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Multivessel Disease in the Modern Era of Percutaneous Coronary Intervention

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1. Introduction

The rapid evolution of medical therapy, percutaneous coronary interventional techniques and cardiac surgery along with the changing patient profile over the last few decades has required the clinician to make increasingly complex decisions. This has led to significant variations in practices that may be discordant with evidence based clinical practice guidelines. Such variations have an unclear clinical impact. There is hope that with growing efforts to apply multidisciplinary care to the management of complex coronary artery disease (CAD), that we will arrive at more consistent and balanced decisions.

In this chapter, we will explore (1) The history of angiography and angioplasty, (2) the current clinical dilemma (3) the evidence supporting the use of cardiac surgery to improve survival above medical therapy alone, (4) the role of percutaneous approach versus surgery in different populations, (5) the impact of changing technologies/techniques in revascularization, (6) the current discordance between guidelines and clinical practice, and (7) the potential role of a multidisciplinary Heart Team to create a more unified, balanced approach to the treatment of complex CAD.

2. The origins of the age of percutaneous revascularization

2.1. Cardiac catheterization

One of the earliest descriptions of cardiac catheterizations was done by Steven Hales, an English chemist, botanist and animal physiologist who cannulated the carotid artery and the jugular vein to access the left and right-sided chambers of the heart respectively in the 17th

century [1]. It was through some of this initial work, that he was able to make the first measurements of blood pressure, describe systole and diastole, characterize the volumes of the heart through wax cast work and correctly describe the function of the aortic and mitral valve [1]. Interestingly, the first human cardiac catheterization was by a Urologist by the name of Werner Forssmann [2]. He performed right heart catheterization on himself in 1929 by advancing a cannula through the left antecubital vein via cut-down access into the right atrium [2].

2.2. Selective coronary angiography and angioplasty

The credit of the first true selective coronary angiogram and much of the initial correlations between angina pectoris and coronary anatomy has to be granted to Mason Sones, a Pediatric Cardiologist, who at the time of discovery was working out of the Cleveland clinic [3-5]. In 1958, whilst performing non-selective aortogram on a patient, Sones inadvertently engaged the right coronary artery [2].

The original technique of angioplasty was born out earlier work by a Vascular Radiologist by the name of Charles Theodore Dotter [6]. Andreas Gruentzig, now known as the father of modern day coronary angioplasty, learned the Dotter technique from a German Radiologist Eberard Zeitler while doing a clinical fellowship in the Radiology Department of Aggertalclinic in Engelskirchen, Germany [6]. He had adopted the Dotter concept of using the balloon approach for angioplasty [6]. After experimenting with a number of materials performed the first procedure in 1977 in a man with stenosis of his left anterior descending artery (LAD) using a polyvinyl chloride balloon mounted onto the Dotter catheter [6].

3. The current dilemma

The treatment of coronary artery disease can be simplified into three major therapeutic approaches: medical therapy alone, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). However, deciding on which approach is optimal for the individual patient is sometimes far from simple. This decision requires not only an in depth understanding of the evidence but also the applicability of this evidence to the individual patient considering the anatomic characteristics of the disease, the clinical context, the patient's preferences, social circumstances, and available resources [ie. local expertise and access to PCI and/or CABG]. Furthermore, because there has been evolution of all of these three approaches, interpretation of the evidence has become quite complex. Comparison of different modes of therapy (eg CABG versus medical therapy or CABG to balloon angioplasty) in the past may not be as relevant in the current clinical milieu.

3.1. Advances in medical therapy

Medical therapy has made remarkable advances from a time when patients may have been treated with nitrates alone to contemporary use of a combination of antiplatelets, lipid lowering therapy (statins), beta-blockers (BB) and Angiotensin Converting Enzyme- inhibitors

(ACEI)/Angiotensin Receptor Blocker (ARB). This combined therapy addresses not only patient symptoms but also modifies the disease process such that prognosis is vastly improved [7]. The growth in our understanding the impact of lifestyle modification has also played a central role in how we manage patients with CAD [8].

3.2. Changing clinical patient profile

Due to advances in medical therapy, patients that are now considered for revascularization are also older and have accrued more co-morbidities [9]. These co-morbidities render the interpretation of relevant symptoms more difficult. For example, in a diabetic patient with chronic obstructive lung disease (COPD), it may be difficult to distinguish between dyspnea as an anginal equivalent versus that caused by the underlying pulmonary pathology. The severity of the patients' COPD may also complicate the eligibility for CABG as a mode of revascularization [10, 11]. In fact, in a recent clinical trial comparing CABG versus PCI in complex CAD, significant burden of co-morbidities was the most common reason that patients were felt not to be suitable for CABG and hence entered into the PCI registry [9].

3.3. Advances in angioplasty

Angioplasty has significantly evolved over the last several decades with respect to four principle areas. First, operator training has advanced from informal training courses to 1-2 year formal clinical fellowships [12, 13]. Second, the equipment to perform PCI has significantly improved from plain old balloon angioplasty (POBA) to second-generation drug-eluting stents (DES) and supporting devices to improve PCI outcomes (filter wires, thrombectomy in ST elevation acute coronary syndrome (STEACS), and rotational atherectomy) [14, 15]. Third, vascular access has evolved from brachial cut-downs with large caliber sheaths (7-8 FR) to increasingly common radial access with smaller caliber sheaths (5 and 6 FR) [5, 15-18]. Finally, concomitant medications have become more sophisticated, from Aspirin (ASA) alone to combination antiplatelets resulting in reduced stent thrombosis [19]. Restenosis has remained in the forefront of limitation to PCI[20]. However, the challenges with restenosis have been significantly reduced with advancement in DES technology [21-23]. Concerns with the thrombosis rates in the setting of discontinuation of dual antiplatelet therapy (DAPT) after DES have been addressed by second-generation DES, which have dramatically reduced this clinical problem [24]. These advances have been paralleled by an increasing use in complex coronary artery disease including left main (LM) disease[25].

3.4. Advances in surgical techniques

From the standpoint of CABG, we have over the years learned the benefits of arterial grafting with the internal mammary artery (IMA) in improving survival [26]. A high long-term patency rate of left internal mammary artery (LIMA) after revascularization of the LAD is well established and is estimated at 88 percent at 10 to 15 years [26]. More recently, to circumvent particular risks associated with sternotomy, there has been some investigation of revascularization of the LAD with the LIMA using a minimally invasive direct coronary artery bypass (MIDCAB) technique [26]. In the setting of multivessel disease (MVD), there has been some

discussion of a hybrid approach with MIDCAB for the LAD and PCI of the other vessels. However, the evidence supporting this approach is still limited; the most recent European Society of Cardiology (ESC) Guidelines give a *Class IIb recommendation* to this approach (*Level of Evidence B*) for those “patients with conditions likely to prevent healing after sternotomy” [26]. This approach does have significant promise and further research is required before it is adopted on a population level.

3.5. Evidence of survival benefit for revascularization in stable ischemic heart disease (SIHD)

The current framework for patient selection in treatment strategy for MVD is largely shaped by early studies comparing medical therapy and CABG. This body of evidence has been best synthesized by a meta-analysis performed by Yusuf et al in the Lancet in 1994 [27]. This meta-analysis was an individual patient data analysis of 2549 patients derived from three large randomized controlled trials, the Coronary Artery Surgery Study (CASS), Veterans Administration (VA) study and the European Coronary Surgery Study (ECSS) as well as four other smaller randomized studies [27]. The population studied consisted of patients with stable symptomatic coronary artery disease of a wide spectrum of severity [27]. However, only 10 percent were single vessel disease (1VD); the remainder consisted of MVD with 59.4% affecting the proximal LAD [27].

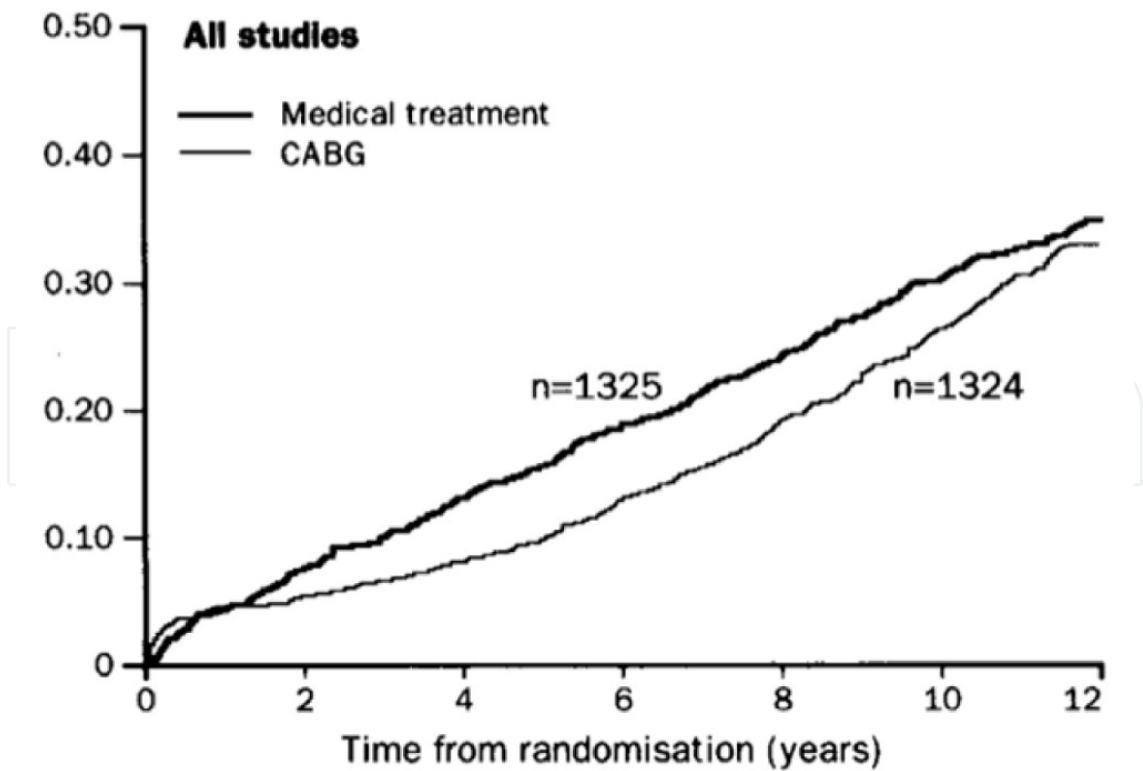


Figure 1. Survival curve for medical therapy versus coronary artery bypass grafting (CABG). Reproduced with permission from Yusuf S. et al. Lancet 1994. 344;8922:563-568

There was an overall statistically significant survival benefit with an **absolute risk reduction (ARR) 5.6% at 5 years, 5.9% at 7 years and 4.1% at 10 years** [Figure 1] [27]. This was likely an overall underestimate of the total treatment effect as there was a 36.4% cross over from the medical group to CABG over that time period whereas 93.7% of those assigned to the surgical group underwent CABG [27]. Subgroup analysis revealed that benefit was largely in those that had *three-vessel disease (3VD)* and *those with involvement of the proximal LAD* with each of those groups demonstrating a 42% relative risk reduction (RRR) in mortality [27]. In contrast, revascularization in two-vessel disease (2VD) in the absence of involvement of the proximal LAD did not result in a significant mortality benefit [27]. Randomized data is fairly consistent with that of registry data, demonstrating survival benefit for revascularization over medical therapy in those with 3VD; its support for benefit in those with 2VD even in those with proximal left anterior descending (LAD) involvement was non-significant [28]. The latter may be related to improvements in medical therapy.

4. Changing landscape in the treatment of CAD

Many of the earlier studies comparing surgical revascularization with medical therapy was during a period in cardiology where the BB and nitrates were the mainstay of medical therapy. Although antiplatelets were available, these were only taken by approximately 20% of the patients at the time [27]. It may hence be important to interpret these results in the context of current medical practice, which include contemporary treatments (standard secondary prevention with antiplatelets, statin therapy, BB and ACEi) that have all made further advancements in the survival and prognosis of patients with CAD [7].

ASA for secondary prevention has an estimated RRR of 18 percent in total serious vascular events (including stroke and major coronary event) with an **annual ARR of 1.5 percent**; the decrease in major coronary event (non-fatal myocardial infarction (MI) and cardiovascular death) is estimated at **annual ARR of 1.0 percent** [29]. As an adjunctive antiplatelet clopidogrel has further reduced death from cardiovascular causes, non-fatal MI and stroke in patients with Non ST elevation acute coronary syndromes (NSTEMI) with an **ARR of 2.1 percent** [30]. Most recently, newer agents such as prasugrel and ticagralor have both shown benefit compared to clopidogrel in patients with acute coronary syndromes (ACS). Prasugrel compared with clopidogrel in PCI treated ACS has demonstrated an **ARR of 2.2 percent** with regards to death from cardiovascular causes, nonfatal MI or non-fatal stroke over the 6-15 month follow up period [31]. Ticagralor has shown similar reduction in the same composite endpoint in patients with ACS over clopidogrel with an **ARR of 1.9 percent** [32]. In addition, ticagralor also showed an overall **reduction in all cause mortality with an ARR of 1.4 percent** [32].

BB's have a longstanding history in the management of CAD [7]. Although BB's can be used in patients post-MI with a normal ejection fraction (EF), the evidence for this is not as strong as that for those with significant Left Ventricular (LV) dysfunction [8]. It was previously shown that Carvedilol compared with placebo in patients with chronic heart failure (HF) and severe LV dysfunction (average EF 22-23 percent) **reduces all cause mortality with an ARR of 4.6 percent** [33].

The introduction of 3-hydroxyl-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors otherwise known as the “statins,” has significantly improved the care of patients with coronary artery disease [34, 35]. Simvastatin 40mg orally daily compared to placebo in patients with known vascular disease was shown in the Heart Protection Study (HPS) to *reduce all cause mortality with an ARR of 1.8 percent* over a five year period [34]. This was paralleled with a **reduction of coronary death with an ARR 1.2%** [34].

ACEi's have also been established to have a significant benefit towards long-term cardiovascular outcomes. It was shown in the Heart Outcomes Prevention Evaluation Study that in high-risk patients (vascular disease or diabetes plus one other risk factor) Ramipril compared with Placebo provides a *relative risk reduction* in myocardial infarction, stroke and death from cardiovascular causes of *21 percent and ARR of 3.8 percent* [36] over the mean follow up period of 5 years. There was also a *reduction in all cause death with an ARR of 1.8 percent* [36].

Concurrently, there was the advent and evolution of percutaneous approaches to revascularization. The first generation of angioplasty that truly adopted popular practice involved serial balloon inflations at the site of stenoses restore normal flow dynamics down the conducting epicardial vessels [6]. This approach, although promising was limited by a high rate of restenoses as a result of localized vascular recoil and epithelial hyperplasia [20, 37]. The bare metal stents (BMS) were created as a scaffolding technique that limited the degree of recoil but still faced significant re-stenosis rates due to mediated by injury to the medial layer, increased inflammation resulting from stent strut penetration into the lipid core and ultimately neointimal growth [38].

Pacitaxel and Sirolimus DES were developed in the next phase to overcome the challenge of restenosis requiring repeat intervention [20]. Although there was no difference in mortality or rates of myocardial infarction seen with DES compared with BMS, there were considerable reductions in restenosis rates with an estimated RRR of 0.44 [21, 22, 39-41].

Early enthusiasm for the use of drug eluting stents was curbed by a significantly higher rate of stent thrombosis, particularly in the face of an initially shorter duration (6 months) of dual antiplatelet therapy (DAPT) [22, 42, 43]. Currently the American College of Cardiology/American Heart Association (ACC/AHA) recommends at least *12 months of DAPT* in patients receiving DES for non-ACS indication and *12 months of DAPT* for ACS indication regardless of the stent type (BMS or DES) (*Class I recommendation, Level B evidence*) [14].

The most recent development in stent technology has been the introduction of second-generation (everolimus and zotarolimus) drug eluting stents. A large Swedish registry observational study containing 94,384 patients demonstrated the advantage of the second-generation stents over its predecessors (first generation DES and BMS) both in terms of *restenosis* and *definite stent thrombosis* [44]. The second generation DES in this study was shown to have lower risk of restenosis compared with both BMS and the first generation DES with **Hazard Ratios (HR) of [0.29, 95% confidence interval (CI) 0.25-0.33]** and **[0.62, CI: 0.53-0.72]** respectively [44]. The Cobalt Chromium Everolimus eluting stents (CoCr EES) have shown the most promise in reducing stent thrombosis. In a recent network meta-analysis of 50844 patients, the CoCr EES was shown to have a lower rate of 1 year definite stent thrombosis compared to both paclitaxel DES and sirolimus DES with odds ratio (OR) of **[0.41 95% CI 0.24-0.70]** and **[0.28 95% CI 0.16-0.48]** respectively [24]. The CoCr EES also had a lower rate of definite stent thrombosis compared with BMS at 1 year and 2 years with an odds ratio [OR] of

[0.23 95% CI 0.13-0.41) and [0.35, 95% CI 0.17-0.69] respectively [24]. Finally, compared to even the zotarolimus second generation DES, the CoCr EES still demonstrated a robust reduction in stent thrombosis with an OR [0.21, 95% CI 0.17-0.69] at one year [24].

5. PCI versus CABG in SIHD

There have been numerous randomized studies comparing PCI with surgical revascularization in MVD. A recent systematic review including 10 major trials over and the individual data from over 7800 patients found similar mortality in patients treated with CABG (15%) compared to patients treated with angioplasty (16%) over median survival of 5.9 years ($p=0.12$) [45]. There was, however a significantly lower rate of death or repeat revascularization in those treated with CABG (9.9%) compared with those treated with PCI (24.5%) [45]. This suggests that in fact the major benefit seen in CABG over PCI in this comparison is a lower need for repeat revascularization and is paralleled by a lower incidence of angina in the CABG group (14%) compared to the PCI group (26%) at one year ($p<0.0001$) [45]. The major caveat to this data is that stenting (which is known to reduce restenosis rates) only represented 37 percent of the total angioplasty group [45].

Subgroup analysis revealed that patients with diabetes have overall *better survival* when treated with surgical revascularization than when treated with angioplasty **with an ARR of 7.7% over 5 years** [45]. More definitive data supporting the use of CABG in patients with diabetes will be presented in Section 6.2. Interestingly, there was also a graded age interaction that was significant ($p=0.002$) [45]. For patients younger than 55 years of age, mortality was lower with PCI (8%) than CABG (10%). In patients between ages 55-64, PCI and CABG had similar mortality rates at 15 and 14 percent respectively [45]. And for patients older than 65 years of age, CABG had a lower overall mortality (20%) compared with PCI (24%) [45]. Prior to this study, this interaction had not been previously reported and we can only speculate whether the effect is a true function of age.

Other subgroups did not prove to contribute any significant interaction to the overall treatment effect [45]. Six of the trials included had POBA as the main mode of PCI whereas four trials used BMS; neither of these groups had significantly different survival rates when compared with surgery [45]. There was no overall interaction contributed by the presence/absence of proximal LAD disease, 3VD, abnormal LV function, previous MI or unstable symptoms [45].

6. Factors favoring surgery as the mode of revascularization

6.1. LV dysfunction

LV function has never been shown to have a significant interaction with mode of revascularization (PCI versus CABG) with regard to survival. In fact, the majority of studies comparing PCI with CABG enrolled a low percentage of patients with abnormal LV function (*20 percent or less*) [45]. However, it has been considered an important variable that favors revascularization with surgery due to historical data showing that patients with significant LV dysfunction

have improved survival with CABG compared to medical therapy. An initial signal for preferential benefit of revascularization in patients with mild to moderate LV dysfunction (LV EF of 35-49%) was seen in subgroup analyses of the CASS randomized study and the VA study [46, 47]. This was further supported by a meta-analysis demonstrating a significantly longer survival time in 10-year follow up with surgical revascularization over medical therapy in patients with LV dysfunction [10.6 months] compared with those with normal LV function [2.3 months] [27]. These studies however did not address whether a similar effect would be seen in severe LV dysfunction.

The Surgical Treatment for Ischemic Heart Failure (STITCH) trial published recently in 2011, designed to address this question in a randomized comparison of medical therapy versus surgical revascularization in patients with an EF of 35 percent or less [48]. There was a non-statistically significant trend ($p=0.12$) towards decreased all-cause mortality in the surgical group with an relative reduction of 24% and an ARR of 5 percent over the six year follow up period [48]. The lack of statistical significance, in the context of intention to treat analysis, may be related to the disproportionate crossover rate with 17 percent of the patients assigned to medical therapy ultimately receiving coronary bypass surgery [48]. Nevertheless, there was still a significant relative reduction of death from cardiovascular causes of 19 percent ($p=0.05$) and a significant relative reduction in death from any cause and hospitalization from cardiovascular causes of 26 percent ($p<0.001$)[48].

It is unclear why surgical revascularization confers clear benefit in mild to moderate LV dysfunction, and only modest benefit severe LV dysfunction, but there are possible explanations. Medical therapy has advanced tremendously since the initial comparisons between medical therapy and surgery, which may decrease the relative mortality benefit between the two treatments during this more contemporary comparison. One could also hypothesize that the beneficial effect of revascularization plateaus at the extremes of LV dysfunction due to irreversible remodelling and/or the progressive increase in associated procedural risk.

There is currently limited data in how revascularization with PCI would affect prognosis in the setting of LV dysfunction[14]. As a result, the most recent ACC/AHA guidelines still recommend CABG for patients with LV EF 35-50 percent with a *Ila recommendation (Grade B evidence)* and a *IIf recommendation (Grade B evidence)* for those with a LV EF of less than 35 percent [49]. And currently, the ACC/AHA guidelines state that there is *insufficient data* to make a recommendation for revascularization with PCI in patients with LV dysfunction [49]. In practice however, if a patient does require revascularization but is not a surgical candidate, that natural decision is that if percutaneous intervention is feasible, that option should be entertained.

6.2. Diabetes favoring surgical revascularization

The Bypass Angioplasty Revascularization Investigation (BARI) was one of the first major landmark studies comparing angioplasty versus coronary bypass in patients with both stable anginal symptoms and unstable angina with MVD. Although there was no significant difference between the two treatments in the overall survival, patients with diabetes tended to have a significantly lower mortality rate with CABG (19.4%) compared with angioplasty (34.5%) with an **ARR of 15.1%** [50]. This finding was further confirmed with a meta-analysis comparing angioplasty with CABG in MVD, albeit with a smaller ARR of 7.7% [45]. In contrast,

in non-diabetics there was no overall benefit of surgery over angioplasty [45]. This relationship was corroborated by significant interaction found for the diabetic subgroup ($p=0.014$) [45]. The interaction was robust and was present even after excluding the data contributed by BARI and when adjusted for various clinical parameters (age, sex, smoking, hypertension, history of MI, heart failure and 3VD) [45].

One hypothesis that may explain why diabetics may have a better outcome with surgery than angioplasty is that restenosis may be more aggressive in this group of patients [20]. It has been well established that one major drawback of percutaneous coronary intervention is the need for repeat revascularization due to restenosis [20]. While restenosis itself may not incur an increased risk of mortality, the repeat exposure to the inherent risk of intervention may be additive. The need for repeat revascularization was certainly more striking in the earlier trials where POBA was used (54 percent within 5 years for the BARI trial) [50]. There has been considerable improvement to both the techniques and technology of PCI first with the development of BMS and now DES which are intended to reduced restenosis rates have been integrated into common practice. However, even in more contemporary trials such as *Synergy between PCI with Taxus and Cardiac Surgery* (SYNTAX), DES conferred a 13.5% need for revascularization compared with 5.9% in patients treated with CABG over a one-year period [51].

BARI 2D is a contemporary trial evaluating revascularization (both PCI and CABG) with intensive medical therapy for SIHD in diabetic patients. No significant difference emerged overall between the two groups in terms of overall mortality, cardiac death or myocardial infarction over the 5-year follow up period [52]. The mode of revascularization was at the discretion of the treating physician and the burden of disease tended to be higher in the CABG group than the PCI group with a mean number of lesions being 5.6 versus 4.3 respectively [52]. Although not specifically designed to compare PCI and CABG as a mode of revascularization, it is still noteworthy that there was a significant difference in death and MI for those revascularized with CABG compared to medical therapy (21.1% versus 29.2% $p=0.010$); the same comparison in the PCI stratum revealed no difference [52].

To date, the trial most relevant in determining whether the difference between PCI and CABG for revascularizing SIHD in diabetic patients in a randomized fashion is the *FREEDOM* trial [53]. There are 1900 diabetic patients with multivessel disease (defined by $>70\%$ stenosis in 2 or more epicardial vessels supplying different vascular territories) that were randomized to CABG versus PCI with DES (Paclitaxel or Sirolimus eluting stent at the discretion of treating physician) with a background of guideline supported optimal medical therapy. The primary endpoint is a composite of all-cause mortality, non-fatal MI or stroke over the mean follow up period of 4.37 years [53]. This consists of a high-risk population with 83% having 3-vessel disease and a significant proportion (32%) requiring insulin therapy [53]. The study results showed that there was a reduction in *primary endpoint all cause death, non-fatal MI and stroke in the CABG group*, with an **ARR of 7.9%** (26.6% in the PCI group and 18.7% in the CABG group, $p=0.005$) and a **Number Needed to Treat (NNT) of 12.5 [Figure 2] [53]**. There was also a reduction in *all-cause mortality* which was 16.3% in the PCI arm and 10.9% in the CABG arm with an **ARR = 5.4% and NNT of 19 [Figure 2] [53]**. This was at the cost of an increase in stroke, as might be expected in the CABG arm of **2.8% Number Needed to Harm (NNH) of 36 [53]**.

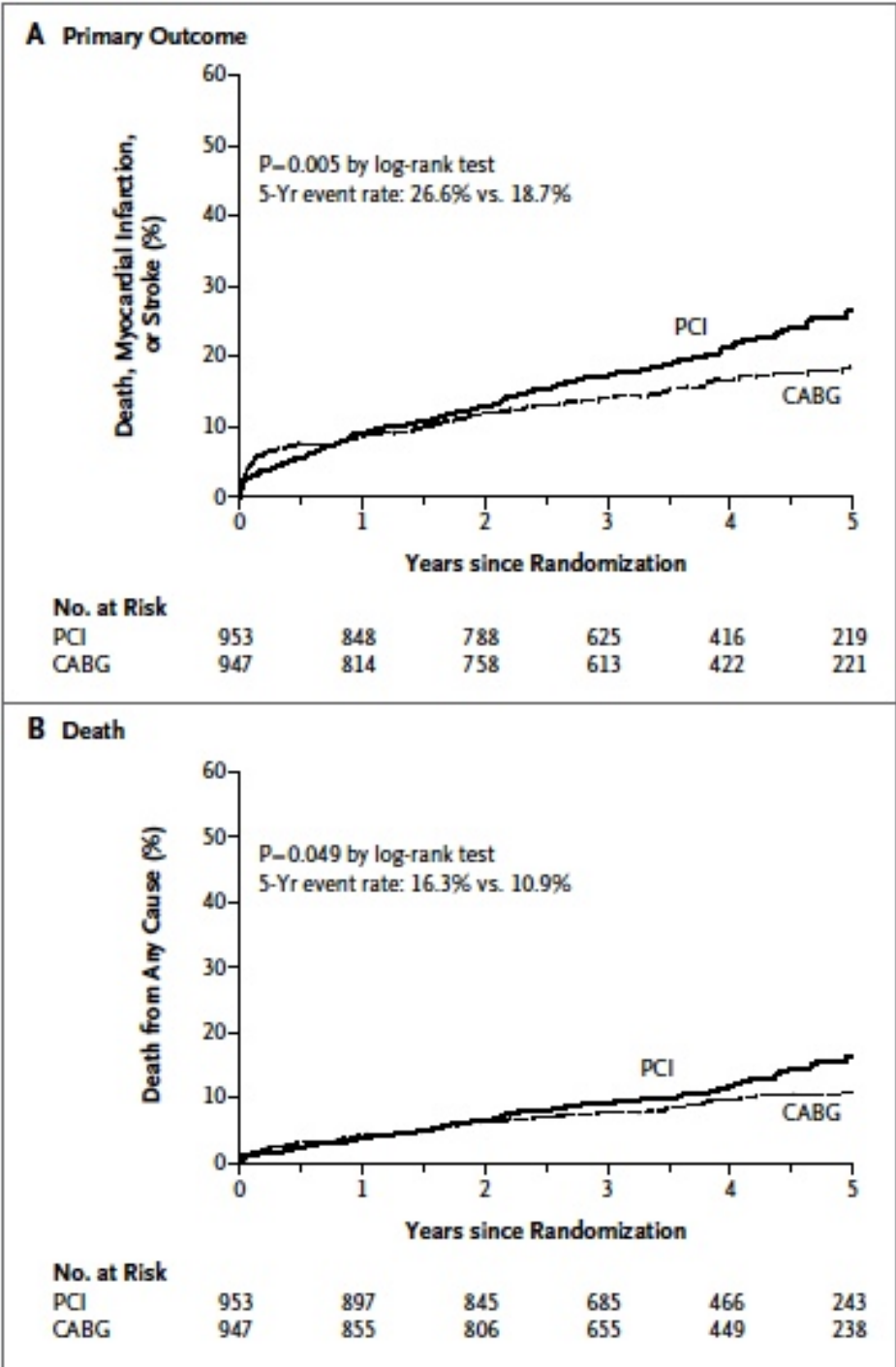


Figure 2. Kaplan-Meier Curves for composite primary outcome (all cause death, non-fatal myocardial infarction or stroke) and all cause death in a comparison between PCI with DES compared with CABG for multivessel disease in diabetic patients. Reproduced with permission from Farkough ME et al. NEJM 2012. DOI 10.1056/NEJMoa1211585.

6.3. Degree of ischemia and revascularization: Is the effect independent of symptoms?

Although there is paucity of randomized data addressing the question of how the degree of functional ischemia relates to the benefit of revascularization, there is observational data that suggests a strong relationship [54, 55]. Adjusted risk models have suggested that patients with *less than a 10-12.5% threshold* of ischemia as demonstrated by stress myocardial perfusion imaging, the survival profile of those treated with medical therapy were similar or even perhaps slightly better than those who are treated with revascularization [54]. However *above the threshold of 10-12.5% of ischemia*, there was a graded incremental survival benefit of revascularization over medical therapy, with a risk adjusted relative risk reduction of 50% [Figure 3] [54].

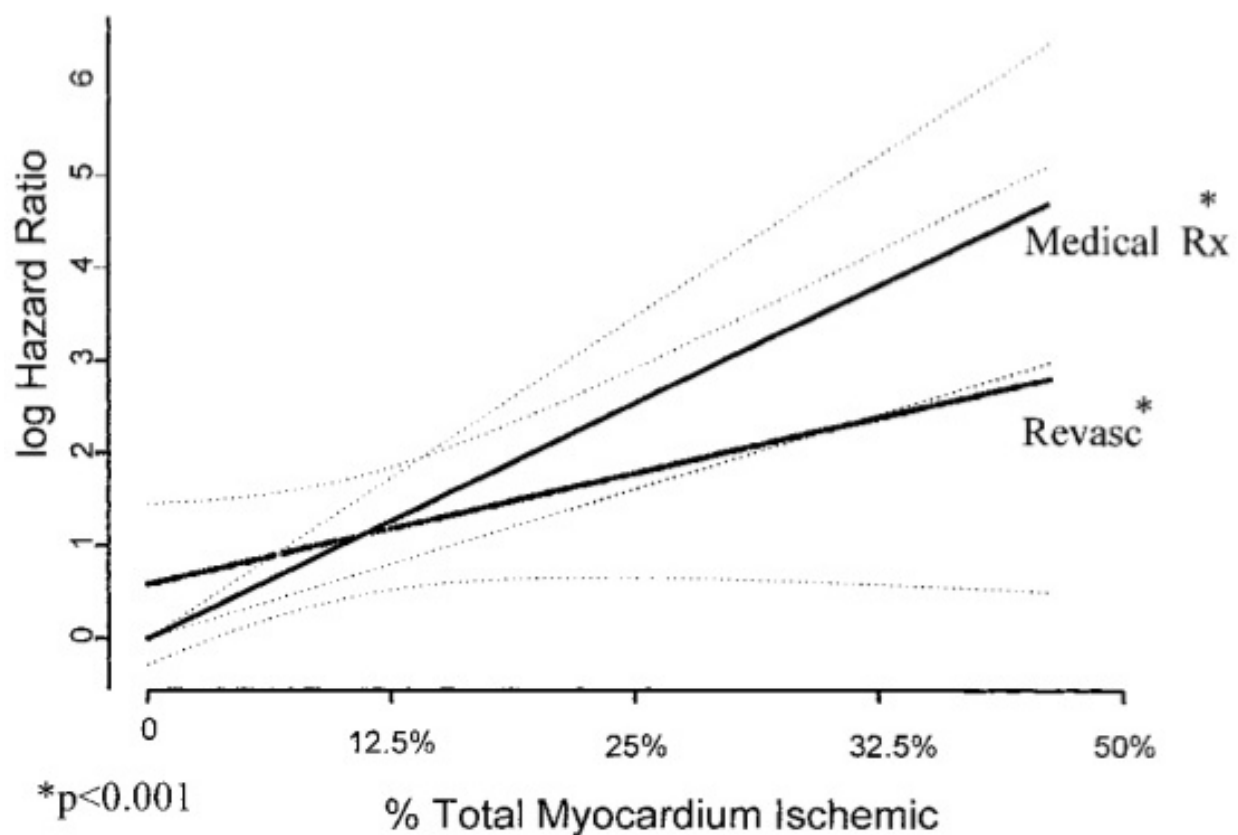


Figure 3. Log hazard ratio for revascularization (Revasc) versus medical therapy (Medical Rx) as a function of % myocardium ischemia based on final cox proportional hazards model. Model, $P < 0.0001$; interaction, $P = 0.0305$ (Reproduced with permission from Hachamovitch et al. Circulation 2003. 107: 2900-2906).

This data was further corroborated by another observational study demonstrating a similar effect in a group of asymptomatic diabetic patients [55]. This study found a *14% survival benefit* in patients with a high-risk myocardial perfusion scan treated with CABG over medical therapy [55]. Patients treated with PCI in the high-risk scan group did not achieve a survival benefit over medical therapy [55]. This may be due to the fact that, this treatment group consisted of only 10.7% three vessel disease and no patients with left main disease whereas in the CABG group, this was 52.1% and 20.8% respectively [55]. The other caveat to this data is

the low overall use of optimal medical therapy, which may overestimate the effect size of revascularization in some anatomic subgroups. The use of ASA, ACEi's and BB's were all 40% or less with no mention of statin therapy [55].

In summary, patients with moderate to high-risk scans by myocardial perfusion have significant survival advantage if treated with revascularization over medical therapy alone *even in the absence of symptoms* [54, 55]. This benefit has more convincingly been demonstrated in patients undergoing CABG [54, 55]. Although the current standard and use of optimal medical therapy has improved over time, this effect is likely still significant. This survival benefit in the high-risk scans has not been clearly demonstrated in patients treated with PCI in stable coronary disease. Recently, the COURAGE trial involving over 2000 patients, which compared optimal medical therapy plus PCI with optimal medical therapy alone in stable CAD included a high prevalence of MVD (over two thirds) associated with the same proportion of multiple reversible defects by myocardial perfusion imaging [56]. This study showed, after exclusion of patients with high-risk anatomy (LM) and markedly positive exercise stress testing (substantial ST depression or hypotensive response in stage I Bruce protocol), no significant difference in all cause death and non-fatal myocardial infarction between the medical therapy and PCI groups [56].

6.4. Impact of complexity of disease

6.4.1. *The synergy between PCI with taxus and cardiac surgery (SYNTAX) score*

The SYNTAX score was designed as a comprehensive tool to classify the anatomic complexity and functional severity of a patients' coronary anatomy [57]. It is in fact an amalgamation of five different scoring/classification systems which can be distilled into three basic guiding principles: the first which describes the segments of the coronary artery tree; the second which describes the relative importance of the lesion based on the location and vascular territory to which the lesion impedes flow; the third which describes the complexity of the lesion [Table 1].

6.4.2. *The SYNTAX trial*

As techniques and technology for percutaneous coronary intervention have evolved, there has been an increasing number of patients with multivessel disease treated with percutaneous intervention [58]. The SYNTAX trial has evaluated the PCI versus CABG in patients with highly complex disease in the contemporary context of paclitaxel drug eluting stenting [51]. At 12 months there was a significantly lower incidence of the primary outcome of major cardiac and cerebrovascular events (MACCE) (ie. all cause death, stroke myocardial infarction or repeat revascularization) CABG group compared than the PCI group with an **ARR of 5.4% or NNT 19** [51]. This was largely driven by an increase need for repeat revascularization as the rates of *all cause death, MI or stroke was similar between the two groups* [51]. In the initial subgroup analysis at 12 months, while there was a trend towards lower MACCE in the CABG group compared to the PCI group as the SYNTAX scores increased, a significantly lower rate of the primary outcome could only be demonstrated at the highest SYNTAX scores (>33) [Figure 4] [51].

Principle	Description
Definition and segmentation of the coronary artery tree	1. The coronary tree can be divided into 16 major segments
Functional significance	2. Functional importance of the particular epicardial vessel is weighted according to the percentage of the left ventricle to which it supplies. For example the left main supplies 5 times the vascular territory compared to that of a dominant RCA; hence the LM will be given a score of 5 whereas the RCA will be given a score of 1.
Lesion Complexity	3. The complexity of the lesion itself can be described in terms of <ol style="list-style-type: none">Degree of involvement of side branches, anatomic configuration of lesionsPresence or absence of a total occlusions and presence of collateralsLesion lengthTortuosity of vesselPresence or absence of heavy calcificationPresence or absence of ThrombusPresence or absence of diffuse disease

Table 1. Principles underlying the development of the SYNTAX score

The 3-year follow-up for this study more definitively demonstrated that PCI and CABG tended to have similar cardiovascular outcomes in patients with lower complexity while at higher levels of anatomical complexity, patients that underwent CABG faired better [Figure 5] [59]. At three-year follow-up, patients with 3VD in the CABG group versus the PCI group with intermediate complexity (SYNTAX Score 23-32) had overall **decrease in MI with an ARR of 5.8%** and those with the highest complexity (SYNTAX Score >33) had a decrease in **all cause mortality (ARR of 6.6%) and a decrease in MI (ARR of 5.3%)** [51, 59]. This was also reflected in an *overall lower all-cause death* in the 3VD patients treated with CABG versus PCI with an *ARR of 3.8% (p=0.02)* and a *lower rate of cardiac death* in those treated with CABG versus PCI *ARR 3.3% (p=0.01)* [59]. Interestingly, there was no significant difference for all-cause death or cardiac death between the CABG group versus the PCI group among patients with LM disease [59]. In contrast to those with 3VD, there were only significantly lower MACCE rates among patients with LM disease treated with CABG compared with PCI at the highest SYNTAX scores (>33) [59]. Although it is difficult to make precise conclusions regarding the subgroup analyses, the overall trends are certainly compelling.

The recent SYNTAX trial has heralded a new era in revascularization. The recent European Guidelines have responded to the findings by giving a **Ila recommendation (level B evidence)** to PCI for revascularization in 3VD with low angiographic complexity (SYNTAX score ≤22) while giving a **class III recommendation (level A evidence)** for revascularization of such patients moderate to high angiographic complexity (SYNTAX score >22) [26]. The most recent ACC/AHA PCI guidelines state that in patients with 3VD with or without proximal LAD, revascularization with PCI for the purposes of prognosis is of **uncertain benefit (IIb recommendation, level B evidence)** [14]. In these populations, CABG is still given **Class I recommendation (level B evidence)** [Table 2 and 3] [14, 26].

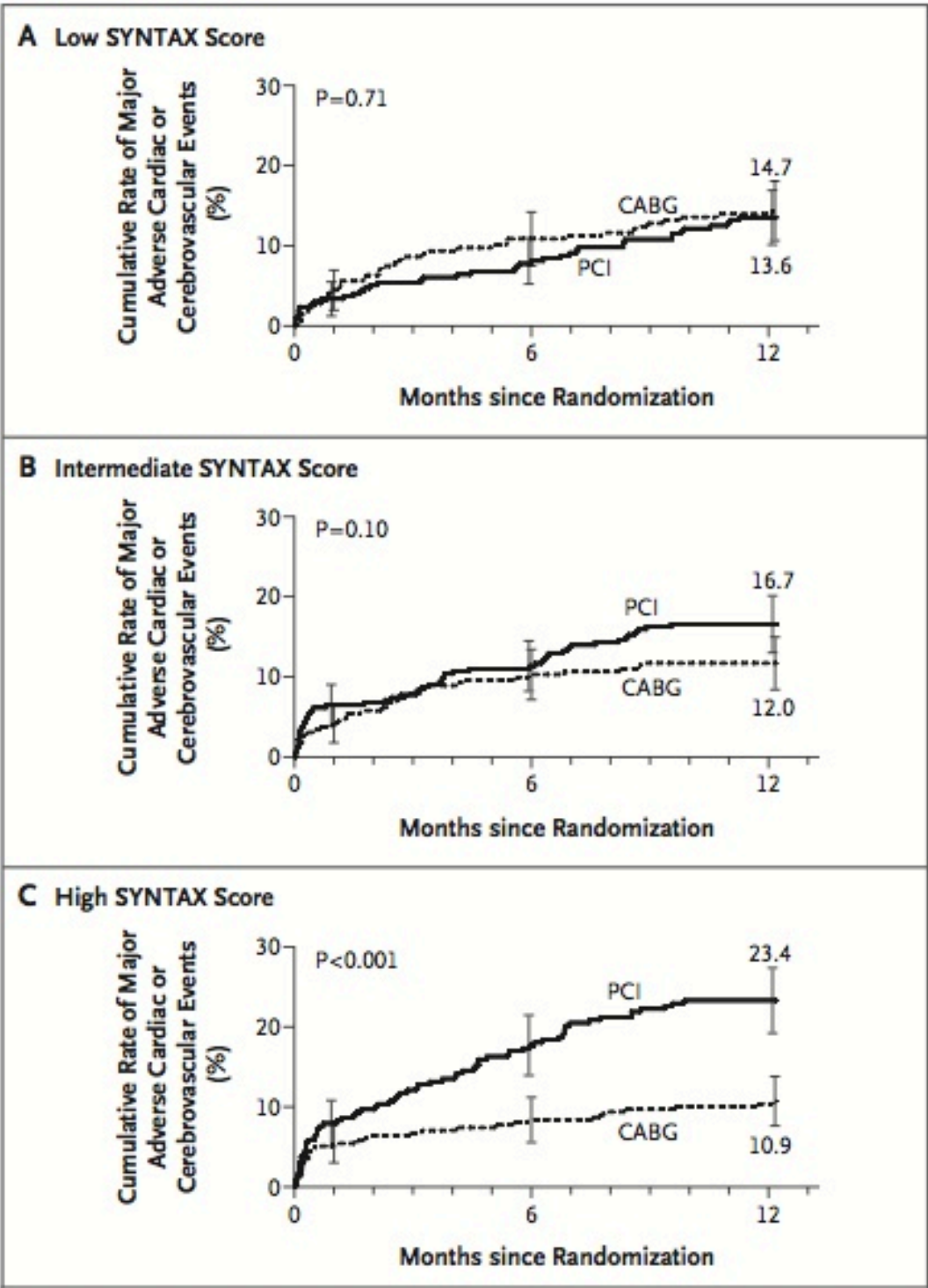


Figure 4. 12-month Subgroup analysis of the rates of (all cause death, stroke, myocardial infarction and repeat revascularization) between those treated by CABG versus PCI stratified by SYNTAX score. A significant difference in the overall rates was not significantly different at low (<22) and intermediate (23-32) SYNTAX scores. At the highest SYNTAX score (>33), there was a significantly lower rate of major cardiac and cerebrovascular events. Reproduced with permission from Serruys PW et al. NEJM 2009. 360;10: 961-972.

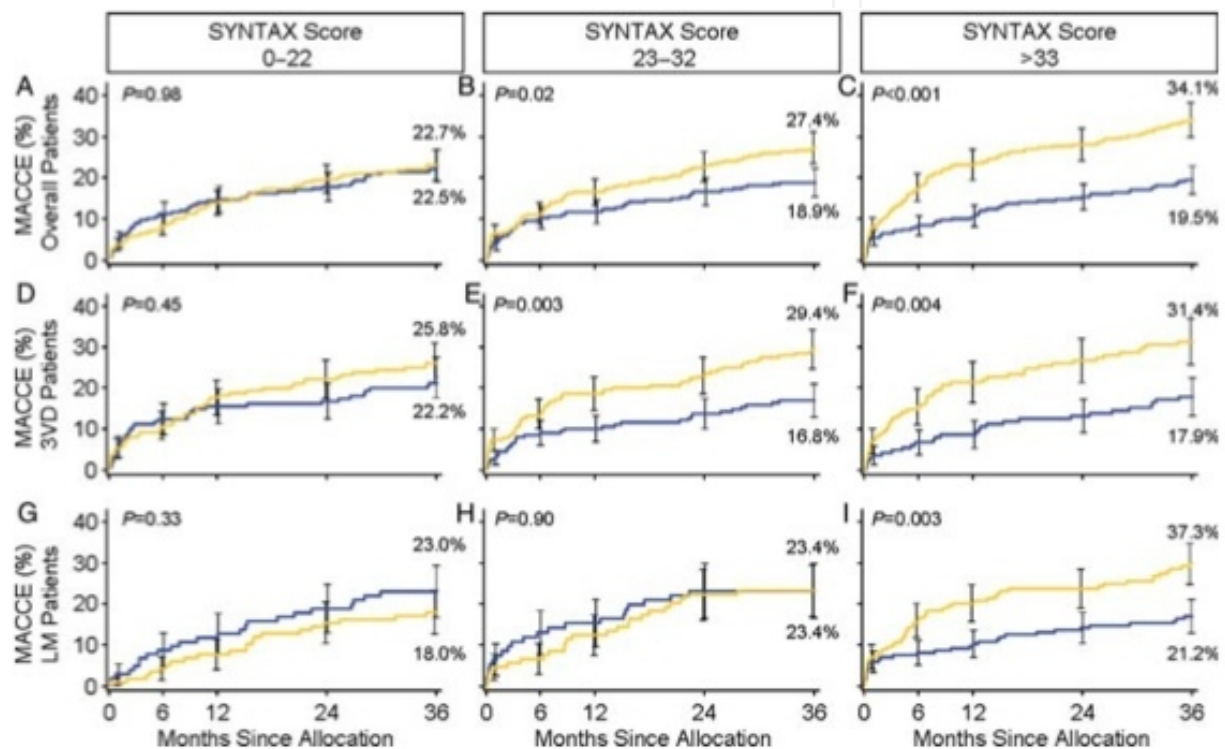


Figure 5. 3-year subgroup analysis of the rates of MACCE (all cause death, stroke, myocardial infarction and repeat revascularization) between those treated by CABG (blue line) versus PCI (yellow line) stratified by SYNTAX score: Low SYNTAX Score (0-22), Intermediate SYNTAX Score (23-32), High SYNTAX Score (>33). Results are provided for overall group (A-C), 3VD patients (D-F) and LM patients (G-I). Reproduced with permission from Kappetein et al. European Heart Journal 2011. 32: 2125-2134.

Subset of CAD by anatomy	Favours CABG	Favours PCI
1VD or 2VD - non-proximal LAD	IIb C	I C
1VD or 2VD - proximal LAD	I A	IIa B
3VD simple lesions, full functional revascularization achievable with PCI, SYNTAX score ≤ 22	I A	IIa B
3VD complex lesions, incomplete revascularization achievable with PCI, SYNTAX score > 22	I A	III A
Left main (isolated or 1VD, ostium/shaft)	I A	IIa B
Left main (isolated or 1VD, distal bifurcation)	I A	IIb B
Left main + 2VD or 3VD, SYNTAX score ≤ 32	I A	IIb B
Left main + 2VD or 3VD, SYNTAX score ≥ 33	I A	III B

Table 2. ESC Guidelines on revascularization for complex coronary disease. Indications for CABG and PCI are tabulated for stable patients with low predicted surgical mortality and lesions suitable for either modes of revascularization. CABG= coronary artery bypass grafting; CAD= coronary artery disease; LAD = left anterior descending; PCI= percutaneous coronary intervention; VD= vessel disease. Reproduced with permission from Wijns W et al. European Heart Journal 2010. 31: 2501-2555.

Anatomical Setting	Class of Recommendation	Level of Evidence
UPLM or complex CAD		
CABG and PCI	I—Heart Team approach recommended	C
CABG and PCI	Ia—Calculation of STS and SYNTAX scores	B
UPLM*		
CABG	I	B
PCI	Ia—For SIHD when both of the following are present <ul style="list-style-type: none"> Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (eg, a low SYNTAX score of ≤ 22, ostial or trunk left main CAD) Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (eg, STS-predicted risk of operative mortality $\geq 5\%$) Ia—For UA/NSTEMI if not a CABG candidate	B
	Ia—For STEMI when distal coronary flow is TIMI flow grade < 3 and PCI can be performed more rapidly and safely than CABG	C
	Ib—For SIHD when both of the following are present <ul style="list-style-type: none"> Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (eg, low-intermediate SYNTAX score of < 33, bifurcation left main CAD) Clinical characteristics that predict an increased risk of adverse surgical outcomes (eg, moderate-severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted risk of operative mortality $> 2\%$) II: Harm—For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B
3-vessel disease with or without proximal LAD artery disease*		
CABG	I	B
	Ia—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (eg, SYNTAX score > 22) who are good candidates for CABG	B
PCI	Ib—Of uncertain benefit	B
2-vessel disease with proximal LAD artery disease*		
CABG	I	B
PCI	Ib—Of uncertain benefit	B
2-vessel disease without proximal LAD artery disease*		
CABG	Ia—With extensive ischemia	B
	Ib—Of uncertain benefit without extensive ischemia	C
PCI	Ib—Of uncertain benefit	B
1-vessel proximal LAD artery disease		
CABG	Ia—With LIMA for long-term benefit	B
PCI	Ib—Of uncertain benefit	B
1-vessel disease without proximal LAD artery involvement		
CABG	II: Harm	B
PCI	II: Harm	B
LV dysfunction		
CABG	Ia—EF 35% to 50%	B
CABG	Ib—EF $< 35\%$ without significant left main CAD	B
PCI	Insufficient data	
Survivors of sudden cardiac death with presumed ischemia-mediated VT		
CABG	I	B
PCI	I	C
No anatomic or physiologic criteria for revascularization		
CABG	II: Harm	B
PCI	II: Harm	B

Table 3. ACC Guidelines on revascularization for complex coronary disease to improve survival. Indications for CABG and PCI are tabulated. CABG = coronary artery bypass grafting; COPD= chronic obstructive pulmonary disease; EF= ejection fraction; LAD=left anterior descending artery; LIMA= left internal mammary artery; LV =left ventricular; N/A= not applicable; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease; STEMI= ST-elevation myocardial infarction; STS= Society of Thoracic Surgeons; SYNTAX = Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery; TIMI= Thrombolysis in myocardial infarction; UA/NSTEMI =unstable angina/ non-ST elevation myocardial infarction; UPLM= unprotected left main disease; VT=ventricular tachycardia. Reproduced with permission from Levine GN et al. Circulation 2011. 124: e574-e651.

For those with unprotected left main disease (UPLM), both the ACC and ESC guidelines still give a **Class I recommendation for CABG in all cases (Classified as Grade A evidence for ESC and Grade B evidence for ACC)** [14, 26]. They have both also given a **IIa recommendation for PCI in Stable Ischemic Heart Disease (SIHD) in UPLM when the SYNTAX is 22 or less (eg isolated ostial or main trunk LM) and IIb recommendation for PCI for low or intermediate SYNTAX score (<33) (Level B evidence)** [14, 26]

It is recognized however, that some populations are not expected to derive prognostic benefit from revascularization. In such groups for the purposes of alleviating symptoms refractory to optimal medical therapy, CABG and PCI have equivalent **Class I recommendation (level A evidence)** unless SYNTAX is >22 in which case CABG is still favored (**Class IIa recommendation, level B evidence**) [14].

7. PCI versus CABG in acute coronary syndromes versus stable ischemic coronary artery disease

7.1. Non-ST-elevation acute coronary syndromes (NSTEMACS)

Although there are limited studies designed to address this specific question, it is generally accepted that the same considerations that are used to decide between PCI and CABG in stable ischemic coronary artery disease would be applied when faced with an NSTEMACS (**Class I recommendation, Level B evidence**) [14]. Comparisons between PCI and CABG have typically included a mixture of patients with stable and unstable symptoms [45]. The ERACI II study contained the highest proportion of patients with unstable symptoms constituting 92% of the randomized patients whereas MASS II included the least with 0% having unstable symptoms [60, 61]. However in a large meta-analysis including individual patient data from 10 large randomized studies (n=7812) did not reveal any significant interaction between the presence or absence of unstable symptoms and mode of revascularization (PCI vs CABG) with respect to mortality outcomes over a 5 year period [45].

The optimal approach to PCI in the setting of a NSTEMACS and MVD is still somewhat uncertain. There are currently no randomized trials in the literature comparing the multivessel PCI to culprit only PCI in NSTEMACS [62].

7.2. ST -elevation acute coronary syndromes (STEMACS)

Primary PCI remains the main modality of revascularization in STEACS (*Class I recommendation, Level A evidence*). It is common to encounter MVD during the index angiogram for STEACS having an estimated incidence of up to 40-50 percent [62]. Current evidence supports primary PCI of the culprit vessel only, in the absence of hemodynamic instability, as the optimal approach [14, 62, 63]. *Multivessel PCI in this setting has been associated with a higher mortality and is not recommended (Class III recommendation, Level B evidence)* [14, 62, 63]. The approach to residual coronary disease has been a subject of controversy and the decisions are likely made clinically on an individual basis.

7.3 Cardiogenic shock

The optimal mode of revascularization in patients with multivessel disease and cardiogenic shock is still under debate due to lack of supporting evidence for or against either PCI or CABG. It has been previously shown in the **Should We Emergently Revascularize Occluded Arteries for Cardiogenic Shock (SHOCK) Trial** that urgent revascularization with PCI or CABG for cardiogenic shock in the setting of STEACS has *mortality benefit* with an **ARR of 13 percent** or **NNT of 8** at 6 months compared with medical management [64]. This difference continued out to one year and remained stable at long-term follow up [Figure 6] [65, 66]. In the revascularization group, 64 percent were treated with angioplasty whereas 36 percent were treated with CABG [64]. Interestingly, because the mode of revascularization was at the discretion of the treating physicians, patients treated with CABG compared with those that received PCI tended to more often have LM disease and 3VD [64]. Nevertheless, there was no significant difference between patients treated with PCI versus CABG at either 30 days or at 1 year [64]. Certainly the advantage of PCI for revascularization over CABG would be a reduced time required to achieve revascularization; the time of randomization to first revascularization attempt was 0.9 hour for PCI and 2.7 hours for CABG [64].

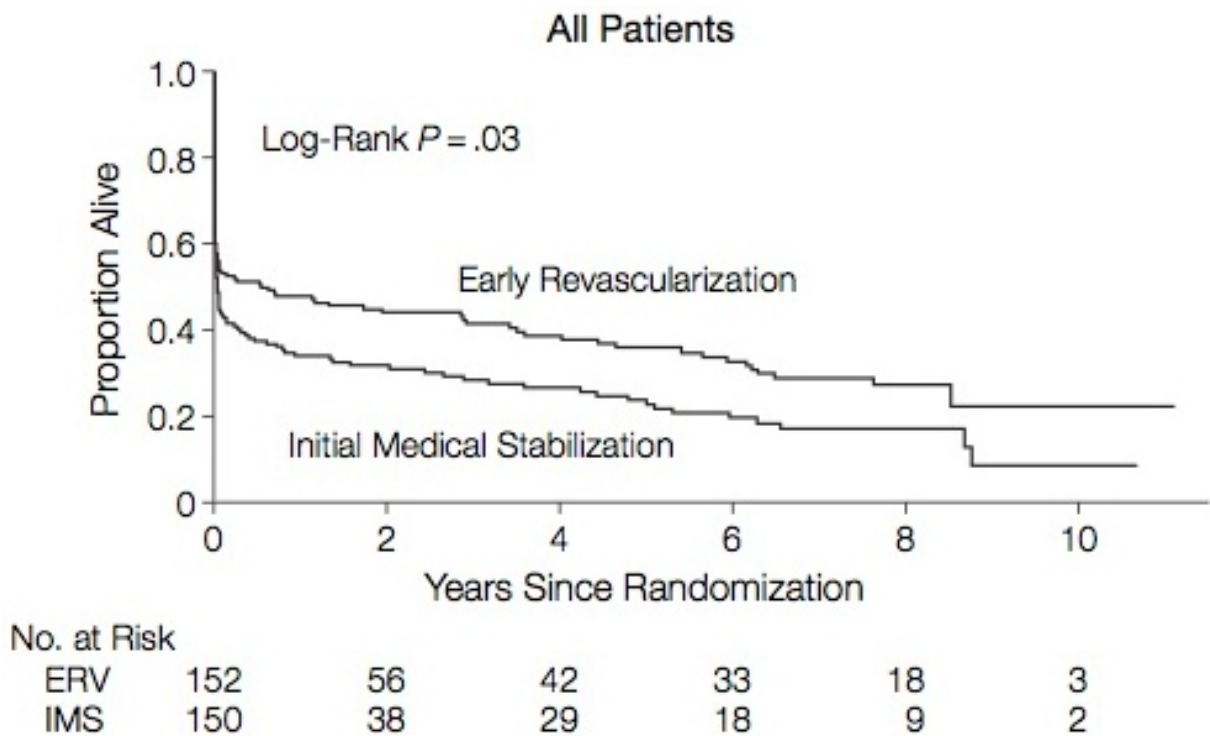


Figure 6. Kaplan-Meier Survival Curves For Early Revascularization Versus Initial Medical Stabilization in Long Term Follow-Up. ERV= Early Revascularization; IMS =Initial Medical Stabilization. Reproduced with permission from Hochman JS. et al. JAMA 2006. 295;21: 2511-2515.

There is a lack of randomized data regarding the optimal mode of revascularization in cardiogenic shock for acute coronary syndromes [67]. Currently, both the ACC and ESC

guidelines recommend that PCI (or emergency CABG) should be performed on patients who candidates for revascularization in the setting of STEMI and severe heart failure or cardiogenic shock (*Class I recommendation, Level B evidence*) [14, 26]. Although the data upon which this recommendation is based does not show a preferential benefit to either mode of revascularization, both guidelines favor PCI as the primary mode of revascularization in cardiogenic shock [14, 26]. The ACC guidelines do recognize however, that “select patients with severe 3VD or LM disease can benefit from emergency CABG” [14].

8. Treatment of hemodynamically significant disease

Currently, the ACC/ AHA defines a significant stenosis as “Greater than or equal to 70% luminal diameter narrowing, by visual assessment, of an epicardial stenosis measured in the “worst view” angiographic projection [68].” The exception is the left main artery in which a significant stenosis is defined as “ greater or equal to 50% luminal diameter narrowing [68].” A challenge in the interpretation of the data surrounding comparisons of PCI versus CABG the variability in definitions of “significant disease.” Interestingly, many of the landmark trials comparing PCI versus CABG actually defined a significant stenosis as greater or equal to 50% [27, 45, 51].

Even in the presence of a significant stenosis, myocardial blood flow can be maintained by compensatory mechanisms at rest [69]. Consequently, hemodynamically significant disease has been defined by those lesions, which produce a reduction in coronary flow reserve under conditions of maximal hyperemia [69, 70]. Reduction of coronary flow reserve is generally observed in lesions with as little as 50 percent stenosis but progressively worsens with the degree of narrowing [70]. There are two implications of this clinically. First, there is a significant interobserver and intraobserver variability in the degree of angiographic stenosis [69]. Second, the hemodynamic significance of a given lesion is dependent on the severity of the stenosis, the length of the lesion as well as the presence of collateral blood flow [71].

Aims to quantify the functional significance of coronary stenosis lead to the development of the concept Fractional Flow Reserve (FFR) [72]. FFR is a hemodynamic construct defined as the maximal blood flow distal to a stenosis compared with the maximal blood flow in the same vessel, hypothetically in the absence of any stenosis, conditions of maximal hyperemia [72]. Flow can be characterized by the following equation: Pressure (P) = Flow (Q) * Resistance (R) [72]. For a given lesion, the FFR is the maximal flow for the stenotic vessel (Qs)/ maximal flow if the vessel were normal (Qn). Since, under maximal hyperemia, the resistance becomes a constant, Q is only dependent on the pressure and fractional flow reserve can be defined by a ratio of aortic pressure (Pa)/ pressure distal to the lesion (Pd) [Figure 7] [72]. FFR allows for the functional assessment of ischemia at the time of coronary angiogram [72].

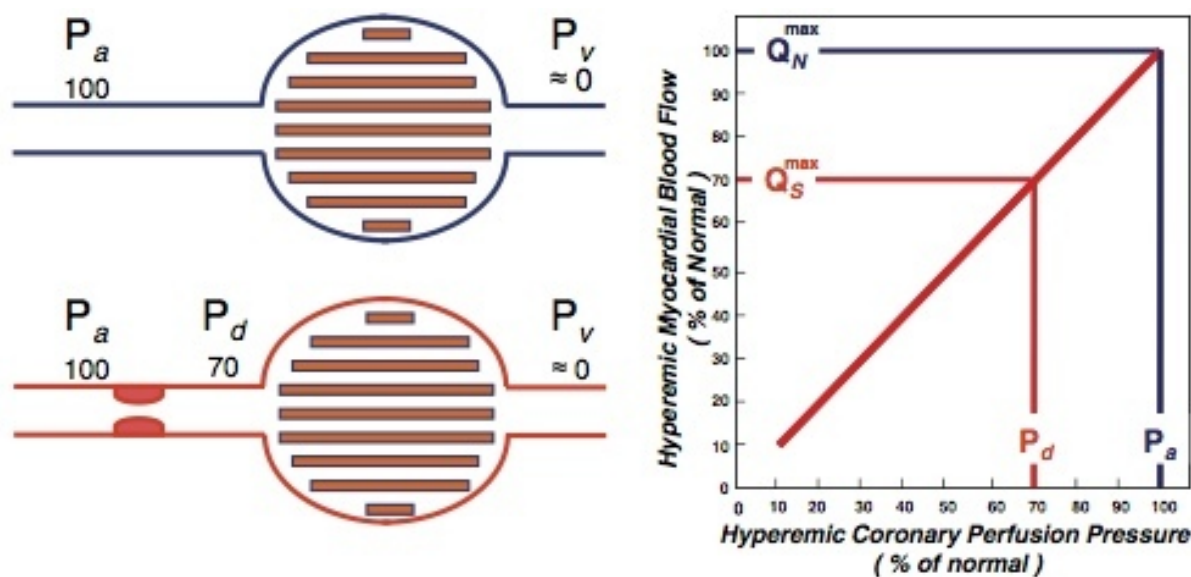


Figure 7. A schematic depiction of the concept of fractional flow reserve. On the right is the graphical correlation between Flow Q and perfusion pressure P under conditions of maximal hyperemia. The maximal blood flow in the stenotic vessel Q_S (Red Lines) is directly proportional to the perfusion pressure distal to the lesion. The maximal blood flow in the same vessel hypothetically without the stenosis Q_N (Blue Lines) is proportional to the perfusion pressure proximal to the stenosis P_a which is the same as aortic pressure. Q_S/Q_N is therefore equal to P_d/P_a . Reproduced with permission from Pijls NHJ et al. JACC 2012. 59: 1045-57.

The use of FFR will become increasingly more relevant in the assessment of patients with multivessel disease. The **Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME)** was a study randomizing 1005 patients to either angiographically guided PCI or PCI guided by fractional flow reserve in patients with multivessel disease of at least moderate severity (greater or equal to 50%) [73]. Patients in the angiographic group were revascularized if PCI was indicated based on visual assessment of angiographic data and clinical data; patients in the FFR group only had PCI if the FFR was < 0.80 [73]. The combined outcome of death, myocardial infarction and repeat revascularization was significantly less in those treated with FFR guided PCI (18.3%) than the angiographically guided PCI (13.2%) [Figure 8] [73]. Death and myocardial infarction, although not a pre-specified outcome, was also significantly less in the FFR group (11.1%) versus the angiographic group (7.3%) [73]. This difference persisted to the two-year follow-up [74].

Although FFR is early in its development, certainly it has the potential to play a role in classifying the severity of disease for decision-making in MVD. Consider a patient with 3VD with a 50 percent lesion at the proximal LAD. If the proximal LAD lesion is FFR is greater than 0.80, this patient may in fact be classified as two vessel disease with no hemodynamic involvement of the proximal LAD and hence should receive PCI. While there is limited research exploring the use of FFR in determining the mode of revascularization, this is certainly an area worthy of further study. Currently the ACC advocates the use of FFR guiding revascularization decisions in stable ischemic heart disease with moderate lesions with 50-70% stenosis (**IIa recommendation, level A evidence**) [14].

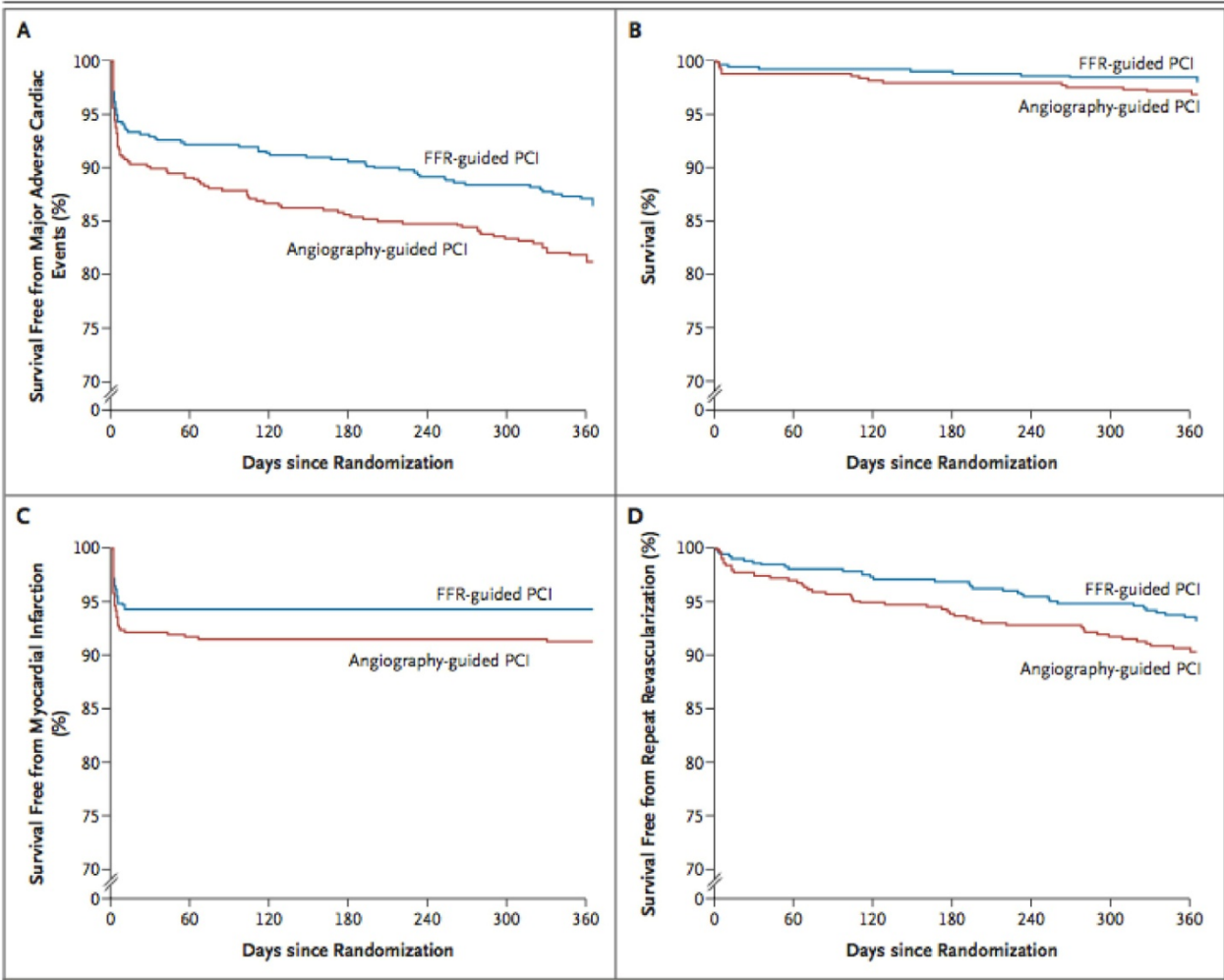


Figure 8. Kaplan-Meier Survival Curves according to study group PCI guided by angiography alone versus PCI guided by FFR in addition to angiography. FFR=fractional flow reserve, PCI=percutaneous coronary intervention. Reproduced with permission from Tonino PAL et al. Fractional flow reserve versus angiography or guiding percutaneous coronary intervention. NEJM 2009. 360(3):213-224.

9. Current trends in PCI versus CABG in North America

The practice patterns regarding PCI and CABG have changed dramatically within the last 10-15 years. In the earlier part of this last decade, rates of PCI have been observed to be on the rise both in the United States and in Canada despite relatively more static rates of CABG over that same period [75, 76]. Furthermore, although there is some signal that the trend in PCI rates have begun to plateau or reverse in the latter part of this decade both in the United states and in Canada, there is still a consistent increase in the overall PCI: CABG ratio [77, 78].

These recent trends have been an area of increasing research interest, as it seems paradoxical in the context of relatively consistent practice guidelines from the ACC and the ESC supporting the use of CABG as the first line mode of revascularization in prognostically important stable

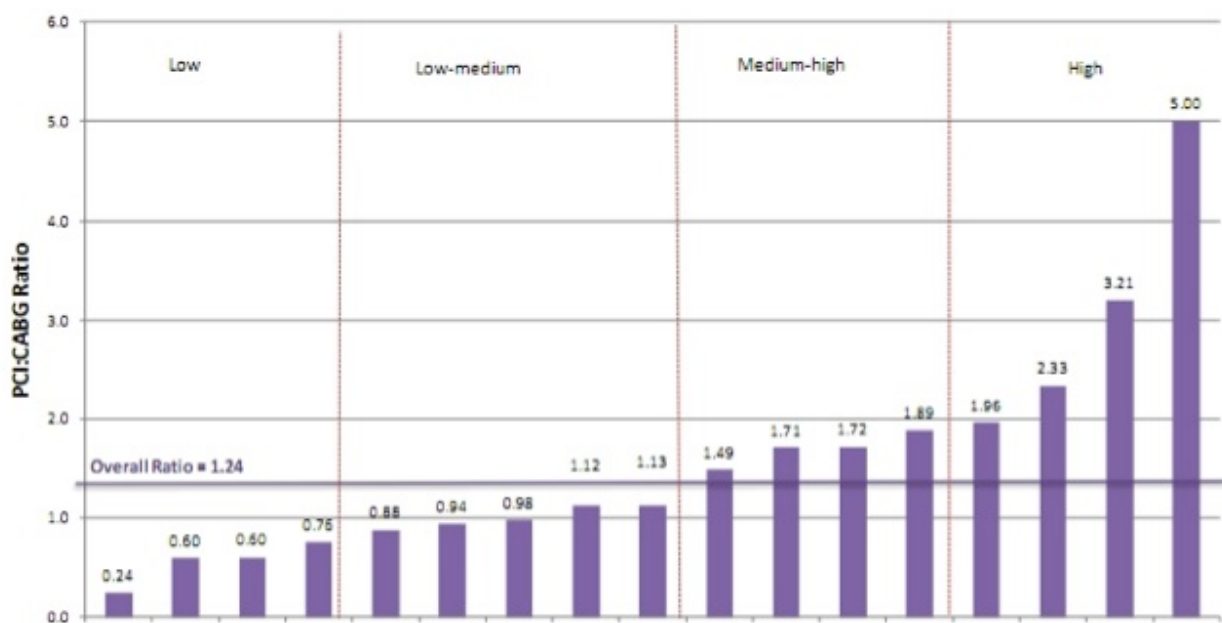


Figure 9. Variation in Revascularization for Multivessel Disease Across 17 Cardiac Centers in Ontario. Reproduced with permission from Schwalm JD et al. SYNTAX Score and Real World Revascularization Patterns. Canadian Cardiovascular Congress 2011 Vancouver, BC. Abstract Presentation.

ischemic coronary artery disease [Figure 9] [14, 26]. In fact, recent data has demonstrated a rise in PCI with DES in patients with Class I recommendation for surgery [25].

Significant variability in PCI: CABG ratio between provinces/states, between hospitals and even between individual interventionalists suggests that the trends in revascularization practices are not entirely explained by changes in population or advancements in revascularization techniques [76-80]. In Ontario, Canada, PCI to CABG ratios vary considerably between hospitals from 1.3 to 6.1 [81]. In multivessel disease, this ratio ranges from 0.24 to 5.0 [figure 9] [82]. The physician performing the diagnostic catheterization (interventional cardiologist versus non-interventional cardiologist), the coronary anatomy (LM, 3VD, 2VD), and the treating hospital were the three strongest determinants of the ultimate therapeutic strategy [58].

Two possible hypotheses for the presence of such dramatic variability in the management of multi-vessel disease include misinterpretation of the evidence and misclassification of disease complexity at the time of diagnostic angiogram. There are complex interacting variables upon which the final therapeutic decision is based, including: (1) complexity of coronary anatomy, (2) presence or absence of prognostically important factors favoring surgery, (3) degree of active functional ischemia, (4) complex co-morbid state of patient, (5) patient preferences and social factors, (6) local resources and expertise. All of these factors may affect the patient's suitability for CABG and likelihood to benefit prognostically from surgical revascularization. Application of the large body of evidence in this variable clinical milieu is a complex process. The management algorithm is further complicated when considering the patient's role in the decision-making process and the steps required to ensure truly "informed" patient consent.

10. Angioplasty versus bypass surgery: An evolving complex decision analysis

10.1. Establishing a general approach

Decisions regarding revascularization are complex and have been founded on decades of evidence. This body of evidence has evolved in parallel with advances in treatment but also a patient population with increasing medical complexity. Therefore, a contemporary approach to MVD and revascularization must be founded on an understanding of the wide spectrum of disease severity, advances in medical/surgical therapy, diversity in patient populations, patient preference and social circumstances. Optimal treatment strategies must apply the most current evidence in an appropriate clinical context. Furthermore, guiding principles of management with a multidisciplinary ‘Heart Team’ approach should be the cornerstone of state of the art treatment of multivessel coronary artery disease as supported by recent revascularization guidelines [14]. The basic approach should address a number of basic clinical questions which address the (1) therapeutic goals of the case, (2) the presence or absence of clinical evidence to support revascularization, (3) the presence/absence of prognostic factors that may make surgical revascularization more favorable, (4) whether the anatomy favor PCI or CABG, (5) is the patient a good surgical candidate should prognostic disease be present, (6) does the patient have any particular preferences and (7) are there ambiguities that would benefit from further discussion by a Heart Team [Table 4].

Fundamental Question	
Therapeutic Goals:	<ul style="list-style-type: none">● Can we improve survival?● Can we improve symptoms?● Can we improve both?
Clinical Evidence to support revascularization	<ul style="list-style-type: none">● Severity of disease● Severity of Symptoms● Degree of Ischemia● Degree of Medical Optimization
Prognostic Factors that may make surgical revascularization more favorable?	LM, 3VD, or 2VD with proximal LAD with <ul style="list-style-type: none">● DM● LV dysfunction● High burden of ischemia (" / ≥12.5 percent)
Does anatomy favor one mode of revascularization versus the other?	<ul style="list-style-type: none">● Surgical targets● Diffuseness of disease● Complexity
Is the patient a good surgical candidate?	Consider: <ul style="list-style-type: none">● Age● Co-morbidities● Anatomy
Patient Preference and Social Factors	Discussed off the catheterization table
Ambiguities in Case?	Would this benefit from discussion with the Heart Team?

Table 4. Key clinical questions forming the basis of the therapeutic decision for management of multivessel coronary artery disease.

The fundamental basis of our decisions rest on what therapeutic goals can be achieved: *improvement of survival, improvement of symptoms or both*. It is important to make this distinction because although the goal would naturally to improve on both; consider the following two clinical scenarios:

- In a 50 year-old asymptomatic patient with 70% distal LM, CABG is the treatment of choice regardless of his symptom profile because of known survival benefit with surgical revascularization (**Class I, Level A evidence**)[14]
- In a 90 year-old, medically optimized, CCS class III patient who has 3VD and normal ejection fraction, his age may undermine any treatment for the purposes of prognosis, hence PCI may be favored if technically feasible as the overriding goal is for relief of symptoms. (**Class I, Level A evidence**)[14]

If the intent is to improve survival, there is good evidence that supports revascularization in certain patient populations: significant left main (>50%) or 3VD, 2VD with proximal LAD with diabetes LV dysfunction and/or high burden of functional ischemia).

If the intent is primarily to *improve symptoms* (eg. *The clinical profile undermines the prognostic benefit of surgical revascularization*), there is good evidence that revascularization with PCI is of benefit in those who are symptomatic despite optimal medical therapy if technically feasible. But with advances in medical therapy, it is reasonable to maximize medical treatment before considering revascularization [56].

10.2. The decision algorithm

Based on existing evidence and guidelines, we have developed an algorithm that may help guide decision-making in the management of MVD [Figure10]. There are a number of factors that support surgical revascularization in SIHD for improving survival over medical therapy or PCI, namely: 1) LM disease, 3VD and likely some subsets of 2VD with proximal LAD; 2) MVD in the presence of mild to moderate LV dysfunction (35-49%) 3) MVD in the presence of diabetes 4) coronary anatomy of intermediate to high level of complexity (SYNTAX >22) and 5) high burden of ischemia (>12.5%). If these are present, then surgery should be considered first unless patient preference dictates otherwise (**Class I recommendation, Level B Evidence**).

If the patient does have prognostic disease, then considering the overall coronary anatomy, patients clinical profile and co-morbidities must be considered to ultimately guide the appropriate therapeutic decision. These factors may alter the likelihood of benefit from revascularization and also affect the patients' potential eligibility CABG and PCI.

If the patient does not appear to have prognostic disease and is not likely to prognostically benefit from revascularization, then the primary goal of treatment would be symptoms. The first goal of alleviating symptoms is medical optimization. If the patient has unacceptable symptoms despite optimal medical therapy, then revascularization (PCI or CABG) would be indicated (**Class I recommendation, Level A Evidence**).

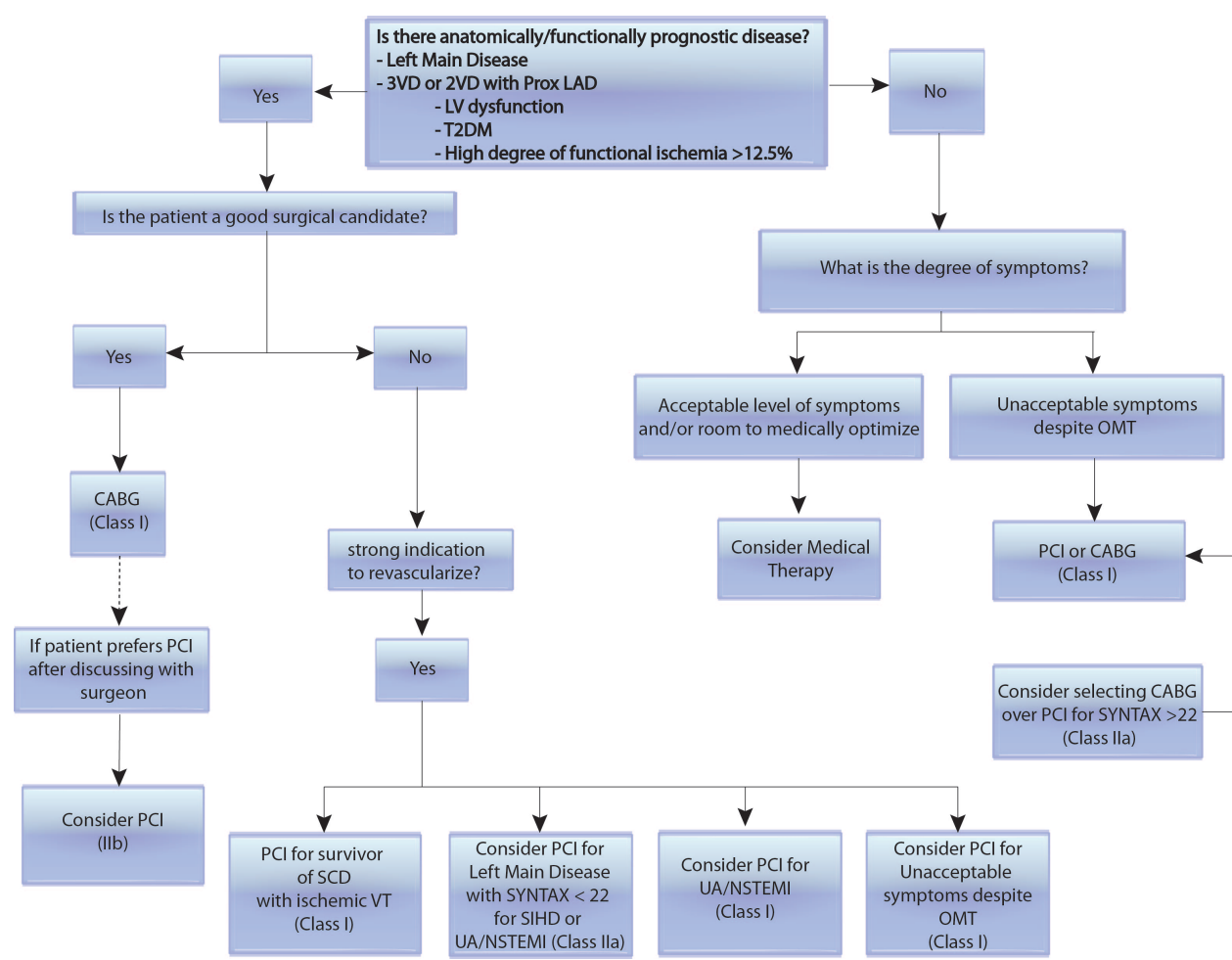


Figure 10. Suggested approach for decision making in multivessel coronary artery disease. CAD= coronary artery disease; CABG= coronary artery bypass grafting; LAD= left anterior descending artery; LM = left main disease; LV= Left Ventricular; OMT= optimal medical therapy; PCI= percutaneous coronary intervention; SCD= sudden cardiac death; SYNTAX = The Synergy between PCI with Taxus and Cardiac Surgery; T2DM= Type 2 Diabetes Mellitis; UA/NSTEMi = unstable angina/Non ST elevation myocardial infarction; VT= ventricular tachycardia; 3VD = Three vessel disease; 2VD = two vessel disease.

11. The Role of the heart team in the future of multivessel disease

The management of CAD with the advances in revascularization techniques and medical therapy, changing patient population and constantly expanding body of knowledge is becoming increasingly more complex. Such complexity would intuitively benefit from a broad spectrum of expertise. There is currently increasing interest in the area of multidisciplinary decision-making and both ACC and ESC have recommended that a Heart Team approach be implemented in the management of UPLM disease or complex CAD (*Class I recommendation, Level C Evidence*) [14, 26]. It is envisioned that with the joint involvement of the interventional cardiologist, the cardiac surgeon and a non-invasive cardiologist, there will be a more balanced, consistent management of these complex cases. From the patient's perspective, this approach would conceivably allow them to be more informed and involved in the ultimate

treatment decision. There is currently limited data on the true impact of the Heart Team and this is certainly an area of worthy future research.

12. The future of research in complex coronary artery disease

The approach to the management of complex CAD will continue to change with exponential growth of knowledge in this area. The majority of clinical trials involving CABG and PCI were largely based on complete revascularization of lesions greater than 50 percent [45]. Use of FFR has shown that PCI with DES of moderately severe lesions (50-70 percent) guided by angiography alone compared with PCI of lesions guided by both angiography and hemodynamic significance (FFR< 0.80) may actually confer a higher rate of death and MI [73]. Given our knowledge of this finding, the SYNTAX trial (where the threshold for revascularization was also a stenosis of 50 percent or greater) may conceivably have different results if FFR was used to guide therapy. Furthermore, investigations with the new second-generation DES, a now better understanding of how to utilize FFR and definition of the impact of coronary complexity may serve as a guide to better define the populations that may benefit from PCI versus CABG.

The other area requiring more research is in the arena of collaboration for decision-making in multivessel disease. The Heart Team, although a promising concept would benefit from formal validation. We also need to better define what type of institutions and what type of cases would most benefit from formal evaluation with a Heart Team approach. Furthermore as these decisions become more complex, we will also need to find better methods/mechanisms of informed balanced patient involvement in the final management decision.

Complex CAD remains a challenging area both from the scientific and the clinical point of view. The goal should be to build on the research foundations in the management of MVD CAD thus far and continue to improve our understanding of how to better manage and care for patients with complex CAD.

Abbreviations

ACC	American College of Cardiology
ACEi	Angiotensin Converting Enzyme inhibitor
ARB	Angiotensin Receptor Blocker
AHA	American Heart Association
ARR	Absolute risk reduction
ASA	Aspirin
BB	Beta Blocker
BMS	Bare metal stent

CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CI	95% Confidence interval
COPD	Chronic obstructive pulmonary disease
DAPT	Dual antiplatelet therapy
DES	Drug eluting stent
ESC	European Society of Cardiology
HMG-CoA	3-hydroxyl-3-methyl-glutaryl-coenzyme A
LAD	Left anterior descending artery
LIMA	Left internal mammary artery
LM	Left main
MID CAB	minimally invasive direct coronary artery bypass
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NSTEACS	Non ST elevation acute coronary syndrome
NSTEMI	Non ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
POBA	Plain old balloon angioplasty
RRR	Relative Risk Reduction
SCD	Sudden cardiac death
SIHD	Stable ischemic heart disease
STEACS	ST elevation acute coronary syndrome
STEMI	ST elevation myocardial infarction
SYNTAX	Synergy between PCI with Taxus and Cardiac Surgery
UA	Unstable angina
UPLM	Unprotected left main disease
VT	Ventricular tachycardia
3VD	Three vessel disease
2VD	Two vessel disease

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