Can red yeast rice & olive extract improve lipid profile and cardiovascular risk in metabolic syndrome?

A double blind randomized controlled trial

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Introduction
• Introduction
• Aim
• Material & methods
  - Study design
  - Biomarkers of metabolic stress
  - Biomarkers of oxidative stress
• Results
• Discussion
• Conclusion
# Introduction

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin resistance</td>
<td>IGT, IFG, T2DM, or lowered insulin sensitivity* plus any 2 of the following</td>
<td>None, but any 3 of the following 5 features</td>
<td>None</td>
</tr>
<tr>
<td>Body weight</td>
<td>Men: waist-to-hip ratio &gt;0.90; women: waist-to-hip ratio &gt;0.85 and/or BMI &gt;30 kg/m²</td>
<td>WC ≥102 cm in men or ≥88 cm in women†</td>
<td>Increased WC (population specific) plus any 2 of the following</td>
</tr>
<tr>
<td>Lipid</td>
<td>TG ≥150 mg/dL and/or HDL-C &lt;35 mg/dL in men or &lt;39 mg/dL in women</td>
<td>TG ≥150 mg/dL</td>
<td>TG ≥150 mg/dL or on TG Rx</td>
</tr>
<tr>
<td></td>
<td>HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
<td></td>
<td>HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women or on HDL-C Rx</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥140/90 mm Hg</td>
<td>≥130/85 mm Hg</td>
<td>≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx</td>
</tr>
<tr>
<td>Glucose</td>
<td>IGT, IFG, or T2DM</td>
<td>&gt;110 mg/dL (includes diabetes)‡</td>
<td>≥100 mg/dL (includes diabetes)</td>
</tr>
</tbody>
</table>

T2DM indicates type 2 diabetes mellitus; WC, waist circumference; TG, triglycerides.
Introduction
• **STATINS**

→ HMGCoA-reductase inhibitors
Double blind placebo controlled randomized trial to study the efficacy of red yeast rice (RYR)– olive fruit extract on

1. LDL and oxidative stress
2. serum lipid parameters, blood pressure, cardiovascular risk, side effects
• Introduction
• Aim
• **Material & methods**
  - Study design
  - Biomarkers of metabolic stress
  - Biomarkers of oxidative stress
• Results
• Discussion
• Conclusion
Material & Methods
Study design

Double blind Placebo-controlled
N=50

Metabolic syndrome:
NCEP ATP III +
LDL > 160 mg/dL
8 weeks

RYR-olive
N=26

Placebo
N=24

• Biomarkers of metabolic syndrome
• Biomarkers of oxidative stress
### Baseline characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n = 26)</th>
<th>Control (n = 24)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (SD)</strong></td>
<td>53.6 (8.4)</td>
<td>49.9 (13.3)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Female: 17</td>
<td>Female: 13</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Male: 9</td>
<td>Male: 11</td>
<td></td>
</tr>
<tr>
<td><strong>Waist circumference (cm)</strong></td>
<td>96.8 (10.2)</td>
<td>96.7 (10.4)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>27.8 (3.2)</td>
<td>27.46 (3.5)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Mean systolic blood pressure (mmHg)</strong></td>
<td>136.2 (14.2)</td>
<td>139.0 (10.4)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Mean diastolic blood pressure (mmHg)</strong></td>
<td>84.0 (7.8)</td>
<td>88.9 (9.2)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Mean total Cholesterol (mg/dL)</strong></td>
<td>247.5 (38.1)</td>
<td>251.2 (39.2)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Mean HDL (mg/dL)</strong></td>
<td>56.3 (14.3)</td>
<td>53.5 (13.9)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Mean LDL (mg/dL)</strong></td>
<td>164.3 (32.2)</td>
<td>171.50 (40.9)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Mean Triglycerides (mg/dL)</strong></td>
<td>134.5 (57.9)</td>
<td>132.7 (49.5)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Mean apoA1 (mg/dL)</strong></td>
<td>162.2 (39.5)</td>
<td>157.3 (30.6)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Mean apoB (mg/dL)</strong></td>
<td>115.5 (25.1)</td>
<td>119.3 (22.1)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Mean glucose (mmol/mol)</strong></td>
<td>89.6 (10.8)</td>
<td>88.1 (13.9)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Mean HbA1c (mg/dL)</strong></td>
<td>35.3 (3.2)</td>
<td>35.9 (6.4)</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Mean oxLDL (U/L)</strong></td>
<td>80.8 (34.5)</td>
<td>69.1 (17.7)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>On hypertension medication</strong></td>
<td>8/26</td>
<td>5/24</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td>1/26</td>
<td>3/24</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Mean level of perceived stress (scale 1–10)</strong></td>
<td>4.9 (26)</td>
<td>5.5 (2.0)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Meat consumption ≥ 5x/week</strong></td>
<td>8/26</td>
<td>7/24</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Vegetarian</strong></td>
<td>2/26</td>
<td>3/24</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Daily alcohol consumption</strong></td>
<td>14/26</td>
<td>10/24</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Menopausal status in women</strong></td>
<td>11/17</td>
<td>6/13</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Mean weight</strong></td>
<td>81.6 (12.8)</td>
<td>78.4 (10.7)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*Independent samples t-test, chi²-test or Fisher’s exact test.
Values in italics are statistically significant.
• Clinical parameters
  • Waist circumference
  • BMI
  • Blood pressure

• Biochemical parameters
  • Total Cholesterol
  • LDL
  • HDL
  • apoA1
  • apoB
  • Triglycerides
  • HbA1c

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Material & Methods
Study design

- **Parameters of oxidative stress**
  - Oxidised LDL (OxLDL)
  - Malondialdehyde (MDA)
  - Lipoprotein-associated phospholipase A₂ (Lp-PLA₂)

“High blood pressure, high cholesterol, high blood sugar, high waist circumference... getting high is no fun at my age!”
Material & Methods
Biomarkers of oxidative stress

MDA

- Oxidative degradation PUFA
- Plasma

\[ \lambda_{(ex)} = 532 \text{ nm} \]
\[ \lambda_{(em)} = 553 \text{ nm} \]
**Material & Methods**

**Biomarkers of oxidative stress**

**OxLDL**
- Plasma OxLDL ELISA (Mercodia)

**Lp-PLA₂**
- Plasma Lp-PLA₂ activity (PLAC-test)
Red yeast rice (RYP)

• Asia - traditional medicine
  - used in food as food colorant, flavour enhancer

• Fermentation of rice by Monascus purpureus:
  secondary metabolites: monacolins
Red yeast rice (RYS)

- 10 mg monacolin K
  → Inhibition HMG-CoA reductase
  → 2 forms

**Material & Methods**

RYS-olive fruit extract

**BIOLOGICAL ACTIVITY**

lovastatin
Olive fruit extract

- Main polyphenolic constituents:

  → Antioxidative activity
  → ↓ oxidation of LDL

- 10 mg hydroxytyrosol

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Material & Methods
RYR-olive fruit extract

Olive fruit extract

- ↓ oxidation of LDL

| Art.13 (1) | Olive oil polyphenols | Olive oil polyphenols contribute to the protection of blood lipids from oxidative stress | The claim may be used only for olive oil which contains at least 5 mg of hydroxytyrosol and its derivatives (e.g. oleuropein complex and tyrosol) per 20 g of olive oil. In order to bear the claim information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 20 g of olive oil. | protection of LDL particles from oxidative damage |

EFSA, EFSA Journal, 9, 2033 (2011)
Material & Methods
RYR-olive fruit extract

- ≠ Randomised Controlled Trials
  - 1 RCT, cross-over, multicenter, 3 weeks (200 men)
    25 ml/day of olive oil:

  - Quantified on main polyphenols
    *LOW PC:* 2.7 mg/kg polyphenols
               no HO-tyrosol
    *MEDIUM PC:* 164 mg/kg polyphenols
                  28.5 mg/kg HO-tyrosol
    *HIGH PC:* 366 mg/kg polyphenols
                63.5 mg/kg HO-tyrosol

- Biomarkers of lipid peroxidation
- Dose-effect relationship

Weinbrenner et al., J Nutr, 134, 2314-2321 (2004);

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• **Dose-effect relationship**

LOW PC: 2.7 mg/kg polyphenols
no HO-tyrosol

MEDIUM PC: 164 mg/kg polyphenols
28.5 mg/kg HO-tyrosol

HIGH PC: 366 mg/kg polyphenols
63.5 mg/kg HO-tyrosol

↑ polyphenols, ↑ HO-tyrosol
↓ antioxidant activity
↓ Lipid peroxidation

Material & Methods
RYR-olive fruit extract
**Dose-effect relationship**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Change due to ROO</th>
<th>Change due to VOO</th>
<th>(P^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL composition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo B</td>
<td>2.4 ± 1.4</td>
<td>0.0 ± 0.0</td>
<td>0.185</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.5 ± 1.2</td>
<td>−1.0 ± 6.7</td>
<td>0.775</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>−5.6 ± 12.53</td>
<td>−7.3 ± 8.2</td>
<td>0.770</td>
</tr>
<tr>
<td>Homovanillic acid sulfate</td>
<td>3.3 ± 4.3</td>
<td>27.9 ± 9.3</td>
<td>0.049</td>
</tr>
<tr>
<td>Hydroxytyrosol sulfate</td>
<td>16.8 ± 12.4</td>
<td>50.8 ± 12.1</td>
<td>0.041</td>
</tr>
<tr>
<td>Tyrosol sulfate</td>
<td>5.3 ± 7.9</td>
<td>20.0 ± 6.9</td>
<td>0.039</td>
</tr>
<tr>
<td>Sum of the 3 phenols</td>
<td>11.1 ± 19.1</td>
<td>27.0 ± 8.8</td>
<td>0.075</td>
</tr>
<tr>
<td>LDL oxidation markers in plasma and serum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma oxLDL</td>
<td>−9 ± 6.4</td>
<td>−22 ± 1.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum conjugated dienes</td>
<td>−8.1 ± 7.1</td>
<td>−11.1 ± 7.2</td>
<td>0.799</td>
</tr>
<tr>
<td>Plasma hydroxy fatty acids</td>
<td>2.3 ± 3.2</td>
<td>−29.6 ± 4.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 Percentage change is the change, expressed as a percentage, from before to after the respective olive oil treatment, \(n = 36\).

2 \(P\) value is for olive oil ingestion differences between treatments using Student’s t-test for paired samples analysis.

**VOO (Virgin olive oil):**
629 mg/l polyphenols - 24,4 mg/l tyrosol; 63,5 mg/l hydroxytyrosol; 327,2 mg/l oleuropein derivatives

**ROO (Refined olive oil):**
0 mg/l polyphenols

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de la Torre-Carbot et al., J Nutr, 140, 501-508 (2010)
Material & Methods
Analysis of test product

HPLC-UV analysis of RYR – 10.82 ± 0.84 mg monacolins/caps
Material & Methods
Analysis of test product

HPLC-UV analysis of hydroxytyrosol – 9.32 ± 0.54 mg / caps
hydroxytyrosol

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  - Biomarkers of oxidative stress
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Table 1: Comparison between alterations in **biochemical parameters** in intervention and control group

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Placebo group</th>
<th>Difference</th>
<th>95% CI of difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Intervention</td>
<td>Baseline</td>
<td>Intervention</td>
<td>(absolute value and %)</td>
</tr>
<tr>
<td><strong>LDL (SD)</strong> mg/dL</td>
<td>164.3 (32.2)</td>
<td>122.6 (19.8)</td>
<td>170.7 (40.9)</td>
<td>171.5 (41.8)</td>
<td>-41.7 (-23.7%) (28.3)</td>
</tr>
<tr>
<td><strong>total CHOL (SD)</strong> mg/dL</td>
<td>247.5 (38.1)</td>
<td>204.0 (26.0)</td>
<td>251.2 (39.2)</td>
<td>255.1 (50.0)</td>
<td>-43.5 (-16.5%) (31.1)</td>
</tr>
<tr>
<td><strong>HDL (SD)</strong> mg/dL</td>
<td>56.3 (14.3)</td>
<td>58.0 (13.8)</td>
<td>53.5 (13.9)</td>
<td>54.3 (14.0)</td>
<td>1.6 (3.5%) (4.3)</td>
</tr>
<tr>
<td><strong>TG (SD)</strong> mg/dL</td>
<td>134.5 (57.9)</td>
<td>117.5 (53.9)</td>
<td>132.7 (49.5)</td>
<td>150.3 (84.4)</td>
<td>-16.1 (-8.7%) (37.4)</td>
</tr>
<tr>
<td><strong>apoA (SD)</strong> mg/dL</td>
<td>162.2 (39.5)</td>
<td>171.2 (5.8)</td>
<td>157.3 (30.6)</td>
<td>161.1 (31.0)</td>
<td>4.7 (2.9%) (9.4)</td>
</tr>
<tr>
<td><strong>apoB (SD)</strong> mg/dL</td>
<td>115.5 (25.1)</td>
<td>96.6 (16.5)</td>
<td>119.3 (22.1)</td>
<td>126.3 (5.4)</td>
<td>-19.0 (-14.7%) (18.3)</td>
</tr>
<tr>
<td><strong>HbA1c (SD)</strong> mmol/mol</td>
<td>35.3 (3.2)</td>
<td>36.1 (2.6)</td>
<td>35.9 (6.4)</td>
<td>36.7 (6.5)</td>
<td>0.9 (2.9%) (1.6)</td>
</tr>
</tbody>
</table>
Table 2: Comparison between alterations in clinical parameters in intervention and control group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intervention group</th>
<th>Placebo group</th>
<th>Diff Intervention group</th>
<th>Diff Placebo group</th>
<th>95% CI of difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (SD) cm</td>
<td>96.8 (10.2)</td>
<td>95.1 (15.0)</td>
<td>-1.7 (12.0)</td>
<td>0.7 (2.8)</td>
<td>-7.3; 2.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Systolic blood pressure (SD) mmHg</td>
<td>136.2 (14.2)</td>
<td>125.8 (10.2)</td>
<td>-10.4 (11.4)</td>
<td>-0.3 (6.3)</td>
<td>-4.3; -0.23</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (SD) mmHg</td>
<td>84.0 (7.8)</td>
<td>76.4 (15.4)</td>
<td>-7.6 (15.9)</td>
<td>-0.4 (5.5)</td>
<td>-3.4; -0.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Weight (SD) kg</td>
<td>81.6 (12.8)</td>
<td>81.2 (13.5)</td>
<td>-0.4 (1.64)</td>
<td>-0.1 (2.65)</td>
<td>-1.5; 0.98</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Plasma MDA-levels at baseline & after 8 weeks of treatment in RYR-olive treated & placebo groups.
Plasma OxLDL-levels at baseline & after 8 weeks of treatment in RYR-olive treated & placebo groups.

***: p<0.001 mean difference placebo-intervention groups.
Biomarkers of oxidative stress

- **Lp-PLA₂**

Plasma Lp-PLA₂-levels at baseline & after 8 weeks of treatment in RYR-olive treated & placebo groups.

***: p<0.001 mean difference placebo-intervention groups.

Correlation between the absolute difference in OxLDL & Lp-PLA2.
• Median CV risk in both groups: 2%

• Intervention group: 1-18%
  Control group: 1-46%

• After the intervention: lower risk in 8/26 in RYR-olive (mainly blood pressure)

  lower risk in 1/24
  higher risk in 2/24 in control group
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Discussion

RYR - olive (Monakolin K 10 mg; Hyroxytyrosol 10 mg) daily – 8 weeks

• Total cholesterol  down 17 %
• LDL down 24 %
• Triglyceride down 9 %
• Blood pressure down 7 % (10 mmHg) systolic
  9 % (7 mmHg) diastolic

• OxLDL down 20 %
• Lp-PLA₂ down 7 %
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>N</th>
<th>Dose</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heber et al., Am J Clin Nutr 1999</strong></td>
<td>RCT-DB, 12 w</td>
<td>Cholesterol-lowering effects of RYR compared to diet</td>
<td>83</td>
<td>2.4 g/dg RYR (~10mg MK)</td>
<td>Reduction of LDL, TC, TG</td>
<td>Significant reduction of TC, TG en LDL.</td>
</tr>
<tr>
<td><strong>Lin et al., Eur J Endocrinol 2005</strong></td>
<td>RCT DB, 8 w</td>
<td>Lipid lowering effects and safety of RYR</td>
<td>79</td>
<td>1.2 g/dg RYR (~11.5 mg MK)</td>
<td>LDL: -28% TC: -22% TG: -16% HDL: NS</td>
<td>Significant reduction of LDL, TC en TG. Well tolerated</td>
</tr>
<tr>
<td><strong>Tetsuo et al. 2008</strong></td>
<td>RCT DB, 8 w</td>
<td>Dose-effect study of RYR</td>
<td>60</td>
<td>100mg RYR (= 2 mg MK), 200mg RYR (= 4 mg MK)</td>
<td>100mg RYR: LDL: -17% TC: -9% 200mg RYR: LDL: -17% TC: -12%</td>
<td>100 mg RYR (2mg MK)/day: reduction of LDL en TC.</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Aim</td>
<td>N</td>
<td>Dose</td>
<td>Results</td>
<td>Conclusion</td>
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<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><em>Gheith et al., Ind J Nephrol 2008</em></td>
<td>Open label, 12 m</td>
<td>Efficacy and safety of RYR compared to fluvastatin in treatment of nephrotic dyslipidemia</td>
<td>72</td>
<td>0.6 g RYR 2x/day, 20 mg statin/day</td>
<td>TC fluva: -31%, TC RYR: -54% ↓Proteinuria</td>
<td>Safe and effective in treatment of nephrotic dyslipidemia</td>
</tr>
<tr>
<td><em>Liu et al., Am J Cardiol, 2008</em></td>
<td>RCT 4,5 j</td>
<td>Effect of XZK in secondary prevention of AMI</td>
<td>4870</td>
<td>0.3 g XZK (= 2.5 – 3.2 mg MK)</td>
<td>TC: -11%, LDL: -18% (8w)</td>
<td><strong>XZK: reduced cholesterol level, 30% coronary events and mortality</strong></td>
</tr>
<tr>
<td><em>Mitchell et al., J Clin Lipidol 2012</em></td>
<td>RCT DB, 12 m</td>
<td>Cholesterol lowering effects of nutritional drink with or without RYR</td>
<td>79</td>
<td>0.6 g/dg RGR (2.4 mg MK)</td>
<td>drink with RYR: at 8w, TC: -14%, at 8w, LDL: -8%</td>
<td>RYR containing drink lowers LDL en TC. Well tolerated.</td>
</tr>
</tbody>
</table>
### Discussion

#### Statin intolerant (SAM) patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Aim</th>
<th>N</th>
<th>Dose</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venero et al., Am J Cardiol, 2010</td>
<td>&gt; 4 w</td>
<td>Dose-effect study and tolerance of RYR</td>
<td>25</td>
<td>1,2 g/day RYR</td>
<td>TC: -15%</td>
<td>Mild reduction of TC and LDL. well-tolerated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LDL: -21%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>TGs: -6%</td>
<td></td>
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<td></td>
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<td></td>
<td>HDL: -0,5%</td>
<td></td>
</tr>
<tr>
<td>Becker et al., Ann Intern Med, 2009</td>
<td>RCT DB 24 w</td>
<td>Effectivity and tolerance</td>
<td>62</td>
<td>3,6 g/dg RYR (3,6 mg MK)</td>
<td>LDL: -21% vs placebo</td>
<td>Therapeutic option for patients with SAM</td>
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</tbody>
</table>
Discussion - side effects

- 20/26 in intervention group: no side effects
- 21/24 participants in placebo group: no side effects

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Intervention group (26)</th>
<th>Placebo group (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle ache</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

- Mild CK elevation (less than twice the cut off) was present in 4/26 vs 2/24.
Discussion - Challenges

- Treatment > 8 weeks
- > study population / statin intolerant patients
- Effect due to combination RYR-olive extract? synergistic,...??

→ Biomarkers of oxidative stress

- Quality: Batch control !!
  - monacolin K levels – monacolin K/lovastatin ratio
  - hydroxytyrosol levels
  - citrinin
• **Citrinin**?

  • Mycotoxin formed during fermentation of rice → may also be formed in stored grains & other plant food products (*beans, fruits, spoiled dairy products, herbs & spices, ...*)

  • Optimisation of RYR fermentation process: ↓↓ citrinin

  • Nephrotoxic?

  • Level of no concern for nephrotoxicity: < 0.2 µg/kg b.w.
    → EC Regulation 212/2014: max 2000 µg/kg RYR

    → Screening of citrinin in RYR of study: <2.5 µg/kg RYR

    → APB: screening RYR supplements on Belgian market: no significant contamination with citrinin
RYR - olive extract (Monakolin K 10 mg; Hyroxytyrosol 10 mg)
daily – 8 weeks

- Total cholesterol ↓ 17 %, LDL ↓ 24 %, Triglyceride ↓ 12 %
- Blood pressure ↓ 10 mmHg systolic ↓ 7 mmHg diastolic
- Anti-oxidative: OxLDL ↓ 20 %, Lp-PLA2 ↓ 7 %

- << long – term studies
  → 4.5 years – secondary prevention - ↓ coronary events/ mortality
  Liu et al.(2008)
- Well-tolerated → statin intollerant patients?
  → >> RCT in statin intollerant patients long-term
  → Case reports Vercelli et al., J Am Geriatr Soc (2006);
    Mueller PS, Ann Int med, (2006); Prasad et al.,
    Transplantation, (2002)
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Thank you for your attention