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Review

ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)^{☆,☆☆}

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BACKGROUND

- **CLASSES OF RECOMMENDATIONS**
- **LEVEL OF EVIDENCE**



Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
<i>Class IIa</i>	<i>Weight of evidence/opinion is in favour of usefulness/efficacy.</i>	Should be considered
<i>Class IIb</i>	<i>Usefulness/efficacy is less well established by evidence/opinion.</i>	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

THE APPROACH

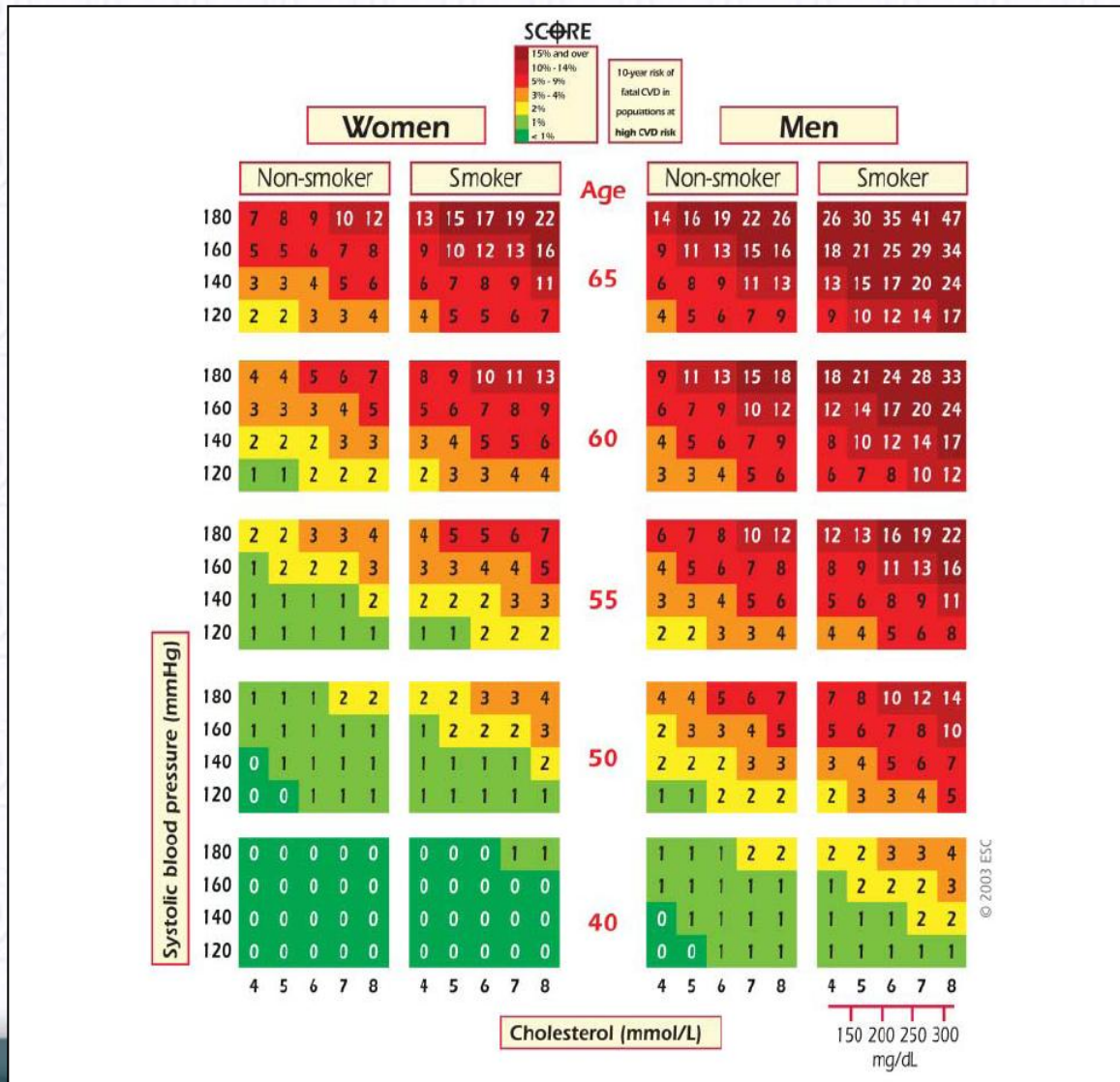
- **GLOBAL RISK**
- LEVELS OF RISK GRADING
- INTERVENTION LEVELS
- TARGETS



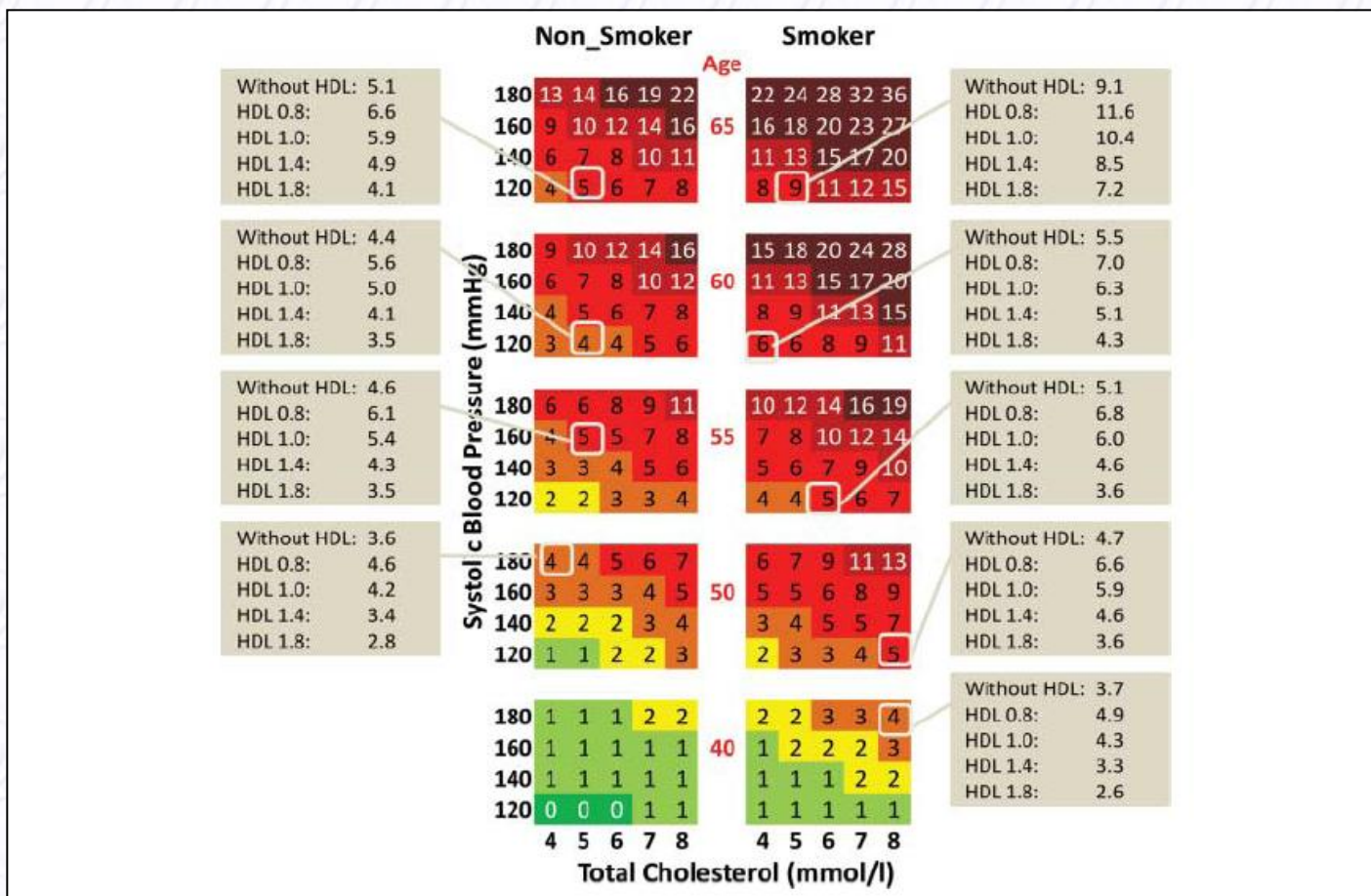
RISK LEVELS

- **THE SCORE RISK OF CV MORTALITY OF 5 CORRESPONDS TO 15 IN THE EQUATIONS CONSIDERING MOTALITY AND MORBILITY**

SCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at high CVD risk

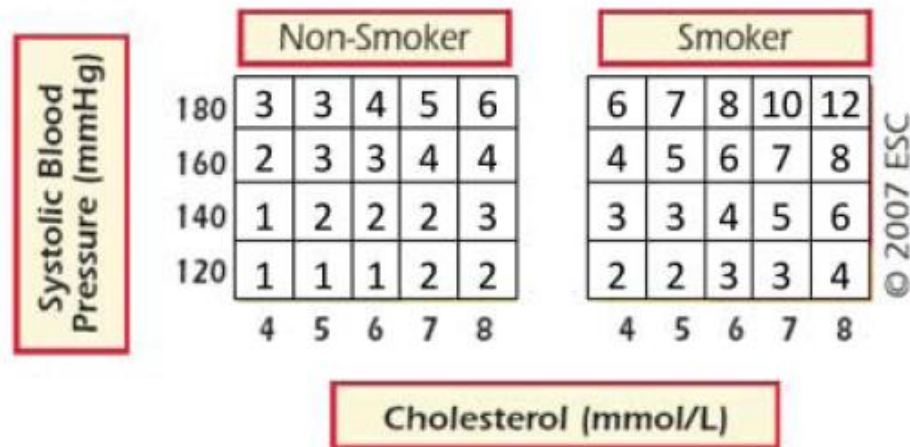


Risk function without high-density lipoprotein-cholesterol (HDL-C) for men in populations at high cardiovascular disease risk



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

Risk will also be higher than indicated in the charts in:

- Socially deprived individuals; deprivation drives many other risk factors.
- Sedentary subjects and those with central obesity; these characteristics determine many of the other aspects of risk listed below.
- Individuals with diabetes: re-analysis of the SCORE database indicates that those with known diabetes are at greatly increased risk; five times higher in women and three 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; these factors indicate a higher level of risk in both genders, all age groups and at all levels of risk. As mentioned above, supplementary material (see Addendum I) illustrates the additional impact of HDL-C on risk estimation.
- Asymptomatic individuals with preclinical evidence of atherosclerosis, for example, the presence of plaques or increased carotid intima-media thickness (CIMT) on carotid ultrasonography.
- 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.
- Conversely, risk may be lower than indicated in those with very high HDL-C levels or a family history of longevity.

THE APPROACH

- GLOBAL RISK
- LEVELS OF RISK GRADING
- INTERVENTION LEVELS
- TARGETS



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

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

THE APPROACH

- GLOBAL RISK
- LEVELS OF RISK GRADING
- INTERVENTION LEVELS
- **TARGETS**



Recommendations for treatment targets for LDL-C

Recommendations	Class ^a	Level ^b	Ref ^c
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level $\geq 10\%$) the LDL-C goal is < 1.8 mmol/L (less than ~ 70 mg/dL) and/or $\geq 50\%$ LDL-C reduction when target level cannot be reached.	I	A	15, 32, 33
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥ 5 to $< 10\%$) an LDL-C goal < 2.5 mmol/L (less than ~ 100 mg/dL) should be considered.	IIa	A	15, 16, 17
In subjects at MODERATE risk (SCORE level > 1 to $\leq 5\%$) an LDL-C goal < 3.0 mmol/L (less than ~ 115 mg/dL) should be considered.	IIa	C	-

THE APPROACH

- **LIPID ANALYSES**

Recommendations for lipid analyses as treatment target in the prevention of CVD

Recommendations	Class ^a	Level ^b	Ref ^c
LDL-C is recommended as target for treatment.	I	A	15, 16, 17
TC should be considered as treatment target if other analyses are not available.	IIa	A	5, 15
TG should be analysed during the treatment of dyslipidaemias with high TG levels.	IIa	B	52
Non-HDL-C should be considered as a secondary target in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	B	48
Apo B should be considered as a secondary treatment target.	IIa	B	48, 53
HDL-C is not recommended as a target for treatment.	III	C	-
The ratios apo B/apo AI and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	C	-

THE APPROACH

- **LIFESTYLE CHANGES**

Definition of central obesity

	Waist circumference
Caucasians (Europids)	Men ≥ 94 cm; women ≥ 80 cm
South Asians, Chinese, Japanese	Men ≥ 90 cm; women ≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and Middle East (Arabic) populations	Use European data until more specific data are available

Dietary recommendations to lower TC and LDL-C

	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Cereals	Whole grains	Refined bread, rice and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables		Vegetables prepared in butter or cream
Legumes	All (including soy and soy protein)		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, fructose, glucose, chocolate, candies	Cakes, ice creams
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork or veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Skimmed milk and yogurt, egg white	Low fat milk, low fat cheese and other milk products	Regular cheese, cream, egg yolk, whole milk and yoghurt
Cooking fat and dressings	Vinegar, ketchup, mustard, fat-free dressings	Vegetable oils, soft margarines, salad dressing, mayonnaise	Butter, solid margarines, trans fats, palm and coconut oils; lard, bacon fat, dressings made with egg yolks
Nuts/seeds		All	Coconut
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

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.



THE APPROACH

- **DRUG THERAPY**



Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class ^a	Level ^b	Ref ^c
Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level.	I	A	15, 16, 17
In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered.	IIa	B	108, 120
A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.	IIb	C	-
If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.	IIb	C	-

Recommendations for drug treatment of HTG

Recommendations	Class ^a	Level ^b	Ref ^c
In particular high risk patients (see above), lowering of HTG by using the following drugs:			
is recommended: fibrates	I	B	127
should be considered: nicotinic acid	IIa	B	131
nicotinic acid + laropiprant	IIa	C	-
<i>n</i> -3 fatty acids	IIa	B	135, 136
statin + nicotinic acid ^d	IIa	A	142, 145
statin + fibrate ^d	IIa	C	-
may be considered: combinations with <i>n</i> -3 fatty acids ^e	IIb	B	146

Recommendations if drug treatment of low HDL-C is considered

Recommendations	Class ^a	Level ^b	Ref ^c
Nicotinic acid is currently the most efficient drug to raise HDL-C and should be considered.	IIa	A	112
Statins and fibrates raise HDL-C with similar magnitude and these drugs may be considered.	IIb	B	141, 151
The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.	IIb	B	127, 141

THE APPROACH

- **GENETIC DYSLIPIDAEMIAS**

Genetic disorders of lipoprotein metabolism

Disorder	Prevalence	Gene(s)	Effect on lipoproteins
HeFH	1 in 500	<i>LDLR</i> <i>PCSK9</i> <i>APO B</i>	↑LDL
HoFH	1 in 10 ⁶	<i>LDLR</i>	↑↑LDL
FCH	1 in 100/200	<i>USF1</i> + modifying genes	↑LDL, ↑VLDL ↑ apo B
Familial dysbetalipoproteinaemia	1 in 5000	<i>APO E</i>	↑↑IDL and chylomicron remnants (βVLDL)
Familial lipoprotein lipase deficiency	1 in 10 ⁶	<i>LPL</i> <i>APO C2</i>	↑↑chylomicrons andVLDL
Tangier disease (analphalipoproteinaemia)	1 in 10 ⁶	<i>ABC-1</i>	↓↓HDL
Familial LCAT deficiency (fish eye disease)	1 in 10 ⁶	<i>LCAT</i>	↓HDL

Diagnostic criteria for the clinical diagnosis of HeFH according to MedPed and WHO

	Criteria	Score
Family history	First-degree relative known with premature CAD ^a and/or first-degree relative with LDL-C >95th centile	1
	First-degree relative with Tx and/or children <18 with LDL-C >95th centile	2
Clinical history	Patient has premature CAD*	2
	Patient has premature cerebral/peripheral vascular disease	1
Physical examination	Tx	6
	Arcus cornealis below the age of 45 years	4
LDL-C	>8.5 mmol/L (more than ~330 mg/dL)	8
	6.5–8.4 mmol/L (~250–329 mg/dL)	5
	5.0–6.4 mmol/L (~190–249 mg/dL)	3
	4.0–4.9 mmol/L (~155–189 mg/dL)	1
Definite FH		Score >8
Probable FH		Score 6-8
Possible FH		Score 3-5
No diagnosis		Score <3

THE APPROACH

- **SPECIFIC POPULATIONS**

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.

Recommendations for treatment of dyslipidaemia in the elderly

Recommendations	Class ^a	Level ^b	Ref ^c
Treatment with statins is recommended for elderly patients with established CVD in the same way as for younger patients.	I	B	15, 16
Since elderly people often have comorbidities and have altered pharmacokinetics, it is recommended to start lipid-lowering medication at a low dose and then titrate with caution to achieve target lipid levels which are the same as in the younger subjects.	I	C	-
Statin therapy may be considered in elderly subjects free of CVD, particularly in the presence of at least one other CV risk factor besides age.	IIb	B	20, 167

Recommendations for treatment of dyslipidaemia in diabetes

Recommendations	Class ^a	Level ^b	Ref ^c
In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL-C lowering (at least 30%) with statins as the first choice (eventually drug combination) is recommended irrespective of the basal LDL-C concentration.	I	C	
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are over the age of 40 years with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (less than ~70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (100 mg/dL) and for apo B is <80 mg/dL.	I	B	15, 16
In all people with type 2 diabetes LDL-C <2.5 mmol/L (less than ~100 mg/dL) is the primary target. Non-HDL-C <3.3 mmol/L (130 mg/dL) and apo B <100 mg/dL are the secondary targets.	I	B	15, 16

Recommendations for lipid lowering drugs in patients with moderate to severe CKD

(stages 2–4, GFR 15–89 mL/min/1.73 m²)

Recommendations	Class ^a	Level ^b	Ref ^c
CKD is acknowledged as a CAD risk equivalent; in these patients LDL-C reduction is recommended as the primary target of therapy.	I	A	189, 190
LDL-C lowering reduces CVD risk in CKD subjects and should be considered.	IIa	B	111, 193
Statins should be considered to slow the rate of kidney function loss modestly and thus protect against the development of ESRD requiring dialysis.	IIa	C	-
Since statins have a beneficial effect on pathological proteinuria (>300 mg/day) they should be considered in patients with stage 2–4 CKD.	IIa	B	194
In moderate to severe CKD statins as monotherapy or in combination with other drugs should be considered to achieve LDL-C <1.8 mmol/L (less than ~70 mg/dL).	IIa	C	-

Recommendations for lipid-lowering drugs in patients with PAD

Recommendations	Class ^a	Level ^b	Ref ^c
PAD is a high risk condition, and lipid-lowering therapy (mostly statins) is recommended in these patients.	I	A	202
Statin therapy is recommended to reduce the progression of carotid atherosclerosis.	I	A	203, 204
Statin therapy is recommended to prevent the progression of aortic aneurysm.	I	C	-

Recommendations for lipid-lowering drugs for primary and secondary prevention of stroke

Recommendations	Class ^a	Level ^b	Ref ^c
Statin therapy to reach established treatment goals is recommended in patients at high global risk.	I	A	210, 211
Statin therapy is recommended in patients with other manifestations of CVD.	I	A	210
Statin therapy is recommended in patients with a history of non-cardioembolic ischaemic stroke or TIA.	I	A	34, 210

THE APPROACH

- **ADHERENCE AND COMPLIANCE**

Hints to help adherence to lifestyle changes

- Develop a good alliance with the patient.
- Make sure that the patient understands how lifestyles affect cardiovascular disease and use this to gain commitment to the change in behaviour.
- Explore potential barriers to the change.
- Design with the patient a lifestyle change plan that is realistic and encouraging.
- Reinforce the patient's efforts to change.
- Involve other experts wherever needed and possible.
- Arrange a schedule of follow-up visits.

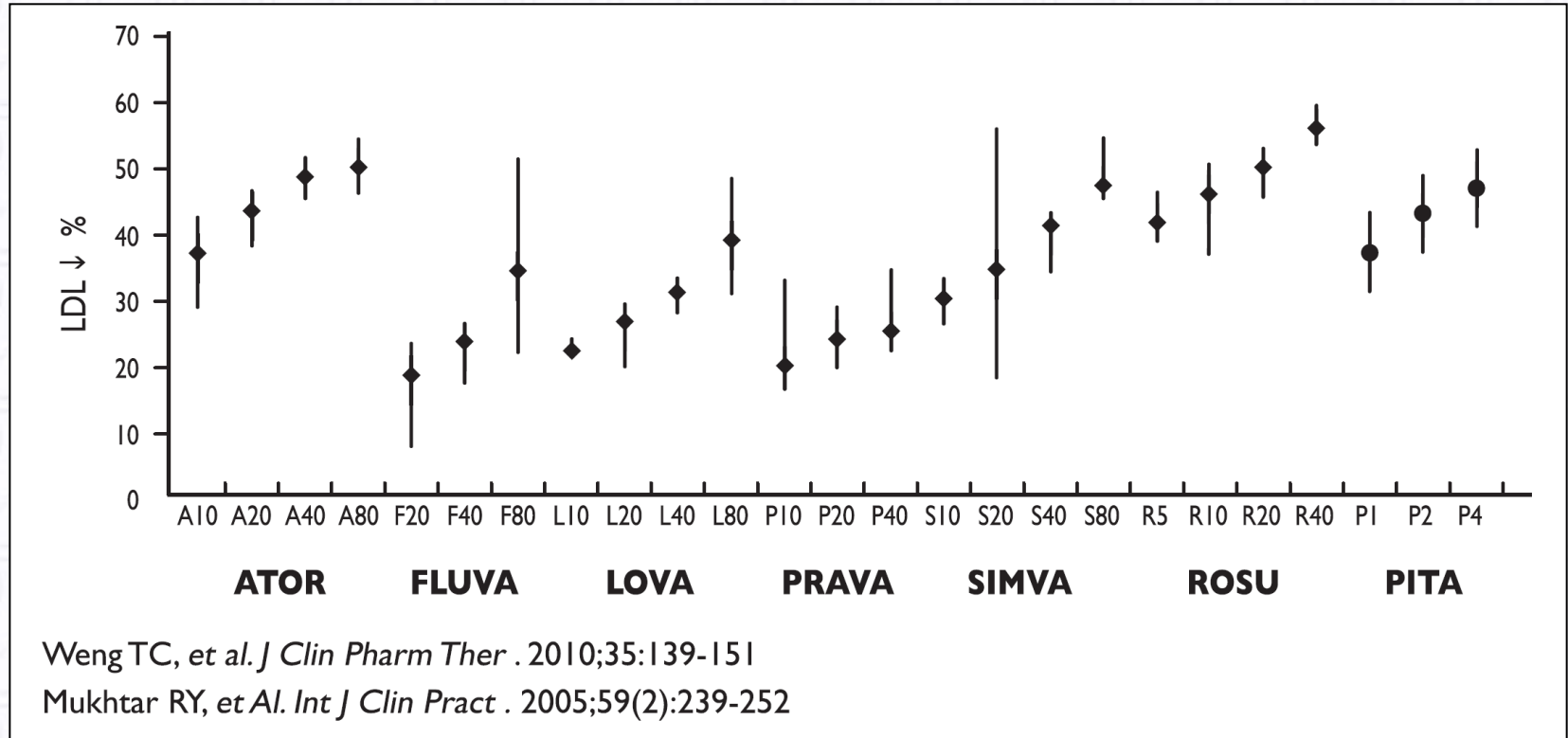
Tips to help compliance with multiple drug therapies

- Simplify the dosing regimen if possible by reducing daily doses and concomitant medications.
- Choose cheaper alternatives.
- Provide clear written and oral instructions.
- Undertake a dialogue with the patient regarding adherence.
- Tailor the regimen to the patient's lifestyle and needs.
- Involve the patient as partner in the treatment.
- Use behavioural strategies (reminder systems, cues, self-monitoring, feedback, reinforcement)

Percentage reduction of LDL-C requested to achieve goals as a function of the starting value

STARTING LDL-C		% REDUCTION TO REACH LDL-C		
		<1.8 mmol/L (~70 mg/dL)	<2.5 mmol/L (~100 mg/dL)	<3 mmol/L (~115 mg/dL)
mmol/L	~mg/dL			
>6.2	>240	>70	>60	>55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	<10
2.3–2.9	90–110	22–35	<10	–
1.8–2.3	70–90	<22	–	–

A systematic review and meta-analysis on the therapeutic equivalence of statins



THE PUBLICATION

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