GLOBAL CARDIOLOGY SCIENCE & PRACTICE
A Qatar Foundation Academic Journal

Discussion

CABG in 2012: Evidence, practice and the evolution of guidelines

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ABSTRACT
In the management of coronary artery disease (CAD) it is important to ensure that all patients are receiving optimal medical therapy irrespective of whether any intervention, by stents or surgery, is planned. Furthermore it is important to establish if a proposed intervention is for symptomatic and/or prognostic reasons. The latter can only be justified if there is demonstration of a significant volume of ischaemia (>10% of myocardial mass). Taking together evidence from the most definitive randomized trial and its registry component (SYNTAX), almost 79% of patients with three vessel CAD and almost two thirds of patients with LMS disease have a survival benefit and marked reduction in the need for repeat revascularisation with CABG in comparison to stents, implying that CABG is still the treatment of choice for most of these patients. This conclusion which is apparently at odds with the results of most previous trials of stenting and surgery but entirely consistent with the findings of large propensity matched registries can be explained by the fact that SYNTAX enrolled 'real life' patients rather than the highly select patients usually enrolled in previous trials. SYNTAX also shows that for patients with less severe coronary artery disease there is no difference in survival between CABG and stents but a lower incidence of repeat revascularisation with CABG. At three years, SYNTAX shows no difference in stroke between CABG and stents for three-vessel disease but a higher incidence of stroke with CABG in patients with left main stem disease. In contrast the PRECOMBAT trial of stents and CABG in patients with left main stem disease showed no excess of mortality or stroke with CABG in comparison to stents in relatively low risk patients. Finally the importance of guidelines and multidisciplinary/heart teams in making recommendations for interventions is emphasised.

Keywords: multivessel coronary artery disease; left main stem; SYNTAX trial; coronary artery bypass grafting; drug eluting stents

http://dx.doi.org/10.5339/gcsp.2012.20

Submitted: 22 September 2012
Accepted: 4 November 2012

Cite this article as: Taggart D. CABG in 2012: Evidence, practice and the evolution of guidelines, *Global Cardiology Science & Practice* 2012:20 http://dx.doi.org/10.5339/gcsp.2012.20

1. INTRODUCTION

For almost half a century now coronary artery bypass grafting (CABG) has been a mainstay in the treatment of coronary artery disease (CAD). Indeed CABG is arguably the most intensively studied surgical procedure of all time. Over the last decade advances in Optimal Medical Therapy (OMT) and Percutaneous Coronary Intervention (PCI) have seen a gradual decline in the number of CABG, particularly in industrialized countries, but it is estimated that up to half a million CABG are still performed annually on a worldwide basis. This article reviews the indications for CABG, contemporary outcomes, comparison of its results to PCI and techniques for optimising its results.

2. INDICATIONS FOR CABG

The two main indications for CABG are in patients with proven coronary artery disease who either are symptomatic or who have prognostic indications. In the ESC/EACTS guidelines of 2010 [1] it is emphasised that CABG should only be considered in patients who remain symptomatic despite optimal medical OMT or who are intolerant of OMT. While it is classically stated that CABG is indicated on prognostic grounds in patients with left main disease or three vessel disease, especially involving the proximal left anterior descending coronary artery, the ESC/EACTS guidelines emphasise that a prognostic indication can only be justified in patients with demonstrable ischaemia which is considered to be ischaemia affecting at least 10% of the myocardial mass or in vessels with a Fractional Flow Reserve (FFR) of less than 0.8 [1].

3. CONTEMPORARY RESULTS OF CABG

The contemporary results of CABG are excellent with an estimated mortality of around 1% in elective patients. This almost certainly reflects significant improvements in the medical and anaesthetic management of patients as well as technical advances in surgical and extracorporeal perfusion techniques. Indeed in the Arterial Revascularisation Trial, a trial of single versus bilateral internal mammary artery grafts plus supplemental conduits as appropriate, the 30 day mortality was 1.2% and the one year mortality 2.4%, with the incidence of stroke, myocardial infarction and repeat revascularisation all around 2% [2]. The ART trial results were produced by 67 surgeons in 28 hospitals in 7 different countries. It is also possible however that the outstanding results in this trial reflected practise of surgeons with a high interest in CABG and in particular arterial revascularisation as it is also noteworthy that there was a relatively high proportion of patients performed with off pump surgery (around 40% of patients) [2].

4. CABG VERSUS PCI: EVIDENCE FROM RANDOMIZED CONTROL TRIALS (RCT)

Over the last two decades there have been significant advances in both the performance of CABG (the use of arterial grafts and off pump CABG) and percutaneous coronary intervention (PCI). Initial attempts at PCI were with simple 'plain old balloon angioplasty (POBA) followed by the introduction of bare metal stents (BMS) and then drug eluting stents (DES). There have been approximately 20 trials of PCI versus CABG over the last two decades and with the exception of the SYNTAX trial (see below) these trials have individually reported no difference in survival between CABG and PCI.

Hlatky and colleagues (Table 1) examined ten of these randomised trials involving 7,812 patients with a median follow up at 6 years and reported the overall hazard ratio for death with CABG in comparison to PCI at 0.9 ($p = 0.12$) [3]. However, they also identified a significant reduction in mortality with CABG in comparison to PCI in patients over 65 years of age ($HR = 0.82$; $p = 0.002$) and in those with diabetes ($HR = 0.7$; $p = 0.014$) [3]. In a separate systematic review Jeremiah and colleagues examined 28 randomised trials of CABG or PCI versus OMT involving approximately 13,000 patients with a median follow up at 3 years. They reported the hazard ratio for death with CABG at 0.62 (95% CI = 0.50 to 0.77) and for PCI HR = 0.82 (95% CI = 0.68 to 0.99) [4]. However, in the most current meta-analysis of RCTs comparing OMT plus stents versus OMT alone for stable CAD, Stergiopoulos and Brown examined 8 trials with 7,729 patients and reported at a mean follow up of over 4 years that an initial strategy of stent implantation showed no additional benefit over OMT for prevention of death, non fatal myocardial infarction, further unplanned revascularisation or angina [5].

Table 1. 5-YEAR EVENT RATE (Reference 3)

	CABG	PCI	HR	p
Death (%)	8.4	10	.91	.12
Death/Myocardial Infarction (%)	15.4	16.7	.97	.47
Death/Repeat Revascularization (%)	20.1	36.4	.52	<0.001

5. CABG VERSUS PCI: EVIDENCE FROM REGISTRIES

Over the last decade data has been reported from several large propensity matched registries comparing survival outcome for CABG and PCI and have consistently reported a survival advantage of around 4 to 5% in favour of CABG at around 3 to 5 years after the respective interventions accompanied by a marked reduction in the need for repeat intervention [6–12]. It is also note worthy that when looking at survival curves between PCI and CABG that at three to five years there is continuing divergence of the survival benefit in favour of CABG suggesting that with even longer duration of follow up the benefits of CABG may be even greater. Indeed in the study with the longest follow up at eight years, the overall survival advantage of CABG was 7% and in the patients with the most severe disease almost 13% [11].

Of particular note data from New York published in 2005 included almost 60,000 patients with at least two-vessel CAD and propensity matched for both cardiac and non cardiac comorbidity. By three years after the initial intervention there was an absolute survival advantage for CABG in the region of 5% accompanied by a seven fold reduction in the need for repeat intervention [7]. In 2011 Wu and colleagues (Table 2) published the long term mortality of CABG versus PCI (predominantly with bare metal stents) and reported that in two propensity matched groups each of 7,235 patients, and matched for 32 risk factors, at 8 year follow up an absolute overall survival benefit of CABG of 7% (mortality for PCI 29% mortality for CABG 22%; $p < 0.001$) [11]. The authors also pointed out that for every category of disease, whether two or three vessel disease with or without proximal LAD disease there was a marked survival benefit of CABG being greatest in the patients with three vessel disease including proximal LAD disease (PCI death 35%, CABG death 22%; $p < 0.001$) [11]. Furthermore although DES have been shown to reduce restenosis they have been shown not to improve clinical outcome in terms of survival or reduced myocardial infarction in comparison to BMS [5].

Table 2. 8-Year Mortality following PCI or CABG (Reference 11)

		Mortality (%)				
	numbers	PCI	CABG	% diff	HR	p
All	14,470	29	22	−7	.68	<0.001
3 vessel + proximal LAD	2692	35	22	−13	.68	<0.001
3 vessel + NO proximal LAD	2784	30	22	−8	.53	<0.001
2 vessel + proximal LAD	5948	24	21	−3	.78	<0.001
2 vessel + NO proximal LAD	1818	30	23	−7	.7	<0.001
2 vessel + NO LAD disease	1228	30	25	−5	.78	<0.05

Most recently the ASCERT Trial [12] (Table 3) has been published comparing survival in 189,793 propensity matched patients aged over 65 years undergoing PCI or CABG from the respective ACC and STS databases. At 4 years there was a highly significant survival benefit of CABG at 4.4% (HR $= 0.79$ 95% CI 0.76 − 0.82). As with the New York Registry databases the survival benefit of CABG appeared to be increasing with time with the greatest divergence in survival apparent at 4 years similar to that reported in the New York Registry data. Furthermore as 78% of the stents used were drug eluting stents (DES) this dismisses previous assertions that DES would improve survival relative to bare metal stents (BMS) in comparison to CABG. As explained subsequently understanding the differing pathophysiological effects of CABG and PCI would in fact predict that DES would not be more effective than BMS in comparison to CABG.

Table 3. Mortality with CABG and PCI at 4 years in ASCERT trial (Reference 12)

	Mortality (%)			
	CABG	PCI	CABG difference (%)	HR
30 day	2.25	1.31	+0.94	1.72
1 year	6.24	6.55	−0.31	0.95
2 year	8.98	11.3	−2.3	0.79
3 year	12.4	15.9	−3.5	0.78
4 year	16.4	20.8	−4.4	0.79

6. SYNTAX TRIAL FOR MULTI-VESSEL AND LEFT MAIN STEM CORONARY ARTERY DISEASE

The SYNTAX Trial (*SYN*ergy between percutaneous coronary intervention with *TAX*us and cardiac surgery) is undoubtedly the most important RCT of PCI and CABG in multi-vessel (MVD) and left main stem (LMS) CAD. While the primary outcome of SYNTAX is the 5 year incidence of major adverse cardiovascular (death, myocardial infarction, repeat revascularization) and cerebrovascular events (stroke) between PCI and CABG the one [13] and three [14] year outcomes have been published. SYNTAX remains a unique RCT for two reasons. First, and in contrast to the highly select enrolment policy of all the previous RCTs of PCI vs CABG, SYNTAX was an 'all comer' trial that recruited 1800 patients with severe multivessel and LMS CAD. Second, SYNTAX also ran a parallel registry to examine outcomes in 1275 patients who were considered ineligible for randomisation. The registry contained 1077 patients of whom 84% underwent CABG because the severity of their disease was considered to preclude any possibility of PCI.

SYNTAX at 1 year [13]: At one year after randomization the rates of MACCE were 18% in the PCI vs. 12% for CABG ($p = 0.002$), meaning that the criterion for noninferiority was not met. While the rates of death and myocardial infarction were similar CABG had a higher rate of stroke (2.2% vs. 0.6%; $p = 0.003$) but a lower rate of repeat revascularization with PCI (6% vs14%; $p < 0.001$). Although the authors concluded that CABG remained 'the standard of care for patients with three-vessel or left main coronary artery disease' nevertheless some clinicians interpreted these results as there being no difference in survival between CABG and PCI but simply a 'trade off' between an increased risk of stroke with CABG and a higher rate of repeat revascularization with PCI.

SYNTAX at 3 years [14]: (Table 4) For the overall cohort there was a markedly lower incidence of MACCE for CABG (20% vs 28%; $p = 0.001$). There was a nonsignificant mortality benefit in favour of CABG (6.7% vs 8.6%; $p = .21$) with no difference in the risk of stroke (CABG 3.4% vs 2.1% for PCI; $p = 0.07$) and accompanied by a marked reduction in both myocardial infarction (3.6% vs. 7.1%; $p = 0.002$) and repeat revascularisation (11% vs. 21% $p = 0.001$).

Table 4. SYNTAX at 3 YEARS (Reference 14)

		CABG (%)	PCI (%)	p
OVERALL (n = 1800)	Death	6.7	8.6	.13
	Myocardial Infarction	3.6	7.1	.002
	Stroke	3.4	2.0	.07
	Revascularization	1.3	4.5	.001
	MACCE	20.2	28	.001
3 Vessel Disease (n = 1095)	Death	5.7	9.5	.02
	Myocardial Infarction	3.3	7.1	.005
	Stroke	2.9	2.6	.64
	Revascularization	10.4	19.4	.001
	MACCE	18.8	28.8	.001
Left Main Disease (n = 705)	Death	8.4	7.3	.64
	Myocardial Infarction	4.1	6.9	.14
	Stroke	4.0	1.2	.02
	Revascularization	11.7	20	.004
	MACCE	22.3	26.8	.2

- **Three Vessel Disease (3VD)** In 1095 patients with 3VD there was a marked reduction in the overall incidence of MACE at 19% for CABG and 29% for PCI ($p = 0.001$). Crucially the mortality was 5.7% for CABG and 9.5% for PCI ($p = 0.002$) with a similar incidence of stroke (2.9% for CABG and 2.6% for PCI; $p = 0.64$). The incidence of myocardial infarction (3.3% vs 7.1%; $p = 0.005$) and repeat revascularisation (10% vs 19.4%; $p = .001$) were both significantly lower with CABG.

- **Left Main Stem (LMS) Disease** In contrast to the findings for three vessel CAD, there was no difference in death (8.4% vs 7.3%; $p = 0.64$) but a higher incidence of stroke with CABG (4% vs 1.2%; $p = 0.02$). For CABG, myocardial infarction (4.1% vs 6.9%; $p = 0.14$) and revascularisation (12% versus 20%; $p = 0.004$) were significantly lower.
- **Diabetes** There was a marked difference in MACCE at 23% for CABG and 37% for PCI ($p = 0.002$). Although there was a 5% mortality benefit for CABG (8.7% for CABG and 13.6% for PCI; $p = 0.11$) the failure of this to reach conventional statistical significance probably reflects the relatively small number of patients. Stroke and myocardial infarction were similar between CABG and PCI but there was a marked reduction in repeat revascularisation with CABG (13% vs 28; $p = 0.001$).
- **Influence of SYNTAX Scores** SYNTAX scores quantify the severity of CAD and to produce similar sized patient numbers, terciles in the trial were arbitrarily classified as low (0–22), intermediate (23–32) and high severity (>32). For 3-VD with low SYNTAX scores there was no difference in MACCE between CABG and PCI whereas, for intermediate and high scores there was a marked reduction in MACCE, and in particular mortality, for CABG (17% vs 29%; $p = 0.003$). For LMS disease there was an overall identical incidence of MACCE of 23.4% for both CABG and PCI. However for LMS disease the incidence of death was higher for CABG than PCI in both the lower (6% vs 2.6%; $p = 0.21$) and intermediate severity groups (12.4% vs 4.9%; $p = 0.06$). In contrast, for SYNTAX scores >32 the mortality was 13.4% for PCI and 7.6% for CABG ($p = 0.10$) and with a three fold increase in repeat revascularization with PCI (28% vs 9%; $p = 0.001$).

7. OTHER TRIALS FOR LMS DISEASE

The PRECOMBAT trial enrolled 600 patients from a total population of 1454 LMS patients in Korea [15]. Trial patients had a mean SYNTAX score of 25 (vs 30 in SYNTAX) and a mean Euroscore of 2.7 (vs 3.8 for SYNTAX). The primary endpoint of death, CVA, MI or repeat revascularisation was 8.1% for CABG and 12.2% for PCI ($p = 0.02$). However when only comparing death, CVA and MI this was 4.7% for CABG and 4.4% for PCI. So in contrast to the findings in SYNTAX for lower and intermediate severity left main there was no excess in mortality or stroke with CABG vs PCI (0.7% vs 0.4%) in these relatively low severity LMS patients.

The results from SYNTAX and PRECOMBAT are at odds with the traditional view that CABG should be the only treatment for LMS disease and that there is no role for PCI. In contrast to the findings for three vessel CAD where CABG is clearly the superior treatment for most patients, for at least lower severity LMS disease PCI produces at least equivalent, if not superior, outcomes to CABG. To resolve this issue definitively the EXCEL trial is a worldwide trial of PCI or CABG in LMS disease with SYNTAX scores below 33 to determine if there is equipoise between the treatments or indeed whether PCI may be superior. The trial is currently enrolling 2600 randomized patients and 1000 registry patients and unlike all previous trials revascularization will be a secondary rather than a primary end point.

8. WHY DOES CABG APPEAR TO HAVE A CONSISTENT SURVIVAL BENEFIT OVER PCI IN MULTIVESSEL DISEASE

Because atheroma is predominantly located in the proximal coronary arteries this has two important implications of treatment by CABG. By placing bypass grafts to the mid-coronary vessel this in effect nullifies the effect of any proximal stenosis regardless of its complexity. Furthermore over the longer-term bypass grafts offer prophylaxis against the effects of development of *de novo* disease either proximal to or within or immediately distal to the stent thereby mitigating its benefit. In contrast, PCI using stents is only effective against localised technically suitable proximal culprit lesions but has no prophylactic benefit against the development of new proximal disease. Further evidence for this prophylactic benefit of CABG to mitigate the effects of new proximal disease is apparent in the reduced incidence of myocardial infarction with CABG in comparison to PCI at 3 years in SYNTAX [14].

These differing patho-physiological effects of CABG and PCI explain why neither plain old balloon angioplasty (POBA), nor bare metal stents (BMS), nor drug eluting stents (DES) have been able to match the survival benefit of CABG for most patients with multi vessel CAD. A second important fact, as reported by Hannan et al in a series of almost 22,000 patients undergoing PCI is that, in contrast to CABG, PCI often results in incomplete revascularization that by itself leads to a decrease in long term survival [16].

How can this apparent difference in outcome with CABG for three-vessel CAD and LMS disease be explained? It is possible that proximal CAD results in less competitive flow for bypass grafts than ostial or mid shaft LMS disease without additional CAD. In contrast distal bifurcation LMS and particularly in the presence of severe proximal CAD (ie those with the highest SYNTAX scores) may reduce competitive flow and produce an optimal environment for bypass grafts.

9. UNDERSTANDING THE DIFFERING DATA BETWEEN RCTS AND REGISTRIES

In the last few years there has been a growing awareness of a marked discrepancy regarding the efficacy and in particular the survival benefit of CABG over PCI reported between RCTs (no benefit) and registries (significant benefit). The results of the SYNTAX trial help resolve this apparent conundrum. While RCTs remain the gold standard form of clinical investigation because of their ability to eliminate bias, their limitations in terms of relevance to everyday clinical practice are also increasingly recognised [17]. RCTs often enrol relatively small numbers of highly selected patients and may therefore not be typical of routine clinical practice. This is often compounded by relatively short durations of follow up and large number of crossovers which, on an intention to treat basis, further complicate interpretation of results. For example a detailed analysis of 15 of these RCTs in 2006 showed that they actually only enrolled approximately 5 to 10% of all potentially eligible patients and often included patients with a single or double vessel disease and normal left ventricular function ie a population in whom it was already known that there was no prognostic benefit of revascularization [17]. Furthermore as few as 40% of patients in some trials had proximal left anterior descending disease and also fewer than 80% of patients received an internal mammary artery graft [17]. In other words the trials largely excluded the patients who were known to have prognostic benefit from CABG such as those with significant left main and/or three vessel coronary disease and especially when involving the proximal left anterior descending coronary artery. The major problem, however, was that although the trials were conducted in very highly selected populations the results were subsequently presented as if relevant to all patients with significant CAD [18].

In contrast to RCTs propensity matched registries are usually composed of several or tens of thousands of patients representative of routine 'every day' clinical practice. In an effort to eliminate selection bias for different interventions (ie PCI or CABG) patients are propensity matched for risk factors known to affect outcomes and in particular longevity. However it must also be stressed that in the absence of randomization such registries cannot exclude both known and unknown confounding factors that could influence outcomes. For example patients in registries may include outcomes in the most frail and sick patients who are likely to be turned down for CABG in favour of PCI-but where frailty index is not captured in registry data.

How can we resolve these apparently conflicting pieces of evidence between RCTs and registries? While the key findings from the SYNTAX trial for 3 vessel CAD are at odds with all the previous trials of PCI versus CABG which, with the exception of the SoS trial [19], reported no survival difference between these interventions they are entirely consistent with several large propensity matched registries which have consistently shown a survival benefit with CABG over PCI [6–12]. In contrast to the previous trials of PCI and CABG, which were populated by highly select patient populations, SYNTAX enrolled a population from everyday clinical practice, similar to those reported in registries, and consequently reported similar findings to the registries. Furthermore the SYNTAX outcomes clearly indicate that with increasing severity and complexity of CAD, CABG offers not only a survival benefit but a marked reduction in MACCE, largely driven by a lower incidence of myocardial infarction and repeat revascularization.

10. IMPLICATION OF CURRENT DATA ON THE NEED FOR MULTI DISCIPLINARY TEAM/HEART TEAM

The ESC/EACTS guidelines are unique being produced by the European Association for Cardiothoracic Surgery (EACTS) and the European Society for Cardiology (ESC) with an equally balanced number of non-interventional cardiologists, interventional cardiologists and cardiac surgeons amongst its 25 members from 13 European countries [1]. Another major strength and unique feature of the guidelines is their emphasis on the importance of multidisciplinary heart teams in ensuring that patients are given appropriate recommendations for particular choices of interventions. The guidelines recommend that the core team should consist of a non-interventional cardiologist, an interventional cardiologist and a cardiac surgeon but that an extended team of experts may be required for more complex patients. The guidelines also emphasise that to prevent the multidisciplinary process becoming unnecessarily cumbersome that local protocols based on the guidelines can be used to avoid systematic case by case review of all patients. However, complex patients who are deemed unsuitable to follow guideline recommendations should be discussed by the multidisciplinary team.

Another major benefit of such an approach is to introduce transparency into how a decision for any intervention was reached in any particular patient thereby ensuring best practice for both patient and doctor. This is also emphasised in the ESC/EACTS guidelines that state that 'ad hoc' PCI procedures should not be the default position for most elective patients except in a few well defined situations because it otherwise, denies appropriate time for the patient to consider all treatment options and, in effect, undermines the principles of informed consent [20].

Recommendations for interventions by the Heart team is also of considerable and growing importance because of several reports in the literature that a significant number of patients undergoing interventions, and in particular PCI, misunderstand its rationale. Indeed up to 70% of patients undergoing PCI reported that it prolonged life and prevented further myocardial infarction, although both are known to be factually incorrect [21]. Although there is also some misunderstanding of CABG this is much less common than for PCI [21].

The importance of this data is also reinforced by a recent report of the National Cardiovascular Data Registry in 1091 US hospitals involving over 500,000 PCIs [22]. In the 29% of patients who underwent elective PCI indications were considered appropriate in 50%, uncertain in 38% and inappropriate in 12% (either because the patient had no angina, no ischaemia, or was on suboptimal medication). The range of inappropriate features varied from 6% to 17% of interventions with a median of 11%. However, the fact that up to 50% of PCI interventions were uncertain or inappropriate is of major concern and the most effective way of regulating this is to ensure that all interventions follow guidelines or if not, there is an MDT/Heart Team documentation of why guidelines have not been implemented.

Conflicts of interest statement

The author ascertains that he:

1. is a cardiac surgeon
2. is one of the 25 ESC/EACTs guideline writers
3. has no nofinancial conflicts

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