Review Article

Should we still have the COURAGE to perform elective PCI in patients with stable myocardial ISCHEMIA?

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Abstract

The main lesson to be learnt from COURAGE, BARI 2D and ISCHEMIA is that optimal medical therapy should be provided to all patients with coronary artery disease as the baseline upon which interventional treatment can be added. We also learnt that a significant percentage of stable coronary artery disease don't immediately progress into ACS and therefore it is safe and appropriate to not perform PCI upfront. Rather, this can be deferred until later if angina symptoms worsen or if ACS develops. Hence, the importance of careful and close follow-up of patients who are medically treated. Elective PCI seems to provide better control of angina symptoms compared to sole optimal medical therapy, and it also seems to reduce the future incidence of ACS admissions. The mortality data from all the three trials contained some uncertainties hence rendering unreliable any conclusions drawn from those data. As such the impact of elective PCI on 'cardiac' mortality so far remains controversial. To answer this question, we suggest a new three-armed large clinical trial to randomize stable angina patients eligible for coronary angiography to receive optimal medical therapy alone or in combination with either PCI or CABG. The trial must include patient with higher risk cardiac profiles, like those with left main stenosis or poor left ventricular systolic function. The three arms must have comparable baseline characteristics and the primary end point should be 'cardiac' mortality only, not all-cause or cardiovascular mortality.

Introduction:

The benefit of performing Percutaneous Coronary Intervention (PCI) in the context of acute ST elevation myocardial infarction (STEMI) is overwhelming and certainly undisputed. Large randomized clinical trials like DANAMI-2 (1-3) , PRAGUE-2 (4, 5), STAT(6), AIR PAMI(7), STOPAMI-1(8), and STOPAMI-2(9) have unequivocally

demonstrated better short and long-term outcomes with primary PCI compared to fibrinolysis. Similarly, other randomized clinical trials (10-12) and meta-analyses (13, 14) have demonstrated the prognostic value of urgent PCI over sole medical therapy for other high risk acute coronary syndromes (ACS); namely, non-ST elevation myocardial infarction (NSTEMI) and unstable angina.

In contrast, there is considerable ambiguity in regard to the benefit or otherwise of elective PCI in patients with stable coronary artery disease. While the available evidence seems to suggest that PCI has no prognostic superiority over optimal medical therapy in this group of patients, deeper scrutiny of the data indicates that the matter is still far from settled. 'COURAGE' (15), 'BARI 2D' (16) and 'ISCHEMIA' (17) are the main randomized clinical trials that examined this issue and have all concluded against the prognostic usefulness of PCI therapy. This article provides critical review of the methodologies of, and the data produced by, those three trials. The authors argue that those studies contained inherent flaws within their design or enrolment courses that substantially impacted on the subsequently obtained results, thereby rendering the final conclusions unreliable. Therefore, the question as to whether PCI is or isn't prognostically beneficial stands yet to be answered. The authors suggest an alternative methodology design to be used in a new large randomized trial so the question can be answered reliably and decisively, once and for all.

The Evidence:

COURAGE

Conducted between 1999 and 2004, and subsequently published in 2007; this randomized study aimed to answer whether, in patients with stable coronary artery disease, an initial management strategy of PCI plus optimal medical therapy is superior to optimal medical therapy alone in reducing the risk of cardiovascular events. Enrolment was based on objective evidence of myocardial ischaemia and the presence of at least 70% stenosis in a proximal epicardial vessel on diagnostic coronary angiography. 2,287 patients with objective evidence of myocardial ischemia and significant coronary artery disease were enrolled from 50 North American centres; 1,149 patients were assigned to the PCI group and 1,138 to

the medical therapy group. The primary outcome was all-cause mortality and non-fatal myocardial infarction (MI) during the follow up period (median 4.6 years). The cumulative primary-event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (P = 0.62). There were no significant differences between the two groups in the composite of death, MI, and stroke (P = 0.62); hospitalization for ACS (P = 0.56), or MI (P = 0.33). As such, the trial investigators concluded that PCI in stable coronary ischaemia confers no additional prognostic benefit over that obtained by optimal medical therapy alone. However, closer examination of trial population and design reveals the following facts:

- Although about 36,000 patients were screened for the trial, yet only 3,071 (8.6%) met the eligibility criteria and 2,287 (6.3%) were subsequently randomised. Thus, indicating significant selective inclusion, which in turn immensely constrains the generalisation of the study findings on the general stable coronary disease population.
- 15.7% of patients assigned to PCI were either not treated or did not complete follow-up. Conversely, 97 (8.5%) of the 1,138 patients assigned to medical therapy were lost to follow-up. Furthermore, while the medical therapy group started the trial with little or no angina symptoms (80% were almost angina free), 32% of them ended up having PCI during the follow up period for worsening angina symptoms that failed to respond to medical therapy, which negates the investigators' claim that angina control was similar in the two trial arms. It is also important to note that the trial design prespecified that no more than 10% of the medically treated patients would cross over to PCI in the first 4 years(18).
- COURAGE seems to be an outlier in concluding that PCI is similar to optimal medical therapy in controlling angina in stable coronary disease, when several other clinical trials have consistently demonstrated the exact opposite (19-24). This is probably due to the fact that the vast majority of the trial's

participants had little or no angina to begin with.

- All-cause mortality as a primary end point was another methodology flaw, for PCI wouldn't be expected to reduce non-cardiac mortality in comparison with medical therapy. During the follow up, 85 patients died in the PCI group compared with 95 patients in the medical therapy group (total of 180 patients). Of this total, only 48 deaths (26.7%) were later confirmed to be cardiac and it remains unclear as to how many of those cardiac deaths belonged to the PCI group.

BARI 2D

Conducted between 2001 and 2005, and later published in 2009; this randomized trial aimed to ascertain whether coronary revascularization has an advantage over medical therapy in patients with type-2 diabetes and stable coronary artery disease. 2,368 patients with both type 2 diabetes and heart disease were randomized to undergo either prompt coronary revascularization plus intensive medical therapy, or intensive medical therapy alone. Primary end points were all-cause mortality and a composite of death, MI, or stroke. Randomization was further stratified according to the choice of revascularization, either PCI or coronary-artery bypass grafting (CABG). A total of 49 sites contributed to the trial (the Americas, the Czech Republic and Austria). Eligibility criteria included a diagnosis of type 2 diabetes and coronary artery disease, which was defined as the presence of ≥50% stenosis of a major epicardial coronary artery associated with a positive stress test, or ≥70% stenosis of a major epicardial coronary artery and classic angina. All patients had to be candidates for elective percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG). Patients were excluded if they required immediate revascularization or had left main coronary disease, class III or IV heart failure, or if they had PCI or CABG within the previous 12 months. Patients in the revascularization group underwent the procedure within 4 weeks after randomization (hence the term 'prompt'), whereas patients in the medical-therapy group were to undergo revascularization during follow-up only if they experienced

progression of angina, severe ischaemia or suffer an ACS event. At 5 years, rates of survival did not differ significantly between the revascularization group (88.3%) and the medical-therapy group (P = 0.97). The rates of freedom from major cardiovascular events also did not differ significantly among the groups (P = 0.70). In the PCI subgroup, there was no significant difference in primary end points between the revascularization group and the medical-therapy group. In the CABG subgroup, the rate of major cardiovascular events was significantly lower in the revascularization group than in the medical-therapy group (P = 0.002). Therefore, the investigators concluded that PCI has no prognostic benefit over medical therapy in diabetic patients with stable coronary disease. However, upon further data scrutiny, we have observed the following facts:

- Of the 1,176 trial participants randomised for revascularisation, the decision to perform either PCI (798 patients) or CABG (378 patients) was determined by the cardiologists' discretion and not by further randomisation. Thus, compared to the PCI arm, the CABG arm contained a much higher risk group of patients (59.7% versus 37.2% myocardial jeopardy, 52% versus 20% 3-vessel coronary disease, 19% versus 10% proximal LAD disease, and 0.84 versus 0.48 mean number of chronic total occlusions).
- The trial investigators themselves stated that their study was designed to compare coronary revascularisation with intensive medical therapy, not to compare CABG with PCI. Indeed, the 5-year mortality among patients who were assigned to the medical-therapy group in the CABG stratum was much higher (16.4%) than that among patients assigned to medical therapy in the PCI stratum (10.2%). Therefore, the PCI group was disadvantaged by being judged against a much lower risk medical therapy comparator, which explains the resultant failure of PCI to demonstrate prognostic value in such low-risk event group.
- The selected patient population group represents a small subset of patients with diabetes and

coronary artery disease. The higher risk group patient who would stand to benefit the most from revascularisation were excluded from the trial.

- Over the 5-year trial follow-up period, 42.1% of patients in the medical therapy arm ended up receiving coronary revascularisation (either CABG or PCI) because of symptom control failure or because of ACS. As such, the trial was more of a comparison between prompt versus delayed coronary revascularisation, at least for 42.1% of patients.

ISCHEMIA

This recently conducted trial involved 320 sites spanning over 37 countries. The research question was: 'In stable patients with at least moderate ischemia on a stress test, is there a benefit to adding cardiac catheterization and, if feasible, revascularization to optimal medical therapy?'. 8,518 patients were initially enrolled, but 3,339 patients were subsequently excluded, either due to insufficient ischaemia or non-obstructive disease identified on CT coronary angiography. The remaining 5,179 patients, who had demonstrable coronary ischaemia on functional testing and appropriate target for intervention on CT coronary angiography, were randomized to receive either conservative (2,591 patients) or interventional (2,588 patients) treatment, namely PCI or CABG. Patients with >50% left main stem stenosis, glomerular filtration rate (eGFR) <30 ml/min, recent MI, left ventricular ejection fraction <35%, or unacceptable angina at baseline were not included in the study. The primary end point was time to cardiovascular (CV) death (defined as deaths attributed to either cardiac or vascular causes), MI, hospitalization for unstable angina (UA), heart failure (HF) or resuscitated cardiac arrest (RCA). 74% of the revascularization arm patients received PCI while the remaining 26% received CABG. The median follow-up period was 3.3 years. Some primary end points were shown to not be statistically different between the medical therapy arm and the revascularization arms, including the cumulative incidence of CV death, MI, UA, HF & RCA (P = 0.50), CV death alone (P = 0.33), all-cause mortality (P = 0.67), cumulative MI (P = 0.38) and RCA (P = 0.98). However, hospitalizations for

UA (P = 0.02) and HF (P < 0.01) were shown to be statistically different in favor of the revascularization arm. The trial investigators therefore concluded that, in patients with stable angina pectoris, revascularization provides no additional prognostic benefit over medical therapy. Furthermore, this message was communicated to the mainstream media before the trial findings were even published or adequately debated within the appropriate international cardiology forums, thereby leading to a significant public concern with regard to usefulness, appropriateness and safety of elective PCI. Notwithstanding this, upon closer data review, the following facts become clear:

- While the trial included patients with demonstrable evidence of both physiological myocardial ischaemia and anatomical coronary artery disease, it nevertheless excluded the high-risk patients, including those with significant left main disease and severe left ventricular systolic dysfunction, who would naturally be expected to benefit the most from coronary revascularisation. As such, mostly the lower risk stable angina patients were included whose expected 5-year risk of morbidity and mortality with optimal medical therapy would be low to begin with, thus making it statistically harder for revascularisation therapy to demonstrate significant benefit in such cohort.
- Cardiovascular death as a primary end point was a methodology flaw, for coronary revascularisation would not be expected to reduce vascular yet non-cardiac mortality (e.g. death from stroke or ischaemic bowel) in comparison with medical therapy. The trial did not measure cardiac death alone as an end point, so it remains unclear as to how many of those cardiovascular deaths in the PCI arm were actually cardiac in origin.
- While the cumulative MI incidence was shown to be similar in both groups, the trial investigators used different Troponin cut-off values for different types of MI. For example, the Troponin value for diagnosing post PCI MI, among other ECG and vessel flow

criteria, was set at >35 times the upper limit of normal (ULN), while for post CABG MI the Troponin value was set at >70 X ULN, which is twice the value required to diagnose post PCI MI. This measurement inequality would be expected to have disadvantaged the PCI group in comparison to the CABG one.

- Although for the first two years, the incident of MI in the revascularisation group was higher than that of the medical therapy group, a sizeable percentage of which could be explained by asymptomatic post-procedural troponin release that reached the cut-off point for MI diagnosis, particularly in the PCI group since their cut-off value was lower. In contrast, the subsequent two years witnessed a higher incidence of spontaneous MI in the medical therapy group, thereby indicating that coronary revascularisation had helped provide some protection against spontaneous MI during that period of time. The two MI occurrences, pre and post two years, were offset against each other to produce the non-statistically significant cumulative MI incidence (P = 0.38), which we argue is difficult to interpret or objectively contextualise.
- 28% of the medical therapy arm patients ended up receiving cardiac catheterisation and 23% actually received coronary revascularisation by 4 years, either to treat failed symptom control or to treat ACS.

Summary:

The main lesson to be learnt from COURAGE, BARI 2D and ISCHEMIA is that optimal medical therapy should be provided to all patients with coronary artery disease as the baseline upon which interventional treatment can be added. We also learnt that a significant percentage of stable coronary artery disease don't immediately progress into ACS and therefore it is safe and appropriate to not perform PCI upfront. Rather, this can be deferred until later if angina symptoms worsen or if ACS develops. Hence, the importance of careful and close follow-up of patients who are medically treated. Elective PCI seems to provide better control of

angina symptoms compared to sole optimal medical therapy, and it also seems to reduce the future incidence of ACS admissions. The mortality data from all the three trials contained some uncertainties hence rendering unreliable any conclusions drawn from those data. As such the impact of elective PCI on 'cardiac' mortality so far remains controversial. To answer this question, we suggest a new three-armed large clinical trial to randomize stable angina patients eligible for coronary angiography to receive optimal medical therapy alone or in combination with either PCI or CABG. The trial must include patient with higher risk cardiac profiles, like those with left main stenosis or poor left ventricular systolic function. The three arms must have comparable baseline characteristics and the primary end point should be 'cardiac' mortality only, not all-cause or cardiovascular mortality.

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