ESC Heart & Brain Workshop

Hypolipidemic drugs in stroke prevention

Supported by Bayer, Bristol-Myers Squibb and Pfizer Alliance, Boehringer Ingelheim, Daiichi Sankyo Europe GmbH and Medtronic in the form of educational grants. The scientific programme has not been influenced in any way by its sponsors.

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BAYER

Boehringer Ingelheim

Daiichi-Sankyo

Bristol-Myers Squibb

Pfizer

Medtronic
Further, Together

Declaration of Interest

DECLARATION

Participation in the « Life Medical Control » company
A medical device company.

STROKE PREVENTION

PHYSICAL ACTIVITY AS A DRUG : LipoProtein Lipase

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ACC/AHA *versus* ESC/EAS

Guidelines

2013 ACC/AHA

Cholesterol is NOT a target.

No treat-to-target strategy. Instead each risk category..

RISK Threshold : Pooled cohorts Equation : 10-year risk from ARIC, CHS, CARDIA, FHS.

Model variables : Age, Sexe, TC, HDLC, SBP & HT, DM, Smoking.

> 13 millions newly eligible

1) Secondary ASCVD - 2) primary LDL-C ≥ 190

2) ASCVD DM @ LDL-C 70-189 - 4) ASCVD LDL-C 70-189 & RISK ≥ 7.5%.

2016 ESC/ESA

Cholesterol is a target

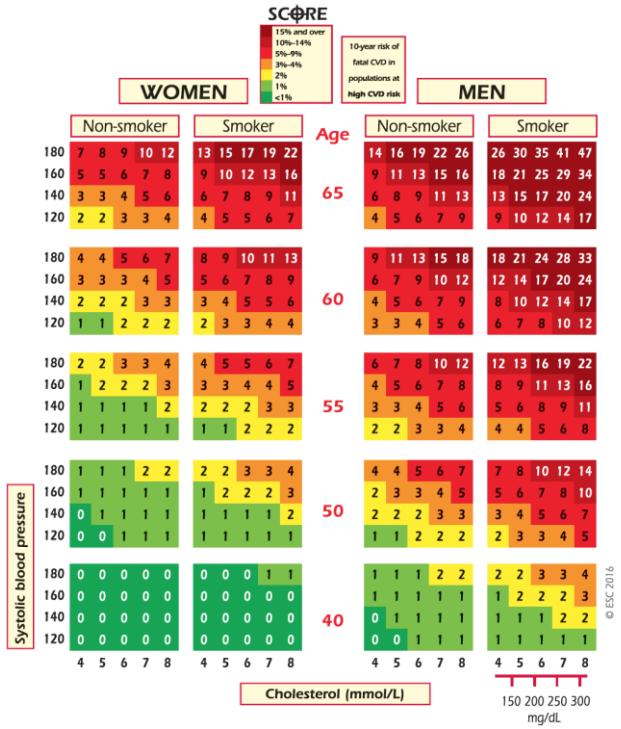
RISK Threshold : SCORE system : age, Total cholesterol (total or HDL-C), SBP, smoking (Fatal).

Low risk charts and high risk charts according to countries.

Recalibration with HDL-C, apoB, Lp(a), TGs, CAC, ABI.

RISK LEVELS ESC/EAS

Total cholesterol, age, SBP



> VERY HIGH-RISK

<u>Documented CVD</u>, clinical or imaging

> HIGH-RISK

Increased risk factors:

Cho > 310 - BP ≥ 180/110 - DM - CKD (30-59)

<u>SCORE 5-10%</u>

> MODERATE-RISK

<u>SCORE</u> 1-5%

> LOW-RISK

<u>SCORE</u> <1%

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SCORE RISK / INTERVENTION

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 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	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a] /Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	No lipid intervention	No lipid 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	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant 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 concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class[a] /Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

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• Stroke Primary Prevention

5 years

Analysis 1.8. Comparison 1 Mortality and Morbidity, Outcome 8 Total Number of Stroke Events.

Review: Statins for the primary prevention of cardiovascular disease

Comparison: 1 Mortality and Morbidity

Outcome: 8 Total Number of Stroke Events

Study or subgroup	Statin Therapy Group n/N	Usual Care or Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ACAPS 1994	0/460	5/459		1.2 %	0.09 [0.01, 1.64]
Adult Japanese MEGA Study	50/3866	62/3966		13.8 %	0.83 [0.57, 1.20]
ASPEN 2006	27/959	29/946		6.6 %	0.92 [0.55, 1.54]
Bone 2007	1/485	0/119		0.2 %	0.74 [0.03, 18.07]
CARDS 2008	30/1429	50/1412		11.3 %	0.59 [0.38, 0.93]
JUPITER 2008	33/8901	64/8901		14.4 %	0.52 [0.34, 0.78]
KAPS 1995	2/214	5/212		1.1 %	0.40 [0.08, 2.02]
PHYLLIS 2004	1/253	0/254		0.1 %	3.01 [0.12, 73.58]
PREVEND IT 2004	7/433	4/431		0.9 %	1.74 [0.51, 5.91]
WOSCOPS	194/3302	223/3293		50.3 %	0.87 [0.72, 1.05]
Total (95% CI)	**20302**	**19993**		**100.0 %**	**0.78 [0.68, 0.89]**

Total events: 345 (Statin Therapy Group), 442 (Usual Care or Placebo)

Heterogeneity: Chi^2 = 12.08, df = 9 (P = 0.21); I^2 =26%

Test for overall effect: Z = 3.56 (P = 0.00037)

Test for subgroup differences: Not applicable

STATINS

Cholesterol decrease of -1.00 mmol/L 40 mg/dL

STROKE DECREASE BY 22%

Cochrane 2013. Taylor F.

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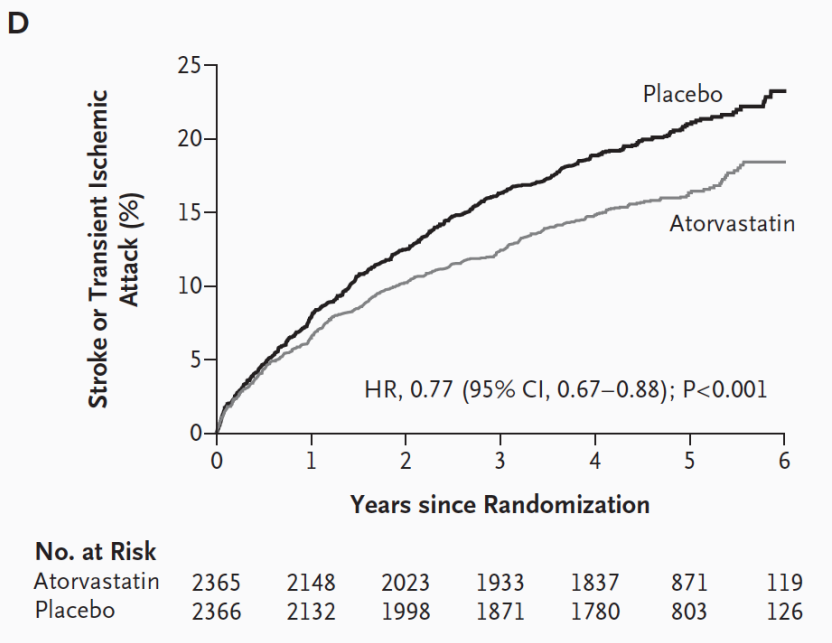
• Stroke Secondary Prevention



NEJM 2006, 355,6:549

Drug choice

STATINS.

EZETIMIBE : inhibits uptake w/o affecting absorption of fat-nutrients

- In association with Statins.

PCKS9 inhibitors When STATINS fails or hereditary hypercholesterolemia

Drug combinations

STATINS and **EZETIMIBE** : 21% less stroke (IMPROVE-IT).

No more consideration

Bile Acid Sequestrants (BAS).
Nicotinic Acid

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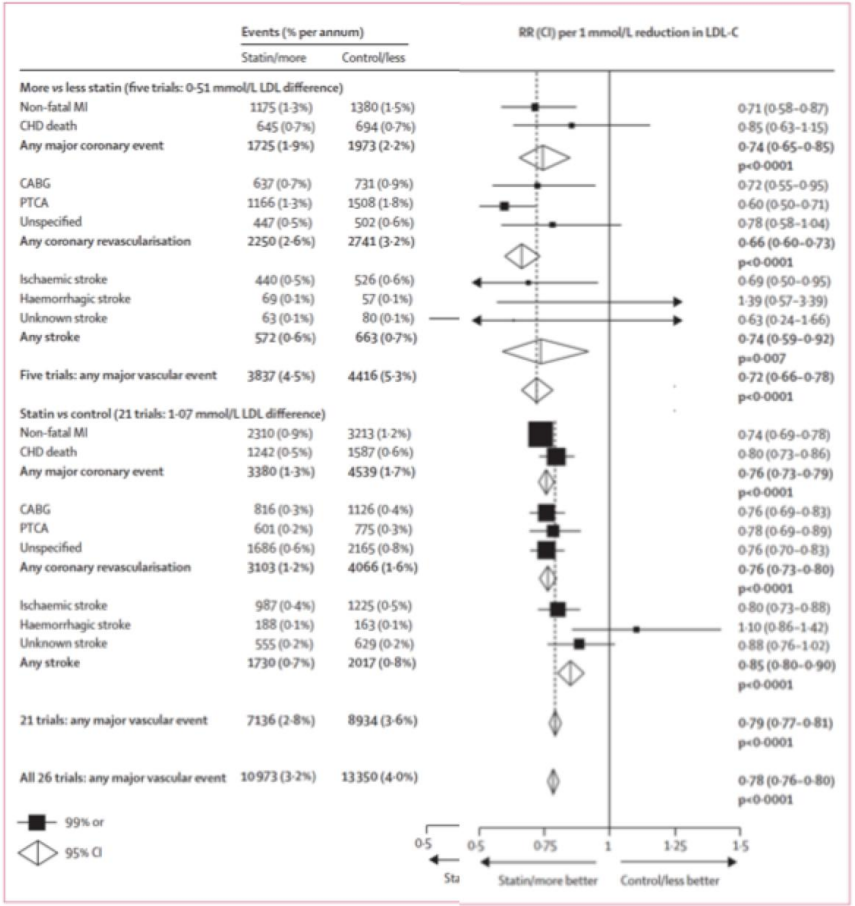
• Stroke Overall Prevention : more or less intensive statins



Initial & More vs Less intensive therapy

Cholesterol down 0,51 mmol/L (mean).

In any case, per 1.0 mmol/L reduction :

Coronary **: -13%**

Coronary revascularisation : **-19%**

Ischemic stroke : **-16%**

Even if …

Initial low cholesterol

CTT. Cholesterol Treatment Trialists
The LANCET 2010, 376:1670-1681

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• TRIGLYCERIDES

Target value **< 1.7 mmol/L (150 mg/dL)**
> 10.0 mmol/L (880 mg/dL)

Recommendations	Class [a]	Level [b]	Ref [c]
Drug treatment should be considered in high-risk patients with TG >2.3 mmol/L (200 mg/dL).	IIa	B	261, 262
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	IIb	B	263, 264
In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins.	IIb	C	261–264

Choice - [Threshold 2.7 mmol/L (200 mg/dL)]

STATINS : strong (atorvastatin, rosuvastatin, pitavastatin)

Less interest

FIBRATES : HHS, (Helsinky Heart Study), VA-HIT, BIP, FIELD, and ACCORD (only ACCORD targeted Fibrates).

NICOTINIC ACID. Unanavailable in Europe.

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- **HDL-C**

TARGET, minimum

- HDL-C Increase ≥ 7.5 %

  and

- LDL-C < 80 mg/dL

Choice

LIFE STYLE : LPL (Lipo Protein Lipase).

STATINS : modest, 5-10%.

Less interest

FIBRATES : Modest.

NICOTINIC ACID.

CPET: deleterious

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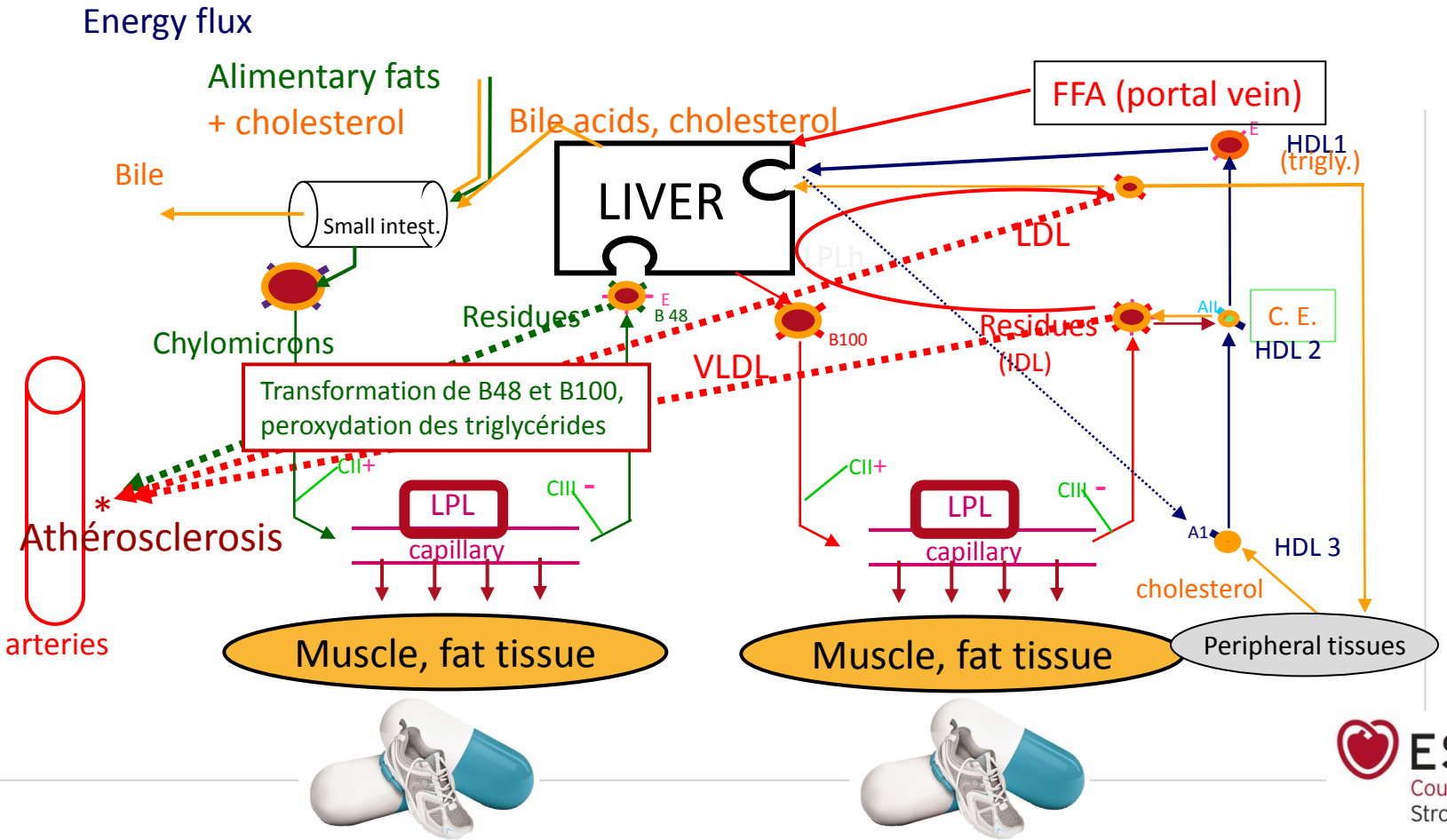

SPECIFIC POPULATIONS

Older adults :

- established CVD : same rules than youngers
- Careful titration
- Free from CVD but many CVRF

METS, STATINS :

- target decrease at least 50 % - regardless of initial LDL-C value

ACS or PTCA : Target cholesterol < 70 mg/dL

- STATINS : Initial HIGH DOSE
- If needed add EZETIMIBE +/- PCKS9 inhibitors
- Short loading or pre-treatment if elective PCI

HEART FAILURE : not an indication by itself

AUTO-IMMUNE DISEASE : no indication

CKD : YES for Very high CV risk (CKD 3-5).

- if dialysis dependent and free of atherosclerotic CVD
- if transplant recipients, considered.

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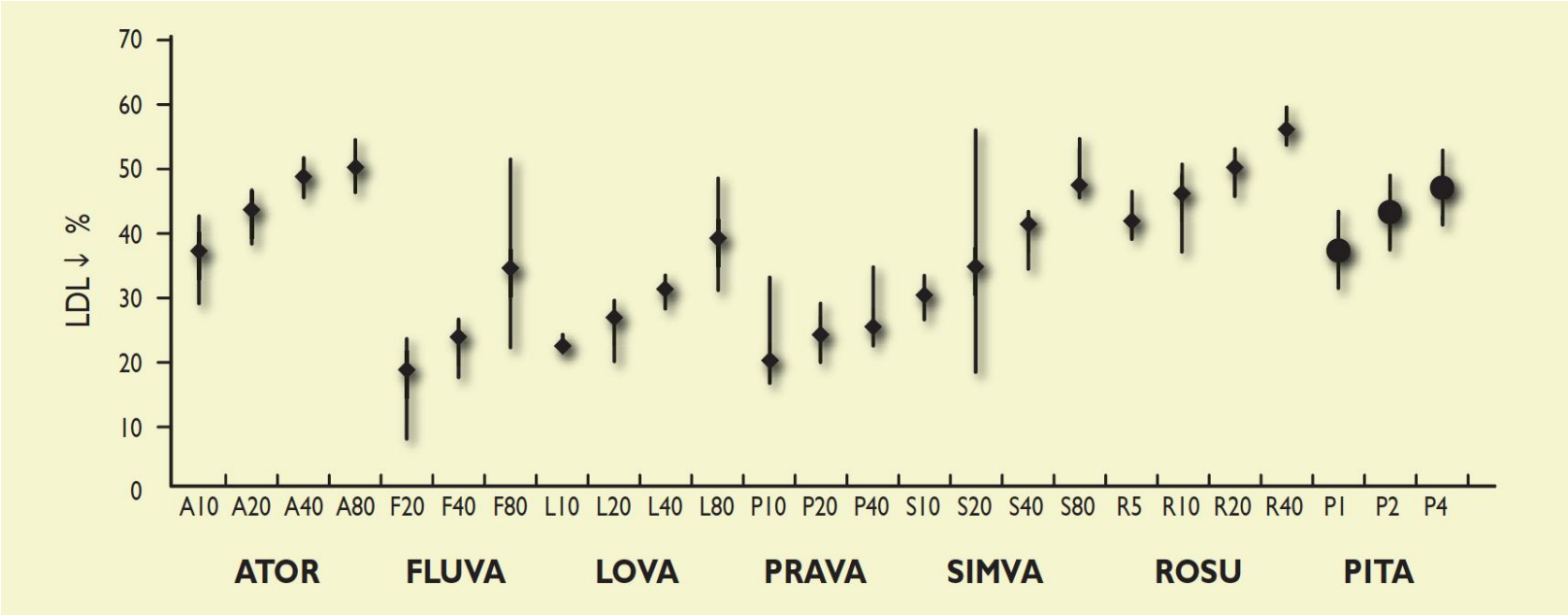
STATINS



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VACCINE AT04A

Antibodies against PCSK9

CLINICAL PHASE 1 (Vienna)

- Running

Animals : mice Western Diet

- **Cholesterol : - 50 %**
- **Atherosclerotic diseases : - 60 %**
- **Inflammation : decrease**

RNAi

Interfering RNA

CHARITE (Berlin) and IMPERIAL COLLEGE (Londres) : « Interfering RNA »

- Inhibition of the PCKS9 mRNA

High Risk PATIENTS (n=500)

- **Cholesterol decrease up to 50 %**
- **Long-term effect of one single administration, still active after a 9-month Follow-Up.**

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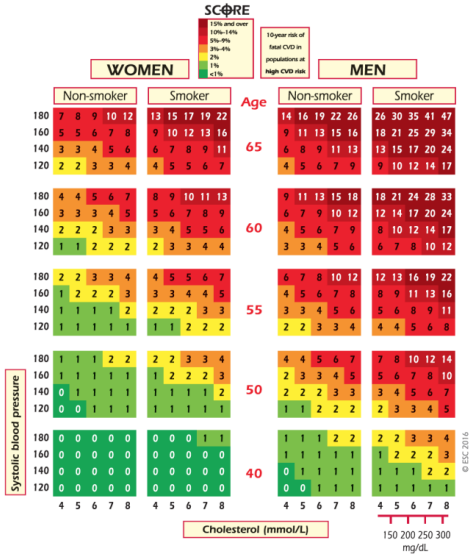
RISK LEVELS ESC/EAS

RISK SCORE :

- Total cholesterol
- age
- SBP



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Recommendations	Class	Level
Lipid-lowering drugs in patients with peripheral arterial disease (including carotid artery disease)		
PAD is a very high-risk condition and lipid lowering therapy (mostly statins) is recommended in these patients.	I	A
Lipid-lowering drugs for primary and secondary prevention of stroke		
Statin therapy to reach established treatment goals is recommended in patients at high or very high CV risk for primary prevention of stroke.	I	A
Lipid-lowering therapy is recommended in patients with other manifestations of CVD for primary prevention of stroke.	I	A
Intensive statin therapy is recommended in patients with a history of non-cardioembolic ischaemic stroke or TIA for secondary prevention of stroke.	I	A

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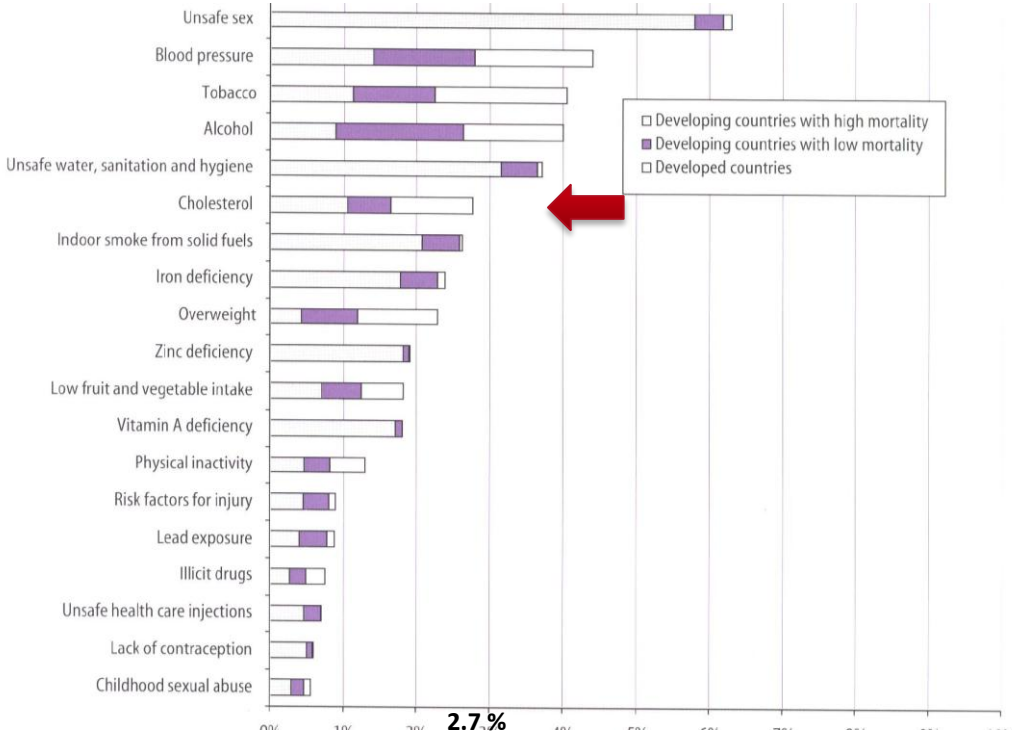
PREVENTION IS COST-EFFECTIVE and would decrease DALYs



Disability Adjusted Life years. OMS 2002

STROKE COST

70.000 € each

Europe : 45 Billions a year or
5 Millions € each hour.

HEALTH RISK BEHAVIOURS WOULD PREVENT AT LEAST 80 % OF CVD

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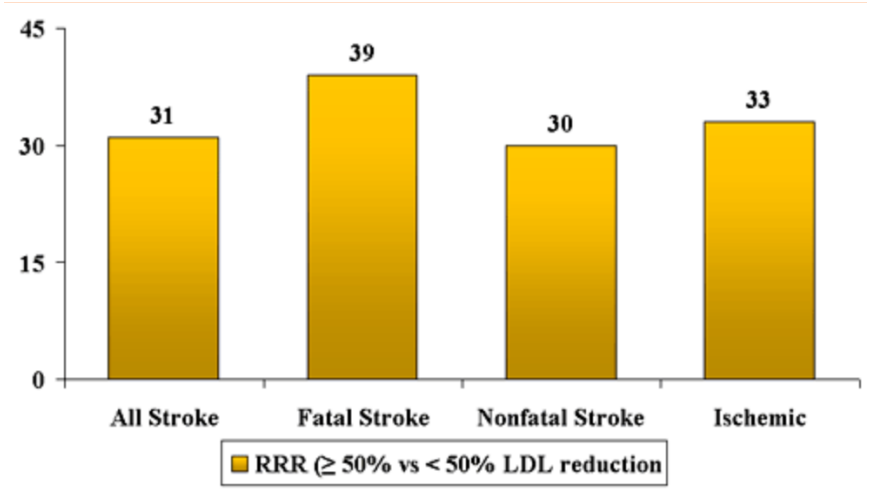
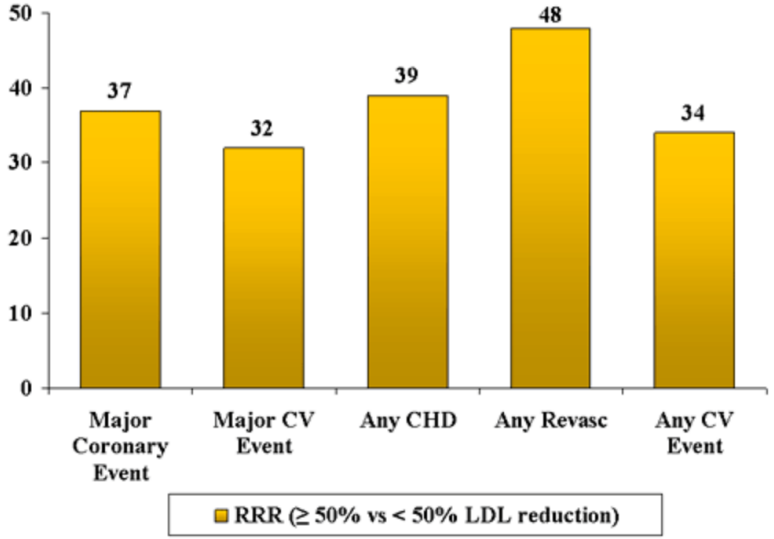
The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators.

High-dose atorvastatin after stroke or transient ischemic attack.

Amarenco (https://www.medscape.com/viewarticle/547087#vp_4)



Brain



Heart

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