REVIEW ARTICLE

Chronic Coronary Syndrome: Medical Therapy or Myocardial Revascularization?

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Abstract

The best therapeutic strategy for chronic coronary syndrome (CCS) is still controversial. The lack of contemporaneity of medical treatment in many randomized clinical trials prior to the large-scale use of statins, antiplatelet agents, anti-diabetic drugs with cardiovascular protection, and changes in life habits with well-established goals limits the applicability of such studies in current clinical practice.

Medical treatment is the only therapeutic option capable of reducing atherosclerotic damage and, therefore, of acting effectively in preventing the progression of this disease.

The purpose of this brief review is to critically analyze the main contemporary studies that confront medical treatment with myocardial revascularization in CCS.

Introduction

The best therapeutic strategy for chronic coronary syndrome (CCS) is still controversial, although several randomized clinical trials (RCTs)[1-4] and some contemporary meta-analyses have shown difficulties in appointing revascularization as the optimal therapeutic option.[5,6]

The lack of contemporaneity of medical treatment in many RCTs prior to the large-scale use of statins, antiplatelet agents, anti-diabetic drugs with cardiovascular protection, and changes in lifestyle habits with well-established goals limits the applicability of such studies in current clinical practices.[7-10]

The optimization of these measures and their influence on the behavior of coronary artery disease (CAD) can be demonstrated by the sharp drop in the percentage of patients with extensive ischemia assessed by myocardial scintigraphy in recent years,[11] as well as by the inverse relationship between mortality and the number of controlled risk factors in the follow-up of the COURAGE study.[12] In the COURAGE trial, at a mean follow-up of 6.8 years, the mortality of patients who presented all six controlled risk factors was 8.0% as compared to 36% of those who had one or no controlled risk factors.[12]

The reduction in atherosclerotic damage from the application of therapeutic measures capable of lowering serum LDL cholesterol levels beyond the benefits provided by statins is evidence of how much medical treatment contributes to the regression of coronary atherosclerotic disease and atherosclerotic plaque stabilization.[13,14] In the GLAGOV randomized trial, the addition of evolocumab, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, together with statins, reduced the percent of atheroma volume (64.3% vs 47.3%) and the total atheroma volume (61.5% vs 48.9%).[13]

Two recent reports unequivocally show how medical therapy can promote regression of CAD. Keraliya et al. reported the improvement of ischemia and regression of coronary atherosclerotic disease assessed by coronary CT angiography in a patient studied over a four-year interval,[15] whereas Kunhali et al. demonstrated the disappearance of angina and the angiographic regression of coronary artery obstruction seven years after the beginning of medical treatment.[16]

Reinforcement for the role of medical treatment in the prognosis of this disease comes from the results of a retrospective, population-based cohort study that included 29,047 residents in the Italian Lombardy region, aged 65 years or older, who were receiving uninterrupted

treatment with statins, blood pressure–lowering, antidiabetic, and antiplatelet agents.[17] Using a matched propensity score, they found that, compared with the maintained group, patients in the discontinuing group presented a 24% increased risk of hospital admissions for heart failure, 14% for any cardiovascular outcome, 15% for deaths from any cause, and 12% for emergency admissions for any cause.[17]

Criticism of systematic reviews and meta-analyses on CCS

Systematic reviews and meta-analyses are methods that support decision-making about the suitability of an intervention; however, results from these studies should be interpreted with caution because of variation in patient selection, studied treatments, outcome definitions, and differences in trial designs and conduct.[18] Consequently, we are critical of the authors who include old RCTs that do not reflect current treatments of CAD in the list of current meta-analyses,[19] as well as authors that highlight individual components of composite outcomes that are usually considered to be hypothesis-generating that need to be proven in RCTs specifically devoted to that outcome.[5,6,18,19]

Another criticism is levied against the inclusion of outcomes such as acute myocardial infarction (AMI) without strict criteria, otherwise the results can be modified in accordance with the adopted criteria as verified in the ISCHEMIA[20] and EXCEL trials.[21] In the ISCHEMIA trial, the authors used two prespecified definitions of AMI, a primary using creatine kinase-MB as the preferred biomarker and a secondary definition using cardiac troponin. According to the two definitions, procedural AMI accounted for 20.1% of all AMI with the primary definition and 40.6% of all AMI using the secondary definition.[20] In the EXCEL trial, the AMI criterion of creatine kinase-MB of 10 times above the upper limit of the normal underestimated the number of percutaneous coronary intervention (PCI) related AMI.[21]

Although we concede that a diversity of outcomes may be relevant for some patients, especially the elderly, for whom quality of life could have a stronger impact than life expectancy, death for any cause should be the primary outcome of RCTs that compare treatment strategies for CCS. Within this context, it is interesting to note that the outcome adopted in many RCTs is death from cardiac or cardiovascular cause rather than death from any cause.[19] Nevertheless, logical reasoning indicates that if a treatment is able to reduce specific death, that is, cardiac or cardiovascular death, this reduction should necessarily reduce death from any cause.

Some studies highlight the fact that early interruption of RCTs enhances the benefits of the studied treatment.[22,23] Therefore, the FAME 2 trial[4] that was interrupted prematurely due to a large number of revascularization guided by acute coronary syndrome rather than death or nonfatal AMI in the group allocated for medical treatment should not be cited or included in any meta-analysis or systematic review that compares revascularization with medical treatment in patients with CCS. In summary, at a mean follow-up of 213 days, the rate of urgent revascularization in the PCI group was lower than in the medical-therapy group (1.6% vs. 11.1%; P<0.001); however, there was no difference in the incidence of death from any cause (0.2% vs 0.7%), myocardial infarction (3.4% vs 3.2%), death or myocardial infarction (3.4% vs 3.9%), or cardiac death (0.2% vs 0.2%).[4]

Nocebo and placebo effects

Another important factor that is not taken into account in RCTs that assess the impact of therapeutic options on the symptoms of CCS is the nocebo effect[24] involved with medical treatment, because the fact that the obstructions present are not "unblocked" causes patients to feel at constant risk of death or AMI. This influence can be seen in the reduction of symptoms when patients are informed about the absence of serious illness, even if no changes in treatment are made.[25] In the DEFER study, the simple act of telling that the physiology test shows no significant ischemia, without any protocol-directed changes to medical therapy, the proportion of patients with chest pain fell from 88% to 54%.[25]

The ORBITA trial, in which patients and physicians were blinded to which patients had received angioplasty, showed no symptom advantage of percutaneous revascularization over nonintervention (that is, a fake procedure), which reinforces the hypothesis that there was no nocebo effect, whereas the sense of benefits provided by the angioplasty was present (placebo effect).[26] In this blinded placebo-controlled randomized study involving patients with stable angina and anatomically and haemodynamically severe coronary stenosis, 105 patients were assigned PCI and 95 the placebo procedure. At the end of 6 weeks of follow-up, there was no significant difference in the primary endpoint of exercise time increments between groups.[26]

The role of ischemia in the prognosis of CCS

Another relevant fact when comparing medical treatment with revascularization is the association between the quantification of ischemia and its prognosis. Before the ISCHEMIA trial,[27] a substudy of the COURAGE trial had already indicated the absence of interaction between the type of treatment and the extension of ischemia regarding the outcomes.[28] In a post hoc analysis of the MASS II trial, the authors assessed the impact of the presence or absence of ischemia on the prognosis of 611 patients randomized to medical treatment, percutaneous or surgical revascularization, and observed that the presence of ischemia did not appear to be associated with an increased incidence of adverse cardiovascular events in long-term follow-up, regardless of what therapy strategy was applied.[29]

Actually, ischemia is a marker of the presence of obstructive or microvascular coronary disease, and pathophysiologically it cannot identify patients at a higher risk of AMI, because there are no significant obstructive lesions prior to this outcome in most cases.[30]

When the ISCHEMIA trial was released, it was expected to conclusively determine the importance of ischemia extension on the prognosis of patients with CCS, but significant changes in patient selection occurred.[31] The study was originally intended to include patients with ≥10% ischemia assessed by imaging techniques. However, the inclusion of patients undergoing conventional exercise testing distorted the essence of the study. Furthermore, by adopting outcomes that are subject to interpretations that rely on the doctors who deal with the patients and by giving them the same degree of clinical importance, the study was weakened, although the authors stand behind the use of these outcomes.[31]

In brief, in the ISCHEMIA trial, 5,179 patients with moderate or severe ischemia were randomly assigned to an initial invasive strategy (angiography and revascularization when feasible) and medical therapy or to an initial conservative strategy of medical therapy alone and angiography if medical therapy failed. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. A key secondary outcome was death from cardiovascular causes or myocardial infarction. Over a median of 3.2 years, there was no difference in the primary outcome

events between the invasive strategy group (318) and the conservative-strategy group (352). At 5 years of follow-up, the cumulative event rate was 16.4% and 18.2%, respectively. Results were similar with respect to the key secondary outcome. There were 145 deaths in the invasive-strategy group and 144 deaths in the conservative-strategy group.[27]

Another detail about the above-mentioned study is that it has been interpreted as an opposition between medical treatment and myocardial revascularization whereas, in fact, it is a confrontation of strategies: a conservative strategy, in which an angiography would be guided by optimized medical treatment failure, and an initial invasive strategy in which, combined with the optimized medical treatment, a coronary angiography would be followed by myocardial revascularization, if feasible. In addition, to be eligible for randomization, patients should undergo a coronary CT angiography to rule out those with left main coronary artery lesion, which contradicts to some extent the assertion of the authors that coronary anatomy evaluation was not required in the ISCHEMIA trial, unlike in other studies.[31]

In any case, the ISCHEMIA trial failed to show the benefit of angiography combined with optimized medical treatment when compared with optimized medical treatment alone, which obscures the importance of ischemia quantification with the prognosis of patients undergoing angiography followed by revascularization,[27] and bringing up the concept of "oculoischemic" reflex.[32]

Another study that casts doubt on the role of ischemia on the prognosis of CCS patients comes from a post hoc analysis of the STICH clinical trial that evaluated the association of myocardial ischemia with mortality and the benefit of coronary artery bypass surgery (CABG) in ischemic cardiomyopathy in the 10 years of follow-up.[33] In this study, 402 patients, representing 33% of the original study population, underwent scintigraphy or echocardiography under stress. The mean age of the patients was 61±10 years and the mean LV ejection fraction was 26±8%. Of the 402 patients, 255 (63%) had stress-induced ischemia. By the end of the 10-year follow-up, no statistically significant difference in mortality was found between those with or without ischemia (69% vs 61%; p=0.15). Although the CABG was associated with lower mortality, the difference was not statistically significant (55% vs 67%; p=0.063).[33]

As previously mentioned, the contemporaneity of the studies that make up a meta-analysis or systematic review is crucial for the practical applicability of the results, because the inclusion of studies that did not include therapies that have been proven effective leads to incorrect conclusions and should therefore be avoided by the authors of such studies.

In this sense, a recently published systematic review and meta-analysis, in which 7 contemporary RCTs were analyzed, Soares et al. concluded that for patients with CCS and myocardial ischemia, initial revascularization with either angioplasty or surgery did not reduce mortality in the long term when compared with medical treatment alone; however, surgery combined with medical treatment reduced the incidence of AMI when compared with medical treatment alone, whereas angioplasty did not show this benefit.[6] This reduction in the incidence of AMI associated with surgical revascularization when compared with medical treatment is intriguing, because one would expect a corresponding reduction in mortality.

The resolution to this dilemma appears to lie in the type of AMI that occurs after revascularization or during medical treatment. An analysis of the impact of different definitions of AMI in the ISCHEMIA trial showed a higher incidence of type I AMI using the conservative strategy than the initial invasive strategy and that the patients with this type of AMI had higher mortality, both cardiac and due to any cause. The authors nevertheless emphasized that it is unclear whether the observed reduction resulted from revascularization itself, dual antiplatelet therapy, calculation bias, or any other mechanism.[20]

However, in contrast to the above analysis De Caterina et al. demonstrated that the excess of spontaneous AMI that occurred in the conservative arm of the ISCHEMIA trial was counterbalanced by the excess of types 4a and 5 AMI that occurred in the invasive arm.[34] Therefore, as there was no difference in all-cause or cardiovascular mortality between the groups, it is intuitive to admit that periprocedural myocardial infarction (MI) is associated with late mortality.[34] Furthermore, a pooled analysis of a patient-level data of elective percutaneous coronary intervention studies demonstrated that periprocedural Type 4a MI was associated with one-year mortality.[35]

We reiterate that ISCHEMIA trial did not compare therapies, but rather management strategies. In fact, of the 2,475 patients who had initial invasive angiography arm, 2,054 (82.9%) underwent revascularization, whereas of the 667 in the noninvasive arm who underwent angiography during the study, 544 (82.3%) underwent revascularization.[27] That is, the percentage of patients that underwent revascularization after angiography was identical regardless of the strategy adopted.

Conclusion

Evidently there are no RCTs, meta-analyses, or systematic reviews that can be used to answer the questions that emerge on a daily basis in clinical practice, such as the best therapeutic alternative for patients with comorbidities, who are not likely to be included in these studies. However, within the context of CCS, initial medical treatment is the best option to be adopted, regardless of the presence and extension of ischemia, leaving initial revascularization as a treatment for very specific groups of patients, such as those with significant obstruction of the left main coronary artery and those with severe LV dysfunction associated with coronary arteries susceptible to surgical myocardial revascularization.

Author contributions

Conception and design of the research: Rocha ASC; Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Rocha ASC, Silva PRD.

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