Advances in Cardiac Research

REVIEW

Optimizing Patient Selection for Revascularization in Chronic Coronary Syndrome: Rethinking Strategies for Improved Outcomes

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Abstract

Current guidelines regarding the revascularization of patients with chronic coronary syndromes remains equivocal and while providing a general opinion, many frequently encountered situations in daily practice are still uncovered. Novel studies and trials are aiming to find the determinants of improved outcomes after revascularization and give an insight to the clinicians in decision making. Despite the controversial results, it seems that more detailed and precise indications are to be defined in the future. This review provides an overview of the current guidelines and clinical trials on revascularization in chronic coronary syndromes. It highlights the importance of complete revascularization, the need for longer follow-up periods, and the value of functional and anatomical assessments in guiding treatment decisions. Furthermore, the review incorporates illustrative figures to aid in comprehending complex concepts.

Keywords: Atherosclerosis, chronic coronary syndrome, revascularization, stable coronary artery disease.

Introduction

Coronary artery disease (CAD) remains a leading cause of mortality and morbidity worldwide. It is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries. The dynamic nature of the CAD process results in various clinical presentations, which can mainly be categorized as acute coronary syndromes (ACS) or chronic coronary syndromes (CCS - also referred to as stable angina or stable ischemic heart disease), and CCS itself has a wide range of presentations. Patients with CCS can present with severe angina or new onset of heart failure symptoms, as well as 'stable' anginal symptoms, or they can be completely asymptomatic, with incidental detection of CAD at screening [1].

Two main goals of therapy in patients with chronic coronary syndrome are to manage symptoms and provide prognostic benefit, such as decreasing the risk of death, heart failure, or myocardial infarction. Despite coronary revascularization being an important therapeutic option for the management of patients with CAD, there are still discrepancies between guidelines when it comes to decision making.

The purpose of this review is to critically evaluate the latest clinical trials and guidelines to optimize patient selection for revascularization in chronic coronary syndromes. We aim to

provide insights into the current controversies and identify areas where more detailed indications are needed.

Clear Indications for Revascularization and Guideline Based Recommendations

Medical treatment is the standard of care in patients with CCS, however a significant part of the cases remain symptomatic despite maximal tolerated doses of optimal guideline directed treatment. Although some studies demonstrated survival benefit with coronary artery by-pass grafting (CABG) compared to medical therapy in patients with CCS, trials with percutaneous coronary intervention (PCI) failed to demonstrate survival benefit. Therefore current guidelines recommend revascularization in selected cases in the light of existing literature. Long term follow up results of FAME-2 trial delineated that revascularization is associated with reduced use of antianginal drugs and improved quality of life[2]. A meta-analysis reported favorable impact of initial PCI on survival and further myocardial infarction compared to medical therapy especially in patients who underwent PCI with newer generation drug eluted stents[3]. Therefore, it should be noted that lack of survival benefit with PCI might be due to the use of older generation stents and should not be generalized to the current era.

ESC/EACTS Guidelines on myocardial revascularization recommends revascularization in chronic coronary syndrome in the following situations: Presence of greater than 50% stenosis in left main (LM) or proximal left anterior descending artery (LAD), greater than 50% stenosis in more than one vessel in conjunction with left ventricular ejection fraction (LVEF) below 35%, significant stenotic lesion in the single remaining patent coronary artery, large ischemic area involving more than 10% of the left ventricle or abnormal results in invasive FFR and finally ongoing symptoms with significant stenosis in any coronary artery despite optimal medical treatment[4].

ACC/AHA/SCAI Guideline for Myocardial Revascularization also has similar recommendations for revascularization in CCS. Revascularization is recommended with Class I level only for CABG in the presence of multivessel coronary artery disease in combination with significantly reduced (less than 35%) LVEF and in patients with significant stenosis in left main coronary artery. CABG for multivessel disease accompanied with mild to moderately depressed (35-50%) LVEF and PCI for left main coronary artery disease are Class II recommendations. Revascularization via either CABG or PCI may be considered in cases with multivessel disease or proximal LAD lesion, whose left ventricular systolic functions are normal (Class IIb recommendation)[5]. (Figure 1)

Deciding the type of revascularization depends on the complexity and extent of coronary anatomy, perioperative mortality risk and the possibility of complete revascularization. Evidence of beneficial effects on outcomes with revascularization in patients with reduced ejection fraction was obtained from the long term follow up results of STICH trial and several registries. CABG resulted in improved survival compared to medical treatment in patients with depressed LV functions[6]. CABG is recommended in patients with left ventricular ejection fraction (LVEF) less than 35% by both ESC and AHA guidelines with Class I indication. CABG is also a Class I recommendation in cases with LVEF between 35-50% and PCI should be considered in these patients if the coronary anatomy is not suitable for CABG[5].

"The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study" randomized patients with CCS (including a significant percent of left main coronary artery disease cases) into medical treatment and CABG arms and demonstrated a significant survival benefit with CABG[7]. Subsequent trials and meta-analyses also yield improved survival in such patients[8]. PCI was compared to medical treatment in patients with stable left main coronary artery disease in several studies and a network meta-analysis concluded the reduced mortality rates with PCI[9]. However most of the trials with PCI included cases with low SYNTAX score. AHA guidelines recommend CABG in left main coronary artery disease by Class I recommendation in all cases and PCI (Class IIa) only for patients without high anatomic complexity. ESC revascularization guideline recommends priorly CABG (Class I) in left main disease and PCI should be avoided (Class III) in patients with SYNTAX score>32. PCI is a Class I recommendation in patients with SYNTAX score between 0-22.

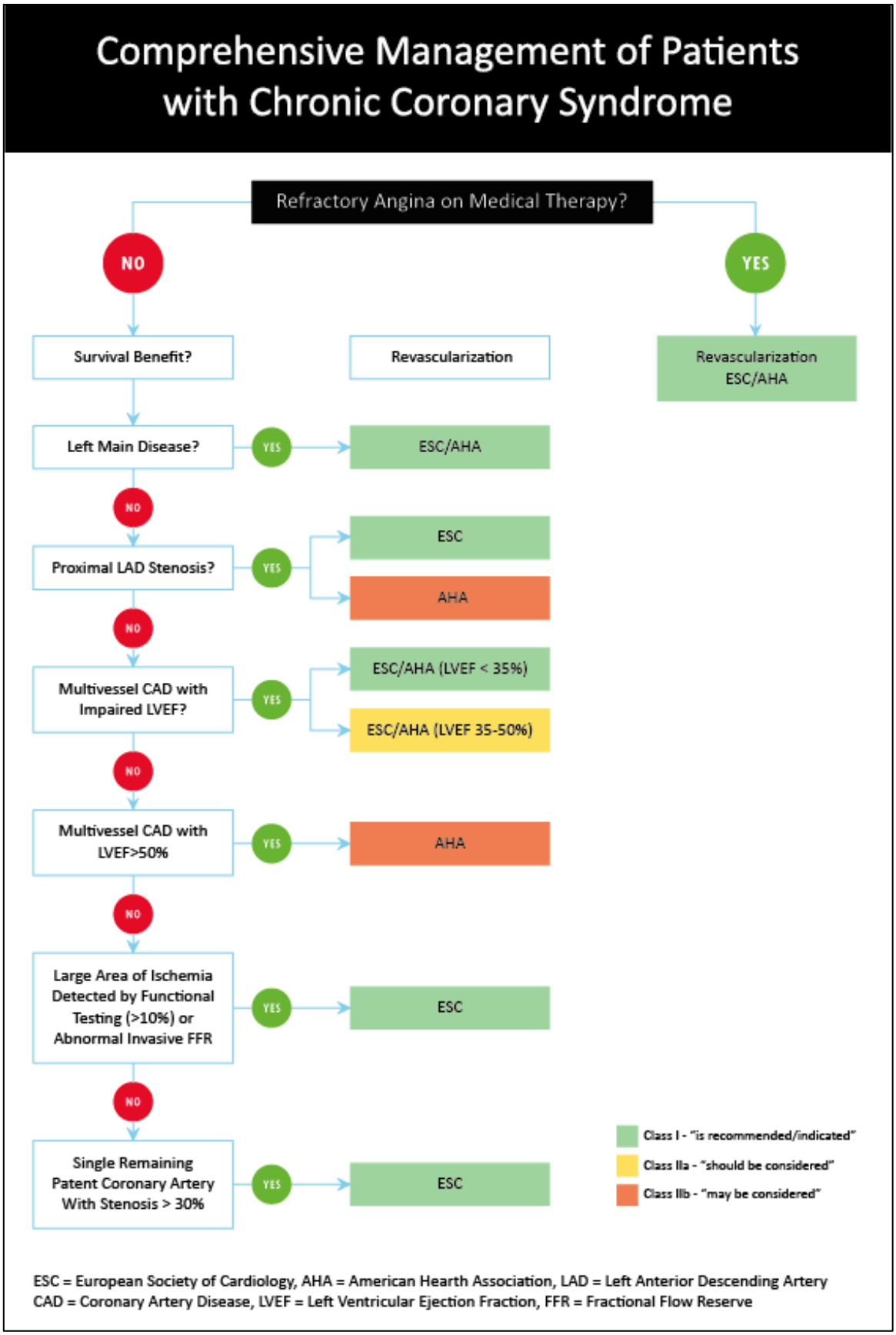

Figure 1. Comprehensive Management of CCS according to the current guidelines.

Although a previous meta-analysis and several studies demonstrated survival benefit with CABG compared to medical treatment in patients with proximal LAD stenosis, recent ISCHEMIA trial concluded similar outcomes between both types of revascularization and medical treatment[8, 10]. ESC revascularization guideline recommends both CABG and PCI as Class I recommendation in cases with single or two vessel disease involving proximal LAD [4].

Deciding the revascularization type in multivessel disease depends on the complexity of anatomy and presence of diabetes. CABG should be preferred in diabetic cases with suitable coronary anatomy and it is delineated below. Pooled analysis of SYNTAX and BEST trials demonstrated that PCI and CABG has similar results in major adverse cardiovascular events (MACE) and survival in non-diabetic multivessel coronary artery disease with low SYNTAX score (0-22), while CABG is superior to PCI with survival benefit in cases with higher SYNTAX score (>22)[11]. ESC guideline recommends CABG as Class I recommendation for all non-diabetic three-vessel disease cases and PCI for only cases with low SYNTAX score (0-22). PCI should be avoided in patients with higher SYNTAX score[4].

Diabetes is associated with worse prognosis in coronary artery disease and CABG (when anatomy is suitable) should be preferred as revascularization strategy in diabetic cases. In FREEDOM study, CABG and PCI were compared in diabetic patients with multivessel coronary artery disease and PCI was demonstrated to be related to 50% increased mortality risk[12]. Therefore CABG is the gold standard revascularization strategy in diabetic patients with multivessel coronary artery disease and it is strongly recommended (Class I) by both ESC and AHA guidelines. PCI may be considered in diabetic cases with low and intermediate complex (SYNTAX score 0-32) multivessel disease[4, 5].

Important Studies

Aside from symptomatic relief, the potential benefit of revascularization depends on the presence and extent of myocardial ischemia[13, 14, 15]. Performing PCI on nonischemic stenoses is not beneficial and is probably harmful[16, 17]. Thus, careful selection of ischemia-inducing stenoses is essential. Several trials have investigated how to make the decision when it comes to revascularization and whether there is a mortality benefit of revascularization for patients with CCS, in addition to optimal medical therapy (OMT) and lifestyle modifications.

In patients with CAD, the degree of luminal narrowing, plaque burden and characteristics, and physiologic significance are prognostic indicators[18, 19]. Intravascular ultrasonography (IVUS) is a common adjunctive technique that can provide detailed anatomical information regarding the lumen, vessel, and plaque. IVUS can guide the PCI procedure to improve stent placement and minimize stent-related problems[20, 21], and IVUS-guided PCI has been reported to improve clinical outcomes in comparison with angiography-guided PCI[22, 23]. Fractional flow reserve (FFR) is a pressure-wire–based index that is used during coronary angiography to assess the potential of a coronary stenosis to induce myocardial ischemia[24], and it has been shown that FFR-guided PCI is associated with fewer clinical events than angiography-guided PCI and medical treatment[17, 24]. Physiological assessment is more effective in ischemia-directed PCI[17, 24], whereas intracoronary imaging is more effective in the assessment of anatomical characteristics and in the planning of the PCI procedure[20, 25].

FLAVOUR trial

The FLAVOUR (Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients with Intermediate Stenosis) trial performed a head-to-head comparison of FFR- and IVUS-guided procedures regarding clinical and patient-reported outcomes in those with intermediate coronary stenosis (de novo intermediate stenosis (40 to 70%) in a target vessel measuring at least 2.5 mm by visual estimation on coronary angiography). Initially, the trial aimed to establish the superiority of the FFR-guided strategy over the IVUS-guided strategy. However, multiple studies published during the trial period demonstrated that IVUS-guided stenting could further enhance clinical outcomes. Therefore, the trial protocol was modified to assess the noninferiority of FFR-guided procedures compared to IVUS-guided procedures[26]. After a follow

up period of two years, the trial findings revealed that FFR-guided procedures were noninferior to IVUS-guided procedures in terms of a composite outcome including death from any cause, nonfatal myocardial infarction, or any revascularization. Notably, the FFR group exhibited a lower incidence of target-vessel PCI compared to the IVUS group, resulting in the implantation of fewer stents and a reduced need for dual antiplatelet therapy. Regarding the angina symptoms (SAQ scores), the two groups had similar results at baseline and during follow-up. The authors commented that these findings may be explained by the fact that the severity of coronary stenosis does not always correlate with clinical symptoms and the influence of guideline-based medical therapy. It should be kept in mind that the study population included low-risk patients so the results may not be applicable to higher-risk patients[27].

FAME 2 trial

Another trial focusing on the functional significance of CAD is FAME 2 trial. FAME 2 trial hypothesized that in patients with functionally significant stenoses, as determined by FFR, PCI plus the best available medical therapy would be superior to the best available medical therapy alone. In patients with CCS, the stenoses were assessed for their significance by measuring FFR. Patients in whom at least one stenosis was functionally significant (FFR ≤0.80) were randomly assigned to FFR-guided PCI plus OMT (PCI group) or OMT alone (medical-therapy group) and followed up for 5 years. This was an "all-comers" trial and conducted at a wide region, therefore expected to be representative of general population. Recruitment was halted prematurely (approximately 1,5 years) because of a significant between-group difference: urgent revascularization rates were significantly lower in the PCI group than in the OMT group (mostly because of myocardial infarction or evidence of ischemia on electrocardiography). Moreover, the percentage of patients with angina of Canadian Cardiovascular Society class II to IV was markedly lower among patients in the PCI group. Due to the unusually short period of follow-up, classical primary outcome of death and any complications related to PCI could not be monitored accurately[24]. However, the 5-year outcomes of the study later revealed a significantly lower rate of the primary composite endpoint, encompassing death, myocardial infarction, or urgent revascularization in the initial FFR-guided PCI strategy arm[2].

COURAGE trial

The COURAGE trial, which involved 2287 patients, aimed to assess the efficacy of PCI combined with OMT versus OMT alone. The trial enrolled patients with objective evidence of ischemia, including classic angina without provocative testing or significant changes in ST-segment depression or T-wave inversion on the resting electrocardiogram, as well as inducible ischemia through exercise or pharmacologic vasodilator stress. Patients were randomized on a 1:1 basis to receive either PCI plus OMT or OMT alone. The patients were followed up for a median of 4.6 years (2,5 to 7) for the primary outcome of death from any cause and nonfatal myocardial infarction. The study resulted in no significant differences between the PCI group and the medical-therapy group in the composite of death, myocardial infarction, and stroke despite a high baseline prevalence of clinical coexisting illnesses, objective evidence of ischemia, and extensive coronary artery disease as seen on angiography. However, the degree of angina relief was significantly higher in the PCI group than in the medical-therapy group. Of note, there was a substantial increase in freedom from angina in patients in the medical-therapy group as well, most of which had taken place at 1 year but with a further improvement at 5 years. Authors concluded that PCI can be safely deferred in patients with CCS, even in those with extensive, multivessel involvement and inducible ischemia, provided that intensive, multifaceted medical therapy is instituted and maintained[28].

COURAGE – Nuclear Substudy

Ischemia reduction is an important therapeutic goal as extent and severity of myocardial ischemia are determinants of risk for patients with coronary artery disease. Accordingly, a substudy of the COURAGE trial aimed to compare changes in ischemic burden with the use of myocardial perfusion single photon emission computed tomography (MPS), after randomization to PCI+OMT compared with OMT alone and to explore associations with patient outcome. The substudy found out that adding PCI to OMT resulted in greater

reduction in ischemia compared with OMT alone, and the benefit was greatest among patients with more severe baseline ischemia. The reduction in ischemic burden was also associated with symptomatic relief. Of note, the majority of patients from both treatment groups with ischemia reduction were angina free at 6 to 18 months of follow-up and regardless of treatment assignment, the magnitude of residual ischemia on follow-up MPS was found to be proportional to the risk for death or MI[29].

ISCHEMIA trial

ISCHEMIA is one of the much-debated studies on this topic. In this trial, 5179 patients with CCS and moderate or severe ischemia (obtained using imaging or exercise stress test (EST)) were enrolled and clinical outcomes of invasive approach plus medical therapy versus medical therapy alone was investigated. Distinguishing itself from previous studies, the ISCHEMIA trial set specific inclusion criteria, focusing on patients with moderate to severe ischemia. This deliberate selection aimed to explore whether an invasive strategy would be particularly advantageous for this subgroup, which was not thoroughly investigated in prior research. Unexpectedly, the study's findings revealed no evidence supporting the notion that an initial invasive strategy, when compared with an initial conservative strategy, reduced the risk of ischemic cardiovascular events or all-cause mortality over a median of follow-up period of 3.2 years. Patients in the invasive-strategy group had more procedural infarctions, and fewer nonprocedural infarctions during follow-up. However, the results should be interpreted in the context of reduced sample size, low than expected event rates, modest follow-up time and expanded primary outcome measures. ISCHEMIA trial was not powered for cardiac mortality and did not focus on long-term follow up[10].

Despite the non-significant difference between an invasive vs. a conservative strategy at a mean of 3.2 years in ISCHEMIA trial, the cumulative difference in the estimates of cardiac death between the invasive and conservative strategies tended to increase numerically over time (e.g., 0.3% in favor of the invasive strategy at 2 years and 1.3% at 5 years). This controversy emerged the rationale for a meta-analysis. At EuroPCR 2021, Navarese et al. presented a new meta-analysis that pooled data from 25 randomized trials, involving 19,806 patients with chronic coronary syndrome who underwent elective revascularization. Outcomes were extracted at the longest available follow-up period. The authors discovered a statistically significant 21% relative risk reduction in late cardiovascular death with revascularization plus medical therapy compared to medical therapy alone. Additionally, for every four-year increase in follow-up duration within the included studies, the risk of cardiac death decreased by 19%. This suggested that, the magnitude of benefit from revascularization increased over time. Notably, there was also a significant 24% reduction in spontaneous myocardial infarction observed with revascularization plus medical therapy. Meta-regression analysis revealed a significant association between the reduction in cardiac death and the reduction in spontaneous myocardial infarction. All in all, the rigorous statistical assessment concluded that an initial strategy of invasive care was superior to an initial strategy of conservative care and that this benefit became more evident with longer follow up. Notably, meta-regression techniques indicated that prior studies may have missed this finding primarily due to insufficient follow-up duration[30].

Concordant with this insight, despite no statistical difference was found in the primary endpoint between initial invasive and conservative management in the ISCHEMIA trial, cardiovascular mortality curves by treatment strategy were suggestive of a late divergence in favour of the invasive strategy over the conservative strategy[31]. In light of this, the ISCHEMIA-EXTEND observational study was planned in order to assess the long-term effect of invasive management strategy on mortality. Surviving participants from the initial phase of the ISCHEMIA trial were included with a projected median follow-up of nearly 10 years. The results of the interim report of 7-year all-cause, cardiovascular (CV) and non-CV mortality revealed an estimated 2.2% absolute reduction in CV mortality in patients treated with an initial invasive strategy, which is consistent with the results of the previously mentioned meta-analysis. This benefit was offset by an estimated 1.2% absolute increase in non-CV mortality over the same timeframe, which was an unexpected finding. These findings brought the authors to the conclusion that there is no clinically meaningful difference in 7-year all-cause mortality between the groups, but there was a lower risk of 7-year CV mortality and a higher risk of non-CV mortality with the

initial invasive strategy when compared with the initial conservative strategy. Unfortunately, the ISCHEMIA-EXTEND study cannot provide detailed data on the specific causes of death. The study is currently ongoing and further follow-up for a maximum of 10 years to monitor for a signal of a mortality difference is planned[32].

ORBITA trial

When it comes to symptomatic relief, ORBITA (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) is a trial aiming to assess the efficacy of percutaneous coronary intervention (PCI) compared with a sham placebo procedure for angina relief among patients with stable angina. The trial enrolled 230 patients with severe single-vessel stenoses of 70% or greater and randomly assigned them in a 1:1 ratio to either the PCI or placebo arms. In addition to conventional assessments, the severity of the lesions was also evaluated using Fractional Flow Reserve (FFR) and instantaneous wave-free ratio (iFR). The results of the study revealed that among patients with medically managed angina and severe coronary stenosis, PCI did not provide a greater increase in exercise time compared to the effect observed with a placebo procedure. In other words, the symptom relief experienced by patients who underwent PCI was not significantly different from that of patients who received a placebo[33].

BARI 2D trial

Some comorbidities indicate a higher mortality in CAD, like diabetes or chronic kidney disease (CKD). Optimal therapeutic strategies for these subset of patients are not well defined. The BARI 2D study is one of the many important studies to offer an insight into the treatment choice for patients with type 2 diabetes mellitus and CCS. Revascularization arm consisted of PCI or coronary artery bypass grafting (CABG), and despite the fact that the study was not designed to compare the two different invasive strategies, the benefit associated with prompt coronary revascularization, as compared with medical therapy, was significantly greater for patients selected for CABG than for patients selected for PCI. That being said, CABG stratum had more extensive coronary disease, with significantly more three-vessel disease, proximal disease of the left anterior descending artery, and chronic coronary occlusions than the patients for whom PCI was intended. Additionally, the CABG stratum had a higher incidence of previous myocardial infarction and a lower likelihood of previous coronary revascularization. Consequently, it can be concluded that patients with diabetes, evidence of myocardial ischemia, and extensive multivessel disease would derive substantial benefits from timely surgical revascularization[34].

ISCHEMIA-CKD trial

Another independent risk factor for CAD is CKD, however this population is under-represented since these patients are mostly excluded from the studies. Only 10 to 40% of patients with CKD and CAD undergo revascularization in clinical practice owing to concerns about acute renal injury and major bleeding events after revascularization[35]. Some observational investigations have provided varied opinions on this controversial issue, and the majority of them supported revascularization[36]. ISCHEMIA-CKD trial is one of the important trials trying to shed light to this topic. The investigators assigned 777 patients with advanced kidney disease and moderate or severe ischemia on stress testing to revascularization added OMT and OMT alone and angiography reserved for those in whom medical therapy had failed. After a follow-up of 2.2 years, no significant difference was found in terms of death or nonfatal myocardial infarction (MI), yet the invasive strategy was associated with a higher incidence of stroke and death or initiation of dialysis than the conservative strategy[37].

In order to provide further evidence-based insights into the treatment of patients with CAD and CKD, a meta-analysis was conducted, incorporating 13 studies and a total of 20,688 patients. The analysis yielded three main results. First, compared to drug therapy alone, revascularization (either through PCI or CABG) reduced the long-term risk of all-cause mortality in patients with CAD and CKD, irrespective of the severity of renal impairment. Second, invasive therapy demonstrated consistent survival benefits, particularly in subgroups with a mean age of over 70 years, predominantly composed of patients with moderate CKD. Third, a lower mortality rate associated with revascularization was

observed in the CCS group. It is important to note that conflicting results observed across studies can be attributed to differences in patient selection and follow-up duration, emphasizing the need for careful interpretation of the findings[36].

Discussion

Despite the well-delineated recommendations of guidelines, real-life practice do not always fall with the literature when it comes to deciding on revascularization of patients with chronic coronary syndrome. It is certain that revascularization is an effective therapeutic option for symptom relief, but reduction in mortality is not ascertained yet. Current guideline suggestions are based on previous evidence obtained from older studies, in which survival benefit was demonstrated with CABG but not with PCI. However, evolving technology leads to newer generation stents, more potent antiplatelet therapy alternatives and more accurate diagnostic methods. Combined with latest developments in stenting techniques, these advances are also making complete revascularization possible with PCI. In parallel with this, results of novel trials and meta-analysis demonstrated beneficial effects of PCI as well as CABG, bringing the actuality of these recommendations into question.

Guideline-based recommendations are mainly based on angiographic assessment of coronary stenoses. Nevertheless, recent clinical trials disclosed the importance of functional tests such as FFR or MPS as well as anatomical evaluation of the lesions. Different modalities were used to assess the severity of CAD, and mortality benefit varied between each of them. Lack of any head-to-head prospective comparison makes it hard to define a superior diagnostic tool, but it is clear that angiographic assessment only is not adequate without functional or anatomical assessment of the lesions.

Findings from the ISCHEMIA-EXTEND study brings up the question of what the primary endpoint in revascularization trials and meta-analyses should be. Despite total mortality has been advocated to be the best endpoint in clinical trials, primary endpoints should be more specific than total mortality for drawing precise treatment effect estimates. Most trials used cause-specific mortality rather than all-cause mortality in their primary composite outcome. Hence, the use of all-cause mortality in myocardial revascularization trials remains debatable.

Whilst the question still remains about whom to perform revascularization, another matter of debate is how to do so. Different revascularization strategies were used in studies, including bare metal stents (BMS), drug-eluting stents (DES), and CABG. Extent and severity of CAD also varied upon each study. Whether any strategy is more beneficial is still controversial. The importance of complete revascularization rather than the treatment itself as the determinant of mortality benefit has been discussed. Thereby, residual myocardial ischemia and disease burden in non-stented segments may play a significant role and future studies should aim to shed light to this argument.

Different subgroups of patients with co-morbidities such as diabetes and chronic kidney disease require specific attention because of their poor prognostic characteristics. In spite of the fewer number of studies conducted in these underrepresented subgroups, the results are in accordance with the guideline recommendations, suggesting a mortality benefit with surgical revascularization.

Lastly, as atherosclerosis is a dynamic and gradual process, potential effects of any treatment on such chronic conditions require longer follow up periods. The longest follow-up of approximately 7 years may provide an insight, even though a longer follow-up may result in superior outcomes in revascularization groups or reveal longer term complications of revascularization.

All in all, many studies are ongoing and more definitive prospective trials are needed for conclusive indications of revascularization in chronic coronary syndrome. By the time recommendations of newer guidelines be inclusive of these uncertainties, each patient should be approached individually, using every diagnostic and therapeutic modality available. The "Heart Team" should discuss each therapeutic option and patients should be involved in the process of decision making with the intent to choose the most beneficial treatment (Figure 2, 3).

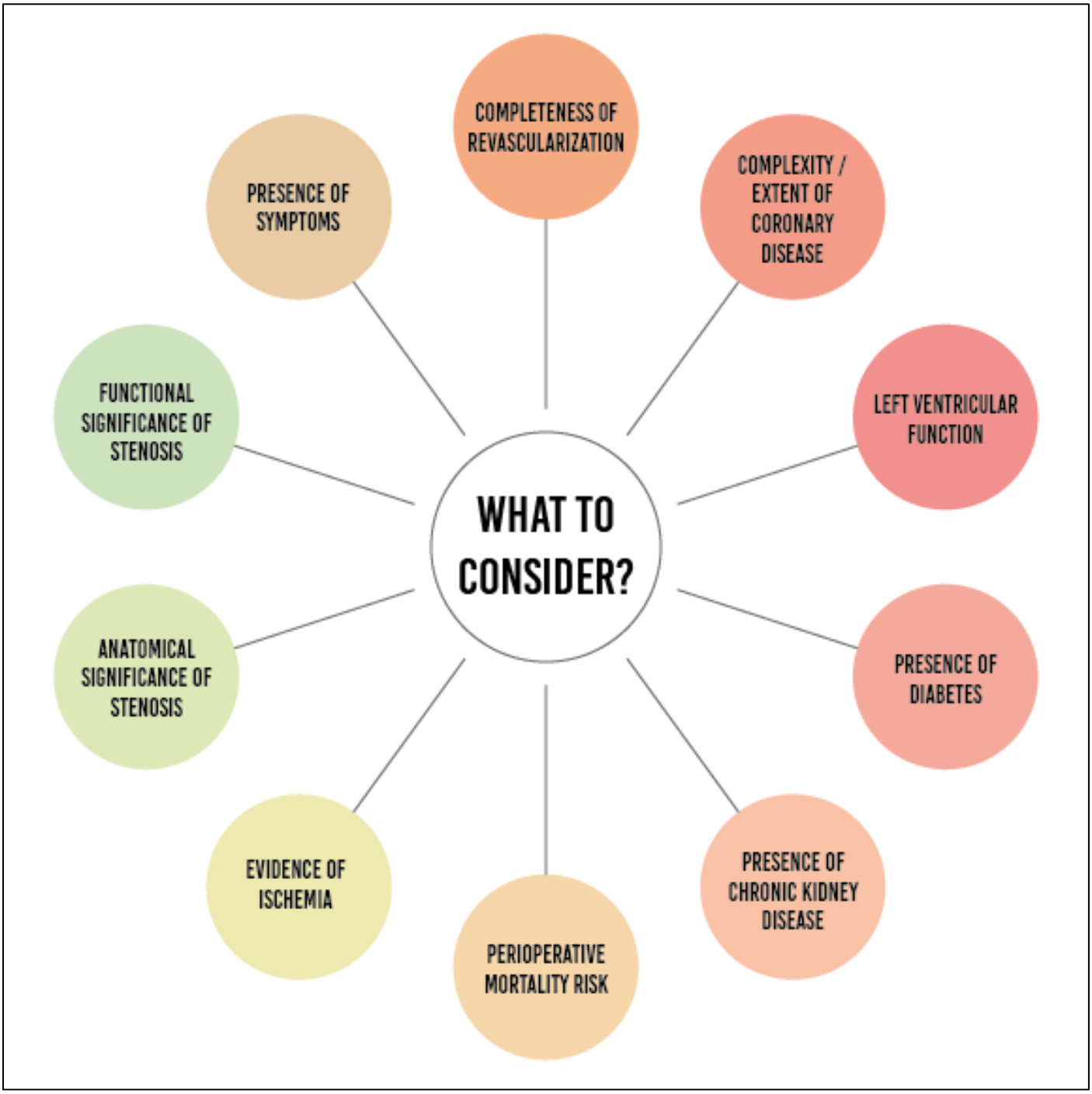

Figure 2. Factors that impact the decision of revascularization.

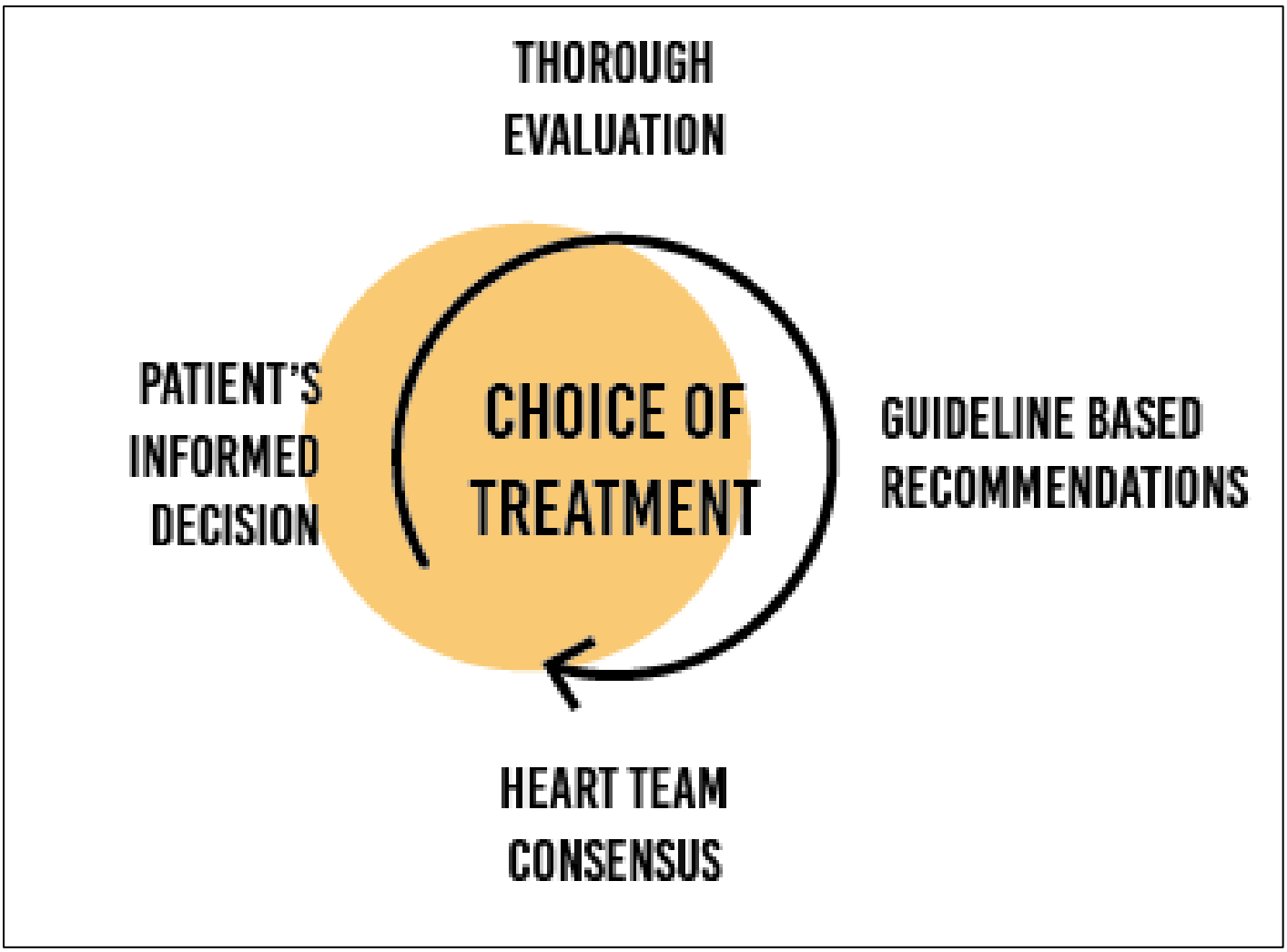

Figure 3. Pathway to the choice of treatment.

Conclusion

In conclusion, the decision-making process for revascularization in patients with chronic coronary syndrome remains complex and subject to ongoing debate. While revascularization provides effective symptom relief, its impact on reducing mortality is still uncertain. Guidelines are based on previous evidence, but newer technological advancements in stenting, antiplatelet therapies, and diagnostic methods are challenging the existing recommendations. The importance of functional tests, such as FFR or MPS, alongside anatomical assessments, has been highlighted in recent clinical trials. It is clear that relying solely on angiographic assessment of coronary stenoses is inadequate. The choice of primary endpoints in revascularization trials also requires careful consideration, as all-cause mortality versus cause-specific mortality can lead to different treatment effect estimates. Different revascularization strategies and patient subgroups, such as those with comorbidities, further complicate the decision-making process. The significance of achieving complete revascularization and the role of residual myocardial ischemia and disease burden in non-stented segments should be further investigated.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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