

## The Attack on Coronary Disease: Should it be before, during or after?

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### Introduction

The meaning of the title is that the control of coronary heart disease can be considered as being focused on prevention (before), during (upon onset of symptoms), or after (long term active treatment). The ideas expressed are based on a large experience of these aspects in a West London hospital cardiology practice between 1995 and 2000.

### Before

The whole idea of primary prevention of arterial disease stems from the Framingham philosophy (Framingham Heart Study, 1948), which is based on an epidemiological approach. There is no doubt that this has been successful in leading to a great reduction in smoking, correlating with a great reduction in coronary disease. Improved control of hypertension was a further important advance. The next great focus was on lipid abnormalities triggered by a correlation between arterial disease and blood cholesterol. This approach remains controversial with enthusiasts wanting the entire population to be fed statins, while others call it the "Great Cholesterol Myth" [1].

Our approach was to simplify the statistical method by measuring a wide range of supposed risk factors immediately upon admission to hospital, of patients with acute coronary syndromes before receiving treatment. We followed these patients up for four years in order to calculate any correlations with outcome, after allowing for such obvious ones as a previous acute coronary syndrome, diabetes, and infarct size as determined by troponin-T release [2]. While finding positive correlations for non-diabetic insulin resistance [3] and hyperhomocysteinaemia [4] (neither of which have penetrated into general practice screening), we did not find a correlation between mixed cholesterol and outcome.

This makes us critical of the still common reliance in general practice on using mixed cholesterol rather than high LDL and/or low HDL as the correct way to assess risk from lipid abnormalities. We also found poor outcome in patients with high lipoprotein (a) [5,6,7]. Our other anxiety is about the use of statins in primary prevention, as we have observed serious side effects of these drugs, which not only leach lipid from fatty arterial lesions but also from normal cell membranes, leading to muscular and neurological defects. Their use in secondary prevention is undoubtedly well proven - see below. Even the recommendation of low fat diet seems misconceived as the cholesterol in the blood are not determined much by what is eaten, and the campaign seems to have led to an increase in carbohydrate consumption and type 2 diabetes, which may be a more serious risk factor than eating some fat or oil.

### During

In the case of stable angina (and stable patients after PCI or CABG), dual anti-platelet therapy is the established treatment and is effective, but leads to concern amongst patients, doctors and regulators because of increased bleeding risk, of which more hereafter. I will focus more on the onset of disease as an acute coronary syndrome. In our practice, following preclinical experimental work [8], we advocated primary angioplasty for treatment of myocardial infarction following Dutch practice [9]. Experimentally, much research has been performed, mainly by the Folts group, using his model of the anaesthetized dog with coronary artery stenosis and endothelial damage, showing a number of influences that inhibit thrombus growth, of which serotonin 5HT<sub>2</sub> antagonism was of particular interest [10]. There are 12 other papers in 1986, 1992 (2), 1993, 1994(2), 1990, 1998, 2001, 2008, 2010, the latest being the paper of Lin et al. [11], confirming the inhibition of arterial thrombus growth by 5HT<sub>2A</sub> receptor antagonists. The pharmaceutical industry, however, has preferred to explore agents inhibiting platelet-rich thrombosis by antagonizing the beginning of the process, i.e., inhibition of initial aggregation and adhesion mediated by thromboxane (hence aspirin) and/or ADP (hence clopidogrel and other P<sub>2</sub>Y<sub>12</sub> receptor antagonists); hence dual anti-platelet therapy.

The problem with this approach is that the mode of action of these drugs inhibits mechanisms of haemostasis and therefore causes excess bleeding. Moreover dosing is difficult as allowance for differences in body weight and individual sensitivity to these drugs is beyond the capacity of routine general practice, or even hospital practice. The industry has also been inhibited from using serotonin antagonists because of the vital functional requirements for serotonin as a neurotransmitter in the brain. A 5HT<sub>2A</sub> antagonist for which this is not a problem was ICI170809, which does not cross the blood-brain barrier. A further advantage is that there is no detectable effect on initial aggregation or adhesion, only inhibition of macro-aggregate growth [12].

### After

One might consider the possibility of attacking the late phase of the thrombotic process rather than the initiation. The most popular idea about that is a plaque rupture leaking material that causes platelet activation and adhesion. However, in our practice coronary angiography showed that approximately only half the culprit lesions were eccentric, and half concentric. Concentric lesions are not likely to respond to statin, and that may explain why non-ST elevation acute coronary syndromes have outnumbered ST elevation infarcts in frequency since 2000. The mechanism of thrombosis in any stenosis, including concentric lesions, is that the velocity of blood flow increases (convective acceleration, Westerhof et al., [13]), which increases the shear stress applied to the blood platelets. This causes platelets to leak

serotonin from the dense granules, and this sets up the growth of the thrombus as serotonin activates other platelets through the 5HT<sub>2A</sub> receptors causing more serotonin release (positive feedback).

The established, successful, clinical management after diagnosis of coronary disease is chronic administration of a statin to reduce the fatty lesions, plus dual anti-platelet therapy (aspirin plus a P<sub>2</sub>Y<sub>12</sub> receptor antagonist) in order to prevent activation and adhesion of platelets [14]. The fact that this management has improved prognosis considerably does not mean that further improvement is not possible. There remain the problems of statin adverse effects and bleeding excess due to anti-platelet therapy.

### Suggestion

The emergence of a 5HT<sub>2A</sub> receptor antagonist that has now been shown (1) to be highly potent in inhibiting coronary artery thrombus growth [14]; (2) not to cross the blood-brain barrier; (3) to have no cerebral effects in humans and (4) to be free of adverse events in patients, suggests that this compound is a candidate for tackling all aspects of coronary disease, i.e., primary prevention (no important adverse events), onset of symptoms (safe to give before definitive diagnosis) and secondary prevention (avoiding cell membrane damage and excess bleeding). BEFORE, DURING AND AFTER!

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