

# Primary prevention and hypercholesterolaemia: 'Doc, please, give me the natural statin'

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The correlation between blood cholesterol levels and cardiovascular risk is characterized by a constantly increased risk as the cholesterol level increases; on the other hand, the risk doesn't increase for very low values of cholesterol (as in the 'J' shaped curves), as it is a well-known pattern, for instance, with the blood pressure. The risk curve shape, combined with the result of the study on cholesterol-lowering drugs, suggest that any intervention aimed at lowering the cholesterol levels, when carried on for sufficient time, will reduce the risk of adverse cardiovascular events, such as myocardial infarction. This concept holds true also for subjects at low cardiovascular risk, or with cholesterol levels not particularly elevated, in whom, according to the available data, lowering the cholesterol will lower the incidence of cardiovascular events; this effect will fade, though, according to the risk of the patient and the pre-treatment cholesterol level. These premises are the basis for the theoretical use, in the general population, of intervention to lower cholesterol levels in primary cardiovascular prevention; when the costs of treatment (statins off note 13, or food supplements with cholesterol-lowering action) are with the patient and not the National Health System, it is reasonable to imagine that their use should be assessed with less attention to the pharmaco-economic impact, whereas the cost/benefit ratio (ratio between adverse effect and protective effects) should be evaluated with the utmost attention. Among the various supplements, particularly popular both for public and sales, are the products based on fermented red rice. There are approximately 200 different brands of the products, reaching sales for over 100 million Euros.

The active substance in fermented red rice is Monacolin K, chemically indistinguishable from Lovastatin.<sup>1</sup>

In the East red rice has been a popular remedy, for many centuries, as intestinal cleanser; only recently its cholesterol lowering effect has been described and studied. The

effects of fermented red rice on lipid profile are well known. The prevalent effect is reduction of LDL cholesterol, which according to the Monacolin K level, decreases by 15% and 25%.<sup>2</sup> The effect on HDL cholesterol is negligible.

Long-term studies confirmed that the reduction of LDL cholesterol is unchanged over time, provided the dose of the compound remains the same. As for the other statins, Monacolin K improves endothelial function and has an anti-inflammatory effect (measured by the plasma level of C reactive protein).<sup>3</sup> The pharmacokinetic of Monacolin K is characterized by a relatively short half-life, a limited intestinal absorption (improved by a full stomach) and is metabolized by cytochrome P450.<sup>4</sup>

Fermented red rice is the only food supplement upon which a control clinical study with 'hard' clinical end points has been conducted. The study confirmed the reduction of LDL cholesterol by about 20%, and documented, during follow-up, a reduction of total cardiovascular events by 37%, and coronary related deaths by 31%. Overall mortality was also lower in treated patients (–32%). It is interesting to notice that the effect of red rice supplement on lipid profile, considering the dose of Monacolin K, is superior, milligram by milligram, to that of lovastatin pills: lovastatin and Monacolin K are chemically indistinguishable. It is possible that the difference resides in the better bio-availability of Monacolin K in fermented red rice, which for the characteristics of the carrying substances, is significantly higher than the chemically purified compound.<sup>5</sup> Overall the effect of fermented red rice containing 3 mg of Monacolin K on LDL cholesterol is equivalent to a dose of 10 mg of lovastatin.

It should be stressed that the European Food Safety Authority released a claim regarding the use of red rice supplement for 'maintenance of normal blood LDL cholesterol': the interesting fact is that the claim is subject to a

dose of Monacolin K of at least 10 mg, which is not the case for the food supplements (widely in use), containing 3 mg of the active compound, whose cholesterol-lowering effect is proven beyond doubt.

In actuality, this food supplement is not without its critical aspects and potential risks. A provocative study published in 2010 investigated a series of fermented red rice products purchased on the Internet which were tested for their content of Monacolin K e Ka (all declared content of 10 mg). The study revealed a wide range of active compound, varying by a factor of 100 (from 0.1 to 10.5 mg)<sup>6</sup>; the same analysis revealed the presence of citrinin, a nephrotoxic alkaloid, in some of the preparations. Monacolin is metabolized, as the lovastatin, by the isoenzyme 3A4 of cytochrome P450 (responsible for the metabolism of about 50% of drugs used in human), hence the theoretical possibility of drug interaction is not negligible, despite the low dose of the compound. The side effects are dose dependent. The risk-benefit ratio of this treatment is essentially dependent from the patient global cardiovascular risk, which should correctly be estimated by a medical professional. Furthermore, the treatment should be continued through the years (the few data available suggest that

the product is used for short periods): the physician contribution to the correct use of these products is therefore essential.

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