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Transcatheter versus surgical intervention: Lessons from trials of coronary revascularization

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Abstract

In this paper, a cardiac surgeon and an interventional cardiologist draw lessons from the trials of PCI/CABG for the TAVI/SAVR era. Both PCI and CABG are effective treatments, but do the trials ask the right questions? They dwell on the 'either/or' decision for selected patients suitable for both treatments, but provide little guidance for the majority of 'real world' patients with comorbidities precluding CABG, or complex CHD precluding PCI. The control group must be meaningful and relevant. The pace of technological and therapeutic change causes trials to date rapidly. Procedures often do not reflect everyday practice, such as performing multi-vessel PCI, copious stenting and full arterial grafting. Composite endpoints such as MACCE provide statistical significance but little insight into patient-orientated needs. There is a variety of temporal, safety, symptomatic and prognostic endpoints, provoking debate over their relative and absolute magnitude and importance; and there are issues of interpretation and inappropriate extrapolation. Trial interpretation, crystallised in the Kaplan-Meier curve, focuses on the relative benefit of one treatment over another, but deserves careful scrutiny. Subgroup analysis tends to exceed its role in dealing with issues such as poor LV function, diabetes, multi-vessel disease and proximal LAD stenosis. Meta-analysis is controversial and guidelines date rapidly, lacking robust evidence in some domains, yet assuming considerable importance. Measures of frailty, physiological measures of blood flow, 'real world' activity levels, and predictions of benefit rarely feature. The multidisciplinary (Heart) Team meeting, now integral to study design, is challenging to deliver in practice. The PCI/CABG trials, and the issues arising from them, provide salutary lessons in the TAVI/SAVR era.

Background

It is unusual to have two excellent alternative treatments for a single condition, such as coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI) for coronary artery disease (CAD), and surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) for aortic stenosis (AS). There is concern that a newer technology may exceed its evidence base, being less invasive and more convenient than the older one; particularly when the results of the tried and tested technology, in selected patients, are excellent.

In the 1970s, the only form of revascularisation for coronary artery disease was CABG, and comparison with the medical therapy of the time revealed superior results to medical therapy (1). When PCI was introduced in the 1980s there were initially no stents or optimal antiplatelet agents, but it provided an instant 'hit' with reasonable safety and durability. The convenience of the procedure outweighed the risks, and its growth was accompanied by development of stents, drug-eluting stents (DES), improved medical therapy, radial approaches and applicability in most syndromes. That made PCI seductive. Developments in CABG were less dramatic but tangible, with widespread adoption of the internal mammary artery conduit, and some surgeons adopting full arterial revascularisation and off-pump surgery. From the 1990s onwards, as both PCI and CABG matured, a number of randomised trials emerged comparing these modes of revascularisation (2-10). Two developments limit applicability of the early trial findings to current practice; later improvements in PCI technology and adjunctive therapy, and an increased focus on emergency patients. This led to coronary angiography with follow-on ('ad hoc') PCI; efficient in many patients with one or two vessel disease and a straightforward clinical syndrome, but controversial in more

complex patients for whom surgery might have been better. Surgical unease is tempered by the sheer numbers, and the capability of PCI to treat the critically ill and those with morbidities that confer high risk for CABG.

Now, with ageing of the population, and many patients with degenerate AS, we have a tried and tested surgical therapy, and a novel, less invasive alternative. The evidence supporting TAVI in patients who are inoperable (11) or at high surgical risk (12) is clear; and excellent results are demonstrable for SAVR in surgically fit patients at intermediate risk (13), whilst we await data in the low risk. In this paper, we examine issues that arose in the PCI/CABG trials that might help inform debate in the TAVI/SAVR era, with specific reference to one of the most studied trials in revascularisation of recent years – the Synergy between percutaneous coronary intervention with Taxus (stent) and cardiac surgery (SYNTAX) study (14).

Big decisions with big implications

The three outcomes for patients with AS are SAVR, TAVI or no intervention, analogous to CABG, PCI or medical therapy, except that the 'no intervention' option is effectively a death sentence, whereas medical therapy for CAD may have a favourable outcome. But patients exist on a 'grey scale' of functionality, illness and co-morbidity: at one extreme, unfit for any intervention; at the other, suitable for any; and, in between, many in whom there is scope for further investigation, discussion and balancing of risks and benefits. Nor is there room for a 'black and white' approach to therapy. Neither SAVR nor TAVI confer immortality. The timecourse of deterioration is related to comorbidities, left ventricular (LV) function and age. The key is quality of life, and elderly patients often prefer quality to longevity. A

technically successful procedure is of little value if the remaining lifespan is spent in a nursing home. Will the operation improve the patient's symptoms, help the LV recover or enable the patient to care for a partner? Does the patient need complete revascularisation with long recovery or fixing of an obvious culprit with partial revascularisation and early discharge? In patients with AS, these issues frequently co-exist.

Are we asking the right questions?

Clinical trials are designed to address specific questions. The title of a study may promise a general conclusion, such as *Percutaneous coronary intervention versus coronary artery bypass grafting for severe coronary artery disease*. This title conceals a specific hypothesis, namely *that for patients with three vessel or left main disease, for whom the local cardiac surgeon and interventional cardiologist determined that equivalent anatomical revascularization could be achieved with either treatment, a non-inferiority comparison will be performed for the primary endpoint – death, stroke, MI or repeat revascularization during the 12 months after randomization*. This example is from SYNTAX (14). Further scrutiny reveals even more specificity. Inclusion criteria comprised *de novo*, previously untreated lesions, ≥50% target vessel stenosis, stable or unstable angina or (interestingly) atypical chest pain. Patients with no symptoms were allowed, provided evidence of myocardial ischemia was documented. Exclusion criteria included previous PCI or CABG, acute myocardial infarction (MI), or the need for concomitant cardiac surgery. Definitions of the primary endpoint comprised MACCE, with equally specific definitions, notably for the MI component. Applying the findings of the trial depends upon an individual patient fitting the inclusion criteria *precisely*, the potential benefit for others being speculative.

The randomised controlled trial (RCT): who is included?

In the Coronary Artery Surgery Study (CASS) in the 1970s, of 16,626 coronary angiograms screened, 2099 met the randomisation criteria and 780 patients were randomised; 5% of the original total (1). In SYNTAX, 4337 patients were 'assessed for eligibility', representing patients with MVD and/or LMS disease that the local cardiologists thought might be suitable for such a study. Of those, 1800 (41%) were randomised. The main reasons for exclusion were inability to offer complete revascularisation due to the complexity of the CHD (usually biasing against PCI) in around 80% or the presence of significant comorbidities (usually biasing against CABG) (14). Examples of randomisable and non-randomisable coronary arteries are shown in Figure 1. Many of the PCI/CABG trials excluded a large proportion of patients seen in everyday practice. Applying the results of such trials to *all* patients is therefore inappropriate.

Do we practise medicine in the trials how we normally do?

The surgical arm of SYNTAX was pragmatic, with an average of 2.8 grafts; and 97% of patients received an arterial graft. These are 'real world' figures (15). In contrast, the PCI arm employed an average of 4.6 DES [a 'real world' average being 1.5 (16)], with an astonishing mean 86 mm stent length; and they were first generation DES, with greater restenosis and thrombosis rates than contemporary DES. The requirement for equivalent revascularisation demanded a 'CABG-like' PCI, so complete revascularisation was achieved in 63% in the surgical arm and in 57% in the PCI arm. It is not surprising, therefore, that PCI in SYNTAX was far removed from everyday practice, and associated with inferior results compared with CABG in terms of the composite endpoint (14). PCI fared better in SYNTAX II, a single-arm study which employed second generation DES; but this was with 84%

intravascular imaging and 83% multi-vessel physiological guidance (17), which are usually deployed in <10% patients (16).

Is the control arm meaningful and relevant?

In the early development of CABG, PCI, SAVR and TAVI, the control group was a non-interventional cohort (1,2,11,18). The early PCI/CABG studies were in low risk patients, whereas TAVI was first studied in those rejected for SAVR (11). Subsequent PCI/CABG trials compared the two interventions, providing guidance on *selection* of treatment modality for the few patients suitable for either. Recent re-exploration of the control group occurred in the Percutaneous Coronary Intervention in Stable Angina (ORBITA) study. The control arm employed a sham procedure and intense physician input, both non-standard, which could have conferred unappreciated benefits (19). The recurring problem that 'real world' patients are suitable for one or other intervention, but not both, raises the possibility of testing strategies of *allocation* to both treatments. In SYNTAX III, for example, randomisation is between two Heart Teams, not two treatments, with patients being allocated to their treatment, whether PCI or CABG, dependent upon CT_{FFR} vs traditional angiographic guidance (20). At the moment, investigation continues using the traditional SAVR vs TAVI type study, in intermediate and low risk groups.

Are the endpoints right?

The traditional cardiovascular trial endpoint is an aggregate of major adverse cardiovascular events, comprising death, myocardial infarction, stroke and unplanned repeat revascularisation (MACCE). Whilst death and stroke are undeniably major and adverse, repeat revascularisation (mostly due to restenosis after PCI) is usually not. But the key

question is whether this combination is meaningful to patients, or a composite formulated to facilitate a statistically significant difference. Similarly, the length of follow-up needs to be considered. Follow-up of less than five years mitigates against the survival benefit of CABG that accrues for multi-vessel disease beyond that, as shown in SYNTAX and other trials, but it successfully captures most of the complications of PCI (14). However, vein graft failure may occur later, and is not generally captured. This is important because restenosis after stenting usually responds to repeat PCI, whereas a patient with failed SVGs presents a more challenging problem. PCI may be readily repeated, in contrast to CABG. Longer timepoints also tend to accrue diverse events which dilute the ability of the study to discriminate the value of one treatment over another.

What does the patient really want?

Patient orientated clinical outcomes outcomes (POCE) have only recently been systematically studied. For most CAD patients, and particularly in those who are robust without other life-threatening co-morbidity, key priorities are to be rid of chest pain and the fear of impending mortality as well as long-term quality of life and survival. They generally wish to avoid a highly invasive procedure and are concerned by the prospect of a disabling complication. A CABG, more than PCI, may durably improve several aspects of health, but the particular toll taken on a frail individual can be considerable. It is therefore easy to frighten a patient with procedural risk, but do we explain the implications of 'conservative' treatment clearly? And what weight should be quoted to patients in their early sixties of the enduring benefits of internal thoracic arteries that have angiographic patencies exceeding 90% after two decades of follow-up? A frequent response to attempts at balanced

explanation is ‘You are the expert, Doctor, you decide.’ Most professionals rise to this challenge, but there is a risk of biased decision-making and paternalism.

Symptoms, prognosis and priorities

A patient surviving a procedure often believes that their life has been saved, but the psychological impact of any procedure, therapeutic or not (19), cannot be over-estimated. After a procedure an individual is either alive or dead, whatever the prior risk profile, whilst population percentages are forgotten. For PCI vs CABG, those initial percent differences are generally small (14), but may diverge with time, whereas for SAVR vs TAVI they may be larger (12). For the elderly and frail with CHD, the evidence base is sparse, and prognosis is of less importance than functionality and independence. The risks of both commission and omission in the elderly and frail are often high; and co-morbidities are key in selecting treatment. So, whilst open heart surgery is effective but hazardous in this group, partial revascularisation with PCI to relieve rest pain may be reasonably effective at far less risk. For the young, different priorities apply, with an emphasis upon efficacy, durability, complete functional recovery and optimal prognosis. Traditional trial outcomes are therefore of limited use in the very elderly, but of more pressing importance in the young.

Misunderstanding the Kaplan-Meier curve

We regard the randomised controlled trial as the ‘gold standard’ comparing two therapies, and we are comfortable reading the accompanying Kaplan-Meier (K-M) survival curve (21). A trial with large numbers of participants and widely divergent curves is ideal. This is seldom achieved, although it has been observed in AS, for example in the treatment of inoperable patients with TAVI (11). More often, there are small numbers, close curves, composite

endpoints and short followup. We must distinguish absolute from relative benefit, and statistical significance from clinical importance. The usual way of reading a K-M curve is vertically, comparing percent survival at a given timepoint, using a hazard ratio and a 95% confidence interval. From the patients' perspective, this is artificial; they want to know if they will feel better or live longer. Longer timepoints are valuable. In SYNTAX there was a negligible difference in mortality at two years, but an advantage for CABG in intermediate and high SYNTAX scoring patients at five years (22). These, and other points to consider when analysing a K-M curve, are shown in Figure 2.

Subgroup analysis

A pre-specified endpoint for a large, well defined group of patients, with a clinically and statistically important inter-treatment difference, provides the ideal basis for guiding therapy. Heterogeneity of the patient population makes this challenging. It is therefore commonplace to employ sub-group analysis; in the PCI/CABG trials these included particular age groups, sexes, presentations, patterns of CHD, levels of LV dysfunction and diabetes. This risks bias, the disadvantages of retrospective analysis, and lacks statistical power (23). In those circumstances, subgroup analysis should be regarded as hypothesis-generating, rather than definitive. An example is diabetes in the Bypass Angioplasty Revascularization Investigation (BARI) (6). Prospective testing is then required (24). One partial solution is to pre-specify subgroups. A good example is the study of patients with left main disease within the overall cohort in SYNTAX (14).

Extrapolating inappropriately

A headline such as 'CABG is better than PCI for patients with diabetes and multi-vessel disease' seems to simplify decision-making. Initial reading of the CABG/PCI trials over the years would tend to suggest this (6), it is reflected in guidelines (25), and many practitioners adopt this as default. Following that guideline in *all* cases, however, may not be appropriate. What is the pattern of the CHD? Does it consist of focal or long lesions? Are the vessels large in calibre or small and diffusely diseased? Is the LV function impaired or infarcted? Is the patient severely obese? Is there evidence of peripheral arteriopathy, neuropathy, nephropathy or other co-morbidities? These are common in diabetics, and would have excluded such a patient from entry into the trials. Other examples of patient groups falling outside the evidence base are the very elderly, ACS after more than a few days of 'settling', prior CABG, renal failure, co-existent lung or stroke disease, bleeding problems, and frailty. These are all common in everyday practice. Almost invariably, discussion of superiority in trials neglects these important considerations.

Pitfalls of the meta-analysis

Meta-analysis seeks to augment the power of individual RCTs by combining them retrospectively and re-analysing the outcomes. It is a controversial approach and, to be performed correctly, PRISMA (referred reporting items systematic reviews and meta-analysis) guidelines must be followed (26). Even so, there are pitfalls. The trials to be included frequently have differing study dates, inclusion criteria, endpoints, timepoints, and definitions. The data may be inhomogeneous, there may be publication bias, subjectivity in selecting eligible studies and statistical challenges such as non-linear correlations and multifactorial effects. A good example is the initial study of stent thrombosis with DES

presented at the European Society of Cardiology in 2007 (27). The analysis was performed without accessing patient-level data from the trials being evaluated.

The multidisciplinary team (MDT) 'Heart Team' meeting

The MDT meeting is indispensable to the design of RCTs that involve procedures performed by different disciplines, and is now established in clinical practice. Guidelines for the conduct of MDT meetings are helpful (28), but challenging to enact, mostly due to finding sufficient time. However MDTs are also a powerful tool to eliminate potentially inappropriate treatment strategies. The majority of patients with straightforward CAD can be treated with PCI effectively and quickly, whereas an MDT meeting is most helpful for patients with complex disease and in whom surgery is a possibility. Its effectiveness, however, depends upon attendance mix, delays, special interests, ownership of the decision, willingness of participants to speak up, cross-refer and seek second opinions, knowledge base, and other subtle factors such as enthusiasm and vulnerability. There is a reliance upon imaging, with poor co-registration of images from diverse sources. The patient, and measures of frailty, activity levels and physiology, are usually conspicuous by their absence.

Guidelines are guidelines

Guidelines synthesize the available evidence to manage a condition, such as stable angina (24) or AS (29), and have to convey a clear message, even if the evidence is diverse. They include a range of sources, and themselves conform to stringent guidelines (30). Guidelines declare classes of recommendation (I-III) and levels of evidence (A-C). If several large, well conducted RCTs are available with a concordant, clear positive outcome for an intervention,

a Class 1A recommendation can be given; but this is not always the case, and 'expert opinion' has to substitute. Guidelines date quickly, lag behind published trials and, being based upon meta-analyses and large RCTs, perpetuate the limitations associated with those.

Conclusion: PCI *and* CABG, surgeon *and* cardiologist

One treatment bypasses stenoses, the other dilates them; one is well established, the other more recently introduced; one is invasive, the other minimally so; one is more complete, the other less so (with important implications for long-term survival); one is rapidly evolving, the other consistent; one is minimally dependent upon comorbidity, the other more so; each has a number of weaknesses; and both are effective. See Figure 3 for a summary. Pitting one *against* the other is only part of the picture. One is better for one patient, and the other for another. Trials clarify the strengths and weaknesses of each in the cohort of patients considered candidates for either. We have considered the issues relevant to scrutinising the trials. See Figure 4 for a summary. In the 'real world', however, CABG and PCI co-exist, enabling us to offer our patients a comprehensive revascularisation service to suit clinical and personal requirements, taking into account age, co-morbidity and activity level. We can now integrate CABG and PCI into a strategy, thinking 'longitudinally' for the individual, rather than 'vertically' for a group. Competition has given way to complementarity. Perhaps we can apply the lessons of 30 years of CABG 'versus' PCI to the treatment of patients with AS.

Conflicts of interest

Professor Gunn has no conflicts (except as an interventional cardiologist). Professor Taggart has no conflicts (except as a cardiac surgeon).

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Figure legends

Fig. 1

Two examples of multi-vessel coronary artery disease; one treatable with PCI or CABG (A), the other with neither (B). These are images taken from left coronary angiograms of two different patients meriting revascularisation because of chest pain inadequately controlled by medical therapy. In case (A), there are proximal, relatively discrete stenoses (arrows) and large calibre distal vessels; the former being suitable for stenting, and the latter for bypass grafting. This patient would have been 'randomisable' in studies of CABG vs PCI. In case (B), there is diffuse, severe atherosclerosis affecting all coronary vessels, which are reduced to minute calibre, and are suitable for CABG or PCI. This patient would not have been randomisable. In both cases, the left anterior descending artery, the most important vessel, is marked (LAD). Any comparative data pertaining to the merits of CABG or PCI would therefore not apply to such a patient as (B).

Fig. 2

Some points to consider when critically evaluating trial results presented in the form of Kaplan-Meier curves. In this hypothetical example, outcomes are displayed following two different interventional treatments for CAD, portrayed in red and black. (A) The Y axis only extends to 30% of patients. The remaining 70% had a favourable outcome and are omitted, which tends to exaggerate the visual impact of the absolute, rather than the relative, benefit. (B) The outcome measure is MACCE. This is a composite endpoint, and it is useful to see the results for the components broken down in a separate table. Often in PCI vs CABG trials, mortality is not significantly different, or only minimally so, between the treatment groups. (C) Individual adverse events appear as steps up in the curves, and appear to be

larger at later timepoints. This is because the number of patients who have reached the later timepoints is lower than the number at earlier ones, so the percentage effect of a single event is relatively greater. (D) This is also reflected in the larger error bars seen at later timepoints. (E) The number of patients studied at each major timepoint (in this case every 12 months would suffice) should be shown clearly on the chart. (F) It is not clear at which timepoint the 'p' value applies. It is unlikely to be at three years. (G) Given all the above limitations, the difference between the two groups at three years may not be as impressive as it appears. (H) Of importance, and rarely discussed, is the residual adverse event rate. Clearly neither treatment is conferring a perfect clinical outcome. There is still room for improvement. (I) Follow-up is only 36 months. In the PCI/CABG trials, this may be long enough to capture problems after PCI, but not necessarily the survival advantage of CABG usually demonstrable by 5 years.

Fig. 3

Comparison of the attributes of PCI and CABG, including some which are not generally addressed in traditional 'head-to-head' trials, but are of practical importance to patients.

Fig. 4

A summary of learning points from the trials of PCI vs CABG.

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