

Treatment Selection for Multivessel Coronary Artery Disease

A practical appraisal for selecting the best revascularization therapy for patients with multivessel CAD.

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Among patients with coronary artery disease (CAD), multivessel stenoses are a more frequent occurrence than single-vessel disease. When compared with single-artery treatment, complete coronary revascularization in these patients is associated with better outcomes, such as improved functional status and higher rates of survival.¹ Coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI) are equally safe, and both are established treatment modalities of revascularization in patients with multivessel CAD.² During the last 3 decades, many studies and registries have shown that in multivessel CAD patients, CABG and PCI using bare-metal stents have been associated with similar clinical outcomes in terms of hard endpoints (ie, death and myocardial infarction), but that CABG has proven to be superior to PCI in terms of the need for repeat interventions.² Consequently, CABG has been considered for many years to be the gold standard therapy in patients with multivessel CAD, especially in those who are considered high risk (eg, diabetics and/or those with impaired left ventricular function).^{3,4} Importantly, both therapies have improved tremendously since their inception. CABG now routinely uses arterial-only grafts and can be performed off-pump, whereas drug-eluting stents (DES) have been increasingly used in PCI during the last decade, providing a safe and less-invasive option for CAD and allowing reduced hospital stay and an early return to daily activities.

Optimal treatment of multivessel CAD is still a subject of debate. This is mainly due to the difficulty of extrapolating data from randomized trials conducted in highly selected patients with multivessel CAD to the general CAD patient population. Clinical outcomes may also differ according to completeness of revascularization, the

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presence or absence of diabetes, whether diabetic patients are insulin dependent or not, the presence of left main disease, and left ventricular function. PCI is the treatment option that most patients prefer because of its less-invasive nature compared to CABG. Even when taking into account the lack of patient education regarding the long-term clinical outcomes of each revascularization strategy, the patient's preference remains an obvious determinant of clinical decision making, especially because PCI does not exclude CABG as a second option in cases of midterm failure requiring repeat intervention.

We aim to address some of these controversial issues by reviewing the most recent clinical data that have led to revised American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines, in an attempt to improve the understanding of the optimal care that should be delivered to patients with multivessel CAD.

SYNTAX SCORE AS A RISK STRATIFICATION SCALE

Whereas clinical variables such as increasing age, diabetes, renal failure, left ventricular dysfunction, and hemodynamic instability were conventionally shown to adversely affect clinical outcomes of multivessel CAD patients requiring revascularization, the main lesson

TABLE 1. INDICATIONS FOR CABG VS PCI^a

Subset of CAD by Anatomy	Favors CABG	Favors PCI
One- or two-vessel disease: nonproximal left anterior descending artery	IIb C	I C
One- or two-vessel disease: proximal left anterior descending artery	I A	IIa B
Three-vessel disease with simple lesions, fully functional revascularization achievable with PCI, SYNTAX score ≤ 22	I A	IIa B
Three-vessel disease with complex lesions, incomplete revascularization achievable with PCI, SYNTAX score > 22	I A	III A
Left main disease (isolated or one-vessel disease, ostium/shaft)	I A	IIa B
Left main disease (isolated or one-vessel disease, distal bifurcation)	I A	IIb B
Left main disease + two- or three-vessel disease, SYNTAX score ≤ 32	I A	IIb B
Left main disease + two- or three-vessel disease, SYNTAX score ≥ 33	I A	III B

^aIn stable patients with lesions suitable for both procedures and low predicted surgical mortality. Adapted from Wijns W et al. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2010;31:2501-2555.⁸

that we learned from the SYNTAX trial⁵ is the strong negative impact of the complexity of coronary disease, as measured by the so-called SYNTAX score,⁶ on PCI outcomes. Interestingly, the SYNTAX score was not predictive of outcomes after CABG.⁷ The SYNTAX trial was the first large trial (N = 1,800) to randomize suitable patients for revascularization to either CABG or PCI using paclitaxel-eluting stents to treat left main and/or three-vessel disease.⁵ The rates of major adverse cardiac and cerebrovascular events (MACCE) at 12-month follow-up were significantly higher among patients treated by PCI who had a high SYNTAX score (≥ 33 ; 23.4%) compared to those with a low (0–20; 13.6%) or intermediate (23–32; 16.7%) score. Indeed, the 12-month event rates were similar after CABG and PCI for patients with low and intermediate SYNTAX scores, whereas

those with high SYNTAX scores who were treated by PCI had a significantly higher event rate than those treated by CABG (23.4% vs 10.9%; $P < .001$). The SYNTAX investigators also showed that the presence of left main disease and nonachievement of complete revascularization were associated with adverse outcomes at 2 years.⁷ This was corroborated by the 3-year results of the SYNTAX trial,⁹ which showed that patients with left main disease had comparable MACCE rates after PCI and CABG (26.8% vs 22.3%; $P = .2$). Additionally, PCI outcomes with regard to MACCE were excellent compared to CABG in patients who were treated for isolated left main disease (11.9% vs 17%), left main plus one-vessel disease (19.4% vs 26.7%), and in patients with a low or intermediate SYNTAX score (20.5% vs 23.2%). The results of SYNTAX prompted the revision of recom-

TABLE 2. METHOD OF REVASCULARIZATION OF ADVANCED CAD^a

	CABG			PCI		
	No diabetes and normal LVEF	Diabetes	Depressed LVEF	No diabetes and normal LVEF	Diabetes	Depressed LVEF
Two-vessel CAD with proximal left anterior descending artery stenosis	A	A	A	A	A	A
Three-vessel CAD	A	A	A	U	U	U
Isolated left main stenosis	A	A	A	I	I	I
Left main stenosis and additional CAD	A	A	A	I	I	I

Abbreviations: A, appropriate; I, inappropriate; U, uncertain; LVEF, left ventricular ejection fraction.

^aAdapted from Patel MR et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: A Report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology. Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation*. 2009;119:1330-1352.¹⁰

mendations both in the United States¹⁰ and in Europe⁸ in 2009 and 2010, respectively.

The ESC recommendations were stratified on the basis of anatomic complexity of CAD, thus applying the results of SYNTAX to patients with stable presentation and low predicted surgical mortality (Table 1). On the other hand, the ACC/AHA recommendations were based on the presence or absence of diabetes, as well as impaired left ventricular function (Table 2). It is noteworthy that the European guidelines were more practical and in line with the results of the SYNTAX trial, whereas the ACC/AHA recommendations were less favorable to PCI and excluded patients with significant left main lesions from this technique, which was not consistent with the latest reported data. Indeed, in the SYNTAX trial, patients with left main disease had better outcomes than patients with multivessel disease when treated by PCI compared to CABG.

Very interestingly, in 16,142 patients who were treated in 19 hospitals in New York state between 2005 and 2007, Hannan et al¹¹ reported that patients with multivessel CAD received more recommendations for PCI and fewer recommendations for CABG than indicated in the ACC/AHA guidelines. These data show that patient referral to a coronary revascularization strategy is mainly guid-

ed by the preference of interventional cardiologists working in hospitals with PCI capability.

COMBINING CLINICAL AND ANATOMICAL SCORES

Another lesson that we learned from the SYNTAX trial is the key role of a heart team. Establishing a multidisciplinary team of clinical cardiologists, anesthesiologists, interventional cardiologists, and cardiothoracic surgeons is essential to ensuring that the most appropriate strategy is proposed to a given multivessel CAD patient. Both the ACC/AHA and ESC recommend a general approach with subsequent application to a given patient after multidisciplinary discussion and debate. Combining clinical and anatomical scores is of interest when selecting the optimal treatment option for a patient with multivessel CAD. Although the SYNTAX score is predictive of outcomes after PCI only, the EuroSCORE, Parsonnet score, and Society of Thoracic Surgeons score are able to predict the perioperative or 30-day mortality rates after CABG. Therefore, combining the EuroSCORE and SYNTAX score may be an appropriate strategy for risk stratification in patients with multivessel CAD. Patients with a high EuroSCORE are usually considered for PCI because of very high post-CABG

TABLE 3. APPRAISAL OF REVASCULARIZATION TECHNIQUES FOR MULTIVESSEL CAD

Indication	High EuroSCORE	Low EuroSCORE
Three-vessel disease, SYNTAX score < 33	PCI > CABG	PCI > CABG
Three-vessel disease, SYNTAX score $\geq$ 33	Case-by-case discussion	CABG > PCI
Isolated left main disease	PCI	PCI > CABG
Left main disease + one-vessel disease	PCI	PCI > CABG
Left main disease + two- or three-vessel disease	Case-by-case discussion	CABG > PCI

mortality. Patients with a low EuroSCORE, a low or intermediate SYNTAX score (< 32), isolated left main disease, or left main plus one-vessel disease may be preferentially referred to PCI, and those with a high SYNTAX score ($\geq$ 33) or left main plus two- or three-vessel disease are referred to CABG (Table 3). In some high-risk patients with very poor physiological status who are frequently deemed unsuitable candidates for both PCI and CABG (elevated EuroSCORE and SYNTAX score), there is no clear consensus, but PCI is usually preferred because of its less-invasive nature.

PRAGMATIC TREATMENT APPRAISAL FOR CTOs

Registry studies have shown that the incidence of chronic total occlusions (CTOs) can be as high as 30% to 50% in patients with significant CAD who are undergoing coronary angiography.^{12,13} The rationale for PCI of CTOs is the improvement in ischemic burden, ejection fraction, quality of life, and survival, as well as the decreased need for CABG, as shown by many retrospective studies comparing successful PCI to failed PCI.¹⁴⁻¹⁶ Although the results of PCI were relatively poor in these patients because of high rates of failure to cross the occlusion or restenosis or reocclusion after successful balloon angioplasty or bare-metal stent implantation, the development of novel technologies and techniques has dramatically improved procedural success rates, and the use of DES has increased long-term vessel patency.¹⁷⁻¹⁹ In 2008, Valenti et al²⁰ showed that successful PCI of CTOs conferred a long-term survival benefit, which was driven by the differences in the outcomes of patients with multivessel CAD who were completely revascularized. Considering these data and the relative higher probability of PCI failure in these patients, we suggest that treatment of the CTO lesion should be attempted first and that the patient should be referred to surgery in cases when the initial strategy proves unsuccessful.

ARE THE RESULTS OF SYNTAX APPLICABLE TO CURRENT PRACTICE?

The results of SYNTAX are sometimes inappropriately applied to all multivessel CAD patients. First of all, it is noteworthy that these results are only applicable to patients with three-vessel disease and/or left main coronary disease, in whom equivalent anatomical revascularization could be achieved with either PCI or CABG as shown in the study population. It is also very important to keep in mind that the SYNTAX trial was a noninferiority comparison of two groups of patients who were treated by PCI or CABG for the primary endpoint (MACCE as defined as death from any cause, stroke, myocardial infarction, or repeat revascularization). Therefore, comparing other endpoints or parts of the primary endpoints (eg, repeat revascularization), comparing data in subgroups of the whole population (except for patients with left main or three-vessel disease, which were prespecified), or underlining the superiority of either of these two techniques would be improper and inaccurate. In addition, one of the main criticisms leveled at the SYNTAX trial is that patients who were referred to PCI were treated using the first-generation paclitaxel-eluting stent (Taxus, Boston Scientific Corporation, Natick, MA), which has recently been associated with a less favorable outcome, including higher rates of occlusion and restenosis, compared to newer-generation DES.²¹ In view of this, we may reasonably think that the rate of adverse events might have been in favor of PCI if patients had received newer-generation DES. In response to the SYNTAX results, the ACC/AHA changed the indication for stenting patients with left main or three-vessel disease from class III to IIb. The revised recommendations still do not represent an unconditional endorsement of PCI, but they may encourage more medical teams to select this revascularization strategy in patients with low-to-intermediate lesion complexity.

The EXCEL trial is designed to randomize 2,500 patients with left main disease who have low or intermediate SYNTAX scores at a 1:1 ratio to panarterial CABG or to complete revascularization by PCI using the everolimus-eluting Xience Prime stent (Abbott Vascular, Santa Clara, CA). The EXCEL trial, which is currently underway, may address some of the limitations of previous studies and be more relevant to contemporary practice, although it will not address the issue of patients with high SYNTAX scores who are currently considered poor candidates for PCI. We have recently reported²² lower rates of events after everolimus-eluting stents compared to paclitaxel-eluting stents in selected patients with significant left main lesions treated by either Taxus²³ or Xience²⁴ DES in multicenter, nonrandomized registries. This comparison, as well as others,²⁵ emphasized the appropriateness of the SYNTAX score in patients treated with newer-generation DES, thus showing that the rate of events after PCI is not only dependent on the complexity score but also on the stent type used.

THE ROLE OF FFR GUIDANCE IN TREATING MULTIVESSEL CAD

Another piece of the coronary revascularization jigsaw puzzle has been provided by the FAME trial.²⁶ The purpose of this randomized trial, which was conducted in patients with multivessel disease, was to compare PCI of angiographically significant lesions with PCI of significant functional lesions as assessed by fractional flow reserve (FFR). The study showed that FFR guidance not only showed a reduction in the number of lesions requiring treatment (only 14% of patients had functional three-vessel disease, 43% had two-vessel disease, and 34% had single-vessel disease) but also led to a decrease in the MACE rate at 1 year (13.2% vs 18.4%; $P = .02$), as well as overall costs. This new approach shed some light on the strategy of PCI treatment in multivessel CAD patients by supporting the evolving paradigm of functionally complete revascularization (ie, stenting of ischemic lesions and medical treatment of nonischemic lesions). This finding has proven to be consistent with the conclusions of the COURAGE trial, which showed that PCI treatment of ischemic lesions is instrumental in improving patient outcomes.²⁷

CONCLUSION

Treatment selection for patients with multivessel CAD has changed during the last 2 years, thanks to the publication of the results of the SYNTAX trial. Risk/benefit stratification may be obtained by combining clinical and anatomical scores (ie, EuroSCORE and SYNTAX score) to select the best revascularization therapy for a given

patient. In addition, the benefit of treating functionally significant lesions alone has been well demonstrated by the FAME trial. These data have been taken into account in the recently updated ACC/AHA and ESC recommendations. ■

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1. Sarno G, Garg S, Onuma Y, et al; ARTS-II Investigators. Impact of completeness of revascularization on the five-year outcome in percutaneous coronary intervention and coronary artery bypass graft patients (from the ARTS-II study). *Am J Cardiol*. 2010;106:1369-1375.
2. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. *Circulation*. 2008;118:1146-1154.
3. King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. *Circulation*. 2008;117:261-295.
4. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation*. 2004;110:1168-1176.
5. Serruys PW, Morice MC, Kappetein AP, et al; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-972.
6. SYNTAX Working Group. SYNTAX score calculator. <http://www.syntaxscore.com>. Accessed November 2009.
7. Mohr FW, Rastan AJ, Serruys PW, et al. Complex coronary anatomy in coronary artery bypass graft surgery: impact of complex coronary anatomy in modern bypass surgery? Lessons learned from the SYNTAX trial after two years. *J Thorac Cardiovasc Surg*. 2011;141:130-140.
8. Wijns W, Kolh P, Danchin N, et al; European Association for Percutaneous Cardiovascular Interventions. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2010;31:2501-2555.
9. Garot P, Morice MC. Controversy, challenges, and landmark clinical trials. The SYNTAX left main analysis: left main PCI for most patients. Presented at: American Heart Association 2010 scientific sessions; November 13-17, 2010; Chicago, IL.
10. Patel MR, Dehmer GJ, Hirshfeld JW, et al. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: A Report of the American College of

Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulation*. 2009;119:1330-1352.

11. Hannan EL, Racz MJ, Gold J, et al; American College of Cardiology and American Heart Association. Adherence of catheterization laboratory cardiologists to American College of Cardiology/American Heart Association guidelines for percutaneous coronary interventions and coronary artery bypass graft surgery: what happens in actual practice? *Circulation*. 2010;121:267-275.

12. Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. *Am Heart J*. 1993;126(3 Pt 1):561-564.

13. Christofferson RD, Lehmann KG, Martin GV, et al. Effect of chronic total coronary occlusion on treatment strategy. *Am J Cardiol*. 2005;95:1088-1091.

14. Suero JA, Marso SP, Jones PG, et al. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. *J Am Coll Cardiol*. 2001;38:409-414.

15. Hoyer A, van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience 1992-2002. *Eur Heart J*. 2005;26:2630-2636.

16. Noguchi T, Miyazaki MD S, Morii I, et al. Percutaneous transluminal coronary angioplasty of chronic total occlusions. Determinants of primary success and long-term clinical outcome. *Cathet Cardiovasc Interv*. 2000;49:258-264.

17. Hoyer A, Tanabe K, Lemos PA, et al. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions. *J Am Coll Cardiol*. 2004;43:1954-1958.

18. Ge L, Iakovou I, Cosgrave J, et al. Immediate and mid-term outcomes of sirolimus-eluting stent implantation for chronic total occlusions. *Eur Heart J*. 2005;26:1056-1062.

19. Orlic D, Bonizzoni E, Stankovic G, et al. Treatment of multivessel coronary artery disease with sirolimus-eluting stent implantation: immediate and mid-term results. *J Am Coll Cardiol*. 2004;43:1154-1160.

20. Valenti R, Migliorini A, Signorini U, et al. Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. *Eur Heart J*. 2008;29:2336-2342.

21. Stone GW, Midei M, Newman W, et al; SPIRIT III Investigators. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. *Circulation*. 2009;119:680-686.

22. Garot P, Morice MC, Salvatella N, et al. A comparison of 12-month follow-up after unprotected left main lesions stenting using the paclitaxel and the everolimus-eluting stent. A post-hoc analysis from the French left main Taxus and the left main Xience registries. *Transcatheter Cardiovascular Therapeutics* 2010; September 21-25, 2010; Washington, DC.

23. Vaquerizo B, Lefèvre T, Darremont O, et al. Unprotected left main stenting in the real world: two-year outcomes of the French left main taxus registry. *Circulation*. 2009;119:2349-2356.

24. Salvatella N, Morice MC, Lefevre T, et al. Unprotected left main stenting with a second-generation drug-eluting stent. One-year outcomes of the LEMAX pilot study. In press.

25. Wykrzykowska JJ, Garg S, Girasis C, et al. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) trial. *J Am Coll Cardiol*. 2010;56:272-277.

26. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation). *J Am Coll Cardiol*. 2010;55:2816-2821.

27. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the clinical outcomes utilizing revascularization and aggressive drug evaluation (Courage) trial nuclear substudy. *Circulation*. 2008;117:1283-1291.

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