Nutritional ingredients for risk reduction in cardiovascular disease

ESC Congress London 2015

DSM Satellite Symposium | Program of events
31st August 2015
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Nutritional ingredients for risk reduction in cardiovascular disease

Foreword

Introduction
Manfred Eggersdorfer, University Groningen and DSM, Switzerland
Rob Winwood, DSM, Switzerland

Marine fatty acids for primary and secondary CVD risk reduction
Philip C. Calder, University of Southampton, UK

The potential of tomato extracts in primary prevention of CVD
Niamh O’Kennedy, University of Aberdeen, Scotland

Panel discussion
All

Key references
Nutritional ingredients for cardiovascular disease prevention

It is a matter of common knowledge that some dietary habits are protective against cardiovascular disease. Almost half a century ago, it was recognised that populations who ate large quantities of marine lipids e.g. the Inuit populations of Greenland and Northern Canada – and the Japanese, had much lower incidence of cardiovascular disease than would have been predicted. It was found in these populations, that their blood was particularly rich in the omega 3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In fact, EPA and DHA beneficially modify and reduce a broad range of cardiovascular disease risk factors, including blood triglycerides, blood pressure and inflammatory markers. Scientific evidence from a number of human studies demonstrates improved blood flow and reduced build up of atherosclerotic plaques.1

The Mediterranean diet also provides protection against cardiovascular disease. This low meat consumption diet is rich in fruit, nuts and vegetables, which in turn are rich in vitamins, fibre and polyphenolics. Scientific evaluations reveal that the humble tomato pervades much of Mediterranean cuisine. Based on these insights an efficacious product from a water soluble tomato extract was developed which improves blood flow and thereby present an effective alternative in the indulgent prevention of ischaemic strokes or deep vein thrombosis. The product demostated efficacy in a number of human studies and the European Food and Safety Authority (EFSA) granted an article 13.5 health “Helps maintain normal platelet aggregation, which contributes to healthy blood flow”. The product is safe and no side effects have been observed in the application to reduce the risk of cardiovascular diseases.

This satellite symposium will discuss the role of two nutritional ingredients in cardiovascular disease prevention: marine omega 3 fatty acids and water soluble tomato concentrates, both of which have approved, relevant, health claims from the European Food Safety Authority (EFSA). The session will be chaired by Dr Manfred Eggersdorfer, Professor for Healthy Ageing at Groningen University and Dr Rob Winwood, chair of the scientific committee of GOEDomega3, both senior scientists at DSM Nutritional Products based at Kaiseraugst in Switzerland. They will introduce two globally respected scientists in their field to present supporting clinical data for both ingredients. Dr Philip Calder, Professor of Nutritional Immunology at Southampton University and Dr Niamh O’Kennedy, Honorary Research Fellow at the Rowett Institute of Nutrition and Health, University of Aberdeen and member of the scientific advisory board to Provexis plc.

Through validation of progressive research, the symposium will demonstrate that nutrition related, natural solutions can play a vital role in an indulgent prevention of cardiovascular health concerns. We look forward to your attendance in this meeting.

Prof. Manfred Eggersdorfer
Dr Rob Winwood

1 Calder PC., European J Lipid Science Technology, 2014; 116; 1280-1300, DOI
Dr. Manfred Eggersdorfer is Senior Vice President for Nutrition Science & Advocacy at DSM Nutritional Products. He studied chemistry at the Technical University Munich and did his PhD in organic chemistry in the field of synthesis and characterization of unusual amino acid. He was post-doc at the Stanford-University, California working with Carl Djerassi on the isolation and characterization of sterols from marine origin.

Dr. Manfred Eggersdorfer is active as professor for Healthy Ageing at the Faculty of Medical Sciences at the University of Groningen. He is member of the Advisory Board of the Johns Hopkins Bloomberg School of Public Health, of the Fraunhofer-Gesellschaft Curatorial for Innovation, and affiliate of various other organizations. He is author of numerous publications in the fields of vitamins, innovation in nutritional ingredients, and renewable resources, reviewer for a variety of journals and associate editor of the “International Journal of Vitamin and Nutrition Research.”

Dr Rob Winwood, CSci FIFST, is the scientific communications manager at DSM Nutritional Products. He is currently chair of the scientific committee of the global trade organisation GOEDomega3. He is a specialist in lipid nutrition. He serves on the lipid group of EUFIC (European Food Information Council), the technical committee of the UK CRN (Council for Responsible Nutrition) and the lipids committee of the SCI (Society of Chemistry for Industry). He has held a series of senior technical and business development positions in various global food ingredient companies including Martek Biosciences, Archer Daniels Midland (ADM), Kelco International and Tunnel Avebe Starches.

Rob has a particular interest with regard to the effects of lipids and micronutrients on diseases associated with ageing. He has authored numerous scientific publications and has been an invited speaker at many conferences around the globe. During the last year, he has also made appearances on UK national radio and television.
Nutritional Solutions for Risk Reduction in CVD

DSM at ESC Congress London 2015

Introduction

- Cardiovascular disease was virtually unknown one hundred years ago
- Today, One in Four of us will die of it.

It is estimated that 90% of CVD is preventable through healthy eating, exercise, avoiding smoking and limiting alcohol intake.


Nutrients support cardiovascular health

- Targeted nutritional interventions can have a major effect in delaying or even preventing the onset of cardiovascular disease
- EFSA has granted Health Claims (13.1 or 13.5) for nutrients relating to cardiovascular health, with particular attention to maintaining good blood circulation and healthy blood lipid profiles.
- Specific attention is given to the mode of action of marine omega-3 fatty acids, Vitamin E, oat beta glucans, water-soluble tomato concentrates and olive polyphenols


Risk factors and potential treatment interventions

CVD is a multi-factorial disease. The efficacy of any nutritional intervention thus needs to be determined by a relevant basket of validated biomarkers

Examples of risk factors:
- Stress
- Smoking
- Obesity
- Sedentary lifestyle
- Dyslipidemia
- Hypertension
- Genetic predisposition
- Metabolic syndrome
- Poor diet (high salt/trans-fats)
- Infection

Proven treatment interventions:
- Exercise
- Reduce blood pressure
- Regularise blood lipid profile
- Reduce inflammation
- Reduce blood viscosity/clotting

Nutritional solutions to support a healthy heart

- 1. Prevents cardiovascular disease progression, which contributes to reduction in heart health risk
- 2. Omega-3 LC PUFA contributes to maintenance of normal blood pressure
- 3. Nuts and seeds contribute to maintenance of normal blood cholesterol

Summary: nutrients for your heart

Heart health benefits
- Blood lipid
- Oxidative stress
- Blood pressure
- Vascular function
- Heart function

Nutrients
- Omega-3 LC PUFA (EPA, DHA), oat beta glucan, olive polyphenols
- Vitamin C and E
- Omega-3 LC PUFA (EPA, DHA), CoQ10, vitamin D
- Omega-3 LC PUFA (EPA, DHA), vitamin E, water soluble tomato concentrate
- Omega-3 LC PUFA (EPA, DHA), CoQ10
In the UK, the prevalence of deaths from cardiovascular disease is 25% yet only 7% of adults aged 35 and over cite heart health as their main health concern. It is estimated that 90% of cardiovascular disease is preventable. Healthy nutrition is key to prevention by decreasing risk factors.

1. **Oat beta-glucan has been shown to lower/reduce blood cholesterol.**
   - High molecular weight oat beta-glucan is released from the food matrix during digestion and forms a viscous gel inside the small intestine, which is responsible for lowering LDL cholesterol.
   - 10% reduction in LDL cholesterol through the consumption of at least 3g/day of oat beta-glucan.

2. **Fruitflow® helps maintain normal platelet aggregation, which contributes to healthy blood flow.**
   - The activation of blood platelets leads to hemostasis and major arterial disorders.
   - 97% of individuals saw a reduction in platelet aggregation within 1.5 hours of consumption.

3. **DHA and EPA contribute to the maintenance of normal blood triglyceride concentrations.**
   - Studies show that populations who eat large quantities of marine lipids have much lower incidence of cardiovascular disease.

Scientifically substantiated evidence based on clinical studies.

FIND OUT MORE Visit stand C720 at the ESC Congress 2015.

Visit stand C720 at the ESC Congress 2015.
Dr Philip C. Calder
Professor at the Faculty of Medicine, University of Southampton, UK

Marine fatty acids for primary and secondary CVD risk reduction

Fatty fish, other seafood, fish oils and their concentrates, and some algal oils are sources of long chain, highly unsaturated omega-3 fatty acids (O3FA), sometimes referred to as marine O3FA. Functionally the most important O3FA appear to be eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), although roles for docosapentaenoic acid (DPAn-3) are emerging. Intakes of EPA and DHA are typically low and much below recommended intakes. Increased intakes are reflected in greater incorporation into blood lipid, blood cell and tissue (including heart) pools. Increased content of EPA and DHA can modify the structure of cell membranes and also the function of membrane proteins. EPA and DHA also modify the production of lipid mediators and through effects on cell signaling can alter patterns of gene expression. Through these actions EPA and DHA act to beneficially modify a number of risk factors for cardiovascular disease (CVD) including blood pressure, platelet reactivity and thrombosis, plasma triglyceride concentrations, vascular function, heart rate and heart rate variability, and inflammation. Consistent with these effects, epidemiological studies show an inverse association between EPA and DHA intake or status and risk of cardiovascular morbidity and mortality. Thus, there is a key role for O3FA in prevention and slowing progression of cardiovascular disease. Furthermore, some, but not all, supplementation studies with O3FA have demonstrated reduced mortality in at risk patients, such as post-myocardial infarction, indicating a therapeutic role. Meta-analyses based upon the inconsistent evidence base produce mixed findings. This will be further explored.
Marine fatty acids for primary and secondary CVD risk reduction

Philip C. Calder
Professor of Nutritional Immunology
University of Southampton
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Very long chain (“marine”) ω-3 polyunsaturated fatty acids

Eicosapentaenoic acid (EPA) 20:5ω-3

Docosapentaenoic acid (DPA) 22:5ω-3

Docosahexaenoic acid (DHA) 22:6ω-3

Fish intake is low
So ... typical intakes of marine ω-3 PUFAs are low

- Mean UK adult intake is about 0.2 g/day (but bimodal distribution since only 25% of the population consumes oily fish)
- Australian data (Meyer et al. (2003) Lipids 38, 391-398):
  - Mean daily intakes of EPA, DPA and DHA = 0.056, 0.026, and 0.106 g (Total = 0.188 g/d)
  - Median daily intakes of EPA, DPA and DHA = 0.006, 0.006, and 0.015 g DHA (Total = 0.029 g/d)

EPA, DPA and especially DHA are poorly synthesised in humans

-> dietary sources are important

Supplemental and prescription preparations of ω-3 PUFAs are available

<table>
<thead>
<tr>
<th>Supplemental &amp; Prescription Preparations</th>
<th>Chemical Form of w-3</th>
<th>Which w-3?</th>
<th>How Much w-3?</th>
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<tr>
<td>Fish oil</td>
<td>TAG</td>
<td>EPA and DHA</td>
<td>25% to 35%</td>
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<tr>
<td>Concentrated Fish Oil</td>
<td>TAG</td>
<td>EPA and DHA</td>
<td>+45% [up to 85%]</td>
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<td>Liver oil (e.g. cod liver oil)</td>
<td>TAG</td>
<td>EPA and DHA</td>
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<td>DHA</td>
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<td>A-DF oil</td>
<td>FL and TAG</td>
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<tr>
<td>Pharmaceutical preparations</td>
<td>Often E3</td>
<td>EPA and DHA</td>
<td>&gt;90%</td>
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</tbody>
</table>

Increasing EPA+DHA intake increases the EPA and DHA content of blood lipids, blood cells, and many tissues including liver, heart & skeletal muscle – effect is dose, time and tissue dependent
Omega-3 Fatty Acids in Cardiac Biopsies From Heart Transplantation Patients
Correlation With Erythrocytes and Response to Supplementation

- Heart transplant recipients
- 6 months
- 1 g EPA/DHA/day

Before
After
EPA
DHA

Prospective study of ω-3 PUFA intake and CHD outcomes:
The Nurse’s Health Study

- Total CHD (P < 0.001)
- Fatal CHD (P = 0.01)
- Non-fatal MI (P = 0.003)

Quintile of marine ω-3 fatty acid intake


Prospective study of ω-3 PUFA status and sudden death:
The Physician’s Health Study

Adjusted for age & smoking
Also adjusted for BMI, diabetes, hypertension, hypercholesterolemia, alcohol, exercise & family history of MI

Relative risk of sudden death
Quartile of whole blood marine ω-3 PUFAs


CVD: Classic and emerging risk factors

CLASSIC:
- Age
- Sex
- Family history (genetics)
- Smoking
- High alcohol consumption
- High blood pressure
- Diabetes
- Obesity
- Lack of physical activity

EMERGING:
- High serum triglycerides
- Elevated post-prandial lipaemia
- Endothelial dysfunction
- Tendency towards thrombosis
- Inflammation
- Cardiac rhythm
- Heart rate variability

High serum (LDL) cholesterol

= Improved by n-3 PUFAs
Marine ω-3 fatty acids most likely slow or limit atherosclerosis due to risk factor reduction ...... (= primary prevention)

...... But marine ω-3 fatty acids may also reduce risk of coronary events in people with advanced atherosclerosis (= secondary prevention)

N-3 Polynsaturated Fatty Acids in Coronary Heart Disease: A Meta-analysis of Randomized Controlled Trials
Heiner C. Bucher, MD, MPH, Peter Henggeler, MD, Christian Schneider, PhD, Gabriela Meier, MD

Considered: Eleven intervention trials with marine ω-3 PUFAs and with follow-up of at least 6 months (2 dietary studies; 9 supplementation studies)

N = 7835 in control group; 7951 in ω-3 PUFA group

Findings:
Risk of nonfatal MI = 0.8 (P = 0.16)
of fatal MI = 0.7 (P < 0.001)
of sudden death = 0.7 (P < 0.01)
of mortality = 0.8 (P < 0.001)

Effect of Different Antilipemic Agents and Diets on Mortality
A Systematic Review
Mark Stadel, MD; Matthias Fehr, MD; Bernd Lohmann, MD; Tracy C. Glass, MD; Heiner C. Bucher, MD, MPH
Arch. Int. Med. (2005) 165, 725-730

Considered: 97 intervention trials with lipid lowering strategies (incl. long chain ω-3 PUFAs) and with follow-up of at least 6 months (for ω-3 PUFAs considered 14 studies)

N = 10138 in control group; 10122 in ω-3 PUFA group

Findings for ω-3 PUFA:
Risk of cardiac mortality = 0.68 (P < 0.001)
of mortality = 0.77 (P = 0.01)

But new studies published from 2010 onwards have challenged this view (But these new studies have been criticised)

Summary

• Typical intakes of marine ω-3 fatty acids are low in most people, resulting in low status
• Intake and status of marine ω-3 fatty acids can be markedly increased through intake of oily fish or supplements
• EPA and DHA act through multiple molecular and cellular mechanisms to affect cell and tissue function
• There is robust evidence that long-term intake of marine ω-3 fatty acids reduces risk of cardiovascular disease – due to beneficial impacts on a range of risk factors – they have an important role in primary prevention
• There is strong evidence from studies conducted pre-2010 for a role in marine ω-3 fatty acids in secondary prevention – this role is challenged by some recent studies
The role of nutrition in lifestyle strategies for improving public cardiovascular health is constantly expanding. For many years, a ‘whole food’ approach, recommending a healthy dietary pattern including fruits, vegetables, whole grains, nuts and some oils, has been advocated. More recently an expansion in the development of specific functional food ingredients targeting CVD mechanisms has taken place. Increasing numbers of such food ingredients, which can often be added extraneously to any desired food matrix, are gaining acknowledgement of health benefits, via regulated health claims. CVD reduction is a target area of particular relevance for this approach, for two reasons: firstly, the increased, and partially preventable, burden of CVD-related events linked to obesity and T2DM, and secondly, the potential utility of a large number of bioactive compounds derived from foods. Representatives of bioactive lipids, peptides, phenolic derivatives and sulphur compounds have all been shown to have potential benefits in CVD prevention by targeting BP reduction, platelet function, endothelial function or cardiovascular inflammation.

While their potential for CVD reduction is exciting, many of these functional food ingredients are insufficiently studied to give consistent, clear evidence of efficacy against a chosen biomarker, and all lack the large scale, long term outcomes-based studies normally used by the medical profession to judge clinical benefit. These limitations can result in withholding of health claim authorisation, as well as slow uptake of the ingredient in use. Water soluble tomato concentrate (WSTC) was awarded an authorised health claim by EFSA in 2009, on the basis of a set of mechanistic and intervention studies demonstrating consistent reduction of human platelet aggregability, resulting in benefits to blood flow. To show the clinical relevance of the measured alteration in platelet function, WSTC was compared directly to low dose (75mg) aspirin in healthy subjects. By examining similarities and differences in responses to the food and drug interventions, an attempt to benchmark the likely relevance of the functional ingredient was made. This approach is not a replacement for outcomes-based studies, but is informative and reduces the data gap. While developing a human study portfolio is not quick or easy, generation of comprehensive data for functional ingredients is essential if they are to realise their potential as dietary adjuncts for CVD reduction.
Lecture by Niamh O’Kennedy

**Nutritional components for the primary prevention of CVD**

**Current global public health focus**

- WHO target: 25% relative reduction in premature mortality from non-communicable diseases (NCD) by 2025.
- NCD - CVD, cancers, chronic respiratory diseases and diabetes – in many cases a preventable burden.
- Natural compounds that occur in plants can target physiological disease mechanisms relevant in particular to CVD.

**Natural plant compounds reported to affect cardiovascular health**

- Natural antioxidants
- Polyphenols
- Bioactive lipids
- Sulfur compounds

**Are natural compounds efficacious enough to be used in primary prevention?**

Evidence from epidemiology suggests **YES**

- High polyphenol
- High fibre
- High natural antioxidant
- Improved CVD health – lower risk of CVD-related events or related deaths
- High healthy fats
- High fruit / vegetable

**Advent of functional ingredients**

**Functional ingredients** - an expanding food sector – seek to simplify achieving meaningful intake of naturally occurring bioactives.

As their use expands, health claims legislation has been introduced by EFSA to protect the consumer from unsubstantiated claims.

- Polyphenols (cocoa)
- Stannol esters
- Tomato extract

**Focus on tomato extract – an example of a functional ingredient approved for use in cardiovascular health**

To achieve an approved health claim, functional ingredients are required to use human studies to show consistent effects on validated biomarkers of disease.

- Tomato extract (Fruitflow™) has shown –
  - Mechanism of action
  - Onset of effect (acute)
  - Dose response (acute)
  - Extent of effect (acute)
  - Chronic effect
  - Effects in different matrices
Lecture by Niamh O’Kennedy

Biomarker reduction vs outcomes data

No functional ingredient has outcomes data similar to that obtained in drugs trials.

This makes it difficult to judge the true benefit of reductions in disease biomarkers.

As an interim solution, it can be useful to compare effects of the dietary component directly with those of a drug with the same physiological target.

Fruitflow (150mg) compared to low dose (75mg) aspirin (ASA).

Preliminary comparison – proteomic study

As a preliminary investigation, a proteomic study was carried out, comparing effects of a maximum theoretical plasma concentration of FF (150mg dose) or ASA (75mg dose) on the platelet proteome before and after stimulation with collagen agonist.

Aspirin Fruitflow

14 11 2

Both treatments affected proteins associated with platelet structure, platelet coagulation, platelet membrane trafficking and platelet secretion - actin-binding proteins, fibrinogen beta chain 5, Ras-related proteins, and HSP90s.

Conclusions and progression to comparison in an intervention study

At the maximum theoretical dose - AA and FF affect the platelet proteome similarly, with many similar actions, although AA appears to have stronger effects with more significant interactions.

Does this hold up ex vivo? A human intervention study was carried out to investigate.

Study protocol

Normal healthy subjects without CVD, but falling within the age range for which a dietary antioxidant might be expected to give benefit. FF (150mg) was compared to low dose aspirin (75mg) as an acute (one dose) and as a chronic (7-day) treatment in a crossover study.

Overall comparison of FF and ASA in healthy subjects

Overall results shown for platelet aggregation, TXA2 generation and overall primary haemostasis show that FF effects ex vivo are similar to those for a single dose of ASA, and about one-third those achieved by daily ASA.

Subgroups with different responses in the population

Overall, results seem similar to those predicted by the proteomics. But looking deeper, some subsets can be seen in the subject group.

Even after 7 days of 75mg ASA, some subjects - 6% of the study population - did not respond at all, while 19% had a less than average response. This group do not metabolise ASA well.

However for 18% of the study population, chronic ASA more than tripled the TTC. This group must metabolise ASA well, and probably reflects the changes seen in the proteomics study.

Fruitflow shows less extreme on both sides of the distribution. The majority experience up to 2-fold increase in TTC. Metabolism is not so polarised.

Summary

There is clear potential for natural ingredients to be used in a functional way to confer health benefits and possibly help in primary prevention.

Lack of outcomes data makes it difficult for clinicians to appreciate whether the scale of effects observed is likely to be as useful as for drug interventions.

Studies comparing natural compounds to drugs can be useful in highlighting similarities and differences which can help to benchmark the effects.
Key references


8. European Food Safety Authority (EFSA), Scientific Opinion of the Panel on Dietetic Priducts, Nutrition and Allergies on a request from Provexis Natural Products Limited on Water-soluble tomato concentrate (WSTC I and II) and platelet aggregation. EFSA Journal 2009, 1101, 1-15.

