

Clinical Conundrum: Three Management Strategies for Three-Vessel Coronary Artery Disease?

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This Commentary relates to the article by H. Zhao and D. Zhang on pages 527–532.

Martin Luther King, Jr. once said “we are now faced with the fact that tomorrow is today. We are confronted with the fierce urgency of now. In this unfolding conundrum of life and history, there “is” such a thing as being too late. This is no time for apathy or complacency. This is a time for vigorous and positive action. We are now faced with the fact that tomorrow is today. We are confronted with the fierce urgency of now. In this unfolding conundrum of life and history, there “is” such a thing as being too late. This is no time for apathy or complacency. This is a time for vigorous and positive action.”

Inspired by King’s word, the goal of optimal pharmacotherapy is optimizing patient outcomes in an appropriate and consistent fashion, integrating itself with other management strategies, when and as appropriate, but this goal cannot be achieved if such therapy is not implemented in a forceful and proactive fashion. Indeed, cardiovascular pharmacotherapy for ischemic heart disease due to coronary artery disease (CAD) represents a unique case study in this sense, given the complex interplay between societal and individual preventive strategies as well as clinical treatments aimed at secondary or tertiary prevention, which may apparently challenge immediate and thorough implementation.^{1,2}

This issue of the Journal offers a poignant synthesis of 2 competing treatments for CAD, which benefit, however, both from comprehensive and state-of-the-art pharmacologic therapy: percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).³ In particular, Zhao and Zhang performed a comprehensive systematic review and meta-analysis pooling randomized and nonrandomized studies comparing PCI versus CABG in patients with three-vessel CAD and highlighting consistent comparative benefits for CABG (ie comparative hazards for PCI) when focusing on all-cause death, myocardial infarction, and repeat revascularization. Evidently, CABG is confirmed as the real winner in the PCI versus CABG contest for complex CAD.⁴

Irrespective of the results of this and similar meta-analysis comparing PCI versus CABG, a number of important issues should be borne in mind. First, any meta-analysis pooling small randomized trials or observational studies risks providing spuriously precise results if small study effects are given excessive statistical weights (such as in the case of publication bias and selective reporting of extreme study results).⁵ Second, outcomes may differ in importance for patients and also subjectively in specific patients. For instance, considering a myocardial infarction equivalent to a stroke may miss the point of the clearly different impact of each outcome on the quality of life and independent lifestyle. Even definitions may matter, with definitions of myocardial infarction proving particularly challenging. Indeed, periprocedural myocardial infarction may be defined differently after PCI versus CABG, and this may impact on comparative analysis. In addition, in some trials periprocedural myocardial infarction had been censored from long-term outcome comparisons, potentially favoring CABG. Symptom control may be

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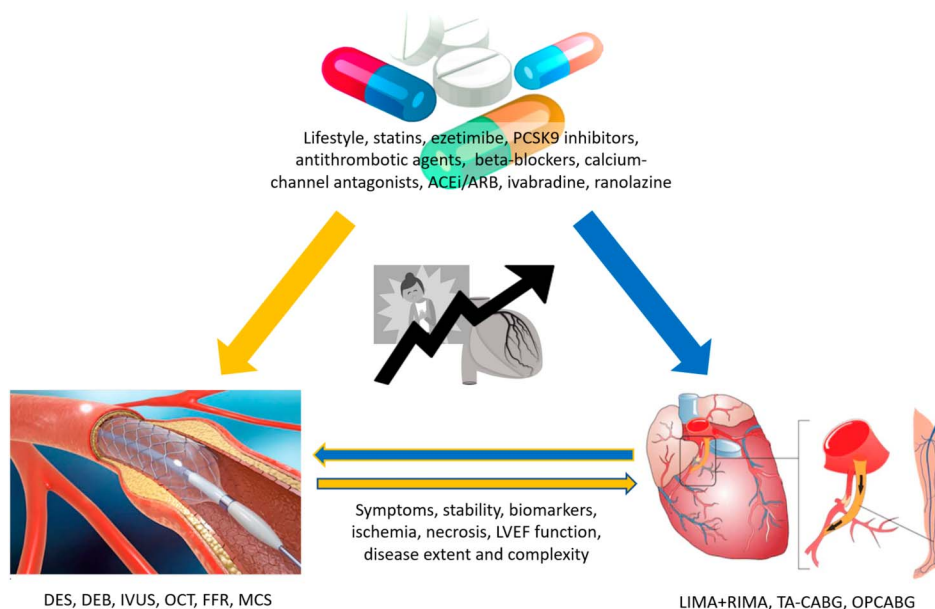
impacted by treatment strategy, and also symptom ascertainment may be difficult in studies lacking any form of actual blinding to patients or caring physicians. This holds even truer, given that CABG may lead to reduced symptom burden simply because of reduced cardiac innervation rather than because of more comprehensive relief from ischemia. Finally, goals of treatment may be altogether different, especially in light of time frames. For instance, PCI may, possibly, prevent myocardial infarction from complex lesions but cannot protect from atherothrombosis progression. This is at odds with CABG, in the sense that a left internal mammary artery to the mid left anterior descending may protect the patient from tightening of an already significant stenosis in the proximal left anterior descending and also from disease progression occurring, for instance, on the left main or the mid left anterior descending.^{6,7} This is most likely the key explanation for the comparative superiority of CABG versus PCI in patients with multivessel or three-vessel disease, left main disease, or left ventricular systolic dysfunction, given the substantial atherosclerotic burden of these patient subsets.

The main conundrum rests, however, not simply on choosing PCI versus CABG or on referring a given patient to an interventional cardiologist versus a cardiac surgeon. The main issue rests with optimizing noninvasive management and adopting state-of-the-art PCI or CABG methods, when choosing one or the other, notwithstanding the possibility to undergo CABG after PCI or PCI after CABG (Fig. 1). First, aggregate-level risk factors such as climate and pollution force us to consider collective interventions to improve global health, a choice which is even more important and potentially beneficial in the coronavirus disease 2019 (COVID-19) era.^{1,2,8} Second, lifestyle interventions ranging from regular

aerobic exercise to a healthy (ie slightly hypocaloric) diet remain key baseline interventions. Third, systematic use of medications with proven prognostic and/or symptomatic benefits is crucial, especially in an era where inexpensive generics abound, ranging from antithrombotic agents, such as aspirin or P2Y12 inhibitors, to statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, ivabradine, ranolazine, and, possibly, colchicine compounded as appropriate by medications with proven benefits in ischemic heart failure, such as mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, sodium/glucose cotransporter 2 inhibitors, and glucagon-like peptide-1 receptor agonists.⁹

Before invasive assessment and management is considered, it is imperative to weigh pros and cons and explicitly define goals (eg symptom control or systolic function improvement). To optimize such decision making, recent results from the pivotal International Study of Comparative Health Effectiveness With Medical and Invasive Approach (ISCHEMIA) trial should be well considered, including, for instance, the increased risk of periprocedural myocardial infarction, the reduced risk of spontaneous myocardial infarction, and the overall greater symptomatic benefit in patients managed invasively.¹⁰ After coronary angiography, joint decision making is best sought by multidisciplinary evaluation with a noninvasive cardiologist, an interventional cardiologist, and a cardiac surgeon. Fit patients with extensive CAD are typically better served by CABG, in terms of prognosis and symptoms, whereas less fit patients or those with more focal lesions may equally benefit from PCI. In any case,

FIGURE 1. Multidimensional management of CAD, beginning with aggressive medical therapy. Patients failing medical management or those with specific clinical features may benefit from PCI (orange arrow) or CABG (blue arrow), choosing revascularization strategy according to a comprehensive appraisal of patient, cardiac, and coronary features. PCI may be followed by CABG in case of restenosis or disease progression, and minimally invasive CABG may be combined with PCI of non-LAD lesions. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DEB, drug-eluting balloon; DES, drug-eluting stent; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LAD, left anterior descending; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; MCS mechanical cardiac support; OCT, optical coherence tomography; OPCABG, off-pump coronary artery bypass grafting; PCSK9, Proprotein convertase subtilisin/kexin type 9; RIMA, right internal mammary artery; TA-CABG, totally arterial coronary artery bypass grafting. The scheme was created using royalty-free images downloaded from shutterstock.com.



it is paramount to continue to offer optimal medical therapy to these patients because both PCI and CABG are simply de facto palliative therapies for coronary atherosclerosis. For instance, fractional flow reserve, instantaneous wave-free ratio, intravascular ultrasound, and optical coherence tomography should be used whenever appropriate to improve decision making and enable PCI optimization, which should be based on thin-strut new-generation drug-eluting stents (with a potential niche role for drug-eluting balloons), exploiting mechanical cardiac support whenever necessary in complex or hemodynamically unstable patients.¹¹ Similarly, CABG-related benefits are clearly greater if a totally arterial revascularization strategy is sought, for instance, with use of both right and left internal mammary arteries and reliance on radial artery grafts for the remaining needs.^{6,7,12}

Notwithstanding the distance between PCI and CABG, in selected cases off-pump CABG with left internal mammary artery grafting to the left anterior descending can be combined with PCI on the other diseased vessels during the same hospitalization. Similarly, PCI can be performed in an emergency for ST-elevation myocardial infarction and followed during the same hospitalization by CABG for residual multivessel disease.^{13,14} Finally, CABG remains a reasonable alternative for patients with disease progression or multivessel restenosis after PCI, whereas PCI is optimally suited to manage disease progression or graft failure after CABG or in case of contraindications to surgery, such as very advanced age.¹⁵

In conclusion, modern management of CAD requires a comprehensive integration of several lifestyle, pharmacologic, and invasive strategies, to maximize prognostic and symptomatic benefits while appropriately using resources. Indeed, quoting a pioneering cardiologist such as Antonio Colombo, “birds fly because they have wings and they flap them”. Similarly, optimal clinical results can only be achieved by using optimal cardiovascular medications in combination with PCI or CABG when each one is appropriate (typically in simpler and more complex cases, respectively).

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