Β΄ ΠΡΟΠΑΙΔΕΥΤΙΚΗ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
ΙΠΠΟΚΡΑΤΕΙΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣ/ΝΙΚΗΣ
Διευθ. Καθηγητής Καραγιάννης Αστέριος

Πολυπαραγοντική αντιμετώπιση του μεταβολικού συνδρόμου

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Ορισμός μεταβολικού συνδρόμου

- **Κεντρική παχυσαρκία**
- **Δυσλιπιδαιμία**
- **Αρτηριακή υπέρταση**
- **Αντίσταση στην ινσουλίνη**

- **ΚΡΙΤΗΡΙΑ ΔΙΑΓΝΩΣΗΣ**
- National Cholesterol Education Program-Adult Treatment Panel-III (NCEP-ATP-III)
- International Diabetes Federation (IDF)
- American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI)
- World Health Organization (WHO)

Μεταβολικό σύνδρομο (WHO)

Clinical Measure	WHO (1998)
Insulin resistance	IGT, IFG, T2DM, or lowered insulin sensitivity* **plus any 2 of the following**
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m^2
Lipid	TG ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women
Blood pressure	≥140/90 mm Hg
Glucose	IGT, IFG, or T2DM
Other	Microalbuminuria

Alberti KG, Zimmet PZ. Diabet Med. 1998; 15(7): 539–53

Μεταβολικό σύνδρομο (NCEP-ATP-III)

3 or more of the following:

Risk Factor	Defining Level
Abdominal Obesity	Waist Circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/85 mmHg
Fasting glucose	≥110 mg/dL

NCEP ATP III. Circulation. 2002; 106(25): 3143–21

Μεταβολικό σύνδρομο (IDF)

Increased WC (population specific) **plus any 2 of the following**
TG ≥150 mg/dL or on TG Rx
HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
≥100 mg/dL (includes diabetes)

Alberti KG, Zimmet P, Shaw J. Lancet. 2005; 366(9491): 1059–62

Μεταβολικό σύνδρομο (AHA/NHLBI)

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical Cutpoints
Elevated waist circumference*†	≥102 cm (≥40 inches) in men ≥88 cm (≥35 inches) in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or On drug treatment for elevated triglycerides‡
Reduced HDL-C	<40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women or On drug treatment for reduced HDL-C‡
Elevated blood pressure	≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL or On drug treatment for elevated glucose

Grundy SM, Cleeman JI, Daniels SR, et al. Circulation. 2005; 112(17): 2735–52

Μεταβολικό σύνδρομο (JIS)

- IDF
- AHA/NHLBI
- World Heart Organization
- International Atherosclerosis Society (IAS)
- International Association for the Study of Obesity (IASO)

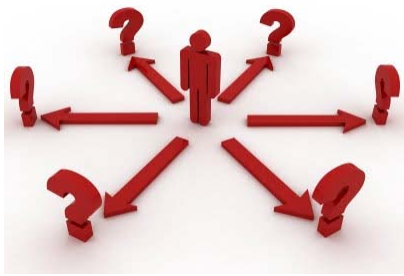
≥ 3 of the following

Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

Alberti KG, Eckel RH, Grundy SM, et al. Circulation. 2009; 120(16): 1640-5

Μεταβολικό σύνδρομο: ορισμός ?

- Μεγαλύτερο ποσοστό ασθενών με μεταβολικό σύνδρομο όταν χρησιμοποιήθηκαν τα κριτήρια JIS συγκριτικά με τους ορισμούς IDF, NCEP-ATP-III και AHA/NHLBI (45.7, 43.4, 24.5 και 26.3%)
- Ωστόσο, τα κριτήρια NCEP-ATP-III και AHA/NHLBI προέβλεπαν καλύτερα τον καρδιαγγειακό κίνδυνο (17.6, 18.3, 23.3 και 22.6%)



ΠΡΟΣΟΧΗ: έλεγχος κριτηρίων διάγνωσης

Athyros VG, Ganotakis ES, Tziomalos K …, Karagiannis A. Int J Cardiol. 2007;117(2):204-10
Athyros VG, Karagiannis A, Mikhailidis DP. Curr Med Res Opin. 2010;26(3):713-9

Μεταβολικό σύνδρομο και καρδιαγγειακός κίνδυνος

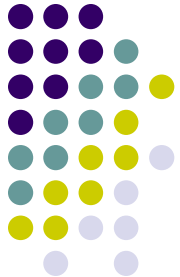
- Μεταβολικό σύνδρομο = αυξημένος κίνδυνος καρδιαγγειακής νόσου και τύπου 2 διαβήτη

- Ο κίνδυνος αυξάνει με τον αριθμό των χαρακτηριστικών του μεταβολικού συνδρόμου

- Μεταβολικό σύνδρομο = αυξημένος κίνδυνος ολικής + καρδιαγγειακής θνητότητας

Gami AS, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49:403-14
Mottillo S, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56:1113-32

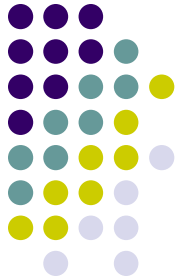
Μεταβολικό σύνδρομο και καρδιαγγειακός κίνδυνος



- Li J, Flammer AJ, Lennon RJ, Nelson RE, et al. Comparison of the Effect of the Metabolic Syndrome and Multiple Traditional Cardiovascular Risk Factors on Vascular Function. Mayo Clin Proc. **2012** Sep 11 [Epub ahead of print]

- "individuals with MetS have a **higher degree of endothelial dysfunction** (reactive hyperemia-induced vasodilation) and **inflammation** (hsCRP) compared with individuals with multiple CV risk factors and may therefore have an increased CV risk beyond the contributions of multiple traditional risk factors".

Μεταβολικό σύνδρομο και καρδιαγγειακός κίνδυνος

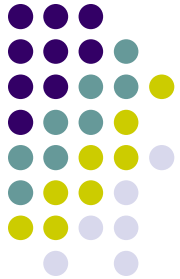


- Hanefeld M, Koehler C, Gallo S, Benke I, Ott P. Impact of the individual components of the metabolic syndrome and their different combinations on the prevalence of atherosclerotic vascular disease in type 2 diabetes: the Diabetes in Germany (DIG) study. Cardiovasc Diabetol. **2007**;6:13

- A population-based study with type 2 diabetes in Germany (n= **4020** unselected patients with type 2 diabetes aged 35 – 80 years)
- MetS: diabetes plus > or = 2 traits of the MetS by **AHA/NHBLI** definition
- AVD: history of myocardial infarction and/or coronary revascularization and/or stroke

- "Overall **MetS increases the risk of AVD in type 2 diabetes** and individual traits in some clusters with hypertension and low HDL-cholesterol may act synergistically as risk factors particularly in women"

Μεταβολικό σύνδρομο και παράγοντες καρδιαγγειακού κινδύνου



- WHR
- Δυσλειτουργία HDL
- sdLDL
- Μεταγευματική υπερτριγλυκεριδαιμία
- Lp (a)
- Ουρικό οξύ
- NAFLD
- Παράγοντες πήξης (PAI-1, ινωδογόνο)
- vit D
- Ενδοθηλιακή δυσλειτουργία
- Κυτοκίνες (CRP, ICAM-1, VCAM-1)
- Αδιποκίνες (λεπτίνη, αδιπονεκτίνη,TNF-a)
- Αρτηριακή σκληρία
- Νεφρική δυσλειτουργία, νεφρολιθίαση
- PCOS
- OSA

Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP. Curr Pharm Design In press

Μεταβολικό σύνδρομο και καρδιαγγειακός κίνδυνος: κλινικές μελέτες

- Athyros VG, Mikhailidis DP, ..., Kakafika AI, Elisaf M; **METS-GREECE** Collaborative Group. Prevalence of atherosclerotic vascular disease among subjects with the metabolic syndrome with or without diabetes mellitus: the METS-GREECE Multicentre Study. Curr Med Res Opin. **2004**;20:1691-1701

- A cross-sectional analysis of a representative sample of Greek adults (n = **4153**), men and women (49% and 51%, respectively), living in urban, semi-urban and rural areas (54%, 25% and 21%, respectively)

  The **NCEP-ATP III** definition of the MetSyn was used
- Prevalence of vascular disease (coronary heart disease/stroke/peripheral arterial disease):
- **29.4% MetS vs 9.6% without MetS** ($p < 0.0001$)
- 24.1% MetS without DM
- 25.4% DM without MetS
- 40.7% both MetS and DM

Αντιμετώπιση? Υπάρχει ανάγκη?

- Athyros VG, …, Papageorgiou AA, Papathanasiou A, Kakafika AI, Mikhailidis DP, Elisaf M; MetS-Greece Collaborative Group. Awareness, treatment and control of the metabolic syndrome and its components: a multicentre Greek study. Hellenic J Cardiol. **2005**;46:380-6.

- A cross-sectional analysis was made of a representative sample of Greek adults (**n=9669**, 49% men and 51% women), living in urban, semi-urban and rural areas (55%, 23% and 22%, respectively)

  NCEP-ATP III and IDF definitions for the MetS were used

- The age-standardised prevalence of the MetS in the general population was **24.5%** [95% CI 23.4-25.7%] (n=2369)
- Only one third of subjects were aware of the MetS component conditions, less than one quarter were on treatment, and very few (< or =10%) were controlled for MetS components
- Only 2% were treated for all component conditions and only 1% were controlled

Αντιμετώπιση? Αποτελεσματική

- Athyros VG, Mikhailidis DP, Liberopoulos EN, Kakafika AI, Karagiannis A, Papageorgiou AA, Tziomalos K, Ganotakis ES, Elisaf M. Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (**GREACE**). Nephrol Dial Transplant. **2007**;22(1):118-27

- Post hoc analysis of the **GREACE** Study
- CHD patients with MetS were divided into: Group A (n = 365) received lifestyle advice, target-driven treatment with statins (mainly atorvastatin) and treatment for hypertension and elevated glucose.

  Group B (n = 347) received the same except for statins
- Patients without MetS were divided into those who received treatment similar to Group A and Group B [Groups C (n = 504) and D (n = 384), respectively]
- All patients were followed for **3 years**
- "Among CHD patients, **those with MetS benefited more from statin treatment** than those without MetS. This benefit could be partially attributed **to favourable changes in e-GFR and SUA levels** probably induced by statin treatment"

Αντιμετώπιση? Ασφαλής

- Athyros VG, Tziomalos K,…, Karagiannis A, Mikhailidis DP; GREACE Study Collaborative Group. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet. **2010**;376:1916-22

- A post-hoc analysis of the **GREACE** study
- 437 patients with **moderately abnormal liver tests** at baseline, of which the 227 who were treated **with a statin** (mainly atorvastatin 24 mg per day) had **substantial improvement in liver tests** ($p<0.0001$) whereas 210 not treated with a statin had further increases of liver enzyme concentrations
- **68% relative CVD risk reduction** in patients with abnormal liver tests on statin compared with patients with abnormal liver tests who did not receive statin
- This cardiovascular disease benefit was greater than in patients with normal liver tests (39% relative risk reduction)
- Seven (<1%) of 880 participants who received a statin discontinued statin treatment because of liver-related adverse effects (transaminase > 3 the upper normal limit)

Πολυπαραγοντική αντιμετώπιση?

- Δίαιτα
- Άσκηση
- Διακοπή καπνίσματος
- Θεραπεία: δυσλιπιδαιμίας
  υπέρτασης
  διαβήτη
  παχυσαρκίας

Μεταβολικό σύνδρομο και δίαιτα

The Effect of Mediterranean Diet on Metabolic Syndrome and its Components

A Meta-Analysis of 50 Studies and 534,906 Individuals

Christina-Maria Kastorini, MSc,*† Haralampos J. Milionis, MD, PhD,†
Katherine Esposito, MD, PhD,‡ Dario Giugliano, MD, PhD,‡ John A. Goudevenos, MD, PhD,†
Demosthenes B. Panagiotakos, PhD*

Athens and Ioannina, Greece; and Naples, Italy

Objectives The aim of this study was to meta-analyze epidemiological studies and clinical trials that have assessed the effect of a Mediterranean diet on metabolic syndrome (MS) as well as its components.

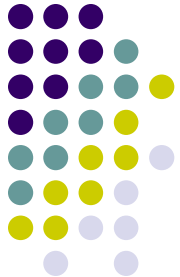
Background The Mediterranean diet has long been associated with low cardiovascular disease risk in adult population.

Methods The authors conducted a systematic review and random effects meta-analysis of epidemiological studies and randomized controlled trials, including English-language publications in PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials until April 30, 2010; 50 original research studies (35 clinical trials, 2 prospective and 13 cross-sectional), with 534,906 participants, were included in the analysis.

Results The combined effect of prospective studies and clinical trials showed that adherence to the Mediterranean diet was associated with reduced risk of MS (log hazard ratio: −0.69, 95% confidence interval [CI]: −1.24 to −1.16). Additionally, results from clinical studies (mean difference, 95% CI) revealed the protective role of the Mediterranean diet on components of MS, like waist circumference (−0.42 cm, 95% CI: −0.82 to −0.02), high-density lipoprotein cholesterol (1.17 mg/dl, 95% CI: 0.38 to 1.96), triglycerides (−6.14 mg/dl, 95% CI: −10.35 to −1.93), systolic (−2.35 mm Hg, 95% CI: −3.51 to −1.18) and diastolic blood pressure (−1.58 mm Hg, 95% CI: −2.02 to −1.13), and glucose (−3.89 mg/dl, 95% CI:−5.84 to −1.95), whereas results from epidemiological studies also confirmed those of clinical trials.

Conclusions These results are of considerable public health importance, because this dietary pattern can be easily adopted by all population groups and various cultures and cost-effectively serve for primary and secondary prevention of the MS and its individual components. (J Am Coll Cardiol 2011;57:1299–313)

Μεταβολικό σύνδρομο και άσκηση



- Dunkley AJ, Charles K, Gray LJ, et al. Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison **meta-analysis**. Diabetes Obes Metab. 2012 Jul;14:616-25

  "**lifestyle interventions were the most clinically effective**"

- Hwang CL, Wu YT, Chou CH. Effect of aerobic interval training on exercise capacity and metabolic risk factors in people with cardiometabolic disorders: **a meta-analysis**. J Cardiopulm Rehabil Prev. 2011;31:378-85

- Strasser B, Siebert U, Schobersberger W. Resistance training in the treatment of the metabolic syndrome: a systematic review and **meta-analysis** of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. Sports Med. 2010;40:397-415

  "Based on our meta-analysis, RT has a clinically and statistically significant effect on metabolic syndrome risk factors such as **obesity, HbA(1c) levels and systolic blood pressure**, and therefore should be recommended in the management of type 2 diabetes and metabolic disorders."

Μεταβολικό σύνδρομο και κάπνισμα

- Saxena AR, Seely EW. Smoking cessation and associated risk of metabolic syndrome in women. Womens Health (Lond Engl). 2012;8:367-9.

  “past smoking was associated with higher odds of metabolic syndrome, regardless of menopausal status”

- Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat distribution, and insulin resistance. Am J Clin Nutr. 2008;87:801-9.

  “**heavy smokers tend to have greater body weight** than do light smokers or nonsmokers, which likely reflects a clustering of risky behaviors (eg, low degree of physical activity, poor diet, and smoking) that is conducive to weight gain. Other factors, such as weight cycling, could also be involved.

  In addition, **smoking increases insulin resistance and is associated with central fat accumulation**. As a result, **smoking increases the risk of metabolic syndrome** and diabetes, and these factors increase risk of cardiovascular disease”

Κλινικές μελέτες πολυπαραγοντικής αντιμετώπισης μεταβολικού συνδρόμου

- Athyros VG, Mikhailidis DP, Papageorgiou AA, …, Karagiannis A, Kakafika AI, Tziomalos K, Elisaf M. Targeting vascular risk in patients with metabolic syndrome but without diabetes. Metabolism. **2005**;54:1065-74

➢ **Prospective, randomized, open-label**, intention-to-treat, and parallel study, with **300** nondiabetic patients **with MetS**, **free of CVD at baseline**, studied for a period of **12 months**. Age- and sex-matched subjects without MetS (n = 100) acted as controls

All patients received lifestyle advice and a stepwise-implemented drug treatment of hypertension, impaired fasting glucose, and obesity

Hypolipidemic treatment: atorvastatin, fenofibrate or both

- By the end of the study, 76% of the patients no longer had MetS, and 46% had only one diagnostic MetS factor
- 10-year- eCVD risk (PROCAM) risk for all patients with MetS at baseline was 14.6% and was reduced in the atorvastatin group to 6.4%, in the fenofibrate group to 9.2%, and in the combination group to 5.5% (P < .0001 for all vs baseline). The 10-year risks of the atorvastatin and combination groups were not different from that of the control group (5.0%)

Κλινικές μελέτες πολυπαραγοντικής αντιμετώπισης μεταβολικού συνδρόμου

- Athyros VG, …, Karagiannis A, …, Mikhailidis DP. Assessing the treatment effect in metabolic syndrome without perceptible diabetes (**ATTEMPT**): a prospective-randomized study in middle aged men and women. Curr Vasc Pharmacol. **2011**;9:647-57.

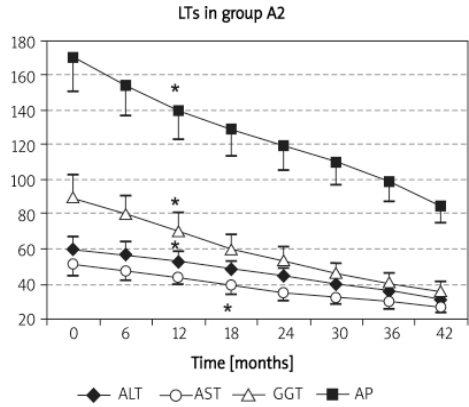
  This **prospective, randomized**, target driven study included **1,123 subjects** (512/611 men/women, aged 45-65 years) with metabolic syndrome (MetS) without diabetes or CVD referred to specialist outpatient clinics. Patients were randomized to two treatment groups: group A with low density lipoprotein cholesterol (**LDL-C) target of < 100 mg/dl** and group B with a target of **< 130 mg/dl**.

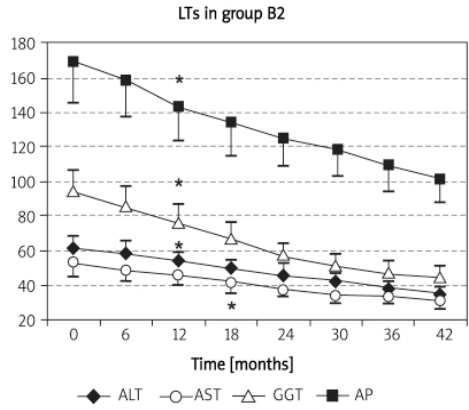
  Follow-up: **42 months**

- **Lifestyle intervention**
- **Atorvastatin** was used in both groups on top of optimal multifactorial treatment (quinapril, amlodipine, hydrochlorothiazide for **hypertension**, metformin for **impaired fasting glucose**, and orlistat for **obesity**).
- **e-CVD**: Framingham, the PROCAM and Reynold's equations.
- Reductions in e-CVD risk at **6 months** were > 50% in all patients, but were superior in group A and in women. Reductions were even greater **during the next 3-years** and were mainly attributed to changes in lipid profile.

Κλινικές μελέτες πολυπαραγοντικής αντιμετώπισης μεταβολικού συνδρόμου

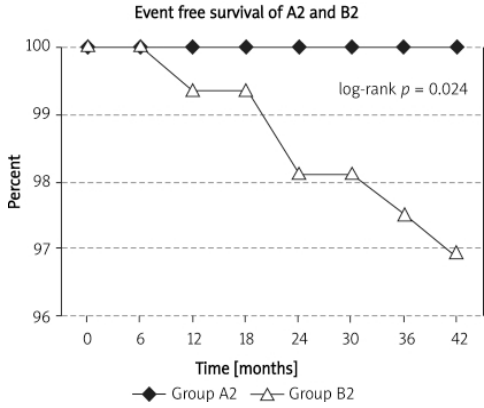
- Athyros VG, …, Tziomalos K,…, Karagiannis A, Mikhailidis DP. Safety and impact on cardiovascular events of long-term **multifactorial treatment** in patients with metabolic syndrome and abnormal liver function tests: a post hoc analysis of the randomised **ATTEMPT** study. Arch Med Sci. **2011**;7:796-805.
  - The **NAFLD** resolved during the 42-month treatment period in 86% of patients in group A (LDL-C target < 100 mg/dl) and in 74% of patients in group B (LDL-C target < 130 mg/dl)
  - In both groups nearly 90% of patients attained lipid goals





- Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP. Hyperuricaemia and non-alcoholic fatty liver disease (NAFLD): a relationship with implications for vascular risk? Curr Vasc Pharmacol. 2011;9:698-705

- Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP. Managing the combination of non-alcoholic fatty liver disease and metabolic syndrome. Expert Opin Pharmacother. 2012;13:287-8



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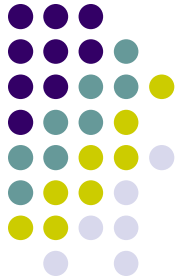
- Athyros VG, Karagiannis A, …,Tziomalos K, …, Mikhailidis DP; Assessing The Treatment Effect in Metabolic syndrome without Perceptible diabeTes (ATTEMPT) Collaborative Group. Association between the changes in renal function and serum uric acid levels during multifactorial intervention and clinical outcome in patients with metabolic syndrome. A post hoc analysis of the **ATTEMPT** study. Curr Med Res Opin. **2011**;27:1659-68.

  - Multifactorial intervention in patients with MetS without established CVD improved **renal function** and **reduced SUA levels**. These changes were more prominent in stage 3 CKD patients and might have contributed to the reduction in eCVD risk and clinical events.

- Katsiki N, Elisaf M. Multifactorial treatment for improvement of renal function and cardiovascular risk: an ATTEMPT for patients with metabolic syndrome and chronic kidney disease. Curr Med Res Opin. 2011;27:1669-72
- **CKD** (eGFR < 60 ml/min/1.73m^2) is regarded as a CVD risk factor by the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS) and the Canadian Cardiovascular Society [Reiner Z, et al. Eur Heart J 2011;32:1769-818; Genest J, et al. Can J Cardiol 2009;25:567-79]
- Athyros VG, Karagiannis A, …, Katsiki N, Tziomalos K, …, Kakafika A, Gossios TD, Mikhailidis DP. IMproving the imPlemEntation of cuRrent guidelines for the mAnagement of major coronary hearT disease rIsk factors by multifactorial interVEntion. The IMPERATIVE renal analysis. Arch Med Sci. 2011;7(6):984-92

Κλινικές μελέτες πολυπαραγοντικής αντιμετώπισης μεταβολικού συνδρόμου



- Athyros VG, …, Karagiannis A, Liberopoulos EN, Tziomalos K, Mikhailidis DP. Assessing the Treatment Effect in Metabolic Syndrome Without Perceptible Diabetes (ATTEMPT) Collaborative Group. Long-term impact of multifactorial treatment on new-onset diabetes and related cardiovascular events in metabolic syndrome: a post hoc **ATTEMPT** analysis. Angiology. **2012**;63:358-66

  - The **incidence of NOD** during the 42-month follow-up was **very low** 0.83/100 patient-years in patients with MetS
  - Older age, increased waist circumference and persistent MetS were determinants of NOD
  - **One CVD nonfatal** event occurred in the 28 patients with NOD

- Sattar N, Preiss D, Murray HM, et al. **Statins and risk of incident diabetes**: a collaborative meta-analysis of randomized statin trials. Lancet 2010;375:735-42
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Take home message

- Μεταβολικό σύνδρομο = κεντρική παχυσαρκία
  δυσλιπιδαιμία
  αρτηριακή υπέρταση
  αντίσταση στην ινσουλίνη

- Καλύτερο αποτέλεσμα = αντιμετώπιση όλων των παραγόντων καρδιαγγειακού κινδύνου

«ΟΛΙΣΤΙΚΗ ΙΑΤΡΙΚΗ»