THE ROLE OF SECONDARY PREVENTION AND NUTRITIONAL COUNSELING IN PRECISION CARDIOLOGY

EXPERT OPINION

HIGHLIGHTS

- The first year after hospitalization is a highly vulnerable stage for patients that have suffered a cardiovascular event. Inadequate secondary management may contribute to relapse and re-admission of these patients, as well as to the onset of other adverse events and even death.
- It has been extensively reported the contribution that psycho-social support, pharmacological adherence, return to everyday activities (related to both employment and recreation) may have to improve the outcomes of these patients
- There is still a need to discuss the role that nutritional management and other forms of secondary prevention may have in post-infarction patients.
- One of the goals of Precision Medicine is to provide an integral, individualized management to patients, even in periods of secondary rehabilitation.

An initiative by
PRECISION-MEDICINE.IN
www.precision-medicine.in

ABSTRACT

Cardiovascular diseases are still among the main causes of morbi-mortality in industrialized countries. One of the reasons behind this may be the scarce importance given to primary and secondary prevention strategies. Our current knowledge about the impact that nutritional risk has on cardiovascular disease patients is still limited. In particular, it was not until quite recently that secondary prevention approaches have started to gain attention in rehabilitation programs. The Precision Medicine paradigm aimed at the integral management of complex diseases has provided medical practice with analytical approaches that consider the genetic background of individuals, as well as the interactions with the environment and lifestyle. It is in this framework that strategies such as nutritional management and secondary prevention may fit best. Here we will discuss how to apply these ideas to patients that have suffered myocardial infarction.

Jessica I. Verduzco-Ramos[1,2] **and Mireya Martínez-García**[1,3*]
[1]Sociomedical Research Department, National Institute of Cardiology "Ignacio Chávez", México City, MÉXICO
[2]Health Sciences School, University of the Valley of México (UVM), México City, MÉXICO
[3]Program in Collective Health, Metropolitan Autonomous University (UAM), Xochimilco, México City, MÉXICO

*Corresponding author: Mireya.Martinez.Garcia@gmail.com, **Tel.:** +52-55552695; **Fax:** +52-5555155665

In the last decades, important public health efforts have been devoted to modify the lifestyle and reduce conditions that contribute as risk factors, to improve survival rates and diminish morbility of cardiovascular diseases (CVDs) [1]. CVDs are still the leading cause of morbi-mortality in industrialized countries, likely because of deficient primary and secondary prevention strategies, poor pharmacological adherence programs, lack of communication between the cardiologists and their patients and relatives, high costs of drug treatments for CVDs and a limited (sometimes inexistent) nutritional management scheme [2, 3].

The Precision Medicine (PM) initiative as a new approach for the treatment and prevention of complex diseases (especially those with high public health impact), considers the effects that inter-individual genetic variability, environmental factors and personal lifestyle have on their health status [1, 4, 5-8]. It can be expected that aspects as the ones mentioned in the previous paragraphs may be naturally incorporated into a Precision Medicine Approach to CVDs. For instance, diagnostics may improve by the introduction of new technologies and the inclusion of sophisticated analysis tools that may enable us to have more precise information about the optimal individualized treatment for a given diseased state (and in the case of chronic illness, also of the periods of relative health), to enhance the health status and to improve clinical research with a view to impact public health [2-4].

In recent times, due to the concerted efforts of many research labs and institutions worldwide, a number of genetic polymorphisms in genes that may be associated with higher risk of CVDs have been found. This has led to the development of probes that allow us to measure gene expression to improve diagnostics and in a few cases to attempts to intervene in order to modify the evolution of the disease in certain patients [3]. The pharmacogenomics component of PM has allowed us to have a positive impact in the management of patients requiring pharmacological treatments for hypertension and dyslipidaemia, among other diseases [5]. This made possible to consider how different patients react differently to the same medication. Therapy is thus precisely adjusted (or fine-tuned) to the individual characteristics of a given patient.

The understanding of the phenotypic expression that comes from the knowledge provided by genomics, epigenetics, transcriptomics, metabolomics and nutrigenomics in combination with information of the lifestyle, social and environmental factors [Figure–1] is useful not only to individualize pharmacological therapeutics and to define the individual's response to this, but also to design 'de novo' intervention strategies (such as secondary prevention and nutritional management) tailored to the needs and characteristics of each patient [5-7, 20].

Cardiovascular and metabolic diseases are strongly linked to genetic and nutritional factors. Nutrigenomics thus provides a natural framework to enhance our understanding of the effects of diet in health and disease, as well as in the development of a disease by analyzing, for instance, how genetic variants and dietary modulation incide on the cardio-metabolic risk. A deep knowledge of gene-diet interactions is thus crucial to allow us to understand the clinical applications of early diagnostic testing, namely allowing for prevention schemes. Currently, most efforts along these lines have been devoted to primary prevention. However, there is also a growing interest to discover how gene-dietary interactions may affect secondary prevention strategies to deal with CVDs in order to provide with proper nutritional counseling to those who already suffered from a cardiovascular event such as myocardial infarction.

On the other hand, just as the components of the diet are able to modify gene expression and metabolism, a number of effects of diet and nutrition are mediated by epigenetic mechanisms that alter the risk of cardio-metabolic diseases by leading to dysfunction of endothelial cells, abnormal blood flow, inflammation and atheroma formation [20].

Hence, one way to reinforce PM approaches to CVDs is by means of secondary prevention. For instance, after an acute coronary event, secondary prevention measures may be incorporated, including lifestyle modification, as well as pharmacological and nutritional therapy for myocardial protection and cardiovascular risk reduction [6]. Evidence based therapies have shown to provide evident clinical benefits, for instance in the case of acute coronary syndrome (ACS) [18]. There are a number of short and long terms risks after suffering ACS. For this reason, a number of interventions to reduce complications after myocardial lesion must be implemented (cardiac protection), but also to diminish recurrent acute coronary events (vascular protection) and to prevent cardiac-related mortality [6, 16].

Prevention of thrombosis of the atherosclerotic plaque by means of anti-platelet agents is the central therapeutic strategy for the treatment of a patient with a recent ACS, especially when patients have been subject to percutaneous intervention such as stent placement. Some evidence-based recommendations for the treatment of thrombosis are the low dose (around 81 mg/day) administration of aspirin as well as 90 mg/day of ticagrelor, a P2Y12 inhibitor, to patients on the first year after ACS. 10 mg/day of prasugrel or 75 mg/day of clopidogrel to patients who have received a coronary stent in the last

12 months or to patients with a very high risk of recurrent cardiovascular events is also recommended [6]. Cardiac rehabilitation have shown to improve on the symptoms of cardiac insufficiency and survival. The Canadian Cardiovascular Society recommends that patients that retain symptoms after opportune medical treatment with a QRS duration over 130 ms, and an ejection fraction < 35 % must be considered for cardiac rehabilitation [6, 14].
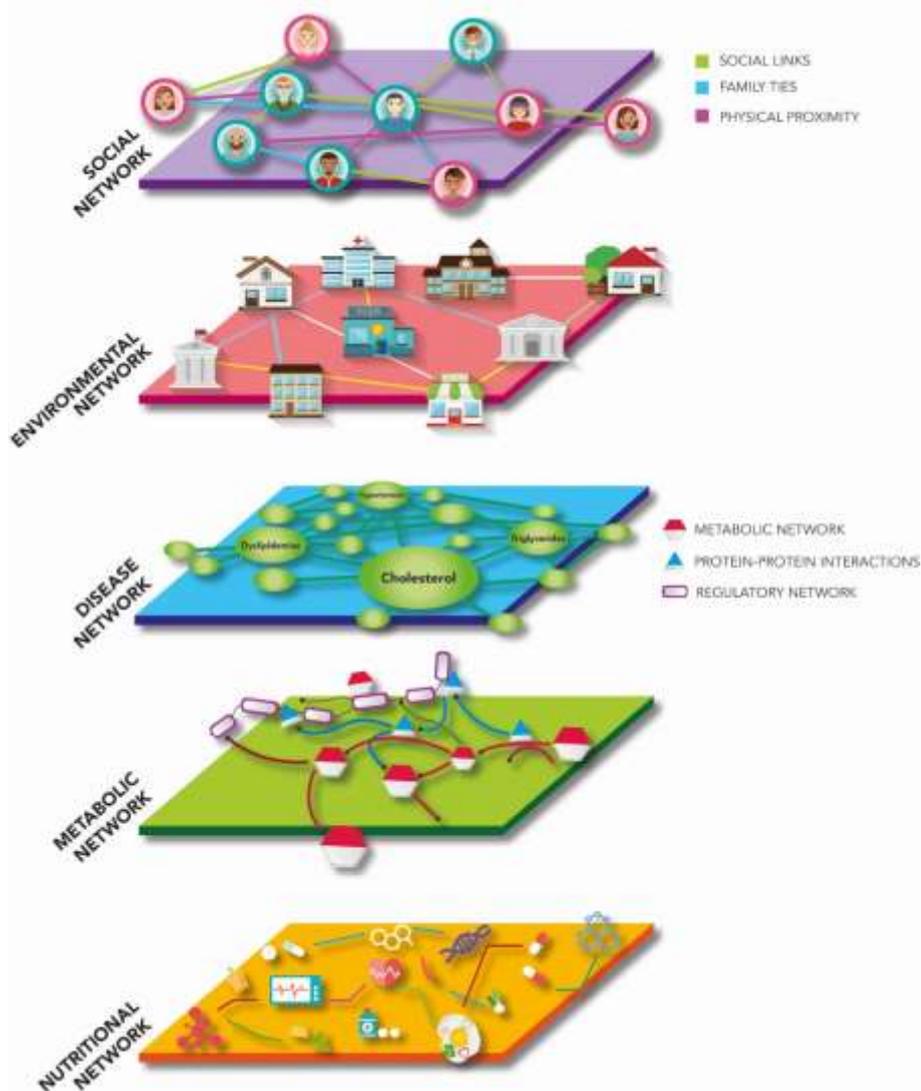
Fig: 1. The Precision Medicine approach to secondary prevention of cardiovascular diseases integrates information coming from several layers of information.

....

CVD risk reduction strategies in secondary prevention also include discontinuing tobacco consumption, controlling arterial pressure, glycaemia and dyslipidaemia; but also changes in eating habits, weight control and the promotion of physical activity [6, 14]. The smoking habit, for instance, is associated with accelerated atherosclerosis and the onset of acute coronary events. A recent meta-analysis shown that persistent smokers present a 20% increase in mortality in the 4 to 8 years after myocardial infarction. Depression diagnosis and treatment is also important since it is known that this mental disease is an important trigger for relapse into tobacco consumption. In the case of post-infarction patients, the same analysis shown that around 60-70% of patients are still showing strong signs of depression for 1 to 4 months after acute myocardial infarction [6].

Hyperglycaemia in ACS patients is associated with additional mortality relative to medium glucose blood levels in the 24 h period around early hospitalization. For this reason arterial pressure control for most patients must be targeted to <140/90mmHg but these levels must be adapted to <130/80mmHg in the case of diabetics [6]. In the case of atherosclerosis, it is frequently the first

manifestation of coronary arterial disease and the event that identifies the need for secondary prevention strategies. One of such strategies can be, for instance, the prescription of a low fat dietary regime (up to 20 % of the total caloric count) in order to diminish the levels of cholesterol and triglycerides. This regime should include dietary fiber (fruits, vegetables and integral cereals), as well as Omega 3 compounds (fish, fish oil, nuts, chia and flaxseed) [10, 15, 18]. A 3 g/day dose of either EPA or DHA (both rich in Omega 3) may improve upon several risk factors of CVDs [17, 18]. On the other hand, statin treatment (say 80 mg of atorvastatin) is quite efficient to reduce cholesterol and triglycerides levels. Unfortunately the cost of this treatment precludes a high percentage of the population at risk from using it so that only about 10 % of the patients reach the desired levels within one year [6, 15, and 19].

Current knowledge about the actual impact of nutritional risk on CVD patients is rather limited. Only a few studies focused on involuntary weight loss or in the detection of nutritional risk during the course of treatment for CVDs exist. Involuntary weight loss is clinically important to evaluate nutritional risk and it is also a relevant parameter for outcome prognostics. As an integral PM management of CVDs, it would be desirable to involve a clinical nutrition specialist in the attention of patients undergoing a cardiovascular rehabilitation program, in particular to support nutritional therapeutics and follow up. Surgical treatments carry out the largest load of nutritional risk, followed by percutaneous coronary interventions. The rise in nutritional risk incides negatively in the potential for recovery and in the quality of life. According to the reproducibility for clinical suppliance in the 2002 Nutritional Risk Screening (NRS-2002), patients with CVDs must be examined 2 to 4 times a year, with additional reevaluation in the case of acute disease due to invasive treatment [9].

Between 25 % and 57 % of the US population and more than a billion persons in the world have either insufficient (20 to 29, 9 ng/ml) or frankly defficient (less than 20 ng/ml) vitamin D concentration levels [12]. Low concentration of 25-hydroxy vitamin D have been associated with CVDs in a large number of observational studies. This association may be the result of dietary unbalance and low levels of solar exposition manifest via a biologically mediated mechanism in which low vitamin D concentrations led to a rise in the risk for cardiovascular events, hypertension, diabetes, depression and to higher levels of A1C haemoglobin, C-reactive protein and parathyroid hormone (PTH). One study in the American Journal of Epidemiology reports that the association between vitamin D levels and cardiovascular risk may be mediated by PTH levels [11]. A recent review suggests that higher PTH levels are associated with higher risk for CVDs, which may imply that there is a chance that by correcting vitamin D deficiency, the hyper risk of CVDs will be reduced via diminished PTH concentration levels that anticorrelate with vitamin D levels.

 Hyperparathyroidism has been proposed as a mechanism by which vitamin D deficiency may mediate cardiovascular events since it can promote cardiac hypertrophy, vascular remodeling and inflammation. The authors also highlight that this association was stronger in patients with diabetes, chronic kidney failure and albuminuria [12]. It is known that an eating plan based on the Mediterranean diet, with proper quantities of diet fiber (mainly of vegetal origins), vitamin D, vitamins of the B complex and Omega 3 will not only help to diminish the risk for CVD and its complications, but also the risk for cognitive diseases such as Alzheimer's [13, 19]. In this regard, aside from aging, a number of modifiable cardiovascular disease risk factors (hypertension, obesity and high homocystein levels) have been associated with dementia risk. Vitamin blood levels may be influenced by environmental, metabolic and genetic factors. However, hyperhomocysteinemia, hypertension and diabetes (all known associates with the risk of dementia) may be modified with diet changes [13, 20].

Currently, most CVD patients are discharged upon 48 to 72 hours after hospital entrance, which gives scarce time for nutritional education [6], for this reason, it is proposed that after an acute event, patients receive individualized nutritional and prevention counseling, proper for their age, gender and mental capabilities, in order that they may regain quality of life, and to keep or maintain their functional capacities. They may also receive support on how to overtake the basic components of cardiac rehabilitation as soon as possible and whenever possible this support strategies should also be communicated to their relatives and caretakers in educational sessions, home visits and telephone follow up calls.

Quite often, dietary information as presented by the treating physician has a rather vague, rutinary character. For this reason, it is suggested that the alimentary plan should be handled by a nutrition specialist to enhance adherence [9, 14, and 15]. By conforming multidisciplinary teams integrating psychological and nutritional support as well as secondary prevention strategies, precision cardiology will allow for better individualized therapies or preventive interventions in order that CVD patients reach a better control of their treatment with obvious benefits for their health.

REFERENCES

[1] Pitt GS. Cardiovascular precision medicine: hope or hype? European Heart Journal, 2015; ehv226.

[2] University Claude Bernard Lyon, France. The precision cardiology medicine platform: Integrated solutions for cardiac diseases. A unique European approach, 2015. http://www.biovision.org/pdf/projects/HCL.pdf

[3] Goldstein S. Precision medicine in cardiology, Cardiology News Digital Network, 2016 http://www.ecardiologynews.com/views/heart-of-the-matter/blog/precision-medicine-in-cardiology/3bf1a1106efda11fcad3afc6a03bcb4e.html

[4] Pepine C J. Precision medicine may change management of CVD for cardiologists, patients, Cardiology Today, 2016. http://www.healio.com/cardiology/practice-management/news/print/cardiology-today/%7B7dfcf99c-bd7b-4bce-91ce-8cc77f1ede02%7D/precision-medicine-may-change-management-of-cvd-for-cardiologists-patients

[5] Squassina A, Manchia M, Manolopoulos VG, et al. Realities and expectations of pharmacogenomics and personalized medicine: impact of translating genetic knowledge into clinical practice. Pharmacogenomics. 2010;11(8), 1149-1167.

[6] Fitchett DH, Goodman SG, Leiter LA, et al. Secondary Prevention Beyond Hospital Discharge for ACS: Evidence-based Recommendations. Can J Cardiol. 2016;32(7 Suppl):S15-34.

[7] Antman EM, Loscalzo J. Precision medicine in cardiology. Nat Rev Cardiol. 2016;13(10):591-602.

[8] Shah SH, Arnett D, Houser SR, et al. Opportunities for the Cardiovascular Community in the Precision Medicine Initiative. Circulation. 2016;133(2):226-31.

[9] Boban M, Laviano A, Persic V, et al. Characteristics of NRS-2002 Nutritional Risk Screening in patients hospitalized for secondary cardiovascular prevention and rehabilitation. J Am Coll Nutr. 2014;33(6):466-73.

[10] Li S, Flint A, Pai JK, et al. Low carbohydrate diet from plant or animal sources and mortality among myocardial infarction survivors. J Am Heart Assoc. 2014;3(5):e001169.

[11] Schneider AL, Michos ED. The association of low vitamin D with cardiovascular disease--getting at the "heart and soul" of the relationship. Am J Epidemiol. 2014;179(11):1288-90.

[12] Welles CC, Whooley MA, Karumanchi SA, et al. Vitamin D deficiency and cardiovascular events in patients with coronary heart disease: data from the Heart and Soul Study. Am J Epidemiol. 2014;179(11):1279-87.

[13] Andreeva VA, Kesse-Guyot E, Barberger-Gateau P, et al. Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial. Am J Clin Nutr. 2011;94(1):278-86.

[14] Piepoli MF, Corrà U, Benzer W, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil. 2010;17(1):1-17.

[15] Martínez S, Zegers Y, Stockins B, et al. Evaluación de una maniobra nutricional tendiente a reducir los niveles de colesterol en pacientes portadores de enfermedad coronaria en el sistema público de salud chileno. Revista médica de Chile. 2014;132(12), 1457-65.

[16] Ergin A, Muntner P, Sherwin R, et al. Secular trends in cardiovascular disease mortality, incidence, and case fatality rates in adults in the United States. Am J Med. 2004; 117(4), 219-227.

[17] Breslow JL. n-3 fatty acids and cardiovascular disease. Am J Clin Nutr. 2006;83(6 Suppl):1477S-1482S.

[18] Hooper L, Griffiths E, Abrahams B, et al. Dietetic guidelines: diet in secondary prevention of cardiovascular disease (first update, June 2003). J Hum Nutr Diet. 2004;17(4):337-49.

[19] Trichopoulou A, Vasilopoulou E, Lagiou A. Mediterranean diet and coronary heart disease: are antioxidants critical? Nutr Rev. 1999;57(8):253-5.

[20] Ferguson JF, Allayee H, Gerszten RE, et al. Nutrigenomics, the Microbiome, and Gene-Environment Interactions: New Directions in Cardiovascular Disease Research, Prevention, and Treatment: A Scientific Statement From the American Heart Association. Circ Cardiovasc Genet. 2016;9(3):291-313.