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17/19 MARZO 2016

Bari, Hotel Majesty

VII
CORSO
NAZIONALE AME
DI ENDOCRINOLOGIA
CLINICA

16.15 - 19.15
VI SESSIONE - CASI CLINICI INTERATTIVI
con divisione in piccoli gruppi

Elvio D'Addato & Giovanni De Pergola

Dislipidemia e ipertensione nella Sindrome Metabolica
quali farmaci per quali target?

Venerdì, 18 Marzo 2016

CASO CLINICO

Donna di 47 anni

Peso: 76 Kg, Altezza: 160 cm, BMI: 29,6, Waist: 98 cm

PA (misurata in ambulatorio): 140/85 mmHg, FC: 80 bpm

PA (misurata a domicilio): 135/80 mmHg,

EOC: toni 2, pause libere EOA: nds

EO generale: nds

Al momento attuale non assume farmaci

ANAMNESI PATOLOGICA

Nega ricoveri per malattie internistiche o chirurgiche

Nega eventi cardiovascolari

LAVORO E ANAMNESI FAMILIARE

Svolge il lavoro di infermiera, alternando turni diurni e notturni

Anamnesi familiare
positiva per diabete mellito tipo 2 (entrambe i genitori e una sorella che ha 55 anni), ipertensione (entrambe i genitori) e obesità (padre e sorella)

Il padre è deceduto alla età di 70 anni per un infarto del miocardio

ANAMNESI FISIOLOGICA

Ha avuto 2 gravidanze portate a termine (1 maschio e 1 femmina)

Ha presentato 7 flussi mestruali negli ultimi 12 mesi e 3 flussi negli ultimi 6 mesi

Fuma una media di 15 sigarette al giorno

Il diario alimentare (dei 3 giorni) mostra un'alimentazione caratterizzata da una media di circa 2400 kcal giornaliere, distribuite abitualmente tra 5 pasti giornalieri (3 principali e 2 spuntini).
Il 60% delle calorie è rappresentato da carboidrati, il 30% da lipidi ed il 10% da proteine. Assume 18 grammi di fibre al giorno

Riferisce di avere saltuariamente un sonno disturbato, con senso di stanchezza al mattino

Cammina per meno di 7000 passi al giorno e non frequenta palestre, piscine o altre sedi dove svolgere attività fisica

ESAMI EMATOCHIMICI DI ROUTINE

Gli esami di laboratorio eseguiti una settimana prima della visita mostrano:

Trigliceridi : 184 mg/dL

Colesterolo totale: 213 mg/dL

Colesterolo HDL: 40 mg/dL

Colesterolo LDL: 136 mg/dL

Glicemia: 109 mg/Dl

HbA1c: 6,4%

Tutti gli altri parametri ematochimici di routine (emocromo, creatininemia; transaminasi, etc) sono nei limiti della norma

SINDROME METABOLICA NCEP-ATPIII

- Obesità addominale
  (waist ≥ 102 cm nell'uomo, ≥ 88 cm nella donna)

- Ipertrigliceridemia (≥ 150 mg/dl)
- Basso colesterolo HDL (<40 mg/dl nell'uomo, <50 mg/dl nella donna)
- Ipertensione arteriosa (≥ 130/85 mmHg)
- Glicemia ≥ 110 mg/dl

NCEP-ATP III, JAMA, 2001

SINDROME METABOLICA IDF

Waist ≥ 94 cm nell'uomo, ≥ 80 cm nella donna

+ almeno 2 tra i seguenti criteri:

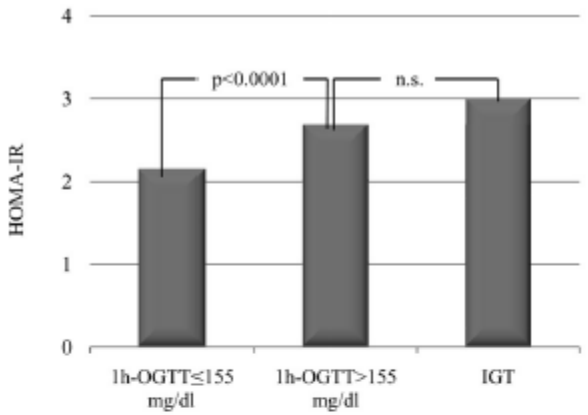
- Trigliceridi ≥150 mg/dl
- HDL-C <40 mg/dl nell'uomo, <50 mg/dl nella donna
- Pressione arteriosa ≥130/85 mmHg
- Glicemia ≥100 mg/dl

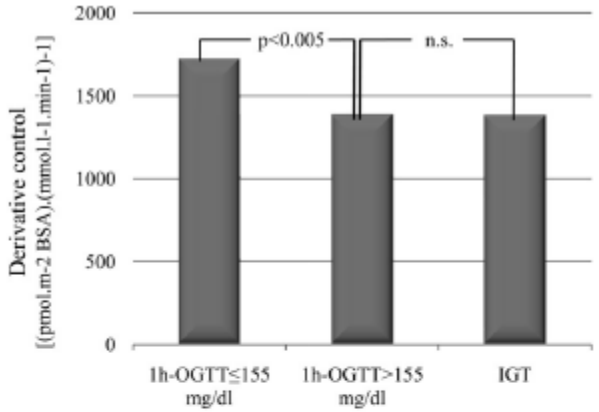
Ruolo essenziale dell'obesità addominale

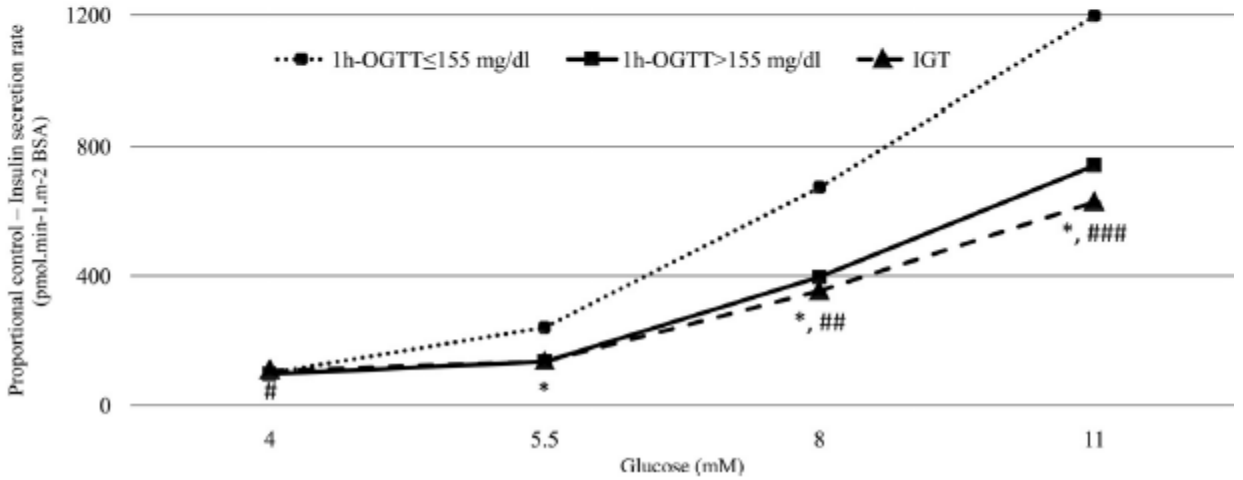
CURVA DA CARICO ORALE CON GLUCOSIO

Glicemia base	109 mg/dL	Insulina base	10 mU/L
Glicemia 30′	154 mg/dL	Insulina 30′	90 mU/L
Glicemia 60′	160 mg/dL	Insulina 60′	120 mU/L
Glicemia 90′	149 mg/dL	Insulina 90′	140 mU/L
Glicemia 120′	136 mg/dL	Insulina 120′	110 mU/L

Elevated 1-Hour Postload Plasma Glucose Levels Identify Subjects With Normal Glucose Tolerance but Impaired β-Cell Function, Insulin Resistance, and Worse Cardiovascular Risk Profile: The GENFIEV Study







Bianchi C et al, J Cin Endocrinol Metab, 98: 2100-2105, 2013

2013 ESH/ESC Guidelines for the management of arterial hypertension

TABLE 3. Definitions and classification of office blood pressure levels (mmHg)[a]

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

TABLE 15. Drugs to be preferred in specific conditions

Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical CV event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
Other	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

TABLE 14. Compelling and possible contra-indications to the use of antihypertensive drugs

Drug	Compelling	Possible
Diuretics (thiazides)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcemia Hypokalaemia
Beta-blockers	Asthma A–V block (grade 2 or 3)	Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive pulmonary disease (except for vasodilator beta-blockers)
Calcium antagonists (dihydropyridines)		Tachyarrhythmia Heart failure
Calcium antagonists (verapamil, diltiazem)	A–V block (grade 2 or 3, trifascicular block) Severe LV dysfunction Heart failure	
ACE inhibitors	Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis	Women with child bearing potential
Angiotensin receptor blockers	Pregnancy Hyperkalaemia Bilateral renal artery stenosis	Women with child bearing potential
Mineralocorticoid receptor antagonists	Acute or severe renal failure (eGFR <30 mL/min) Hyperkalaemia	

Treatment strategies in hypertensive patients with metabolic syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
Lifestyle changes, particularly weight loss and physical exercise, are to be recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset.	I	B	369, 519, 520
As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating beta-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent.	IIa	C	-

It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg.	I	B
BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP.	III	A

Clinical indications for HBPM or ABPM
• Suspicion of white-coat hypertension
– Grade I hypertension in the office
– High office BP in individuals without asymptomatic organ damage and at low total CV risk
• Suspicion of masked hypertension
– High normal BP in the office
– Normal office BP in individuals with asymptomatic organ damage or at high total CV risk
• Identification of white-coat effect in hypertensive patients
• Considerable variability of office BP over the same or different visits
• Autonomic, postural, post-prandial, siesta- and drug-induced hypotension
• Elevated office BP or suspected pre-eclampsia in pregnant women
• Identification of true and false resistant hypertension
Specific indications for ABPM
• Marked discordance between office BP and home BP
• Assessment of dipping status

2013 ESH/ESC Guidelines for the management of arterial hypertension

Specific indications for ABPM
• Marked discordance between office BP and home BP
• Assessment of dipping status
• Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, CKD, or diabetes
• Assessment of BP variability

The Task Force for the management of the arterial hypertension, Eur Heart J, 2013

2013 ESH/ESC Guidelines for the management of arterial hypertension

Table 3 Definitions and classification of office blood pressure levels (mmHg)[a]

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Grade 1 hypertension	140–159	and/or	90–99
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Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

140/85

The Task Force for the management of the arterial hypertension, Eur Heart J, 2013

2013 ESH/ESC Guidelines for the management of arterial hypertension

Table 6 Definitions of hypertension by office and out-of-office blood pressure levels

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP	≥140	and/or	≥90
Home BP	≥135	and/or	≥85

135/80

The Task Force for the management of the arterial hypertension, Eur Heart J, 2013

2013 ESH/ESC Guidelines for the management of arterial hypertension

Table 6 Definitions of hypertension by office and out-of-office blood pressure levels

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake)	≥135	and/or	≥85
Nighttime (or asleep)	≥120	and/or	≥70
24-h	≥130	and/or	≥80
Home BP	≥135	and/or	≥85

The Task Force for the management of the arterial hypertension, Eur Heart J, 2013

HOLTER PRESSORIO (ABPM)

Un Holter pressorio, eseguito 2 mesi prima della visita attuale, mostra valori pressori medi delle 24 ore di 132/85 mmHg;

I valori pressori medi nelle ore diurne sono 140/90 mmHg;

I valori pressori medi nelle ore notturne sono 120/80 mmHg;

Adoption of lifestyle changes

Recommendations	Class[a]	Level[b,d]	Level[b,e]	Ref.[c]
Salt restriction to 5–6 g per day is recommended.	I	A	B	339, 344–346, 351
Moderation of alcohol consumption to no more than 20–30 g of ethanol per day in men and to no more than 10–20 g of ethanol per day in women is recommended.	I	A	B	339, 354, 355
Increased consumption of vegetables, fruits, and low-fat dairy products is recommended.	I	A	B	339, 356–358
Reduction of weight to BMI of 25 kg/m² and of waist circumference to <102 cm in men and <88 cm in women is recommended, unless contraindicated.	I	A	B	339, 363–365

per day in women is recommended.				
Increased consumption of vegetables, fruits, and low-fat dairy products is recommended.	I	A	B	339, 356–358
Reduction of weight to BMI of 25 kg/m² and of waist circumference to <102 cm in men and <88 cm in women is recommended, unless contraindicated.	I	A	B	339, 363–365
Regular exercise, i.e. at least 30 min of moderate dynamic exercise on 5 to 7 days per week is recommended.	I	A	B	339, 369, 373, 376
It is recommended to give all smokers advice to quit smoking and to offer assistance.	I	A	B	384–386

ESC/EAS LINEE GUIDA SULLE DISLIPIDEMIE 2011

CATEGORIA DI RISCHIO	PUNTEGGIO (SCORE)	CARATTERISTICHE DEI SOGGETTI
Molto alta	≥10%	Soggetti con: • malattia CV documentata mediante test invasivi e non invasivi; • precedente infarto del miocardio; • sindrome coronarica acuta; • rivascolarizzazione coronarica; • stroke ischemico; • arteriopatia periferica; • diabete di tipo II, diabete di tipo I con markers di danno d'organo; • patologia renale cronica moderata-severa (FG <60 ml/min/1.73m^2).
Alta	≥5% e <10%	Soggetti con: • SCORE ≥5% e <10% • singoli fattori di rischio marcatamente elevati come dislipidemie familiari e ipertensione severa.
Moderata	≥1% e <5%	Soggetti con: • SCORE ≥1% e <5% Il rischio è ulteriormente influenzato da: • storia familiare di patologia coronarica precoce; • obesità addominale; • attività fisica; • Col-HDL, TG, CRP ad alta sensibilità, Lp(a), fibrinogeno, omocisteina, Apo B; • classe sociale.
Bassa	<1%	

CV = cardiovascolare
FG = filtrato glomerulare
Col-HDL = colesterolo a lipoproteine ad alta densità
TG = trigliceridi
CRP = proteina C reattiva
Lp = lipoproteina
Apo = apolipoproteina

Tabella 1. Categorie di rischio cardiovascolare secondo il punteggio SCORE.

Table 5 Comparison of Cholesterol Guidelines

Guideline	ATP III	Canadian	European	IAS	ACC/AHA
LDL-C goal(mg/dL)	Low risk: < 160IntermediateRisk < 130 High risk: <100Very high risk: <70	Low riskIntermediate and high risk:< 77(or 50% lowering)	Moderate risk:< 115High risk:<100 Very high risk <70	Primary prevention:< 100 mg/dLSecondaryPrevention: <70	None
Non-HDL-C goal (mg/dL)	(with high TG)30 mg/dL higher than LDL-C goal	Alternate target	30 mg/dL higher than LDL-C goal	30 mg/dL higher than LDL-C goal	None
Risk Assessment	Modified Framingahm	Modified Framingham	SCORE	Framingham adjusted for population	5-population risk tool
End points	Hard CHD events	CHD events	CHD mortality	CHD	ASCVD events
Risk projection	10-year	10-year	10-year	Long-term(to age 80)	10-year
Drug treatment threshold	≥ 10% 10-year risk	≥ 10% 10-year risk			≥ 7.5% 10-year risk
First-line drug therapy	Statins (dose adjusted to LDL-C goal)	Statins	Statins	Statins	Statins(high-intensity preferred)
Second-line drugs	Bile acid resinsNicotinic acidFibratesEzetimibe	Bile acid resinsNicotinic acidFibratesEzetimibe	Bile acid resinsNicotinic acidFibratesEzetimibe	Bile acid resinsNicotinic acidFibratesEzetimibe	Discouraged
MetabolicSyndrome	Emphasized: denotes higher risk for ASCVD	Recognized as higher risk condition	Emphasized: denotes higher risk for ASCVD	Emphasized: denotes higher risk for ASCVD	Ignored
Lifestyle intervention	Backbone of therapy	Backbone of therapy	Backbone of therapy	Backbone of therapy	Component of ASCVD

Table 2 Cholesterol Lowering Drugs

Drug Class	Mechanism of Action	Effects on Plasma Lipids	LDL-C lowering	Side effects
Statins	Inhibit HMG CoA reductaseRaise LDL receptor activity	Reduce LDL and VLDLMinimal effect on HDL	30-55% depending on dose	MyalgiaCognitivedysfunctionRaises plasma glucose
Bile acid sequestrants	Impairs reabsorption of bile acidsRaise LDL receptor activity	Reduces LDLRaises VLDLMinimal effect on HDL	15-25%, depending on dose	ConstipationGI distressRaiseTriglycerides
Ezetimibe	Impairs absorption of cholesterolRaises LDL receptor activity	Reduces LDLReduces VLDLMinimal effect on HDL	15-25%	Rare
Niacin	Reduces hepatic secretion of VLDL	Reduces VLDLReduces LDLRaises HDL	5-20%	Flushing, rash, raise plasma glucose, hepatic dysfunction, others
Fibrates	Reduces secretion of VLDLEnhances degradation of VLDL	Reduces VLDL(lowers TG 25-35%)Small effect on LDLRaises HDL	5-15%	Myopathy (in combination with statins)GallstonesUncommonly various others
MTP inhibitors	Reduces hepatic secretion of VLDL	Reduces VLDL and LDL	50+%	Fatty liver
Mipomersen(RNA antisense)	Reduces hepatic secretion of VLDL	Reduces VLDL and LDL	50+%	Fatty liver
CETP inhibitors	Blocks transfer of cholesterol from HDL to VLDL&LDL	Raises HDLLowers LDL	20-30%	Under study
PCSK9 inhibitors	Blocks effects of PCSK9 to destroy	Lowers LDL	45-60%	Under study

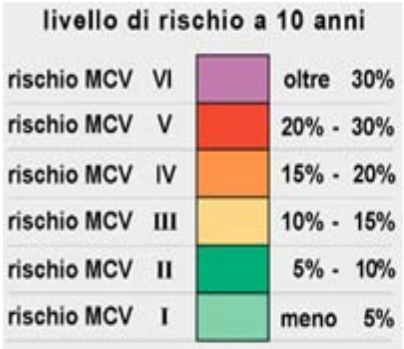
Table 22 Management of dyslipidaemia in women

• Statin treatment is recommended for primary prevention of CAD in high risk women.[16]
• Statins are recommended for secondary prevention in women with the same indications and targets as in men.[15, 164]
• Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy or during the breast feeding period.

CAD = coronary artery disease.

STIMA DEL RISCHIO CARDIOVASCOLARE

- Il progetto SCORE, a differenza del Framingham, prende in considerazione solo gli eventi fatali
- A rischio elevato i soggetti che hanno una probabilità di eventi fatali >0,5% per anno nei successivi 10 anni
- Approssimativamente, il fattore di conversione tra punteggio SCORE e probabilità di eventi fatali e non fatali è 3, per cui un punteggio SCORE di 0,5 corrisponde alla probabilità di avere 1,5% di eventi cardiovascolari per anno



I fattori di rischio considerati sono:

1 ***genere*** espresso in due categorie, uomini e donne

2 ***diabete*** espresso in due categorie, diabetico e non diabetico; viene definita diabetica la persona che presenta, in almeno 2 misurazioni successive nell'arco di una settimana, la glicemia a digiuno **uguale o superiore a 126 mg/dl** oppure è sottoposta a trattamento con **ipoglicemizzanti orali o insulina** oppure **presenta storia clinica personale** di diabete

3 ***età*** espressa in anni e considerata in decenni, 40-49, 50-59, 60-69

4 ***abitudine al fumo*** di sigaretta espressa in due categorie, fumatori e non fumatori; si definisce fumatore chi fuma regolarmente ogni giorno (anche una sola sigaretta) oppure ha smesso da meno di 12 mesi. Si considera non fumatore chi non ha mai fumato o ha smesso da più di 12 mesi

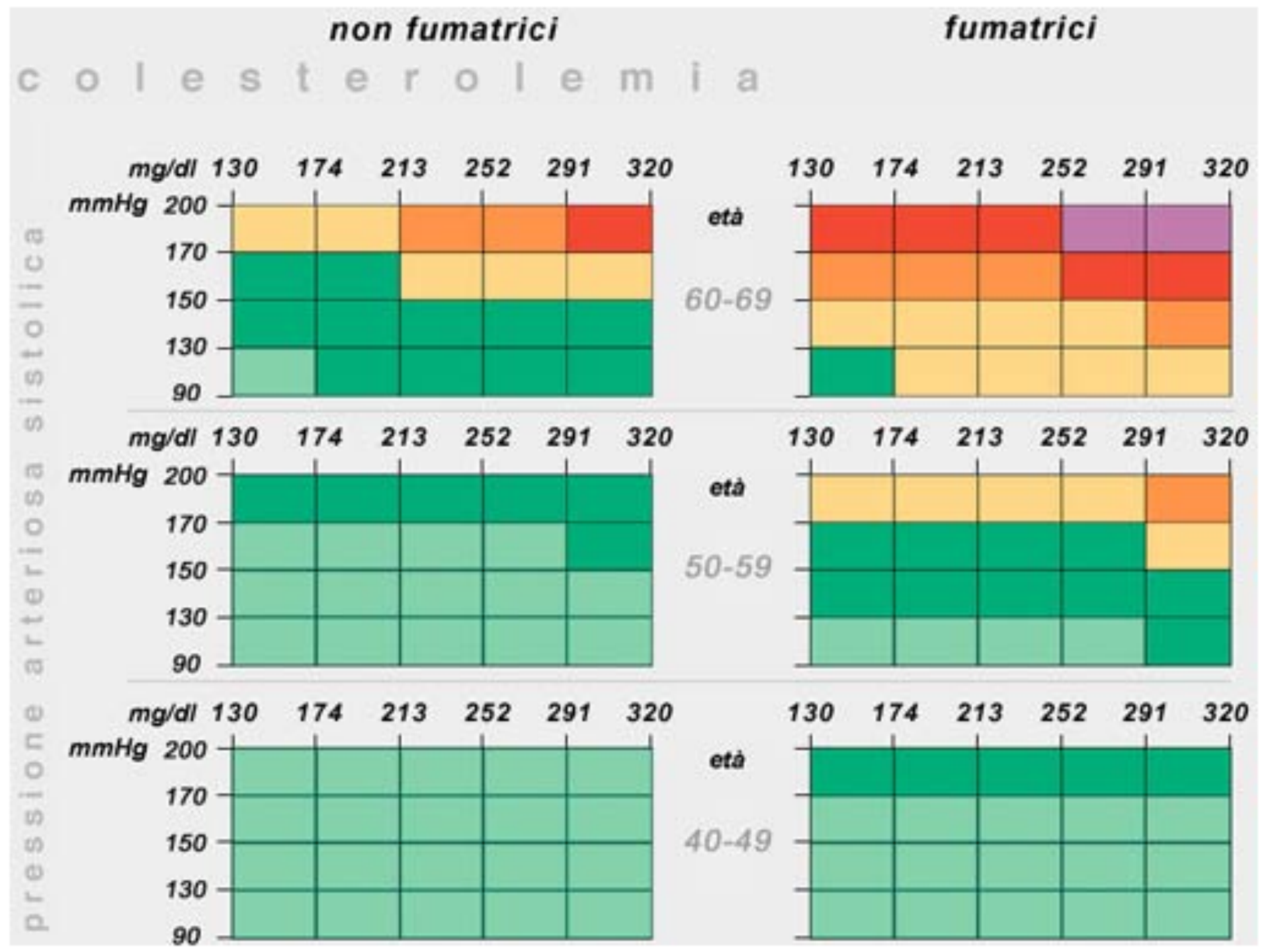
5 ***pressione arteriosa sistolica*** espressa in mmHg; rappresenta la pressione sistolica come media di due misurazioni consecutive eseguite secondo la metodologia standardizzata. È suddivisa in quattro categorie:

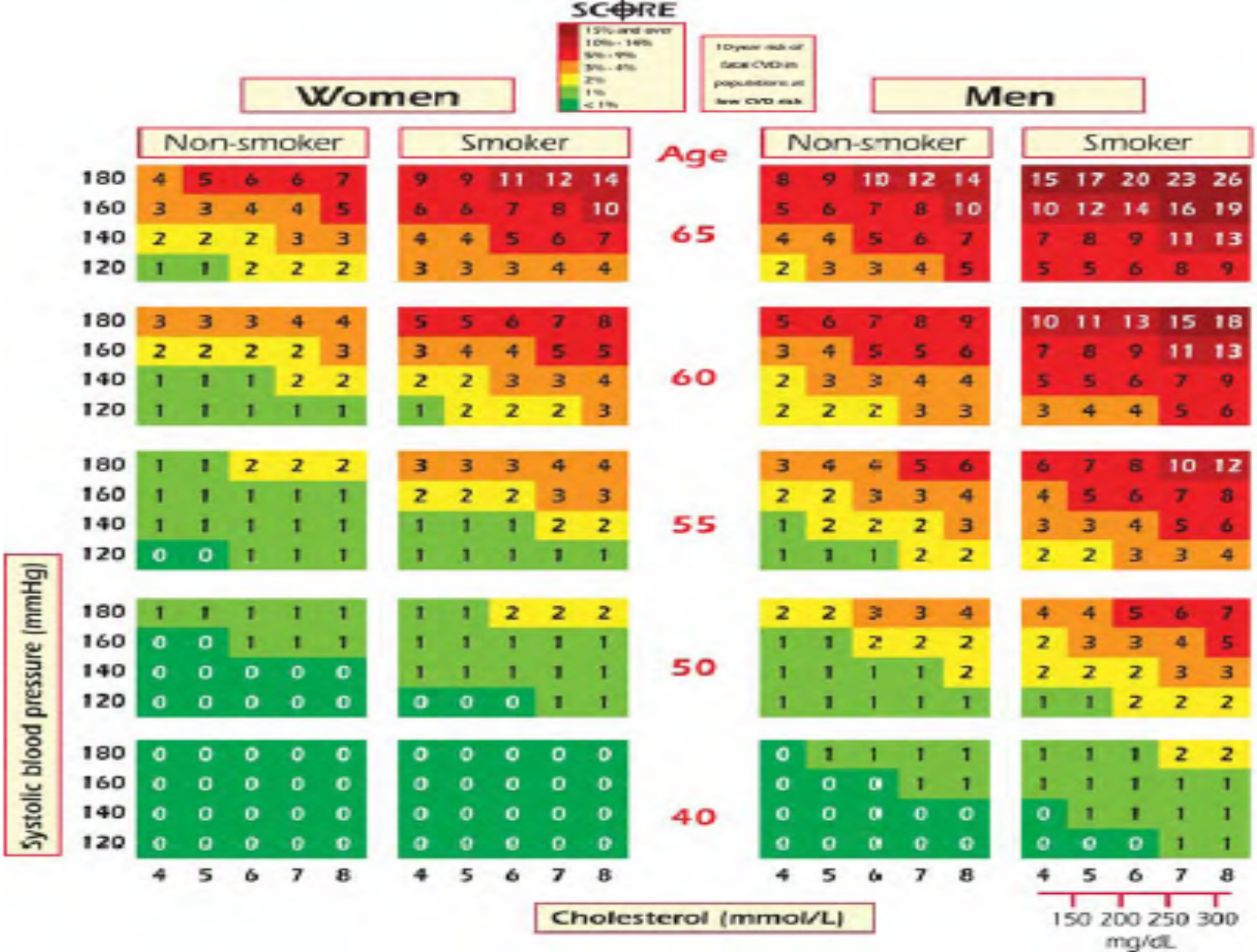
- uguale o superiore a 90 mmHg e inferiore a 130 mmHg
- uguale o superiore a 130 mmHg e inferiore a 150 mmHg
- uguale o superiore a 150 mmHg e inferiore a 170 mmHg
- uguale o superiore a 170 mmHg e inferiore o uguale a 200 mmHg.

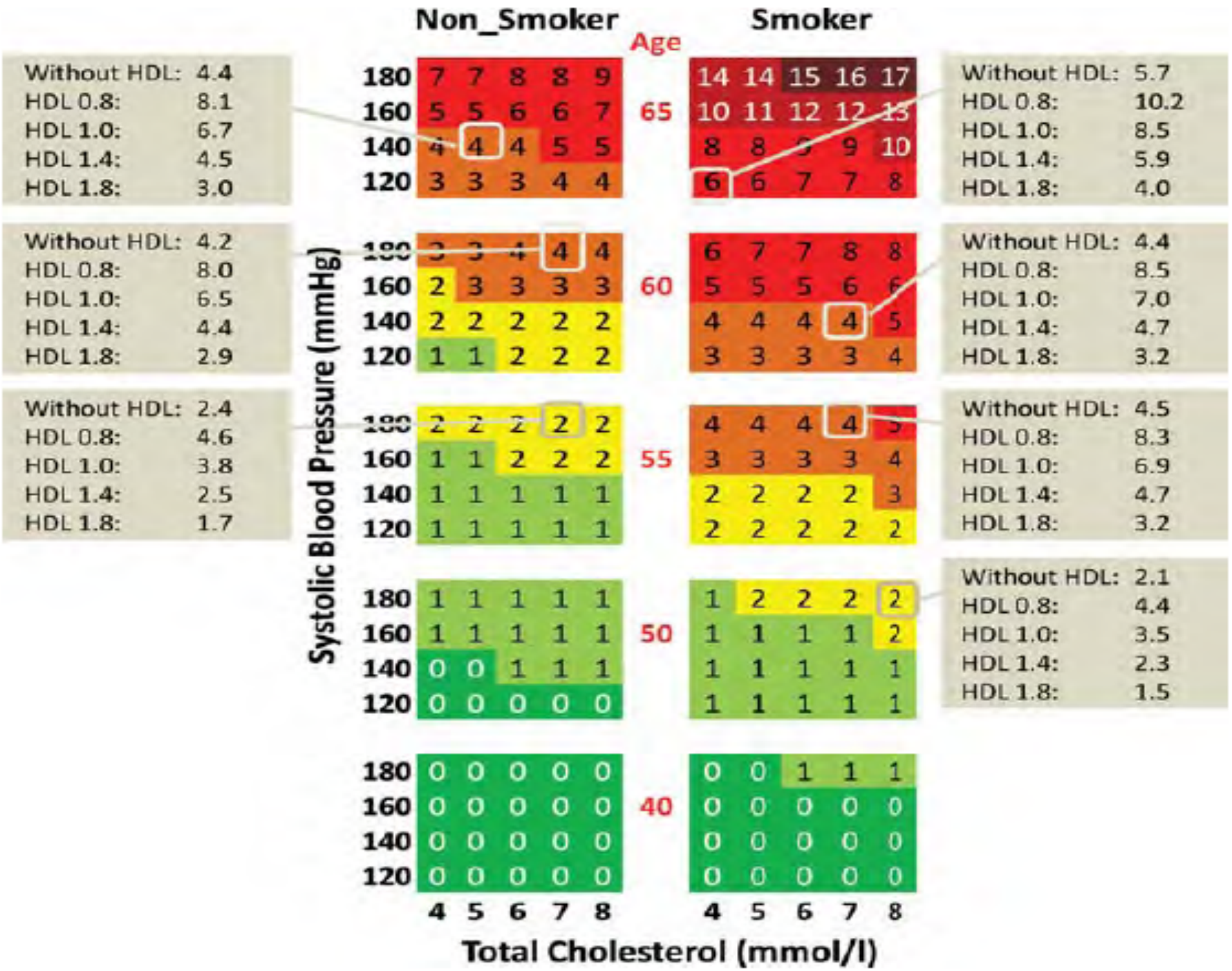
Per persone che hanno il valore della pressione arteriosa sistolica superiore a 200 mmHg o inferiore a 90 mmHg non è possibile utilizzare la carta per la valutazione del rischio

6 ***colesterolemia*** espressa in mg/dl; è suddivisa in cinque intervalli:

- uguale o superiore a 130 mg/dl e inferiore a 174 mg/dl
- uguale o superiore a 174 mg/dl e inferiore a 213 mg/dl


non fumatrici
fumatrici
colesterolemia
pressione arteriosa sistolica
mg/dl 130 174 213 252 291 320
mmHg 200 170 150 130 90
età
60-69
50-59
40-49


SCORE
15% and over
10% - 14%
8% - 9%
5% - 7%
2%
1%
< 1%
10-year risk of fatal CVD in populations at low CVD risk
Women
Men
Non-smoker
Smoker
Non-smoker
Smoker
Age
65
60
55
50
40
180 160 140 120
4 5 6 7 8 | 9 9 11 12 14 | 6 6 7 8 10 | 4 4 5 6 7 | 3 3 3 4 4
3 3 4 4 5 | 2 2 2 3 3 | 1 1 2 2 2
8 9 10 12 14 | 5 6 7 8 10 | 4 4 5 6 7 | 2 3 3 4 5
15 17 20 23 26 | 10 12 14 16 19 | 7 8 9 11 13 | 5 5 6 8 9
3 3 3 4 4 | 2 2 2 2 3 | 1 1 1 2 2 | 1 1 1 1 1
5 5 6 7 8 | 3 4 4 5 5 | 2 2 3 3 4 | 1 2 2 2 3
5 6 7 8 9 | 3 4 5 5 6 | 2 3 3 4 4 | 2 2 2 3 3
10 11 13 15 18 | 7 8 9 11 13 | 5 5 6 7 9 | 3 4 4 5 6
1 1 2 2 2 | 1 1 1 1 1 | 1 1 1 2 2 | 0 0 1 1 1
3 3 3 4 4 | 2 2 2 3 3 | 1 1 1 2 2 | 1 1 1 1 1
3 4 4 5 6 | 2 2 3 3 4 | 1 2 2 2 3 | 1 1 1 2 2
6 7 8 10 12 | 4 5 6 7 8 | 3 3 4 5 6 | 2 2 3 3 4
1 1 1 1 1 | 1 1 1 1 1 | 1 1 1 1 1 | 0 0 0 0 0
1 1 2 2 2 | 1 1 1 1 1 | 1 1 1 1 1 | 0 0 0 0 0
2 2 3 3 4 | 1 1 2 2 2 | 1 1 1 1 2 | 1 1 1 1 1
4 4 5 6 7 | 2 3 3 4 5 | 2 2 2 3 3 | 1 1 2 2 2
0 0 0 0 0 | 0 0 0 0 0 | 0 0 0 0 0 | 0 0 0 0 0
0 0 0 0 0 | 0 0 0 0 0 | 0 0 0 0 0 | 0 0 0 0 0
0 1 1 1 1 | 0 0 0 0 0 | 0 0 0 0 0 | 0 0 0 0 0
1 1 1 2 2 | 1 1 1 1 1 | 1 1 1 1 1 | 0 0 0 0 0
4 5 6 7 8
Systolic blood pressure (mmHg)
Cholesterol (mmol/L)
150 200 250 300
mg/dL

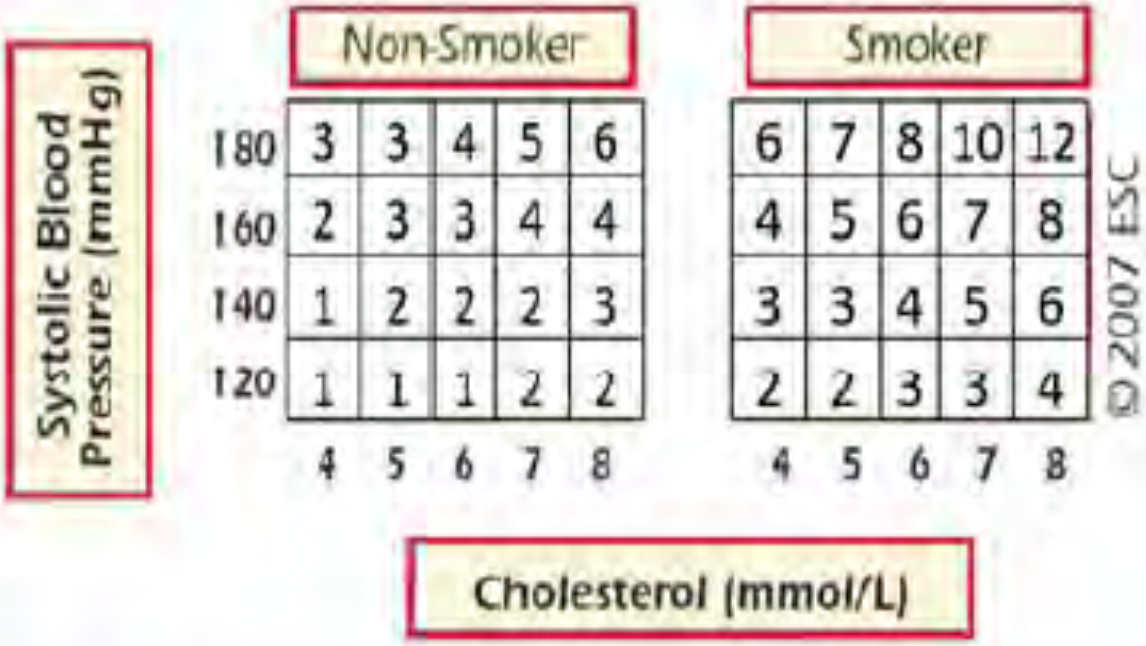

Non_Smoker
Smoker
Age
65
60
55
50
40
Systolic Blood Pressure (mmHg)
180 7 7 8 8 9
160 5 5 6 6 7
140 4 4 4 5 5
120 3 3 3 4 4
14 14 15 16 17
10 11 12 12 13
8 8 9 9 10
6 6 7 7 8
Without HDL: 4.4
HDL 0.8: 8.1
HDL 1.0: 6.7
HDL 1.4: 4.5
HDL 1.8: 3.0
Without HDL: 5.7
HDL 0.8: 10.2
HDL 1.0: 8.5
HDL 1.4: 5.9
HDL 1.8: 4.0
Without HDL: 4.2
HDL 0.8: 8.0
HDL 1.0: 6.5
HDL 1.4: 4.4
HDL 1.8: 2.9
Without HDL: 4.4
HDL 0.8: 8.5
HDL 1.0: 7.0
HDL 1.4: 4.7
HDL 1.8: 3.2
Without HDL: 2.4
HDL 0.8: 4.6
HDL 1.0: 3.8
HDL 1.4: 2.5
HDL 1.8: 1.7
Without HDL: 4.5
HDL 0.8: 8.3
HDL 1.0: 6.9
HDL 1.4: 4.7
HDL 1.8: 3.2
Without HDL: 2.1
HDL 0.8: 4.4
HDL 1.0: 3.5
HDL 1.4: 2.3
HDL 1.8: 1.5
4 5 6 7 8
Total Cholesterol (mmol/l)

FATTORI CHE AUMENTANO IL RISCHIO

- Socially deprived individuals;
- Sedentary subjects and those with central obesity;
- Individuals with diabetes: 5 times higher in women and 3 times higher in men;
- Individuals with low HDL-C or apolipoprotein A1 (apo A1), increased TG, fibrinogen, homocysteine, apolipoprotein B (apo B), and lipoprotein(a) [Lp(a)] levels, familial hypercholesterolaemia(FH), or increased hs-CRP;
- Asymptomatic individuals with plaques or increased carotid intima–media thickness (CIMT);
- Those with impaired renal function;
- Those with a family history of premature CVD, which is considered to increase the risk by 1.7-fold in women and by 2.0-fold in men

Relative Risk Chart

This chart may be used to show younger people at low absolute risk that, relative to others in their age group, their risk may be many times higher than necessary. This may help to motivate decisions about avoidance of smoking, healthy nutrition and exercise, as well as flagging those who may become candidates for medication



Please note that this chart shows RELATIVE not absolute risk. The risks are RELATIVE to 1 in the bottom left. Thus a person in the top right hand box has a risk that is 12 times higher than a person in the bottom left

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug*	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

Lifestyle interventions to reduce TG levels	
Reduce excessive body weight	+++
Reduce alcohol intake	+++
Reduce intake of mono- and disaccharides	+++
Increase habitual physical activity	++
Reduce total amount of dietary carbohydrate	++
Utilize supplements of *n*-3 polyunsaturated fat	++
Replace saturated fat with mono- or polyunsaturated fat	+
Lifestyle interventions to increase HDL-C levels	
Reduce dietary trans fat	+++
Increase habitual physical activity	+++
Reduce excessive body weight	++
Reduce dietary carbohydrates and replace them with unsaturated fat	++
Use alcohol with moderation	++
Among carbohydrate-rich foods prefer those with low glycaemic index and high fibre content	+
Quit smoking	+
Reduce intake of mono- and disaccharides	+

	Da preferire	Da usare con moderazione	Da scegliere occasionalmente in quantità limitate
Cereali	Farina integrale	Pane raffinato, riso, pasta, biscotti, corn flakes	Dolci, muffins, torte, croissants
Verdure	Verdure crude e cotte		Verdure preparate con creme e burro
Legumi	Tutti (incluso soia e proteine di soia)		
Frutta	Frutta fresca o congelata	Frutta secca, gelatina, marmellata, frutta candita, sorbetti, ghiaccioli	
Dolci e dolcificanti	Dolcificanti non calorici	Saccarosio, miele, fruttosio, glucosio, cioccolata, dolciumi	Torte, gelati
Carne e pesce	Pesce, pollame senza pelle	Tagli magri di manzo, agnello, maiale o vitello, frutti di mare, crostacei	Salsicce, salami, pancetta, costolette di maiale, hot dog, frattaglie
Prodotti caseari e uova	Latte scremato, yogurt con latte scremato, albume d'uovo	Latte parzialmente scremato e suoi derivati	Formaggio, crema, tuorlo d'uovo, latte intero, yogurt con latte intero
Cibi grassi e condimenti	Aceto, ketchup, mostarda, condimenti con pochi grassi	Oli vegetali, margarina a basso contenuto di grassi, condimenti per insalate, maionese	Burro, margarina, grassi trans, olio di palma e olio di cocco, strutto, grasso di pancetta, condimenti prodotti con tuorlo d'uovo
Noci/semi		Tutti	Cocco
Tipo di cottura	Alla griglia, bollito, al vapore	Saltato in padella, arrostito	Fritto

Col-LDL = Colesterolo a lipoproteine a bassa densità.
TC = colesterolo totale.

Tabella 4. Raccomandazioni dietetiche per abbassare i livelli di CT e Col-LDL.

ESC/EAS Guidelines for the management of dyslipidaemias

Table 12 Summary of lifestyle measures and healthy food choices for managing total cardiovascular risk

• Dietary recommendations should always take into account local food habits; however, interest in healthy food choices from other cultures should be promoted.
• A wide variety of foods should be eaten. Energy intake should be adjusted to prevent overweight and obesity.
• Consumption of fruit, vegetables, legumes, nuts, wholegrain cereals and bread, fish (especially oily) should be encouraged.
• Saturated fat should be replaced with the above foods and with monounsaturated and polyunsaturated fats from vegetable sources, in order to reduce energy intake from total fat to <35% of energy, saturated fat to <7% of total energy, trans fats to <1% of total energy, and dietary cholesterol to <300 mg/day.
• Salt intake should be reduced below 5 g/day by avoiding table salt and limiting salt in cooking, and by choosing fresh or frozen unsalted foods; many processed and convenience foods, including bread, are high in salt.
• For those who drink alcoholic beverages, moderation should be advised (<10–20 g/day for women and <20–30 g/day for men) and patients with hypertriglyceridaemia (HTG) should abstain.
• The intake of beverages and foods with added sugars, particularly soft drinks, should be limited, particularly for patients with HTG.
• Physical activity should be encouraged, aiming at regular physical exercise for at least 30 minutes/day every day.
• Use and exposure to tobacco products should be avoided.

Task Force for the management of dyslipidaemias, Eur Heart J, 32: 1769- 1818, 2011

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• Use and exposure to tobacco products should be avoided.

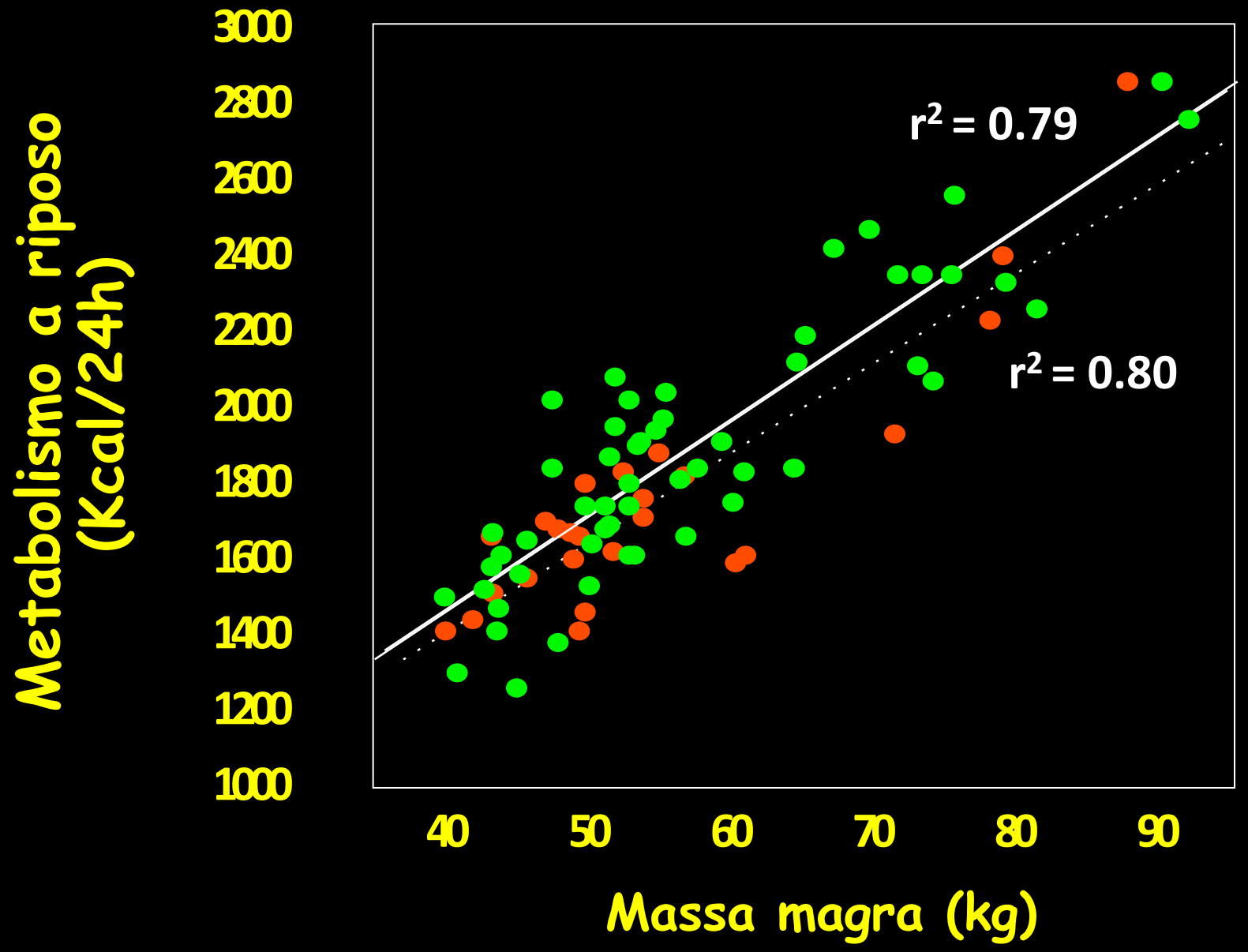
Table 9 Impact of specific lifestyle changes on lipid levels

	Magnitude of the effect
Lifestyle interventions to reduce TC and LDL-C levels	
Reduce dietary saturated fat	+++
Reduce dietary trans fat	+++
Increase dietary fibre	++
Reduce dietary cholesterol	++
Utilize functional foods enriched with phytosterols	+++
Reduce excessive body weight	+
Utilize soy protein products	+
Increase habitual physical activity	+
Utilize red yeast rice supplements	+
Utilize polycosanol supplements	-

NUTRACEUTICI

- Innovative nutritional strategies changing some ‘risky’ dietary components or on encouraging the consumption of specifically targeted ‘healthy’ functional foods and/or dietary supplements; these so-called ‘nutriceuticals’
- The principal phytosterols are sitosterol, campesterol, and stigmasterol, in vegetable oils and, in smaller amounts, in vegetables, fresh fruits, chestnuts, grains, and legumes. The dietary intake of plant sterols ranges between an average of 250 mg/day in Northern Europe to 500 mg/day in Mediterranean countries. Phytosterols compete with cholesterol for intestinal absorption, thus modulating TC levels.

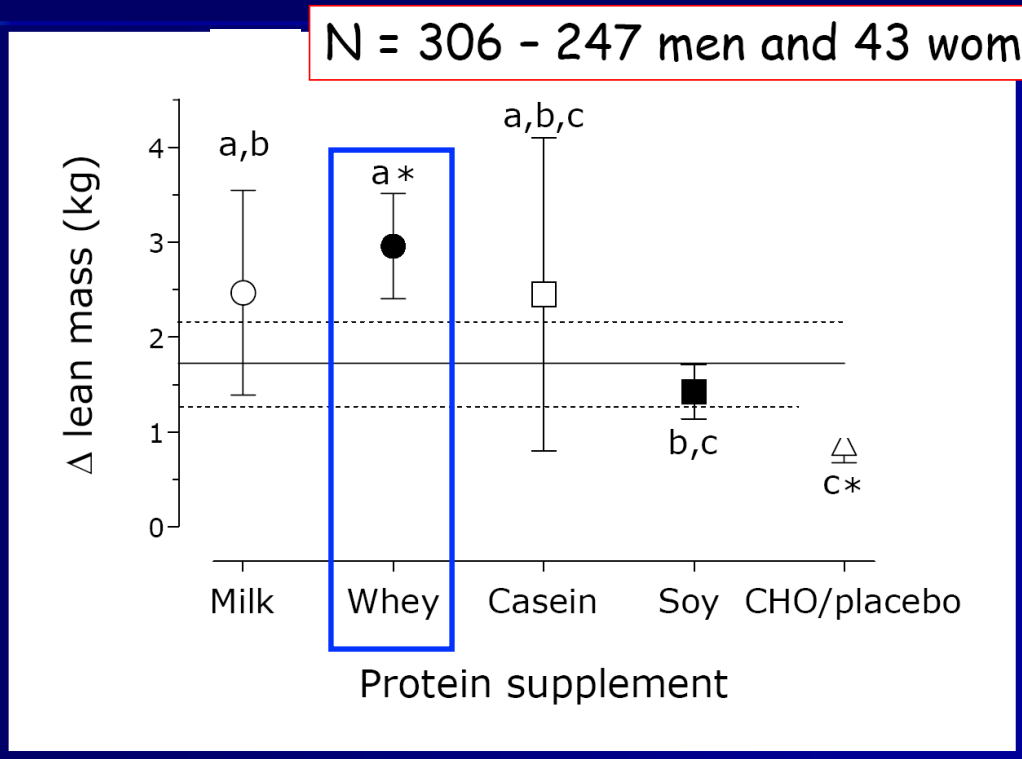
RELAZIONE TRA MASSA MAGRA E METABOLISMO A RIPOSO



FONTI PROTEICHE E ANABOLISMO MUSCOLARE

Whey promotes superior gains in muscle mass versus other proteins

N = 306 - 247 men and 43 women



Phillips et al, J. Am. Coll. Nutr., 2008, in

EFFETTI DELLE PROTEINE DEL SIERO DEL LATTE

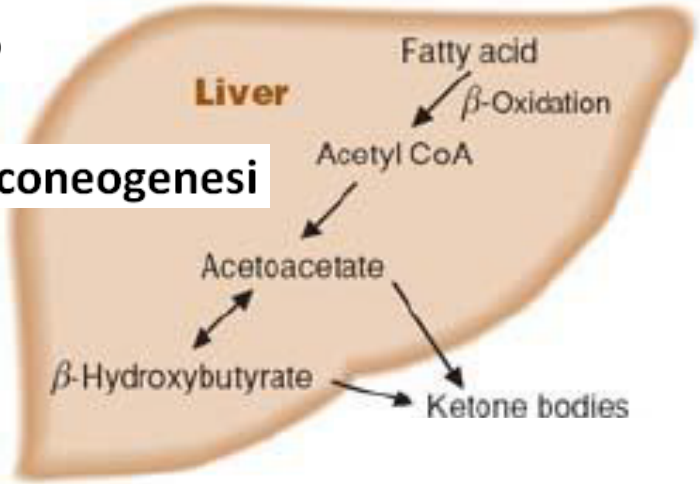
- Composizione AA simile a quella dei muscoli umani
- Contengono tutti gli AAE
- Contengono oligopeptidi e polipeptidi a rapido assorbimento
- Stimolano la sintesi proteica
- Favoriscono un profilo ormonale adatto alla protezione e alla crescita della FFM: GH/IGF-1

  Inducono maggiore senso di sazietà rispetto alle caseine
- Fungono da substrato per la gluconeogenesi
- Stimolano la sintesi di NO e quindi la vasodilatazione

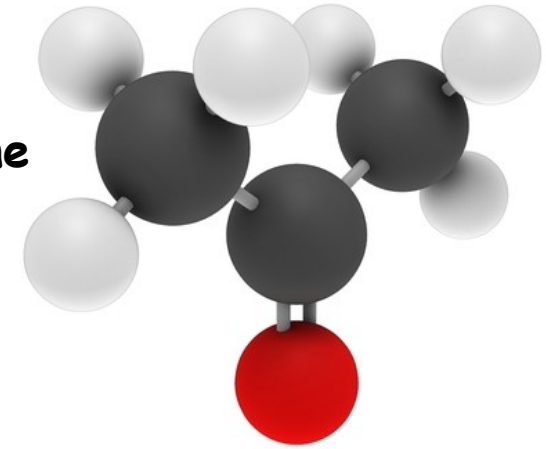
CHETOSI

Carboidrati della dieta < 50 g al giorno

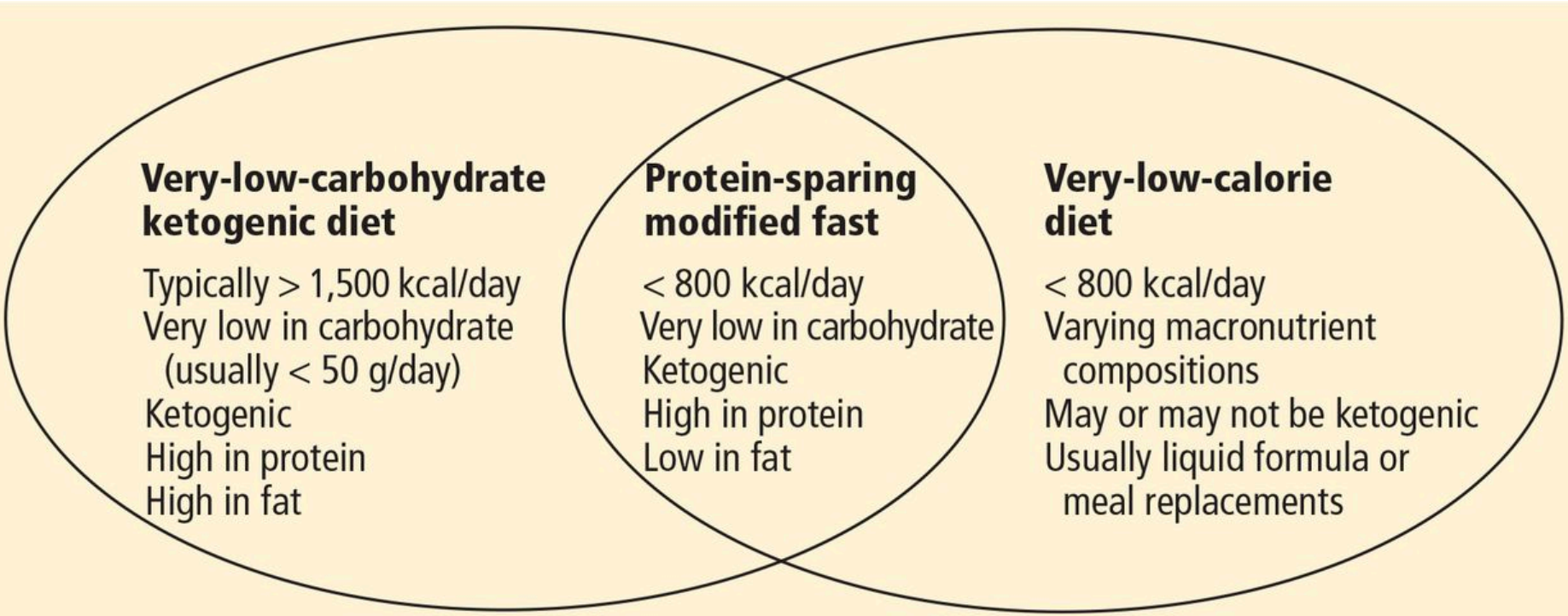
Glicerolo → **Gluconeogenesi**



Acetone



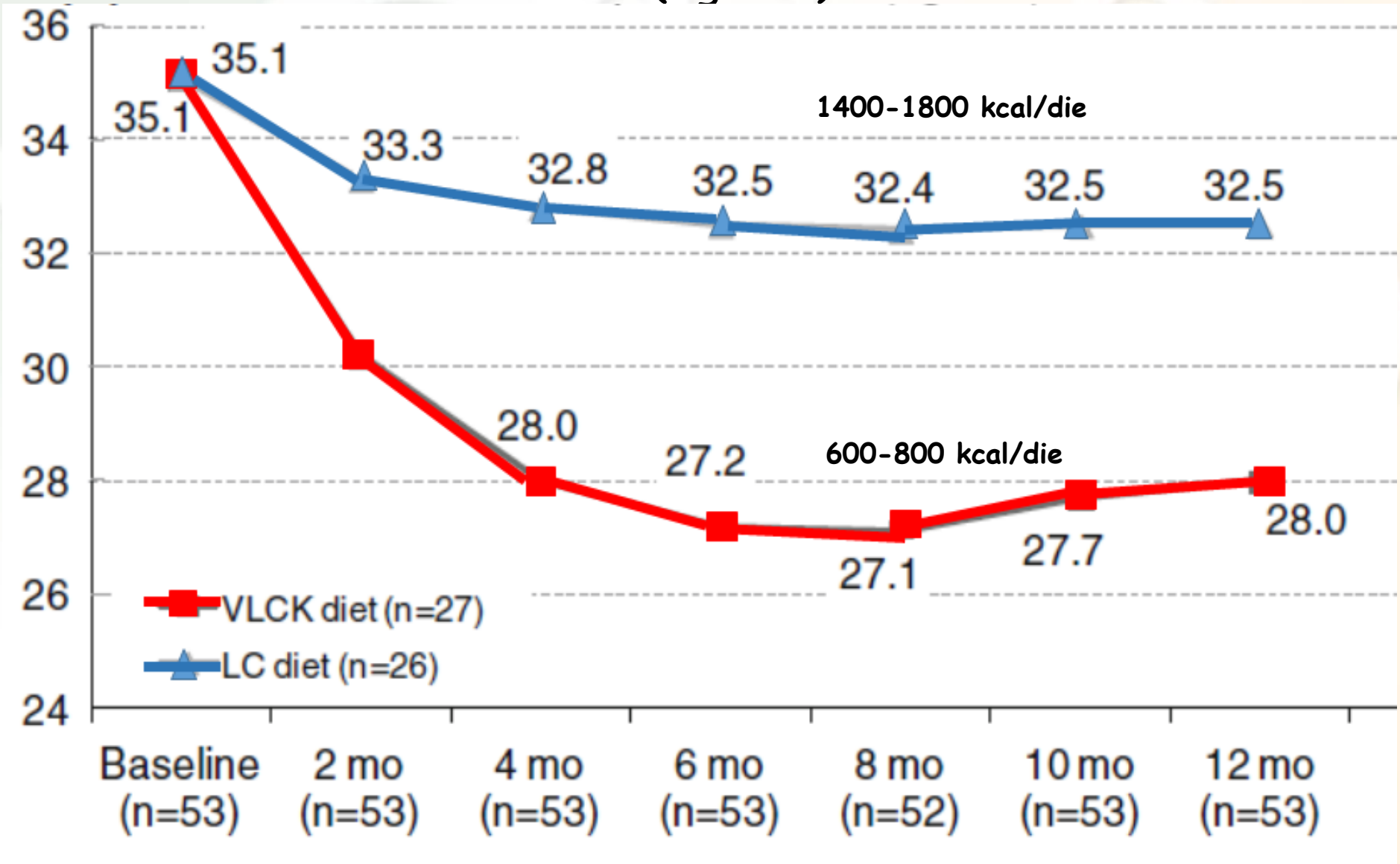
0.5 mM



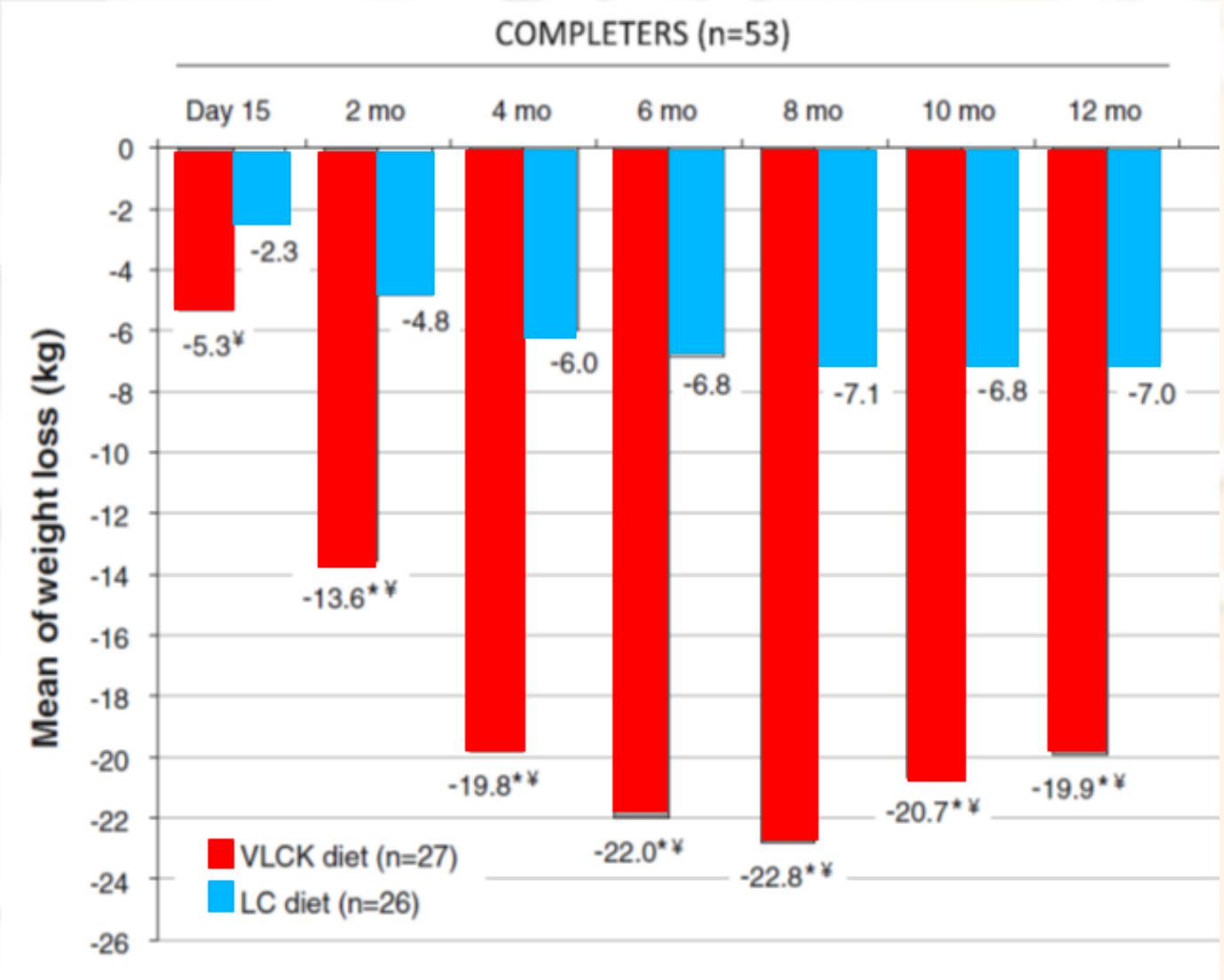
A ketogenic diet is a highly muscle-sparing diet

Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity

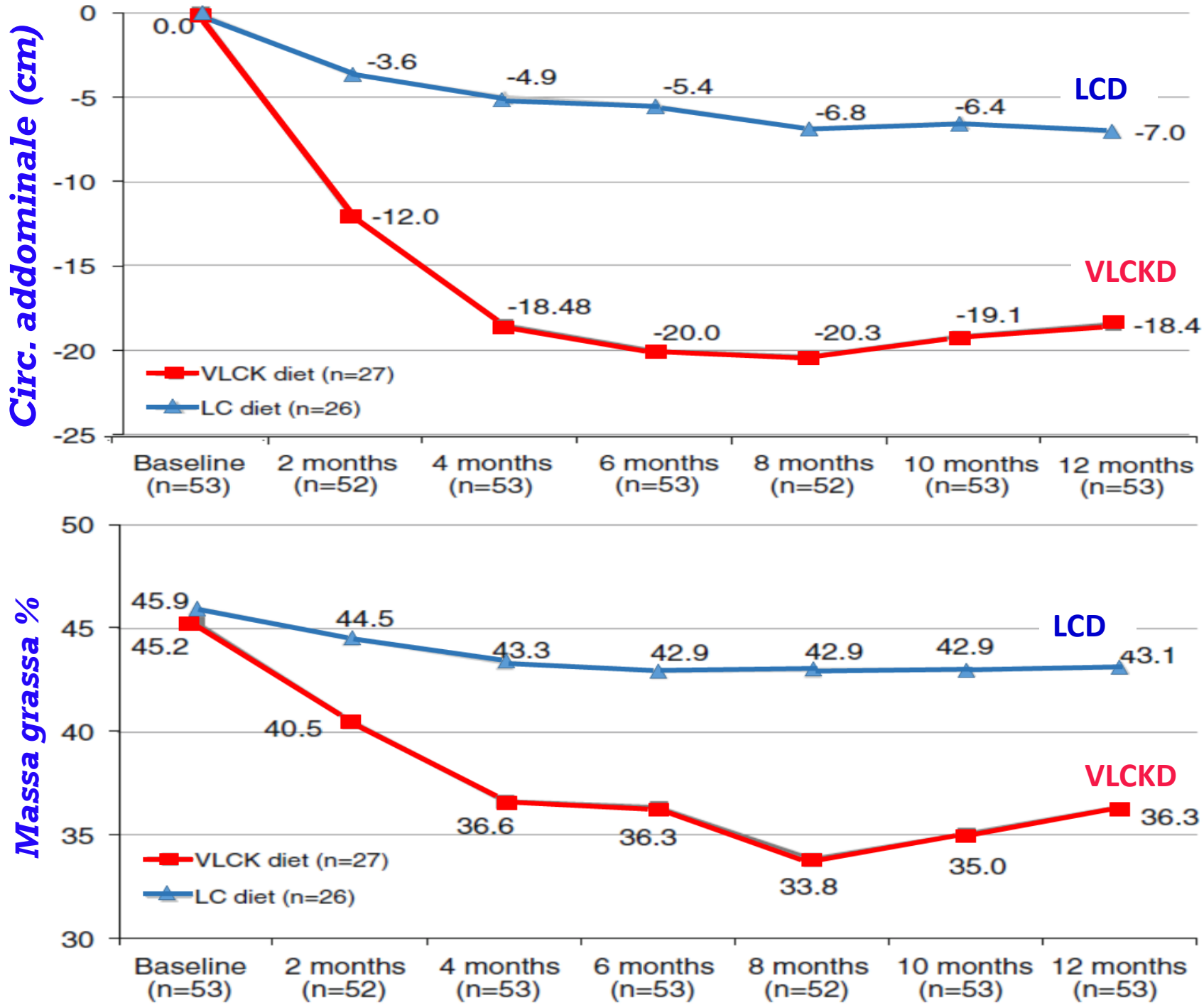
Riduzione BMI (Kg/m^2) valore assoluto



Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity



Moreno B et al, Endocrine, 2014


Circ. addominale (cm)
0
-5
-10
-15
-20
-25
0.0
-3.6
-4.9
-5.4
-6.8
-6.4
-7.0
LCD
-12.0
-18.48
-20.0
-20.3
-19.1
-18.4
VLCKD
VLCK diet (n=27)
LC diet (n=26)
Baseline (n=53)
2 months (n=52)
4 months (n=53)
6 months (n=53)
8 months (n=52)
10 months (n=53)
12 months (n=53)
Massa grassa %
50
45
40
35
30
45.9
45.2
44.5
43.3
42.9
42.9
42.9
43.1
LCD
40.5
36.6
36.3
33.8
35.0
36.3
VLCKD
VLCK diet (n=27)
LC diet (n=26)
Baseline (n=53)
2 months (n=52)
4 months (n=53)
6 months (n=53)
8 months (n=52)
10 months (n=53)
12 months (n=53)

PROPORRESTI FARMACI PER IL PESO?

……

LA PERDITA DI PESO PUO' MIGLIORARE LE COMORBIDITA' CORRELATE ALLA OBESITA'

L'obiettivo fissato dall'FDA per i farmaci per i quali viene richiesta l'approvazione per la perdita di peso è una differenza del 5% tra il trattamento attivo e il placebo.

BENEFICI DELLA PERDITA DEL 5-10% DEL PESO CORPOREO

- Riduzione del rischio di diabete tipo 2

- Riduzione dei fattori di rischio CV

- Miglioramento del profilo lipidico

- Riduzione dei valori della pressione arteriosa

- Riduzione della gravità dell'OSAS

- Miglioramento della qualità della vita

FARMACI PER IL PESO?

Standard Italiani per la Cura dell'Obesità

Società Italiana dell'Obesità

Adulti

Il trattamento farmacologico dovrebbe essere preso in considerazione solo dopo che è stata valutata l'efficacia della dieta, dell'esercizio fisico e, dove indicato, della terapia cognitivo-comportamentale e tali approcci terapeutici si siano dimostrati inefficaci o nell'indurre perdita di peso o nel mantenimento del peso perso.

- un BMI di 28,0 kg/m^2 o maggiore con fattori di rischio associati
- un BMI di 30,0 kg/m^2 o maggiore.

La terapia dovrebbe essere continuata oltre i 3 mesi solo se il paziente ha perso almeno il 5 % del peso dall'inizio della terapia farmacologica.

Prosecuzione della terapia e sospensione del farmaco

Il trattamento farmacologico può essere indicato al fine di mantenere la perdita di peso, piuttosto che per indurre un'ulteriore perdita del peso. In questo contesto si inserisce il concetto di terapia ciclica o intermittente[c]

ORLISTAT

TABLE 1 Medications Approved for Chronic Weight Management: Mechanism of Action, Dosing and Response Evaluation

	Mechanism of Action	Dosing	Response Evaluation
Orlistat (1)	Pancreatic lipase inhibitor	120 mg orally with each meal containing fat	Not addressed in label

Fujioka A et al, Obesity, 23: S7-S11, 2015

TABLE 1 Comparison of Weight Loss Efficacy of Medications for Chronic Weight Management

Medication	Mechanism of Action	Average weight lost at 1 year (kg)	Percentage of patients achieving >5% loss of body weight at 1 year
Orlistat	Gastrointestinal lipase inhibitor	10.3 kg vs. for placebo	68.5% vs. for placebo
Phentermine/ topiramate	Adrenergic agonist/taste aversion via unclear mechanisms	8.1 kg (7.5/46 mg) vs. for placebo 10.2 kg (15/92 mg) vs. for placebo	62% vs. for placebo 70% vs. for placebo
Lorcaserin	5-HT2C Agonist	5.8 kg vs. for placebo	47.5% vs. for placebo
Bupropion/naltrexone	Reuptake inhibitor of dopamine and/or norepinephrine/opioid antagonist	6.1 kg (360/32 mg) vs. for placebo	39% vs. for placebo
Liraglutide 3.0 mg	GLP-1 Receptor agonist	7.4% (vs. 3.0% for placebo)	62.3% (vs. 34.4% for placebo)

Ryan DH et al, Obesity, 2015

LIRAGLUTIDE (SAXENDA)

La Commissione Europea ha concesso l'autorizzazione al commercio di Liraglutide 3 mg (Saxenda – Novo N) per il trattamento dell'obesità. Saxenda è il primo analogo GLP-1 in mono-somministrazione giornaliera per il trattamento dell'obesità approvato in Europa.

La dose è 3.0 mg rispetto a 1.2 o 1.8 mg approvate per la terapia del diabete con il marchio Victoza.

È indicato come trattamento in aggiunta a dieta ed esercizio fisico per la gestione del peso in pazienti adulti con BMI iniziale:
≥ 30 kg/m2 (obesi) oppure
compreso tra 27 e 30 kg/m2 (sovrappeso) in presenza di almeno una comorbilità correlata al peso

EFFETTI METABOLICI DEL GLP-1

Appetite

- ↑ Satiety
- ↑ Fullness
- ↓ Hunger
- ↓ Prospective food consumption
- ↓ Energy intake

Glucose regulation

(Glucose-dependent)

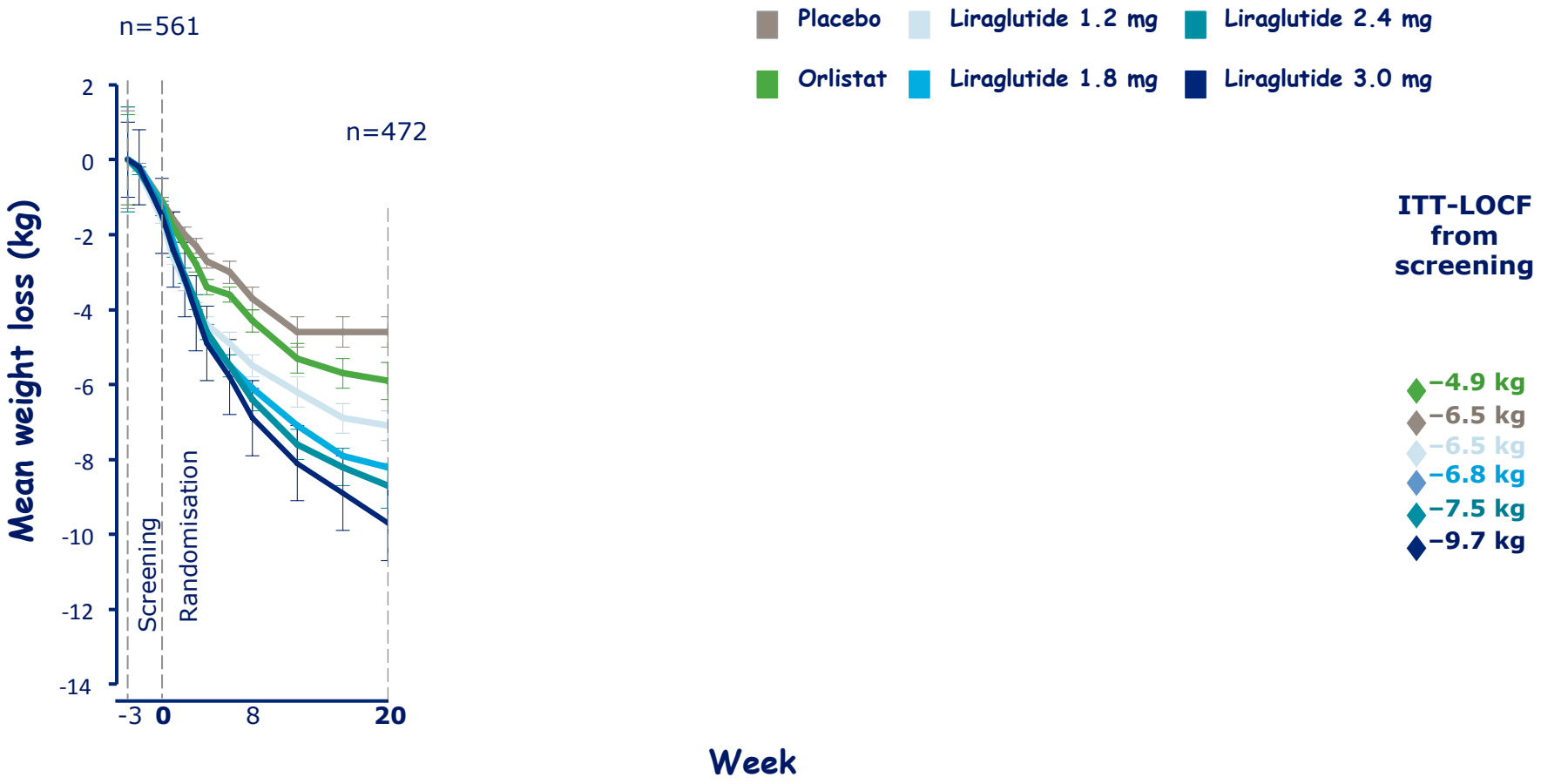
- ↑ Insulin secretion
- ↓ Glucagon secretion

Mild gastric effects

- ↓ Gastric acid
- ↓ Gastric emptying

Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide

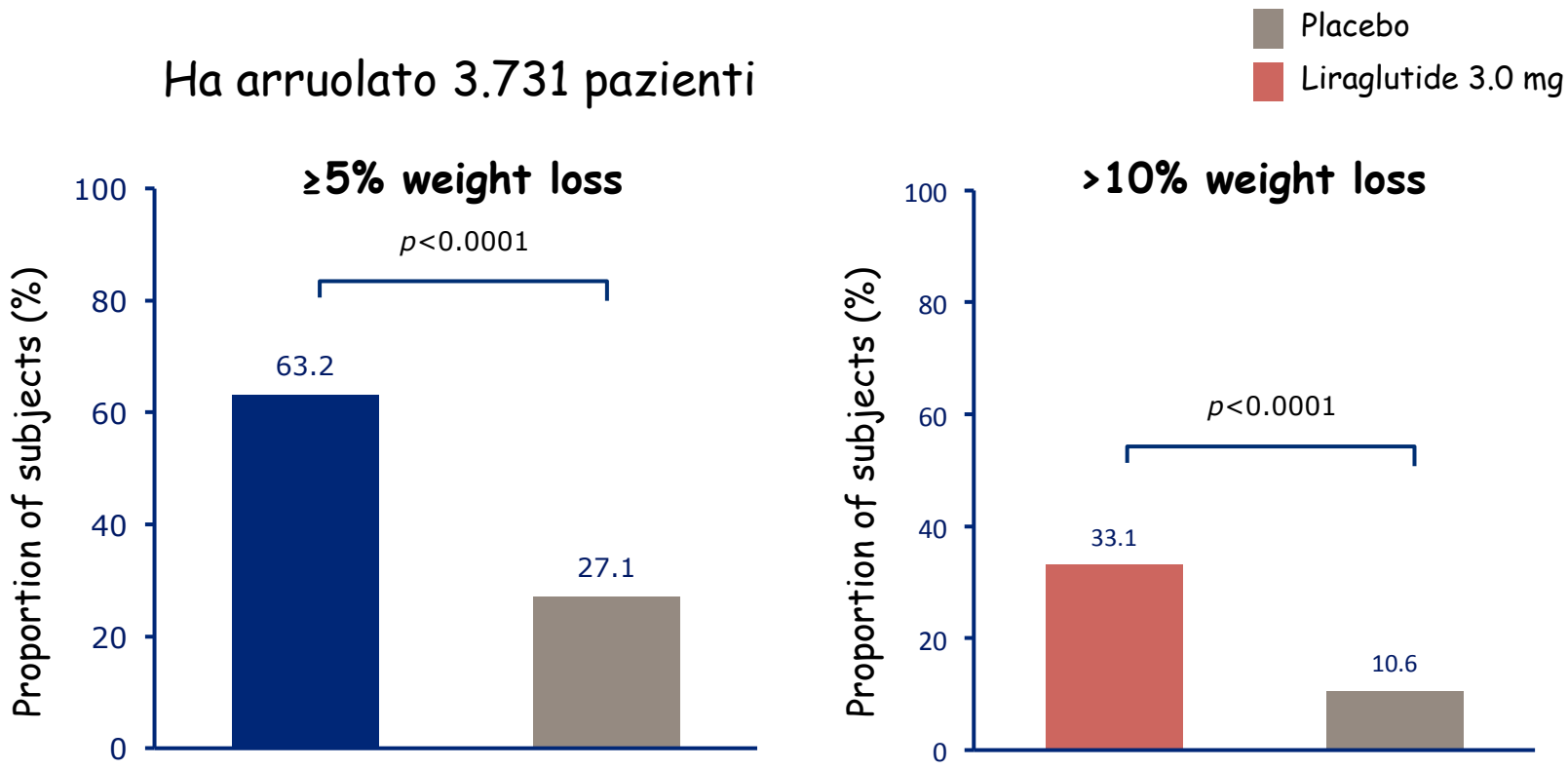
Lifestyle intervention: –500 kcal/day hypocaloric diet + increased physical activity



Astrup et al, Int J Obesity, 36: 843-854, 2012

A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Ha arruolato 3.731 pazienti

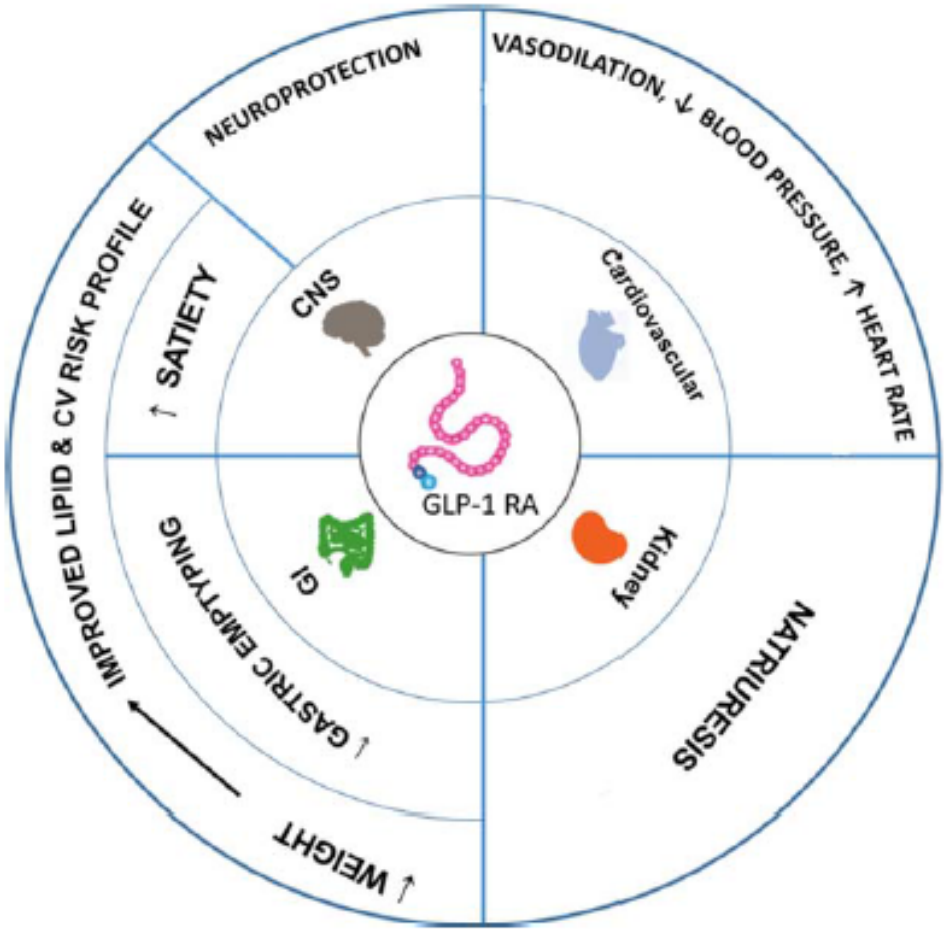


Il gruppo liraglutide ha perso una media dell'8% del peso corporeo a 56 settimane vs il 2.6% del gruppo placebo

La perdita di peso media è stata del 10.8% nel gruppo che aveva mostrato una precoce risposta alla liraglutide, contro 3% nel gruppo che non aveva risposto rapidamente.

Pi-Sunyer X et al, NEJM, 373: 11-22, 2015

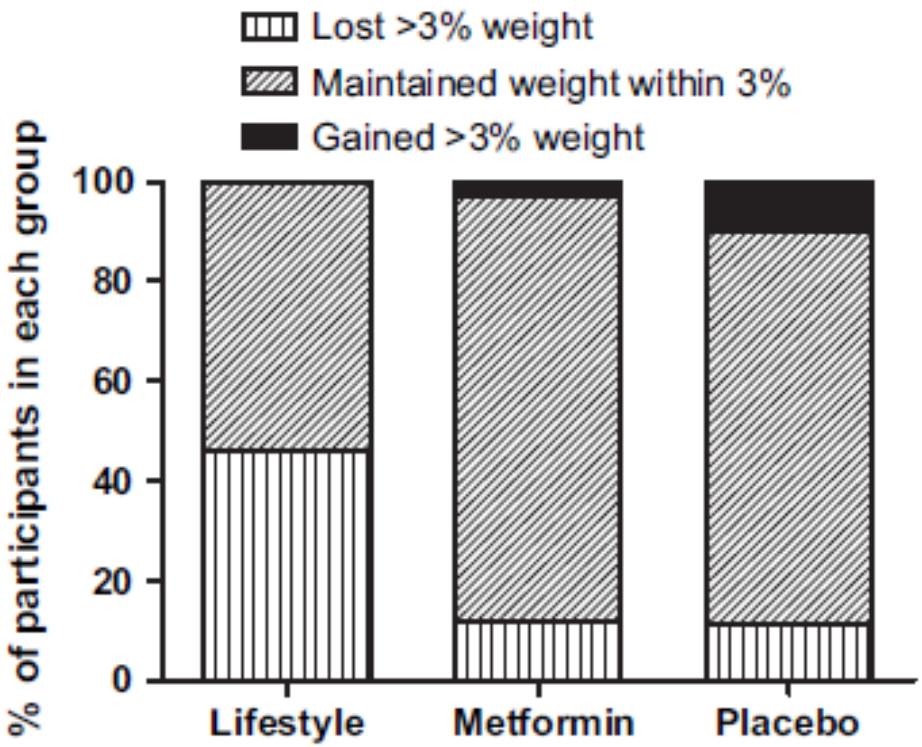
GLP-1 Receptor Agonists: Nonglycemic Clinical Effects in Weight Loss and Beyond



Ryan e Acosta, Obesity, 23: 1119-1129, 2015

The effect of comprehensive lifestyle intervention or metformin on obesity in young women☆

Weight outcomes of participants after 12-weeks on comprehensive lifestyle program (n = 59), metformin (n = 65), or placebo (n = 79). P < 0.05 for chi-square analysis.



Lim SS et al, NMCD, 21: 261-268, 2011

CAMMINARE

10.000 passi al giorno garantiscono il rispetto delle Raccomandazioni per la prevenzione delle patologie croniche e 10.000 passi al giorno ad un'andatura veloce (marcia) equivalgono ad una spesa energetica di circa 350-400 calorie.

Livello di attività fisica	Numero di passi quotidiano
Molto attivo	≥ 12.500
Attivo	10.000 – 12.499
Poco attivo	7.500-9.999
Pochissimo attivo	5.000-7.499
Sedentario • Attività limitata • Attività di base	< 5.000 2.500 – 4.999 < 2.500

Il cammino normale corrisponde a 80-85 passi al minuto (4.800-5.100/h)

Il cammino normale corrisponde a 4 km/h e il cammino veloce a 5-6 km/h

Si consuma 1 kcal per km di camminata a passo svelto e per Kg di peso: una persona di 70 Kg che cammina a passo svelto per 10 km ossida 700 kcal

CRITICITA'

Holter pressorio

Diabete gestazionale macrosomia

Metformina

Dieta chetogenica

Carte del rischio

TAKE HOME MESSAGES

-Nella sindrome metabolica la variazione dello stile di vita è fondamentale
-La diagnostica può trovare nell'holter pressorio un valido strumento
-La tx farmacologica dell'obesità/sovrappeso può precedere l'uso di farmaci diretti (controverso),contro le varie componenti della sindrome
-Le carte del rischio possono non dare una valutazione accurata del rischio cardiovascolare individuale
-Nuove opportunità possono essere fornite dalla nutraceutica
-Il concetto di adattamento sartoriale va applicato alla diagnostica, all'inquadramento del rischio cardiovascolare globale e naturalmente alla terapia

Modigliani

Botero