Metabolic syndrome

MUDr. Yvona Pospíšilová
Department of Internal Medicine, Hematology and Oncology FN Brno and
Masaryk University Brno
pospisilova.yvona@fnbrno.cz
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Metabolic syndrome (MetSy)

- Reaven‘s syndrome
- Syndrome of insulin resistance
- Syndrome X

  - about 30 - 50 % of population
  - the main reason of death in developed countries

Metabolic syndrome

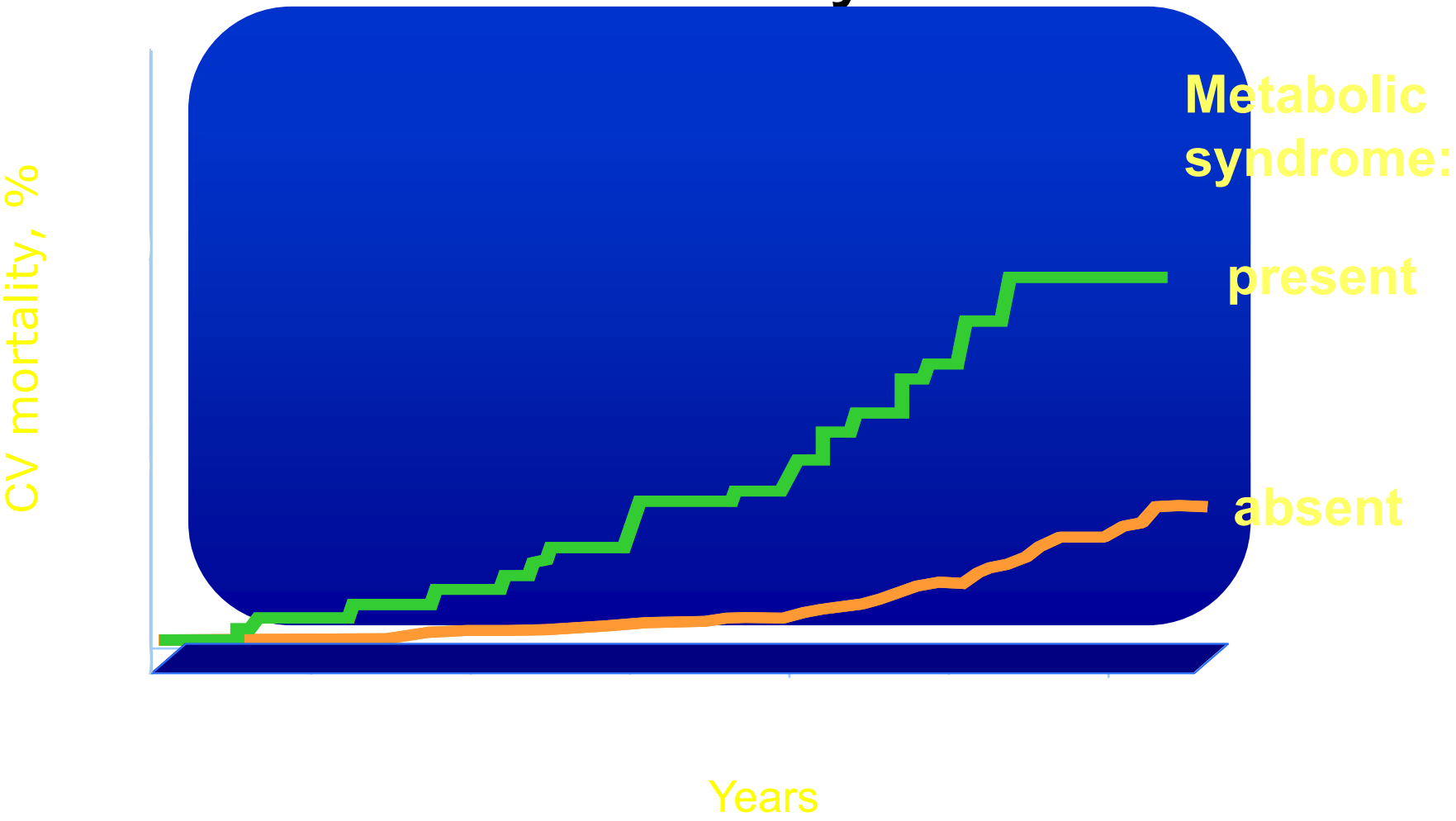
- Type 2 diabetes mellitus or impaired glucose tolerance or impaired fasting glucose
- Central (abdominal) obesity
- Arterial hypertension
- Dyslipidemia

Metabolic syndrome

- Metabolic syndrome occurs in people with increased risk of Type 2 DM and CVD

- Since there is a global epidemic of MetSy, an epidemic of Type 2 DM and CVD is also likely in the near future

Metabolic syndrome **3,5x** increases the risk of cardiovascular mortality



Lakka HM et al. *JAMA* 2002;288:2709-2716.

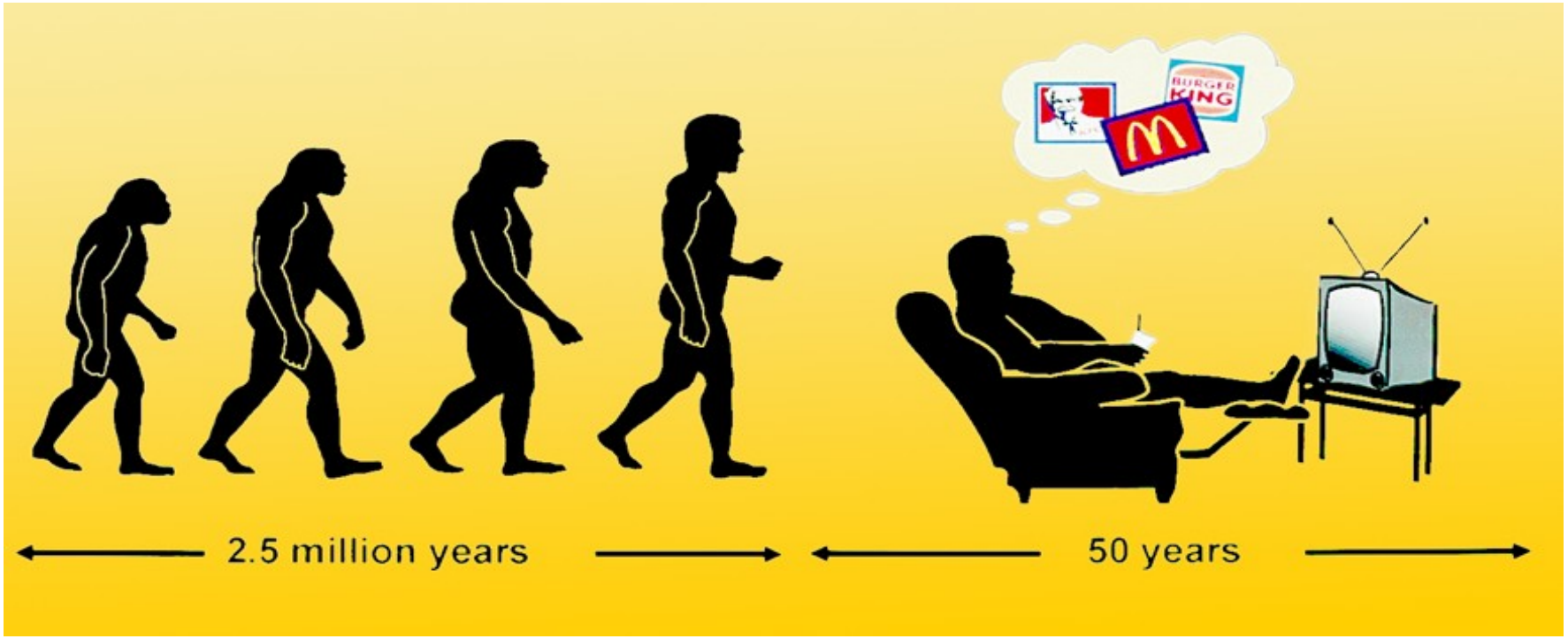
Prevalence of metabolic syndrome

- USA: Caucasian 23 % F and 25 % M, Hispanic and Native Americans - almost 55 %
- Palestinians - 70%, Aborigines in Australia, Mauritius, Asian-Indians in urban areas, Native -Americans – nearly 90%
- CR (2001): 32 % M and 24,5 % F

- Genetic predisposition for metabolic sy: 50% of population („thrifty“ genotype):

„In previous times, when people did not have enough to eat, when hunger and starving were prevalent, only those people that possessed the “thrifty gene” were well equipped for survival because the gene enabled them to fatten quickly and efficiently during those short spells of time when they had food. But nowadays when in most parts of the world we have food in abundance, the thrifty genotype continues to prepare individuals for famine, which, however, never comes. The result is widespread chronic obesity and related health problems like metabolic syndrome…“

Genes cannot keep up with changes in life style



Definiton of metabolic syndrome by NCEP-ATP III

(The National Cholesterol Education Program - 2001)

- waist circumference:
  - males > 102 cm
  - females > 88 cm
- triglycerides ≥ 1,7 mmol/l
- HDL-cholesterol:
  - males < 1,0 mmol/l
  - females < 1,3 mmol/l
- blood pressure ≥ 130/85 mmHg
- fasting glucose ≥ 6,1 mmol/l

3 or more factors

Zdroj: Expert Panel on Detection, JAMA 2001

Definiton of metabolic syndrome – 2009 (Alberti KG et al, Circulation 2009:120:1640-1645)

- waist circumference:
  - males > 102/94 cm
  - females > 88/80 cm
- triglycerides ≥ 1,7 mmol/l
- HDL-cholesterol:
  - males < 1,0 mmol/l
  - females < 1,3 mmol/l
- blood pressure ≥ 130/85 mmHg
- fasting glucose ≥ 5,6 mmol/l

3 or more factors

- treatment of dyslipidaemia or hypertension or DM

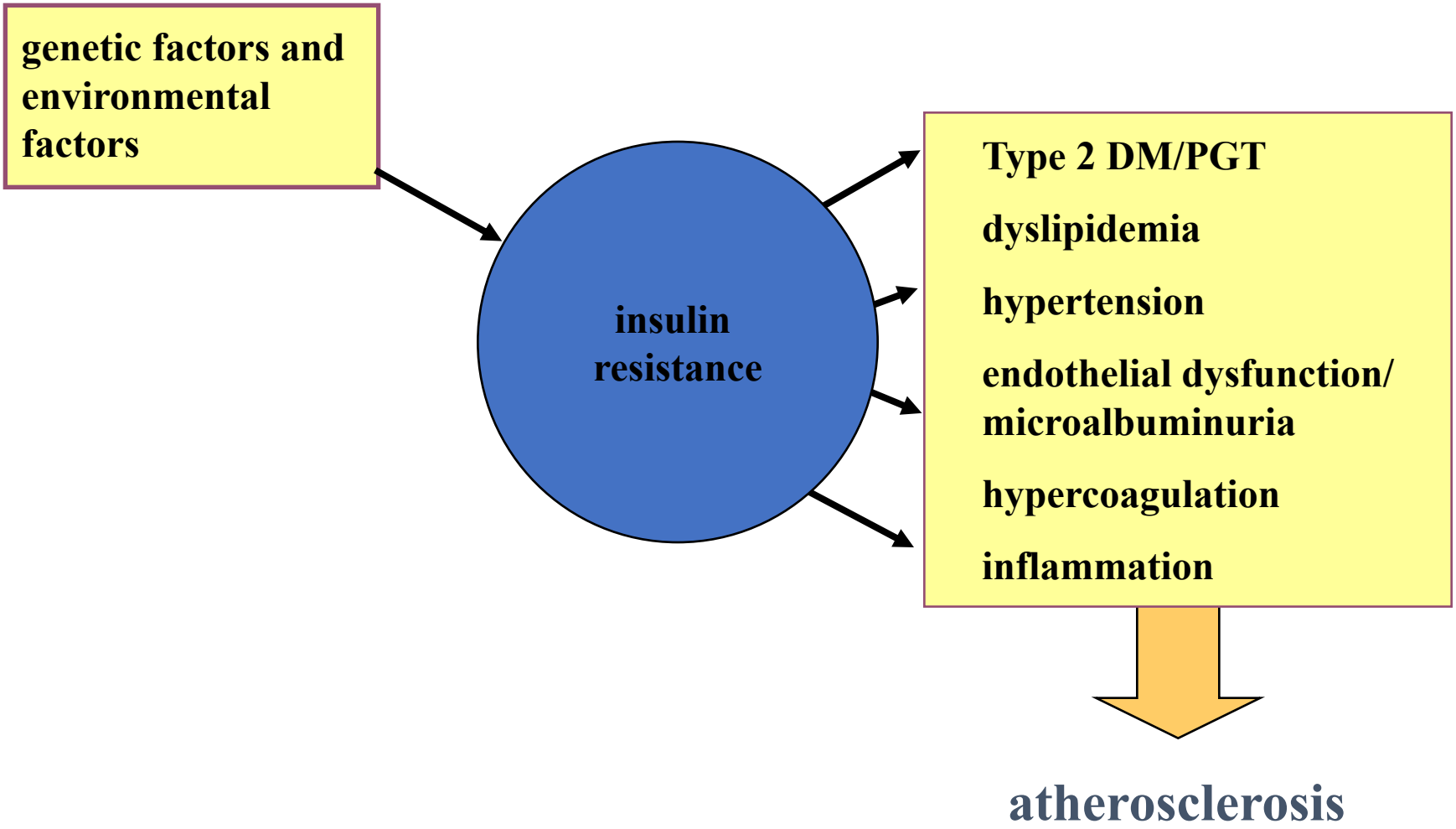
Patogenesis of Metabolic Sy

- ….“more and more complicated“…..

- 1) Insulin resistance
- 2) Chronic inflamation of lipid tissue in the abdomen
- 3) Hormones of lipid tissue
- 4) Hormones of muscle tissue
- 5) Intestinal flora

1) Insulin resistance

Metabolic syndrome



Adapted from McFarlane S, *et al. J Clin Endocrinol Metab* 2001; 86:713–718.

Gerald Reaven - 1988

- **1) insulinoresistance**

- 2) hypertension, hypertriglycidemia, diabetes mellitus
- 3) coagulopathy
- 4) ischemic heart disease and abdominal obesity

Insulin resistance

- physiological level of insulin in blood is not accompanied with physiological response
- decreased capability of insulin-mediated processing of glucose in insulinosensitive tissue

Insulin resistance

- Primary (inherited, genetically given) - e.g. in South Asian populations
- Secondary (acquired) – e.g. in Caucassians, Africans and Native Americans (Pima Indians)

2) CHRONIC INFLAMATION OF LIPID TISSUE IN THE ABDOMEN

3) HORMONES OF LIPID TISSUE

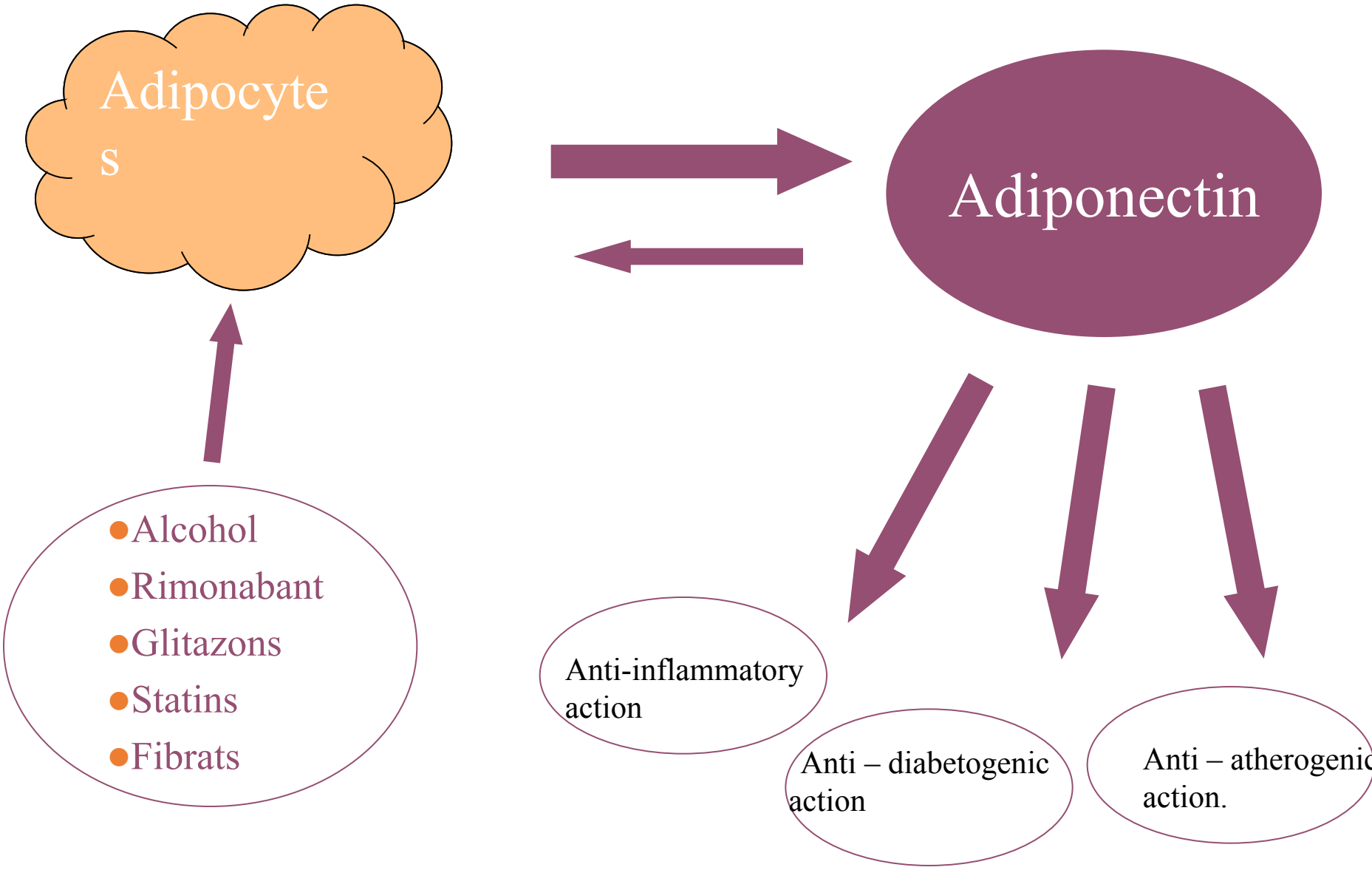
Adipose tissue (visceral fat) - adipocytes produce adipo(cyto)kinies (hormonally active substances)

- Resistin
- Vaspin
- Apelin
- IL-6
- TNF-alfa
- Retinal-binding –protein-4
- Plasminogen – aktivátor – inhibitor – 1
- Angiotenzinogen
- Growth factors (tumor GF, epidermal GF, fibroblast GF

- Adiponectin
- LCN2 (neutrophil gelatinase-associated lipocalin) ?

- Leptin ?
- Visfatin ?

Adiponectin



4) Hormones of muscle tissue

Hormones of muscles - myokines

- Increasing by physical activity
- 50-500?
- Regeneration of tissues
- Increase insulin sensitivity
- Pozitive influence on gut
- Immunosupressive activity

5) Intestinal flora

Intestinal flora

- Genetics
- Epigenetics
- Influence of childbirth – vaginal or section
- Nutrition

Positive influence on intestinal flora

- Metformin
- Physical activity
- Fruit and vegetables
- Natural childbirth – vaginal
- Breastfeeding

Metabolic syndrome

- Type 2 diabetes mellitus or impaired glucose tolerance or impaired fasting glucose
- Central (abdominal) obesity
- Arterial hypertension
- Dyslipidemia

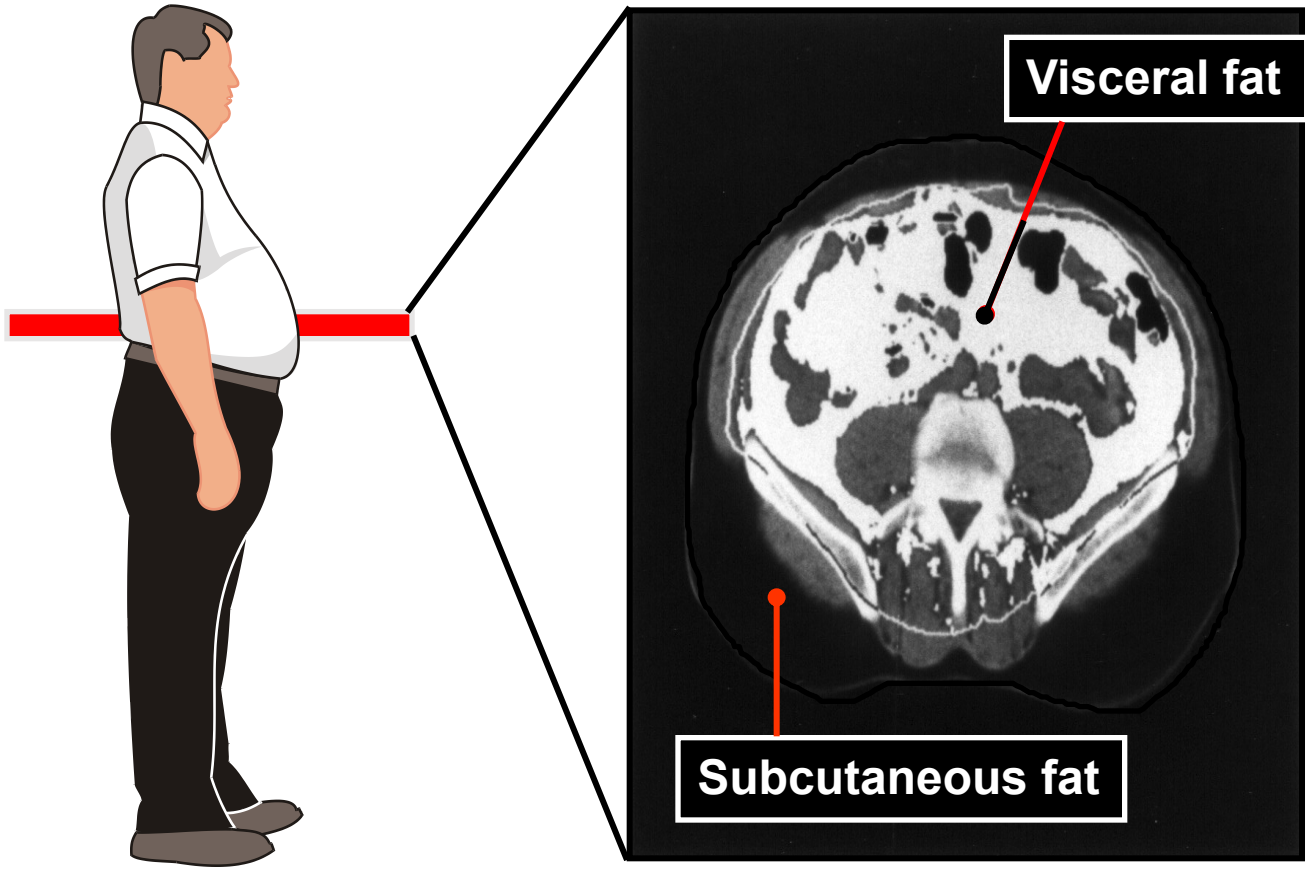
Type 2 Diabetes Mellitus

- 90 % of all diabetics in developed countries
- nearly 100 % of all diabetics in developing countries

- „coca-colonization“, „pandemic“

Obesity

- android type (central)
- BMI (body mass index) more than 30 kg/m^2
- more than 30 % fat in females and more than 25 % in males
- waist circumference – females more than 80-88 and males more than 94-102 cm
- **visceral fat** (decrease insulin sensitivity, increase sympatic sensitivity, increase endothelial dysfunction)



Lemieux I et al. Ann Endocrinol (2001) 62:255-261

Hypertension: 20-50 % adults in developed countries

- „treatment of hypertension decreases stroke by about 38 % and ischemic heart disease by about 22 %“
    - (Cobanian, JAMA 2003)

- 2018 ESC/ESH Guidelines for the management of arterial hypertension
  The Task Force for the management of arterial hypertension of the
  European Society of Cardiology (ESC) and the European Society of
  Hypertension (ESH)

- Authors/Task Force Members: Bryan Williams* (ESC Chairperson) (UK), Giuseppe Mancia* (ESH Chairperson) (Italy), Wilko Spiering (The Netherlands), Enrico Agabiti Rosei (Italy), Michel Azizi (France), Michel Burnier (Switzerland), Denis L. Clement (Belgium), Antonio Coca (Spain), Giovanni de Simone (Italy), Anna Dominiczak (UK), Thomas Kahan (Sweden), Felix Mahfoud (Germany), Josep Redon (Spain), Luis Ruilope (Spain), Alberto Zanchetti † (Italy), Mary Kerins (Ireland), Sverre E. Kjeldsen (Norway), Reinhold Kreutz (Germany), Stephane Laurent (France), Gregory Y. H. Lip (UK), Richard McManus (UK), Krzysztof Narkiewicz (Poland), Frank Ruschitzka (Switzerland), Roland E. Schmieder (Germany), Evgeny Shlyakhto (Russia), Costas Tsioufis (Greece), Victor Aboyans (France), and Ileana Desormais (France

Lifestyle – changes as a non-farmacological treatment of hypertension

- Smoking cessation
- Weight reduction
- Reduction of excessive alcohol intake
- Regular physical exercise
- Sodium restriction
- Other dietary changes: increase in fruit and vegetable intake and decrease in saturated and total fat intake

- Start with one drug or two drugs and after about 3-4 weeks increase the dose if the response is satisfactory and the patient tolerates the drug

- If the response is insufficient replace with drug from different class, do not increase the original drug

- Use long-acting drugs (once daily)

New aspects (2007→2013 → 2018)

- Prognostic value of home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM), not office blood pressure monitoring

- Prognostic value of night-time BP, white-cot and masked hypertension

- More evidence –based criteria and no drug treatment of high normal BP in low risk persons with hypertension

- More evidence –based criteria for target BP for treatment (under 140 mm Hg systolic)

- ACE-I and CA-A better than diuretics and BB (metabolic positive), 2018 – are the same…..

Definitions and Classification of blood pressure – Europe 2007, 2013, 2018

- Optimal (< 120/80 mm Hg)
- Normal (120-129/80-84 mm Hg)
- High normal (130-139/85-89 mm Hg)
- Grade 1 hypertension (140-159/90-99 mm Hg)
- Grade 2 hypertension (160-179/100-109 mm Hg)
- Grade 3 hypertension (> 180/110 mm Hg)
- Isolated systolic hypertension (> 140 mm Hg syst. and < 90 mm Hg diast.)

Secondary hypertension (10 %)

- **Renal** (parenchymal or renovascular)
- **Endocrinal (**hyperaldosteronism, feochromocytoma, Cushing sy, thyreotoxicosis, acromegaly, hyperparathyreosis)
- **Coarctation of the aorta**
- **Drug, chemically or food induced hypertension**
- **Gestational hypertension** (after 20. week of pregnancy)
- **Neurogennic hypertension**
- **Acute hypertension induced by acute stress**

Pharmacological therapy – Europe 2018

- Diuretics (mostly indapamid and chlorthalidon)
- Beta-blockers
- Calcium antagonists
- Inhibitors of angiotensin-converting enzyme (ACE-I)
- Angiotensin receptor antagonists

Hypertension

- metabolic positive - ACE-I, angiotensin receptor antagonists
- metabolic neutral – calcium -antagonists
- metabolic negative - diuretics, beta - blockers

Centrally influencing blood pressure: alfa metyl dopa, rilmetidin, moxonidin

Alfa-blockers: prazosin

Vasodilatans: dihydralazin, endralazin, minoxidil

Inhibitors of renin: aliskiren (?)

Inhibitors of mineralocorticoid receptors: aldosteron antagonist

Catheter-based sympathetic renal denervation procedures (RDN) (?)

Dg of hypertensis (2018):

- Office blood pressure
  - 140/90 mm Hg
- Home blood pressure
  - 135/85 mm Hg

24-hours ambulatory blood pressure monitoring

- Day – no more than 135/85 mmHg
- Night – no more than 120/70 mmHg
- Average – no more than 130/80 mmHg

- - normally decreasing during the night („dipping“)

When to initiate pharmacological antihypertensive treatment (2018)

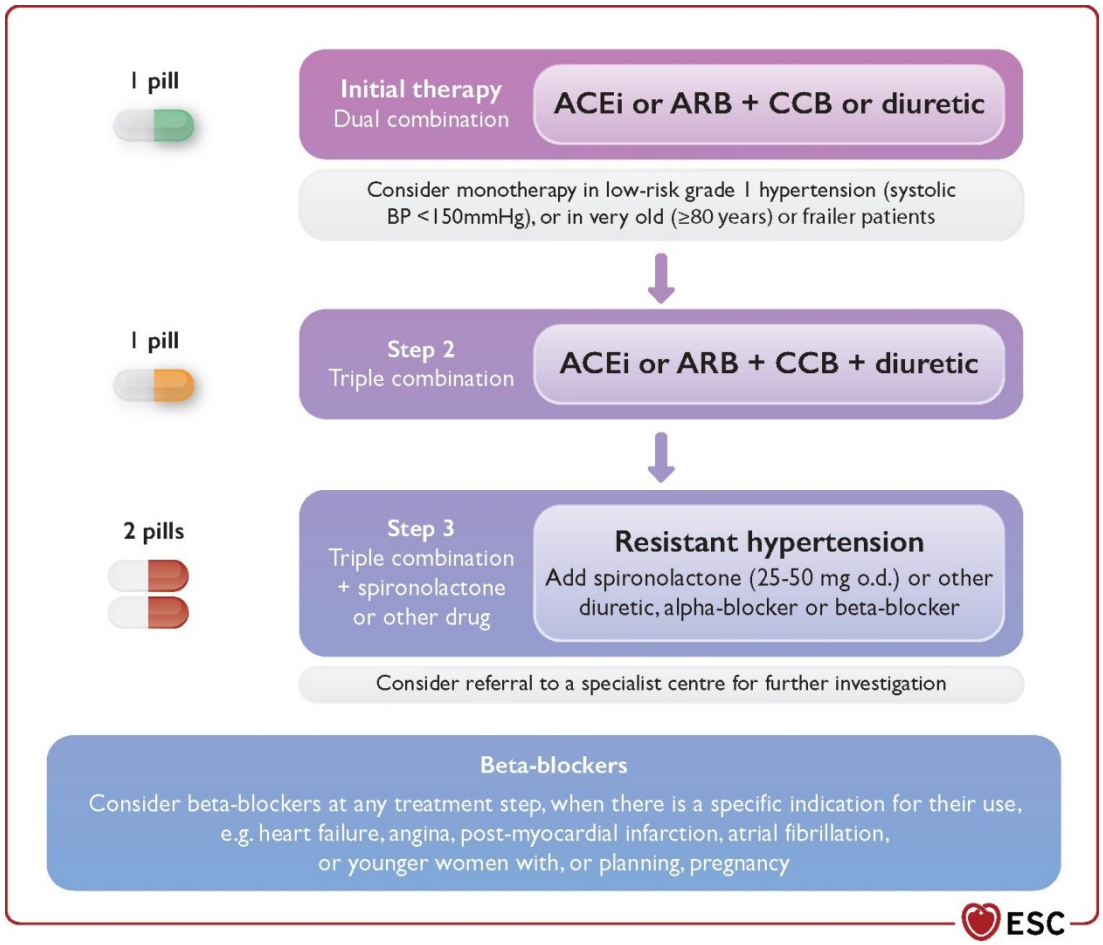
- More than 180/110 mmHg : immediately
- 160-179/100-109 mmHg: immediately
- 140-159/90-99 mmHg: after 3 month, when high risk is present – immediately
- 130-139/85-89 – treatment when very high risk is present

Blood pressure targets in hypertensive patients (2018)

- To 65 years old persons: 120-129 mm Hg syst.
- More than 65 let years old persons: 130-139 mm Hg syst., in some persons can be 150 mm Hg syst., no below 120 mm Hg syst. and no below 70 mm Hg diast.
- Diabetics and praediabetics and patients with CVD:
  - Europe – 130/syst. mm Hg

Diast. blood pressure target: 70-80 mm Hg.

Figure 16 Core drug treatment strategy for hypertension. This algorithm is ap for most patients with ...



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https://doi.org/10.1093/eurheartj/ehab484

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Table 13

Definitions of hypertension according to office, ambulatory, and home blood pressure

Category	SBP (mmHg)		DBP (mmHg)
Office BP[a]	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24-h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

a Refers to conventional office BP rather than unattended office BP.

;

Table 18

Recommended office blood pressure target ranges. The first step in all groups is a reduction to systolic blood pressure <140 mmHg. The subsequent optimal goals are listed below.

Age group	Office SBP treatment target ranges (mmHg)				
	Hypertension	**+ DM**	**+ CKD**	**+ CAD**	**+ Stroke/TIA**
18–69 years	120–130	120–130	<140–130	120–130	120–130
	Lower SBP acceptable if tolerated				
≥70 years	**<140 mmHg, down to 130 mmHg if tolerated** *Lower SBP acceptable if tolerated*				
DBP treatment target (mmHg)	<80 for all treated patients				

CAD = coronary artery disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; DM = diabetes mellitus; SBP = systolic blood pressure; TIA = transient ischaemic attack.

Resistant hypertension

- “When a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) in adequate doses has failed to lower systolic and diastolic blood pressure to goal.“
  - (poor adherence to therapeutic plan, obesity, obstructice sleep apnea ,unsuspected secondary cause, volume overload, white-coat hypertension, high sodium intake, drug induced hypertension, heavy alcohol intake etc….)

- + mineralocorticoid receptor antagonists, alpha-1-blockers, (renal denervation??)….

Hypertension in pregnancy - 2018

- Normal diet without salt and weight restriction
- Methyldopa, Labetalol, Nifedipin
- (other Calcium antagonists)
- (Beta blockers)
- KI: ACE-inhibitors, angiotensin receptor antagonists (teratogenicity)
- + acetylosalicylic acid in eclampsia

Hypertension in breast-feeding - 2018

- any hypotensive drug pass to breast – milk
- to give various drugs in small amount (to potentiate the effect and to decrease adverse events)
- not necessary strictly normotension – usually mothers are not in high risk of complications of hypertension
- no methyldopa - depression

Dyslipidaemias

- Hypercholesterolaemias
- Hypertriglyceridaemias (part of „metabolic syndrome“)
- Combined hyperlipidaemias

European Guidelines on cardiovascular disease prevention in clinical practice – version 2021

- Frank L.J. Visseren et al.: ESC Guidelines on cardiovascular disease prevention in clinical practice (version 2021). Developed by Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies

European Heart Journal, 2021 42, 3227-3337,
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Published: 22 September 2021

The risk of cardiovascular fatal and non-fatal events in the future 10 years:

2021

Age, gender, smoking, systolic blood pressure level, **level of non-HDL-CH and country (SCORE2 and SCORE OP)**

- help us to prevent cardiovascular events

2021

- Low risk:

Andorra, Belgium, Denmark, France, Luxembourg, Monaco, the Nederlands, Norway, Spain, Switzerland, United Kingdom

- Moderate risk:

Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, San Marino, Slovenia, Sweden

2021

- High risk:

Albania, Bosnia and Herzegovina, croatia, Czech Republic, Estonia, Hungary, Kazaghstan, Poland, Slovakia, Turkey

- Very-high risk:

Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Kyrgyzstan, Latvia, Lithuania, Libya, Montenegro, Morocco, Romania, Macedonia, Moldova, Russia, Ukraine, Uzbekistan, Georgia,Serbia, Syria, Macedonia, Tunisia,

Figure 4 Risk regions based on World Health Organization cardiovascular mortality ...

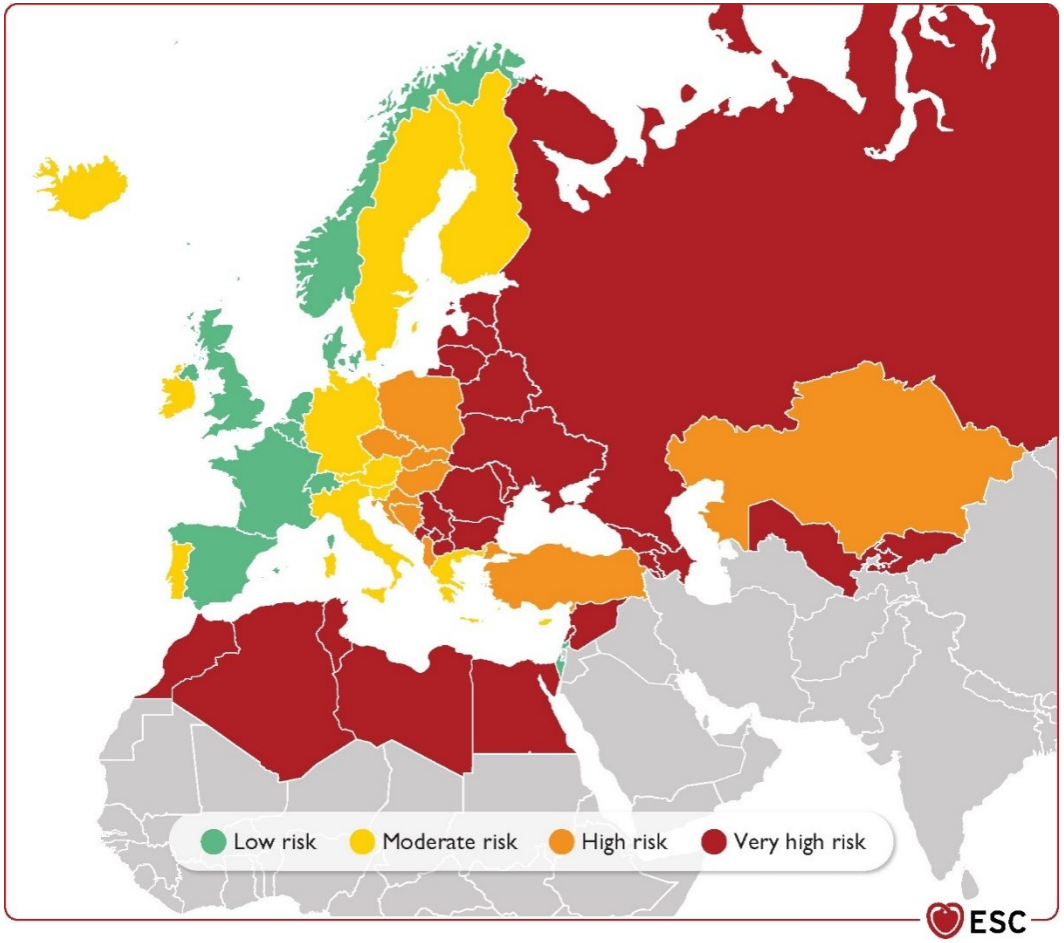

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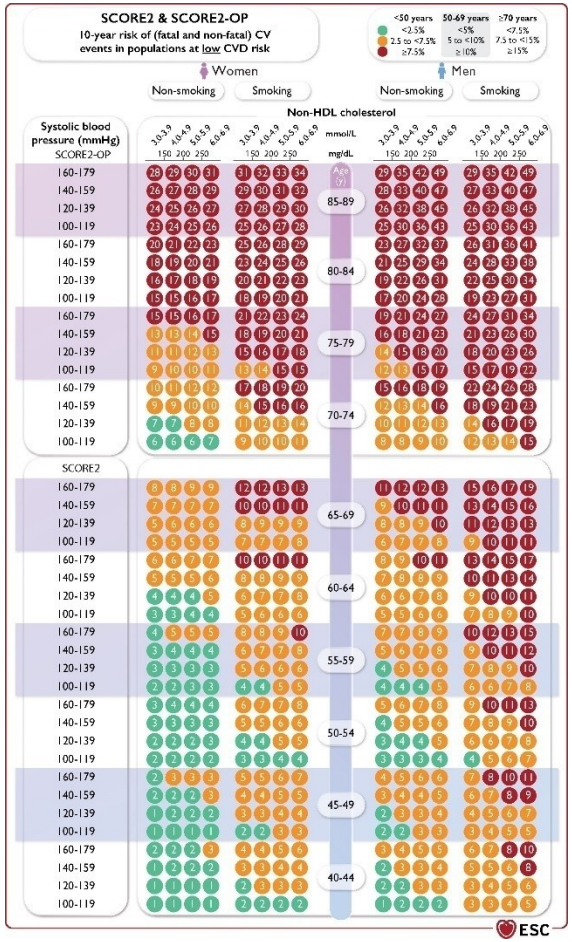
Figure 3 Systematic Coronary Risk Estimation 2 and Systematic Coronary Risk Estimation 2-Older Persons risk charts for ...



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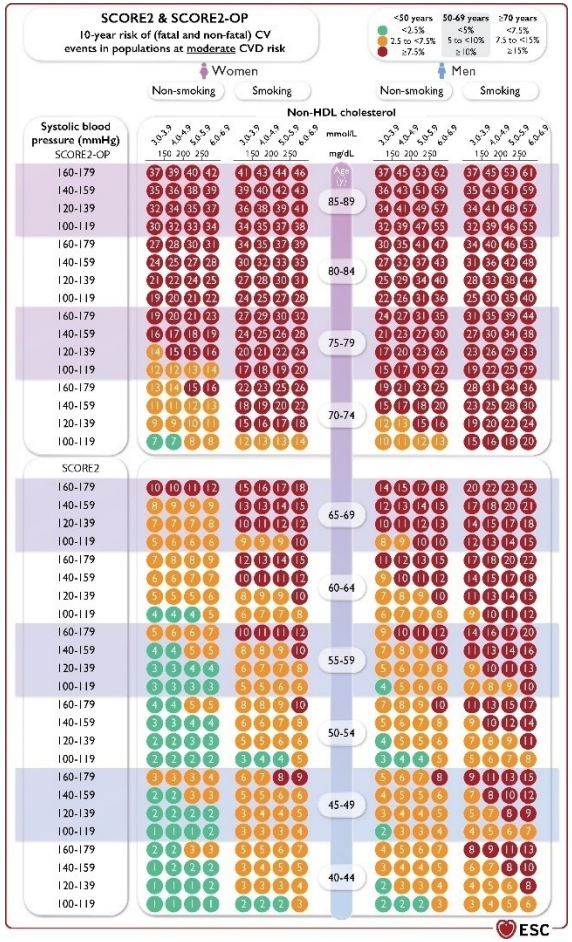

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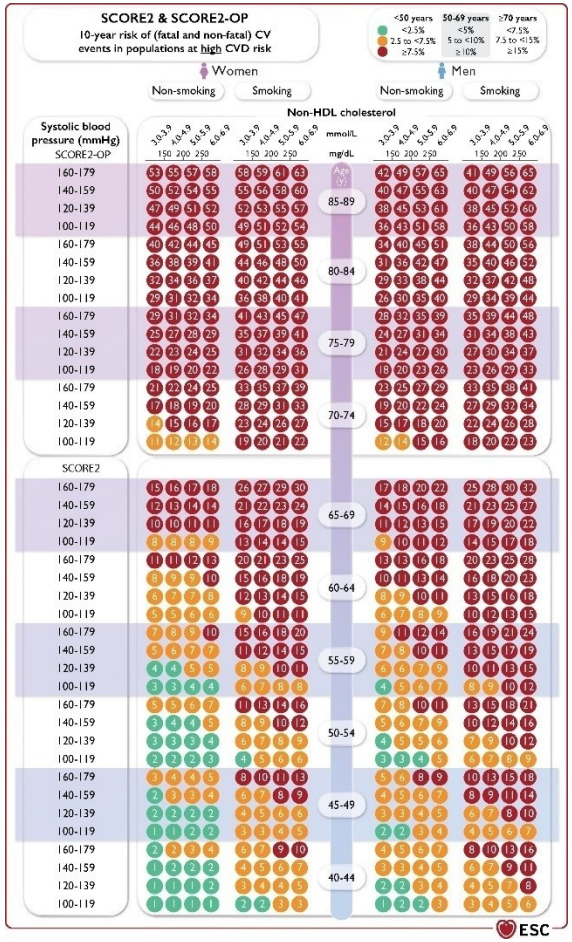

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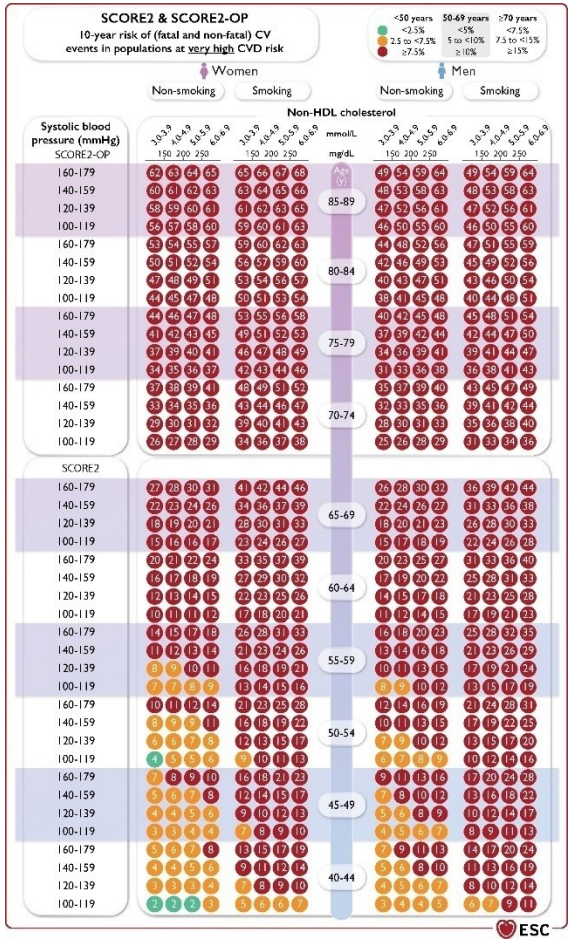

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Apparently healthy people – no reccomended treatment

- SCORE 2 < 2,5% for age < 50
- SCORE 2 < 5% for age 50-69
- SCORE OP < 7,5% for age >70

Apparently healthy people – treatment should be reccomended

- SCORE 2 - 2,5-7,5% for age < 50
- SCORE 2 - 5-10% for age 50-69
- SCORE OP - 7,5-15% for age ≥ 70

Apparently healthy people – treatment is reccomended

- SCORE 2 ≥ 7,5% for age < 50
- SCORE 2 ≥ 10% for age 50-59
- SCORE OP ≥ 15% for age ≥ 70

CVD Risk Calculator app

- https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/esc-cvd-risk-calculation-app
- http://www.hearstscore.org
- http://www.u-prevent.com

People at very high total CV Risk (no use of SCORE)

Subjects with cardiovascular disease (heart or brain vessel disease, peripheral artery disease)

Subjects with very high levels of individual risk factors

Subjects with chronic kidney disease (CKD)

Subjects with Type 1 diabetes mellitus with microalbuminuria

Subjects with Type 2 diabetes mellitus

Target levels in „healthy persons“

- Total CH < 5,0 mmol/l
- LDL-CH < 3,0 mmol/l
- HDL-CH > 1,0 mmol/l
- TG < 2,0 mmol/l

Targets of LDL-C levels

- Very, very high risk (repeated CV event): 1,0 mmol/l
- Very high risk: 1,4 mmol/l or decrease 50 %
- High risk : 1,8 mmol/l or decrease 50%
- Moderate risk: 2,6 mmol/l or decrease o 50%
- Low risk: 3,0 mmol/l

Pharmacotherapy of dyslipidaemias

- **Statins** (reduce synthesis of cholesterol in the liver by competitively inhibiting HMG-CoA reductase activity)
- **Ezetimibe** (inhibits intestinal uptake of cholesterol)
- **Nicotinic acid** (intolerance) – not practically used
- **Fibrates** (agonists of PPAR-alfa)
- **Omega-3-fatty acids** (components of fish oil)
- **Bile acid sequestrants** (intolerance) – not practicelly used

New hypolipidaemics

- Inhibitors PCSK9:

(proprotein convertase subtilisin/kexin type 9

a new class of cholesterol busters:

- crucial protein in LDL cholesterol (LDL-C) metabolism
- pivotal role in the degradation of the LDL receptor)

- Inhibitors PCSK9 increase effect of statins (HMG-CoA reductase inhibitors)

Pharmacotherapy of hypertriglycaridemia

- High risk: Tg > 2,3 mmol/l …statin
- Very high risk: TG 1,5-5,6 mmol/l…statin + eicosapent. acid 2 x 2g/day
- Tg > 2,3 mmol/l and target level of LDL-CH… statin + fibrate

Pharmacotherapy of dyslipidaemia (in practice)

Statins!!

- **in combination:**
  - + **Fibrates** **(increased TG, decreased HDL-CH – as a first step: DM Type 2 with TG > 4 mmol/l**
  - + **Ezetimibe** **(increased LDL-C) – as a monotherapy: intolerance of statins**
  - + **PCSK9 inhibitors**

Dyslipidaemia as a part of metabolic sy („atherogenic lipid triad“) consists of:

- increased triglycerides
- decreased HDL-CH
- normal levels of total and LDL-CH, but increased small dense LDL-CH particles

Coagulopathy

- increasing of plasminogen activator inhibitor-1 (PAI-1) – an independent risk factor of atherosclerosis
- increasing aggregability of trombocytes

Cancers

- males – colorectal carcinoma
- females – breast cancer

How to treat MetSy?

…..have we any single drug?…….

Endocannabinoid system

(Endo)cannabinoid system - endogenic system

- 1988 – discovery of CB1 - receptor
- 1992 – discovery of endogenic agonist of CB1-receptor - anandamide („ananda“ in sanskrt – „joy“)
- THC (terpenoid derivative tetrahydrocannabinol) - the main part of marijuana
- agonists of CB1- rp influence positively production of serotonin, dopamin etc. in neural synapsis…

(Endo)cannabinoid system

- Smoking, overeating, overweight – lead to increased activity of endocannabinoid system…

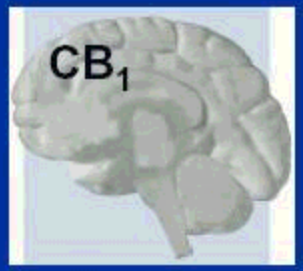
- RIMONABANT (selective inhibitor of CB1 receptors in the brain) (Acomplia-Sanofi Aventis)

Rimonabant, the first CB_1 blocker
A multi-impact drug

Rimonabant

CENTRAL

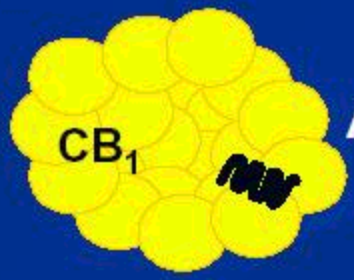
Brain



↓ Food intake

↓ Tobacco dependance

PERIPHERAL



Adipocyt

↑ Adiponectin

↓ Insulin resistance

↓ Triglycerides

↑ Glucose tolerance

↑ HDL-cholesterol

(Endo)cannabinoid system

- RIMONABANT (selective inhibitor of CB1 receptors in the brain) (Acomplia-Sanofi Aventis)

- 10/2008 treatment by this drug was discontinued…..

(Endo)cannabinoid system

- ….adverse events – suicides…..

How to treat MetSy?

- There is no single drug
- We must change life style of population
- But that usually means to deprive people of what they like and to force them to do things they hate…….

„When the World was a simple place, the rich were fat, the poor were thin, and right-thinking people worried about how to feed the hungry. Now, in much of the World, the rich are thin, the poor are fat, and right-thinking peple are worrying about obesity.“

Economist, December 11, 2003

Patient with metabolic syndrome walking a dog ...