HYPERLIPIDEMIA
DIAGNOSIS, MANAGEMENT AND TREATMENT

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Hyperlipidemia

- Primary/genetic/Hereditary/FH
- Polygenic Hyperlipidemia
- Secondary (2°)
- Combined Hyperlipidemia

Simon-Broome's criteria

- D**efinite** familial hypercholesterolaemia (FH) :
- Total cholesterol LDL-C
- Child> 6.7 mmol/l > 4.0 mmol/l
- Adults> 7.5 mmol/l > 4.9 mmol/l

and tendon xanthomas, or evidence of these signs in first- or second-degree relative **or**

- DNA-based evidence

Contd..

- **Possible FH** if they have cholesterol concentrations as defined in table 1 **and** at least one of the following.
- Family history of myocardial infarction @/c 50 years in second-degree relative or </c 60 years in first-degree relative.
- Family history of Total cholesterol>7.5 mmol/l in adult first- or second-degree relative or >6.7 mmol/l in child, brother or sister aged younger than 16 years.

Diagnosis contd..

- Dutch Lipid Clinic Network (DLCN) criteria/score

(Based on personal and family medical history, clinical signs, LDL-C concentration and DNA testing. A score is attributed to each component; the higher the score, the higher the likelihood of the person having FH)

Secondary Hyperlipidemia (2°)

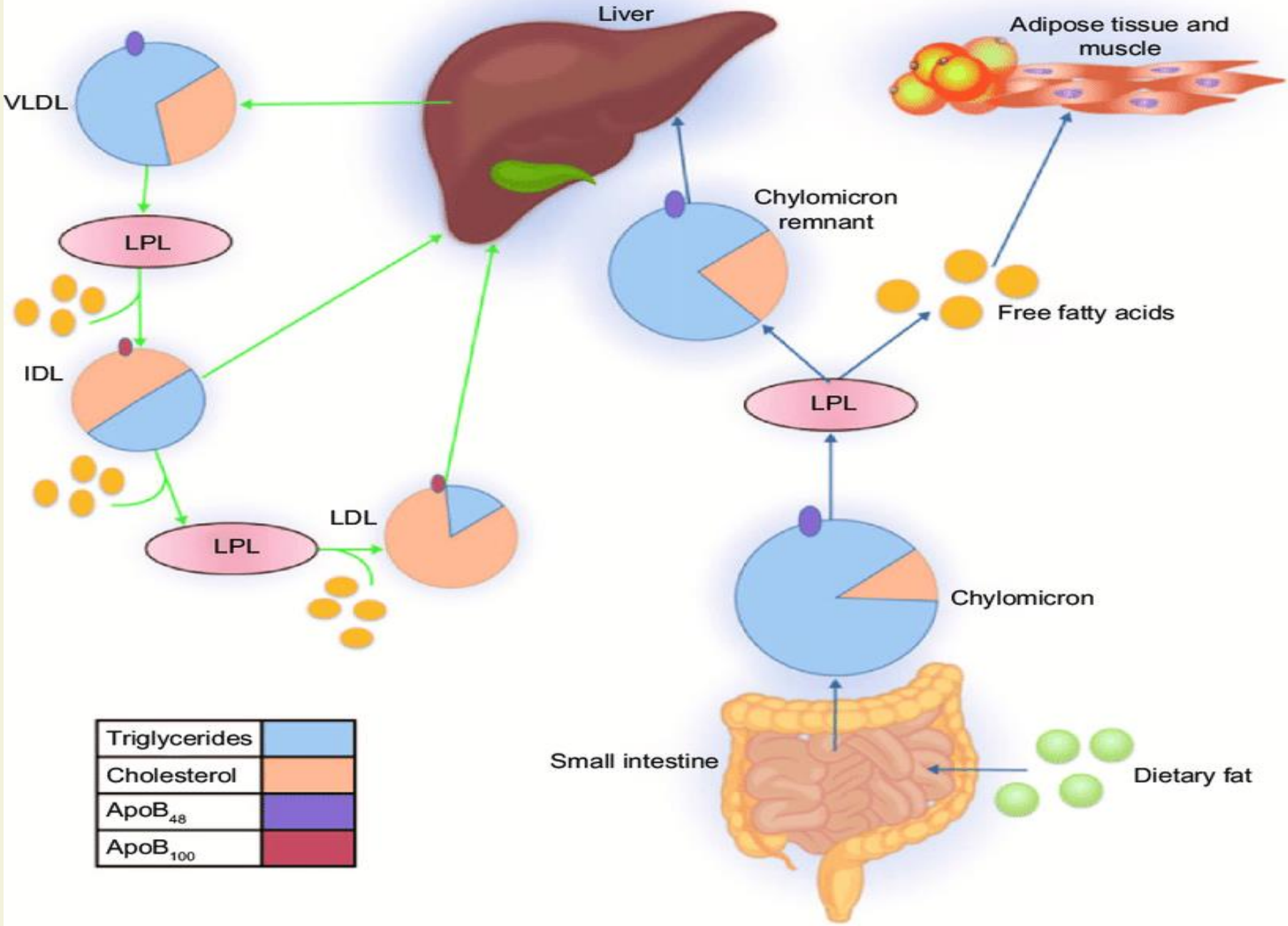
- Hepatic
- Renal
- Thyroid
- Diabetes
- Drugs
- Smoking
- Alcohol
- Obesity/overweight
- Sedentary lifestyle
- Diet
- Ongoing inflammation

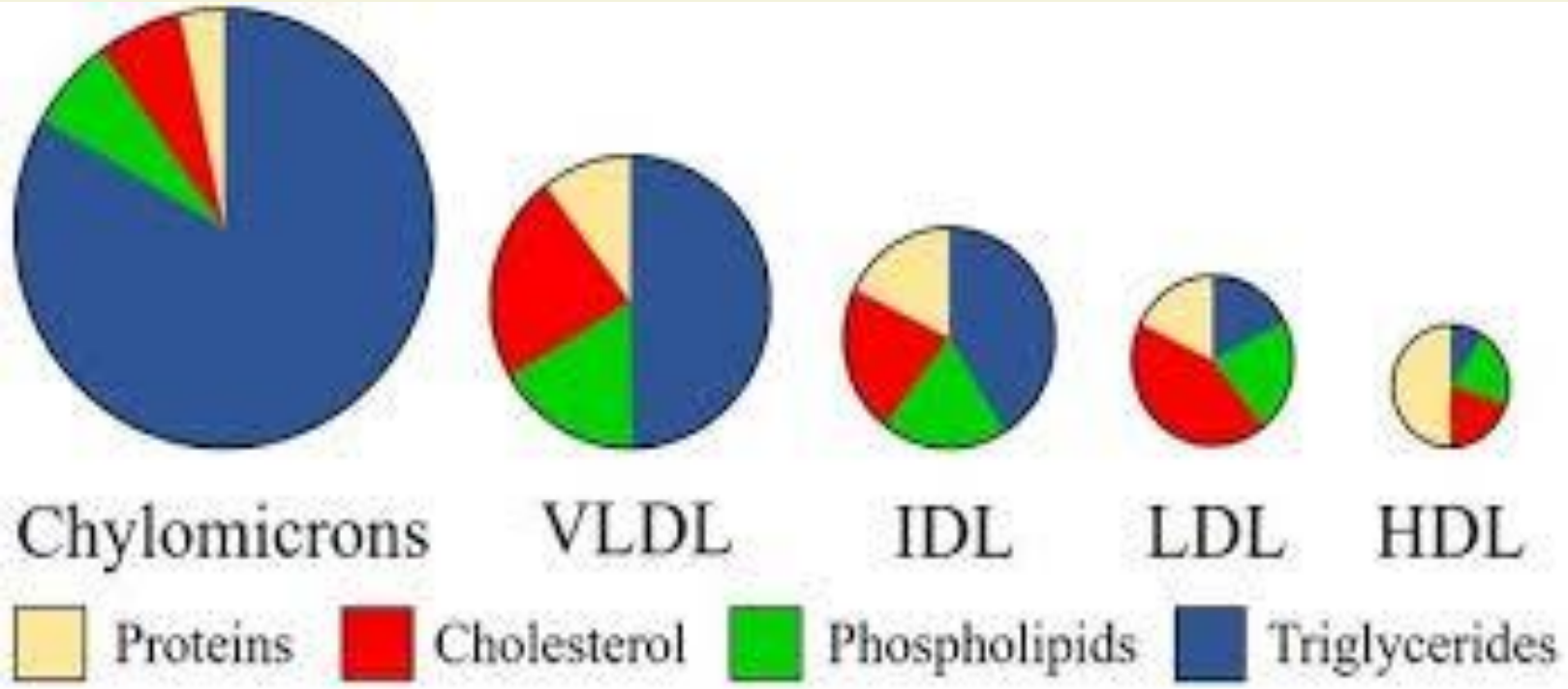
Lipoproteins

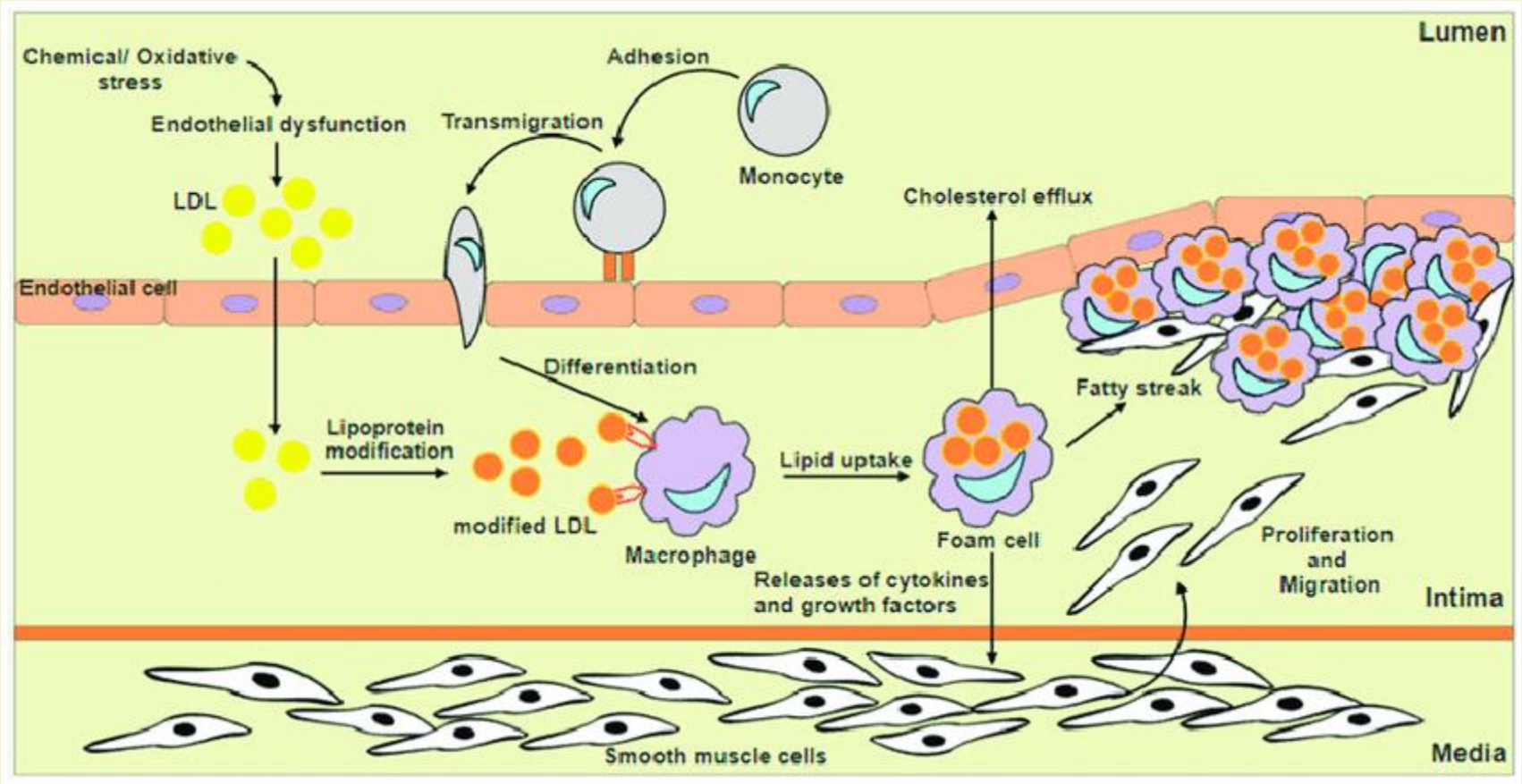
- Chylomicrons
- VLDL
- IDL
- LDL
- HDL

Fasting or non Fasting Cholesterol

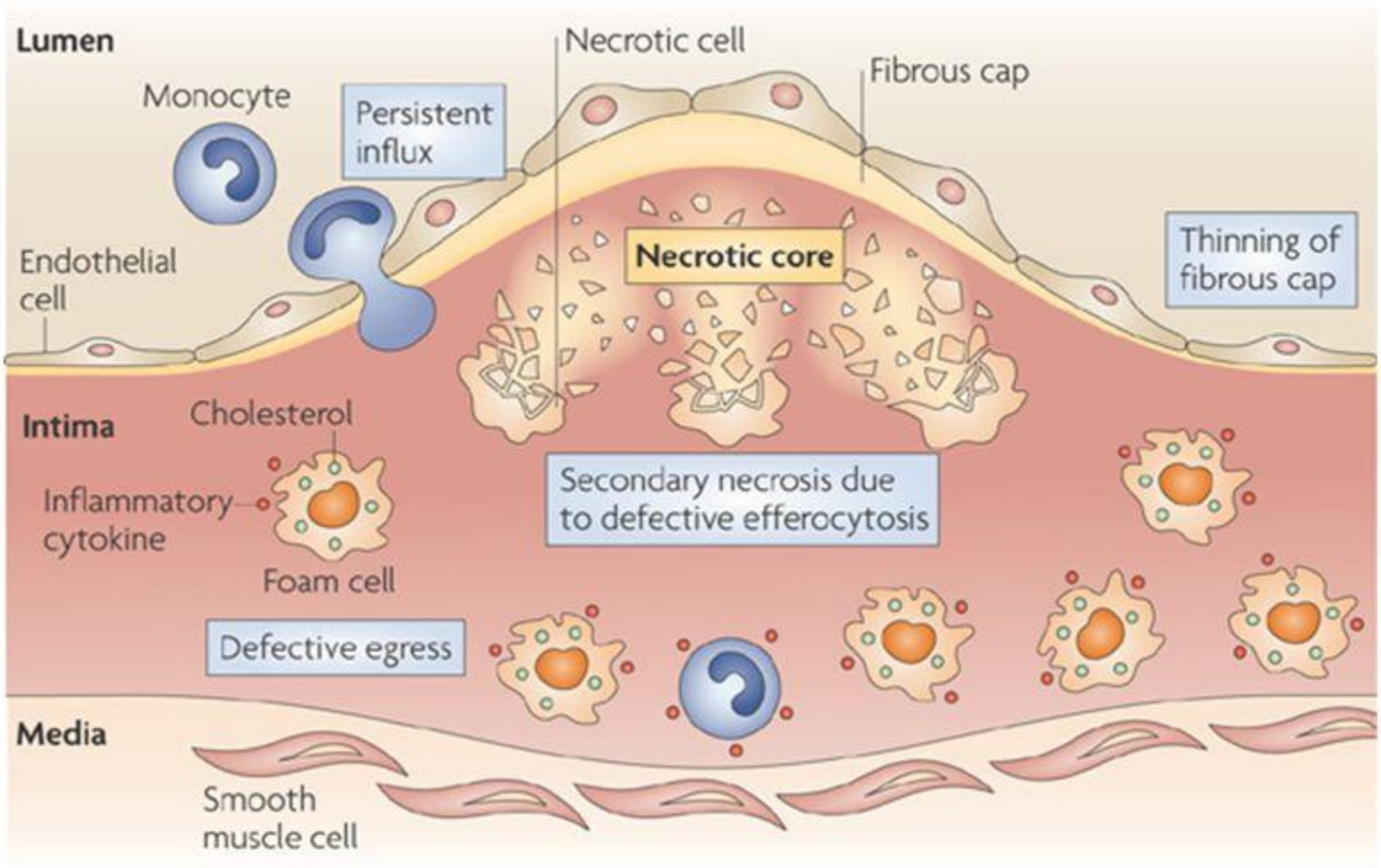
- Depends upon what is the eaten in the last in the last 12 hours?
- A smaller target to chase


Liver
Adipose tissue and muscle
VLDL
LPL
IDL
LPL
LDL
Chylomicron remnant
Free fatty acids
LPL
Chylomicron
Small intestine
Dietary fat
Triglycerides
Cholesterol
ApoB48
ApoB100

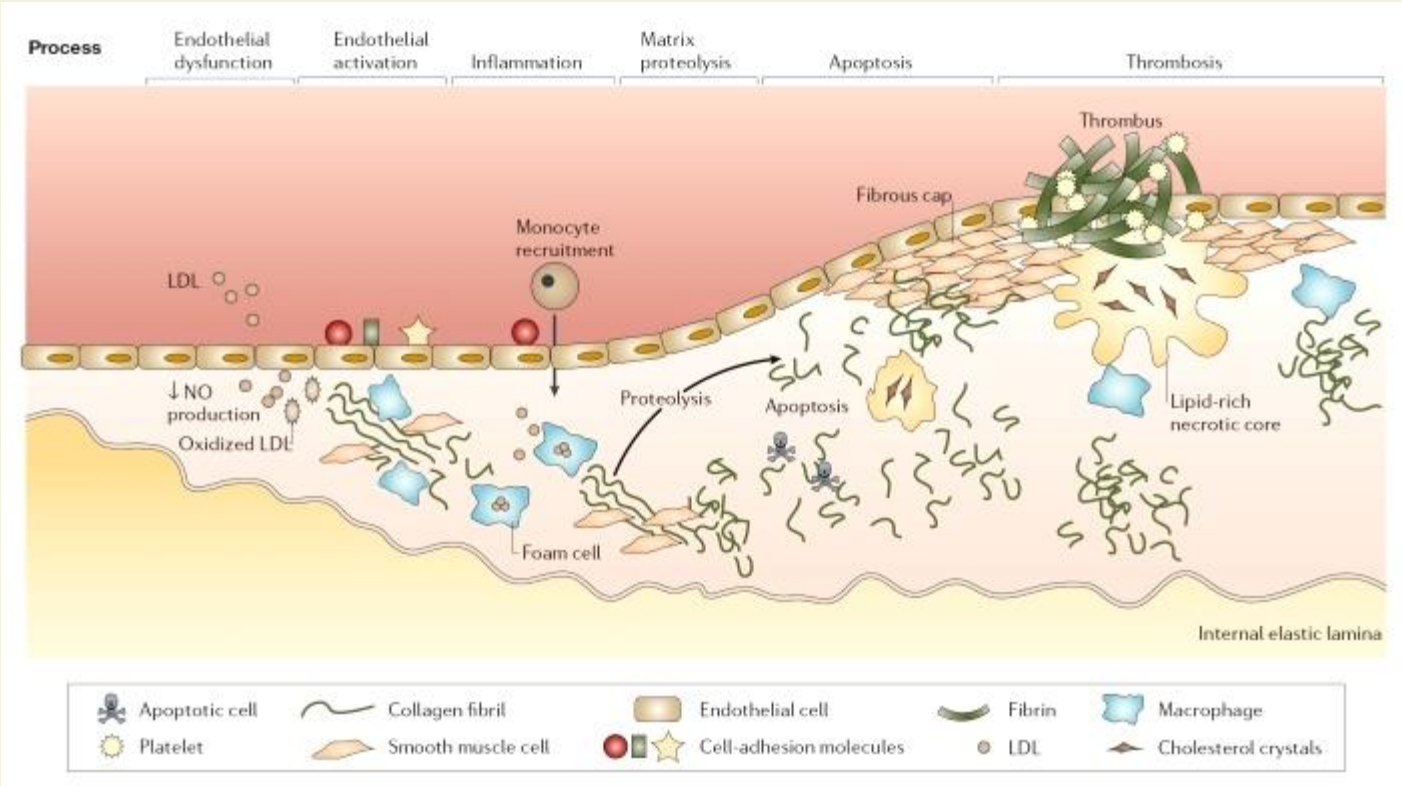

Chylomicrons
VLDL
IDL
LDL
HDL
Proteins
Cholesterol
Phospholipids
Triglycerides


Lumen
Chemical/ Oxidative stress
Endothelial dysfunction
LDL
Endothelial cell
Adhesion
Transmigration
Monocyte
Cholesterol efflux
Differentiation
Lipoprotein modification
modified LDL
Macrophage
Lipid uptake
Foam cell
Fatty streak
Releases of cytokines and growth factors
Proliferation and Migration
Intima
Smooth muscle cells
Media

Atherosclerotic Plaque



Nature Reviews | Immunology


Process
Endothelial dysfunction
Endothelial activation
Inflammation
Matrix proteolysis
Apoptosis
Thrombosis
Thrombus
Fibrous cap
Monocyte recruitment
LDL
↓ NO production
Oxidized LDL
Proteolysis
Apoptosis
Lipid-rich necrotic core
Foam cell
Internal elastic lamina
Apoptotic cell
Collagen fibril
Endothelial cell
Fibrin
Macrophage
Platelet
Smooth muscle cell
Cell-adhesion molecules
LDL
Cholesterol crystals

Lipoprotein pattern	Major elevation in plasma		Ocular features
	Lipoprotein	TGL	
Type I	Chylomicrons	TGL	Lipemia retinalis; iris and retinal xanthomas; lipidkeratopathy; adult onset Coats'disease
Type II a and b	LDL/VLDL	Cholesterol, TGL	Xanthelasma; corneal arcus in fourth to fifth decades; xanthomas of retina, choroid or conjunctiva with lipid keratopathy
Type III	Remnants	TGL, cholesterol	Early onset of arcus senilis; rarely lipemia retinalis; xanthomas
Type IV	VLDL	TGL	Lipemia retinalis; xanthomas
Type V	VLDL, chylomicrons	TGL, cholesterol	Lipemia retinalis; xanthomas not uncommon

TGL: Triglycerides, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein

Interpretation of risk

- Total Cholesterol
- LDL-Cholesterol
- TC:HDL ratio
- Non HDL cholesterol
- TC:LDL ratio

Interpretation of risk

- Triglyceride level

Why rule out 2^{o} causes?

- Good medicine - treat the cause, not the resulting condition
- Improves tolerance
- Better compliance
- Improves quality of care

Target Lipids

- For Primary prevention

Reduce LDL level to at least 50 % from baseline or from the total cholesterol level every time.

- For secondary prevention:

Reduce LDL cholesterol to c2.0 mmol/L.

(‘*Patients who fail to reach this target should be referred to a specialist clinic*’)

Joint British Recommendations
Dec 1998

What class of drugs?

- ‘The best evidence of cholesterol lowering in secondary prevention comes from randomised controlled trials using statins; these drugs are thus the preferred class for CHD patients’

Joint British Recommendations
Dec 1998

What class of drugs?

- ‘Generally a statin should not be the initial choice of therapy in combined hyperlipidaemia, certainly when the triglycerides are more than 5.0 mmol/L’

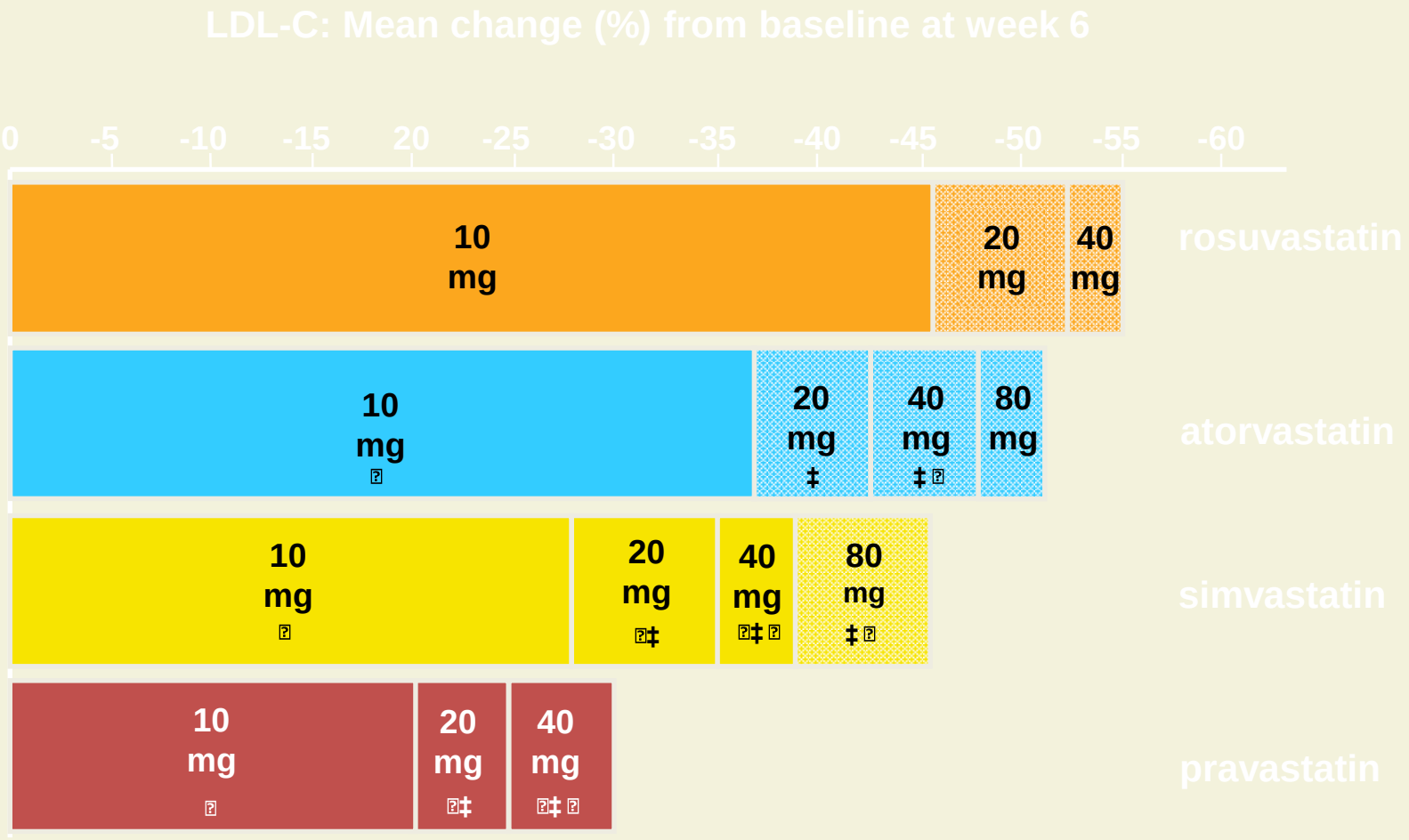
Joint British Recommendations
Dec 1998

Rule of 5 & Rule of 7

- A doubling of each statin lowers Total cholesterol an additional 5%
- A doubling of each statin lowers LDL cholesterol an additional 7%

Am J Cardiol 1997; 80: 166-167

LDL-C reduction and statins



p<0.002 vs. rosuvastatin 10mg ‡ p<0,002 vs, rosuvastatin 20mg p<0.002 vs. rosuvastatin 40mg

Jones PH for the STELLAR Study Group. JACC 2003;41:in press.

Raised ALT

- ALT usually is sufficient.
- Baseline normal ALT rules out bias
- Stop statin if consistently above 3 times upper reference limit
- Individuals with Gilbert's syndrome might benefit from lipid profile
- If pre-treatment ALT is raised then rule out possible cause by doing:

Chronic liver dysfunction screen

Ultrasound abdomen

Muscle Problems

- ‘If the creatine kinase concentration is markedly elevated (>10 times upper limit of normal), and myopathy is suspected or diagnosed, treatment should be discontinued’
- Monitoring of creatine kinase is required if patients of lipid-lowering medications have muscle symptoms
- Myalgia may not increase CK levels but myositis will.

BNF March 2001 p125

Muscle Problems

- Myositis, defined as muscle inflammation with CK levels 10 times normal (> 2,000 U/l in men, >1,500 U/l in women), is rarely reported.
- It is important to note that the CK level returns to normal within 48 hours of discontinuing lipid lowering medication.

Muscle Problems

- Rhabdomyolysis associated with lipid lowering drugs is rare (1 case in every 100,000 treatment years) but may be increased in those with renal impairment and possibly those with hypothyroidism
- Concomitant treatment with cyclosporin/calcium channel blockers/antiretrovirals or in combined statin and fibrate therapy may be associated with increased risk of serious muscle toxicity
- Subclinical or untreated hypothyroidism may induce myalgia and myositis.

BNF March 2001 p125

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis	
Interacting agents	Prescribing recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Nefazodone Ciclosporin Danazol Gemfibrozil	Contraindicated with simvastatin
Amiodarone Amlodipine Verapamil Diltiazem	Do not exceed 20 mg simvastatin daily
Fusidic acid	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

Table 1: Effect of co-administered medicinal products on the pharmacokinetics of Atorvastatin

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[a]	Clinical Recommendation[a]
Grapefruit Juice, 240 mL OD *	40 mg, SD	↑37%	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	↑51%	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10mg, SD	↑33%^	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10mg, single dose	80 mg, SD	↑18%	No specific recommendation.
Cimetidine 300 mg QID, 2 weeks	10mg OD for 4 weeks	↓less than 1%^	No specific recommendation.
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks	10mg OD for 4 weeks	↓35%^	No specific recommendation.
Gemfibrozil 600 mg BID, 7 days	40mg SD	↑35%	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40mg SD	↑3%	Lower starting dose and clinical monitoring of these patients is recommended.
Antiretrovirals		2.3-9.4%↑	

Effect of co-administered medicinal products on Rosuvastatin exposure

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	**1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1.2-fold ↑
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Antiretrovirals		1.2-3.4% ↑

Most commonly asked questions

- What is cholesterol?
- What is a good level?
- Is it required for normal body functioning?
- Why do I need statins?
- Can I manage by diet and lifestyle?
- Why do I need to exercise if I am good with diet?
- I do not have even one meal in the day?

Contd..

- I only drink alcohol over weekends
- What is the recommendation for Alcohol intake?
- Are my drugs interfering with my Cholesterol?
- I eat healthy stuff
- I like my fruit
- I feel well so why should I take tablets
- I only smoke 2-5 cigarettes/roll ups per day

contd

- I am physically active
- Are over the shelf fish oil beneficial
- When can my children be tested and is it needed?
- What if the Lipids are of no concern?
- When can my child have treatment if needed.

Mrs A-58Y

- TC 7.45
- TG 1.48
- LDL 5.40
- HDL
- 1.07

Mr B

- TC 24.56
- TG 120
- HDL 0.07
- LDL
- NC

Case

- CH 7.14
- TG 10.71
- LDL-C NC

- Treatment provided was Atorvastatin 40 mg

Mr C- 42 Y

- TC 6.65
- LDL 4.05
- TG 1.05

Mrs D- 56

- TC 8.40
- TG 3.00
- LDL 5.00
- HDL
- 1.12

Mr E-48y

- TC 6.34
- TG 5.78
- HDL 0.89
- LDL NC

Diagnosis of Hyperlipidemia

- Differentiate Primary from Secondary Hyperlipidemia
- Use Simon Broome's criteria/Dutch score to screen for FH
- Any disproportionately raised LDL ie >50% of total cholesterol needs a folllow up
- Treat Hypertriglyceridemia before treating cholesterol.

Management

- Use low potency low dose statins initially to avoid muscle related side effects
- All lipid lowering drugs(LLD) target cell membranes
- Replace VitD3 before commencing LLD.
- Combined Hypertriglyceridemia is the most common cause of liver dysfunction caused by Statins.

Take home points

- One size does not fit all-custom made advice.
- Treat the Cause and not the resulting Condition.
- Target the source of calories.
- Hypertriglyceridemia is mostly secondary in nature and encourages lipoprotein build up.
- Fatty infiltration may induce liver dysfunction, pancreatitis and diabetes with most lipid lowering drugs.
- Tolerance to statins varies individually
- Raised HDL-Cholesterol does not always reduce cardiovascular risk. (Lancet. 2012 Aug 11;380(9841):572-80. doi: 10.1016/S0140-6736(12)60312-2. Epub 2012 May 17)