Stents or surgery in coronary artery disease in 2013

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In addition to optimal medical therapy, some patients with coronary artery disease also require intervention on symptomatic and/or prognostic grounds. The debate over the relative efficacies of coronary artery bypass grafting (CABG) and stenting has recently been settled by the publication of the five-year outcomes of the SYNTAX and FREEDOM (in patients with diabetes) trials accompanied by supportive data from several large registries. There is also current evidence that stenting is still carried out in patients who would be better served by CABG, emphasizing the need for recommendations for intervention to be overseen by a multidisciplinary team rather than the individual practitioner.

**Keywords:** Coronary artery bypass grafting; stents; SYNTAX; FREEDOM; heart team

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**Introduction**

The two key indications for revascularization in patients with coronary artery disease (CAD) are symptoms unresponsive to optimal medical therapy and/or prognosis in those who demonstrate a substantial burden of ischemia (1). For almost half a century, coronary artery bypass grafting (CABG) has been regarded as the most effective revascularization therapy. However, its role has been increasingly challenged over the last two decades by percutaneous coronary intervention (PCI) and particularly with the introduction of drug eluting stents (DES). The question of whether PCI is equally efficacious as CABG in terms of survival, and freedom from myocardial infarction and recurrent angina has been fiercely debated over the last decade (2). In the last few years significant new data has emerged from the SYNTAX (3,4) and FREEDOM (5) trials that finally help resolve the relative efficacies of both interventions.

**Evidence from previous Randomized Control trials of CABG vs. PCI**

Over the two decades prior to the publication of the five-year outcomes of the SYNTAX (3,4) and Freedom trials (5), approximately 20 trials of PCI versus CABG have been conducted (2). During that period PCI has evolved from plain old balloon angioplasty (POBA), to the use of bare metal stents (BMS), and then to DES. Similarly, the overall results of surgery have also improved substantially, with better medical therapy allied to improvements in anesthesia and surgical techniques, such as the increasing use of arterial grafts and off-pump surgery. Consequently the 30-day risk of death from CABG in the ART trial was just over 1% (6).

The most definitive analysis of CABG vs. PCI to date has been a collaborative analysis of individual patient data from ten randomized trials involving 7,812 patients (7). The overall hazard ratio for death with CABG versus PCI was 0.9 (P=0.12). The implication, therefore, that CABG has no survival benefit over PCI, has however been disputed because the trials only enrolled very highly selected populations largely unrepresentative of routine clinical practice (2). Despite this, there was a significant reduction in mortality with CABG in patients aged over 65 years of age (HR=0.82; P=0.02) and in patients with diabetes (HR=0.7; P=0.014) (7).

**Evidence from registries comparing CABG vs. PCI**

Over the last decade at least five large propensity matched...
registries containing tens of thousands of patients have consistently reported a survival benefit of CABG over PCI of around 4% to 5% at three to five years (8-12). It is also striking that in all of these registries survival curves continue to diverge at five years, suggesting that there may be an even greater benefit from surgery with further durations of follow-up. Indeed, Wu and colleagues reported in the study with the longest follow-up at eight years an overall survival advantage of CABG by 7%, with the magnitude of benefit being greatest in those with the most severe disease (11). These authors also reported that the survival benefit was apparent for patients with both two- and three-vessel CAD and with or without proximal left anterior descending disease. Most recently, the ASCERT study reported survival in 86,244 CABG and 103,549 PCI propensity matched patients with two- or three-vessel CAD. At 4 years follow-up there was increased mortality with PCI compared to CABG (12).

Recent landmark trials of CABG vs. PCI: SYNTAX and FREEDOM

The most important trial of CABG versus PCI is the SYNTAX Trial, whose 5-year outcomes have recently been published (4). Before examining the actual results of SYNTAX it is worth emphasizing that this study was unique for two reasons. First, and in contrast to all the previous randomized trials of CABG versus PCI, which had enrolled only highly selected patient groups, SYNTAX was a relative ‘all comer’ trial in patients with multi-vessel and/or left main stem disease. The second major strength of SYNTAX is its nested parallel registry that looked at outcomes in 1,078 patients who were deemed ineligible for randomization. Over 80% of these patients had CAD of such severity that it was considered they would not be appropriate candidates for stenting and were therefore referred directly for CABG. Only 16% of the registry patients actually underwent PCI having been deemed prohibitively high risk for surgery.

Overall, at one-year, 12.4% of CABG and 17.8% of PCI patients reached the respective primary composite endpoint (P<0.002) of death (3.5% vs. 4.4%; P=0.37), myocardial infarction (MI, 3.3% vs. 4.8%; P=0.11), cerebrovascular accident (CVA, 2.2% vs. 0.6%; P=0.003), or repeat revascularization (5.9% vs. 13.5%; P<0.001) (3). Overall, at five-years, 26.9% of CABG and 37.3% of PCI patients reached the composite endpoint (P<0.001) of death (11.4% vs. 13.9%; P=0.10), MI (3.8% vs. 9.7%; P<0.001), CVA (3.7% vs. 2.4%; P=0.09), or repeat revascularization (13.7% vs. 25.9%; P<0.001) (4).

Because PCI failed to reach the pre-specified criteria for non-inferiority, all other findings can only be regarded as observational and hypothesis generating. Nevertheless, in 1095 patients with three-vessel CAD, CABG reduced the risk of death (9.2% vs. 14.6%; P=0.006), MI (3.3% vs. 10.6%; P<0.001) and need for repeat revascularization (12.6% vs. 25.4%; P<0.001) without an increase in the risk of stroke (3.4% vs. 3%; P=0.66). When analyzed by severity of CAD, as judged by SYNTAX scores, patients with intermediate (between 23-32) and higher (>32) scores had an absolute survival advantage with CABG (by 6.7% and 9% respectively) as well as highly significant reductions in the incidence of MI and need for repeat revascularization. Only in those with scores <22 was there a similar mortality between CABG and PCI, although CABG still resulted in significantly fewer MI and repeat revascularization. This is an important distinction as 79% of all patients with three-vessel CAD in SYNTAX (1,095 in the RCT and 570 in the registry) had SYNTAX scores >22.

However, when the SYNTAX results are analyzed according to patients with three-vessel CAD without left main disease to the 705 patients with left main disease a different pattern of response emerges. In contrast to the situation for three-vessel CAD the respective 5-year rates of death (14.6% vs. 12.8%; P=0.53) and MI (4.8% vs. 8.2%; P=0.10) were similar whereas CABG had a lower risk of repeat revascularization (15.5% vs. 26.7%; P<0.001) but a higher rate of stroke (4.3% vs. 1.5%; P=0.03). In patients with SYNTAX scores >32 CABG resulted in lower mortality (14.1% vs. 20.9%; P=0.11) and the need for repeat revascularization (11.6% vs. 34.1%; P<0.001) but at a higher risk of stroke (4.9% vs. 1.6%; P=0.13). In contrast, in the lower two SYNTAX score terciles PCI appeared to have superior outcomes to CABG in terms of reduced mortality and these patients are currently the subject of the EXCEL trial.

As for multi-vessel CAD, the optimal revascularization strategy in patients with diabetes had also been controversial but has recently been settled by the Freedom trial (5). This trial randomized 1900 patients with diabetes and multivessel CAD already receiving aggressive medical therapy, to CABG or DES. The 5-year primary composite outcome occurred in 26.6% of the PCI group and 18.7% of the CABG group (P=0.005). Crucially, the benefit of CABG was driven by highly significant absolute reductions in both death (5.4%; P=0.049) and myocardial infarction (7.9%;
P<0.001), but with a higher risk of stroke in the CABG group (5.2% vs. 2.4%; P=0.03). Some reassurance that these findings are likely to be real is that they are entirely consistent with the previous collaborative analysis reporting a hazard ratio for death of 0.7 in patients with diabetes undergoing CABG rather than PCI (7).

**Need for enforceable guidelines and multidisciplinary teams**

Despite the availability of internationally recognized guidelines and recommendations for PCI and CABG in differing anatomical patterns of CAD, it is increasingly recognized that individual practitioners still follow personal preferences even when these are not evidence-based (1), and may be influenced by ‘perverse’ incentives (13). This is particularly so in the scenario of ‘ad-hoc’ PCI i.e., when stenting is performed immediately after diagnostic angiography and, in effect, denying the patient any opportunity to discuss possible surgical options with a cardiac surgeon. Consequently it has been recently reported that not only may the documented indications for PCI be uncertain or inappropriate in almost half of all elective PCI patients (14), but that as many as one third of patients with Class I indications for CABG are still submitted to stenting instead (15). Finally, the fact that as many as 70% of patients undergoing elective PCI erroneously believe that it is to improve life expectancy and prevent further myocardial infarction (16) raises serious concerns about the whole consent process and emphasizes the need for recommendations for interventions to be overseen by a multidisciplinary team rather than an individual practitioner.

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