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Revisiting the role of percutaneous coronary interventions in stable angina: The landscape after the COURAGE trial

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The release of the COURAGE trial results has fuelled the debate over the benefits of percutaneous coronary interventions (PCI) in stable angina [1]. To date PCI, when compared to medical therapy, has been demonstrated as efficient in this context in relieving symptoms and improving short-term exercise performance [2–6]. Although previous randomised studies did not show any reduction in either mortality or myocardial infarction rates in the interventional arms, the trials may have been underpowered to detect such differences, as stents and evidence-based medical therapies were also underutilised [2–6]. Their limitations have raised considerable concerns as to whether the results obtained are applicable to contemporary clinical practice. Many cardiologists therefore extrapolated the evidence for a favourable impact of coronary angioplasty on the hard clinical end points observed in acute coronary syndromes to the population with non-acute coronary artery disease.

According to recent data, elective PCI procedures account for approximately 85% and 40% of all coronary angioplasties in the United States of America and Poland, respectively [7, 8]. Additionally, increasing numbers of asymptomatic patients are being referred for PCI with the advent of reliable non-invasive coronary imaging.

The COURAGE study was designed as a strategy trial to compare the long-term outcomes of elective PCI and provisional revascularisation (i.e. PCI or coronary artery bypass grafting when angina cannot be adequately controlled medically or an acute coronary syndrome occurs) in stable angina subjects. In this multicentre study a total of 2287 patients, 85% of whom were male and with a mean age of 61 years, with documented myocardial ischemia and angiographically confirmed single or multivessel coronary artery disease were randomised to coronary angioplasty with intensive medical therapy and lifestyle interventions (n = 1149) or intensive medical therapy and lifestyle interventions alone (n = 1138). An intention-to-treat analysis was applied. The study participants were followed for a median of 4.6 years. The median time from the first episode of angina before randomisation was 5 months. Of these patients 58% had Canadian Cardiovascular Society class II or III angina, while 38% of participants had suffered a prior myocardial infarction. Multivessel disease was present in 69% of patients, with only 31% having single-vessel disease. Complete revascularisation was intended in the PCI group. In these patients 59% received one stent and 41% more than one stent. Drug-eluting stents were implanted in only 31 subjects, as they were not approved until the final 6 months of the study. Antiplatelet drugs in the trial comprised aspirin and clopidogrel in the periprocedural period or clopidogrel indefinitely if aspirin intolerance was present. Medical antiischemic therapy was based on long-acting metoprolol, amlodipine, and isosorbide mononitrate, alone or in combination. All participants with prior myocardial infarction were treated with long-acting metoprolol and those with depressed left ventricular function (an ejection fraction below 40%) or anterior location of the myocardial infarction were also given lisinopril. Lisinopril was also considered a first-line antihypertensive treatment, although

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amlodypine, losartan and diuretics might be used. Moreover, simvastatin alone or in combination with ezetimibe was started to lower the low-density lipoprotein (LDL) cholesterol level to a target level of 60 to 85 mg/dl. After this level was achieved, the attending physicians made an attempt to raise the high-density lipoprotein cholesterol levels above 40 mg/dl and reduce triglyceride levels to below 150 mg/dl. If necessary they ordered exercise, extended-release niacin or fibrate, alone or in combination. The goal of the antihypertensive therapy was to achieve and maintain a target blood pressure of ≤ 130/85 mm Hg in the general population and < 130/80 mm Hg in patients with diabetes or chronic renal disease [9]. The goals for diabetes management were to maintain fasting blood glucose between 80 and 125 mg/gl and hemoglobin A_{1c} < 7.0%. Smoking cessation along with regular aerobic exercise, a low-fat diet and weight loss were strongly advised.

Optimal medication use during the study was high in both treatment groups, with use at 5 years of angiotensin-converting enzyme inhibitors in 64% of patients, statins in 93%, aspirin in 95% and beta-blockers in 85%. LDL levels were reduced to a median of 71 mg/dl. Blood pressure was also very well controlled in both study arms. The hemoglobin A_{1c} level in diabetic patients fluctuated around 7.0% during the study period. High rates of adherence to diet, regular exercise, and smoking cessation were demonstrated in both groups. However, the mean body-mass index did not decrease and most of the patients remained overweight. In terms of the primary end point in non-acute patients the study failed to demonstrate any advantage of elective PCI over initial intensive medical therapy combined with aggressive modification of risk factors alone. The composite of death from any cause and non-fatal myocardial infarction was similar in the two groups, at 211 in the PCI group and 202 in the medical therapy only group (the cumulative event rate was 19.0% and 18.5%, respectively). The secondary end point including death from any cause and non-fatal myocardial infarction and stroke also occurred at similar frequencies in each group, with respective rates of 20.0% and 19.5%. Corresponding rates of hospitalisation for acute coronary syndrome (12.4% and 11.8%) and myocardial infarction (13.2% and 12.3%) were also comparable. Although the degree of angina relief was significantly higher in the PCI group than in the medical-therapy group one year and three years after randomisation, the magnitude of the difference was rather modest (66% *vs.* 58% and 72% *vs.* 67%, respectively). Furthermore, freedom from angina was almost equal in the two groups at 5 years (74% *vs.* 72%; p = 0.35). However, as a result of refractory angina or acute coronary syndrome, approximately one third of the patients crossed over from medical therapy to revascularisation during the study period, a figure that was higher than anticipated. In a cost-economic analysis reported by William Weintraub at the American College of Cardiology 2007 Scientific Sessions [10] PCI costs averaged $6,020 higher than medical therapy during the index hospitalisation (p < 0.0001), a difference that narrowed slightly over time, but remained at an increased cost of $5,295 by 3 years (p < 0.0001). In a cost-effectiveness analysis, PCI was estimated at $217,000 per quality-adjusted life-year gained, while $50,000 is often used as the benchmark for acceptable cost--effective therapies in the United States of America.

The results of the COURAGE trial are compatible with the current concept of the pathogenesis of acute coronary syndromes. Tight stenoses, dilated during PCI procedures, are markers of the extent of the process rather than substrates for acute events. These stable plaques are associated with constrictive remodelling of the arterial wall and, as a consequence, they limit the coronary flow reserve and induce exertional angina. Stable lesions consist of small lipid cores, few macrophages and a relatively large number of smooth-muscle cells and collagen fibres, which are covered by thick fibrous caps. By contrast, vulnerable plaques, usually hardly visible on angiography, promote expansive remodelling. These are characterised by high lipid content, extensive macrophage accumulation, paucity of smooth muscle cells and collagen. Their thin fibrous caps are prone to erode or rupture with superimposed thrombosis, which manifests itself clinically in acute coronary syndrome or sudden cardiac death [11]. On the other hand, on the surface of plaques with severe stenosis, shear stress imposes a significant risk of thrombosis and sudden occlusion [11]. Nevertheless, non-stenotic lesions are far more frequent than stenotic plaques and account for the majority of culprit ruptured plaques [12]. The common appearance of more than one disrupted plaque in many patients with an acute coronary syndrome suggests the systemic nature of the disease [13]. The medical therapy, along with lifestyle interventions, implemented in the COURAGE study were aimed at diminishing patient vulnerability. Numerous mechanisms were proposed to mediate a plaque-stabilising effect: anti-inflammatory properties, reduction of lipid content and thrombotic potential, improvement of endothelial dysfunction, inhibition of plaque neovascularisation and a decrease

in the hemodynamic stress on plaque [14]. Ambrose and D'Agate [14] assessed the likelihood that a given systemic therapy was plaque-stabilising. They classified statins, angiotensin-converting enzyme inhibitors, beta-blockers and aspirin as therapies with biological plausibility and positive clinical evidence. This plaque-stabilising effect exerted by various drugs may be poorly correlated with angiographic surrogates of atherosclerosis regression. For example, statins successfully reduce death and non-fatal myocardial infarction rates with only a slight decline in the severity of stenosis [15].

It should be emphasised that chronic stable angina with appropriate medical management possesses a relatively benign prognosis. Average annual mortality rates range from 1% to 2%, with 1.4% observed in the optimal medical therapy arm of the COURAGE study, which is only twice that of age-matched controls [1, 16, 17]. It is an important consideration when determining the merits of revascularisation treatment [18]. However, an individual's prognosis may vary considerably. Higher risk subgroups include patients with poor exercise capacity and those with easily inducible ischemia or a poor hemodynamic response to exercise, angina of recent onset, depressed left ventricular function and multivessel coronary disease, especially with involvement of the left main stem or proximal left anterior descending artery [18]. Current European guidelines on stable angina recommend referring for coronary angiography subjects at high risk (expected annually mortality > 2% per year), while in the intermediate risk group (expected annually mortality 1–2% per year) the examination is optional, depending on the level of symptoms and clinical judgment [19]. Eugene Braunwald, in a recent interview on the COURAGE results, suggests basing the risk stratification process on stress perfusion imaging and assessment of left ventricle function. He also supposes that increasingly available multi-detector computed tomography will be routinely performed in the immediate future to exclude stenosis of the left main coronary artery [20].

Most of the landmark trials comparing medical treatment with surgical and percutaneous revascularisation pre-date the widespread use of potent antiplatelet and cholesterol-lowering drugs, arterial grafts and coronary stents. Coronary artery bypass grafting (CABG) is generally recommended for patients with severe left main stenosis, significant proximal stenosis of the three major coronary arteries, significant stenoses of two major coronary arteries, including high-grade stenosis of the proximal left anterior descending artery, and for those with concomitant valvular heart disease [19]. Additionally, a meta-analysis conducted by Yusuf et al. [21] indicated a more pronounced survival gain in subjects with left ventricular dysfunction undergoing CABG when compared with individuals who had received medical treatment alone. According to recently published 10-year clinical outcomes of the BARI trial, surgery conferred a survival advantage over balloon angioplasty exclusively among patients with diabetes mellitus [22]. There is general agreement that CABG gives more sustained relief from angina, and the need for repeated procedures is reduced after bypass surgery compared with percutaneous interventions with bare metal stents or without stents [23, 24]. Evidence in favour of drug-eluting stents so far is based on short-term follow-up and mostly on patients with single-vessel disease [23].

On the other hand, according to current PCI guidelines, objective evidence of large ischemia is mandatory to perform coronary angioplasty in stable angina [25]. It may be considered in almost every lesion subset, with the exception of chronic total occlusions, which cannot be crossed. However, in non-acute patients with diabetes or multivessel disease CABG is a preferred method of treatment. PCI of a left main stenosis in stable patients should only be performed in the absence of other revascularisation options. PCI can be also recommended in these subsets when bypass surgery poses a very high perioperative risk.

In the largest meta-analysis comparing the long-term outcomes of PCI (n = 1476) and conservative therapy (n = 1474) in non-acute coronary artery disease, elective invasive strategy did not offer any benefit in terms of death, myocardial infarction or the need for subsequent revascularisation [26]. However, many of the studies included showed numerous limitations besides a small sample size. These limitations included low rates of patients who met the eligibility criteria, the application of balloon angioplasty, single vessel PCI only, restriction of a dilated lesion to the particular anatomical localisation, medical therapy left at the discretion of an attending physician and the utilisation of a single pharmacological intervention directed against one risk factor) [2–6]. Moreover, many cardiologists have questioned whether the conclusions can be generalised. The results of the meta-analysis performed by Katritsis and Ioannidis [26] are concordant with the COURAGE outcomes and to date in an overall population of over 5000 patients no effect of elective PCI on subsequent cardiovascular events has been demonstrated. Similarly, in a recently

published Occluded Artery Trial, PCI provided no benefit in stable patients after myocardial infarction with persistent occlusion of the infarct-related artery [27].

The COURAGE trial highlights the benefits of the initial non-invasive approach, including optimal pharmacological treatment and implementation of lifestyle modifications in patients with chronic stable angina. It provides evidence in support of the safe deferral of PCI in non-acute patients, and this can even be avoided in more than two thirds of subjects. In the light of the study, preventive interventions in asymptomatic and mildly symptomatic patients result in a threat of complications and generate substantial costs. A considerable change in the treatment pattern and substantial health care savings are expected. Subjects with left main disease or with refractory angina despite optimal medical therapy, as well as those in a clinically unstable condition, still remain candidates for revascularisation [28]. Further trials are warranted to evaluate the role of CABG in contemporary practice, especially in the treatment of multivessel disease. The COURAGE study underscores how effective medical therapy and risk factor modification are in secondary prevention as well as angina alleviation, even in those subjects with extensive multivessel involvement and inducible ischemia. The COURAGE findings parallel a tendency recently reported in the OAT and ICTUS trials, in which observed clinical event rates associated with intensive medical treatment were lower than expected [27, 29]. Moreover, Mahmarian et al. [30], using intensive medical therapy, successfully suppressed scintigraphic ischemia in high-risk but stable survivors of acute myocardial infarction with preserved left ventricular function. The effect was as powerful as that derived from revascularisation procedures. On the other hand, there is considerable doubt concerning the reproducibility of the COURAGE results in the real-world setting owing to the high degree of use of evidence-based medical therapies and the achievement of the treatment goals by a vast majority of the study participants. It is noteworthy that in the Euro Heart Survey of 3779 patients with a clinical diagnosis of stable angina 78% were treated with aspirin, 48% with statins, 67% with beta-blockers and 37% with angiotensin-converting enzyme inhibitors [31]. The adherence to guidelines could be enhanced by close co-operation between patients and health care providers in the treatment process.

Patients with depressed left ventricular function, women and non-white individuals, were underrepresented in the COURAGE trial. Furthermore, subjects with left main stenosis, very early ST-segment depression or hypotension on stress testing, restenosis and coronary artery bypass grafting or PCI in the preceding 6 months were excluded. The majority of the PCI group received bare-metal stents, since most of the enrolment was completed prior to the introduction of drug-eluting stents. However, there is no reason to indicate that the use of drug-eluting stents would alter the findings of the trial, as, to our knowledge, these stents have never been shown to reduce the rates of death or myocardial infarction in comparison with bare-metal stents. The COURAGE results therefore apply to most, but not all, stable angina patients.

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