE REVASCULARIZATION INDICATIONS ATTAINED IN THE 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH CHRONIC CORONARY DISEASE.

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RESUMO

Este estudo faz uma critica as recomendações sobre revascularização em pacientes portadores de doença arterial coronariana crônica contidas na diretriz de 2023 da *American Heart Association e American College of Cardiology*. Na maioria das recomendações, os autores da diretriz utilizaram desfechos que não foram os primários dos ensaios clínicos randomizados e que seriam no máximo geradores de hipóteses para novos ensaios clínicos, além de reportarem estudos que carecem de contemporaneidade e outros que envolveram pacientes com sindrome coronariana aguda ou oclusão crônica das coronarias.

Palavras-chave: Doença arterial coronariana cronica, Doença arterial coronariana estável, Angina estável, Doença isquêmica do coração, Isquemia cronica

ABSTRACT

This study criticizes the recommendations on revascularization in patients with chronic coronary artery disease contained in the 2023 guideline from the American Heart Association and American College of Cardiology. In most of the recommendations, the authors of the guideline used outcomes that were not the primary outcomes of contemporary randomized clinical trials and that would, at best, be hypotheses' generating for new clinical trials, in addition to reporting studies that lack contemporaneity and others that involved patients with acute coronary syndrome or chronic coronary total occlusion.

Keywords: Chronic coronary artery disease, Stable coronary artery disease, Stable angina, Ischemic heart disease, Chronic ischemia

RESUMEN

Este estudio hace una crítica a las recomendaciones sobre la revascularización en pacientes con enfermedad arterial coronaria crónica contenidas en la directriz de 2023 de la *American Heart Association y el American College of Cardiology*. En la mayoría de las recomendaciones, los autores de la directriz utilizaron desenlaces que no fueron los principales en los ensayos clínicos aleatorizados y que, en el mejor de los casos, servirían como generadores de hipótesis para nuevos ensayos clínicos. Además, se citaron estudios que carecen de contemporaneidad y otros que involucraron a pacientes con síndrome coronario agudo o con oclusión crónica de las coronarias.

Palabras clave: Enfermedad arterial coronaria crónica, Enfermedad arterial coronaria estable, Angina estable, Enfermedad isquémica del corazón, Isquemia crónica

INTRODUCTION

Clinical practice guidelines are valuable tools that guide doctors' conduct in a series of diseases with high prevalence in the population. The 2023 guideline on chronic coronary disease (CCD), written by the American Heart Association and the American College of Cardiology in conjunction with other American entities is no exception to this rule and although it is designed for application in American medical practice, it gains relevance for use in care of patients affected by this disease worldwide (1).

The guidelines help healthcare professionals make the best decision-making, with the aim of offering the best possible care to patients, aligned with their expectations, needs and interests. Furthermore, they are important documents for governments, payers and healthcare providers by providing a set of recommendations that help and guide decisions about coverage of diagnostic and therapeutic procedures related to diseases with high prevalence in the population.

In this 2023 guideline, the authors say that revascularization is an evolving topic and emphasize that recommendations are typically based on the results of larger randomized controlled trials (RCTs), meta-analyses, or both encompassing a wide range of knowledge on the subject. but they recognize that RCTs do not cover all the nuances involved with the topic, nor do they address all issues comprehensively. Based on this, they made a concentrated effort to stay within the strongest evidence to define these revascularization recommendations in patients with CCD.

Within this principle, reviewing chapter 5 dedicated specifically to myocardial revascularization, we are concerned, among other things, with the recommendations resulting from the analysis of some studies that do not clearly reflect the reality of contemporary care provided to patients with CCD, in addition to events that do not reflect the primary outcomes of many of these studies. For this reason, we performed a careful review of the references used by authors of the guideline for revascularization recommendations.

Because the chapter is long, the criticism will be restricted to the indications for revascularization set out in the table of the document, page e61, which is, in fact, the core of the document.

Starting with the goals of revascularization, in the table there are six recommendations and two statements on the cost-effectiveness of revascularization (Table-1).

The first indication has Class of Recommendation (COR) 1, Level of Evidence (LOE) A for improvement of symptoms in patients with CCD, obstructive coronary artery disease (CAD) amenable to revascularization, and lifestyle-limiting angina despite guideline-directed management and therapy (GDMT). Seven references support these recommendations.

Reference number (1) is the quality of life analysis of the ISCHEMIA study (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) published by Spertus et al, in which the advantage of the invasive strategy over the conservative strategy in relation to improving quality of life was modest, even for very symptomatic patients. In this study, the angina summary score, assessed by the Seattle questionnaire, was higher after 36 months with the invasive strategy than with the conservative one, and this difference was more pronounced in patients with more frequent angina (2). Although this observation is correct, it is necessary to emphasize that, upon analyzing Table 4 in the study's supplementary appendix, we observed that the differences are very modest at the end of 48 months of follow-up. Taking all patients together, the

difference in favor of the invasive strategy is only 3.3 points (86 versus 89.3), while in patients with several episodes of monthly angina the difference is 3.7 points (85.2 versus 88.9), and in patients with daily or weekly angina the difference is 6.3 points (78.9 versus 85.2) (2). Intuitively, one would expect a much more pronounced difference in favor of the invasive strategy.

Table 1 - Goals of revascularization.

COR	LOE	Recommendations
1	A	In patients with CCD and lifestyle-limiting angina despite GDMT and with significant coronary artery stenoses amenable to revascularization, revascularization is recommended to improve symptoms
1	B-R	In patients with CCD who have significant left main disease or multivessel disease with severe LV dysfunction (LVEF ≤ 35%), CABG in addition to medical therapy is recommended over medical therapy alone to improve survival
Cost Value Statement: Intermediate Value	B-NR	In patients with CCD and multivessel disease with severe LV dysfunction, CABG added to optimal medical therapy is of intermediate economic value compared with medical therapy alone
2a	B-R	In patients with CCD and multivessel CAD appropriate for either CABG or PCI, revascularization in addition to GDMT is reasonable to lower the risk of cardiovascular events such as spontaneous MI, unplanned urgent revascularizations, or cardiac death
2a	B-NR	In selected patients with CCD and significant left main stenosis for whom PCI can provide equivalent revascularization to that possible with CABG, PCI is reasonable to improve survival

Decision-making for revascularization

1	A	In patients with CCD who have angina or an anginal equivalent, no previous evaluation for ischemia, and angiographically intermediate stenoses, the use of FFR or other proven nonhyperemic pressure ratios (eg, iFR) is recommended before proceeding with PCI
Cost Value Statement: High Value	B-NR	In patients with CCD undergoing coronary angiography without previous stress testing, the use of invasive FFR to evaluate angiographically intermediate coronary stenosis before proceeding with PCI is a high economic value intervention
1	B-NR	In patients with CCD with complex 3-vessel disease or for whom the optimal treatment strategy is unclear, a Heart Team approach that includes representatives from interventional cardiology and cardiac surgery is recommended to improve patient outcomes

Adapted from de 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines;CCD, chronic coronary disease; GDMT, guideline-direct medical treatament; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio.

Goals of revascularization on page e61

Some points are important when analyzing the quality of life of patients included in the ISCHEMIA study. Firstly, this study is a RCT involving 5,179 patients with stable CAD, moderate to severe myocardial ischemia and EF≥35% that verified whether the addition of rotine coronary angiography followed by revascularization, if feasible, associated with GDMT was superior to the conservative strategy in which angiography was indicated in failure of GDMT to protect against a primary outcome consisting of cardiovascular death, nonfatal acute myocardial infarction (AMI), or hospitalization for heart failure (HF), unstable angina, or aborted sudden death. The analysis of angina-related quality of life was part of the study's key secondary analysis, along with death from cardiovascular causes and non-fatal AMI (3). In other words, the study was not designed to specifically analyze the quality of life related to angina. Secondly, it is necessary to take into account that in patients allocated to the invasive strategy, in a median of 3.2 years of follow-up, 95,6% underwent conventional angiography, but 79.4% underwent revascularization (data taken from table S7 in the supplementtary appendix). Therefore, 20.6% of patients in the invasive strategy did not undergo revascularization, and according to table S8 in the supplementary appendix, of the 421 patients who were not revascularized during follow-up, 221 (52.5%) did not have obstructive CAD, that is, 8.5% of the total number of patients allocated to the invasive strategy, while 111 (26.4%) had unfavorable anatomy for both revascularization surgery (CABG) and percutaneous coronary angioplasty (PCI). Therefore, 4.3% of patients in the invasive strategy did not have anatomy favorable to any revascularization technique. Although the authors did not mention the quality of life of those effectively revascularized, with the data available in the study publication, it can be speculated that this would be one of the reasons for the modest difference found between the two strategies. Thirdly, the ISCHEMIA trial is not a study that compares revascularization associated with GDMT with GDMT alone, it is a comparison between strategies, considering that almost 21% of patients allocated to the invasive strategy did not undergo revascularization most because there was no significant coronary obstruction (Table-2).

Table 2 - ISCHEMIA trial – proportion of revascularized and reason for no revascularization during the follow-up.

Strategy (N)	Angiography N (%)	Revascularization N (%)	Reason for no revascularization	
			Unfavorable anatomy	No obstructive disease
Conservative	667 (25.7)	544 (21.0)	NA	NA
Invasive (2588)	2475 (95.6)	2054 (79.4)	111 (26.4)	221 (52.5)

NA, not available

The reference number (2) deals with the results of five years of follow-up of the FAME 2 study (Fractional flow reserve versus Angiography for Multivessel Evaluation 2) published by Xaplanteris et al (4). This study, which aimed to demonstrate the superiority of PCI guided by fractional flow re-

serve (FFR) associated with GDMT (PCI+GDMT) compared to GDMT alone in patients with CCD and at least one vessel with functionally significant obstruction (FFR <0.80), was designed to randomize 1,632 patients. However, it was prematurely stopped after including only 888 patients due to the "superiority" of PCI in reducing adverse cardiovascular events (MACE), mainly by reducing the need for urgent revascularization (5). In summary, the study was interrupted with only 54.4% of patients randomized and did not reduce mortality or the incidence of acute myocardial infarction (AMI) in five years of follow-up. It is widely known that RCTs interrupted early tend to increase the effects of one intervention over the other, especially when the number of events is less than 200, as was the case with FAME 2. According to Table-2 of the study, 62 primary events occurred in the PCI+GDMT group and 119 in the GDMT alone, that is, a total of 181 events (4). As Guyatt et al. stated about prematurely interrupted studies, the tendency to overestimate the effects of a treatment is particularly harmful because its apparent results are often published in prominent journals, have rapid dissemination in the media, accelerated incorporation into practical guidelines, such as the guideline in question, and in quality assurance initiatives (6). Therefore, guideline authors should be very careful in using FAME 2 results as a basis for decision-making in CCD. However even with the limitations imposed by early interruption, this study shows that in patients with CCD and FFR ≤0.80, starting GDMT and following them for five years does not increase the incidence of non-fatal AMI or death. Actually, this is the "take home message" of the study. Furthermore, there was no formal assessment of the patients' quality of life in this study.

Reference number (3) is an analysis of the quality of life of the EXCEL study (Evaluation of Xience versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) in which there was no comparison between GDMT and revascularization, but between PCI with the use of an Everolimus-eluting stent and CABG in patients with left main coronary artery disease (LMCAD) (7). Therefore, this study should not be used to support the indication of revascularization in comparison to GDMT. The same applies to reference number (4), which is an analysis of the quality of life between PCI and CABG in diabetic patients involved in the FREEDOM study (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease). In this study there was no comparison between GDMT and revascularization (8).

Reference number (5) deals with a study on quality of life in the BARI 2D study (the Bypass Angioplasty Revascularization Investigation Diabetes 2), in which GDMT was compared with revascularization by PCI or CABG (9). Revascularization promoted a statistically significant improvement in quality of life, but as the authors themselves concluded, this difference was too modest to have a clinical impact. Furthermore, in the main study, no difference in the primary outcome (all-cause deaths) was observed between GDMT and revascularization. There was also no difference in the incidence of non-fatal AMI between the two types of treatment. As quality of life was not the primary outcome of the study, any difference observed between treatments is only hypothesis generating (10).

Reference number (6) refers to the "crossover" substudy of the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive DruG Evaluation) published by Spertus et al. In this study, at the end of the first year, quality of life, confirmed by the Seattle questionnaire, was similar between patients treated by revascularization and GDMT, the difference observed in hospitalizations for unstable angina, greater in revascularization (12.4% vs 11.8%) was not statistically significant and there was no difference in the incidence of non-fatal AMI or mortality between treatments (11). Upon reviewing the study, it was observed that these patients represented only 16.1% of the total number

of patients included in the GDMT group. Although in this group of GDMT patients that crossover to revascularization the extent of CAD was identical to those that underwent to revascularization, there were more women and more patients with high cholesterol, more advanced Canadian Cardiovascular Society (CCS) functional class (FC), worse health status, greater physical limitations, greater dissatisfaction with treatment and lower health and quality of life scores among them. In addition, Spertus et al. conclude that among patients allocated to isolated OMT, dissatisfaction with current treatment, degree of angina and, to a lesser extent, health status were associated with early revascularization, but this fact was not associated with an increase in irreversible ischemic events or worsening health status, which according to them, supports the adoption of initial GDMT in CCD with more frequent monitoring of the most symptomatic patients (11).

The last reference, number (7), is a substudy of the ORBITA study (The Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) in which the authors studied the ability of the stress echocardiogram score (echo-stress) pre- randomization in predicting the effectiveness of PCI compared to placebo (sham PCI) (12). There was little evidence that PCI improved angina frequency than placebo, but there was an effect of PCI on angina frequency score in patients with higher echo-stress scores. As the authors emphasize, due to the number of patients studied, there was no evidence that PCI improved physical limitation score, quality of life score, or EuroQOL 5 score compared to placebo. Furthermore, there was no evidence that PCI improved CCS functional class, and that patients with a pre-randomization echo-stress score $\geq$1 had improvements in exercise time. Therefore, although this substudy of the ORBITA trial demonstrated that there was an improvement in the frequency of angina with greater degrees of ischemia detected on stress echo, in general, the quality of life of patients did not improve with PCI compared to the sham procedure. It is surprising that PCI did not produce a greater effect on the quality of life of patients involved in the study, which reinforces how much the placebo effect promoted by PCI has on patients (13).

In summary, it is not understood why the authors used these seven references to support COR I and LOE A to indicate revascularization in the failure of GDMT and using clinical trials such as EXCEL and FREDOOM that did not compare GDMT with revascularization. It would be enough to use the results of the BARI 2D (10), COURAGE (14), MASS II (the Medicine, Angioplasty or Surgery Study II) (15) and ISCHEMIA (3) studies to indicate revascularization in GDMT failure, as in none of these studies a reduction in mortality was demonstrated between the two types of treatment or management strategy (Table-3).

The second recommendation has a COR 1 LOE B-R in favor of CABG to improve the survival of patients with significant left main coronary artery disease (LMCAD) or multivessel CAD associated with severe LV dysfunction ($\leq$35%). Four studies are cited to support the recommendation.

The first reference number (8) is the meta-analysis carried out by Yusuf et al based on RCTs from the 70s and 80s, in which CABG was compared to medical treatment (MT) in patients with CCD with different inclusion criteria. In this meta-analysis, it was demonstrated that CABG prolonged the survival of patients with LMCAD compared to MT. However, at that time MT was restricted to the use of anti-ischemic drugs, without acting to reduce atherosclerotic damage or platelet aggregation as recommended by current guidelines and the number of patients included in the meta-analysis with LMCAD was small (150 patients according to the table 4 of Yusuf's study) (16). In fact, there are no contemporary RCTs that support the reduction in mortality by CABG compared to GDMT in patients with LMCAD. There is only the suggestion that the results of old RCTs could be replicated today.

Table 3 – results of contemporary Randomized Clinical Trials

RCT (year of publication)	All-cause mortality	Cardiovascular death	Outcome	Nonfatal AMI	Stroke
COURAGE (2007):			(primary outcome: death or AMI)		
MT	8.3%	2.1%	18.5%	12.3%	1.8%
PCI	7.6%	2.0%	19.0%	13.2%	2.1%
BARI 2 D (2009):	(primary outcome)		(death, AMI or stroke)		
MT	13.5%	N/A	23.7%	11.6%	2.8%
PCI and CABG	13.2%	N/A	22.6%	10.0%	2.6%
MASS II (2010):			(primary outcome: death, AMI or revascularization)		
MT	31.0%	20.7%	59.1%	20.7%	6.9%
PCI	24.1%	14.3%	42.4%	13.3%	5.4%
CABG	25.1%	10.8%	33.0%	10.3%	8.4%
FAME 2 (2018):			(primary outcome: death, AMI or urgent revascularization)		
MT	5.2%	1.6%	27.0%	12.0%	1.6%
PCI	5.1%	2.5%	13.9%	8.1%	2.7%
ISCHEMIA (2020):			(primary outcome: cardiovascular death, AMI or hospitalization for UA, HF or resuscitated cardiac arrest)		
CONS	8.3%	6.5%	18.2%	11.9%	2.4%
INV	9.0%	5.2%	16.4%	10.3%	2.3%
ISCHEMIA EXTENDED (2023)	13.4%	8.6%	NA	NA	NA
CONS	12.7%	6.4%	NA	NA	NA
INV					

AMI denotes acute myocardial infarction; CABG, coronary artery bypass graft; CONS, conservative strategy; INV, invasive strategy; HF, heart failure; MT, medical treatment; PCI, percutaneous coronary intervention; RCT, randomized clinical trial; UA, unstable angina; ISCHEMIA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; FAME2, Fractional flow reserve versus Angiography for Multivessel Evaluation 2; BARI2D, the Bypass Angioplasty Revascularization Investigation Diabetes 2, COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; MASS II, the Medicine, Angioplasty or Surgery Study II,.

Reference number (9) of the guideline is an observational study from the CASS study, also from the 1980s, in which CABG prolonged the survival of the majority of patients with LMCAD, especially those with severe obstruction and LV dysfunction (17). The same criticisms of Yusuf et al's meta-analysis are applied to this study, because, as already emphasized, the MT of the time lacked contemporaneity and there was no randomization.

The next reference, number (10), is about the STICH trial (Surgical Treatment for Ischemic Heart Failure), in which 1,212 patients with EF≤35 and CAD amenable to CABG were randomized to GDMT alone (602 patients) or CABG associated with GDMT (610 patients) (18). Although in five years

of follow-up there was no statistically significant difference in mortality between the two types of treatment (41% vs 36%; P=0.12), in ten years of follow-up there was lower mortality in those undergoing CABG (66.1% vs 58.9%; P=0.02) (19). It is important to emphasize that patients with single-vessel CAD were also included in the study, that is, there is no study comparing CABG with GDMT in patients with exclusively multivessel CAD associated with severe LV dysfunction.

The ideal would be to separate the recommendation into two, one for LMCAD and the other for significant CAD (not multivessel CAD) associated with severe LV dysfunction. For patients with CCD and significant LMCAD, as there are no contemporary studies comparing revascularization with GDMT and based on the available literature, the recommendation should be CABG with COR 2b LOE C-EO. And for patients with significant CAD associated with severe LV dysfunction (F≤35%), the recommendation should be COR 1, LOE B-R.

Regarding cost-effectiveness, the authors say that in patients with CCD and multivessel CAD associated with severe LV dysfunction, CABG associated with OMT has an intermediate economic value compared to GDMT alone with LOE B-NR and they cite the cost-effectiveness analysis of the STICH trial (20). Again, it is necessary to emphasize that patients with single-vessel CAD were also included in the STICH study.

The next indication is to consider as reasonable revascularization in addition to GDMT with COR 2a LOE B-R for patients with CCD and multivessel CAD amenable to CABG or PCI with the intention of reducing the risk of cardiovascular events such as spontaneous AMI, unplanned revascularization or cardiac death. Supporting this recommendation, the authors of the guideline were based on eight studies.

The first reference is from the ISCHEMIA trial whose results demonstrated that there was no difference between invasive and conservative strategies in relation to the outcome composed of cardiovascular death, non-fatal AMI, non-fatal stroke or hospitalizations for unstable angina, heart failure (HF) or resuscitated cardiac arrest. This trial has no statistical power to analyze isolated components of the primary outcome, therefore differences in any of these components will be only hypothesis-generating. Despite this, no statistically significant difference was found between the strategies with regard to the primary outcome or the individual components of the outcome (3).

Although in the ISCHEMIA trial there was a suggestion of a reduction in spontaneous AMI with the invasive strategy, this was overshadowed by the increase in procedural MI, making the incidence of non-fatal AMI identical in both strategies. Chaitman et al, when analyzing the impact of different definitions of AMI on the incidence, prognosis and comparisons between strategies, showed that the incidence of type 4a or 5 AMI was higher in the invasive strategy, but the incidence of type 1 AMI (spontaneous), type 2 or associated with thrombosis (4b) or restenosis (4c) was reduced by the invasive strategy compared to the conservative strategy (21). However, in the conclusions of the study the authors say: “in contrast to procedural AMI, type 1 AMI (spontaneous) was associated with an increased risk of death and significantly reduced in patients allocated to the invasive strategy, but it was not clear to the study authors whether this reduction could be attributed to revascularization, dual antiplatelet therapy, ascertainment bias or other mechanisms. AMI types 4b and 4c were relatively infrequent, but associated with a higher risk of subsequent death. Longer follow-up may determine whether different types and rates of AMI related to the type of treatment will affect cardiovascular mortality” (21).

A detail not explored by the authors of the guideline is that the incidence of complicated AMI, an event most associated with ST-segment elevation MI, was similar between both invasive and conservative strategies (2.05% versus 2.78%, respectively) (21). In addition, two recent studies attributed higher mortality to patients who developed procedural AMI. Hara et al, analyzing data from the extended SYNTAX trial (The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery), demonstrated that post-PCI AMI, regardless of the diagnostic criteria, is associated with higher mortality in 10 years of follow-up (22). Also, Silvain et al, analyzing 9,081 patients with CCD undergoing PCI who had normal troponin T pre-procedure and who developed type 4a AMI had higher mortality in one year of follow-up (23).

There are at least two problems with including the ISCHEMIA study to support the indication of revascularization for patients with CCD and multivessel disease with the intention of protecting them against spontaneous AMI. The study involved both patients with single- and multivessel disease and was not specifically designed to analyze this outcome, therefore is only hypotheses--generating.

The next study mentioned is MASS II trial, which involved 611 patients with CCD and multivessel CAD with preserved LV function randomized to GDMT, PCI or CABG. At the end of 10 years of follow-up, it was demonstrated that CABG reduced the composite risk of death, non-fatal AMI and the need for revascularization compared to PCI and GDMT, but there was no difference between PCI and GDMT. Although it was not designed and did not have statistical power to compare the incidence of individual components of the primary outcome, CABG reduced the incidence of non--fatal AMI and the need for new or additional revascularization compared to PCI and GDMT, but did not reduce the incidence of all-cause death. Furthermore, there is no mention of the incidence of spontaneous AMI among the three types of treatment and it was not designed to analyze the incidence of cardiovascular death or unplanned revascularization as isolated events (15).

The next study mentioned is a meta-analysis and systematic review by Navarese et al, in which a reduction in cardiac death and spontaneous AMI was observed with revascularization compared to GDMT (24). In this study, the authors included 25 clinical trials with different inclusion criteria, many of which were outdated, such as studies from the 70s and 80s and others involving patients with chronic coronary occlusions and, in at least one of the studies included, the ORBITA trial did not evaluate mortality or incidence of AMI. In this meta-analysis that included more than 19 thousand patients, no difference was demonstrated in all-cause death, non-fatal AMI or stroke between the two types of treatment, but the authors of the guideline emphasized the difference in favor of revascularization for the outcomes of cardiac death, cardiac arrest and spontaneous AMI. In addition to outdated studies regarding GDMT and contemporary revascularization techniques, Navarese et al included trials that did not involve multivessel CAD exclusively and most importantly, the two events were not isolated primary outcomes in any of the studies in the meta-analysis (24).

The other study mentioned was that carried out by Chaitman et al on how different definitions of AMI impact the incidence, prognosis and response to management strategies in the ISCHEMIA trial (21). As previously noted, although spontaneous AMI was more common in the conservative strategy, procedural AMI was more common in the invasive strategy, making the incidence of non-fatal AMI identical in both strategies. Furthermore, it is argued that spontaneous

AMI would be associated with an increased risk of death, but as mortality was identical between the strategies in 7 years of follow-up, it can be speculated that procedural AMI, more common in the invasive strategy, it would also be associated with increased mortality (25).

The next reference is about the FAME 2 study which, as previously mentioned, was prematurely interrupted due to less need for urgent revascularization in patients allocated to PCI+GDMT compared to GDMT alone (5). The results of this study deserve special care because it was interrupted after just over 54% of patients were randomized, greatly reducing the statistical power of the study. Despite this, mortality and the incidence of non-fatal AMI were identical in both treatments. An important fact about this study is that approximately 23% of the patients included were in FC III or IV of the CCS, making them potential candidates for urgent revascularization, especially in the first months of follow-up, which in fact seems to have occurred. Analyzing the 5-years follow-up, in figure 2C it is evident that urgent revascularization was approximately 15% during the first year of follow-up and only 5% between the first and fifth year of follow-up. Therefore, the inclusion of patients in CCS FC III and IV must have contributed to the greater need for urgent revascularization in those allocated to GDMT during the first year of follow-up. Furthermore, it is observed that, although not statistically significant, there were numerically more cardiac deaths in patients undergoing PCI+GDMT than in GDMT alone (11 versus 7, respectively) (4).

The last two references are meta-analyses published by Laukkanen et al and VIj et al. In the meta-analysis by Laukkanen et al, it was concluded that revascularization associated with GDMT did not confer an advantage in the survival of patients with CCD compared to GDMT alone. However, it reduced the risk of combined events, including death, AMI, unplanned revascularization, rehospitalization or stroke, mainly by reducing the risk of unplanned revascularization or fatal AMI (26). A careful reading of this meta-analysis shows that RCTs involving patients with recent AMI were included, such as the OAT, DANAMI3-PRIMULTI, TOAT and DECOPI studies (27-30) which is not in line with the guideline under discussion. Furthermore, in the ISCHEMIA (3) and COURAGE (14) studies, no reduction in hospitalization for ACS was observed with revascularization.

The meta-analysis carried out by Vij et al, in which 7 RCTs were included, demonstrated that revascularization did not reduce mortality, but suggested a reduction in the incidence of adverse cardiac events such as death, AMI and stroke compared to GDMT. This meta-analysis has several limitations, as the authors themselves admit. They did not have access to individual patient data, the results primarily reflect PCI revascularization, and AMI criteria varied greatly among the RCTs included in the meta-analysis. The studies were not designed to analyze isolated events such as AMI or stroke, and analyzing figure 3 of the meta-analysis, it can be seen that the differences in the outcomes of cardiovascular death, 4.41% in revascularization and 4.71% in GDMT (P=0.05), MACE, 19% vs 19, 5%, respectively (P=0.01), and AMI, 9.4% vs 10.5%, respectively (P=0.01) were too small to have a clinical impact, although statistically significant (31).

As verified, none of the studies listed by the guideline' authors had sufficient power to justify COR 2a and LOE B-R for patients with CCD and multivessel CAD to reduce cardiovascular events, such as spontaneous AMI, unplanned revascularization or cardiac death. Many of the studies included in the 8 references did not deal only with CCD or multivessel CAD, especially the FAME 2 and ISCHEMIA studies. Furthermore, these outcomes were not considered primary in any of the aforementioned trials. Therefore, they are at best hypothesis-generating for future studies. The correct indication would be COR 2b, LOE C-LD.

The next recommendation is one of the pearls of the guideline when considering the indication of PCI with COR 2a, LOE B-NR to be reasonable to improve the survival of patients with CCD and LMCAD. The authors were based on a Bayesian analysis performed by Bitti et al, in which the authors concluded that, although there are no studies directly comparing PCI with GDMT in LMCAD, based on the premise that CABG reduces mortality compared to GDMT, PCI would also reduce it (32). In addition to the lack of contemporary data comparing CABG versus GDMT in LMCAD, several problems arise with this analysis. The Bayesian analysis performed to compare CABG with PCI produced a very wide 95% confidence interval, raising doubts about the equivalence between PCI and CABG and, perhaps the most important data, recent RCTs such as EXCEL (33) and NOBLE trials (34) were not included, which would have the potential to modify the conclusion of the analysis. This analysis cannot support any argument that PCI improves the life expectancy of patients with LMCAD compared with GDMT. In summary, there is no way to attribute an advantage of PCI over GDMT in patients with LMCAD based on studies that did not directly compare the two treatments. The guideline authors give the impression that they are more inclined to favor PCI over GDMT, regardless of the existing evidence. Therefore, this indication is purely speculative and should have a maximum of COR 2b, LOE C-EO.

In the decision making for revascularization, the authors of the guideline state that in patients with CCD who have angina or angina equivalent, without prior assessment of ischemia, and obstructions considered intermediate angiographically, the use of FFR or another non-hyperemic measure, such as iFR, is recommended before proceeding with PCI with COR 1, LOE A. They were based on two publications. The first evaluated the use of iFR-guided PCI compared with FFR-guided PCI (35) and the second the comparison between FFR-guided PCI and angiography-guided PCI (36). Although FFR-guided PCI brings more benefits than angiography-guided PCI, the equivalence between FFR and iFR is controversial due to the degree of discordance between these techniques that can reach 20% (37).

After an economic analysis between FFR-guided PCI and angiography-guided PCI in which there is a high economic value in favor of FFR, the authors report that in patients with CCD and complex three-vessel CAD for whom the GDMT strategy is uncertain, a heart-team approach including interventional cardiology representatives and surgeons is recommended to improve outcomes with COR 1, LOE B-NR. The authors relied on four studies for the recommendation. Although the importance of the "heart´team" is unquestionable, there are no randomized clinical studies that provide robustness to this approach. Furthermore, it is necessary to remember the importance of clinical judgment, especially when there is disagreement between the decisions of the "heart-team" and the opinion of experienced clinical cardiologists in decision-making, as observed in the study by Pereira et al. In this study, the authors examined the predictive value of clinical judgment on the incidence of cardiovascular events in patients involved in the MASS II study. Samples were separated into concordant and discordant according to the decision guided by the clinician and randomization. The authors found a significant difference in the incidence of combined events (primary outcome of the study) when there was disagreement between the experts' opinion and what determined randomization, especially in the group that underwent PCI (P=0.003) (38). Therefore, the suggestion for this indication would be COR 2b and LOE B-NR.

Reinforcing the conviction that the authors of the guideline made a "concentrated" effort to place revascularization as the best option for managing patients with CCD, in the synopsis that

supports the recommendations set out in the table, they make contradictory considerations regarding GDMT. They say that GDMT is an effective option, but inferior to revascularization in terms of symptomatic relief and improvement in quality of life and that revascularization reduces cardiovascular mortality, AMI and urgent revascularization, particularly in multivessel disease, but not all-cause mortality, with few exceptions. Actually, only the MASS II study involved patients with multivessel disease (15) and only CABG reduced mortality in single- or multivessel CAD associated with severe LV dysfunction as demonstrated in the STICHES trial (19), because in the REVIVED-BCIS2 study (REVascularisation for Ischaemic VEntricular Dysfunction – British Cardiovascular Intervention Society 2) PCI did not reduce cardiovascular events compared to GDMT in patients with CCD, significant CAD and severe LV dysfunction (39). Furthermore, in the COURAGE study, the improvement in symptomatic relief observed initially was not maintained at the end of five years of follow-up (14). Also, as already demonstrated in this article, in the ISCHEMIA study the improvement in quality of life only occurred in very symptomatic patients and the difference in favor of the invasive strategy was very modest (2).

The authors also report that most RCTs involved patients with low atherosclerotic damage, but this is not true in several contemporary studies. In MASS II, 68% of patients had three-vessel CAD and more than 90% had proximal left anterior descending artery (LAD) disease (3). The STICH (18) and REVIVED-BCIS2 (43) studies involved patients with severe single or multivessel CAD and severe LV dysfunction, which placed them at high risk of death. And, once again, the authors insist on using outdated studies, from the 70s and 80s, to state that CABG prolongs the survival of patients with LMCAD although there are no contemporary RCTs comparing GDMT with CABG or PCI.

CONCLUSIONS

The ACC/AHA 2023 guideline on CCD adds important contributions in the approach to patients affected by this disease, reinforcing the importance of patient-centered care, respecting their values, needs and priorities. However, as described in this article, the chapter related to revascularization is a source of controversy.

In this context, in a text written by members of STS/AATS, in relation to the recommendations of this guideline, Bakaeen et al. write that they do not agree with the downgrading of the indications for CABG compared to GDMT in patients with three-vessel CAD and EF≤35% of COR 1 to 2a and from 2a to 2b in patients with normal LV EF recommended by the 2021 revascularization guideline of the AHA/ACC and ratified in the guideline under discussion (40). Actually, regarding the recommendation of surgical revascularization in patients with CCD, significant obstructive CAD and severe LV dysfunction (EF≤35%), there is no reason to downgrade COR 1 to 2a, given the results of the STICHES trial, in which there was a reduction in mortality in favor of CABG compared to GDMT (19). On the other hand, in patients with significant CAD and preserved left ventricular function there are no studies demonstrating a clear advantage of revascularization over GDMT in CCD, which contributes to the downgrade of COR 2a to 2b.

Analyzing the revascularization recommendations in this guideline free from any type of conflict of interest, one gets the impression that the authors made a “concentrated” effort to position revascularization as a better therapeutic option for CCD than GDMT. As “the devil lies in the details”, in the last sentence of chapter 5, item 8, page e63, the authors of the guideline wrote the following:

"treatment decisions should be patient-centered, incorporate their preferences and goals, and include shared decision-making between doctors and patients", and gave the following example: "there may be patients who may prefer revascularization even if not on GDMT". This paragraph deserves two comments. Firstly, it goes against good medical practices and evidence-based medicine by not offering the patients a form of treatment for CCD, which, with rare exceptions, does not expose them to the risk of death, even in the long term. Secondly, there are patients who prefer GDMT rather than surgical or percutaneous revascularization. Obviously, this statement lacks any scientific evidence to be incorporated into a guideline. Although the final word always belongs to the patient, the difference of opinion lies in the way the cardiologist or the "heart-team" approaches patients and does not hide from them the true results of the studies that support the conduct to be taken.

CONFLITO DE INTERESSE

Nenhum declarado

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