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Advances in Management of Stable Coronary Artery Disease: the Role of Revascularization?

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Abstract

Purpose of review Coronary artery disease remains the most common cause of death worldwide. In patients with biomarker-positive acute coronary syndrome, the combination of guideline-directed medical therapy with routine revascularization is associated with improved outcomes. However, the role of routine revascularization in stable ischemic heart disease, in addition to medical therapy, remains a matter of debate. In this review, we aimed to describe the role of revascularization in stable ischemic heart disease.
Recent findings Revascularization is indicated in patients with stable ischemic heart disease and progressive or refractory symptoms, despite medical management. When guided by ischemia presence, revascularization has failed to show survival benefit, compared with medical therapy alone in multiple clinical trials. On the other hand, revascularization guided by coronary lesion severity, assessed by FFR or iFR, has been shown to offer survival benefit and improvement in symptom severity. PCI-revascularization of unprotected left main disease is feasible with comparable to surgical approach outcomes.
Summary Clinical decision to perform revascularization in stable ischemic heart disease necessitates a heart team approach, and no simple algorithm can guide this process. Further studies are required to assess the benefit of routine revascularization, in combination to medical therapy, in this population.

Introduction

Coronary artery disease remains the most common cause of death worldwide, responsible for about one in every seven deaths. Eighty percent of cardiovascular disease related deaths take place in low- and middle-income countries occurring almost equally in males and females [1]. It is estimated that 16.5 million Americans over the age of 20 years have coronary artery disease with the prevalence being higher for males than females for all ages [2]. Patients with atherosclerotic coronary artery disease may be asymptomatic or present with symptoms ranging from stable angina to acute coronary syndromes (unstable angina, non-ST-elevation acute coronary syndrome, ST-elevation acute coronary syndrome) or cardiogenic shock. Advances in coronary revascularization techniques in conjunction with improvements in drug therapy and risk-factor control have revolutionized the treatment of both stable and unstable angina [3]. Based on the American Heart Association statistics, 954,000 inpatient percutaneous coronary intervention (PCI) procedures and 397,000 coronary artery bypass graft (CABG) procedures were performed in the USA in 2010 [2]. The number of PCI procedures performed declined by 38% between 2006 and 2011. Among patients with stable ischemic heart disease (SIHD), the decline in PCI rates was 61% [4]. In patients with biomarker-positive ACS, the combination of guideline-directed medical therapy with routine revascularization reduces the long-term rates of death and myocardial infarction compared to conservative approach with medical therapy alone [5–7]. However, the optimal therapeutic approach for patients with stable angina remains a matter of debate with significant medical and financial implications. A meta-analysis of 15 randomized trials estimated costs for patients with SIHD as lowest for medical therapy ($3069 and $13,864 at 1 and 3 years, respectively) and highest for CABG ($27,003 and $28,670 at 1 and 3 years, respectively). PCI costs were between medical therapy and CABG and were higher with drug-eluting stents (DES) than with bare-metal stents and balloon angioplasty [8].

Since the inception of PCI in the late 1970s, there has been no convincing evidence that PCI alone improves survival, in patients with stable ischemic heart disease who have no clear indication for CABG, compared with the combination of medications for secondary prevention and lifestyle modifications, such as cigarette cessation, diet, and regular moderate-to-high intensity exercise [9]. Clinical practice guidelines from the USA as well as Europe endorse optimal medical therapy as the initial approach for all patients with stable coronary artery disease. For those with significant ischemia or symptoms that persist despite medical therapy, revascularization is recommended with various levels of support [10•, 11].

Over the past years, multiple studies have questioned the benefits of routine revascularization in SIHD. Results from large clinical trials have demonstrated similar outcomes in guideline-directed medical therapy–treated patients with and without revascularization, PCI, or CABG. The purpose of this review is to describe the advances in management of SIHD and describe the role of revascularization in this evolving field.

Indications for revascularization

Early randomized clinical trials of CABG versus conservative medical management in patients with SIHD demonstrated a survival benefit for CABG in patients with left main disease [12], multivessel disease, and left ventricular dysfunction but not overt heart failure (ejection fraction 35–50%) [13, 14] and proximal left anterior descending coronary artery disease, severe angina, and left ventricular ejection fraction more or equal to 50% [15]. Nevertheless, these findings from the early CABG trials are now considered primarily obsolete as the invasive approach rarely included use of mammary grafts, and the disease-modifying pharmacologic approach applied in the medical management cohort did not reflect current knowledge and evidence.

Prior clinical trials have demonstrated a greater benefit from revascularization compared with medical therapy in those with greater angiographic disease and more severe, clinically significant coronary artery disease, especially with

CABG. In the SYNTAX trial, 1800 patients with three-vessel or left main coronary artery disease were randomized in a 1:1 ratio to undergo CABG or PCI. For all patients, the local cardiac surgeon and interventional cardiologist determined that equivalent anatomical revascularization could be achieved with either treatment. A non-inferiority comparison of the two groups was performed for the primary endpoint—a major adverse cardiac or cerebrovascular event (MACCE) during the 12-month period after randomization. At 12 months, the rates of death and myocardial infarction were similar between the two groups; however, rates of MACCE were significantly higher in the PCI group (17.8%, vs. 12.4% for CABG; $P = 0.002$), in large part because of an increased rate of repeat revascularization (13.5% vs. 5.9%; $P < 0.001$). Stroke was significantly more likely to occur with CABG (2.2%, vs. 0.6% with PCI; $P = 0.003$). Additionally, a significant interaction between SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score and treatment group was noted; patients with low or intermediate scores in the CABG and PCI group had similar rates of MACCE, whereas among patients with high scores, the event rate was significantly increased in the PCI group [16]. At 3-year follow-up, the incidence of death in those undergoing left main coronary artery disease revascularization with low or intermediate SYNTAX scores (< 33) was 3.7% after drug-eluting stenting and 9.1% after CABG ($P = 0.03$); whereas in those with a high SYNTAX score (≥ 33), the incidence of death after 3 years was 13.4% after drug-eluting stenting and 7.6% after CABG ($P = 0.10$) [17]. At 5-year follow-up, MACCE rates did not differ significantly between groups of patients with low or intermediate SYNTAX scores, but significantly more patients in the PCI group with high SYNTAX scores had MACCE (46.5% versus 29.7%, respectively; $P = 0.003$) [18]. Long-term advantage of CABG revascularization over PCI in patients with multivessel disease was also demonstrated in the 10-year follow-up analysis of the initial BARI trial where CABG revascularization had higher survival compared to the PCI assigned group (57.8% vs. 45.5%; $P = 0.025$) [19].

A similar benefit of CABG over PCI in the management of multivessel coronary artery disease in diabetics has also been well described. In the FREEDOM trial, the primary outcome defined as a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke occurred more frequently in the PCI group, with 5-year rates of 26.6% in the PCI group and 18.7% in the CABG group. The benefit of CABG was driven by differences in rates of both myocardial infarction and death from any cause. Stroke was more frequent in the CABG group, with 5-year rates of 2.4% in the PCI group and 5.2% in the CABG group [20]. In the BARI 2D trial, which was neutral in patients with diabetes and SIHD, a strategy of prompt CABG surgery, but not PCI, significantly reduced the rate of death, MI, or stroke in those at high risk, as determined by the extent of coronary artery disease, myocardial jeopardy index, impaired left ventricular function (left ventricular ejection faction < 50%), and the Framingham score [21]. CABG surgery was also beneficial in patients with diabetes and reduced left ventricular function (left ventricular ejection fraction < 50%) but not class III or IV heart failure, as well as in patients with diabetes and a high SYNTAX score [22]. A patient-level meta-analysis (using data from the COURAGE, FREEDOM, and BARI PCI/CABG trials) further demarcated the benefit of CABG surgery over either optimal medical therapy or PCI in patients with type 2 diabetes and multivessel coronary disease; no incremental benefit of PCI over optimal medical therapy was observed [23].

Current guidelines as well as appropriate use criteria support the incorporation of a heart team approach to revascularization in patients with diabetes mellitus and complex multivessel coronary artery disease [10•]. A joint decision from a cardiologist and a heart surgeon allows for thorough evaluation of available revascularization approaches and shared decision-making between the patient and the heart team.

Given the abovementioned findings, the general consensus is that for all patients with a low burden of coronary disease (e.g., single-vessel disease), low-risk findings on noninvasive testing, and/or no antianginal therapy, guideline-directed medical therapy is the initial step to reduce progression of atherosclerosis and prevent coronary thrombosis. As a disease burden progresses, CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel coronary artery disease for which revascularization is likely to improve survival (3-vessel coronary artery disease or complex 2-vessel coronary artery disease involving the proximal left anterior descending artery), particularly if a left-internal mammary artery graft can be anastomosed to the left anterior descending artery, provided the patient is a good candidate for surgery [10•] (Table 1).

Revascularization guided by ischemia presence

It has been long believed that the presence of clinically significant ischemia in the setting of SIHD can assist in identifying patients who would prognostically benefit from revascularization. Several small clinical trials and registry analysis have shown survival benefit in patients with clinically significant inducible ischemia (> 10% of the left ventricular myocardium) undergoing PCI or CABG revascularization [25–27]. However, the reported survival benefit has not been confirmed in larger studies. Recent clinical trials have suggested that the degree of ischemia in patients with SIHD does not correlate with the risk of death or myocardial infarction. Furthermore, revascularization has not been shown to confer improved prognosis compared with guideline-directed medical therapy, raising the question of appropriateness of regular revascularization in this population.

In a metanalysis of 11 randomized trials published by Katritsis et al. comparing PCI to conservative treatment in patients with SIHD, PCI revascularization did not offer any benefit in terms of mortality, myocardial infarction, or the need for subsequent revascularization [9]. Investigators in the COURAGE trial randomized 2287 patients with stable coronary artery disease, initial Canadian Cardiovascular Society class IV angina subsequently stabilized medically, and objective evidence of myocardial ischemia and significant coronary artery disease to either undergo PCI with optimal medical therapy or receive optimal medical therapy alone [28]. The primary outcome of the study was death from any cause and nonfatal myocardial infarction during the follow-up period. After a median follow-up period of 4.6 years, no significant difference was observed in the cumulative primary-event rates (19.0% vs. 18.5%, respectively; $P = 0.62$), as well as in the rates of the composite of death, myocardial infarction, stroke (20.0% vs. 19.5%; $P = 0.62$), hospitalization for acute coronary syndrome (12.4% vs. 11.8%; $P = 0.56$), and myocardial infarction (13.2% vs. 12.3; $P =$

Table 1. Current indications for revascularization in SIHD

	To improve survival		To improve symptoms	
	Class of recommendation	Level of evidence	Class of recommendation	Level of evidence
2012/2014 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guidelines				
Left main disease				
CABG	I	B	–	–
PCI	IIa, IIb, or III[a]	B or C[a]	–	–
3-vessel disease with PLAD disease				
CABG	I	B	–	–
PCI	IIb	B	–	–
2-vessel disease with PLAD disease				
CABG	I	B	–	–
PCI	IIb	B	–	–
2-vessel disease without PLAD disease				
CABG	IIa	B	–	–
CABG	IIb	C	–	–
SPCI	IIb	B	–	–
1-vessel disease with PLAD disease				
CABG	IIa	B	–	–
PCI	IIb	B	–	–
1-vessel disease without PLAD disease				
CABG	III	B	–	–
PCI	III	B	–	–
Left ventricular dysfunction				
CABG	IIa or IIb[b]	B	–	–
CABG	IIb	B	–	–
PCI	–[c]	–	–	–
Unacceptable angina despite GDMT				
PCI or CABG	–	–	I	A
PCI	–	–	IIa[d]	C
CABG	–	–	IIb[d]	C
Unacceptable angina with GDMT noncompliance or side effects or patient preference[e]				
PCI or CABG	–	–	IIa	C
2013/2014 ESC/EACTS guidelines				
Left main disease	I	A	I	A
Proximal LAD disease	I	A	I	A
Multivessel disease with LVEF < 40%	I	B	IIa	B
Large area of ischemia (> 10% LV)	I	B	I	B
Single remaining vessel	I	C	I	A
	–	–	I	A

Table 1. (Continued)

	To improve survival		To improve symptoms	
	Class of recommendation	Level of evidence	Class of recommendation	Level of evidence
Limiting symptoms or symptoms not responsive/intolerant to GDMT				
Heart failure with > 10% ischemia/viability	IIb	B	IIa	B
No limiting symptoms with GDMT and with none of the above or with FFR > 0.80	III	A	III	C

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[a]Varies according to associated clinical conditions and anatomic complexity
[b]IIa for LVEF 35 to 50%; IIb for LVEF < 35% without left main disease
[c]Insufficient data for a recommendation
[d]In patients with prior CABG
[e]In patients with significant anatomic (> 50% left main or > 70% non-left main disease) or physiological (FFR < 0.80) coronary artery stenoses
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0.33) between the PCI and the medical therapy groups. The rates of angina were significantly lower during most of the follow-up period in the PCI group, and similar at 5 years. Revascularization rates were lower in the PCI group compared to the optimal medical therapy group. During the extended follow-up period of 15 years, no difference in mortality was observed between the two groups [29••].

In the COURAGE nuclear sub-study analysis of 314 patients with baseline and follow-up nuclear studies available, combined use of PCI with optimal medical therapy was associated with a greater decrease in ischemia and ischemic myocardium compared with optimal medical therapy alone as measured by quantitative stress single-photon emission computed tomography (SPECT). The described ischemia reduction appeared to benefit the most patients with moderate-to-severe pretreatment ischemia [30]. However, in a subsequent analysis of all patients ($n = 1381$) for whom pre-randomization SPECT information was available, no difference in death or MI was reported among patients with absent-to-mild and moderate-to-severe ischemia treated with either optimal medical therapy and PCI or optimal medical therapy alone [31]. Finally, in the STICH trial, inducible myocardial ischemia in patients with coronary artery disease and severe left ventricular dysfunction failed to identify those with worse prognosis or those with greater benefit from revascularization over optimal medical therapy [32].

In the ORBITA trial, 200 patients with SIHD and severe (≥ 70%) single-vessel stenosis were randomized to receive either PCI and intensive optimal therapy or intensive optimal therapy and a sham procedure. After a short follow up period of 6 weeks, no significant difference in the primary endpoint of exercise time increment between the groups was observed [33••].

Revascularization strategy has also failed to demonstrate improved prognosis in high-risk subgroups with SIHD. In the BARI 2D study, 5-year survival rates in type 2 diabetic patients with heart disease did not significantly differ between the revascularization group and the optimal medical therapy group (88.3% vs. 87.8%, respectively; $P = 0.97$); MACCE rates were also similar (77.2% vs. 75.9%, respectively; $P = 0.70$). Major cardiovascular events were significantly lower in the CABG-revascularization stratum compared to the medical therapy group (22.4% vs. 30.5%,;$P = 0.01$; $P = 0.002$ for interaction between stratum and the study group) [34]. Most importantly, BARI 2D patients that achieved excellent control of multiple risk factors through protocol-guided intensive medical therapy had a decrease in risk of death or cardiovascular disease events by half at 1-year follow-up, compared with those who had 0 to 2 risk factors controlled [35••].

Finally, in a metanalysis of five randomized clinical trials involving 5286 patients with SIHD and objectively documented myocardial ischemia, in which stents and statins were used in more than 50% of patients, PCI revascularization with optimal medical therapy was not associated with a reduction in death, nonfatal myocardial infarction, unplanned revascularization, or angina when compared with optimal medical therapy alone [36].

Revascularization guided by coronary lesion severity

The benefit of fractional flow reserve (FFR)–guided revascularization in patients with stable coronary artery disease was demonstrated in the FAME II trial. One thousand two hundred twenty patients with stable coronary artery disease involving up to three vessels (as determined on angiography) and at least one stenosis with an FFR of 0.80 or less were randomly assigned to undergo FFR-guided PCI plus medical therapy or to receive medical therapy alone. At 2 years, FFR-guided PCI was associated with a significantly lower rate of the primary endpoint (a composite of death from any cause, nonfatal myocardial infarction, or urgent revascularization) compared to medical therapy alone (8.1% vs. 19.5%; $P < 0.001$). This reduction was primarily driven by a lower rate of urgent revascularization in the PCI group (4.0% vs. 16.3%; $P < 0.001$), with no significant between-group differences in the rates of death and myocardial infarction. Urgent revascularizations that were triggered by myocardial infarction or ischemic changes on electrocardiography were less frequent in the PCI group. In a landmark analysis, the rate of death or myocardial infarction from 8 days to 2 years was lower in the PCI group compared to the medical-therapy group (4.6% vs. 8.0%; $P = 0.04$) [37].

In the prematurely halted FUTURE trial, use of FFR to guide treatment choice in patients (stable or unstable coronary artery disease) with multivessel disease was associated with higher risk of death within the first year (3.7% vs. 1.5%; $P = 0.036$). No significant difference was observed in the primary composite outcome of all-cause mortality, myocardial infarction, repeat revascularization, or stroke through 1 year. Conversely, the trial was stopped early by the data and safety monitoring board with only 938 patients enrolled due to high mortality in the FFR group, limiting the ability to draw significant conclusions. In the exploratory analysis, increased mortality was believed to be the result of three factors: lower-than-expected rate of CABG considering that all patients had multivessel disease, higher rate of PCI in severe patients with a SYNTAX score over 32, and the high rate of ad hoc PCI [38].

The efficacy of FFR and instantaneous wave-free ratio (iFR) in predicting response to subsequent PCI in patients with stable coronary artery disease was evaluated in the physiology-stratified analysis of the ORBITA trial including 196 patients from the original ORBITA trial. PCI improved stress echocardiography score more than placebo; the effect of PCI on stress echocardiography score increased progressively with decreasing FFR and decreasing iFR. No significant difference on between-arm prerandomization-adjusted total exercise time in the two arms was observed. Interestingly, PCI did not improve angina frequency score when compared to placebo, but did result in more patient-reported freedom from angina than placebo; neither FFR nor iFR modified these effects [39••].

The use of coronary CT angiography and FFR_{CT}-guided management in the treatment of stable chest pain was demonstrated in a recent study by Nørgaard et al. CTA and FFR_{CT} testing were successful in differentiating patients who did not require further diagnostic testing or intervention ($FFR_{CT} > 0.80$) from higher-risk patients ($FFR_{CT} \leq 0.80$) in whom further testing with invasive coronary angiography and possibly intervention may be required [40•]. Although these findings are promising, further studies comparing the optimal revascularization approach for these higher-risk patients ($FFR_{CT} \leq 0.80$) are required.

Revascularization of unprotected left main disease

Unprotected left main disease (> 50% stenosis) had traditionally been treated with CABG revascularization. Since 1979, when Andreas Grüntzig reported that PCI was not suitable for the management of unprotected left main disease [41], significant advancements in the stent technology and revascularization techniques have occurred. All clinical trials presented over the past decade evaluating therapeutic approaches for left main disease have compared CABG with PCI revascularization without including a medical management-only arm. In the subpopulation of SYNTAX trial with unprotected left main disease, the investigators demonstrated similar rates of major adverse cardiac or cerebrovascular events between CABG and PCI in patients with low or intermediate SYNTAX score. While non-inferiority was not proven in the total cohort rendering the subgroup results observational, these findings led the way to further randomized clinical trials [16].

In the Excel trial, 1905 eligible patients with left main coronary artery disease of low or intermediate anatomical complexity were randomized to undergo either PCI with fluoropolymer-based cobalt–chromium everolimus-eluting stents or CABG. At the 3-year follow-up period, PCI revascularization was non-inferior to CABG with respect to the composite endpoint of death from any cause, stroke, or myocardial infarction [42]. Similar results were reported in the PRECOMBAT trial with wider non-inferiority margins [43].

Long-term comparison of stenting over CABG for the management of unprotected left main disease has also been reported. At the 10-year follow-up period of the LE MANS trial, PCI revascularization was associated with a trend toward higher ejection fraction compared with surgery. No significant difference in mortality, MACCE, occurrence of myocardial infarction, stroke, or repeated revascularization rates was observed. The probability of very long-term survival up to 14 years was comparable between PCI and CABG; however, there was a trend toward higher MACCE-free survival in the PCI group [44]. In the recently published results of the MAIN-COPARE trial, no difference in mortality and a composite outcome of death, Q-wave myocardial infarction, or stroke was observed in the first 5 years. After the 5-year period, PCI with drug-eluting stent implantation was associated with higher mortality and serious composite outcome rates compared with CABG. Target-vessel revascularization rates were consistently higher in the PCI with drug-eluting stenting cohort over the 10-year follow-up [45].

In a metanalysis of 11 randomized trials including 11,518 patients selected by the heart teams to undergo revascularization with PCI or CABG, CABG was shown to have a mortality benefit over PCI in patients with multivessel disease, particularly those with diabetes and higher coronary complexity. Interestingly, in patients with left main disease, all-cause mortality at 5 years was similar between the two interventions (10.7% after PCI vs. 10.5% after CABG; $P = 0.52$), regardless of diabetes status and SYNTAX score [46••].

Future perspective

In current clinical practice, how to best utilize ischemia to guide revascularization remains an area of debate. Previously described studies provide evidence to support both strategies of invasive management as well as conservative medical therapy. In this context, the ongoing ISCHEMIA trial is expected to provide further evidence and assist with decision-making. ISCHEMIA trial is designed to determine whether an initial invasive strategy of cardiac catheterization and optimal revascularization (with PCI or CABG, as determined by the local heart team) plus optimal medical therapy will reduce the primary composite endpoint of cardiovascular death or nonfatal MI in SIHD patients with moderate or severe ischemia and medically controllable or absent symptoms. This is compared with an initial conservative strategy of optimal medical therapy alone, with catheterization reserved for failure of optimal medical therapy. The study excluded patients with significant left main disease as well as those with no obstructive coronary artery disease as evaluated by a blinded coronary CT angiogram. Recruitment has been completed and study results are expected in 2019 [24•].

Conclusion

Conservative approach with guideline-directed medical therapy is now the cornerstone of management for SIHD. Revascularization in addition to optimal medical therapy is deemed appropriate in patients with refractory symptoms despite medical therapy, patients with high-risk features, and significant coronary disease burden. Multiple imaging modalities assessing both extent of ischemia as well as coronary lesion severity have attempted to identify the population that would benefit the most from revascularization. Current available trials provide arguments for both conservative and invasive approach underlying the complexity involved in decision-making. The process of reaching a therapeutic decision often necessitates a heart team approach, and no simple algorithm can be offered to guide the process. The addition of further clinical trials designed to address the question of revascularization in SIHD and identify differences in major adverse clinical events will hopefully add to our current understanding and guide therapeutic recommendations.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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