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## Has preventive medicine entered the realm of the interventional cardiologist?

The result of the Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial<sup>(1)</sup> released at the recent ESC meeting held in Amsterdam has attracted enormous interest and rightly so: if the conclusions drawn by the researchers prove correct, the management of patients presenting with a ST segment elevation myocardial infarction (STEMI) is about to undergo a major change. The authors provide evidence to support "preventive PCI" in non-infarct related coronary arteries in patients with multivessel disease undergoing angiography with the objective of opening the infarct related coronary artery. These findings challenge the long-held view, reflected in international guidelines, that PCI in this setting should be aimed only at the so-called culprit lesion. It also challenges the view that the likelihood of atheromatous plaque rupture is primarily related to the properties of the plaque (degree of inflammation, cap thickness, cholesterol content) and not the degree of stenosis.

The trial enrolled 465 patients with acute STEMI who were undergoing infarct-artery related PCI. Patients were randomised to "preventive PCI" (234 patients; lesions of more than 50% stenosis in non-infarct related arteries were treated by PCI) or "no preventive PCI" (231 patients; lesions of more than 50% in non-infarct related arteries were present but only the culprit lesion was treated by PCI). The primary endpoint was a composite of death from cardiac causes, non-fatal myocardial infarction or refractory angina. The trial was stopped early (mean follow up 23 months) as the data and safety monitoring committee detected a clear advantage in the "preventive PCI" group (hazard ratio in the "preventive PCI" group, 0.35;  $P < 0.001$  which equates to an absolute risk reduction of 14%). The authors suggest that this study settles the debate regarding the best strategy for the management of patients presenting with a STEMI by establishing that "preventive PCI" is a better strategy than restricting further intervention to patients presenting with refractory angina or a subsequent myocardial infarction. They concede that the strategy of delayed or staged PCI for lesions in non-culprit vessels had not been addressed in this study. They also pose the provocative question if the benefits of "preventive PCI" may extend to lesions less than 50% in non-culprit vessels.

Extrapolation of the findings of this study to the patients we manage in our practices every day without due consideration of all the available information may put our patients at risk. So what are the available facts? Patients presenting with a STEMI are at significant risk of suffering another myocardial infarction and/or dying from a cardiac cause. The determinants of this risk include the age and sex of the patient, the presence and the management of risk factors for coronary artery disease, location of the infarct

**Editor, Anton Doubell**

(e.g. inferior vs anterior), size of the infarct and degree of impairment of left ventricular function. The authors state that "the results were not materially affected by... age, sex, the presence or absence of diabetes, infarct location or the number of coronary arteries with stenosis". One cannot however ignore the fact that more patients in the group not receiving "preventive PCI" were diabetic (21% vs 15%) and more patients in this group suffered anterior myocardial infarctions (39% vs 29%). Diabetic patients have significantly worse outcomes compared to non-diabetic patients and the larger number of anterior infarcts may have led to more systolic dysfunction (an important determinant of outcome) in this group. Although the differences in infarct related artery between the "preventive PCI" and "non-preventive PCI" did not reach statistical significance it is conceivable that the resulting differences in left ventricular ejection fraction (LVEF) did, and that the difference in LVEF between the two groups contributed to the difference in outcome. However this does not explain the higher infarction rate in patients where the non-culprit lesions were not treated as reported in this trial. The mechanism of this observation remains unexplained. The principle investigator has indicated that the subsequent infarctions occurred in the non-culprit vessels but it was not stated if the occlusions occurred at the untreated lesions or proximal or distal to these lesions. The lower infarction rate in patients who had the non-culprit lesions treated suggests that these lesions were the site of subsequent occlusions. However, altered flow proximal or distal to significant lesions, resulting in an alteration of endothelial function and subsequent risk of plaque rupture, may also be a plausible mechanism for a protective effect conferred by relieving the obstructions. The findings of this study have highlighted the fact that our knowledge of the mechanisms of plaque rupture leading to myocardial infarction is still incomplete.

To extrapolate the findings of this single trial to our everyday practices without further verification would be premature. It certainly would not be appropriate to use this trial as justification to generate full metal jacket coronary trees in our patients presenting with a STEMI, a scenario that is not far-fetched if you consider the view posed by the authors of the PRAMI trial that consideration must be given to treating non-culprit stenosis less than 50%. In patients with multivessel disease, decisions regarding further revascularisation would have to include the risk factor profile of the patient (e.g. diabetic vs non-diabetic), the location and size of the infarct being treated, the number, severity and complexity of non-culprit lesions (e.g. patients with high Syntax score vs low Syntax score; the FFR values vs visual estimates of lesions) as well as the relative advantages/disadvantages of ischaemia driven or deferred intervention strategies.

Let us assume that the findings of the PRAMI trial will be borne out by further studies designed to validate these findings. What is the explanation for this observation? In patients with stable angina protection against myocardial infarction and cardiac death is earned by good risk factor control and not by interventional revascularisation strategies. The reason for this is that protection is afforded by pacifying all the inflamed atheromatous plaques that could potentially rupture and lead to coronary occlusion. The majority of these plaques are non-obstructive and therefore a preventive strategy aimed at the obstructive lesions does not afford protection. To suggest that targeting the non-obstructive lesions in patients with stable angina, where most of the plaque burden would be non-inflamed and stable, would have no scientific basis and therefore no justification. Can we present a different case for the patient who presents with a STEMI? The plaque rupture that led to the infarct serves as a marker for the inflamed nature of the total plaque burden in these patients and one may reason that any number of the plaques in the rest

of the culprit vessel or in non-culprit vessels will be equally inflamed and potentially on the verge of rupture. Based on this argument PCI of non-culprit lesions may well confer protection. However, based on the knowledge that plaque rupture is not clearly linked to the degree of obstruction, one may assume that the protective advantage of stenting non-culprit lesions may be because it targets the sections of vessels with the highest plaque burden. Extrapolating this argument may well argue in favour of the full metal jacket approach to “preventive PCI” but any potential advantage of such a strategy is likely to be offset by the risks conferred by multiple and long stents. A future strategy of truly preventive stenting would have to be based on a better understanding of the pathogenesis of reinfarction and death following a STEMI and in particular a better selection of lesions likely to rupture, possibly by considering inherent properties of the plaque such as lipid content and cap thickness (detected by IVUS or OCT) or plaque inflammation (e.g. detected by assessing plaque temperature) in addition to the degree of stenosis. The PRAMI study should be valued not so much for the answer it has provided but for the questions it has raised.

## REFERENCES

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1. Wald DS, Morris JK, Wald NJ, et al. Randomised trial of preventive angioplasty in myocardial infarction. *NEnglJMed* 2013 Sep 1 (Epub ahead of print).