

The Emperor has no clothes: reading between the lines of the COURAGE report

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Abstract

Large clinical trials have consistently shown that PCI has limited if any impact on prognosis in patients with chronic ischemic heart disease. Most reports suggest that a large fraction of patients with effort angina remains symptomatic after coronary recanalization. The recently released COURAGE trial has confirmed the persistence of angina in one third of the patients after a “successful” angioplasty procedure and that a similar fraction of patients becomes asymptomatic at follow-up despite they did not undergo PCI. This data underscore the complexity of the pathogenesis of myocardial ischemia and emphasize the need for innovative approaches to the treatment of IHD.

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“Many, many years ago lived an emperor, who thought so much of new clothes that he spent all his money in order to obtain them; his only ambition was to be always well dressed . . .”.

This is the beginning of a tale that Hans Christian Andersen wrote back in 1837. The story was about people who denied even the most obvious evidence and pretended not to see what was in front of their eyes, just to follow the prevailing trend, and for fear of contradicting the “Emperor”.

Turning now to present-day cardiology... The obvious aesthetic benefit of re-opening obstructed arteries has fuelled great expectations in cardiologists, and in patients with ischemic heart disease. In recent decades we have witnessed an enormous increase in the use of percutaneous transluminal coronary angioplasty for the treatment of acute and chronic coronary syndromes [1,2]. Surprisingly enough, although there is evidence that percutaneous coronary intervention (PCI) reduces the incidence of death and non fatal myocardial infarction in acute coronary syndromes

[3–8], similar beneficial effects have not been observed in patients with stable coronary artery disease [9–14].

The widespread use of percutaneous transluminal coronary angioplasty in chronic stable ischemic syndromes is thus not supported by conclusive evidence. However, despite official guidelines recommending limiting the use of PCI to those patients with angina refractory to medical therapy, our “Emperors” have carried on dilating arteries whenever possible.

A recent paper by Boden et al [15] reporting the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial presented further, and possibly conclusive, evidence against this approach.

Between 1999 and 2004 in the COURAGE trial, 2287 patients with objective evidence of myocardial ischemia and significant coronary artery disease were allocated randomly to groups to receive PCI plus optimal medical therapy, or optimal medical therapy alone. The primary outcomes were death from any

New therapeutic approaches

Does PCI relieve chronic stable angina?

cause, and non fatal myocardial infarction, during a follow-up period of 2.5–7.0 years. The authors reported no significant difference between the two groups in the composite of death, myocardial infarction, and stroke ($P=0.62$), in the rate of admission to hospital for acute coronary syndrome ($P=0.56$), and in non fatal myocardial infarction ($P=0.33$). They concluded that, despite the presence of a high baseline prevalence of clinical coexisting illnesses, objective evidence of ischemia, and extensive coronary artery disease, PCI, when added to optimal medical therapy as an initial management strategy, is no better than medical therapy alone.

The conclusions of the COURAGE Trial are fully consistent with those of previous reports. Kastrati and Ioannidis [16] performed a meta-analysis of the findings of 11 studies (Randomised Intervention Treatment of Angina-2 [RITA-2], ACME-1, ACME-2, AVERT, Dakik, the Medicine, Angioplasty, or Surgery Study [MASS], Medicine, Angioplasty, or Surgery Study II [MASS II], ALKK, Sievers, Hambrecht, Bech). Among a total of 2950 patients (1476 of whom received PCI and 1474 of whom received conservative treatment), it was concluded that there was no difference between PCI and conservative treatment with regard to the risk of death, the rate of non fatal myocardial infarction, or the need for coronary artery bypass grafting.

One obvious objection to these conclusions is that the COURAGE Trial has included few patients treated with drug-eluting stents (they were not approved for clinical use until the final 6 months of the study), and that no trial included in the meta-analysis [16] included the use of drug-eluting stents. However, it is very unlikely that a liberal use of these stents would have modified the findings. Analyzing individual data of 4958 patients enrolled in 14 randomized trials comparing sirolimus-eluting stents with bare-metal stents, Kastrati et al [17] concluded that drug-eluting stents do not have a significant effect on long-term survival and on survival free of myocardial infarction, as compared with bare-metal stents. A similar conclusion was reached by Spaulding et al, who analyzed data from four trials comparing sirolimus-eluting stents and bare-metal stents [18].

We all must therefore accept that PCI has no significant impact on prognosis in chronic ischemic syndromes, regardless of the use of stents and of the type of stent used. Indeed, most of the debate that has followed the presentation of the findings of the COURAGE trial at the American College of Cardiologists' meeting has focused on these points.

To return to the analogy of Andersen's tale: we must make an additional effort to dissect other relevant information from the COURAGE Trial; otherwise, we would be behaving like the citizens of the "Emperor who had no clothes"!

The most disturbing data included in the report of the COURAGE Trial [15] are those presented in its Table 2 (p. 1510) concerning the effects of optimal medical therapy, plus or minus PCI, on clinical status, risk, lifestyle factors, and the use of medications. At 1 year, 66% of the patients in the group given PCI plus optimal medical therapy were free of angina, compared with 58% in the group who received medical therapy alone. These rates have been substantially confirmed at 3 and 5 years, with minor, non significant variations.

With few and unheard exceptions, nobody to date has dared to question the superiority of PCI over medical therapy in relieving angina. This assumption is clearly challenged by the figures presented in Table 2 of the COURAGE Trial report. If we open our eyes and minds to these figures, some provocative questions arise spontaneously:

- (1) Which is the cause of persisting angina in the patients receiving PCI on top of optimal medical therapy?
- (2) Why angina disappears in 58% of the patients still carrying a coronary obstruction?
- (3) Which therapeutic alternative can be offered to all those patients who, despite "optimal medical therapy", plus or minus PCI, continue to complain of angina?

These questions may sound very disturbing to many clinical and interventional cardiologists, not to mention the pharmaceutical industry and companies manufacturing interventional devices. Nevertheless, these questions deserve answers: too many patients are still waiting for a satisfactory response to their therapeutic needs.

A better understanding of the mechanism causing angina is urgently needed, innovative pharmacological agents must be actively sought, and cardiologists must fully realize the complexity of the pathogenetic and therapeutic implications of chronic ischemic syndromes. The problem is far from being solved. ■

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New therapeutic approaches

Mario Marzilli

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