Multivessel Coronary Artery Disease and Stable Ischemic Heart Disease: CABG or PCI?

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Completeness of coronary artery revascularization and preservation of viable myocardium are the goals of coronary artery disease (CAD) treatment. The ARTS trial first reported that complete revascularization was more frequently accomplished by coronary artery bypass graft surgery (CABG) than stent implantation.[1,2] Since then, there have been major advancements in medical treatment, drug eluting stents, physiology-based approaches with fractional flow reserve (FFR) for target lesion identification, and post stent optimization with intravascular ultrasound (IVUS) or optical coherence tomography (OCT). The ISCHEMIA trial enrolled patients with moderate to severe ischemia proven by stress imaging or non-imaging exercise tolerance test with a study design to assimilate into clinical practice. The study found no additional benefit with early percutaneous coronary intervention (PCI) on top of optimal medical therapy. This optimal medical therapy could be classified into behavioral (smoking cessation, physical activity and saturated fat intake reduction), physiological (SBP, LDL-C, BMI, HbA1c target) and pharmacological intervention (aspirin, statin, ACEi/ARB, beta blocker, P2Y2 receptor antagonist, Evolocumab, Ezetimibe).[3,4] The initial SYNTAX I trial was designed to test first-generation drug eluting stents (DES) with paclitaxel-eluting stents and CABG.[5] The SYNTAX score was also developed to characterize the complexity of CAD for patient stratification. CABG was found to be superior to PCI with lower all-cause death, myocardial infarction and repeat revascularization at 5 years. There has also been major technical and procedural advancement in PCI since then. When the SYNTAX II trial was done, it incorporated clinical manifestation into the SYNTAX II Score, a physiology-based revascularization approach, use of second-generation DES with thin struts, IVUS-guided optimization of stent deployment, novel chronic total occlusion (CTO) revascularization techniques and guideline-directed medical therapy. While SYNTAX II was a single arm study that compared PCI arm and CABG arm in SYNTAX I, the result shed light, in terms of the lower stent thrombosis, target vessel revascularization, spontaneous myocardial infarction (MI) and cardiovascular death, on the SYNTAX II PCI approach. In addition, MACCE rates were not statistically significant (but trending toward significance), when comparing SYNTAX II data with the original SYNTAX I CABG group.[6]

Diabetes is a risk factor for CAD. Diabetes

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patients commonly present with a more aggressive form of atherosclerosis and with extensive CAD.[7] There is higher cardiovascular event risk in patients with diabetes compared to those without.[8] The SYNTAX I cohort was stratified into those with and without diabetes, and the comparison of PCI and CABG showed a higher repeat revascularization rate in the PCI group.[9] The BEST trial showed similar results in the diabetes subgroup.[10] The FREEDOM trial compared patients with multivessel CAD and type 2 diabetes. The result showed higher myocardial infarction and death from any cause in the PCI group.[11] Nonetheless, stroke occurred more frequently in the CABG group.[11] The BARI 2D trial was designed to compare coronary revascularization with intensive medical therapy, not to compare CABG with PCI. There was no reduction of cardiovascular risk in the PCI group.[12] It is noteworthy that there is still a huge gap between clinical trials evidence and current clinical PCI techniques for patients with diabetes and multivessel CAD. There is still opportunity to incorporate image-based assessment such as OCT and IVUS with physiology-based approaches like FFR. There are better guidance systems and CTO techniques. SGLT-2 and GLP-1 were not included in previous studies. The DEFINE-DM trial (NCT05831085) is currently underway and expected to be completed in the year 2027. The trial uses a noninferiority design and double arm comparison of imaging- and physiology-guided state-of-the art PCI with standard CABG for 1,200 diabetes patients with multiple CAD with LAD involvement. Hopefully, this trial will answer the key question of whether PCI or CABG is better in patients with diabetes and multivessel CAD.

Summary of related trials

International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) 2020[3,4]

The ISCHEMIA trial was set to evaluate if the addition of coronary revascularization to optimal medical therapy would improve prognosis in patients with stable ischemic heart disease. All patients were evaluated with stress imaging or non-imaging exercise tolerance test. Stress imaging included nuclear perfusion via SPECT or PET (with ≥ 10% myocardium ischemic), echocardiography (≥ 3/16 segments with stress-induced severe hypokinesis or akinesis) or cardiac magnetic resonance (perfusion: ≥ 12% myocardial ischemic, and/or wall motion: ≥ 3/16 segments with stress-induced severe hypokinesis or akinesis). Exercise test without imaging is positive when all four criteria are met: (1) angina, (2) absence of resting ST-segment depression or non-interpretable such as LBBB, pacemaker or LVH with repolarization, (3) ST change was compared with baseline, (4) workload at which ST- segment criteria are met but not exceeding stage 2 of the Bruce protocol or 7 METs for a non-Bruce protocol or ST segment criteria are met at < 75% of maximum predicted HR. Patients were excluded if they had acute coronary syndrome within 2 months, EF < 35%, NYHA class III-IV HF, unacceptable angina despite medical therapy, PCI or CABG within 1 year, severe left main disease or EGFR < 30 mL/min/1.73m^2. Blinded, core laboratory-interpreted coronary computed tomographic angiography was used to assess anatomic eligibility for randomization. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure or resuscitated cardiac arrest. The initial invasive strategy did not reduce the risk of ischemic cardiovascular events or death from any cause over a median of 3.2 years. There was only a modest reduction in cardiac death of 0.3%/year.

The guideline-based medical therapy goals in ISCHEMIA included behavioral, physiological and pharmacological aspects. The behavioral intervention included smoking cessation, ≥ 30 minutes of moderate intensity physical activity ≥ 5 times/week, and intake of < 7% calories of saturated fat. Physiological goals included systolic blood pressure < 130 mmHg, LDL-C < 70 mg/dL, target BMI < 25 when the initial BMI was 25-27.5, target of 10% body weight loss when BMI > 27.5 and HbA1c target of < 8% or < 7% in selected individuals. Pharmacological agents

included aspirin and statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) for all participants, ACEi/ARB for hypertension, diabetes, EGFR < 60 or LVEF < 40%, beta blocker when there was a history of myocardial infarction or LVEF < 40%. P2Y2 receptor antagonist was used for participants with contraindication to aspirin or in combination with aspirin for those who received PCI and post-myocardial infarction for 1 year. Evolocumab was used when LDL-C goal was not reached despite using maximally tolerated statin dose. Ezetimibe was used when LDL-C goal was not reached despite maximally tolerated statin dose and without access to Evolocumab.

Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) 2009[5], 2022[6], 2013[9]

The Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX I) trial was originally designed to compare first-generation drug eluting stent with paclitaxel-eluting stents and CABG for patients with untreated 3-vessel disease and/or left main disease. The PCI group was associated with higher rates of all-cause death, myocardial infarction and repeat revascularization at 5 years.

The SYNTAX II trial was designed with the consideration of improved patient stratification according to the SYNTAX II score, which included coronary artery anatomical complexity, participants' clinical characteristics and comorbidities. The SYNTAX II score included anatomical SYNTAX score, age, renal function, LVEF, left main involvement, sex, COPD and peripheral vascular disease. In addition, the trial also incorporated coronary physiology with hybrid use of instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR), second-generation drug-eluting stent with thin-strut biodegradable polymer drug-eluting stents, intravascular ultrasound guided optimization of stent deployment, enhanced treatments of chronic total occlusions and optimized medical therapy. It was postulated that thin strut stent resulted in less pressure gradient across the stent and contributed to laminar flow and less chance of platelet aggregation.[13] SYNTAX II was a single arm study that compared the primary outcome of major adverse cardiac or cerebrovascular events (MACCE) with a matched cohort treated with PCI and CABG in the SYNTAX I trial. The MACCE rate per year in SYNTAX II was significantly lower than in the SYNTAX I PCI cohort (21.5% vs. 36.4%, P < 0.001). This was reflected by lower rates of revascularization and myocardial infarction consisting of both procedural MI and spontaneous MI. All-cause mortality was lower in SYNTAX II (8.1% vs. 13.8%, P = 0.013), reflecting a lower rate of cardiac death (2.8% vs. 8.4%, P < 0.001). Major adverse cardiac and cerebrovascular event outcomes at 5 years among patients in SYNTAX II and predefined patients in the SYNTAX I CABG cohort were similar (21.5% vs. 24.6%, P = 0.35).

In the SYNTAX I DM subgroup analysis, 1800 patients were stratified into 452 patients with DM and 1348 patients without DM. At five year follow-up the composite of death, myocardial infarction, stroke, or repeat revascularization was significantly higher in the PCI group than in the CABG group (46.5% vs 29.0%, p < 0.001, HR 1.81; 95% confidence interval of 1.31-2.48). There was no difference in the composite of all-cause death, stroke and myocardial infarction (23.9% vs 19.1%, p = 0.26, HR 1.27; 95% confidence interval of 0.84-1.92). The repeat revascularization rate was significantly higher in the PCI group (35.3% vs 14.6%, p < 0.001, HR 2.01; 95% confidence interval of 1.04-3.88).

Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease (BEST) 2022[10]

The BEST trial was conducted to compare PCI with everolimus-eluting stents and CABG in patients with multivessel coronary artery disease. The study was terminated early because of slow enrollment, after inclusion of 880 patients. There were 438 in the PCI group and 442 in the CABG group. The primary end point was the composite of death from any cause, myocardial infarction

or target vessel revascularization. Although the study did not reach the target of 1776 patients, it offered a long median follow-up of 11.8 years and interquartile range of 10.6-12.5 years. The primary end point occurred in 151 patients (34.5%) in the PCI group and 134 patients (30.3%) in the CABG group (HR 1.18; 95% confidence interval 0.88-1.56, p = 0.26). There were no significant differences in the occurrence of a safety composite of death, myocardial infarction or stroke (28.8% vs 27.1%, p = 0.70, HR 1.07; 95% confidence interval 0.75-1.53). There were no significant differences in the occurrence of death from any cause (20.5% vs 19.9%, p = 0.86, HR 1.04; 95% confidence interval of 0.65-1.67). More frequent after PCI were spontaneous myocardial infarction (7.1% vs 3.8%, p = 0.031, HR 1.86, 95% confidence interval 1.06-3.27) and any repeat revascularization (22.6% vs 12.7%, p < 0.001, HR 1.92, 95% confidence interval 1.58-2.32). In the subgroup analysis with diabetes stratification, patients with diabetes who received PCI experienced a higher primary endpoint with no difference for composite of death, stroke, myocardial infarction and all-cause mortality. The only difference was from repeat revascularization. With this result, it is important to bear in mind that the study is underpowered.

Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) 2012[11]

The FREEDOM trial enrolled patients with diabetes and angiographically confirmed multivessel coronary artery disease with stenosis ≥ 70% in two or more major epicardial vessels without left main coronary stenosis. Of the patients, 83% had three vessel disease. Sirolimus-eluting and paclitaxel-eluting stents were the predominant types of stents. Abciximab was recommended and provided. Dual antiplatelet therapy with aspirin and clopidogrel was used for at least 12 months. Low-density lipoprotein cholesterol target was < 70 mg/dL, BP < 130/80 mmHg, HbA1C < 7%. SGLT-2 and GLP-1 were not available when the trial was done. 1900 patients were enrolled with 953 patients in the PCI group and 947 patients in the CABG group. The primary outcome was a composite of death from any cause, nonfatal myocardial infarction and nonfatal stroke. The primary outcome occurred more frequently in the PCI group (26.6% vs 18.7%, p = 0.005). The beneficial effect of CABG was driven by differences in rates of both myocardial infarction (p < 0.001) and death from any cause (p = 0.049). Stroke was more frequent in the CABG group (2.4% vs 5.2%, p = 0.03).

Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) 2009[12]

The BARI 2D trial included patients with diagnosis of both type 2 diabetes and coronary artery disease. The diagnosis of coronary artery disease was established when there was ≥ 50% stenosis of a major epicardial coronary artery associated with a positive stress test, or ≥ 70% stenosis of a major epicardial coronary artery and classic angina. Excluded were patients who required immediate revascularization or had left main coronary disease, with a creatinine level of ≥ 2.0 mg/dL, HbA1C ≥ 13.0%, class III or IV heart failure, or hepatic dysfunction or who had undergone PCI or CABG within the last 12 months. There was no 5-year survival difference between the revascularization group and medical therapy group (88.3% vs 87.8%, p = 0.97). Primary end points were the rate of death and a composite of death, myocardial infarction or stroke. In the PCI stratum, there was no significant difference in primary endpoints between the revascularization group and medical therapy group. In the CABG stratum, the rate of major cardiovascular events was significantly lower in the revascularization group than in the medical therapy group (22.4% vs 30.5, p = 0.01). Patients in the CABG stratum had more extensive coronary disease than patients in the PCI stratum (triple vessel disease: 52.4% vs 20.3%; proximal LAD disease: 19.4% vs 10.3%). The study was designed to compare coronary revascularization with intensive medical therapy, not to compare CABG with PCI. It is noteworthy that revascularization did not reduce the risk of cardiovascular events in

patients in the PCI stratum who had less extensive coronary disease when PCI was believed to be the better choice. Approximately one third of patients in the PCI stratum received a first-generation drug-eluting stent. Guideline directed medical therapy was not optimized. SGLT-2 inhibitors and GLP-1 were not included in the practice.

Conclusion

The advancement of PCI tools and medicine is changing the role of PCI in multivessel CAD treatment. ARTS trial supported CABG as a better treatment option for patents with multivessel CAD. ISCHEMIA trial revealed no beneficial advantage of PCI on top of optimal medical therapy. SYNTAX I trials compares first generation DES with CABG and found inferiority of PCI. SYNTAX II trial was a single arm study for second generation DES. When compared with the CABG and PCI arm, there is no inferiority of revascularization and MACCE. Nevertheless, it is still not a head-to-head comparison. In patients with diabetes and multivessel CAD, SYNTAX I cohort, BEST and FREEDOM trials showed higher mortality of PCI group. However, it is worth of noticing that all of these trials were conducted without OCT, IVUS or FFR guided strategy for coronary intervention. On the other hand, novel medical therapeutic agents such as SGLT-1 or GLP-1 receptor agonists were also not included patients receiving optimal medical control. Therefore, there is still a huge gap existing between currently accepted clinical practice and scientific evidence. Further clinical research is still needed in the future to confirm whether the latest PCI concepts and technique can lead to better clinical outcomes when comparing to optimal medical control in most CCS patients. For left main and multi-vessel CAD patients, we also need more clinical study to identify the appropriate specific populations, for whom PCI could be the priority therapeutic choice over bypass surgery.

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