Percutaneous coronary intervention for stable coronary artery disease

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Abstract

The adverse consequences of stable coronary artery disease (CAD) are death, myocardial infarction (MI) and angina. Trials in stable CAD show that PCI does not reduce mortality. PCI does appear to reduce spontaneous MI rates but at the expense of causing some periprocedural MI.

Therefore, the main purpose of PCI is to relieve angina. Indeed, patients and physicians often choose PCI rather than first attempting to control symptoms with anti-anginal medications as recommended by guidelines.

Nevertheless, it is unclear how effective PCI is at relieving angina. This is because whereas anti-anginal medications are universally required to be tested against placebo, there is no such requirement for procedural interventions such as PCI.

The first placebo-controlled trial of PCI showed a surprisingly small effect size. This may be because it is overly simplistic to assume that the presence of a stenosis and inducible ischaemia in a patient means that the clinical chest pain they report is caused by ischaemia. In this article we review the evidence base and argue that if we as a medical speciality wish to lead the science of procedures for symptom control, we should recognise the special merit of placebo-controlled experiments.

Introduction

Coronary artery disease (CAD) is a leading cause of mortality in the UK and worldwide.[1] Stable CAD leads to angina, primary care consultations, and hospital admissions, significantly impacting quality of life and increasing costs.[2]

All patients should receive event prevention medication. For symptoms, however, there are two approaches: (1) anti-anginal medication, and (2) revascularisation with percutaneous coronary intervention (PCI) in the majority and coronary artery bypass graft (CABG) surgery in the remainder.

Event prevention

Aspirin and a statin form the basis of prescriptions for event prevention as these are well proven to reduce myocardial infarction (MI) and mortality rates.[3,4] This is routinely coupled with blood pressure medications and lifestyle advice to promote healthy diet, exercise and smoking cessation.[5]

Symptom relief

Many classes of anti-anginal medication have been proven to reduce angina against placebo.[6-8] This is not merely a coincidence: it is a regulatory requirement for a drug to be licensed for angina treatment.

In contrast, procedures have not been required to be tested against placebo. Therefore, the clinical data supporting PCI in angina relief has mainly been unblinded, i.e. with no control or with only an unblinded control group. It may be this concern that causes guidelines to generally recommend anti-anginals to be used as first line with PCI reserved for patients in whom symptoms are not adequately controlled with anti-anginals.[5]

Percutaneous coronary intervention

Four decades ago PCI was introduced to relieve angina in stable CAD.[9] Today over 500,000 PCI procedures are performed annually worldwide for this indication.[10] While in the setting of acute coronary syndrome, PCI reduces death and subsequent MI,[11] in stable CAD its role is less clear.

Despite its initial remit, as time passed, we slipped into assuming PCI achieved more than symptom relief. We formed an expectation of reduction in mortality, MI and other sequelae of CAD such as left ventricular dysfunction.

Several randomised controlled trials (RCT) have compared event rates between PCI and no PCI. (We prefer this form of words rather than the conventional term "optimum medical therapy" for the no-PCI group because both groups received event prevention medications.) These trials (Table 1), the most prominent amongst them Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), showed no evidence of reduced mortality.[12]

Curiously in subsequent guidelines, the pendulum swung away from PCI towards recommending anti-anginal medications as first line treatment instead.[13,14] This is difficult to explain. Neither anti-anginal medications in general nor PCI reduce mortality in stable CAD. So why should a neutral result for PCI on mortality affect the placing of PCI? Both anti-anginal medications and PCI were always intended for symptom relief.

An alternative explanation might be that the guideline committees knew that PCI had not been tested against placebo while anti-anginal medications had. However, if this was the case perhaps PCI should have been deleted rather than reshuffled.

PCI is nevertheless still commonly performed in stable CAD. Physicians and patients are confident that PCI provides symptomatic relief.[15] Some continue to assume that PCI reduces the risk of MI and death.[16] Physicians often assert that medication is less efficacious than shown in placebo-controlled trials or that an anti-anginal medication approach is impractical and poorly tolerated. An upfront procedure with only a very small risk is therefore a preferable alternative for many patients and physicians.[17]

The impact of PCI on MI and mortality rates
The first RCT to report MI and mortality rates of PCI in stable CAD was in the plain balloon angioplasty (POBA) era. The Angioplasty Compared to Medicine (ACME) trial randomised

patients with angiographically severe single vessel CAD to POBA versus no POBA. It found no significant difference in MI or mortality at 6 months,[18] but with only 212 randomised patients there was still wide uncertainty.

The next step was to randomise patients who should have had a much better chance of benefit from PCI, and to follow-up up for the longer period of 3 years. The Medicine Angioplasty and Surgery Study (MASS) randomised only patients with angiographically severe lesions in the proximal left anterior descending artery (LAD), again to POBA versus no POBA. However, even still there was no effect on MI or death.[19]

Suspecting the lack of stents or the sample size (about 200 in both trials) as the cause of the failure of PCI to reduce MI or death, later trials used stents and larger samples. The Randomised Intervention Treatment of Angina (RITA-2) trial randomised patients to PCI versus no PCI. Although stenting was now available still 91% of PCI patients received only POBA and the remainder received stents which in that era were all bare metal.[20]

RITA-2 produced a surprise result in that there was a significantly higher rate of death and MI with PCI (6.3% versus 3.3%, p=0.02). This was the primary endpoint, although the conclusion of the abstract diplomatically put the emphasis on angina relief.

The next hope was that the MI rate might have only been high in RITA-2 because almost all the angioplasty patients did not receive a stent and therefore would have been vulnerable to vessel occlusion. The next trial, MASS-II, therefore mandated the PCI patients receive stents. It was a 3-armed trial in which the other 2 arms were CABG and no revascularisation. To ensure adequate risk, it enrolled patients with multi-vessel disease or proximal disease in the LAD.[21] At 1, 5 and 10 years there was no significant benefit of PCI on cardiac death or MI.[22,23]

Drug eluting stents were the next hope. In retrospect since their major benefit is reduction in restenosis which does not typically cause death or MI, this was optimistic. Nevertheless, the largest trial completed to-date of PCI in stable CAD, COURAGE addressed many of the perceived limitations of previous trials.[12] With a combined primary endpoint of death and MI,

COURAGE randomised 2287 patients with CAD and evidence of ischaemia to PCI versus no PCI. At median follow-up of 4.6 years there were no reduction in events.

Desperately seeking significance

These results disappointed interventional cardiologists.[12,24-26] The search was on for "limitations" of those trials.

A common complaint was that event prevention medication in trials was now too good for PCI to show a benefit.[12,23,24,26] Oddly this was never argued by interventional cardiologists as a reason to stop doing PCI for stable CAD, but only a criticism of the trials.

Another complaint was that the previous trials inevitably did not use the latest generation of stents. Eventually a 93,000 patient network meta-analysis managed to suggest survival benefit with PCI with new generation drug eluting stents by a chain of indirect comparisons.[27]

The last hope for PCI for death and MI benefit is the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial (NCT01471522). Apart from being double the size, ISCHEMIA introduced 2 major advances over COURAGE. First, it required convincing non-invasive evidence of ischaemia before randomisation. Second, it randomised before angiography which prevented physicians from withdrawing patients based on the oculostenotic reflex having seen a tight lesion that they felt compelled to stent. Both of these innovations will help the trial to have a higher event rate.

On reflection, mortality reduction may not be a suitable aspiration for PCI in stable CAD. Annual mortality rates are around 2% and given the data so far it is unrealistic to expect a relative risk reduction of more than 10% for PCI. This means a trial adequately powered for mortality would need to enroll over 150,000 patients.

Dawn of "urgent revascularisation" in trials

With death and MI being difficult to reduce by PCI, and symptoms themselves seeming too soft as an endpoint, our community then selected "urgent revascularisation" as a compromise solution. This has the merit of sounding solid as it as an objective event, even though what it

contributes extra beyond MI is the clinician and patient response to symptoms. The ISCHEMIA trial itself recently found itself having to add new components to the primary endpoint.[28]

There is of course a fundamental problem in testing PCI for its ability to prevent having to do PCI later. However effective it may be, the arm which does PCI now on 100% of patients will end up doing more PCIs in total than the arm which does not do PCI now but only does it if required later. Therefore, such a trial using total PCI as an endpoint will always be adverse for the PCI arm.

The solution to this problem is to blank out the first PCI in the PCI arm. To do this one needs the readership to accept that the first PCI in the PCI arm must be ignored but the first PCI in the control arm must not. Interventional cardiologists generally accept this approach. The explanation usually given is that the first PCI in the PCI arm is done in a controlled circumstance whereas the first PCI in the control arm might be performed in an emergency situation with greater cost, risk and long term adverse prognostic significance.

Many trials have tested PCI for reduction in urgent revascularisation. This event type sounds important. The mind turns to a patient with continuous rest pain or dramatic dynamic ECG changes because this is the situation which in normal clinical practice one would consider revascularisation urgent outside of the context of MI. However, we do not know whether the patients reported to have undergone urgent revascularisation in trials were like these patients we tend to imagine. There are 2 reasons to think they may not be. First, the rate of urgent revascularisation in trials seems higher than in clinical practice. Second, no trial has systemically detailed symptom characteristics or displayed ECGs of the patients who underwent urgent revascularisation.

Therefore, when interpreting trials of urgent revascularisation we must bear in mind that the threshold for this endpoint may differ between protocols and between investigators. More importantly, all of the trials with this endpoint were unblinded. Patients in the control arm knew that they had not received a stent for a lesion for which outside the trial they would probably have had a stent. This may have coloured the intensity of their symptoms or their desire to act upon them: "subtraction anxiety".[28] Their physicians were also vulnerable to this.

The impact of unblinding is best seen in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial. It showed long term benefits from PCI in patients with evidence of ischaemia defined as FFR≤0.80.[29] However, the primary endpoint of FAME 2 was a composite of urgent revascularisation, MI and death. The trial was halted early as the data safety monitoring board felt that higher rates of urgent revascularisation in the control arm were evidence of harm. Unfortunately, over 50% of these events were caused by presentation with chest pain in the absence of cardiac marker rise or ECG changes. Therefore, many of these control arm events could have been influenced by the unblinded knowledge that a physiological significant lesion had been left untreated.The impact that blinding may have had on the results remains unknown.

Two years later the FAME 2 investigators took the approach of deleting the 10 peri-procedural or early post-procedural events in the first 7 days. This allowed a clear advantage to be seen in death and MI in the subsequent time period.[30] From what is published there is no sign that this form of analysis or precise cutting time was pre-specified. By 5 years death was neutral but MI showed significant reduction in the PCI arm even without special handling of the events in the first 7 days.[31]

Table 2 summarises the mortality, MI and unplanned revascularisation outcomes in RCTs for stable CAD.

PCI for symptomatic relief

When patients are aware that they have had PCI, they have clear reduction in angina and improved quality of life.[26,27,30,32,33] However, not all angina is eliminated. In routine clinical practice doctors report that 5 to 15% of patients with stable CAD continue to have refractory angina.[34,35] Curiously, in trials this proportion is higher. This might reflect more meticulous documentation of residual symptoms in a trial protocol.

Symptoms are subjective. This does not mean that they are inaccurate; it only means that they are reported by the patient rather than a member of staff or a machine. The problem

with subjective assessment arises solely because the patient is unblinded to whether they have had a stent.[29,36]

Randomisation alone does nothing to mitigate this bias. What is needed is blinding. Blinding allows estimation of the placebo-controlled effect size and assessment of the contribution of the true physical effect and the placebo effect to the overall treatment effect.[37,38] Unblinded trials of intervention are known to be susceptible to large, most frequently unintentional, levels of bias.[39] Placebo effects are known to be larger for invasive than non-invasive treatments.[40]

For surgical revascularisation before our current approach of coronary artery bypass grafting, the leading concept was internal mammary artery ligation. At the time it was believed that closing the internal mammary would cause blood to divert into the coronary arteries. Like PCI for stable angina unblinded data verified its efficacy. Only when a blinded RCT was done was the true efficacy found to be nil.[41]

Similarly, laser myocardial revascularisation which had been promoted based on unblinded data for stable angina, finally underwent blinded testing which showed no difference between the intervention and placebo.[42-44] More recently, a placebo-controlled trial of a novel coronary sinus reducing device in patients with refactpry angina showed angina reduction in the intervention arm but no difference in treadmill exercise time change.[45] Table 3 illustrates the necessity for blinded data.

Blinded evaluation of symptom relief
Anti-anginal medication is only taken seriously if there is blinded evidence of symptom relief. Anti-anginal procedures, however, can become commonplace without being tested in this way.

The Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial was designed to provide this evidence.[46] Disappointingly, the effect size on the primary endpoint, improvement beyond placebo in treadmill exercise time,

was smaller than expected and not statistically significant. This was despite clear resolution of ischaemia on stress echocardiography.

In a non-prespecified secondary analysis, dichotomising patient reported angina as present or absent, there was a statistically significant increase in patients free of angina (absolute risk reduction approximately 20%).[47]

This was surprising to a clinical community that reports routine practice to achieve 90% or more freedom from angina. Critics of PCI have interpreted ORBITA as evidence that PCI should no longer be carried out routinely for stable angina.[10]

We may have come to this position because of a failure to resolve a contradiction that has grown over the last 40 years. When asked about their beliefs in principle, most cardiologists would state that the pathway from anatomical stenosis to angina symptoms is complex and has many steps which will vary from patient to patient and vessel to vessel. In contrast, in clinical practice a dichotomy is presented: some patients have "ischaemia" and are therefore entitled to have angina of epicardial origin, and others do not and therefore their pain is non-cardiac or caused by "microvascular disease", a diagnosis that can never be disproven.

Dichotomous thinking is ingrained in our understanding of CAD. Why do we describe ischaemia tests as positive versus negative? This contradicts the considered beliefs of most cardiologists that ischaemia must be a continuous variable if not more complex.

A bigger problem is our inherent bias as interventional cardiologists. So much do we want the procedures we have spent so much time mastering to be effective that we are angry with any experiments that suggest a smaller effect size.[48]

What ORBITA suggests is that our dichotomous thinking is incorrect and our biases are much more powerful than we may have guessed. It is not true that a patient presenting with angina, positive ischaemia test and severe epicardial stenosis, will consistently have angina resolution from PCI. In reality the difference between successful PCI with resolution of ischaemia and a placebo procedure with no effect on ischaemia is very much smaller than we supposed.

Table 4 summarises the unblinded and blinded RCT data of symptom and quality life endpoints.

The paradigm trap

Figure 1 illustrates the cognitive trap that we have fallen into. Once sufficient anatomical stenosis is present to reduce haemodynamics "significantly", there is insufficient perfusion of the myocardium which causes pain that the patient expresses, and the doctor interprets and also causes exercise limitation.

In the dichotomous simplistic paradigm that we present to patients and medical students and inadvertently absorb ourselves, once the first step happens all others fall into place automatically. Likewise, once the anatomical stenosis is eliminated, all the other steps must certainly undo themselves.

This is a myth. To explain the results of ORBITA needs only one simple change. There is no reason to suppose that the threshold at which one step causes the next is the same in every patient or every vessel. This simple insight allows interventional cardiologists to discuss the surprising results of ORBITA without personal anguish.

Conclusions

PCI is unlikely to ever be shown to reduce mortality for stable CAD, not because of a failing of the procedure but because the event prevention element of "medical therapy" is so effective in the types of patients that can be recruited into trials. The FAME 2 trial provides the first suggestion, after many years of trying, that it might reduce the total number of MI. The ongoing ISCHEMIA trial will resolve this definitively.

The final remaining question is over its efficacy in relieving angina. If we as interventional cardiologists wish to lead the process of answering this, we should demonstrate a mature understanding of how to proceed. The first step is to stop resisting what the anti-anginal

medication field has considered obvious for decades, namely that we should routinely conduct our experiments with double blind placebo control.

Contributors

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Figure legends

Figure 1

Why PCI is so successful in relieving angina: a paradigm that is clear, simple and incorrect

Panel A shows the conventional paradigm: an anatomical stenosis (1) causes the haemodynamic disturbance (depicted in (2) as the pressure drop) that leads to an abnormality of myocardial function visualized in (3). This myocardial ischaemia is detected by sensory neurones which root through the spinal cord (4) to the pain centres in the brain (5). In the cerebral cortex (6), the patient prepares a description of the nature and location of the sensation (7) which the doctor interprets and documents (8).

Panel B shows the events in a clinical consultation when a patient has residual symptoms after anatomically and haemodynamically successful PCI and the influence of unblinded knowledge of the PCI result on the interpretation of symptoms.