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# Overview on pharmacological and nutraceutical strategies for treatment of borderline dyslipidemia

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**Cardiovascular system pathologies are responsible for 30-35% of deaths in industrialized countries thus making cardiovasculopathy the leading cause of disease-induced death. Many risk factors and the presence of a chronic inflammatory state represent the substrate for the development of cardiovascular disease. Hypercholesterolemia is considered one of the most important risk factors and consequently a primary therapeutic target. Numerous therapeutic strategies, mainly based on the use of statins, have been developed for hypercholesterolemia management. Unfortunately, those established drug therapies may present low effectiveness and low compliance by the patients.**

**In this overview we discuss the results of a cohort observational prospectic clinical trial with active control which aims to evaluate the effectiveness of the experimental treatment with Omega Formula™ compared to conventional treatment with atorvastatin.**

**The study was conducted in Italy on 30 subjects aged over 18 years enrolled according to defined criteria, divided into two homogeneous groups and treated for 3 consecutive months with 10 mg/die of atorvastatin (control group) or 3 tablets/die of Omega Formula™ (experimental group) and followed up with evaluation of biophysical and haematic parameters. The study highlights the expected result of reduction of total cholesterol plasmatic levels in the group of subjects treated with Omega Formula™ (-17.82%) and the effectiveness of the treatment with Omega Formula™ compared to treatment with atorvastatin in reducing hyperlipidemia.**

**KEY WORDS:** Risk factors - Inflammation - Homocysteine - Atorvastatin - Red yeast rice - Vitamin $B_6$ - Omega fatty acids.

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Cardiovascular diseases (coronary artery disease, CAD and cardio-vascular disease, CVD) are the main cause of death in developed countries (30-35% of total deaths according to ISTAT data – Ministry of Health, 2009) and the forecasts indicate an increase in these pathologies on a worldwide scale. It is estimated that the global population will rise from 5.5 billion in 1995 to 8.5 billion in 2025. Combining this demographic growth with the diffusion of the Western lifestyle will result in an increase in adults potentially at risk of developing CAD and CVD.[1]

Above age 40 the risk affects 50% of males and 33% of females, whereas from age 70 the percentage of risk respectively drops to 33% and 25%;[2, 3] numerous factors affect the onset of CAD and CVD and significantly determine the result: poor nutrition, smoke and alcohol abuse are predisposing behaviours associated to lifestyle, which are

added to independent factors such as familiarity, ethnicity and age. The copresence of obesity, type 2 diabetes and hypertension, together with dyslipidemia, is a multiple risk factor classified as metabolic syndrome.

## Hypercholesterolemia: risk assessment and therapy

All epidemiological studies concerning cardiovascular risk agree in considering hypercholesterolemia an essential causal factor in the onset of chronic low-grade inflammation fundamental to the development of CAD and CVD due to its ability to alter the homeostasis of the vessel endothelium with consequent predisposition to the onset of thrombotic [4] events. A diagnosis of hypercholesterolemia is formulated when there is an elevated level of triglycerides and LDL cholesterol in the blood associated to reduced levels of HDL cholesterol. The correlation between increasing levels of circulating cholesterol and an increase in mortality due to cardiovascular pathologies is exponential: compared to non-hypercholesterolemic individuals, in subjects with total cholesterolemia values of 20 mg/dL, the rate of mortality for CAD doubles at 6 years; the copresence of 2 or more factors makes this triple, while the presence of full-blown CAD multiplies this rate five times.

The first step in managing a patient affected by hyperlipidemia is assessment of the cardiovascular risk level. Cardiovascular risk is defined as the possibility of being struck by a fatal cardiovascular event within the space of 10 years and is assessed through the analysis of blood lipoproteins and the identification of risk factors which may be present; the analysis of data collected allows to attribute a score which represents the risk level of the patient. In the USA, the NHLBI (National Heart, Lungs and Blood Institute, Department of the National Institutes of Health), has standardised several parameters within the NCEP programme (National Cholesterol Education Program, launched in 1985, protocol ATP III updated to 2004) specifying the maximum levels of LDL cholesterol according to the different types of patient; in diabetics for example, considered at high cardiovascular risk, the level of maximum LDL (CVD at 10 years ≥20%) is fixed at 100 mg/dL, in medium-risk individuals the limit is 130 mg/dL, while for patients considered at low risk it rises to 160 mg/dL. In Europe, two scales of multifactorial risk are generally used to take into account the differences in the geographical distribution of the pathologies (Italy and other countries of the Alpine-Mediterranean area are included within a low risk protocol, the remaining countries of the EU, are considered high risk [5]).

In the UK, the guidelines dictated by the Joint British Society [6] suggest classifying, similar to other protocols, as high risk those individuals with a likelihood of CVD at 10 years ≥20% and to adopt appropriate corrections to lifestyle in asymptomatic individuals with CVD at 10 years <20%, excluding the need for them to resort to preventive pharmaceutical therapy.

The NICE [7-9] guidelines also maintain that in addition to the purpose of exercising a primary effective preventive function, it is essential to apply specific procedures to calculate the risk of CVD for individuals who are difficult to categorise within the guidelines of use, for example the elderly or diabetics belonging to restricted ethnic groups.

Unlike glycemic levels in diabetes mellitus, it is difficult to establish clear and unequivocal limits for the theoretical lipid levels usable in calculating the risk of CVD and this implies difficulty in assessing the cost/benefit ratios of the pharmaceutical therapies that can be adopted for dyslipidemia. The American College of Physicians [10, 11] suggests beginning preventive therapy with statins (inhibitors of HMG-CoA reductase, key enzymes in cholesterol biosynthesis) for all patients with type 2 diabetes independently of the presence of other risk factors and to treat dyslipidemic patients with statins to return blood lipid levels to parameters considered normal independently of the starting values of the same.

The developments in pharamcogenetics

TABLE I.—*Summary of parameters for inclusion/exclusion from the OMEGASTAT study.*

| Inclusion criteria | Exclusion criteria |
|---|---|
| Males and females who respond to the following criteria are "eligible": adult out-patients affected by hypercholesterolemia with the following characteristics:<br>• Age >20<br>• In primary prevention: individuals with total cholesterol values ≤280 mg/dL<br>• Individuals who follow a hypolipidic diet during the trial<br>• Patients able to comply to the study procedures<br>• Patients able to understand and sign the consent form and to allow treatment of personal data | Males and females with the following characteristics are "not eligible":<br>• Individuals with liver or kidney failure<br>• Individuals with a positive family history for cardiovascular accidents<br>• Pregnant women<br>• Individuals suffering from neoplasia<br>• Individuals with serious viral infections (HIV-HCV, etc.)<br>• Individuals potentially allergic to the ingredients of Omega™ formula |

have allowed to attribute to precise human genotypes a greater predisposition to the development of hyperlipidemia; the concept of pharmacogenetic-guided treatment of hypercholesterolemia has been proposed as a new tool for the targeted administration of individual therapies with statins. In April 2013, PharmacoEconomics published a review [12] concerning a series of in-depth analysis on the cost/effective ratio of the pharmacogentic approach to treating hyperlipidemia with statins; the authors concluded their analysis by indicating a favourable cost/effective ratio for a single genotype (SLCO1B1) and highlighting the many limits of the studies carried out on the subject.

The use of statins as a preventive and therapeutic tool still remains mostly bound to the large number of protocols and national and international guidelines which were mentioned earlier. Atorvastatin is one of the most recommended [13, 14] statins by the various guidelines for treating hypercholesterolemia. The molecule carries out its action, in addition to a hypolipidic diet, by reducing the levels of total cholesterol, of LDL-C and apolipoprotein B. Nevertheless, atorvastatin (like the other statins) reduces but does not eliminate the cardiovascular risk: though the management of LDL-C levels is essential, numerous tests indicate that high TG and low levels of HDL-C are further independent factors of cardiovascular risk. Treating lipid parameters in addition to the LDL-C can require the addition of niacin or fibrates to the therapy with statins with the consequent reduction in the compliance of the patient towards the multi-therapy compared with the therapy which uses a single drug. The use of statins can also encounter other two important obstacles: intolerance of the patient to the active ingredient and the onset of collateral effects, myopathy being the most relevant. Myopathy includes the phenomena of myalgia and rhabdomyolysis (rarer and more serious) which are considered the typical adverse effects of therapy with statins (a reason why Cerivastatin was withdrawn from the market in 2001 [15, 16]).

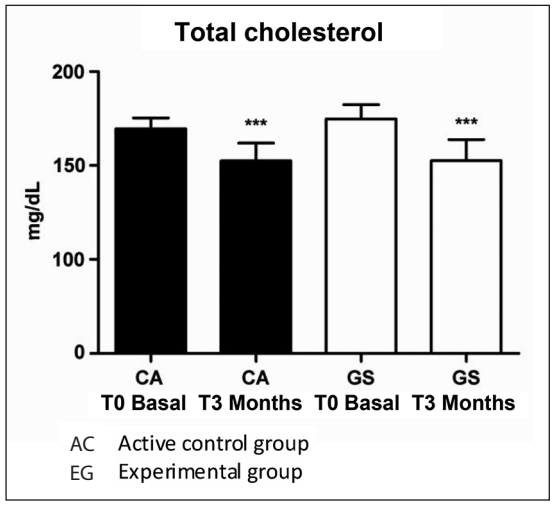


Figure 1.—Treatment with Omega Formula™ leads to the achievement of the primary endpoint (A) of the study. In EG group total cholesterolemia is reduced on average by 17.82% with P<0.0001). In the AC group the levels of total cholesterol are reduced on average by 14.25%. with similar statistical significance.

## New prospects in the field of prevention and treatment of borderline hyperlipidemia

In recent years, there has been a strong shift to complementary and/or alternative therapies to treat "borderline" hyperlipidemia and great focus has been put on food supplements associated with good nutrition and healthy lifestyle.

Within this constantly evolving environment, a clinical study is analysed conducted on a food supplement (Omega Formula™, Guna S.p.a., Milan, Italy) to evaluate its abilities to manage hyperlipidemia compared to those of a traditional classic statin.[17]

The supplement, subject of the study, contains micronised seed of *Adansonia digitata L.* (which contributes unsaturated fatty acids Omega-3, -6 and -9, polyphenols and free sterols), red yeast rice (*Monascus purpureus*) titrated in monacolin K, Pyridoxine hydrochloride (vitamin B6), pteroylglutamic acid, bitter Cocoa powder and maltodextrin.

The prospective cohort observational

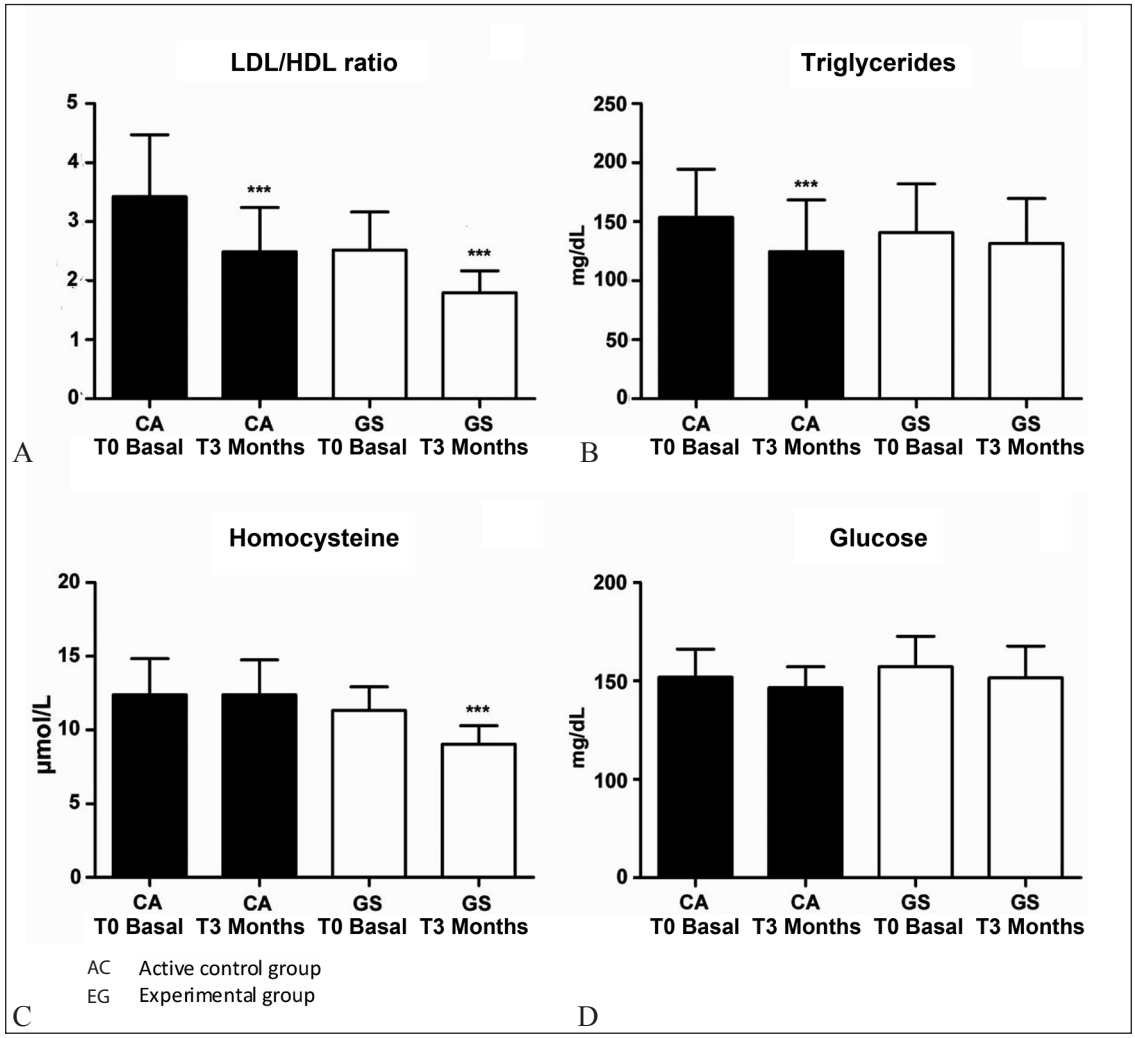


Figure 2.—Set of data on secondary endpoints shows a substantially equivalent picture between treatment with Atorvastatin and Omega Formula™. The parameters: LDL/HDL ratio (-28.41%) (A) and circulating homocysteine (-20.17%) (C) show how Omega Formula™ is effective in modulating these values. Treatment with Atorvastatin proves to be beneficial in managing the levels of triglycerides (-18.83%) (B).

study with active control, published in 2014, was conducted on 30 individuals under the family medicine regime belonging to the ASL (Local Health Authority) of Lodi (District Codogno). The purpose of the study was to assess the different clinical outcomes of a group of hypercholesterolemic patients (the criteria of inclusion and exclusion are described in Table I) undergoing treatment for three months with Omega Formula™, taking 1 chewable tablet 3 times a day (EG: experimental group) compared with those of patients suffering from the same pathology treated with conventional pharmacological therapy (atorvastatin 10 mg/day) of equal length (AC: active control group).

The study proposed to assess a primary endpoint, or rather the total cholesterolemia, and a panel of secondary endpoints. The secondary endpoints analysed were the LDL/HDL ratios, the levels of circulating triglycerides (TG), homocysteinemia, glycemia and the levels of circulating fibrinogen.

The data gathered have been analysed statistically applying a confidence interval of 95%, allowing to compare the effective use of the food supplement with the active control.

The results collected in the study show how the assumption of the tested food supplement allows to obtain superimposable results with respect to those obtained by the traditional pharmacological therapy used as active control. The primary outcome, the reduction in total cholesterolemia, has been fully achieved marking an average value of -17.82%, in line (statistically equivalent) with that reached with pharmacological therapy (-14.25%) during the monitoring period of the patients (Figure 1).

The assessment of the secondary outcomes within the timeframe has recorded a greater efficacy of treatment with the food supplement in managing the LDL/HDL ratio (-28.41% *vs*. -27.22%) and a greater efficacy of the statin in reducing the level of circulating TG (-18.83% *vs*. -6.48%) (Figure 2).

The study highlights the substantial equivalence of action between the food supplement and the drug in improving dyslipidemia; where the supplement seems to have a competitive advantage with respect to the pharmacological treatment is in managing chronic low-grade inflammation. The pharmacological therapy used in the study does not present significant effects on the blood inflammatory parameters assessed, particularly on homocysteine; no direct action was observed on the chronic low-grade inflammation while the use of the supplement leads to a medium reduction of circulating homocysteine of 20.17%. The study also highlights the absence of adverse secondary effects to the use of the supplement and the excellent compliance reported by patients in assuming it.

## Conclusions

From data examined in the present study it can be concluded that:

— alteration of the lipid profile and the presence of low-grade chronic inflammation are essential factors in increasing the risk of the onset of fatal cardiovascular events;

— at the current time the therapy of hyperlipidemia with statins is the elective strategy, though it is not free of side effects;

— the numerous guidelines and therapeutic protocols are a considerable aid in choosing the best pharmacological therapy but they present several limits, especially in suggestions for treating borderline patients and in defining preventive strategies;

— the evolution of pharmacogenomics is a considerable aid to the development of individual and targeted therapies, but the current state of the art does not allow to achieve this objective.

The overview of the described facts highlights how useful it can be to avail of therapeutic tools which are alternative to the standard drug to treat and prevent borderline dyslipidemia.

Though the data deserve to be extended, it appears clear how the food supplement in question exercises a good control action at various levels on non-severe hyperlipidemia and has an added therapeutic value

in the ability to intervene on low-grade chronic inflammation. This allows to consider that the development of food supplements able to regulate cholesterolemia levels, the LDL/HDL ratio and reduce low-grade chronic inflammation is desirable in replacing (in borderline cases), assisting and/or delaying, through preventive use, the conventional pharmacological therapy of hyperlipidemia.

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