



PRESENT
AND FUTURE
APPROACHES TO
THE CONTROL OF
DYSLIPIDAEMIAS

S.I.Te.C.S.
SOCIETÀ ITALIANA DI TERAPIA CLINICA E SPERIMENTALE

A practical approach to nutraceuticals

Matteo Pirro - Università degli Studi di Perugia, Italy

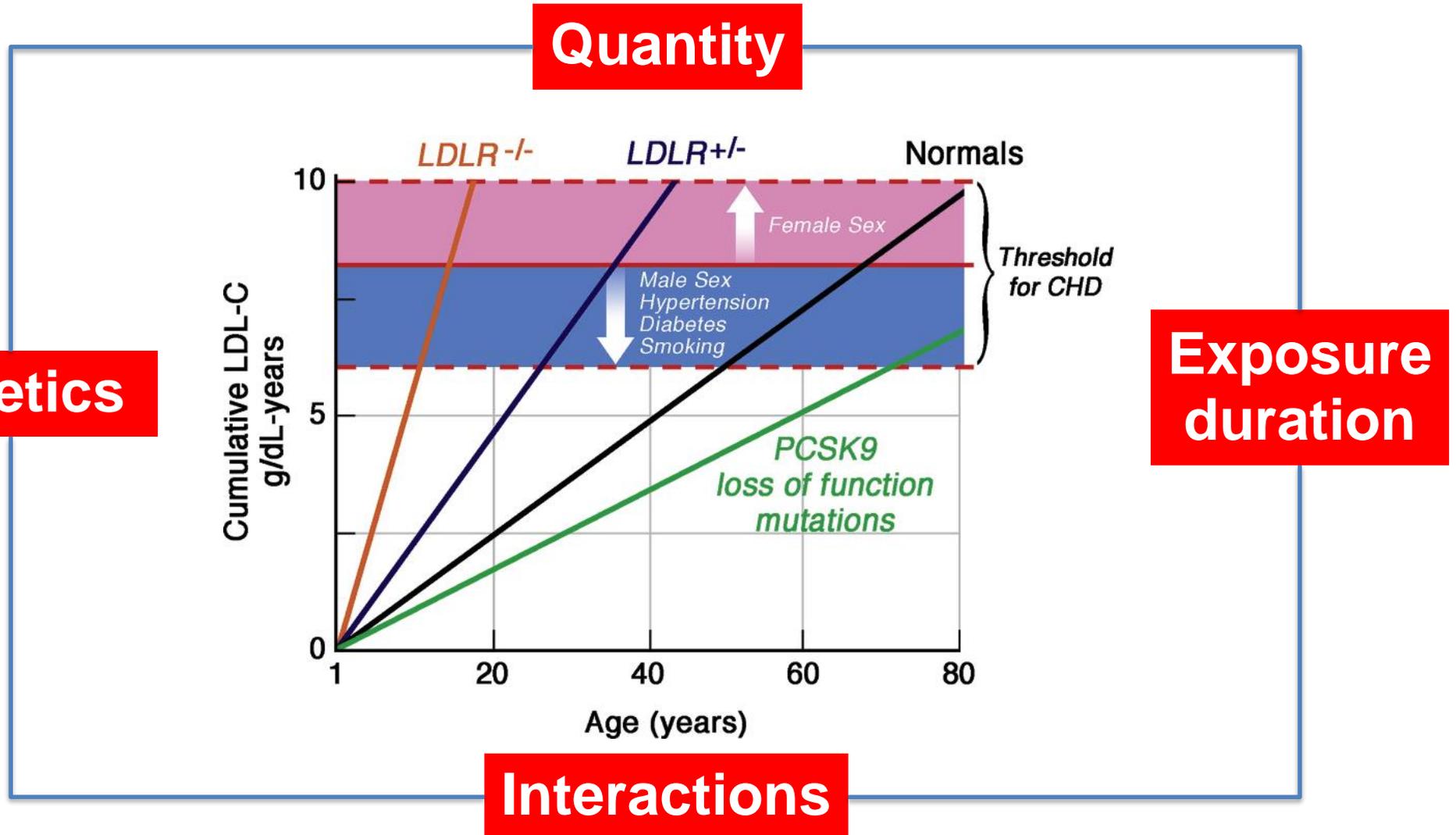
Disclosure of potential conflicts of interest

Matteo Pirro - Università degli Studi di Perugia, Italy

EMPLOYEMENT	//
RESEARCH GRANT / RESEARCH SUPPORT	Amgen, MEDA, Mylan
SPEAKER BUREAU	//
HONORARIA	//
EXPERT WITNESS	//
OWNERSHIP INTEREST	//
CONSULTANT/ ADVISORY BOARD	Bayer, Daiichi Sankyo
OTHER	

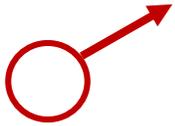
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LDL cholesterol atherogenicity is influenced by different factors...



Modified from: Sniderman AD et al. J Am Coll Cardiol. 2014;63(19):1935-1947.

Interactions may have a significant long-term impact on CV prognosis



45-y

- FAMILY HISTORY:

- mother 73-y: LDL-C 106 mg/dL with SIMVA 20 mg/d
- father 80-y: ischemic stroke at 79-y
- 2 healthy brothers
- sister 53-y: LDL-C 144 mg/dL, otherwise healthy
- 2 healthy sons

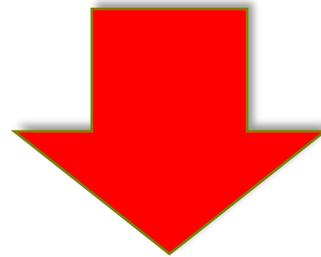
- PERSONAL CLINICAL HISTORY:

- Recent diagnosis of **hypertension** (no drug therapy)

- PATIENT CHARACTERISTICS:

- non smoker
- BP 144/90 mmHg
- Weight/Height 81-Kg/170 cm; **BMI 28; WC103 cm**
- No evidence of xanthomas, corneal arch

Therapeutic Lifestyle Changes



TC.....	227	mg/dl
TGs.....	145	mg/dl
LDL-C.....	148	mg/dL
HDL-C.....	50	mg/dl
FPG.....	89	mg/dl

Fasting lipid profile

```
graph TD; A[Fasting lipid profile] --> B[Try to make an etiological diagnosis]; A --> C[Search for other CV RFs or CHD equivalents]; A --> D[Estimate 10-y CV risk and...]; B --> E[Define the most appropriate treatment goals]; C --> E; D --> E; E --> F[Choose the right therapy];
```

Try to make an etiological diagnosis

Search for other CV RFs or CHD equivalents

Estimate 10-y CV risk and...

Define the most appropriate treatment goals

Choose the right therapy

Some causes of dyslipidemias

Severe Primitive Dyslipidemia

- FH

LDL-C > 195 mg/dl

- FCH

LDL-C > 160 mg/dl and/or TG > 200 mg/dl

- Dysbetalipoproteinemia

CT > 300 mg/dl and TG > 300 mg/dl (TC/TG ~ 0.5-1)

- Familial HTG

TG > 800 mg/dl

- Other...

Secondary dyslipidemias



NO



Hypothyroidism

Paraproteinemia



NO



Cholestatic liver disease

Nephrotic syndrome



NO



CKD

Nervous anorexia



NO



Drugs

Alcohol

Yes



Obesity, DM

 hypercholesterolemia

 hypertriglyceridemia

Fasting lipid profile

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Try to make an etiological diagnosis

Search for other CV RFs or CHD equivalents

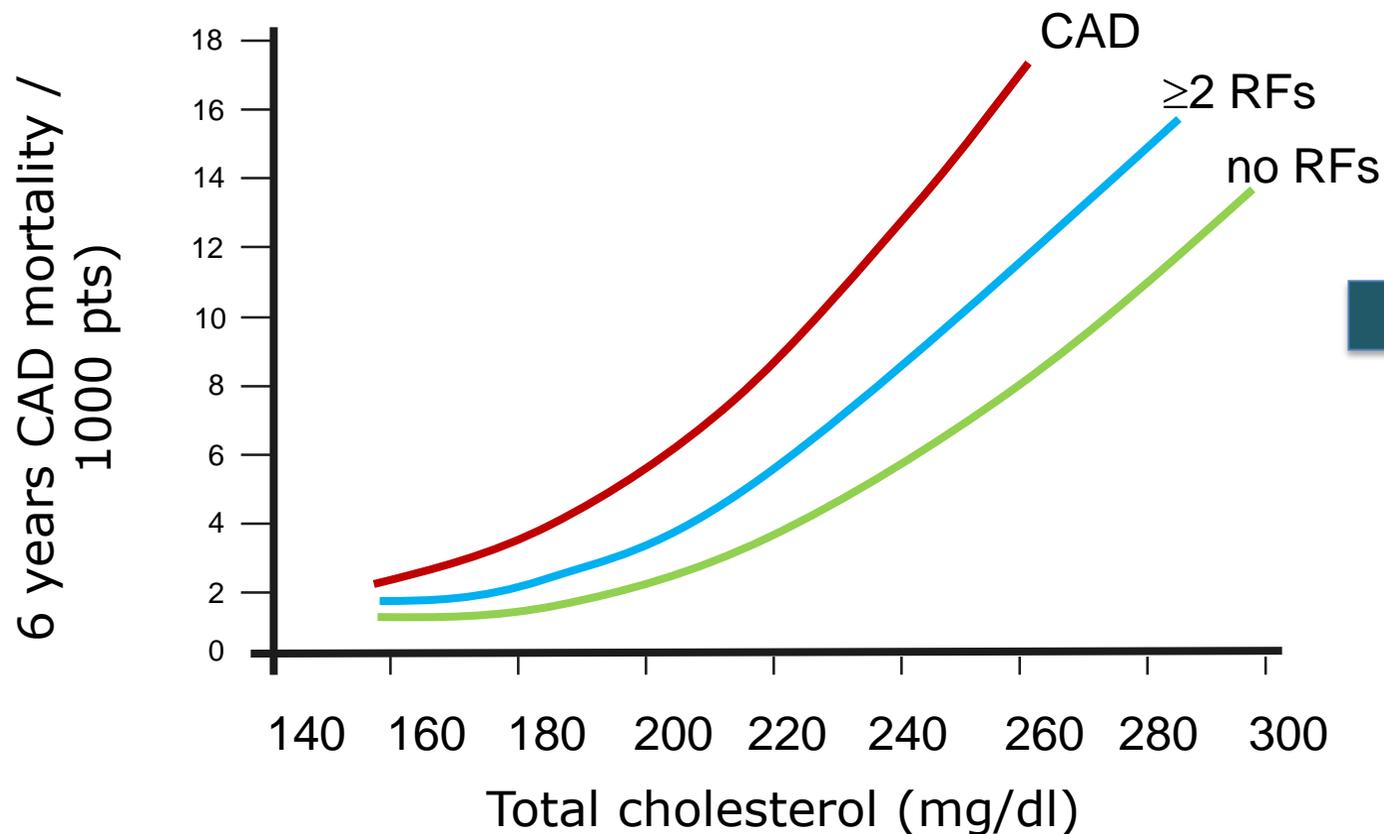
Estimate 10-y CV risk and...

Define the most appropriate treatment goals

Choose the right therapy

Interaction between measurable risk factors and CAD mortality in the MRFIT

For 6-12-25 years, 350,977 men aged 35 to 57 years who had been screened for the **Multiple Risk Factor Intervention Trial** were followed up



This relationship persisted over the 12/25-year follow-up period

Main CV risk factors

Age male >45 years
 female >55 years

Family history of premature CHD (< 55 years in male first-degree relatives, or <65 years of age in female first degree relatives)

Current cigarette smoking

Hypertension (>140/90 mmHg or on anti-hypertensive medication)

Low HDL cholesterol (<40 mg/dl in men and <50 mg/dl in women)

Negative (protector) risk factor: HDL cholesterol > 60mg dl



CV High Risk Equivalents

CHD, CVD, PAD, AAA, ATS



NO

CKD



NO

Diabetes



NO

FH



NO

**Multiple or very high level
of individual RFs**



NO

Fasting lipid profile

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Try to make an etiological diagnosis

Search for other CV RFs or CHD equivalents

Estimate 10-y CV risk and...

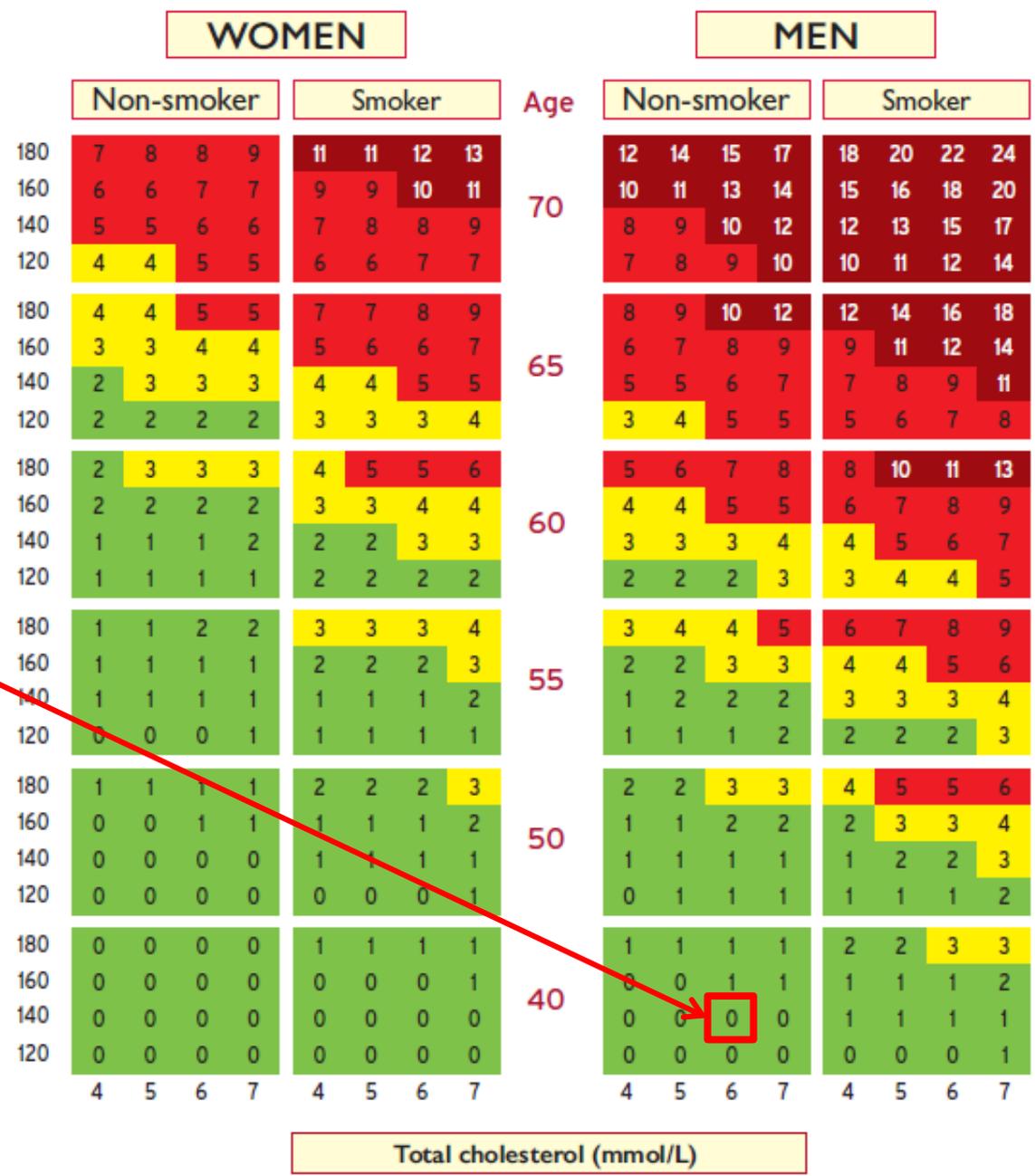
Define the most appropriate treatment goals

Choose the right therapy

Cardiovascular risk estimation

10-y CV risk: <1%

Systolic blood pressure (mmHg)

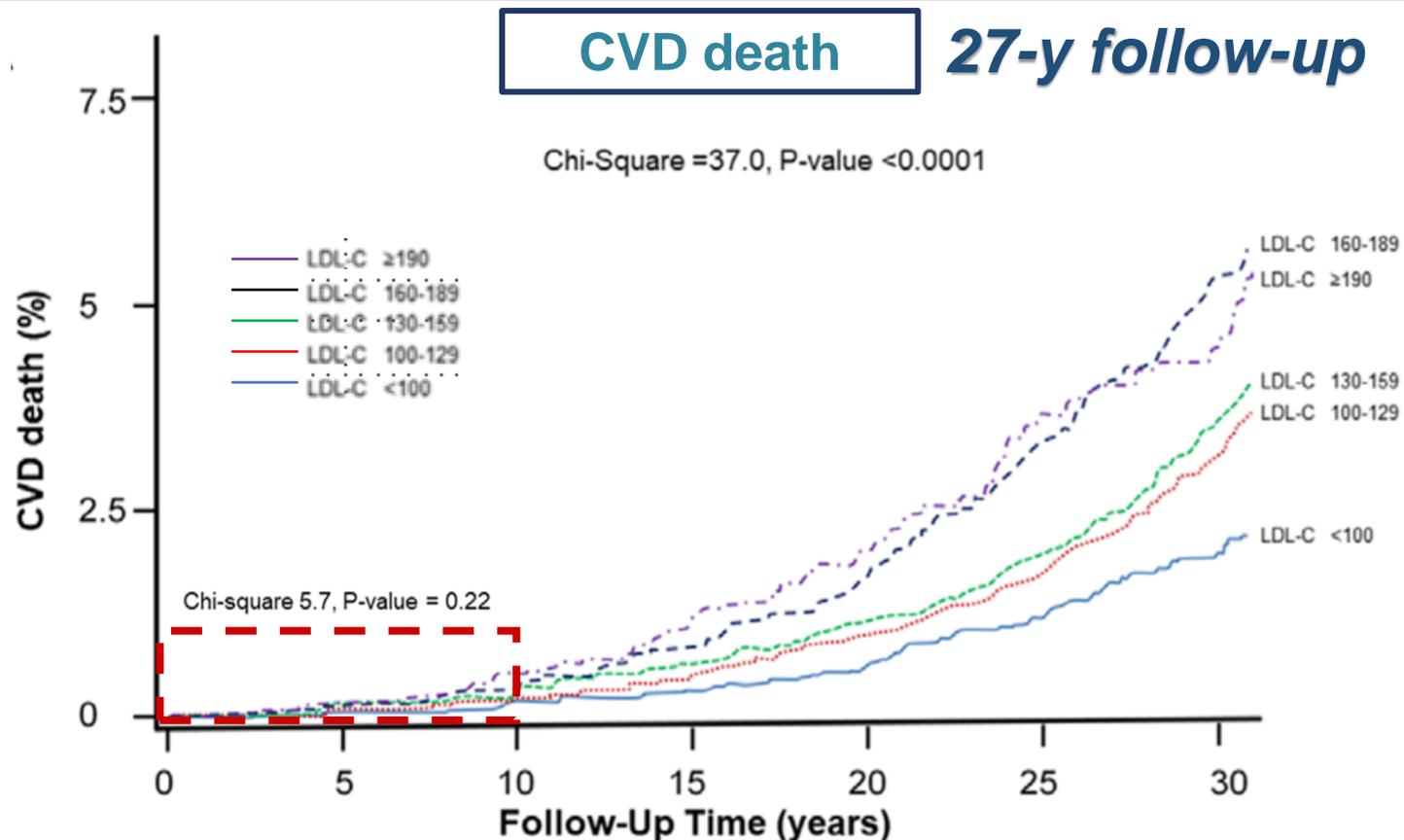


Total cholesterol (mmol/L)



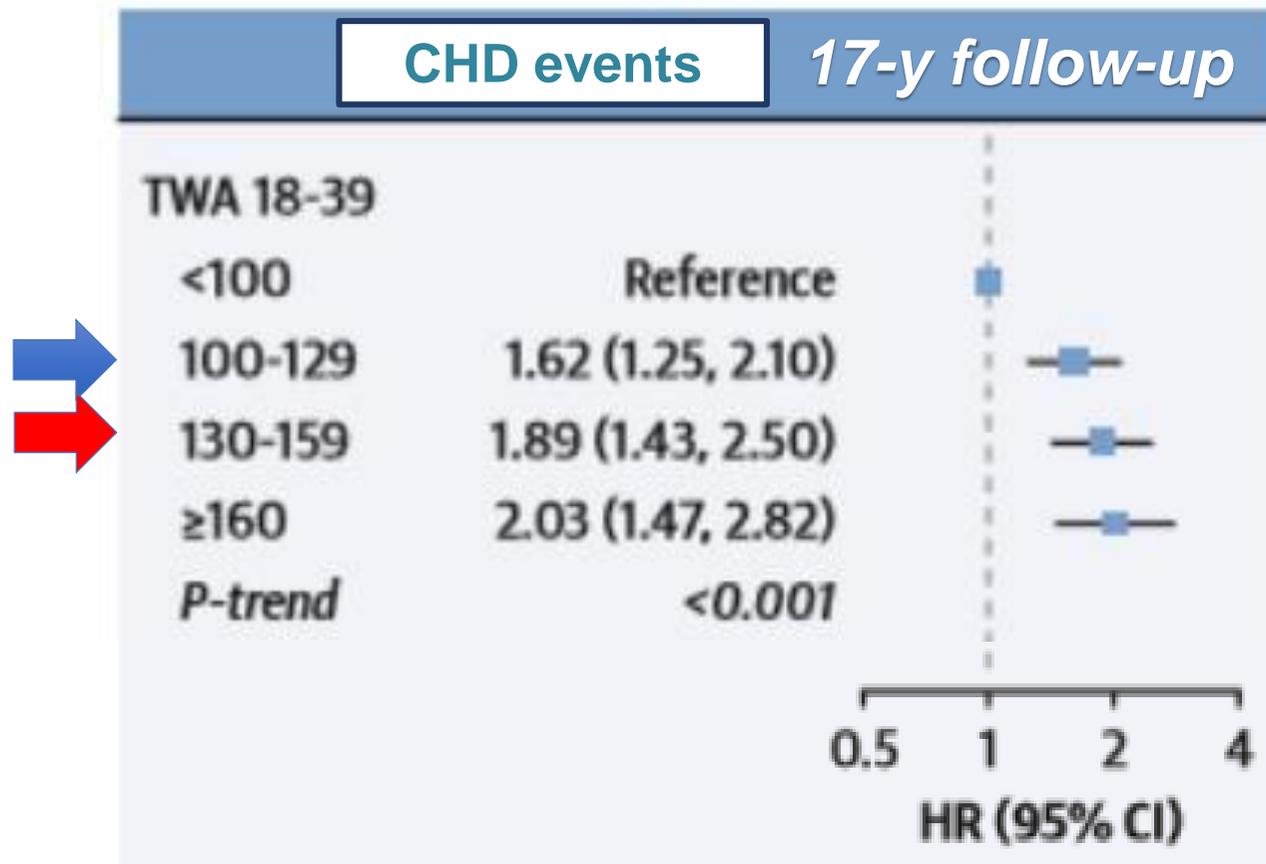
A follow-up longer than 10 years is necessary to discriminate the negative prognostic value of elevated LDL-C levels in low-risk individuals

Long-Term Association of LDL-C With Cardiovascular Mortality in 36,375 Individuals (median age 42-y) at Low 10-Year Risk of Atherosclerotic Cardiovascular Disease. Results From the Cooper Center Longitudinal Study



The association between LDL-C and CHD event risk in individuals aged less than 40-y

6 U.S. cohorts: a total of 36,030 participants were included. During a *median follow-up of 17 years*, there were 4,570 CHD, and 2,862 stroke events



Lifetime CV risk



AMERICAN COLLEGE of CARDIOLOGY



American Heart Association

ASCVD Risk Estimator

3.1%
Low

Current 10-Year ASCVD Risk**

Lifetime ASCVD Risk: 46% Optimal ASCVD Risk: 1.2%

Current Age ⓘ *

45

Age must be between 20-79

Sex *

✓ Male

Female

Race *

✓ White

African American

Other

Systolic Blood Pressure (mm Hg) *

144

Value must be between 90-200

Diastolic Blood Pressure (mm Hg) ○

90

Value must be between 60-130

Total Cholesterol (mg/dL) *

227

Value must be between 130 - 320

HDL Cholesterol (mg/dL) *

50

Value must be between 20 - 100

LDL Cholesterol (mg/dL) ⓘ ○

148

Value must be between 30-300

History of Diabetes? *

Yes

✓ No

Smoker? ⓘ *

Current ⓘ

Former ⓘ

✓ Never ⓘ

On Hypertension Treatment? *

Yes

✓ No

On a Statin? ⓘ ○

Yes

✓ No

On Aspirin Therapy? ⓘ ○

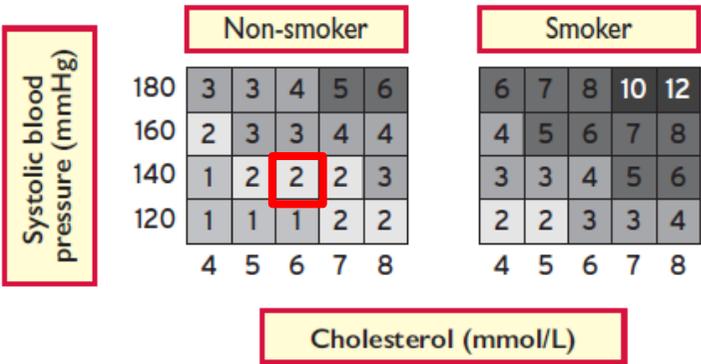
Yes

✓ No

Cardiovascular risk estimation

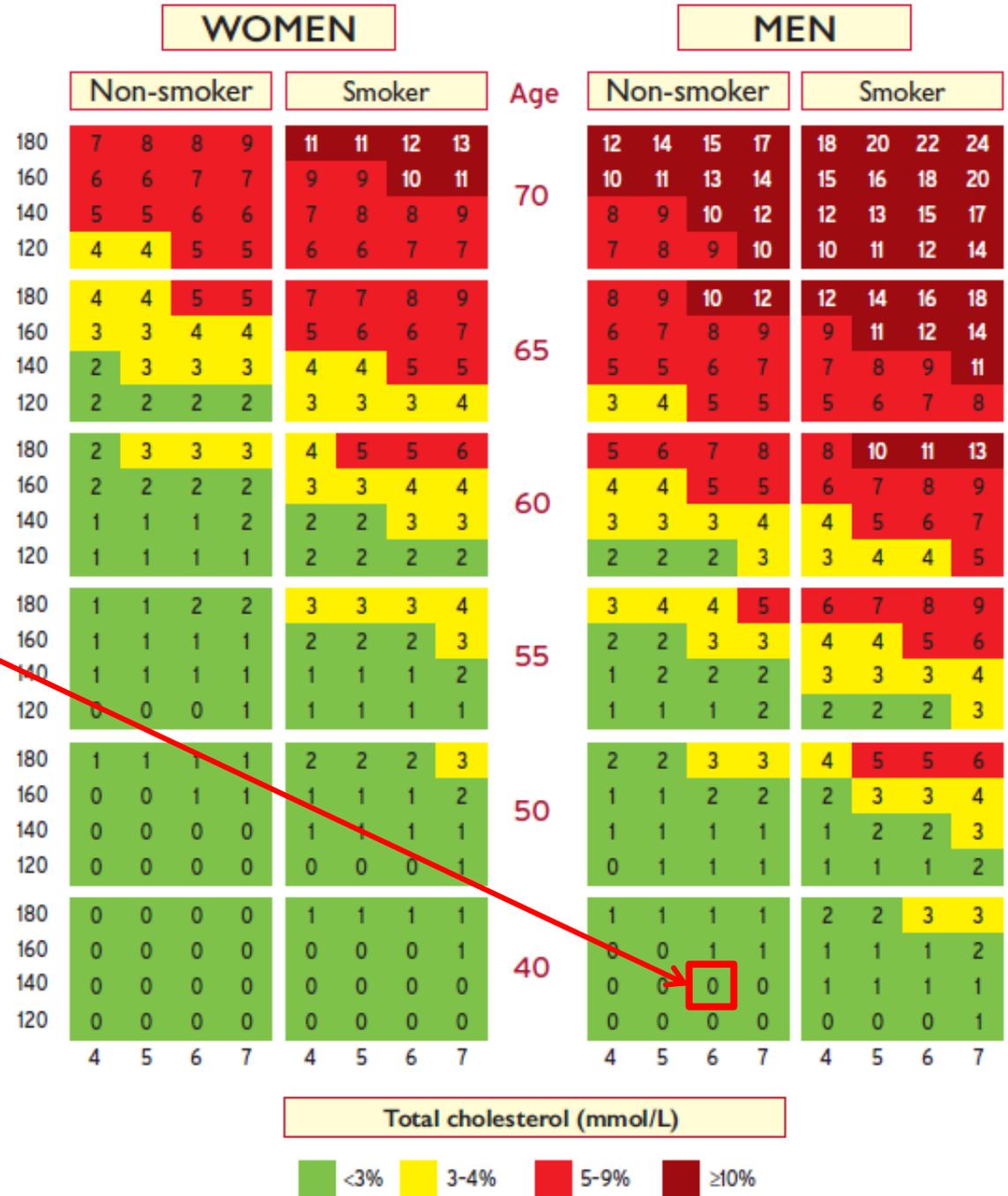
10-y CV risk: <1%

RR: x2



Systolic blood pressure (mmHg)

Low-risk regions of Europe



Total cholesterol (mmol/L)



Fasting lipid profile

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graph TD; A[Fasting lipid profile] --> B[Try to make an etiological diagnosis]; A --> C[Search for other CV RFs or CHD equivalents]; A --> D[Estimate 10-y CV risk and...]; B --> E[Define the most appropriate treatment goals]; C --> E; D --> E; E --> F[Choose the right therapy];
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Try to make an etiological diagnosis

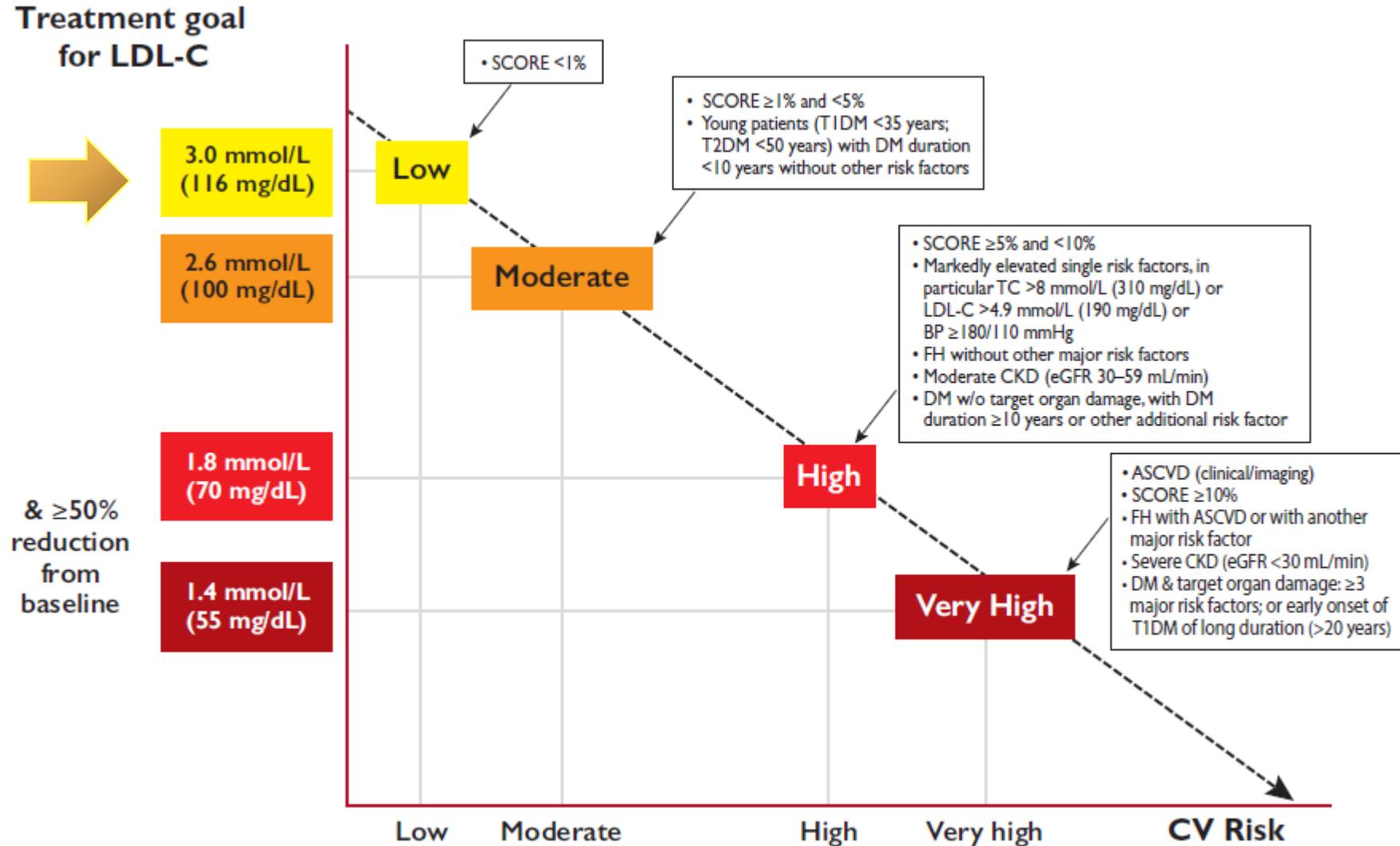
Search for other CV RFs or CHD equivalents

Estimate 10-y CV risk and...

Define the most appropriate treatment goals

Choose the right therapy

LDL-C treatment goals



Starting Fasting Lipid Profile

TC	227	mg/dl
TGs	145	mg/dl
LDL-C	148	mg/dl
HDL-C	50	mg/dl

10-y CV risk: <1%

LDL-C treatment goals

Low-risk : <116 mg/dL

Requested % LDL-C reduction to reach the goals

Low-risk: $148 - 115 = 33 \text{ mg/dL} \dots 33/148 = > -22\%$

Fasting lipid profile

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Try to make an etiological diagnosis

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Intervention strategies as a function of total CV risk and untreated LDL-C levels

		Total CV risk (SCORE) %	Untreated LDL-C levels				
			<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk (see Table 4)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention

Expected LDL-C reductions with specific dietary advices

Advice to reduce fat intake (total and saturated fatty acids) and to increase dietary fibre, fruit and vegetable consumption

VS

No advice

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
Total cholesterol (mmol/l), change from baseline	22	3044	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.21, -0.05]
LDL cholesterol (mmol/l), change from baseline	17	1654	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.24, -0.08] -6.2 mg/dL
HDL cholesterol (mmol/l), change from baseline	16	1700	Mean Difference (IV, Random, 95% CI)	-6.89 [-0.02, 0.02]
Triglycerides (mmol/l), change from baseline	8	648	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.08]

Nutraceuticals for cholesterol-lowering ?

Phytosterols

Soluble fibers

RYR

Berberine

Soy and lupin proteins

Bergamot

Chitosan

Green Tea extract

Artichoke

Garlic

Spirulina

Soy and lupin proteins

Probiotics

Anthocyanins

Curcumin

Gamma-oryzanol

Others

Nutraceutical as part of TLC for reducing cholesterol levels ?

Lifestyle interventions to reduce TC and LDL-C levels

Avoid dietary trans fats

Reduce dietary saturated fats

Increase dietary fibre

Use functional foods enriched with phytosterols

Use red yeast rice nutraceuticals

Reduce excessive body weight

Reduce dietary cholesterol

Increase habitual physical activity

Red yeast rice is the most studied nutraceutical for cholesterol-lowering

Type of study	Subjects (number, type)	Content of monacolin K	Mean duration (range)	Observed effect
Meta-analysis of 93 RCT	n: 9625 Dyslipidemia	3–12.4 mg/day	8 weeks (4–24 weeks)	↓ LDL-C: –28 mg/dl ↓ TG: –36 mg/dl ↑ HDL-C: 5.8 mg/dl
Meta-analysis of 13 RCT	n: 804 Dyslipidemia	2–11.4 mg/day	12 weeks (4–24 weeks)	↓ LDL-C: –34 mg/dl ↓ TG: –20 mg/dl No effect on HDL-C
Meta-analysis of 20 RCT	n: 2811 Dyslipidemia Type 2 diabetes CHD, Hypertensive	4.8–24 mg/day	23 weeks 4–168 weeks	↓ LDL-C: –39 mg/dl ↓ TG: –23 mg/dl ↑ HDL-C: 2.7 mg/dl
Meta-analysis of 21 RCT	n: 4558 Hypertensive	(RYR 1200–1800 mg/day)	4–234 weeks	↓ LDL-C: –24 mg/dl No effect on TG and HDL-C

↓ LDL-C
-24 mg/dL

↓ LDL-C
-39 mg/dL

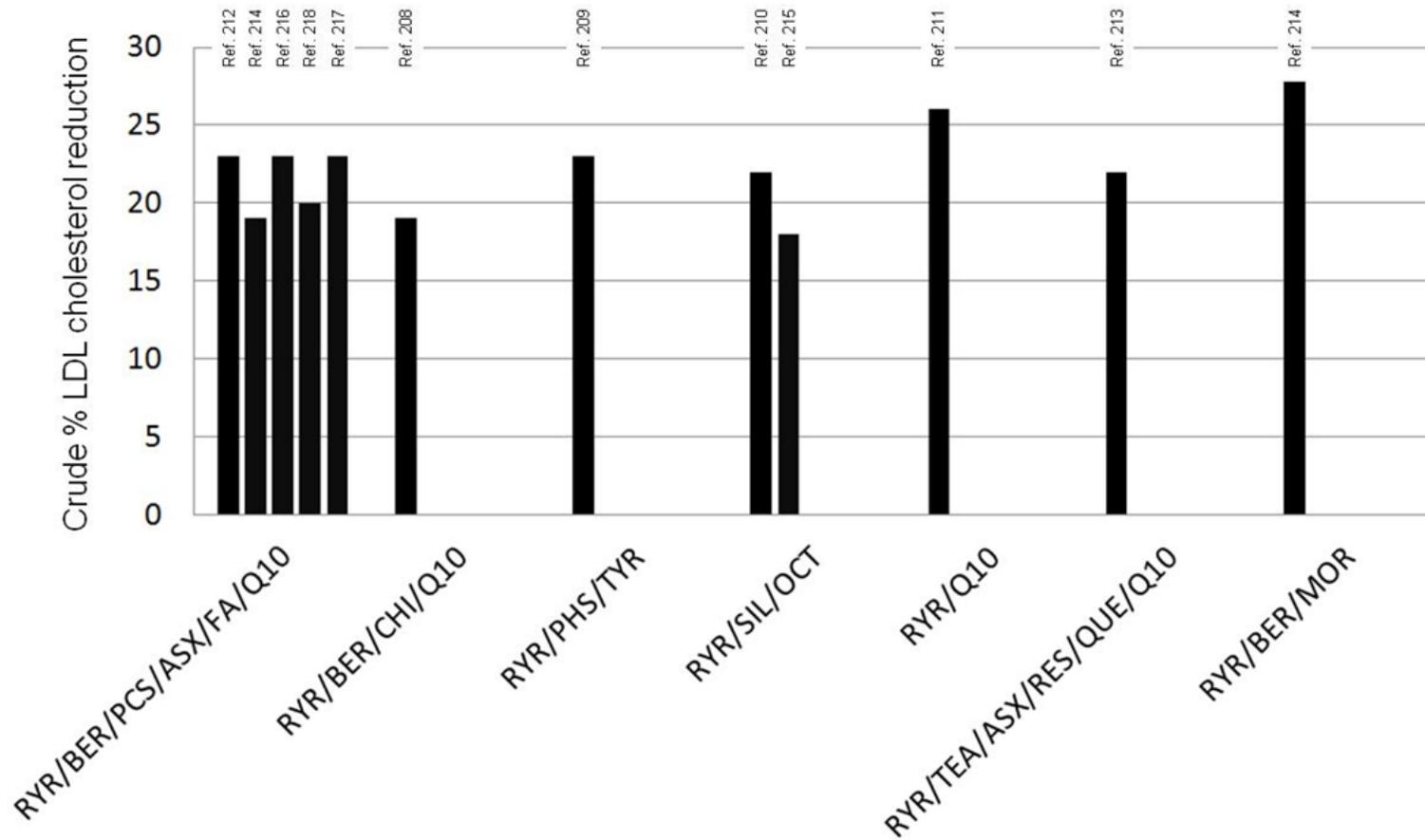
Pros

LDL-C reduction by 16–25%
Good safety profile
Reduction of cardiovascular risk

Cons

Variability of composition and purity of OTC products
Self purchasing by patients and risk of no medical supervision
Higher cost compared to generic statins
Possible side effects at high doses

Red yeast rice is the most studied component in nutraceutical combinations for cholesterol-lowering



Bianconi V, Pirro M, et al. *Curr Cardiol Rep.* 2018 May 25;20(7):53.

Red yeast rice is the most controversial nutraceutical for cholesterol-lowering



SCIENTIFIC OPINION

ADOPTED: 25 June 2018

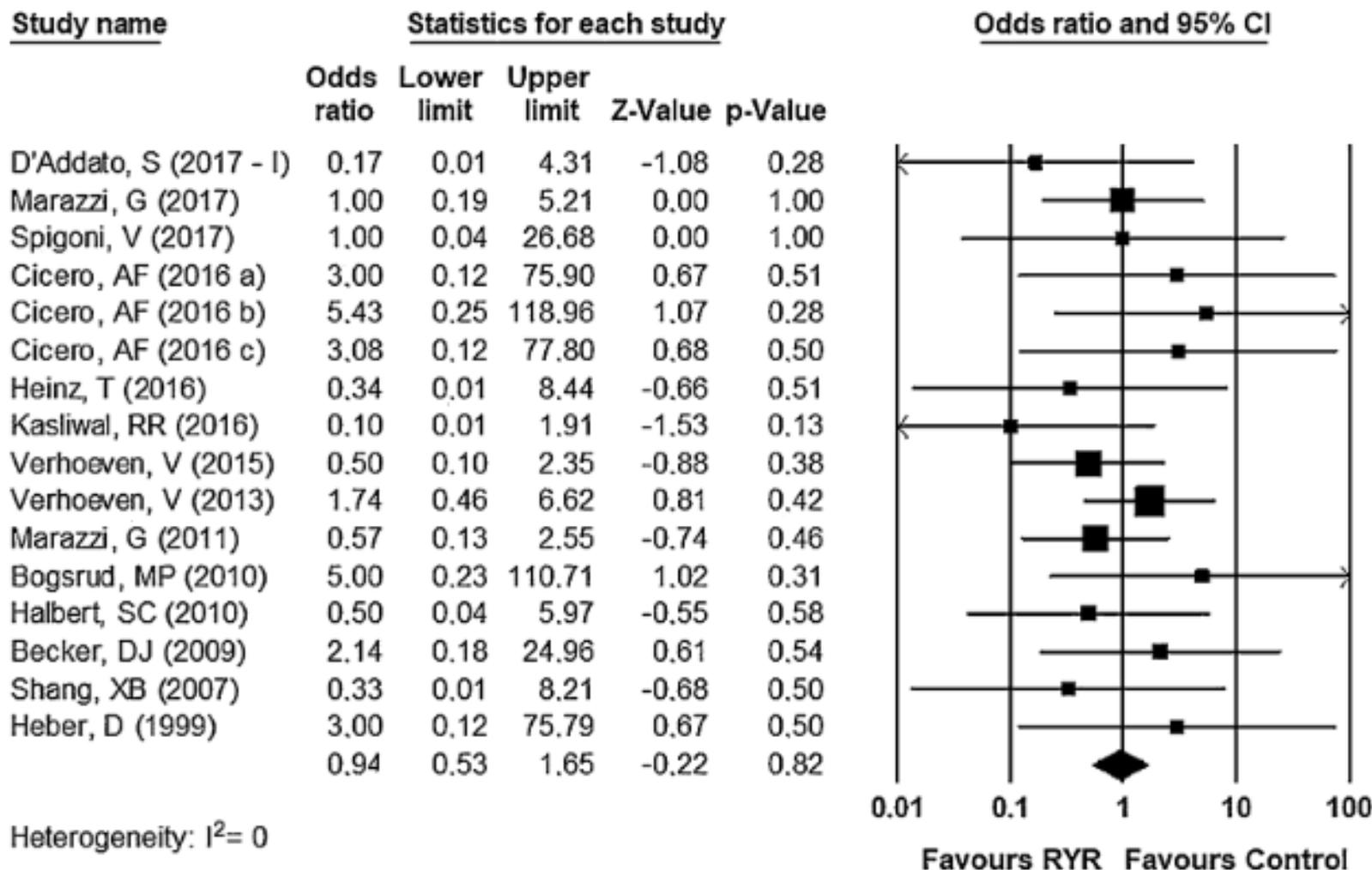
doi: 10.2903/j.efsa.2018.5368

Scientific opinion on the safety of monacolins in red yeast rice

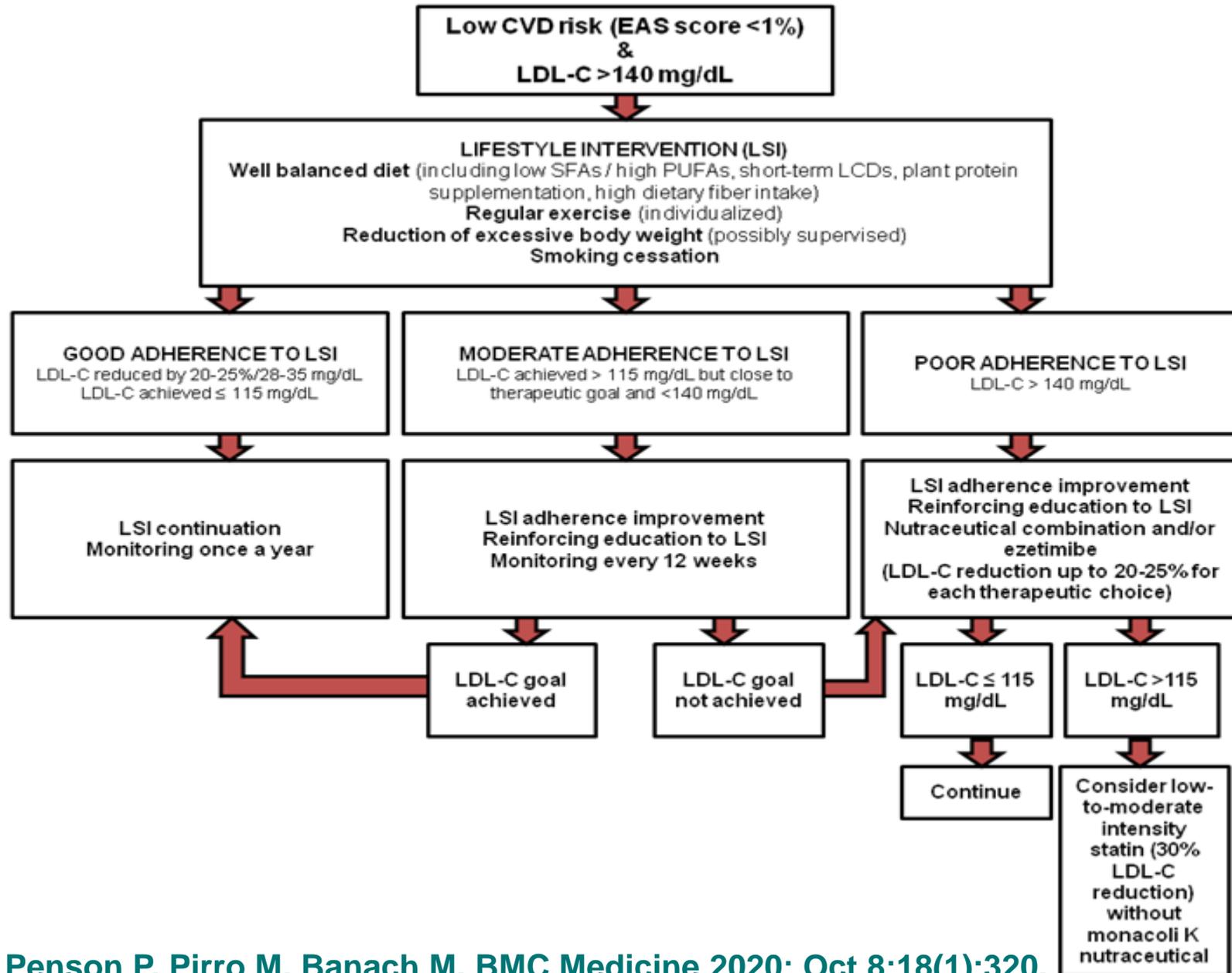
“...monacolins from RYR when used as food supplements were of significant safety concern at the use level of 10 mg/day. The Panel further considered that individual cases of severe adverse reactions have been reported for monacolins from RYR at intake levels as low as 3 mg/day.

The Panel concluded that exposure to monacolin K from RYR could lead to severe adverse effects on musculoskeletal system, including rhabdomyolysis, and on the liver...”

...controversial irrespective of the overall documented safety



Is there an ideal candidate for cholesterol-lowering nutraceuticals ?



Starting Fasting Lipid Profile

TC	227	mg/dl
TGs	145	mg/dl
LDL-C	148	mg/dl
HDL-C	50	mg/dl

10-y CV risk: <1%

Suggested Treatment

BP-lowering (ARB)

TLC + Nutraceutical combination (low-dose RYR + BBR)

4-month visit + FLP

Weight 77 Kg
BMI 26.6
WC 97 cm
BP 134/78 mmHg



TC	190 mg/dl	(-16%)
TGs	135 mg/dl	
LDL-C	112 mg/dl	(-24%)
HDL-C	51 mg/dl	

***What should we keep in
mind ?***

Nutraceuticals are an option: how and when?

How

As an early cholesterol-lowering treatment in patients with elevated cholesterol levels or as a safe and sustainable CV prevention strategy (primordial prevention) before frank hypercholesterolemia occurs

When

When their use is supported by efficacy and safety studies, standardized production methods and strict quality controls

In lower CV risk individuals, when the expected beneficial effect on lipid profile allows to predict a possible achievement of the recommended therapeutic goals