Review Article

Revascularization Strategies in Multivessel and Left Main Coronary Artery Disease: SYNTAX and Beyond

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Key words:
Multivessel coronary artery disease, percutaneous coronary intervention, coronary artery bypass grafting, optimal medical treatment.

Manuscript received:
February 17, 2014;
Accepted:
April 29, 2014.

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Despite tremendous medical progress over the last 20 years in the fields of conservative, interventional and surgical treatment, the selection of therapy in stable coronary artery disease (CAD) remains a challenge. Specifically, the optimal revascularization mode in complex CAD has been a matter of continuous debate between cardiologists and cardiac surgeons.[1] Recent studies have elucidated some issues but have also fueled the controversy concerning the best management strategy in patients with multivessel and left main (LM) CAD.

The impact of myocardial ischemia

The CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes) study examined 15,223 individuals without known CAD using multidetector computed coronary angiography.[2] High-risk patients were defined as those with 2-vessel disease (VD) with proximal involvement of the left anterior descending (LAD) artery, 3-VD or disease of the LM stem. This anatomy was encountered in 7.3% of these subjects. Revascularization was an independent predictor of survival at 2.1 years as compared with non-revascularized patients (hazard ratio, HR: 0.38; 95% confidence interval, CI: 0.38-0.83). However, neither ischemia burden nor ischemia reduction were ascertained. In fact the impact of ischemia *per se* or ischemia reduction on outcome remains an unsettled issue. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) nuclear substudy indicated that percutaneous coronary intervention (PCI) gave better results than optimal medical treatment (OMT) in suppressing ischemia, and that patients with ischemia reduction had a lower unadjusted risk for death or myocardial infarction.[3] Notwithstanding that, in a COURAGE *post hoc* analysis, the extent of site-defined ischemia did not predict death or myocardial infarction (MI) and did not alter treatment effectiveness.[4]

Likewise, in the BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) nuclear substudy, the severity of baseline ischemia predicted a dismal outcome and revascularization resulted in less ischemia compared with OMT;[5] however, the outcome did not differ between the revascularized and non-revascularized study groups.[6]

Revascularization versus OMT

In contrast to coronary artery bypass grafting (CABG), the benefit of PCI over OMT in stable CAD has been difficult to establish. This was reinforced by the

COURAGE trial.[7] A recent meta-analysis suggested that PCI, although associated with periprocedural MI, may be advantageous over OMT as it prevents spontaneous, remote MI.[8]

In the FAME 2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2) trial, PCI guided by fractional flow reserve (FFR) in comparison with OMT reduced the composite primary endpoint of death, MI or urgent revascularization at 12 months by 68% (HR: 0.32; 95% CI: 0.19-0.53; p<0.001). In this study, patients with 1-, 2- and 3-VD were included and FFR<0.80 was considered abnormal.[9] The results were driven exclusively by the high rates of urgent revascularization in the OMT group. Therefore, in stable, relatively low-risk CAD patients, the FFR revascularization approach appears important to improve prognosis compared with OMT alone. The clinical impact of FFR on outcome is further corroborated by observational data from South Korea and France.[10,11] The recent broad implementation of FFR was associated with less stent use, better outcomes, and fewer repeat revascularizations compared to the era without FFR use (relative risk reduction 29-51%).[11] Performing FFR during diagnostic angiography may result in reclassification of the revascularization decision in about half of the patients. Pursuing an FFR-dictated revascularization strategy divergent from that suggested by angiography was safe in 1075 patients.[10]

The advantage of CABG as compared with OMT has been evident in patients with normal or moderate left ventricular (LV) systolic dysfunction but not in those with an LV ejection fraction (EF) ≤35%. In the STICH (Surgical Treatment for Ischemic Heart Failure) trial, 1212 patients with CAD and LVEF≤35% were randomized to CABG + OMT vs. OMT alone. Patients with angina pectoris class III or IV were excluded from the STICH study.[12] About 30% had 2-VD and 60% 3-VD. In the surgical and the conservative group there was a crossover rate of 9% and 17%, respectively, to the other treatment arm. The primary endpoint of total mortality after a median follow up of 56 months did not differ between groups (36% vs. 41%, HR with CABG: 0.86; 95% CI: 0.72-1.04; p=0.12). The secondary endpoint of cardiovascular mortality (28% vs. 33%, p=0.05) and the combined endpoint of total mortality and hospitalization for cardiovascular causes (58% vs. 68%, p<0.001) were lower in the CABG + OMT group.

In the STICH-viability substudy, 601 of the 1212 patients of the STICH trial underwent viability assessment with stress echocardiography or myocardial perfusion imaging.[13] Patients with viability demonstrated better survival than those without viability, a finding which no longer remained significant after adjustment for baseline variables. Surgery did not improve prognosis as compared with OMT, whether patients showed or did not show viability. Viable myocardium *per se* seems to place the patients at lower risk, but the combination of viability and ischemia would likely elevate future ischemic events if left without revascularization. This combination was analyzed *post hoc* in a subset of patients in the STICH-viability trial. Of the 399 study patients with a mean EF of 26%, roughly two thirds had inducible ischemia on either imaging stress test. Inducible myocardial ischemia did not identify patients with a worse prognosis or those with greater benefit from CABG over OMT.[14] Several hypothetical factors may have accounted for the neutral results of revascularization in the STICH patients, including methodological problems inherent in the study design and stress test information, as well as a possible shift in the relative contributions of scarring, rather than ischemia, to mortality in severe ischemic cardiomyopathy.[15] Furthermore, the relevance of viability may critically depend on the coronary anatomy (i.e. occluded vs. stenosed artery) and the presence or not of angina or residual large ischemic myocardial territory.

In the recent American guidelines on stable CAD in the subset of patients with LV systolic dysfunction, surgery has a class IIa level of recommendation (LoR) for LVEF 35-50% and IIb for LVEF<35% without LM disease. For PCI there are insufficient data.[16]

For heart failure, the European guidelines, specify LoR I for LM disease with angina to reduce mortality, and for multivessel disease to reduce cardiovascular morbidity and mortality. Alternatively, PCI may be considered in the above patients (LoR IIb).[17] The American guidelines recommend CABG or OMT for patients with severe LV dysfunction (EF<35%) to improve morbidity and mortality with LoR IIa, and CABG whether or not viable myocardium is present with LoR IIb.[18]

The effect on prognosis of treating silent ischemia was recently reviewed.[19] The STICH and COURAGE trials did not address the evaluation of silent ischemia burden with ambulatory electrocardiographic monitoring after treatment. Remaining silent ischemia despite OMT may identify high-risk individuals for ischemic complications. Newer antianginal drugs,

such as ivabradine or ranolazine, and FFR-guided PCI should be tested prospectively for silent ischemia reduction and outcome improvement.

PCI versus CABG

The comparison of these two revascularization strategies has been examined in randomized control trials (RCTs) and registries. The characteristics of the patients indicated lowest risk in the RCTs before the SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) trial, intermediate risk in the registries, and highest risk in SYNTAX.[1,20]

With the exception of the SYNTAX trial and the New York State registry, the previous investigations have provided an equipoise in the PCI vs. surgical controversy.[1] New data have elucidated this topic. A meta-analysis of older RCTs revealed that the CABG-to-PCI HR for mortality was <1.0 (i.e. favored CABG) at age >63 years among patients without diabetes mellitus (DM) and at age >47 years among patients with DM.[21] Two recent studies showed a greater mortality for PCI compared with surgery. The first study evaluated combined data from the Centers for Medicare and Medicaid Services for the years 2004 through 2008. Among patients ≥65 years of age with 2- or 3-VD, but without acute MI, 86,244 underwent CABG and 103,549 underwent PCI.[22] The median follow-up period was 2.7 years. At 4 years but not at 1 year, mortality was lower with CABG than with PCI (HR: 0.79; 95% CI: 0.76-0.82) In the second cohort study, among 105,156 propensity score-matched patients the improvement in survival for surgery over PCI was concentrated among patients with diabetes, tobacco use, heart failure, or peripheral arterial disease.[23]

Additionally, the impact of completeness of revascularization has been reinforced by a large number of patients and the SYNTAX trial. Complete over incomplete revascularization was more commonly achieved by CABG rather than PCI and was associated with a reduction of 29%, 22%, and 26% in mortality, incident MI, and repeat revascularization, respectively, with a consistent effect in patients with or without total occlusions.[24,25] These data indicate that: (i) PCI should be considered for younger and surgery for older or multi-morbid patients; (ii) surgery may take several years to show a mortality benefit over PCI; and (iii) complete revascularization should be achieved whenever possible.

The 5-year results of the SYNTAX trial among patients with 3-VD confirmed that the primary endpoint of major cardiovascular events (MACE), i.e. death, MI, stroke or repeat revascularization, was met less frequently by CABG as compared with paclitaxel-eluting stent PCI.[26] Mortality (p=0.006), incident MI (p<0.001) and the triple ischemic endpoint of death, MI or stroke (p<0.001) were also lower in the surgical group. The rate of stroke was no longer different between the 2 revascularization groups of patients with 3-VD. These results magnified the surgical superiority over PCI, which was already obvious at 3 years.[1] The more complex the anatomy, the more advantageous was CABG (p=0.008 for SYNTAX score 23-32; p=0.005 for SYNTAX score ≥33). Only patients with a SYNTAX score ≤22, i.e. in the lowest tertiles, treated with PCI had similar outcomes to those treated surgically.[26]

The 5-year results of the SYNTAX trial among patients with LM disease lent support to the 3-year report, as mortality, MI and the triple ischemic endpoint did not differ between CABG and PCI.[26] The stroke rate was lower in the PCI group (p=0.03) but repeat revascularization was more frequent than for surgery (p<0.001). The rate of MACE was similar between groups in the first and second SYNTAX tertiles, but higher among patients undergoing PCI with very complex anatomy i.e. SYNTAX score ≥33 (p=0.003).

In the DELTA registry of unprotected LM CAD, 1874 patients were treated with first generation drug-eluting stents (DES) and PCI vs. 901 with CABG.[27] At 3.5 years, there were no differences, according to the adjusted analysis, in the primary composite endpoint of death, MI and stroke. An advantage of CABG over PCI was observed in the composite secondary endpoint of MACE (adjusted HR: 1.64; 95% CI: 1.33-2.03; p<0.0001), driven exclusively by the higher incidence of target vessel revascularization with PCI. The PRECOMBAT (Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease) trial from South Korea enrolled 600 patients with unprotected LM disease.[28] This RCT compared CABG with PCI using sirolimus DES. At 1 year, PCI was found to be non-inferior to surgery regarding mortality, incident MI, stroke or the triple ischemic endpoint. However, non-inferiority margins were wide. Rates of repeat revascularization favored CABG (p=0.02). A smaller RCT from Leipzig found favorable results of PCI for death or MI, but higher rates of repeat revascularization (14% vs. 5.9%) at 1 year.[29]

In a meta-analysis, PCI compared with CABG for unprotected LM CAD reduced the rate of death/MI/stroke by 30% (HR: 0.70, 95% CI: 0.49-1.00) and increased the rate of repeat revascularization by 3.5 times.[30] The ongoing EXCEL trial (comparing everolimus-eluting stent systems to CABG in subjects with unprotected left main coronary artery disease), which recruited patients with LM disease and SYNTAX score ≤32 will provide further important information on this topic.[31]

PCI versus CABG in patients with DM

Diabetic patients with CAD as compared with non-diabetics show higher long-term mortality, regardless of revascularization mode.[32] In a meta-analysis of all RCTs before SYNTAX, the subgroups of patients with DM undergoing CABG had a lower probability of death than those undergoing PCI.[33] This held true even after exclusion of the BARI trial.

Moreover, the diabetic subset of patients in the SYNTAX trial demonstrated at 5 years: (i) significantly higher rates of MACE ($p<0.001$), death ($p=0.003$) and repeat revascularization ($p<0.001$) than non-diabetic patients among those who underwent PCI;[34,35] and (ii) similar death/infarction/stroke rates between the two revascularization groups, but higher rates of repeat revascularization for PCI than for surgical patients.[1]

The issue of optimal revascularization approach in patients with DM was specifically addressed in three recently published RCTs with a 2-5 year follow up. (Table 1)

The CARDia (Coronary Artery Revascularization in Diabetes) trial included 510 diabetic patients with relatively complex CAD, of whom 69% received a DES. The primary endpoint of death, MI and stroke at 5 years was non-inferior in the PCI group. However, the study was underpowered, with a wide non-inferiority margin at 12%. Rates of MI and repeat revascularization were higher in the PCI than in the CABG patients.

The FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial enrolled 1900 patients with DM. At 2 years, the primary endpoint of death, MI and stroke was similar between groups, but at 5 years it was more frequent in the PCI than in the surgical group ($p=0.005$).[38] Likewise, mortality ($p=0.049$) and incident MI ($p<0.001$) at 5 years were lower in the surgical than in the PCI

Table 1. Overview of baseline characteristics and outcomes in patients with multivessel coronary artery disease and diabetes mellitus randomized to percutaneous coronary intervention or coronary artery bypass surgery.

Trial	N/Duration of follow-up (yrs)	Age (yrs)	Insulin requiring DM (%)	MVD	3-VD	SS (%)	LVEF (%)	Death, MI, Stroke or Death, MI§ (%)	Death (%)	MI (%)	Stroke (%)	RRevasc at 1 year (%)	Death, MI, Stroke, RRevasc (%)
SYNTAX diabetic subset	452/5	65	40	100		29	71‖	23.9/19.1	19.5/12.9	9.0/5.4	3.0/4.7	20.3/6.4‡	46.5/29‡
CARDia	510/5	64	38	100	63	NA	59.5	26.6/20.5	14.0/12.5	14.0/6.3†	4.3/3.1	11.8/2.0‡	37.5/26†
FREEDOM	1900/5	63.1	32	100	83	26.1	66	26.6/17.0†	16.3/10.9*	13.9/6.0‡	2.4/5.2*	12.6/4.8‡	
VA	198/2	62	48	NA	NA	22	NA	25.3/18.4	21/5	6.2/15.0	1.0/1.2	11.6/11.3	NA

*$p<0.05$; †$p<0.01$; ‡$p<0.001$; §The primary endpoint in the VA trial. ‖Two percent of the SYNTAX patients with DM had left main disease only. DM – diabetes mellitus; LVEF – left ventricular ejection fraction; MI – myocardial infarction; MVD – multivessel disease; NA – non-applicable; RRevasc – repeat revascularization; SS – SYNTAX score; 3-VD – 3-vessel disease; VA – Veterans' Administration.

patients, but stroke rates were double (p=0.049). However, only one fourth of the study patients had a 5-year follow up. Subgroup analysis demonstrated no significant interaction of either treatment modality and outcome. Thus, the surgical benefit in comparison with PCI in patients with DM appears similar across the examined subgroups. The FREEDOM trial was adequately powered to make obvious the increasing propensity of diabetic patients for death or MI in the long term when they have undergone PCI rather than CABG.[38] This trend was also apparent in the CARDia trial for incident MI.

To summarize these 3 studies, the rates of the triple ischemic endpoint appeared remarkably similar, within a narrow range of 23.9-26.6% for PCI and 17-20.5% for CABG.[34-38] Similarly, the frequency of repeat revascularization at 1 year was quite high at 12-20% for PCI in the DES era, as compared with the 2-6% rate in the surgical groups of diabetic patients.

A surgical strategy may be a cost-effective approach in patients with DM and multivessel disease. Cost-effectiveness analysis in FREEDOM revealed higher surgical cumulative 5-year costs per patient, but an economically attractive relationship of CABG relative to DES-PCI over a lifetime horizon, with incremental cost-effectiveness ratios <$10,000 per life-year across a broad range of assumptions regarding the surgical effect on post-trial survival and costs.[39]

The Veterans' Administration study included 198 patients with DM and severe CAD.[40] This RCT was stopped prematurely because of slow recruitment after enrolling only 25% of the intended sample size, leaving it severely underpowered for the primary composite endpoint of death plus non-fatal MI (HR for CABG vs. PCI: 0.89; 95% CI: 0.47-1.71; p=NS). Notably, there was an strikingly higher 2-year mortality rate of 21% in the PCI vs. 5% in the surgical group (HR: 0.30; 95% CI: 0.11-0.80) and a more than threefold higher incidence of MI in the CABG group.

Interestingly, among the 297 diabetic patients of the SYNTAX trial, the impact of revascularization mode on MACE at 4 years in the 3 SYNTAX score tertiles was similar to the overall study results.[41] While surgery was superior in patients with SYNTAX score >23, the outcome was almost identical between PCI and CABG in the low-score category. These findings were similar to the FREEDOM results. In a meta-analysis, revascularization of patients with diabetes and multivessel disease by CABG decreased long-term mortality by about a third compared with PCI using either bare-metal stents or DES.[42]

SYNTAX & SYNTAX II scores

The SYNTAX score was shown to affect the outcome of PCI but not CABG patients.[20] We have previously reported that SYNTAX suffers from interobserver variability[1,43] and does not incorporate clinical risk factors. For example, in the 1-year results of the SYNTAX trial, the incidence of MACE was more than 30% lower in non-diabetics than in diabetics, despite similar SYNTAX scores.[1] The SYNTAX score II was developed as a more individualized approach to the appropriate revascularization mode. The SYNTAX score II contains 7 clinical variables in addition to the anatomical SYNTAX score.[44] SYNTAX score II discriminated well in all patients who underwent CABG or PCI, with concordance indices for internal (SYNTAX trial[20,26]) validation of 0.725 and for external (DELTA registry[27]) validation of 0.716, which were substantially higher than for the anatomical SYNTAX score alone. Notably, the presence of diabetes was not important for decision making between CABG and PCI (p for interaction: 0.67). This finding may be explained by the interrelation of DM with age (as a surrogate of more advanced CAD and longer duration of DM in older patients), CAD complexity (as assessed in the SYNTAX score), LVEF, and kidney disease.[44] For example, a more robust association was found between chronic kidney disease, rather than diabetes mellitus, with both incident CAD and all-cause mortality in subjects with or without a history of MI.[45]

Will the recent studies facilitate the management of patients with multivessel or LM disease?

Although the link between ischemia treatment and prognosis improvement awaits more data to be definitely established, observational studies convergently depict the hazards of severe, non-revascularized CAD. In general, recent knowledge has made more obvious the impact of complete revascularization, the advantage of surgery over PCI in complex CAD and patients with DM, and the potential for LM treatment with PCI in patients with increased surgical risk.

The American guidelines give CABG a class I LoR for 3-VD, I for 2-VD with proximal LAD involvement, and IIa for 2-VD without proximal LAD disease but extensive ischemia, or IIb without extensive ischemia. For PCI, the LoR is only IIb for all categories of multivessel disease.[16]

The recent European guidelines recommend PCI

for 1- or 2-VD without proximal LAD involvement and either revascularization mode if proximal LAD disease is present, after discussion with the Heart Team. In patients with 3-VD and SYNTAX score <23, the revascularization options should be analyzed by the Heart Team; low surgical risk patients with higher SYNTAX scores should receive CABG without formal multidisciplinary discussion.[46]

For LM disease, the LoR for PCI in the American guidelines varies between IIa, for ostial/shaft disease in the presence of significantly increased surgical risk, IIb for bifurcation lesions or SYNTAX score <23 in the presence of increased surgical risk, and III for complex coronary anatomy in good surgical candidates.[16]

The European guidelines recommend PCI for patients with LM and no additional disease or 1-VD, if both ostial or shaft disease and high surgical risk are present, and either PCI or CABG for bifurcation LM disease. If 2- or 3-VD with SYNTAX score <32 is evident, PCI or surgery should be considered; CABG is the preferred therapy if the SYNTAX score is >32 and may be selected without Heart Team discussion if the patient is of low surgical risk.[46]

Patients with viable myocardium or severely depressed LVEF may have some or no advantage if treated surgically rather than with OMT.[12,13] Moreover, OMT may be preferred either in patients with unsuitable anatomy for revascularization or in those with features of low-risk multivessel disease (with or without DM), in the context of a crossover revascularization strategy for many of them, as shown in BARI 2D and COURAGE.[1]

The SYNTAX score should probably be used routinely in every patient with CAD of intermediate severity. It appears that in diabetic patients with multivessel disease and simple anatomy, i.e. with SYNTAX score <22, PCI is a viable option for revascularization. The SYNTAX II score represents a substantial advance, but it creates the major dilemma of how to manage diabetic patients, for whom the new trials have provided an important framework for decision making. An analysis of coronary risk prediction by SYNTAX and derived scores has recently been reviewed.[47]

A case-by-case discussion and final counseling of the "gray zone" patients by the Heart Team appears crucial, although admittedly the interventional cardiologist may be the ultimate decision maker in many institutions. Cardiologists and cardiac surgeons should therefore strive to set up a Heart Team in every institution, to ensure more balanced counseling of patients with multivessel CAD.[48]

There will remain a broad gray decision zone. As previously stated,[1] in intermediate-to high CAD severity, more complex algorithms have to take into account diabetes status, renal function, biological age, achievement of complete revascularization, bleeding risk, patient's preference, local expertise and the convenience of PCI over CABG.

Preliminary data from a small study suggest that a hybrid revascularization approach is feasible and safe in a selected population of patients with multivessel disease and LAD involvement. In comparison with classical CABG, revascularization of the LAD with the left internal mammary artery by means of a mini thoracotomy, followed 36 hours later by PCI of the remaining vessels with everolimus-eluting stents, showed a similar rate of the primary endpoint of death, MI, stroke, target vessel revascularization and major bleeding at 1 year.[49]

Ongoing trials such as ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches)[50] and EXCEL[31] are expected to clarify several issues in the complex topic of optimal revascularization strategies in multivessel CAD.

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